Trastuzumab deruxtecan (gastric or gastroesophageal junction adenocarcinoma)

Benefit assessment according to §35a SGB V[1] (new scientific findings)

EXTRACT

Project: A25-128 Version: 1.0 Status: 29 Dec 2025 DOI: 10.60584/A25-128_en

[1] Translation of Sections I 1 to I 6 of the dossier assessment *Trastuzumab deruxtecan (Adenokarzinom des Magens oder des gastroösophagealen Übergangs) – Nutzenbewertung gemäß § 35a SGB V*. 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 (gastric or gastroesophageal junction adenocarcinoma) – Benefit assessment according to §35a SGB V

Commissioning agency

Federal Joint Committee

Commission awarded on

30 September 2025

Internal Project No.

A25-128

DOI-URL

https://doi.org/10.60584/A25-128_en

Address of publisher

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Recommended citation

Institute for Quality and Efficiency in Health Care. Trastuzumab deruxtecan (gastric or gastroesophageal junction adenocarcinoma); Benefit assessment according to §35a SGB V (new scientific findings); Extract [online]. 2025 [Accessed: DD.MM.YYYY]. URL: https://doi.org/10.60584/A25-128_en.

Keywords

Trastuzumab deruxtecan, Stomach Neoplasms, Esophageal Neoplasms, Benefit Assessment, NCT04704934

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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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Part I: Benefit assessment

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

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CTCAE	Common Terminology Criteria for Adverse Events
DGHO	German Society for Haematology and Medical Oncology
ECOG PS	Eastern Cooperative Oncology Group Performance Status
FACT-G	FACT-General
FACT-Ga	Functional Assessment of Cancer Therapy-Gastric
GaCS	gastric cancer subscale
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HER2	human epidermal growth factor receptor 2
IHC	immunohistochemistry
ILD	Interstitial lung disease
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
ISH	in situ hybridization
MMRM	mixed-effects model with repeated measures
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SmPC	summary of product characteristics
SMQ	Standardized Medical Dictionary for Regulatory Activities Query
SOC	System Organ Class
VAS	visual analogue scale

I 1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug 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 30 September 2025.

Research question

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

The research question shown in Table 2 was defined in accordance with the ACT specified by the Federal Joint Committee (G-BA).

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

Therapeutic indication	**ACT**[a]
Adult patients with advanced HER2-positive gastric or gastroesophageal junction adenocarcinoma who have received one prior trastuzumab-based regimen in first-line therapy[b]	▪ docetaxel or ▪ irinotecan or ▪ paclitaxel or ▪ **ramucirumab in combination with paclitaxel**
a. Presented is the ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company according to the inclusion criteria in Module 4 Section 4.2.2 is printed in **bold**. b. According to the G-BA, the therapeutic indication includes patients with unresectable, locally advanced or metastatic disease. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2	

The company deviated from the G-BA's definition of the ACT in that it identified the option of ramucirumab in combination with paclitaxel (hereinafter referred to as ramucirumab + paclitaxel) as the sole ACT. This deviation from the G-BA's ACT had no bearing on the benefit assessment, as ramucirumab + paclitaxel was 1 of the 4 options included in the ACT defined by the G-BA, and the company provided evidence versus the option ramucirumab + paclitaxel.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) were used to derive the added benefit.

Study pool and study design

The DESTINY-Gastric04 study was included for the benefit assessment.

DESTINY-Gastric04 is an ongoing, open-label RCT comparing trastuzumab deruxtecan with ramucirumab + paclitaxel. The study included adult patients with HER2-positive, unresectable, locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma who had experienced disease progression during or after first-line therapy containing trastuzumab. The study only included patients with an Eastern Cooperative Oncology Group Performance Status of 0 or 1 (ECOG PS). Patients were not allowed to have received any further antineoplastic therapy after trastuzumab-containing treatment. Neoadjuvant or adjuvant therapy with a trastuzumab-containing regimen could be counted as a line of therapy if disease progression occurred during therapy or within 6 months of completing therapy.

Overall, 494 patients were included in the study and randomly allocated in a 1:1 ratio either to treatment with trastuzumab deruxtecan (N = 246) or to ramucirumab + paclitaxel (N = 248).

Treatment with trastuzumab deruxtecan was largely in compliance with the specifications of the summary of product characteristics (SmPC). There were possible deviations in the use of concomitant medication with corticosteroids and antiemetics for the prophylaxis of nausea and vomiting. Treatment with ramucirumab + paclitaxel was also largely carried out in accordance with the specifications set out in the respective SmPCs. However, it was unclear to what extent patients had had prior treatment with platinum and fluoropyrimidine chemotherapy, as required by the marketing authorization. However, based on the information in the dossier, it could be assumed that, for a large proportion of the patients, treatment in the control arm was carried out in accordance with the marketing authorization and in line with the guidelines. Furthermore, the study protocol did not provide for the mandatory pretreatment with corticosteroids, H1 antihistamines and H2 receptor antagonists to prevent hypersensitivity reactions to paclitaxel, nor for the recommended pretreatment with H1 antihistamines to prevent infusion-related reactions to ramucirumab. These uncertainties were taken into account in the risk of bias for the respective AE outcomes and, where applicable, for the patient-reported outcomes.

The study's primary outcome is overall survival. Patient-relevant secondary outcomes comprised outcomes in the categories morbidity, health-related quality of life and adverse events (AEs).

Data cut-off

For the ongoing DESTINY-Gastric04 study, data from a prespecified interim data cut-off of 24 October 2024 were available, which was conducted following 266 deaths.

Risk of bias

The risk of bias was rated high for the results of the outcome overall survival and the outcomes in the side effect category. The main reasons for this (apart from discontinuation due to AEs) were, in the absence of blinding, a relevant difference in the rate of study discontinuation at own request (3.3% in the intervention arm vs. 8.9% in the control arm). Another reason for the overall survival outcome was a relevant difference among patients who did not receive treatment after randomization (0.8% in the intervention arm vs. 6.0% in the control arm). However, it was unclear to what extent the patients in the control arm who did not receive treatment after randomization contributed to the reported study discontinuations, nor was it clear for how long the patients were followed up or when the study discontinuations occurred. Furthermore, with regard to the overall survival outcome, there was a relevant difference in the proportion of censorings between the treatment arms already at an early stage. In Months 3, 6 and 9, the difference in the proportion of censored patients between the treatment groups ranged from 4.4 to 7.6 percentage points. The number of censorings in Month 3 was similar to the number of events and remained at a high level thereafter. These differences cannot be explained solely by administrative censorings.

The results of the specific AEs nausea (PT, severe AEs) and vomiting (PT, AEs) additionally had a high risk of bias due to uncertainties regarding the antiemetic premedication required in accordance with the SmPC.

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

Summary assessment of the certainty of conclusions

Irrespective of the aspects described under ‘risk of bias’, the certainty of conclusions regarding the study results for the outcome of overall survival was further limited by the uncertainties regarding the subsequent therapies used.

Based on the study results, at most hints, e.g. of an added benefit, can be derived for all outcomes.

Results

Mortality

Overall survival

A statistically significant difference in favour of trastuzumab deruxtecan was shown for the outcome of overall survival. There is a hint of an added benefit of trastuzumab deruxtecan in comparison with ramucirumab + paclitaxel.

Morbidity

Symptoms (PGIS) and health status (EQ-5D VAS and PGIC)

No suitable data were available for the outcomes symptoms, recorded using PGIS, and health status, recorded using EQ-5D VAS and PGIC. There is no hint of an added benefit of trastuzumab deruxtecan in comparison with ramucirumab + paclitaxel; an added benefit is therefore not proven.

Health-related quality of life

FACT-Ga

No suitable data were available for the outcome of health-related quality of life, recorded using the FACT-Ga. There is no hint of an added benefit of trastuzumab deruxtecan in comparison with ramucirumab + paclitaxel; an added benefit is therefore not proven.

Side effects

SAEs and severe AEs (CTCAE grade ≥ 3)

No suitable data were available for the outcomes SAEs and severe AEs (CTCAE grade ≥ 3). The effect in favour of trastuzumab deruxtecan in the outcome severe AEs (CTCAE grade ≥ 3) was not sufficiently large to be interpreted with sufficient certainty. However, based on the available data, it was possible to make a qualitative assessment of the side effects when weighing up the overall picture.

Discontinuation due to AEs

A statistically significant difference in favour of trastuzumab deruxtecan compared with ramucirumab + paclitaxel was shown for the outcome discontinuation due to AEs.

There was an effect modification for the characteristic of age, however. For patients < 65 years of age, there is a hint of lesser harm from trastuzumab deruxtecan in comparison with ramucirumab + paclitaxel. For patients ≥ 65 years, there is no hint of greater or lesser harm of trastuzumab deruxtecan in comparison with ramucirumab + paclitaxel; greater or lesser harm is therefore not proven.

Cardiac disorders (severe AEs)

The company presented no calculations on hazard ratio or p-value for this outcome. Due to the low number of events, it cannot be assumed that there would be a statistically significant effect in case of suitable analyses. There is no hint of greater or lesser harm of trastuzumab deruxtecan in comparison with ramucirumab + paclitaxel; greater or lesser harm is therefore not proven.

Platelet count decreased (severe AEs) and ILD/pneumonitis (SAEs)

For the outcomes platelet count decreased (severe AEs) and ILD/pneumonitis (SAEs), there was no statistically significant difference between the treatment groups in either case. For both outcomes, there is no hint of greater or lesser harm of trastuzumab deruxtecan in comparison with ramucirumab + paclitaxel; greater or lesser harm is therefore not proven.

Stomatitis (AEs), epistaxis (AEs), musculoskeletal and connective tissue disorders (AEs), renal and urinary disorders (AEs), hypertension (severe AEs) and nervous system disorders (severe AEs)

There was a statistically significant difference in favour of trastuzumab deruxtecan compared with ramucirumab + paclitaxel for the outcomes stomatitis (AEs), epistaxis (AEs), musculoskeletal and connective tissue disorders (AEs), renal and urinary disorders (AEs), hypertension (severe AEs) and nervous system disorders (severe AEs). In each case, there is a hint of lesser harm of trastuzumab deruxtecan in comparison with ramucirumab + paclitaxel.

Vomiting (AEs)

A statistically significant difference to the disadvantage of trastuzumab deruxtecan compared with ramucirumab + paclitaxel was shown for the outcome vomiting (AEs). There is a hint of greater harm of trastuzumab deruxtecan in comparison with ramucirumab + paclitaxel.

Nausea (severe AEs)

A statistically significant difference to the disadvantage of trastuzumab deruxtecan compared with ramucirumab + paclitaxel was shown for the outcome nausea (severe AEs). There is a hint of greater harm of trastuzumab deruxtecan in comparison with ramucirumab + paclitaxel.

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

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

Overall, there is a majority of positive effects and a few negative effects of trastuzumab deruxtecan compared with ramucirumab plus paclitaxel. Data across the entire observation period were only available for overall survival. All other effects referred exclusively to the shortened observation period (until the end of treatment [plus 40 days]). The analyses presented on the outcome categories morbidity and health-related quality of life, and on the outcomes SAEs and severe AEs are not suitable for the benefit assessment. However, based on the available data, it was not anticipated that the intervention would show disadvantages in terms of the SAEs and severe AEs outcomes to an extent that would call into question the advantage observed in the overall survival outcome.

In terms of positive effects, there is a hint of considerable added benefit of trastuzumab deruxtecan in comparison with ramucirumab + paclitaxel for the outcome of overall survival. In addition, in terms of side effects there were various positive effects resulting from lesser harm, both for outcomes in the severe/serious side effects category and in the non-severe/non-serious side effects category, to varying extents. These positive effects are offset only by isolated negative effects in terms of specific AEs: in the category of severe/serious side effects for the specific AE nausea with a non-quantifiable extent, and for the non-severe specific AE vomiting with a considerable extent. Overall, the positive effects therefore clearly outweigh the negative ones.

In summary, there is a hint of a considerable added benefit of trastuzumab deruxtecan versus ramucirumab + paclitaxel for adult patients with advanced HER2-positive gastric or gastroesophageal junction adenocarcinoma who have received one prior trastuzumab-based regimen in first-line therapy.

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

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

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

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adult patients with advanced HER2-positive gastric or gastroesophageal junction adenocarcinoma who have received one prior trastuzumab-based regimen in first-line therapy[b]	▪ docetaxel or ▪ irinotecan or ▪ paclitaxel or ▪ **ramucirumab in combination with paclitaxel**	Hint of considerable added benefit[c]

a. Presented is the ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company according to the inclusion criteria in Module 4 Section 4.2.2 is printed in **bold**.
b. According to the G-BA, the therapeutic indication includes patients with unresectable, locally advanced or metastatic disease.
c. Only patients with an ECOG PS of 0 or 1 were included in the DESTINY-Gastric04 study, with the exception of 2 patients. 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

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

I 2 Research question

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

The research question shown in Table 4 was defined in accordance with the ACT specified by the Federal Joint Committee (G-BA).

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

Therapeutic indication	**ACT**[a]
Adult patients with advanced HER2-positive gastric or gastroesophageal junction adenocarcinoma who have received one prior trastuzumab-based regimen in first-line therapy[b]	▪ docetaxel or ▪ irinotecan or ▪ paclitaxel or ▪ **ramucirumab in combination with paclitaxel**
a. Presented is the ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company according to the inclusion criteria in Module 4 Section 4.2.2 is printed in **bold**. b. According to the G-BA, the therapeutic indication includes patients with unresectable, locally advanced or metastatic disease. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2	

The company deviated from the G-BA's definition of the ACT in that it identified the option of ramucirumab in combination with paclitaxel (hereinafter referred to as ramucirumab + paclitaxel) as the sole ACT. This deviation from the G-BA's ACT had no bearing on the benefit assessment, as ramucirumab + paclitaxel was 1 of the 4 options included in the ACT defined by the G-BA, and the company provided evidence versus the option ramucirumab + paclitaxel.

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

I 3 Information retrieval and study pool

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

Sources used by the company in the dossier:

- Study list on trastuzumab deruxtecan (status: 28 July 2025)
- Bibliographical literature search on trastuzumab deruxtecan (last search on 28 July 2025)
- Search of trial registries/trial results databases for studies on trastuzumab deruxtecan (last search on 28 July 2025)
- Search on the G-BA website for trastuzumab deruxtecan (last search on 12 August 2025)

To check the completeness of the study pool:

- Search of trial registries for studies on trastuzumab deruxtecan (last search on 9 October 2025); for search strategies, see I Appendix A of the full dossier assessment

The search did not identify any additional relevant studies.

I 3.1 Studies included

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

Table 5: Study pool – RCT, direct comparison: trastuzumab deruxtecan vs. ramucirumab + paclitaxel

Study	Study category			Available sources		
	Study for the marketing authorization of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication (yes/no [citation])
Study DS8201-A-U306 (DESTINY-Gastric04[c])	No	Yes	No	Yes [3]	Yes [4-6]	Yes [7]

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

CSR: clinical study report; G-BA: Federal Joint Committee; RCT: randomized controlled trial

The study pool for the benefit assessment concurred with that of the company.

I 3.2 Study characteristics

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

Table 6: Characteristics of the included study – RCT, direct comparison: trastuzumab deruxtecan vs. ramucirumab + paclitaxel

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
DESTINY-Gastric04	RCT, open-label, parallel	Adults with HER2-positive[b], unresectable, locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma and: ▪ Disease progression during or after first-line therapy containing trastuzumab[c, d] ▪ ECOG PS 0 or 1	trastuzumab deruxtecan (N = 246) ramucirumab + paclitaxel (N = 248)	Screening: up to 28 days Treatment: until disease progression, unacceptable toxicity or treatment discontinuation following the physician's or patient's decision Follow-up[e]: outcome-specific, at most until death	117 centres in Argentina, Belgium, Brazil, Chile, China, France, Germany, Hong Kong, Ireland, Israel, Italy, Japan, Poland, Portugal, Romania, Singapore, South Korea, Spain, Taiwan, Turkey and the United Kingdom 5/2021–ongoing[f] Data cut-off: ▪ 24 October 2024[g]	Primary: overall survival Secondary: morbidity, health-related quality of life, AEs

a. Primary outcomes include information without taking into account the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b. Locally or centrally confirmed HER2-positive status (IHC 3+ or IHC 2+ and evidence of HER2 amplification by ISH) based on a tumour biopsy obtained after disease progression on or after a trastuzumab-containing first-line regimen.
c. Previous neoadjuvant or adjuvant therapy with a trastuzumab-containing regimen was counted as a line of therapy if disease progression occurred during therapy or within 6 months of completing therapy. If the neoadjuvant or adjuvant therapy did not include trastuzumab, it was not counted as a line of therapy.
d. Patients were not to have received any further antineoplastic therapy after trastuzumab-containing treatment.
e. Outcome-specific information is described in Table 8.
f. In accordance with the study design, the study will end when all patients have died, patients have discontinued treatment or long-term follow-up for overall survival, patients are eligible to join an alternative study with trastuzumab deruxtecan, or the study is terminated by the company. In Module 4 A, the company states that the expected completion date is May 2026.
g. Prespecified interim data cut-off (planned after approximately 237 deaths, carried out after 266 events). In accordance with the study design, this served as both the primary and final data cut-off, as evidence of superiority in the overall survival outcome had already been provided at that stage.

AE: adverse event; ECOG PS: Eastern Cooperative Oncology Group Performance Status; HER2: human epidermal growth factor receptor 2; IHC: immunohistochemistry; ISH: in situ hybridization; N: number of randomized patients; RCT: randomized controlled trial

Table 7: Characteristics of the intervention – RCT, direct comparison: trastuzumab deruxtecan vs. ramucirumab + paclitaxel

Study	Intervention	Comparison
DESTINY-Gastric04	Treatment in 21-day cycles: trastuzumab deruxtecan 6.4 mg/kg BW[a] IV on Day 1	Treatment in 28-day cycles: ramucirumab 8 mg/kg BW IV on Days 1 and 15 + paclitaxel 80 mg/m^2 BSA IV on Days 1, 8 and 15
	Dose modification: ▪ Dose interruption for up to 126 days allowed ▪ Dose reductions due to toxicity were permitted as follows[b]: 1st dose level: 5.4 mg/kg BW 2nd dose level: 4.4 mg/kg BW	▪ Dose modifications according to local marketing authorization
	Prior treatment ▪ Trastuzumab-containing first-line treatment **Disallowed prior treatment** ▪ Further antineoplastic therapy following trastuzumab-containing first-line treatment ▪ Total pneumonectomy ▪ Antibody-drug conjugate consisting of an exatecan derivative (topoisomerase I inhibitor) **Allowed concomitant treatment** ▪ Before each infusion of trastuzumab deruxtecan: a combination of 2 or 3 drugs to prevent nausea and vomiting, e.g. dexamethasone with 5-hydroxytryptamine receptor antagonists and/or neurokinin-1 receptor antagonists ▪ Haematopoietic growth factors for prophylaxis or treatment **Disallowed concomitant treatment** ▪ Other antineoplastic therapies (excluding use of hormones for non-cancer-related conditions) and other experimental interventions ▪ Radiotherapy (excluding palliative radiation to known sites other than the thorax) ▪ Systemic corticosteroids or other immunosuppressive medications (except for the treatment of AEs) ▪ Chloroquine or hydroxychloroquine	

a. If during the course of treatment the patient's weight changes by ≥ ±10% of the baseline weight, the patient's dose will be recalculated based on the patient's updated weight.
b. Subsequent cycles after dose reduction due to toxicity should be continued at the reduced dose; a dose increase is not allowed. If toxicity persists after 2 dose reductions, the study treatment should be discontinued.

AE: adverse event; BSA: body surface area; BW: body weight; IV: intravenous; RCT: randomized controlled trial

Study design

The DESTINY-Gastric04 study is an ongoing, open-label RCT comparing trastuzumab deruxtecan with ramucirumab + paclitaxel. The study included adult patients with HER2-positive, unresectable, locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma who had experienced disease progression during or after first-line therapy containing trastuzumab. HER2 status had to be determined on the basis of a tumour biopsy obtained after disease progression and had to show a score of 3+ or 2+ by

immunohistochemistry (IHC). If IHC 2+ was present, in situ hybridization (ISH) had to be positive. The study only included patients with an Eastern Cooperative Oncology Group Performance Status of 0 or 1 (ECOG PS). Patients were not allowed to have received any further antineoplastic therapy after trastuzumab-containing treatment. Neoadjuvant or adjuvant therapy with a trastuzumab-containing regimen could be counted as a line of therapy if disease progression occurred during therapy or within 6 months of completing therapy.

Overall, 494 patients were included in the study and randomly allocated in a 1:1 ratio either to treatment with trastuzumab deruxtecan (N = 246) or to ramucirumab + paclitaxel (N = 248). Randomization was stratified according to HER2 status (IHC 3+ versus IHC 2+/ISH+), region (Asia [excluding mainland China] versus Western Europe versus mainland China / rest of the world) and time to disease progression following first-line treatment (< 6 months vs. ≥ 6 months).

Treatment with trastuzumab deruxtecan was largely in compliance with the specifications of the summary of product characteristics (SmPC) [8]. Possible deviations may arise when using concomitant medication with corticosteroids and antiemetics for prophylaxis of nausea and vomiting (see p. I.17, Concomitant treatment for nausea and vomiting [intervention arm]). Treatment with ramucirumab + paclitaxel was also largely carried out in accordance with the specifications set out in the respective SmPCs [9,10]. However, it was unclear to what extent patients had had prior treatment with platinum and fluoropyrimidine chemotherapy, as required by the marketing authorization (see below, Prior treatment of patients with platinum and fluoropyrimidine chemotherapy). Furthermore, the study protocol did not provide for the mandatory pretreatment with corticosteroids, H1 antihistamines and H2 receptor antagonists to prevent hypersensitivity reactions to paclitaxel, nor for the recommended pretreatment with H1 antihistamines to prevent infusion-related reactions to ramucirumab (see p. I.18, Pretreatment to prevent hypersensitivity reactions [control arm]).

Treatment with the study medication continued until disease progression, unacceptable toxicity, or treatment discontinuation at the patient's or physician's decision. The study did not provide for any switching between study arms. There were, however, no limitations regarding the choice subsequent therapies.

The study's primary outcome is overall survival. Patient-relevant secondary outcomes are outcomes in the morbidity, health-related quality of life and adverse event (AE) categories.

Prior treatment of patients with platinum and fluoropyrimidine chemotherapy

According to the SmPC [9], the ACT option relevant to this benefit assessment, i.e. ramucirumab + paclitaxel, in the control arm of DESTINY-Gastric04 should only be used if prior treatment with platinum and fluoropyrimidine chemotherapy has been administered.

However, according to the study protocol, platinum- and fluoropyrimidine-containing chemotherapy was not a prerequisite for inclusion in the study.

The company's dossier contained details of previous systemic antineoplastic therapies (see also Table 9). In the control arm, 63% of patients had been treated with oxaliplatin, 34% with cisplatin and 3% with carboplatin in a previous line of treatment. A prior fluoropyrimidine-containing chemotherapy treatment was given to 50% of patients with fluorouracil, 42% with capecitabine and 18% with tegafur. In both the current S3 guideline 'Diagnosis and treatment of gastric and gastroesophageal junction adenocarcinoma' [11] and the recommendation by the German Society for Haematology and Medical Oncology (DGHO) [12], platinum- and fluoropyrimidine-based chemotherapy in combination with trastuzumab is recommended for patients with HER2-overexpressing tumours as first-line treatment for advanced or metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma. In accordance with the inclusion criteria, all patients had received trastuzumab as prior antineoplastic therapy.

It can therefore be assumed that, for almost all patients in the control arm, prior treatment had been carried out on-label and in line with the guidelines.

Concomitant treatment for nausea and vomiting (intervention arm)

According to the SmPC, patients should receive a combination regimen of 2 or 3 drugs (e.g. dexamethasone with either a 5-HT3 receptor antagonist and/or an NK1 receptor antagonist and other drugs as per therapeutic indication) before each dose of trastuzumab deruxtecan to prevent chemotherapy-induced nausea and vomiting [8]. The antiemetic premedication required in accordance with the SmPC prior to each dose of trastuzumab deruxtecan was originally listed in the study design as a recommendation within the scope of permitted concomitant treatments, and was only described as a requirement in Amendment 3 to the study protocol dated 12 January 2023. It was unclear why the necessary antiemetic treatment was not specified until Amendment 3 of the study protocol. No precise details were available regarding the extent to which premedication in accordance with the SmPC was administered in DESTINY-Gastric04; such details can only be derived approximately from the information on concomitant treatments (due to the possibility of multiple responses). Overall, 92% of patients in the intervention arm received at least one form of concomitant antiemetic treatment, although it was unclear to what extent this was administered as premedication. It therefore remained unclear how many patients in total in the intervention arm were pretreated with antiemetics in accordance with the SmPC. This uncertainty was taken into account in the risk of bias for the respective AE outcomes and, where applicable, for the patient-reported outcomes (see Section I 3.2).

Pretreatment to prevent hypersensitivity reactions (control arm)

According to the SmPC, all patients must be pretreated with corticosteroids, H1 antihistamines and H2 receptor antagonists prior to the use of paclitaxel in order to prevent hypersensitivity reactions [10]. For ramucirumab, according to the SmPC [9], premedication with an H1 antihistamine, and as needed in combination with a corticosteroid, is recommended prior to the first infusion and, if required, for all subsequent infusions to prevent infusion-related reactions. In the study protocol premedication with corticosteroids, H1 antihistamines and H2 receptor antagonists to prevent hypersensitivity reactions to paclitaxel, and H1 antihistamines to prevent infusion-related reactions to ramucirumab, was not explicitly described; instead, reference was made to the relevant local marketing authorizations. As described above, information regarding the use of premedication can only be inferred approximately from the details of concomitant treatments. Overall, in the control arm, a maximum of 79% of patients received corticosteroids, around 75% received antihistamines any kind, and around 50% received H2 antagonists. Based on this information, it was assumed that only around 50% of patients in the control arm received premedication for paclitaxel, which according to the SmPC should contain all 3 drug classes. It is also reasonable to assume that not all patients in the control group received premedication to prevent infusion-related reactions. This uncertainty was taken into account in the risk of bias for the respective AE outcomes and, where applicable, for the patient-reported outcomes.

Data cut-off

For the ongoing DESTINY-Gastric04 study, data from a prespecified interim data cut-off of 24 October 2024 were available, which was conducted following 266 deaths. As the prespecified statistical threshold for providing evidence of the superiority of trastuzumab deruxtecan in terms of the overall survival outcome had already been exceeded by this timepoint, this became the primary and final data cut-off in accordance with the study design.

Planned duration of follow-up

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

Table 8: Planned duration of follow-up – RCT, direct comparison: trastuzumab deruxtecan vs. ramucirumab + paclitaxel

Study **Outcome category** **Outcome**	**Planned follow-up**
DESTINY-Gastric04	
Mortality	
Overall survival	Until death, withdrawal of consent, lost to follow-up, or end of study (whichever occurs first)
Morbidity	
Symptoms (PGIS) Health status (EQ-5D VAS, PGIC)	40 days (+ 7 days) after the last dose of the study medication or the start of subsequent antineoplastic therapy (whichever occurs first)
Health-related quality of life	
FACT-Ga	40 days (+ 7 days) after the last dose of the study medication or the start of subsequent antineoplastic therapy (whichever occurs first)
Side effects	
All outcomes in the side effects category	40 days (+ 7 days) after the last dose of the study medication or the start of subsequent antineoplastic therapy (whichever occurs first)[a]
a. SAEs suspected to be related to the study medication are followed up beyond this period.	
FACT-Ga: Functional Assessment of Cancer Therapy-Gastric; PGIC: Patient Global Impression of Change; PGIS: Patient Global Impression of Severity; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale	

The observation periods for the outcomes of morbidity, health-related quality of life and side effects were systematically shortened, as data were recorded only for the duration of treatment with the study medication (plus 40 + 7 days or the start of subsequent antineoplastic therapy). However, to draw a reliable conclusion on the total study period or the time to patient death, it would also be necessary to record these outcomes for the total period, as was done for survival.

Characteristics of the study population

Table 9 shows the patient characteristics of the included study.

Table 9: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: trastuzumab deruxtecan vs. ramucirumab + paclitaxel (multipage table)

Study Characteristic Category	trastuzumab deruxtecan N = 246	ramucirumab + paclitaxel N = 248
DESTINY-Gastric04		
Age [years], mean (SD)	62 (11)	63 (11)
Sex [F/M], %	24/76	17/83
Family origin		
White	116 (47)	130 (52)
Asian	101 (41)	97 (39)
Black or African American	0 (0)	2 (1)
Other	29 (12)	19 (8)
Region as a stratification factor, n (%)		
Asia (excluding mainland China)	57 (23)	60 (24)
Western Europe	140 (57)	139 (56)
Mainland China / rest of the world	49 (20)	49 (20)
ECOG PS, n (%)		
0	97 (39)	88 (35)
1	148 (60)	158 (64)
2	1 (< 1)	1 (< 1)
Missing	0 (0)	1 (< 1)
Smoking status, n (%)		
Ex-smoker	108 (44)	114 (46)
Current smoker	28 (11)	30 (12)
Location of the primary tumour, n (%)		
Stomach	153 (62)	149 (60)
Gastroesophageal junction	93 (38)	99 (40)
HER2 status, n (%)		
IHC 2+/ISH+	39 (16)	40 (16)
IHC 3+	207 (84)	208 (84)
Disease stage at the time of initial diagnosis, n (%)		
Metastatic	187 (76)	198 (80)
Locally advanced / localized / unknown	59 (24)[a]	50 (20)[a]
Disease stage at baseline, n (%)		
Metastatic	230 (93)	228 (92)
Locally advanced / localized / unknown	16 (7)[a]	20 (8)[a]
Disease duration: time from first diagnosis to randomization [months]		
Mean (SD)	17.5 (14.5)	18.1 (13.5)
Median (min; max)	12.9 (3.7; 135.1)	13.6 (2.2; 89.5)

Table 9: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: trastuzumab deruxtecan vs. ramucirumab + paclitaxel (multipage table)

Study Characteristic Category	**trastuzumab deruxtecan N = 246**	**ramucirumab + paclitaxel N = 248**
Prior systemic antineoplastic therapy, n (%)[b]	246 (100)	248 (100)
trastuzumab	244 (99)	248 (100)
oxaliplatin	177 (72)	157 (63)
fluorouracil	120 (49)	123 (50)
capecitabine	110 (45)	103 (42)
cisplatin	77 (31)	85 (34)
tegafur/gimeracil/oteracil (S-1)	45 (18)	45 (18)
carboplatin	6 (2)	8 (3)
Previous surgical intervention for gastric cancer, n (%)	64 (26)	58 (23)
Partial gastrectomy	21 (9)	14 (6)
Total gastrectomy	19 (8)	19 (8)
Endoscopic resection	2 (< 1)	5 (2)
Other	25 (10)	27 (11)
Time to disease progression in the first-line setting (according to IRT[c]), n (%)		
< 6 months	61 (25)	61 (25)
≥ 6 months	185 (75)	187 (75)
Treatment discontinuation, n (%)[d]	198 (81)	190 (82)
Study discontinuation, n (%)[e]	129 (52)	155 (63)

a. Institute's calculation.
b. The drugs shown are limited to those relevant to this benefit assessment.
c. Discrepancies between the eCRF and the IRT.
d. Frequent reasons for treatment discontinuation in the intervention arm vs. the control arm (percentages refer to randomized patients with at least one dose of study medication): disease progression (57% vs. 54%), AEs (10% vs. 7%), clinical progression (6% vs. 4%). An additional < 1% vs. 6% of randomized patients never started treatment. The data also include patients who died during treatment with the study medication (intervention arm: 5% vs. control arm: 8%).
e. Frequent reasons for study discontinuation in the intervention arm vs. the control arm (percentages refer to randomized patients): withdrawal of consent (3% vs. 9%), lost to follow-up (< 1% vs.< 1%). The data additionally include patients who died during the course of the study (intervention arm: 48% vs. control arm: 53%).

AE: adverse event; ECOG PS: Eastern Cooperative Oncology Group Performance Status; eCRF: electronic case report form; F: female; HER2: human epidermal growth factor receptor 2; IHC: immunohistochemistry; IRT: interactive response technology; ISH: in situ hybridization; M: male; n: number of patients in the category; N: number of randomized patients; RCT: randomized controlled trial; SD: standard deviation

The patient characteristics were largely balanced between the 2 treatment arms of DESTINY-Gastric04. The mean age of the patients was about 63 years. The vast majority of patients (around 80%) were men, and around 57% of patients were from Western Europe. In

approximately 61% of patients, the primary tumour was localized in the stomach, and in approximately 39% of patients, it was localized in the gastroesophageal junction. At around 93%, the patients almost exclusively had metastasized disease at baseline. Surgical treatment for gastric cancer was conducted in around 25% of patients, of whom 8% underwent a total gastrectomy. There were no relevant differences between the treatment arms in terms of treatment discontinuation, with the most common reason being disease progression, followed by adverse events.

Information on the course of the study

Table 10 shows the patients' mean/median treatment duration and the mean/median observation period for individual outcomes.

Table 10: Information on the course of the study – RCT, direct comparison: trastuzumab deruxtecan vs. ramucirumab + paclitaxel

Study **Duration of the study phase** **Outcome category/outcome**	**trastuzumab deruxtecan** **N = 246**	**ramucirumab + paclitaxel** **N = 248**
DESTINY-Gastric04		
Treatment duration [months][a, b]	N = 244	N = 233
Median [min; max]	5.4 [0.7; 30.3]	4.6 [0.9; 34.9]
Mean (SD)	6.6 (5.2)	5.3 (4.4)
Observation period [months]		
Overall survival[c]		
Median [min; max]	9.7 [0.3; 39.7]	7.5 [0.03; 35.0]
Mean (SD)	11.4 (7.5)	9.3 (7.2)
Morbidity		
Median [min; max]	ND	ND
Mean (SD)	ND	ND
Health-related quality of life		
Median [min; max]	ND	ND
Mean (SD)	ND	ND
Side effects		
Median [min; max]	ND	ND
Mean (SD)	ND	ND

a. Defined as the period between the first administration of the study medication and the date of the last administration of the study medication, + 21 days for trastuzumab deruxtecan, + 14 days for ramucirumab, and + 28, 21 or 14 days (depending on the number of doses in the last cycle) for paclitaxel.
b. Data are based on patients who received at least one dose of study medication.
c. Defined as the time between randomization and the date of study discontinuation or the date of the data cut-off.

max: maximum; min: minimum; N: number of patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation

The median treatment duration at the time of the final data cut-off was 5.4 months in the intervention arm and 4.6 months in the control arm, meaning it was approximately 17% longer in the intervention arm.

The median observation period for the outcome overall survival was 9.7 months in the intervention arm and 7.5 months in the control arm. No information on the observation period was available for the outcomes of morbidity, health-related quality of life and side effects. For these outcomes, the observation period was linked to the end of treatment (plus 40 [+ 7] days) and was therefore systematically shortened in comparison to overall survival.

Subsequent therapies

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

Table 11: Information on subsequent antineoplastic therapies – RCT, direct comparison: trastuzumab deruxtecan vs. ramucirumab + paclitaxel (multipage table)

Study Drug	Patients with subsequent therapy, n (%[a])	
	trastuzumab deruxtecan N = 246	ramucirumab + paclitaxel N = 248
DESTINY-Gastric04		
Number of subsequent therapies		
1	122 (49.6)	111 (44.8)
2	39 (15.9)	37 (14.9)
3	15 (6.1)	10 (4.0)
Systemic therapies in the first subsequent therapy, n (%[b])		
BDC 1001	0 (0)	1 (0.9)
bevacizumab	0 (0)	1 (0.9)
calcineurin subunit B	0 (0)	1 (0.9)
calcium folinate	4 (3.3)	2 (1.8)
calcium folinate + fluorouracil + irinotecan	1 (0.8)	0 (0)
calcium folinate + fluorouracil + irinotecan hydrochloride	8 (6.6)	11 (9.9)
capecitabine	4 (3.3)	0 (0)
capecitabine + cisplatin	1 (0.8)	0 (0)
capecitabine + irinotecan	0 (0)	1 (0.9)
capecitabine + oxaliplatin	1 (0.8)	0 (0)
carboplatin	1 (0.8)	0 (0)
cisplatin	1 (0.8)	1 (0.9)
disitamab vedotin	3 (2.5)	11 (9.9)
docetaxel	4 (3.3)	1 (0.9)
fluorouracil	7 (5.7)	6 (5.4)
sodium fluorouracil	1 (0.8)	0 (0)
fluorouracil + folinic acid + oxaliplatin	1 (0.8)	0 (0)
fluorouracil + oxaliplatin	1 (0.8)	0 (0)
folinic acid	2 (1.6)	1 (0.9)
fruquintinib	3 (2.5)	0 (0)
gimeracil + oteracil potassium + tegafur	3 (2.5)	0 (0)
immunotherapy	1 (0.8)	0 (0)
investigational product	3 (2.5)	7 (6.3)
irinotecan	12 (9.8)	11 (9.9)
irinotecan hydrochloride	1 (0.8)	3 (2.7)

Table 11: Information on subsequent antineoplastic therapies – RCT, direct comparison: trastuzumab deruxtecan vs. ramucirumab + paclitaxel (multipage table)

Study	Patients with subsequent therapy, n (%[a])	
Drug	trastuzumab deruxtecan	ramucirumab + paclitaxel
	N = 246	N = 248
irinotecan hydrochloride trihydrate	1 (0.8)	0 (0)
nivolumab	1 (0.8)	4 (3.6)
oxaliplatin	5 (4.1)	1 (0.9)
paclitaxel	53 (43.4)	5 (4.5)
nab-paclitaxel	10 (8.2)	0 (0)
paclitaxel + ramucirumab	11 (9.0)	1 (0.9)
pyrotinib maleate	1 (0.8)	1 (0.9)
ramucirumab	39 (32.0)	5 (4.5)
regorafenib	0 (0)	1 (0.9)
rivoceranib mesylate	1 (0.8)	2 (1.8)
runimotamab	0 (0)	1 (0.9)
sintilimab	3 (2.5)	1 (0.9)
tegafur	0 (0)	1 (0.9)
tipiracil hydrochloride + trifluridine	2 (1.6)	6 (5.4)
tipiracil + trifluridine	0 (0)	1 (0.9)
tislelizumab	0 (0)	1 (0.9)
toripalimab	0 (0)	1 (0.9)
trastuzumab	7 (5.7)	7 (6.3)
trastuzumab deruxtecan	2 (1.6)	42 (37.8)
trastuzumab mafodotin	0 (0)	1 (0.9)
trifluridine	1 (0.8)	0 (0)
tumour necrosis factors (unspecified)	1 (0.8)	0 (0)

a. Relates to the number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line.
b. Institute's calculation; relates to patients with at least one subsequent therapy.

n: number of patients with subsequent therapy; N: number of analysed patients; RCT: randomized controlled trial

DESTINY-Gastric04 did not specify any restrictions regarding subsequent antineoplastic therapies. According to the study design, treatment switching from ramucirumab + paclitaxel to trastuzumab deruxtecan was not planned as part of the study.

In total, 122 (49.6%) of all randomized patients in the intervention arm and 111 (44.8%) in the control arm of DESTINY-Gastric04 received at least one subsequent therapy. In relation to patients with disease progression (153 in the intervention arm and 135 in the control arm), approx. 80% of the patients in the intervention arm and approx. 82% of the patients in the

control arm received subsequent therapy after disease progression. As the first subsequent therapy, patients in the intervention arm were most commonly treated with paclitaxel (43%), ramucirumab (32%), irinotecan (10%) and ramucirumab + paclitaxel (9%). In the control arm, however, the most commonly used first subsequent therapy was trastuzumab deruxtecan (38%), followed by irinotecan combination therapy and irinotecan monotherapy, as well as disitamab vedotin (each at approximately 10%). Disitimab vedotin is an antibody-drug conjugate that has so far received marketing authorization in China but not in the European Union. However, the data on subsequent therapies included information at both the drug level and the level of drug combinations, which means that drugs were listed multiple times, making it difficult to perform an assessment of the subsequent therapies used.

According to the current S3 guideline [11], the choice of third-line treatment in this therapeutic indication should be based on HER2 status and consist of either trastuzumab deruxtecan or the combination of tipiracil and trifluridine. The DGHO also recommends treatment with tipiracil + trifluridine, provided that oral treatment is still an option [12]. Furthermore, according to the DGHO guideline, taxanes or irinotecan may be considered as intravenous options, although these drugs do not have marketing authorization for the therapeutic indication in question. In DESTINY-Gastric04, only a small proportion of patients in both study arms who were treated with at least one subsequent therapy received tipiracil + trifluridine (approximately 4% in the third-line setting and approximately 10% across all subsequent lines of therapy). The choice of treatment depends on the patient's general condition and HER2 status, and, in the case of tipiracil + trifluridine, also on whether it can be administered orally. It was not clear from the study documents how many patients were no longer able to take the medication orally or did not wish to do so. However, it cannot be assumed that this was the case for the vast majority of patients. Overall, the use of tipiracil + trifluridine in both study arms, as well as the use of trastuzumab deruxtecan in the comparator arm, should be regarded as low in light of the recommendations.

In summary, the subsequent therapies used in the DESTINY-Gastric04 study do not adequately represent the current standard of care. At the same time, when the first subsequent therapy is administered as part of the third line of treatment, patients are in a palliative care situation with a very poor prognosis. Overall, therefore, the results for the overall survival outcome were rated as interpretable. The uncertainties described were taken into account in the certainty of conclusions of the results on overall survival (see Section I 3.2).

Risk of bias across outcomes (study level)

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

Table 12: Risk of bias across outcomes (study level) – RCT, direct comparison: trastuzumab deruxtecan vs. ramucirumab + paclitaxel

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	Absence of other aspects	Risk of bias at study level
			Patients	Treating staff			
DESTINY-Gastric04	Yes	Yes	No	No	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes for DESTINY-Gastric04 was rated as low.

Limitations resulting from the open-label study design are described in Section I 3.2 under outcome-specific risk of bias.

Transferability of the study results to the German health care context

In Module 4 A, the company stated that the DESTINY-Gastric04 study included adult patients with advanced HER2-positive gastric or gastroesophageal junction adenocarcinoma who had experienced disease progression following trastuzumab-based first-line treatment but who had not yet received any further antineoplastic therapy as a result.

According to the company, the results of DESTINY-Gastric04 relevant to the benefit assessment are transferable to the German health care context. It stated that the study population concurs with the demographic and disease-specific characteristics of the target population in Germany.

The company described that the population of DESTINY-Gastric04 comprised a high proportion of patients (around 50%) of Caucasian origin. It continued that most patients were randomized into the study in Western Europe (around 56%). The company stated that this also reflects the broader context of the German health care system.

In the overall view of the company, the study results of DESTINY-Gastric04 are fully transferable to the German health care context.

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

I 4 Results on added benefit

I 4.1 Outcomes included

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

- Mortality
  - Overall survival
- Morbidity
  - Symptoms recorded using the Patient Global Impression of Severity (PGIS)
  - Health status, recorded using the EQ-5D visual analogue scale (VAS)
  - Health status recorded using the Patient Global Impression of Change (PGIC)
- Health-related quality of life
  - Recorded using the Functional Assessment of Cancer Therapy-Gastric (FACT-Ga)
- Side effects
  - Serious adverse events (SAEs)
  - Severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)
  - Discontinuation due to AEs
  - Cardiac disorders (System Organ Class [SOC], severe AEs [CTCAE grade ≥ 3])
  - Platelet count decreased (Preferred Term [PT], severe AEs [CTCAE grade ≥ 3])
  - Interstitial lung disease (ILD)/pneumonitis (SAEs)
  - Other specific AEs, if any

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

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

Table 13: Matrix of outcomes – RCT, direct comparison: trastuzumab deruxtecan vs. ramucirumab + paclitaxel

Study	Outcomes										
	Overall survival	Symptoms (PGIS)	Health status (EQ-5D VAS, PGIC)	Health-related quality of life (FACT-Ga)	SAEs	Severe AEs[a]	Discontinuation due to AEs	Cardiac disorders (SOC, severe AEs[a])	Platelet count decreased (PT, severe AEs[a])	ILD/pneumonitis[b] (SAEs)	Other specific AEs[c]
DESTINY-Gastric04	Yes	No[d]	No[d]	No[d]	No[d]	No[d]	Yes	Yes	Yes	Yes	Yes

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. For details on operationalization, see the text below
c. The following events (coded according to MedDRA) are considered: vomiting (PT, AEs), stomatitis (PT, AEs), epistaxis (PT, AEs), musculoskeletal and connective tissue disorders (SOC, AEs), renal and urinary disorders (SOC, AEs), injury, poisoning and procedural complications (SOC, AEs), nausea (PT, severe AEs), hypertension (PT, severe AEs) and nervous system disorders (SOC, severe AEs).
d. No suitable data available; for the reasoning, see the following text sections of this dossier assessment.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; FACT-Ga: Functional Assessment of Cancer Therapy-Gastric; ILD: interstitial lung disease; MedDRA: Medical Dictionary for Regulatory Activities; PGIC: Patient Global Impression of Change; PGIS: Patient Global Impression of Severity; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; VAS: visual analogue scale

Notes on the included outcomes

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

Health-related quality of life

In the DESTINY-Gastric04 study, health-related quality of life was recorded using the FACT-Ga instrument. The FACT-Ga questionnaire comprises the FACT-General (FACT-G) and the gastric cancer subscale (GaCS), which is specific to gastric cancer. In Module 4 A of the dossier, the company provided post-hoc analyses of responder analyses for the time to first deterioration for both the FACT-G and the FACT-Ga, as well as their individual subscales. Furthermore, Appendix 4-G of the dossier contained the prespecified analyses of mean differences from a mixed-effects model with repeated measures (MMRM) for the change compared with baseline. FACT-Ga was developed for patients with gastric cancer. Overall, the majority of patients in DESTINY-Gastric04 had gastric cancer, and around 39% had gastroesophageal junction cancer. However, an assessment of the questions suggested that they are likely to be relevant to this patient group as well. It therefore seemed appropriate to include the recording of this instrument for the whole study.

Data on patient-reported outcomes from the symptoms, health status and health-related quality of life categories not suitable

In the DESTINY-Gastric04 study, patient-reported outcomes regarding symptoms (using the PGIS), health status (using the EQ-5D VAS and PGIC) and health-related quality of life (using the FACT-Ga) were recorded initially every 3 weeks and from Day 64 every 6 weeks until disease progression or the start of subsequent antineoplastic therapy. In Module 4 A of the dossier, the company provided post-hoc analyses of responder analyses for the time to first deterioration for all patient-reported outcomes. Furthermore, Appendix 4-G of the dossier contained MMRM analyses for the EQ-5D VAS and the FACT-Ga.

However, the data provided by the company could not be interpreted in a meaningful way. This was partly due to the sharply declining and varying response rates: as early as the first follow-up survey after study begin (Day 22), the response rates for the EQ-5D VAS and the FACT-Ga showed a difference of around 16% between the treatment arms. For the PGIS and the PGIC, there was a large difference in the response rate of around 23% for the 2nd follow-up survey after study begin (Day 43). However, by the 2nd follow-up survey (Day 43), the overall response rate for all patient-reported outcomes had already fallen below 70%. What was striking here was the at times substantially more pronounced decline in response rates observed in the control arm (for the EQ-5D VAS, for example, the response rate fell by 10% from the 1st to the 2nd survey, to 57%, before rising again to around 66% by the 3rd survey on Day 64). By way of comparison, the response rates for the questionnaires in the intervention arm at these points in time were consistently around 79 to 83%. It was not clear from the available information what caused these sporadic failures to respond in the control arm. The missing surveys from the control arm at the time of the 1st (Day 22) and 2nd follow-up surveys (Day 43) meant that, at these time points, the responder analyses could not reliably detect a potential first deterioration in the control arm at an early stage of the study . Furthermore, given the response rates in the control arm over the entire study period, it could not be assumed that a missing at random assumption was justified in this case. The MMRM analyses presented by the company were therefore unsuitable for the benefit assessment.

Furthermore, due to the different treatment regimens between the intervention arm and the control arm (see also Table 7), the patient-reported outcomes were also recorded at different time points within the treatment cycles in the 2 study arms. As a result, the study arms differed in terms of their representation of treatment-related burden over the course of the cycle. Additional analyses disregarding the surveys of these time points (with unequal treatment burden), for example, would be required to check the influence the different representations of the burden have on the results. However, this would only be possible if a sufficient number of surveys continue to be included in the analyses. Overall, in this case, more frequent recording of patient-reported outcomes during the treatment phase would allow for an adequate assessment, even when different treatment regimens are used.

Due to the strongly decreasing and varying response rates as well as different time points of recording of the patient-reported outcomes within the treatment cycles, the analyses presented by the company on the patient-reported outcomes could not be interpreted meaningfully and were therefore not suitable for the benefit assessment.

Side effects

Overall rates SAEs and severe AEs

According to the study design, events related to the progression of the underlying disease were not to be recorded as AEs. However, the data on common AEs indicated that events were recorded under the PT disease progression (see Table 21 and Table 22 of the full dossier assessment). It is unclear which events were recorded under the PT disease progression and why this recording deviated from the study design. The company presented no information on this. However, based on the available information, it could be assumed that these events – which were also unevenly distributed across the study arms (8 vs. 18 patients with an event) – were included in the calculation of the overall rates of SAEs and severe AEs. In this data situation, therefore, effects on the overall rates of SAEs and severe AEs can only be interpreted if they are sufficiently large. To arrive at a reliable assessment, analyses would be required that do not take these events into account.

ILD/pneumonitis (SAEs)

In Module 4 A, the company presented results for the outcome ILD/pneumonitis. The dossier contained no details regarding the precise operationalization of this AE of special interest prespecified by the company. However, the study documents indicated that the events to be classified as ILD or pneumonitis were predefined in an 'adjudication charter' and that all events that occurred were to be adjudicated by an independent adjudication committee. An 'adjudication charter' was not included in the dossier. Furthermore, the company stated in Module 4 A that ILD/pneumonitis was operationalized using a Standardized Medical Dictionary for Regulatory Activities Query (SMQ). However, it was unclear whether this referred to the SMQ ILD, which also includes the PT pneumonitis, or to a PT collection prespecified by the company based on the SMQ ILD, as there is no SMQ ILD/pneumonitis. Nevertheless, the results of DESTINY-Gastric04 showed that the event rates for the outcome ILD/pneumonitis corresponded to the events for the respective PTs ILD and pneumonitis. It was therefore unlikely that a relevant number of events went unreported.

For this benefit assessment, the SAEs ILD/pneumonitis were used, as these were considered to represent patient-relevant events.

I 4.2 Risk of bias

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

Table 14: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: trastuzumab deruxtecan vs. ramucirumab + paclitaxel

Study	Study level	Outcomes										
		Overall survival	Symptoms (PGIS)	Health status (EQ-5D VAS, PGIC)	Health-related quality of life (FACT-Ga)	SAEs	Severe AEs[a]	Discontinuation due to AEs	Cardiac disorders (SOC, severe AEs[a])	Platelet count decreased (PT, severe AEs[a])	ILD/pneumonitis[b] (SAEs)	Other specific AEs[c]
DESTINY-Gastric04	L	H[d, e]	–[f]	–[f]	–[f]	–[f]	–[f]	H[g]	H[d]	H[d]	H[d]	H[d]

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. For operationalization, see Section I 3.1.
c. The following events (coded according to MedDRA) are considered: vomiting (PT, AEs), stomatitis (PT, AEs), epistaxis (PT, AEs), musculoskeletal and connective tissue disorders (SOC, AEs), renal and urinary disorders (SOC, AEs), injury, poisoning and procedural complications (SOC, AEs), nausea (PT, severe AEs), hypertension (PT, severe AEs) and nervous system disorders (SOC, severe AEs).
d. Incomplete observations for potentially informative reasons (a relevant difference between the treatment groups [> 5 percentage points] in study discontinuations at the request of the patient, in the absence of blinding).
e. A relevant difference in the proportion of censorings between the treatment arms at an early stage (a difference of 4.4 to 7.6 percentage points at Months 3, 6 and 9).
f. No suitable data available; for the reasoning, see Section I 3.1 of this dossier assessment.
g. Lack of blinding in the presence of subjective decision on treatment discontinuation.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; FACT-Ga: Functional Assessment of Cancer Therapy-Gastric; H: high; ILD: interstitial lung disease; L: low; MedDRA: Medical Dictionary for Regulatory Activities; PGIC: Patient Global Impression of Change; PGIS: Patient Global Impression of Severity; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; VAS: visual analogue scale

The risk of bias was rated high for the results of the outcome overall survival and the outcomes in the side effect category. The main reasons for this (apart from discontinuation due to AEs) were, in the absence of blinding, a relevant difference in the rate of study discontinuation at own request (3.3% in the intervention arm vs. 8.9% in the control arm). Another reason for the overall survival outcome was a relevant difference among patients who did not receive treatment after randomization (0.8% in the intervention arm vs. 6.0% in the control arm). However, it was unclear to what extent the patients in the control arm who did not receive treatment after randomization contributed to the reported study discontinuations, nor was it clear for how long the patients were followed up or when the study discontinuations occurred. Furthermore, with regard to the overall survival outcome, there was a relevant difference in the proportion of censorings between the treatment arms already at an early stage. In Months 3, 6 and 9, the difference in the proportion of censored patients between the treatment groups ranged from 4.4 to 7.6 percentage points. The number of censorings in Month 3 was

similar to the number of events and remained at a high level thereafter (see also Figure 1 in I Appendix B of the full dossier assessment). These differences cannot be explained solely by administrative censorings.

The results of the specific AEs nausea (PT, severe AEs) and vomiting (PT, AEs) additionally had a high risk of bias due to uncertainties regarding the antiemetic premedication required in accordance with the SmPC (see p. I.17, Concomitant treatment for nausea and vomiting [intervention arm]).

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

Summary assessment of the certainty of conclusions

Irrespective of the aspects described under 'risk of bias', the certainty of conclusions regarding the study results for the outcome of overall survival was further limited by the uncertainties regarding the subsequent therapies used, as described in Section I 3.2.

Based on the study results, at most hints, e.g. of an added benefit, can be derived for all outcomes.

I 4.3 Results

Table 15 summarizes the results of the comparison of trastuzumab deruxtecan with ramucirumab + paclitaxel in adult patients with advanced HER2-positive gastric or gastroesophageal junction adenocarcinoma who have received one prior trastuzumab-based regimen in first-line therapy. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier. For the outcome nausea (severe AEs) with 0 events in the control arm, no data were available for the effect estimate of the time-to-event analyses. One way to obtain point and interval estimates for time-to-event analyses in such situations is to use the Firth correction to the Cox model [13-16] in combination with profile likelihood methods for the 95% confidence intervals.

The Kaplan-Meier curves for the outcomes shown are included in I Appendix B of the full dossier assessment, provided that the company submitted them in the dossier. The company did not provide Kaplan-Meier curves for the outcomes of specific AEs (except for the outcome ILD/pneumonitis [SAEs]) or for common AEs at the SOC/PT level. It was therefore not possible

to determine when the relevant events occurred during the course of the study, nor to perform a more detailed assessment of the data situation to potentially derive a higher level of certainty of conclusions with regard to specific outcomes.

Results on common AEs, SAEs, severe AEs, and discontinuations due to AEs are presented in I Appendix C of the full dossier assessment.

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: trastuzumab deruxtecan vs. ramucirumab + paclitaxel (multipage table)

Study Outcome category Outcome	trastuzumab deruxtecan		ramucirumab + paclitaxel		trastuzumab deruxtecan vs. ramucirumab + paclitaxel
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[a]
DESTINY-Gastric04					
Mortality					
Overall survival	246	14.7 [12.1; 16.6] 124 (50.4)	248	11.4 [9.9; 15.5] 142 (57.3)	0.70 [0.55; 0.90]; 0.004
Morbidity					
Symptoms (PGIS)				No suitable data[b]	
Health status (EQ-5D VAS, PGIC)				No suitable data[b]	
Health-related quality of life					
FACT-Ga				No suitable data[b]	
Side effects					
AEs (supplementary information)	244	0.1 [0.1; 0.2] 244 (100)	233	0.2 [0.2; 0.2] 228 (97.9)	–
SAEs				No suitable data[b]	
Severe AEs[c]				No suitable data[b]	
Discontinuation due to AEs[d]	244	22.1 [17.1; NC] 35 (14.3)	233	NA 40 (17.2)	0.61 [0.39; 0.98]; 0.038[e]
Cardiac disorders (SOC, severe AEs[c])	244	ND 1 (0.4)	233	ND 4 (1.7)	–[f]
Platelet count decreased (PT, severe AEs[c])	244	NA [23.1; NC] 17 (7.0)	233	NA 8 (3.4)	1.88 [0.81; 4.37]; 0.139[e]
ILD/pneumonitis (SAEs)[g]	244	NA 5 (2.0)	233	NA 3 (1.3)	1.49 [0.36; 6.22]; 0.585[h]
Vomiting (PT, AEs)	244	NA 64 (26.2)	233	NA 33 (14.2)	1.92 [1.26; 2.93]; 0.002[e]
Stomatitis (PT, AEs)	244	NA 14 (5.7)	233	NA 31 (13.3)	0.38 [0.20; 0.71]; 0.002[e]
Epistaxis (PT, AEs)	244	NA 4 (1.6)	233	NA 34 (14.6)	0.10 [0.03; 0.27]; < 0.001[e]
Musculoskeletal and connective tissue disorders (SOC, AEs)	244	NA 41 (16.8)	233	14.6 [14.6; NC] 63 (27.0)	0.51 [0.34; 0.76]; < 0.001[e]
Renal and urinary disorders (SOC, AEs)	244	NA 12 (4.9)	233	NA 31 (13.3)	0.30 [0.15; 0.58]; < 0.001[e]

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: trastuzumab deruxtecan vs. ramucirumab + paclitaxel (multipage table)

Study Outcome category Outcome	trastuzumab deruxtecan		ramucirumab + paclitaxel		trastuzumab deruxtecan vs. ramucirumab + paclitaxel
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[a]
Nausea (PT, severe AEs[c])	244	NA 13 (5.3)	233	NA 0 (0)	NC; < 0.001[i]
Hypertension (PT, severe AEs[c])	244	NA 1 (0.4)	233	NA 25 (10.7)	0.03 [0.004; 0.24]; < 0.001[e]
Nervous system disorders (SOC, severe AEs[c])	244	NA 8 (3.3)	233	NA 16 (6.9)	0.41 [0.18; 0.96]; 0.034[e]

a. Effect and CI: Cox proportional hazards model, stratified by HER2 status (IHC 3+ vs. IHC 2+ / ISH+); p-value: log-rank test stratified by HER2 status (IHC 3+ vs. IHC 2+ / ISH+).
b. See Section I 4.1 of this dossier assessment for the reasoning.
c. Operationalized as CTCAE grade ≥ 3.
d. Discontinuation of at least one component.
e. Effect: unstratified Cox proportional hazards model with treatment as the sole categorical variable; CI: based on the Wald test; p-value: based on the unstratified log-rank test.
f. The company did not present any calculations on the HR, CI or p-value.
g. For operationalization, see Section I 4.1.
h. Effect: Cox proportional hazards model with treatment as a categorical variable; inclusion of stratification factors according to a prespecified pooling strategy; CI: based on the Wald test; p-value: based on the log-rank test; inclusion of stratification factors according to a prespecified pooling strategy.
i. p-value: based on an unstratified log-rank test.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; FACT-Ga: Functional Assessment of Cancer Therapy-Gastric; HER2: human epidermal growth factor receptor 2; HR: hazard ratio; IHC: immunohistochemistry; ILD: interstitial lung disease; ISH: in situ hybridization; n: number of patients with event; N: number of analysed patients; NA: not achieved; NC: not calculable; ND: no data; PGIC: Patient Global Impression of Change; PGIS: Patient Global Impression of Severity; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

Based on the available information, at most hints, e.g. of an added benefit, can be determined for all outcomes (for reasoning, see Sections I 3.2. and I 4.2).

Mortality

Overall survival

A statistically significant difference in favour of trastuzumab deruxtecan was shown for the outcome of overall survival. There is a hint of an added benefit of trastuzumab deruxtecan in comparison with ramucirumab + paclitaxel.

Morbidity

Symptoms (PGIS) and health status (EQ-5D VAS and PGIC)

No suitable data were available for the outcomes symptoms, recorded using PGIS, and health status, recorded using EQ-5D VAS and PGIC. There is no hint of an added benefit of trastuzumab deruxtecan in comparison with ramucirumab + paclitaxel; an added benefit is therefore not proven.

Health-related quality of life

FACT-Ga

No suitable data were available for the outcome of health-related quality of life, recorded using the FACT-Ga. There is no hint of an added benefit of trastuzumab deruxtecan in comparison with ramucirumab + paclitaxel; an added benefit is therefore not proven.

Side effects

SAEs and severe AEs (CTCAE grade ≥ 3)

No suitable data were available for the outcomes SAEs and severe AEs (CTCAE grade ≥ 3) (for reasoning, see Section I 4.1). The effect in favour of trastuzumab deruxtecan in the outcome severe AEs (CTCAE grade ≥ 3) was not sufficiently large to be interpreted with sufficient certainty (see Table 24 in I Appendix D of the full dossier assessment). However, based on the available data, it was possible to make a qualitative assessment of the side effects when weighing up the overall picture.

Discontinuation due to AEs

A statistically significant difference in favour of trastuzumab deruxtecan compared with ramucirumab + paclitaxel was shown for the outcome discontinuation due to AEs.

However, there was an effect modification for the characteristic age (see Section I 4.4). For patients < 65 years, there is a hint of lesser harm of trastuzumab deruxtecan compared with ramucirumab + paclitaxel. For patients ≥ 65 years, there is no hint of greater or lesser harm of trastuzumab deruxtecan in comparison with ramucirumab + paclitaxel; greater or lesser harm is therefore not proven.

Cardiac disorders (severe AEs)

The company presented no calculations on hazard ratio or p-value for this outcome. Due to the low number of events, it cannot be assumed that there would be a statistically significant effect in case of suitable analyses. There is no hint of greater or lesser harm of trastuzumab deruxtecan in comparison with ramucirumab + paclitaxel; greater or lesser harm is therefore not proven.

Platelet count decreased (severe AEs) and ILD/pneumonitis (SAEs)

For the outcomes platelet count decreased (severe AEs) and ILD/pneumonitis (SAEs), there was no statistically significant difference between the treatment groups in either case. For both outcomes, there is no hint of greater or lesser harm of trastuzumab deruxtecan in comparison with ramucirumab + paclitaxel; greater or lesser harm is therefore not proven.

Stomatitis (AEs), epistaxis (AEs), musculoskeletal and connective tissue disorders (AEs), renal and urinary disorders (AEs), hypertension (severe AEs) and nervous system disorders (severe AEs)

There was a statistically significant difference in favour of trastuzumab deruxtecan compared with ramucirumab + paclitaxel for the outcomes stomatitis (AEs), epistaxis (AEs), musculoskeletal and connective tissue disorders (AEs), renal and urinary disorders (AEs), hypertension (severe AEs) and nervous system disorders (severe AEs). In each case, there is a hint of lesser harm of trastuzumab deruxtecan in comparison with ramucirumab + paclitaxel.

Vomiting (AEs)

A statistically significant difference to the disadvantage of trastuzumab deruxtecan compared with ramucirumab + paclitaxel was shown for the outcome vomiting (AEs). There is a hint of greater harm of trastuzumab deruxtecan in comparison with ramucirumab + paclitaxel.

Nausea (severe AEs)

A statistically significant difference to the disadvantage of trastuzumab deruxtecan compared with ramucirumab + paclitaxel was shown for the outcome nausea (severe AEs). There is a hint of greater harm of trastuzumab deruxtecan in comparison with ramucirumab + paclitaxel.

I 4.4 Subgroups and other effect modifiers

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

- Sex (men/women)
- Age (< 65/≥ 65 years)

The characteristics mentioned were prespecified. No suitable characteristic for disease severity was available.

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

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup

results are only presented if there is a statistically significant and relevant effect in at least one subgroup.

The results are presented in Table 16. In the dossier, the company did not provide any Kaplan-Meier curves for the time-to-event analyses presented.

Table 16: Subgroups (side effects) – RCT, direct comparison: trastuzumab deruxtecan vs. ramucirumab + paclitaxel

Study Outcome	trastuzumab deruxtecan		ramucirumab + paclitaxel		trastuzumab deruxtecan vs. ramucirumab + paclitaxel	
Characteristic Subgroup	N	Median time to event in months [95 % CI] Patients with event n (%)	N	Median time to event in months [95 % CI] Patients with event n (%)	HR [95% CI][a]	p-value[b]
DESTINY-Gastric04						
Discontinuation due to AEs[c]						
Age						
< 65 years	139	NA [18.0; NC] 9 (6.5)	123	NA 19 (15.4)	0.32 [0.14; 0.72]	0.004
≥ 65 years	105	17.1 [13.6; NC] 26 (24.8)	110	NA [10.1; NC] 21 (19.1)	0.93 [0.51; 1.69]	0.811
Total					Interaction[d]:	0.021

a. Effect: unstratified Cox proportional hazards model with treatment as the only categorical variable; CI: based on the Wald test.
b. Based on an unstratified log-rank test.
c. Discontinuation of all components.
d. Based on an unstratified Cox proportional hazards model with treatment, subgroup and treatment-by-subgroup interaction as categorical variables.

CI: confidence interval; HR: hazard ratio; n: number of patients with event; N: number of analysed patients; NA: not achieved; NC: not calculable; RCT: randomized controlled trial

Side effects

Discontinuation due to AEs

There was an effect modification for the characteristic age for the outcome of discontinuation due to AEs. A statistically significant difference in favour of trastuzumab deruxtecan compared with ramucirumab + paclitaxel was shown for patients < 65 years. There is a hint of an added benefit of trastuzumab deruxtecan in comparison with ramucirumab + paclitaxel for this patient group.

However, no statistically significant difference between treatment groups was found for patients ≥ 65 years. There is no hint of an added benefit of trastuzumab deruxtecan in

comparison with ramucirumab + paclitaxel for this patient group; an added benefit is therefore not proven.

I 5 Probability and extent of added benefit

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

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

I 5.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level was assessed based on the results presented in Chapter I 4 (see Table 17).

Determination of the outcome category for the outcomes on side effects

It could not be inferred from the dossier whether the following side effects outcome was serious/severe or non-serious/non-severe. The classification of this outcome is explained below.

Discontinuation due to AEs

The DESTINY-Gastric04 study documents showed that the recorded AEs that led to discontinuation of the study medication were predominantly of CTCAE grade ≥ 3. The outcome discontinuation due to AEs was therefore assigned to the outcome category serious/severe side effects.

Table 17: Extent of added benefit at outcome level: trastuzumab deruxtecan vs. ramucirumab + paclitaxel (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**trastuzumab deruxtecan vs. ramucirumab + paclitaxel** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Outcomes with observation over the entire study duration		
Mortality		
Overall survival	14.7 vs. 11.4 HR: 0.70 [0.55; 0.90]; p = 0.004 Probability: hint	Outcome category: mortality $0.85 \leq CI_u < 0.95$ Added benefit, extent: considerable
Outcomes with shortened observation period		
Morbidity		
Symptoms (PGIS)	No suitable data[c]	Lesser benefit not proven/added benefit not proven
Health status (EQ-5D VAS, PGIC)	No suitable data[c]	Lesser benefit not proven/added benefit not proven
Health-related quality of life		
FACT-Ga	No suitable data[c]	Lesser benefit not proven/added benefit not proven
Side effects		
SAEs	No suitable data[c]	Greater/lesser harm not proven
Severe AEs	No suitable data[c]	Greater/lesser harm not proven
Discontinuation due to AEs Age < 65 years	NA vs. NA HR: 0.32 [0.14; 0.72]; p = 0.004 Probability: hint	Serious/severe side effects $CI_u < 0.75$, risk ≥ 5% Lesser harm, extent: major
≥ 65 years	17.1 vs. NA HR: 0.93 [0.51; 1.69]; p = 0.811	Greater/lesser harm not proven
Cardiac disorders (severe AE)	ND HR: –[d] p: –[d]	Greater/lesser harm not proven
Platelet count decreased (severe AE)	NA vs. NA HR: 1.88 [0.81; 4.37]; p = 0.139	Greater/lesser harm not proven

Table 17: Extent of added benefit at outcome level: trastuzumab deruxtecan vs. ramucirumab + paclitaxel (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**trastuzumab deruxtecan vs. ramucirumab + paclitaxel** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
ILD/pneumonitis (SAE)	NA vs. NA HR: 1.49 [0.36; 6.22]; p = 0.585	Greater/lesser harm not proven
Vomiting (AE)	NA vs. NA HR: 1.92 [1.26; 2.93] HR: 0.52 [0.34; 0.79][e] p = 0.002 Probability: hint	Outcome category: non-serious/non-severe side effects CI_u < 0.80 Greater harm, extent: considerable
Stomatitis (AE)	NA vs. NA HR: 0.38 [0.20; 0.71]; p = 0.002 Probability: hint	Outcome category: non-serious/non-severe side effects CI_u < 0.80 Lesser harm, extent: considerable
Epistaxis (AE)	NA vs. NA HR: 0.10 [0.03; 0.27]; p < 0.001 Probability: hint	Outcome category: non-serious/non-severe side effects CI_u < 0.80 Lesser harm, extent: considerable
Musculoskeletal and connective tissue disorders (AE)	NA vs. 14.6 HR: 0.51 [0.34; 0.76]; p < 0.001 Probability: hint	Outcome category: non-serious/non-severe side effects CI_u < 0.80 Lesser harm, extent: considerable
Renal and urinary disorders (AE)	NA vs. NA HR: 0.30 [0.15; 0.58]; p < 0.001 Probability: hint	Outcome category: non-serious/non-severe side effects CI_u < 0.80 Lesser harm, extent: considerable
Nausea (severe AE)	NA vs. NA HR: NC; p < 0.001 Probability: hint	Outcome category: serious/severe side effects Greater harm, extent: non-quantifiable
Hypertension (severe AE)	NA vs. NA 0.03 [0.004; 0.24]; p < 0.001 Probability: hint	Outcome category: serious/severe side effects CI_u < 0.75, risk ≥ 5% Lesser harm, extent: major
Nervous system disorders (severe AE)	NA vs. NA 0.41 [0.18; 0.96]; p = 0.034 Probability: hint	Outcome category: serious/severe side effects 0.90 ≤ CI_u < 1.00 Lesser harm, extent: minor

Table 17: Extent of added benefit at outcome level: trastuzumab deruxtecan vs. ramucirumab + paclitaxel (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**trastuzumab deruxtecan vs. ramucirumab + paclitaxel** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
a. Probability provided if there is a statistically significant and relevant effect. b. Depending on the outcome category, the effect size is estimated using different limits based on the upper limit of the confidence interval (CI_u). c. See Section I 4.1 for reasons. d. The company did not present any calculations on the HR, CI or p-value. e. Institute's calculation; inverse direction of effect to enable use of limits to derive the extent of the added benefit. AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; NA: not achieved; NC: not calculable; ND: no data; SAE: serious adverse event		

I 5.2 Overall conclusion on added benefit

Table 18 summarizes the results taken into account for the overall conclusion on the extent of the added benefit.

Table 18: Positive and negative effects from the assessment of trastuzumab deruxtecan in comparison with ramucirumab + paclitaxel

Positive effects	**Negative effects**
Outcomes with observation over the entire study duration	
Mortality ▪ Overall survival: hint of an added benefit – extent: considerable	–
Outcomes with shortened observation period	
Serious/severe side effects ▪ Discontinuation due to AEs ▫ Age (< 65 years) Hint of lesser harm – extent: major ▪ Hypertension (severe AE): hint of lesser harm – extent: major ▪ Nervous system disorders (severe AE): hint of lesser harm – extent: minor	Serious/severe side effects ▪ Nausea (severe AE): hint of greater harm – extent: non-quantifiable
Non-serious/non-severe side effects ▪ Stomatitis (AE): hint of lesser harm – extent: considerable ▪ Epistaxis (AE): hint of lesser harm – extent: considerable ▪ Musculoskeletal and connective tissue disorders (AE): hint of lesser harm –extent: considerable ▪ Renal and urinary disorders (AE): hint of lesser harm – extent: considerable	Non-serious/non-severe side effects ▪ Vomiting (AE): hint of greater harm – extent: considerable
No suitable data were available for the morbidity and health-related quality of life outcomes, or for the side effect outcomes (SAEs and severe AEs).	
AE: adverse event	

Overall, there is a majority of positive effects and a few negative effects of trastuzumab deruxtecan compared with ramucirumab plus paclitaxel. Data across the entire observation period were only available for overall survival. All other effects referred exclusively to the shortened observation period (until the end of treatment [plus 40 days]). The analyses presented on the outcome categories morbidity and health-related quality of life, and on the outcomes SAEs and severe AEs are not suitable for the benefit assessment. However, based on the available data, it was not anticipated that the intervention would show disadvantages in terms of the SAEs and severe AEs outcomes to an extent that would call into question the advantage observed in the overall survival outcome.

In terms of positive effects, there is a hint of considerable added benefit of trastuzumab deruxtecan in comparison with ramucirumab + paclitaxel for the outcome of overall survival. In addition, in terms of side effects there were various positive effects resulting from lesser harm, both for outcomes in the severe/serious side effects category and in the non-severe/non-serious side effects category, to varying extents. These positive effects are offset only by isolated negative effects in terms of specific AEs: in the category of severe/serious side effects for the specific AE nausea with a non-quantifiable extent, and for the non-severe

specific AE vomiting with a considerable extent. Overall, the positive effects therefore clearly outweigh the negative ones.

In summary, there is a hint of a considerable added benefit of trastuzumab deruxtecan versus ramucirumab + paclitaxel for adult patients with advanced HER2-positive gastric or gastroesophageal junction adenocarcinoma who have received one prior trastuzumab-based regimen in first-line therapy.

The result of the assessment of the added benefit of trastuzumab deruxtecan in comparison with the ACT is summarized in Table 19.

Table 19: Trastuzumab deruxtecan – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adult patients with advanced HER2-positive gastric or gastroesophageal junction adenocarcinoma who have received one prior trastuzumab-based regimen in first-line therapy[b]	▪ docetaxel or ▪ irinotecan or ▪ paclitaxel or ▪ **ramucirumab in combination with paclitaxel**	Hint of considerable added benefit[c]

a. Presented is the ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company according to the inclusion criteria in Module 4 Section 4.2.2 is printed in **bold**.
b. According to the G-BA, the therapeutic indication includes patients with unresectable, locally advanced or metastatic disease.
c. Only patients with an ECOG PS of 0 or 1 were included in the DESTINY-Gastric04 study, with the exception of 2 patients. 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

The assessment described above deviates from that of the company, which derived an indication of considerable added benefit based on DESTINY-Gastric04.

The G-BA decides on the added benefit.

I 6 References for English extract

Please see full dossier assessment for full reference list.

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