Trastuzumab deruxtecan (gastric or gastroesophageal junction adenocarcinoma)

Addendum to Project A25-128 (dossier assessment)[1]

ADDENDUM (DOSSIER ASSESSMENT)

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[1] Translation of the addendum *Trastuzumab deruxtecan (Adenokarzinom des Magens oder des gastroösophagealen Übergangs) – Addendum zum Projekt A25-128 (Dossierbewertung)*. Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CTCAE	Common Terminology Criteria for Adverse Events
DGHO	Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie (German Society for Haematology and Medical Oncology)
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HER2	human epidermal growth factor receptor 2
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse events
SGB	Sozialgesetzbuch (Social Code Book)
SmPC	summary of product characteristics
SOC	System Organ Class

1 Background

On 10 February 2026, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A25-128 (Trastuzumab deruxtecan – Benefit assessment according to §35a Social Code Book V) [1].

The commission comprises the assessment of the analyses from the DESTINY-Gastric04 randomized controlled trial (RCT) submitted by the company during the commenting procedure, taking into account the information contained in the dossier:

- Censoring of the overall survival outcome for patients who discontinued the study
- Censoring for the overall survival outcome for patients who did not receive treatment following randomization
- Details of the reasons for censoring for each censoring timepoint for the Kaplan-Meier curves for the overall survival outcome (data cut-off 24 October 2024), taking into account all randomized patients
- Supplementary data on subsequent therapies
- Sensitivity analysis for serious adverse events (SAEs) and severe adverse events (AEs), excluding the Preferred Term (PT) ‘disease progression’
- Kaplan-Meier curves for common AEs at the System Organ Class (SOC)/PT level

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

2 Assessment

For the benefit assessment 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 RCT DESTINY-Gastric04 [2-6] presented by the company was included (see also dossier assessment A25-128 [1]). The benefit assessment described, amongst other things, uncertainties regarding the censoring for the overall survival outcome and regarding subsequent therapies in the RCT; reference was also made to analyses missing in the company's dossier. The company addressed these points of criticism in its comments [7] and submitted new analyses.

In accordance with the G-BA's commission, the assessment of the supplementary data is set out below, taking into account the information contained in the dossier.

2.1 Censoring for the overall survival outcome

In the dossier assessment the risk of bias in the results for the overall survival outcome was rated as high. The reasons for this were, in the absence of blinding, a relevant difference

- in study discontinuations at patient's own request (3.3% in the intervention arm versus 8.9% in the control arm)
- among patients who did not receive treatment following randomization (0.8% in the intervention arm versus 6.0% in the control arm; it is unclear to what extent the patients in the control arm who did not receive treatment following randomization contributed to the reported study discontinuations, nor how long the patients were followed up or when the study discontinuations occurred)
- in the proportion of censored patients between the treatment arms even at an early stage (at 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), which could not be explained solely by administrative censoring

In response to this, the company submitted new analyses as part of the commenting procedure. Table 1 describes study discontinuations at the patient's own request and reasons for censoring for the overall survival outcome for Months 3, 6 and 9, whilst Table 2 shows the disposition of patients who did not receive treatment following randomization.

Table 1: Study discontinuations at the patient's own request and reasons for censoring for the overall survival outcome for Months 3, 6 and 9 – RCT, direct comparison: trastuzumab deruxtecan vs. ramucirumab + paclitaxel

Study	trastuzumab deruxtecan N = 246	ramucirumab + paclitaxel N = 248
DESTINY-Gastric04		
Patients who discontinued the study at their own request, n (%)	8 (3.3)	22 (8.9)
Reason for censoring for overall survival: study discontinuation at the patient's own request	4 (1.6)	12 (4.8)
3 months		
Censored patients, n (%)	13 (5.3)	24 (9.7)
Alive	13 (5.3)	14 (5.6)
Study discontinuation at the patient's own request	0 (0)	10 (4.0)
Lost to follow-up	0 (0)	0 (0)
6 months		
Censored patients, n (%)	23 (9.3)	42 (16.9)
Alive	22 (8.9)	32 (12.9)
Study discontinuation at the patient's own request	1 (0.4)	10 (4.0)
Lost to follow-up	0 (0)	0 (0)
9 months		
Censored patients, n (%)	47 (19.1)	60 (24.2)
Alive	45 (18.3)	49 (19.8)
Study discontinuation at the patient's own request	2 (0.8)	11 (4.4)
Lost to follow-up	0 (0)	0 (0)

n: number of patients in the category; N: number of analysed patients; RCT: randomized controlled trial

Table 2: Disposition of patients who did not receive treatment following randomization – RCT, direct comparison: trastuzumab deruxtecan vs. ramucirumab + paclitaxel

Study	trastuzumab deruxtecan N = 246	ramucirumab + paclitaxel N = 248
DESTINY-Gastric04		
Patients who did not receive treatment following randomization, n (%)	2 (0.8)	15 (6.0)
Primary reason for study discontinuation, n (%[a])		
Death	1 (50.0)	5 (33.3)
Study discontinuation at the patient's own request	1 (50.0)	10 (66.7)
Reason for censoring for overall survival: study discontinuation at the patient's own request	0 (0)	6 (40.0)
Traceable based on publicly available data sources	1 (50.0)	4 (26.7)
Lost to follow-up	0 (0)	0 (0)
Other	0 (0)	0 (0)

a. Relates to patients who did not receive treatment following randomization.

n: number of patients who did not receive treatment following randomization; N: number of analysed patients; RCT: randomized controlled trial

The data subsequently submitted show, firstly, that fewer than half of the study discontinuations at patient's own request in the comparator arm occurred early in the study (10 out of 22 patients at Month 3; see Table 1). Secondly, in the comparator arm, only two-thirds of the patients who did not receive treatment following randomization discontinued the study at their own request (10 out of 15 patients; see Table 2). However, the survival status of some of these patients (4 out of 10) could be further tracked using publicly available data sources. According to information provided by the company, patients who discontinued the study at their own request were also followed up, but it was unclear how many patients this applies to.

Furthermore, in the dossier assessment it was noted that the high number of censorings for overall survival at Month 3 was similar to the number of events. In its comments, the company explained that this was due to the inclusion of patients shortly before the database lock for the interim analysis, which accounted for the high number of patients censored as alive. The last patient was randomized on 16 October 2024, whilst the database lock for the interim analysis took place on 24 October 204. Ultimately, the study was terminated early because the primary outcome (overall survival) was reached ahead of schedule, meaning that the interim analysis constituted the final analysis.

Based on the information provided by the company in its comments, it was assumed that the early censorings were largely non-informative (see Table 1). In addition, patients who discontinued the study at their own request were still followed up to some extent. Overall, the differences between the treatment arms in terms of censoring and study discontinuation at patient's own request at Months 3, 6 and 9 were < 5%. There was therefore a low risk of bias in the results for the overall survival outcome. Nevertheless, the certainty of conclusions for the results for this outcome remained limited due to the subsequent therapies used in the study (see Section 2.2).

Impact on the risk of bias in other outcomes

As there were therefore no incomplete observations for potentially informative reasons (a relevant difference between the treatment groups [> 5%] in the number of study discontinuations at the patient's own request in the absence of blinding), the risk of bias in the results on side effects (with the exception of the outcome discontinuation due to AEs) changed from high to low. The certainty of results for the outcome discontinuation due to AEs remained limited by the fact that premature treatment discontinuation may also be for reasons other than AEs. For the specific AEs nausea and vomiting, the risk of bias was rated as high due to continuing uncertainties regarding the antiemetic premedication required in accordance with the summary of product characteristics (SmPC) (for details, see dossier assessment A25-128).

2.2 Supplementary data on subsequent therapies

In dossier assessment A25-128 it was described that according to the S3 guideline [8], 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 German Society for Haematology and Medical Oncology (DGHO) also recommends treatment with tipiracil/trifluridine, provided that oral treatment is still possible [9]. It was noted in the dossier assessment that 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. During the commenting procedure, the company provided additional information on subsequent therapies. However, these related exclusively to the use of tipiracil/trifluridine (see Table 3).

Table 3: Information on tipiracil/trifluridine as subsequent therapies – RCT, direct comparison: trastuzumab deruxtecan vs. ramucirumab + paclitaxel

Study Drug	Patients with subsequent therapy, n (%[a])	
	trastuzumab deruxtecan N = 246	ramucirumab + paclitaxel N = 248
DESTINY-Gastric04		
Number of subsequent therapies		
Any	126 (51.2[b])	118 (47.6[b])
1	122 (49.6)	111 (44.8)
2 or more	39 (15.9)[c]	37 (14.9)[c]
Any subsequent therapy		
tipiracil/trifluridine, n (%[d])	13 (10.3)	12 (10.2)
1st subsequent therapy		
tipiracil/trifluridine, n (%[d])	2 (1.6)	7 (6.3)
2nd or later subsequent therapy		
tipiracil/trifluridine, n (%[d])	11 (28.2)	5 (13.5)

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.
c. Identical values were reported in the dossier for patients who had received 2 subsequent therapies.
d. Relates to patients with subsequent therapy in the relevant line of treatment

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

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 company argued that tipiracil/trifluridine is used particularly in later lines of treatment, but even in the second or subsequent lines of treatment only a small number of patients overall received this combination. Furthermore, in its comments, the company referred to an updated version of the S3 guideline [10]. However, trastuzumab deruxtecan or tipiracil/trifluridine are still recommended as third-line treatments in that version.

The analyses subsequently submitted by the company, as well as the written explanation in its comments, did not alter the assessment regarding the use of tipiracil/trifluridine as subsequent therapy. Overall, the subsequent therapies used in the DESTINY-Gastric04 study do not adequately represent the current standard of care. For this reason, the certainty of conclusions regarding the results for the overall survival outcome remained limited; consequently, for this outcome, at most a hint of an added benefit can be derived.

2.3 Kaplan-Meier curves for common AEs at SOC/PT level

In its dossier, the company had only provided Kaplan-Meier curves for the side effects relating to the outcomes discontinuation due to AEs and interstitial lung disease / pneumonitis (SAEs). The dossier assessment therefore stated that, for the remaining AEs at SOC/PT level, it was not possible to determine when the respective events occurred during the course of the study, nor whether a higher certainty of conclusions could be derived on an outcome-specific basis. In its comments, the company provided further Kaplan-Meier curves for AEs. These can be found in Appendix A for the common AEs at SOC/PT level shown in the dossier assessment. It should be noted, however, that the Kaplan-Meier curves for the outcome cardiac disorders (severe AEs) were still missing.

Based on the information provided by the company during the commenting procedure on censoring, there is a low risk of bias for each of the AE outcomes at SOC/PT level (see also the information on 'Impact on the risk of bias in other outcomes' in Section 2.1). Consequently, the certainty of conclusions was also not reduced for any AE outcome. This meant that even a large effect could not increase the certainty of conclusions. It was therefore not necessary to further examine the Kaplan-Meier curves for this purpose in the given situation.

2.4 SAE and severe AE analyses

In the company's original analyses of SAEs and severe AEs, events related to the PT disease progression were included in each case. According to the module templates, in such situations additional AE analyses should be submitted that do not take these events into account. In its comments, the company presented new analyses of SAEs and severe AEs, in which the PT disease progression was not taken into account. These were used for this assessment.

The risk of bias in the results relating to common SAEs and severe AEs, without taking into account the PT disease progression, was assessed as low (see also Section 2.1).

Table 4 presents the results for common SAEs and severe AEs, without taking into account the PT disease progression. No Kaplan-Meier curves were available for common SAEs and severe AEs.

Table 4: Results (side effects) – RCT, direct comparison: trastuzumab deruxtecan vs. ramucirumab + paclitaxel

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					
Side effects					
SAEs	244	13.7 [6.6; NA] 99 (40.6)	233	8.5 [6.3; 12.3] 96 (41.2)	0.91 [0.69; 1.21]; 0.510
Severe AEs[b]	244	2.3 [1.6; 3.5] 166 (68.0)	233	1.6 [1.0; 2.3] 169 (72.5)	0.81 [0.65; 1.00]; 0.052

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. Operationalized as CTCAE grade ≥ 3.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; HER2: human epidermal growth factor receptor 2; HR: hazard ratio; IHC: immunohistochemistry; ISH: in situ hybridization; n: number of patients with event; N: number of analysed patients; NA: not achieved; RCT: randomized controlled trial; SAE: serious adverse event

For the outcomes SAEs and severe AEs, without taking into account the PT disease progression, there was no statistically significant difference between trastuzumab deruxtecan and ramucirumab + paclitaxel in either case. There is no hint of an added benefit of trastuzumab deruxtecan in comparison with ramucirumab + paclitaxel; an added benefit is therefore not proven in either case.

The company did not subsequently submit any subgroup analyses for the outcomes SAEs and severe AEs which did not take the PT disease progression into account.

2.5 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* [11].

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.

2.5.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in benefit assessment A25-128 [1] and in the previous sections (see Table 5).

Table 5: 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

Table 5: 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]
Side effects		
SAEs	13.7 vs. 8.5 HR: 0.91 [0.69; 1.21]; p = 0.510	Greater/lesser harm not proven
Severe AEs	2.3 vs. 1.6 HR: 0.81 [0.65; 1.00]; p = 0.052	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
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: indication	Outcome category: non-serious/non-severe side effects CI_u < 0.80 Lesser harm, extent: considerable

Table 5: 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]
Epistaxis (AE)	NA vs. NA HR: 0.10 [0.03; 0.27]; p < 0.001 Probability: indication	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: indication	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: indication	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: indication	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: indication	Outcome category: serious/severe side effects 0.90 ≤ CI_u < 1.00 Lesser harm, extent: minor

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. For justification see Section I 4.1 of dossier assessment A25-128 [1].
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; FACT-Ga: Functional Assessment of Cancer Therapy-Gastric; HR: hazard ratio; ILD: interstitial lung disease; NA: not achieved; NC: not calculable; ND: no data; PGIC: Patient Global Impression of Change; PGIS: Patient Global Impression of Severity; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

2.5.2 Overall conclusion on added benefit

Table 6 summarizes the results taken into account for the overall conclusion on the extent of the added benefit.

Table 6: 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): indication of lesser harm – extent: major ▪ Nervous system disorders (severe AE): indication 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): indication of lesser harm – extent: considerable ▪ Epistaxis (AE): indication of lesser harm – extent: considerable ▪ Musculoskeletal and connective tissue disorders (AE): indication of lesser harm –extent: considerable ▪ Renal and urinary disorders (AE): indication 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 outcomes of morbidity and health-related quality of life.	
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 of morbidity and health-related quality of life were not suitable for the benefit assessment.

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 (indications and hint) 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. As only overall survival was monitored throughout the entire study duration, and the positive effects of the side effects relate only to a shorter observation period, the effect in overall survival is the key factor in the overall conclusion on added benefit.

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

2.6 Summary

The data subsequently submitted by the company in the commenting procedure did not change the conclusion on the added benefit of trastuzumab deruxtecan from dossier assessment A25-128.

Table 7 below shows the result of the benefit assessment of trastuzumab deruxtecan, taking into account dossier assessment A25-128 and this addendum.

Table 7: 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 G-BA decides on the added benefit.

3 References

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Appendix A Kaplan-Meier curves on side effects

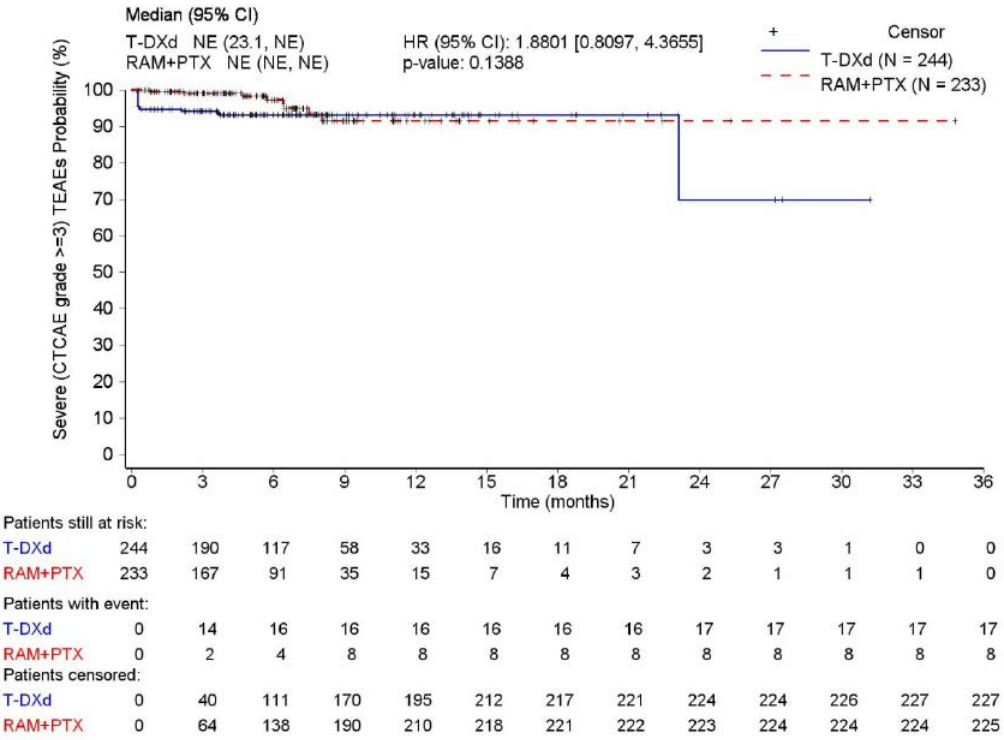
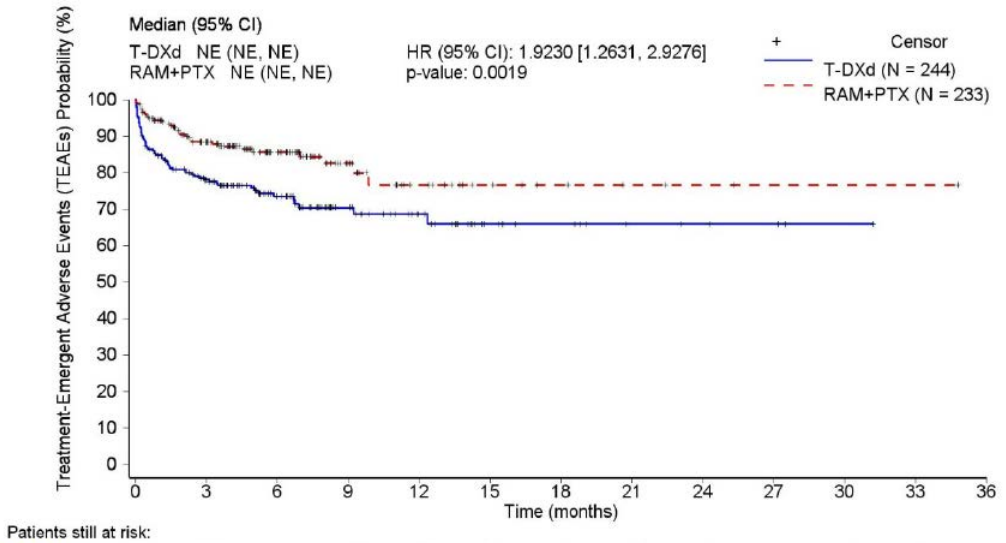
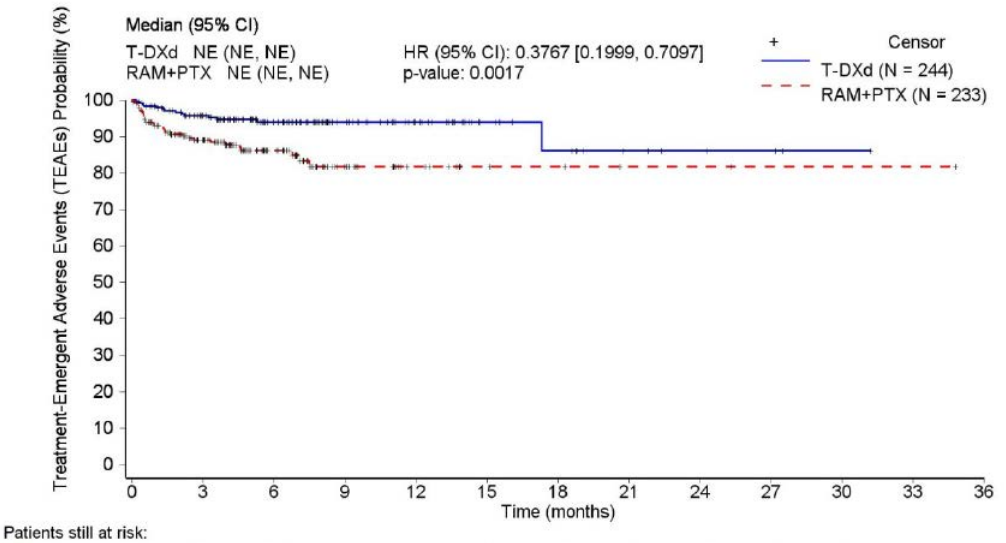


Figure 1: Kaplan-Meier curves for the outcome platelet count decreased (severe AEs [CTCAE grade ≥ 3]) of RCT DESTINY-Gastric04, data cut-off 24 October 2024



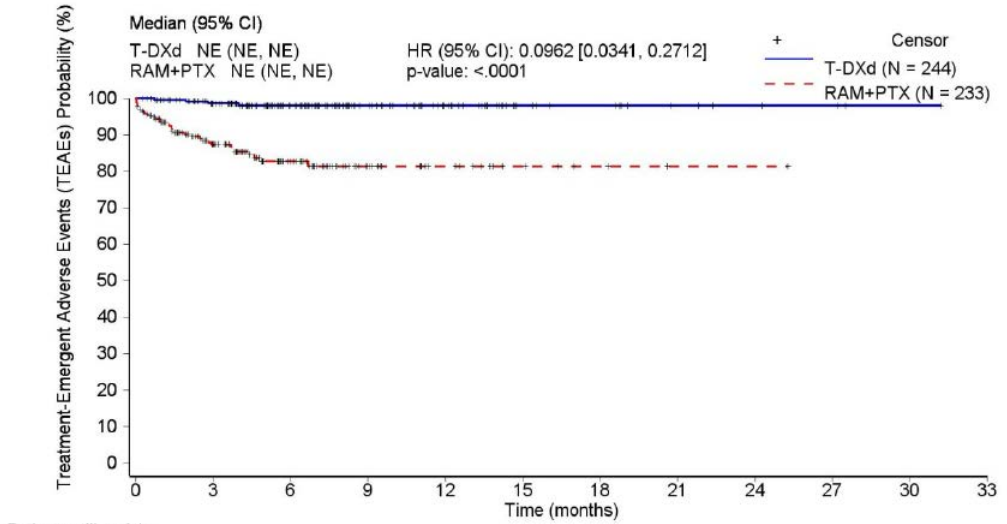
Patients still at risk:													
T-DXd	244	154	84	43	27	13	9	5	4	3	1	0	0
RAM+PTX	233	153	87	34	16	8	5	3	2	1	1	1	0
Patients with event:													
T-DXd	0	52	59	62	63	64	64	64	64	64	64	64	64
RAM+PTX	0	25	29	31	33	33	33	33	33	33	33	33	33
Patients censored:													
T-DXd	0	38	101	139	154	167	171	175	176	177	179	180	180
RAM+PTX	0	55	117	168	184	192	195	197	198	199	199	199	200

Figure 2: Kaplan-Meier curves for the outcome vomiting (AEs) of RCT DESTINY-Gastric04, data cut-off 24 October 2024



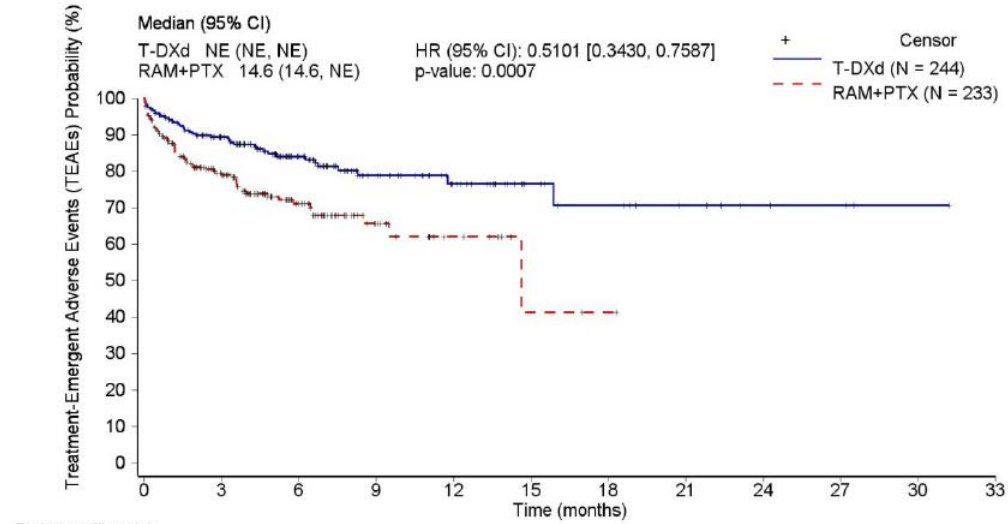
Patients still at risk:													
T-DXd	244	190	112	56	32	16	11	6	4	3	1	0	0
RAM+PTX	233	148	80	30	12	5	4	2	2	1	1	1	0
Patients with event:													
T-DXd	0	10	13	13	13	13	14	14	14	14	14	14	14
RAM+PTX	0	24	28	31	31	31	31	31	31	31	31	31	31
Patients censored:													
T-DXd	0	44	119	175	199	215	219	224	226	227	229	230	230
RAM+PTX	0	61	125	172	190	197	198	200	200	201	201	201	202

Figure 3: Kaplan-Meier curves for the outcome stomatitis (AEs) of RCT DESTINY-Gastric04, data cut-off 24 October 2024



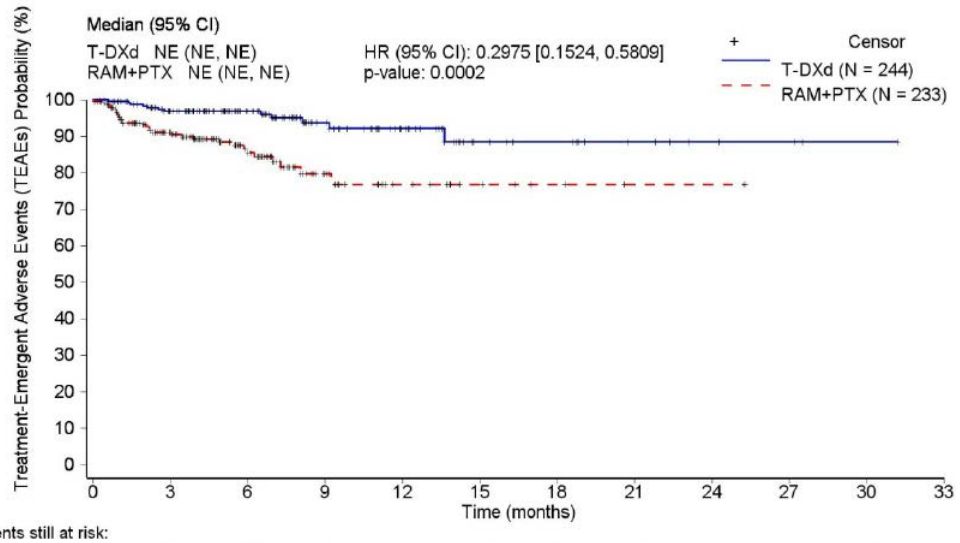
Patients still at risk:												
T-DXd	244	196	118	58	33	15	11	6	4	3	1	0
RAM+PTX	233	143	71	28	13	6	3	1	1	0	0	0
Patients with event:												
T-DXd	0	3	4	4	4	4	4	4	4	4	4	4
RAM+PTX	0	27	33	34	34	34	34	34	34	34	34	34
Patients censored:												
T-DXd	0	45	122	182	207	225	229	234	236	237	239	240
RAM+PTX	0	63	129	171	186	193	196	198	198	199	199	199

Figure 4: Kaplan-Meier curves for the outcome epistaxis (AEs) of RCT DESTINY-Gastric04, data cut-off 24 October 2024



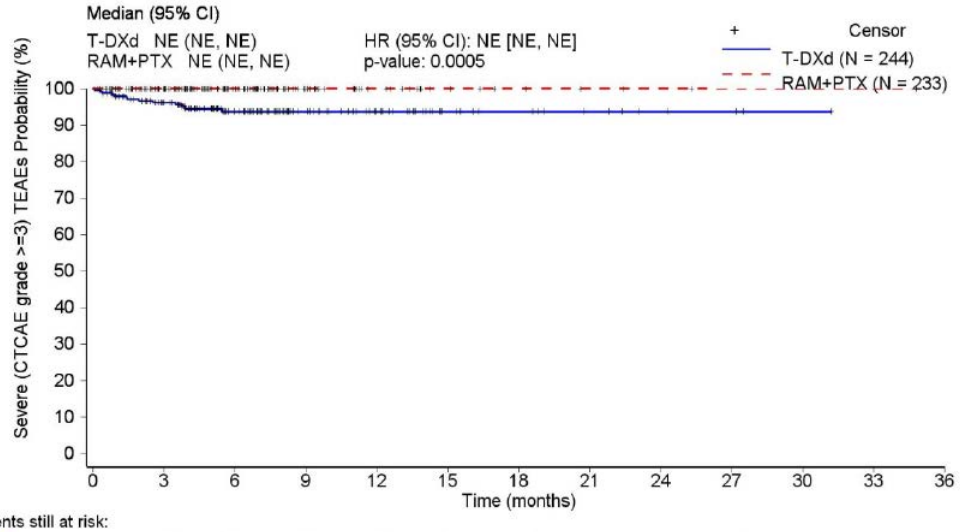
Patients still at risk:												
T-DXd	244	178	101	49	30	15	11	7	4	3	1	0
RAM+PTX	233	138	70	27	9	2	1	0	0	0	0	0
Patients with event:												
T-DXd	0	25	34	39	40	40	41	41	41	41	41	41
RAM+PTX	0	45	57	61	62	63	63	63	63	63	63	63
Patients censored:												
T-DXd	0	41	109	156	174	189	192	196	199	200	202	203
RAM+PTX	0	50	106	145	162	168	169	170	170	170	170	170

Figure 5: Kaplan-Meier curves for the outcome musculoskeletal and connective tissue disorders (AEs) of RCT DESTINY-Gastric04, data cut-off 24 October 2024



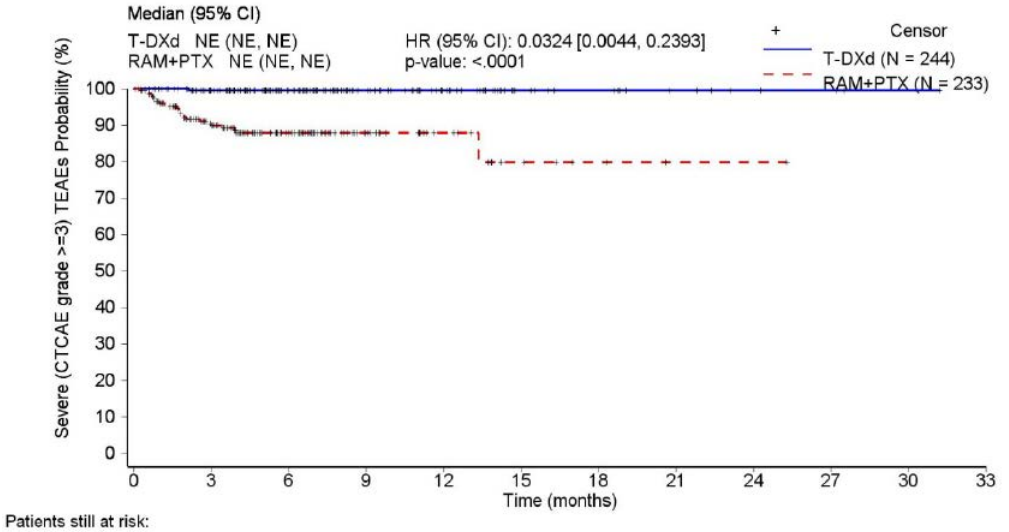
Patients still at risk:												
T-DXd	244	198	120	59	34	16	12	7	4	3	1	0
RAM+PTX	233	155	84	30	13	6	3	1	1	0	0	0
Patients with event:												
T-DXd	0	7	7	10	11	12	12	12	12	12	12	12
RAM+PTX	0	19	25	30	31	31	31	31	31	31	31	31
Patients censored:												
T-DXd	0	39	117	175	199	216	220	225	228	229	231	232
RAM+PTX	0	59	124	173	189	196	199	201	201	202	202	202

Figure 6: Kaplan-Meier curves for the outcome renal and urinary disorders (AEs) of RCT DESTINY-Gastric04, data cut-off 24 October 2024



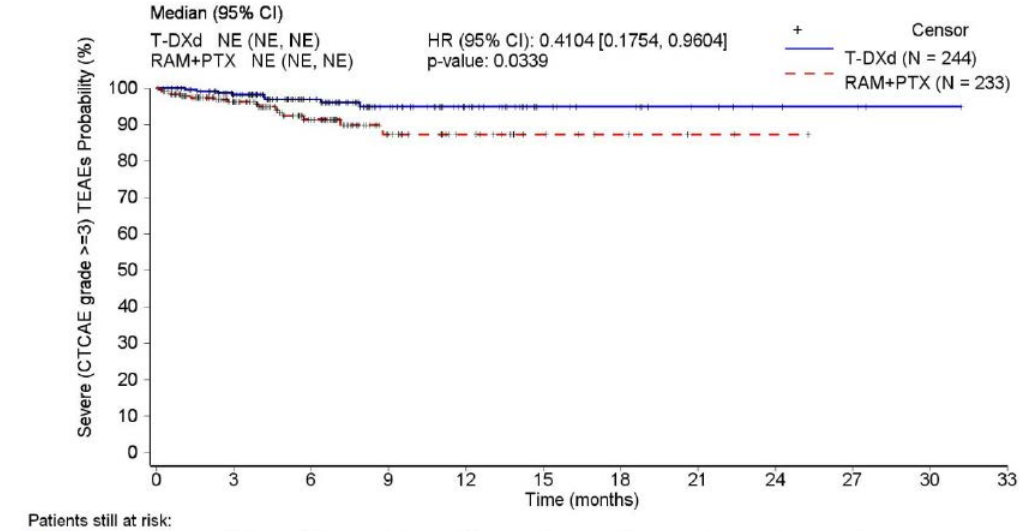
Patients still at risk:													
T-DXd	244	192	113	56	33	16	11	7	4	3	1	0	0
RAM+PTX	233	168	92	37	17	8	5	3	2	1	1	1	0
Patients with event:													
T-DXd	0	9	13	13	13	13	13	13	13	13	13	13	13
RAM+PTX	0	0	0	0	0	0	0	0	0	0	0	0	0
Patients censored:													
T-DXd	0	43	118	175	198	215	220	224	227	228	230	231	231
RAM+PTX	0	65	141	196	216	225	228	230	231	232	232	232	233

Figure 7: Kaplan-Meier curves for the outcome nausea (severe AEs [CTCAE grade ≥ 3]) of RCT DESTINY-Gastric04, data cut-off 24 October 2024



Patients still at risk:												
T-DXd	244	198	120	61	36	17	12	7	4	3	1	0
RAM+PTX	233	152	80	33	15	6	3	1	1	0	0	0
Patients with event:												
T-DXd	0	1	1	1	1	1	1	1	1	1	1	1
RAM+PTX	0	20	24	24	24	25	25	25	25	25	25	25
Patients censored:												
T-DXd	0	45	123	182	207	226	231	236	239	240	242	243
RAM+PTX	0	61	129	176	194	202	205	207	207	208	208	208

Figure 8: Kaplan-Meier curves for the outcome hypertension (severe AEs [CTCAE grade ≥ 3]) of RCT DESTINY-Gastric04, data cut-off 24 October 2024



Patients still at risk:												
T-DXd	244	195	118	58	34	17	12	7	4	3	1	0
RAM+PTX	233	160	86	32	16	7	4	2	1	0	0	0
Patients with event:												
T-DXd	0	4	6	8	8	8	8	8	8	8	8	8
RAM+PTX	0	8	14	16	16	16	16	16	16	16	16	16
Patients censored:												
T-DXd	0	45	120	178	202	219	224	229	232	233	235	236
RAM+PTX	0	65	133	185	201	210	213	215	216	217	217	217

Figure 9: Kaplan-Meier curves for the outcome nervous system disorders (severe AEs [CTCAE grade ≥ 3]) of RCT DESTINY-Gastric04, data cut-off 24 October 2024