Trastuzumab deruxtecan (NSCLC)

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

EXTRACT

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

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

Medical and scientific advice

- Jochem Potenberg, Waldkrankenhaus Protestant Hospital Berlin, Berlin, Germany

IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

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

IQWiG employees involved in the dossier assessment

- Stefanie Reken
- Merlin Bittlinger
- Katharina Frangen
- Simone Heß
- Kirsten Janke
- Maximilian Kind
- Katrin Nink
- Anke Schulz

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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
EMA	European Medicines Agency
ERBB2	erythroblastic oncogene B receptor tyrosine kinase 2
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)
NSCLC	non-small cell lung cancer
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics

I 1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug trastuzumab deruxtecan. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 29 November 2023.

Research question

The aim of this report is to assess the added benefit of trastuzumab deruxtecan as monotherapy compared with the appropriate comparator therapy (ACT) in adult patients with advanced non-small cell lung cancer (NSCLC) whose tumours have an activating human epidermal growth factor receptor 2 (HER2) erythroblastic oncogene B receptor tyrosine kinase 2 (ERBB2) mutation and who require systemic therapy following platinum-based chemotherapy with or without immunotherapy.

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

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

Research question	Therapeutic indication	ACT[a, b]
1	Adults with advanced NSCLC whose tumours have an activating HER2(ERBB2) mutation following prior treatment with platinum-based chemotherapy without immunotherapy	▪ Docetaxel[c] or ▪ pemetrexed[c, d] or ▪ nivolumab or ▪ pembrolizumab[e] or ▪ atezolizumab or ▪ docetaxel in combination with nintedanib[c, f]
2	Adults with advanced NSCLC whose tumours have an activating HER2(ERBB2) mutation following prior treatment with a PD-1/PD-L1 antibody[g] in combination with platinum-based chemotherapy or after sequential therapy with a PD-1/PD-L1 antibody[g] and platinum-based chemotherapy	▪ Docetaxel or ▪ docetaxel in combination with nintedanib[f] or ▪ docetaxel in combination with ramucirumab or ▪ pemetrexed[d] or ▪ vinorelbine[h]

a. Presented is the respective ACT specified by the G-BA.
b. According to the G-BA, for the present therapeutic indication, it is assumed that patients have no medical indication for definitive local therapy. In addition, it is currently assumed that molecularly stratified therapy (directed against EGFR, ALK, BRAF, ROS1, or others) is not an option for the patients at the time of treatment with trastuzumab deruxtecan. Patients were further assumed to be generally eligible for active antineoplastic therapy, and therefore, best supportive care was not an ACT option in the present case.
c. Only for patients with PD-L1-negative tumours.
d. Except for patients with mainly squamous histology.
e. Only for patients with PD-L1 expressing tumours, TPS ≥ 1%.
f. Only for patients with adenocarcinoma histology.
g. Use of a PD-1/PD-L1 inhibitor in prior treatment is not interpreted as a line of therapy to be taken into account with regard to the approval of pemetrexed.
h. Only for patients for whom docetaxel is not suitable.

ALK: anaplastic lymphoma kinase; BRAF: rapidly accelerated fibrosarcoma – isoform B; EGFR: epidermal growth factor receptor; HER2 (ERBB2): human epidermal growth factor receptor 2 (erythroblastic oncogene B receptor tyrosine kinase 2); G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer; PD-1: programmed cell death receptor 1; PD-L1: programmed cell death ligand 1; ROS1: c-ros oncogene 1; TPS: tumour proportion score

In the dossier, the company stated that it was following the ACT specified by the G-BA, referring to a consultation meeting with the G-BA on 21 July 2023. For research question 1, the company's ACT corresponds to the specification of the G-BA. For research question 2, in deviation from the specification of the G-BA, the company defined individualized treatment choosing from different treatment options, taking into account prior therapy and histology, as comparator therapy . In addition to the treatment options specified by the G-BA in the ACT for research question 2, the company also listed afatinib and erlotinib. Besides, in deviation from the G-BA specification, the company limited its research questions to patients after first-line therapy with the treatment options and sequences mentioned. However, the present research questions relate to patients with a corresponding previous treatment, irrespective of

the line of therapy this took place in. The present benefit assessment is conducted in comparison with the ACT specified by the G-BA for the patient groups with previous treatment according to Table 2. These deviations are of no consequence for the present assessment, as the company did not present any data on the comparison of trastuzumab deruxtecan with the ACT.

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

Results

Concurring with the company, no RCT was identified that would allow a direct comparison of trastuzumab deruxtecan with the ACT. As the company did not identify any RCT for the direct comparison of trastuzumab deruxtecan versus the ACT, it conducted an information retrieval for further investigations on trastuzumab deruxtecan and identified the randomized, non-controlled dose-finding study DESTINY-Lung02, which compared 2 different dosages of trastuzumab deruxtecan with each other (6.4 mg/kg versus 5.4 mg/kg body weight). From this study, the company used the study arm with the dosage in accordance with the Summary of Product Characteristics (SPC) (5.4 mg/kg body weight) to assess the added benefit. However, as the DESTINY-Lung02 study does not allow a comparison with the ACT, it is unsuitable for assessing the added benefit of trastuzumab deruxtecan.

Results on added benefit

Since no suitable data are available for the benefit assessment, there is no hint of an added benefit of trastuzumab deruxtecan in comparison with the ACT; an added benefit is therefore not proven.

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

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

[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

Research question	Therapeutic indication	ACT[a, b]	Probability and extent of added benefit
1	Adults with advanced NSCLC whose tumours have an activating HER2(ERBB2) mutation following prior treatment with platinum-based chemotherapy without immunotherapy	▪ Docetaxel[c] or ▪ pemetrexed[c, d] or ▪ nivolumab or ▪ pembrolizumab[e] or ▪ atezolizumab or ▪ docetaxel in combination with nintedanib[c, f]	Added benefit not proven
2	Adults with advanced NSCLC whose tumours have an activating HER2(ERBB2) mutation following prior treatment with a PD-1/PD-L1 antibody[g] in combination with platinum-based chemotherapy or after sequential therapy with a PD-1/PD-L1 antibody[g] and platinum-based chemotherapy	▪ Docetaxel or ▪ docetaxel in combination with nintedanib[f] or ▪ docetaxel in combination with ramucirumab or ▪ pemetrexed[d] or ▪ vinorelbine[h]	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. According to the G-BA, for the present therapeutic indication, it is assumed that patients have no medical indication for definitive local therapy. In addition, it is currently assumed that molecularly stratified therapy (directed against EGFR, ALK, BRAF, ROS1, or others) is not an option for the patients at the time of treatment with trastuzumab deruxtecan. Patients were further assumed to be generally eligible for active antineoplastic therapy, and therefore, best supportive care was not an ACT option in the present case.
c. Only for patients with PD-L1-negative tumours.
d. Except for patients with mainly squamous histology.
e. Only for patients with PD-L1 expressing tumours, TPS ≥ 1%.
f. Only for patients with adenocarcinoma histology.
g. Use of a PD-1/PD-L1 inhibitor in prior treatment is not interpreted as a line of therapy to be taken into account with regard to the approval of pemetrexed.
h. Only for patients for whom docetaxel is not suitable.

ALK: anaplastic lymphoma kinase; BRAF: rapidly accelerated fibrosarcoma – isoform B; EGFR: epidermal growth factor receptor; HER2 (ERBB2): human epidermal growth factor receptor 2 (erythroblastic oncogene B receptor tyrosine kinase 2); G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer; PD-1: programmed cell death receptor 1; PD-L1: programmed cell death ligand 1; ROS1: c-ros oncogene 1; TPS: tumour proportion score

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 as monotherapy compared with the ACT in adult patients with advanced NSCLC whose tumours have an activating HER2(ERBB2) mutation and who require systemic therapy following platinum-based chemotherapy with or without immunotherapy.

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

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

Research question	Therapeutic indication	ACT[a, b]
1	Adults with advanced NSCLC whose tumours have an activating HER2(ERBB2) mutation following prior treatment with platinum-based chemotherapy without immunotherapy	▪ Docetaxel[c] or ▪ pemetrexed[c, d] or ▪ nivolumab or ▪ pembrolizumab[e] or ▪ atezolizumab or ▪ docetaxel in combination with nintedanib[c, f]
2	Adults with advanced NSCLC whose tumours have an activating HER2(ERBB2) mutation following prior treatment with a PD-1/PD-L1 antibody[g] in combination with platinum-based chemotherapy or after sequential therapy with a PD-1/PD-L1 antibody[g] and platinum-based chemotherapy	▪ Docetaxel or ▪ docetaxel in combination with nintedanib[f] or ▪ docetaxel in combination with ramucirumab or ▪ pemetrexed[d] or ▪ vinorelbine[h]

a. Presented is the respective ACT specified by the G-BA.
b. According to the G-BA, for the present therapeutic indication, it is assumed that patients have no medical indication for definitive local therapy. In addition, it is currently assumed that molecularly stratified therapy (directed against EGFR, ALK, BRAF, ROS1, or others) is not an option for the patients at the time of treatment with trastuzumab deruxtecan. Patients were further assumed to be generally eligible for active antineoplastic therapy, and therefore, best supportive care was not an ACT option in the present case.
c. Only for patients with PD-L1-negative tumours.
d. Except for patients with mainly squamous histology.
e. Only for patients with PD-L1 expressing tumours, TPS ≥ 1%.
f. Only for patients with adenocarcinoma histology.
g. Use of a PD-1/PD-L1 inhibitor in prior treatment is not interpreted as a line of therapy to be taken into account with regard to the approval of pemetrexed.
h. Only for patients for whom docetaxel is not suitable.

ALK: anaplastic lymphoma kinase; BRAF: rapidly accelerated fibrosarcoma – isoform B; EGFR: epidermal growth factor receptor; HER2 (ERBB2): human epidermal growth factor receptor 2 (erythroblastic oncogene B receptor tyrosine kinase 2); G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer; PD-1: programmed cell death receptor 1; PD-L1: programmed cell death ligand 1; ROS1: c-ros oncogene 1; TPS: tumour proportion score

In the dossier, the company stated that it was following the ACT specified by the G-BA, referring to a consultation meeting with the G-BA on 21 July 2023. For research question 1,

the company's ACT corresponds to the specification of the G-BA. For research question 2, in deviation from the specification of the G-BA, the company defined individualized treatment choosing from different treatment options, taking into account prior therapy and histology, as comparator therapy . In addition to the treatment options specified by the G-BA in the ACT for research question 2, the company also listed afatinib and erlotinib. Besides, in deviation from the G-BA specification, the company limited its research questions to patients after first-line therapy with the treatment options and sequences mentioned. However, the present research questions relate to patients with a corresponding previous treatment, irrespective of the line of therapy this took place in. The present benefit assessment is conducted in comparison with the ACT specified by the G-BA for the patient groups with previous treatment according to Table 4.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs are used to derive added benefit. This deviates from the approach of the company, which also considered other studies besides RCTs in its inclusion criteria.

The deviations described above are of no consequence for the present assessment, as the company did not present any data on the comparison of trastuzumab deruxtecan with the ACT (see Chapter I 3 for details).

I 3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on trastuzumab deruxtecan (status: 21 September 2023)
- bibliographical literature search on trastuzumab deruxtecan (last search on 21 September 2023)
- search in trial registries/trial results databases for studies on trastuzumab deruxtecan (last search on 21 September 2023)
- search on the G-BA website for trastuzumab deruxtecan (last search on 21 September 2023)

To check the completeness of the study pool:

- search in trial registries for studies on trastuzumab deruxtecan (last search on 12 December 2023); for search strategies, see I Appendix A of the full dossier assessment

Concurring with the company, the check of the completeness of the study pool identified no RCT that would allow a direct comparison of trastuzumab deruxtecan versus the ACT.

As the company did not identify any RCT for the direct comparison of trastuzumab deruxtecan in comparison with the ACT, it conducted an information retrieval for further investigations on trastuzumab deruxtecan. The company identified the randomized, non-controlled dose-finding study DESTINY-Lung02 [3], which compared 2 different dosages of trastuzumab deruxtecan with each other (6.4 mg/kg versus 5.4 mg/kg body weight). From this study, the company used the study arm with the dosage in accordance with the SPC (5.4 mg/kg body weight) to assess the added benefit [4]. The company neither conducted an information retrieval nor presented data on the ACT. The completeness of the study pool for further investigations was not checked.

The data presented by the company are unsuitable for drawing conclusions on the added benefit of trastuzumab deruxtecan in comparison with the ACT. This is justified below.

Evidence presented by the company – DESTINY-Lung02 study

The DESTINY-Lung02 study is an ongoing, 2-arm, randomized, non-controlled, dose-finding study in adults with metastatic NSCLC with a known activating HER2 mutation. The study included patients who had received previous treatment including platinum-based therapy in the metastatic setting and who were not amenable to curative surgery or radiation. The study

compared 2 different dosages of trastuzumab deruxtecan (6.4 mg/kg versus 5.4 mg/kg body weight), of which the study arm with treatment with 5.4 mg/kg body weight investigated the dosage specified for patients in the present therapeutic indication according to the SPC of trastuzumab deruxtecan [4]. The study was the basis for the conditional approval by the European Medicines Agency (EMA), where the EMA stipulated as a condition for approval the submission of results from an ongoing RCT investigating treatment with trastuzumab deruxtecan in the first-line treatment of NSCLC and thus in another line of therapy [5].

For its benefit assessment, the company used results from the DESTINY-Lung02 study on treatment with 5.4 mg/kg body weight according to the SPC [4] from a single study arm. The company did not aim for a comparison with the ACT and presented neither information retrieval nor data on the ACT.

DESTINY-Lung02 study unsuitable for the benefit assessment

The DESTINY-Lung02 study is unsuitable for the derivation of an added benefit because it does not permit a comparison with the ACT. Hence, there are no suitable data for deriving an added benefit in comparison with the ACT.

I 4 Results on added benefit

No suitable data are available for the assessment of the added benefit of trastuzumab deruxtecan as monotherapy compared with the ACT in adult patients with advanced NSCLC whose tumours have an activating HER2(ERBB2) mutation and who require systemic therapy following platinum-based chemotherapy with or without immunotherapy. There is no hint of an added benefit of trastuzumab deruxtecan in comparison with the ACT; an added benefit is therefore not proven.

I 5 Probability and extent of added benefit

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

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

Research question	Therapeutic indication	ACT[a, b]	Probability and extent of added benefit
1	Adults with advanced NSCLC whose tumours have an activating HER2(ERBB2) mutation following prior treatment with platinum-based chemotherapy without immunotherapy	▪ Docetaxel[c] or ▪ pemetrexed[c, d] or ▪ nivolumab or ▪ pembrolizumab[e] or ▪ atezolizumab or ▪ docetaxel in combination with nintedanib[c, f]	Added benefit not proven
2	Adults with advanced NSCLC whose tumours have an activating HER2(ERBB2) mutation following prior treatment with a PD-1/PD-L1 antibody[g] in combination with platinum-based chemotherapy or after sequential therapy with a PD-1/PD-L1 antibody[g] and platinum-based chemotherapy	▪ Docetaxel or ▪ docetaxel in combination with nintedanib[f] or ▪ docetaxel in combination with ramucirumab or ▪ pemetrexed[d] or ▪ vinorelbine[h]	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. According to the G-BA, for the present therapeutic indication, it is assumed that patients have no medical indication for definitive local therapy. In addition, it is currently assumed that molecularly stratified therapy (directed against EGFR, ALK, BRAF, ROS1, or others) is not an option for the patients at the time of treatment with trastuzumab deruxtecan. Patients were further assumed to be generally eligible for active antineoplastic therapy, and therefore, best supportive care was not an ACT option in the present case.
c. Only for patients with PD-L1-negative tumours.
d. Except for patients with mainly squamous histology.
e. Only for patients with PD-L1 expressing tumours, TPS ≥ 1%.
f. Only for patients with adenocarcinoma histology.
g. Use of a PD-1/PD-L1 inhibitor in prior treatment is not interpreted as a line of therapy to be taken into account with regard to the approval of pemetrexed.
h. Only for patients for whom docetaxel is not suitable.

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The above assessment departs from that by the company, which derived a hint of non-quantifiable added benefit on the basis of the results of the individual study arm from the DESTINY-Lung02 study for all patients in the therapeutic indication.

The G-BA decides on the added benefit.

I 6 References for English extract

Please see full dossier assessment for full reference list.

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

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The full report (German version) is published under https://www.iqwig.de/en/projects/a23-115.html.