IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Osimertinib (non-small cell lung cancer) –

Benefit assessment according to §35a Social Code Book V[1] (expiry of the limitation period)

Extract

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

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AEs	adverse events
AUC	area under the curve
BSC	best supportive care
CI	confidence interval
CTCAE	Common Terminology Criteria for AEs
EGFR	epidermal growth factor receptor
EGFR-TKI	EGFR tyrosine kinase inhibitor
EORTC	European Organization for Research and Treatment of Cancer
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MMRM	mixed-effects model with repeated measures
NSCLC	non-small cell lung cancer
PFS	progression-free survival
QLQ-C30	Quality of Life Questionnaire-Core 30
QLQ-LC13	Quality of Life Questionnaire-Lung Cancer 13
RECIST	Response Evaluation Criteria in Solid Tumours
SAEs	serious adverse events
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
VAS	visual analogue scale
WHO PS	World Health Organization Performance Status

2 Benefit assessment

2.1 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 osimertinib. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 2 May 2017.

Research question

The aim of this report was to assess the added benefit of osimertinib compared with the appropriate comparator therapy (ACT) in adult patients with locally advanced or metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer (NSCLC). According to the G-BA's commission, the present benefit assessment exclusively refers to patients who were pretreated with an EGFR tyrosine kinase inhibitor (EGFR-TKI) and for whom cytotoxic chemotherapy is an option. The described patient population corresponded to subpopulation 1a from the first assessment of osimertinib.

For the benefit assessment of osimertinib, the research question presented in Table 2 resulted from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of osimertinib

Subindication	**ACT**[a]
Adult patients with locally advanced or metastatic NSCLC and a positive T790M epidermal growth factor receptor (EGFR) mutation after pretreatment with an EGFR tyrosine kinase inhibitor (EGFR-TKI) for whom cytotoxic chemotherapy is an option	▪ physician's choice of cytotoxic chemotherapy (under consideration of the approval status together with the prescribability of drugs in off-label indications in accordance with Appendix VI of the Pharmaceutical Directive) or, if applicable, ▪ BSC for patients who have already received cytotoxic chemotherapy as an alternative for further cytotoxic chemotherapy.
a: Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; BSC: best supportive care; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer; TKI: tyrosine kinase inhibitor	

The company deviated from the G-BA's specification of the ACT insofar as it exclusively specified the combination therapies of cisplatin and pemetrexed or carboplatin and pemetrexed as comparator therapy. Moreover, the company did not include best supportive care (BSC) in its comparator therapy and did not consider that cytotoxic treatment was to be conducted under consideration of the approval status together with the prescribability of drugs in off-label indications in accordance with Appendix VI of the Pharmaceutical Directive.

The present benefit assessment was conducted in comparison with the ACT specified by the G-BA. The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

Results

Study characteristics

The AURA3 randomized, open-label, controlled study was used for the benefit assessment.

The study included adult patients with locally advanced or metastatic T790M mutation-positive non-small lung cancer with non-squamous histology, who had disease progression after prior first-line treatment with EGFR-TKI.

Patients had to be in good general condition (corresponding to a World Health Organization Performance Status [WHO PS] of 0 or 1) and had to be free of uncontrolled systemic diseases such as hypertension. Moreover, patients had to have adequate functions of the bone marrow, the kidneys and the liver.

In this study, a total of 419 patients were randomly assigned in a ratio of 2:1, 279 of them to the osimertinib arm and 140 to the comparator arm. The participants in the comparator arm received platinum-based chemotherapy consisting of cisplatin + pemetrexed or carboplatin + pemetrexed. Before randomization, the investigator specified the platinum-based chemotherapy that was to be administered to the patients of both study arms.

Patients in the osimertinib arm received 80 mg osimertinib once daily. Patients in the comparator arm received a maximum of 6 cycles of one of the two platinum-based combination chemotherapies every 3 weeks. The interventions in both study arms were used in compliance with the respective Summaries of Product Characteristics (SPCs).

Primary outcome of the study was progression-free survival (PFS). Patient-relevant secondary outcomes were overall survival, symptoms, health status, health-related quality of life and AEs.

Treatment with the randomized study medication was continued until a criterion for discontinuation occurred, e.g. disease progression. The patients in both treatment arms could continue to receive the randomized study medication beyond disease progression if the investigator considered the treatment to be beneficial to them. In the chemotherapy arm, the patients could switch to osimertinib when disease progression was confirmed.

Implementation of the ACT in the AURA3 study

Treatment with cisplatin + pemetrexed was specified prior to randomization for about one third of the patients (approx. 31% [n = 87] of the osimertinib arm and approx. 33% [n = 45] of the comparator arm) in case of allocation to the comparator arm, the remaining patients were to receive treatment with carboplatin + pemetrexed.

Whereas pemetrexed and cisplatin are approved in the investigated therapeutic indication, carboplatin is not approved for the treatment of NSCLC.

Based on the study documents it cannot be assumed that the majority of the patients who were treated with carboplatin had an increased risk of cisplatin-induced side effects (according to the criteria of the Pharmaceutical Directive for off-label use). Overall, the decision criteria for the choice between treatment with carboplatin or cisplatin remained unclear.

The G-BA specified a cytotoxic chemotherapy chosen by the physician as ACT. In the AURA3 study, the investigators could choose between the options cisplatin + pemetrexed or carboplatin + pemetrexed. Further treatment options have actually been approved within the therapeutic indication (as combination therapy or monotherapy); the cytotoxic chemotherapy specified by the physician therefore presents one choice among these options.

Relevant subpopulation of the study

In summary, the subpopulation for whom treatment with cisplatin + pemetrexed was specified before randomization was used for the benefit assessment. The conclusions on the added benefit versus cisplatin + pemetrexed were drawn on the basis of the AURA3 study.

Risk of bias

The risk of bias at study level for the AURA3 study was rated as low. The risk of bias at outcome level was rated as high for all outcomes.

Results

Mortality

There was no statistically significant difference between the treatment groups for the outcome "overall survival". Hence, there was no hint of an added benefit of osimertinib in comparison with cisplatin + pemetrexed; an added benefit is therefore not proven.

Morbidity

- Symptoms

Outcomes of symptoms were recorded with the symptom scales of the disease-specific instruments European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) and EORTC Quality of Life Questionnaire-Lung Cancer 13 (QLQ-LC13). The mean change of the values at week 24 compared with the start of the study was considered (mixed-effects model with repeated measures [MMRM analysis]).

Statistically significant differences in favour of osimertinib versus cisplatin + pemetrexed were found for the outcomes fatigue, nausea and vomiting, pain, appetite loss, dyspnoea, insomnia and constipation (measured with EORTC QLQ-C30) as well as dysphagia,

dyspnoea, alopecia, haemoptysis and pain (arm/shoulder), pain (other), pain (chest) and sore mouth (measured with EORTC QLQ-LC13) respectively.

For the outcomes "fatigue", "nausea and vomiting", "insomnia" and "alopecia" (measured with EORTC QLQ-C30) as well as dyspnoea (measured with EORTC QLQ-C30 and EORTC QLQ-LC13), the confidence interval (CI) of Hedges' g was fully outside the irrelevance range [−0.2; 0.2]; this was interpreted as relevant effect. This resulted in a hint of an added benefit of osimertinib in comparison with cisplatin + pemetrexed for each of these outcomes.

For the outcomes pain, appetite loss, constipation (measured with EORTC-QLQ-C30) as well as dysphagia, haemoptysis, pain (arm/shoulder), pain (other) pain (chest) and sore mouth (measured with EORTC QLQ-LC13) the CI of Hedges' g was not fully outside the irrelevance range [−0.2; 0.2]; it can therefore not be inferred that the effect is relevant. This resulted in no hint of an added benefit of osimertinib in comparison with cisplatin + pemetrexed for these outcomes; an added benefit is therefore not proven.

No statistically significant differences between the treatment groups were shown for the further outcomes on symptoms (diarrhoea, coughing and peripheral neuropathy). This resulted in no hint of an added benefit of osimertinib in comparison with cisplatin + pemetrexed for these outcomes, an added benefit is therefore not proven for any further symptom outcome.

- Health status

The outcome "health status" was recorded with the EQ-5D-5L visual analogue scale (VAS). The present benefit assessment considers the mean change of the values at week 24 compared with the start of the study (MMRM analysis). This analysis showed a statistically significant difference in favour of osimertinib in comparison with cisplatin + pemetrexed. However, the CI for the of Hedges' g was not fully outside the irrelevance range [−0.2; 0.2]; it can therefore not be inferred that the effect is relevant. This resulted in no hint of an added benefit of osimertinib in comparison with cisplatin + pemetrexed for the outcome "health status"; an added benefit is therefore not proven.

Health-related quality of life

Health-related quality of life was recorded with the functional scales and with the scale for recording global health status of the instrument EORTC-QLQ-C30. The mean change of the values at week 24 compared with the start of the study is considered (MMRM analysis).

There was a statistically significant difference in favour of osimertinib for all outcomes.

The CI of Hedges' g for the outcomes global health status, physical functioning, role functioning and social functioning was fully outside the irrelevance range [−0.2; 0.2]; this was interpreted as relevant effect. This resulted in a hint of an added benefit of osimertinib in

comparison with cisplatin + pemetrexed for each of these components of health-related quality of life.

For the outcomes emotional functioning and cognitive functioning, in contrast, the CI of Hedges' g was not fully outside the irrelevance range [−0.2; 0.2]; it can therefore not be inferred that the effect is relevant.

An added benefit for these outcomes is therefore not proven.

Side effects

- Serious adverse events (SAEs), discontinuation due to adverse events (AEs)

There were no statistically significant differences between the treatment groups for the outcomes "SAEs" and "discontinuation due to AEs". Hence, for these outcomes there was no hint of greater or lesser harm from osimertinib in comparison with cisplatin + pemetrexed; greater or lesser harm for these outcomes is therefore not proven.

- Severe AEs (Common Terminology Criteria for AEs (CTCAE) grade ≥ 3)

There was a statistically significant difference in favour of osimertinib versus cisplatin + pemetrexed for the outcome "severe AEs (CTCAE grade ≥ 3)". This resulted in a hint of lesser harm from osimertinib in comparison with cisplatin + pemetrexed for this outcome.

- Specific AEs

The dossier contained no data for the relevant subpopulation for the choice of specific AEs. Information on the total population are also partially missing. The effects observed in the total population were chiefly in favour of osimertinib. There were effects to the disadvantage of osimertinib regarding individual specific AEs (e.g., infections and diarrhoea). The effects of specific AEs in the relevant subpopulation were unclear. However, based on the information available on the total population, disadvantages of osimertinib versus the comparator therapy for the subpopulation can in summary be excluded.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[4]

On the basis of the results presented, the probability and the extent of the added benefit of the drug osimertinib compared with the ACT is assessed as follows:

[4] 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, no added benefit, or less benefit). For further details see [1,2].

In summary, only positive effects are found for osimertinib. A hint of an added benefit with the extent "non-quantifiable" was shown for several outcomes in the categories "morbidity" and "health-related quality of life". For the outcome "severe AEs" (CTCAE grade ≥ 3), there is a hint of lesser harm of osimertinib with the extent "major".

Due to missing information on the specific AEs for the relevant subpopulation, the negative effects are subject to uncertainty. However, based on the present results it cannot be assumed that the effects in the subpopulation raise doubts about the extent that are strong enough to result in only a minor added benefit of osimertinib.

In summary, there is a hint of a non-quantifiable, at least considerable added benefit of osimertinib versus cisplatin + pemetrexed for patients with locally advanced or metastatic NSCLC and a positive T790M EGFR mutation as well as pretreatment with an EGFR-TKI for whom cytotoxic chemotherapy is an option.

Table 3 presents a summary of the probability and extent of the added benefit of osimertinib.

Table 3: Osimertinib – probability and extent of added benefit

Subindication	**ACT**[a]	**Probability and extent of added benefit**
Adult patients with locally advanced or metastatic NSCLC and a positive T790M EGFR mutation as well as pretreatment with an EGFR-TKI for whom cytotoxic chemotherapy is an option	▪ physician's choice of cytotoxic chemotherapy (under consideration of the approval status together with the prescription of drugs in off-label indications in accordance with Appendix VI of the Pharmaceutical Directive) or, if applicable, ▪ BSC for patients who have already received cytotoxic chemotherapy as an alternative for further cytotoxic chemotherapy	Hint of non-quantifiable, at least considerable added benefit[b]

a: Presentation of the respective ACT specified by the G-BA.
b: In the relevant subpopulation of the AURA3 study cisplatin + pemetrexed were examined in the comparator therapy. Conclusions in comparison with further therapies included in the treatment specified by the physician cannot be drawn on the basis of the study.
ACT: appropriate comparator therapy; BSC: best supportive care; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer; SPC: Summary of Product Characteristics; TKI: tyrosine kinase inhibitor

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

2.2 Research question

The aim of this report was to assess the added benefit of osimertinib compared with the ACT in adult patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC. According to the G-BA's commission, the present benefit assessment exclusively refers to patients who had been pretreated with an EGFR-TKI and for whom a cytotoxic chemotherapy was an option. The described patient population corresponded to subpopulation 1a from the first assessment of osimertinib [1].

For the benefit assessment of osimertinib, the research question presented in Table 4 resulted from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of osimertinib

Subindication	**ACT**[a]
Adult patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC after pretreatment with an EGFR-TKI for whom cytotoxic chemotherapy is an option	▪ physician's choice of cytotoxic chemotherapy (under consideration of the approval status together with the prescription of drugs in off-label indications in accordance with Appendix VI of the Pharmaceutical Directive) or, if applicable, ▪ BSC for patients who have already received cytotoxic chemotherapy as an alternative for further cytotoxic chemotherapy
a: Presentation of the respective ACT specified by the G-BA. BSC: best supportive care; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer; TKI: tyrosine kinase inhibitor	

The company deviated from the G-BA's specification of the ACT insofar as it exclusively specified the combination therapies cisplatin and pemetrexed or carboplatin and pemetrexed as comparator therapy. It considers this treatment option to be an adequate implementation of the ACT specified by the G-BA. Moreover, the company did not include BSC in its comparator therapy and did not consider in its definition of the comparator therapy that cytotoxic treatment was to be conducted under consideration of the approval status together with the prescribability of drugs in off-label indications in accordance with Appendix VI of the Pharmaceutical Directive (see Section 2.7.1 of the full dossier assessment).

The present benefit assessment was conducted in comparison with the ACT specified by the G-BA. The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

2.3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study lists on osimertinib (last status: 3 March 2017)
- bibliographical literature search on osimertinib (last search on 7 March 2017)
- search in trial registries for studies on osimertinib (last search on 3 February 2017)
- bibliographical literature search on the ACT (last search on 7 March 2017)
- search in trial registries for studies on the ACT (last search on 3 March 2017)

To check the completeness of the study pool:

- search in trial registries for studies on osimertinib (last search on 5 May 2017)

The check identified no additional relevant study.

2.3.1 Studies included

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

Table 5: Study pool – RCT, direct comparison: osimertinib versus cisplatin + pemetrexed or carboplatin + pemetrexed

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
D5160C00003 (AURA3[b])	Yes	Yes	No

a: Study for which the company was sponsor.
b: In the following tables, the study is referred to with this abbreviated form.
RCT: randomized controlled trial; versus.: versus

The AURA3 study was used for the benefit assessment of osimertinib. This corresponded to the company's approach. However, unlike the company that based its assessment on the total population of the study, the present benefit assessment considered a subpopulation (a detailed explanation can be found in Section 2.3.2). The results of the total population of the AURA3 study are presented in Appendix D of the full dossier assessment as supplementary information.

Section 2.6 of the full dossier assessment contains a reference list for the study included.

2.3.2 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: osimertinib versus cisplatin + pemetrexed or carboplatin + pemetrexed

Study	Study design	Population	Interventions (numbers of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
AURA3	RCT, open-label, parallel, with treatment switching[b]	Adult patients with locally advanced or metastatic T790M mutation-positive non-small lung cancer, who had disease progression after prior first-line treatment with EGFR-TKI. with WHO PS 0 or 1	osimertinib[c] (N = 279) platinum-based chemotherapy[c, d] (N = 140) Relevant subpopulation thereof: osimertinib (n = 87) cisplatin + pemetrexed (n = 45)	Screening: 28 days Treatment: ▪ Osimertinib: until occurrence of one of the criteria for treatment discontinuation[e, f] ▪ Chemotherapy: maximum of 6 cycles[d, e, f] Observation: ▪ Outcome-specific, at most until death	126 centres in Australia, Canada, China, France, Germany, Hong Kong, Hungary, Italy, Japan, Mexico, the Netherlands, Russia, South Korea, Spain, Sweden, Taiwan, United Kingdom, USA 8/2014–ongoing First data cut-off: 15 April 2016 Second data cut-off: 2 September 2016	Primary: progression-free survival Secondary: overall survival, symptoms, health status, health-related quality of life, AEs

a: Primary outcomes contain information without consideration of its relevance for the present benefit assessment. Secondary outcomes exclusively include information on the relevant available outcomes for the present benefit assessment.
b: After the introduction of amendment 1 to the study protocol (22 December 2014), patients in the chemotherapy arm could switch to treatment with osimertinib after confirmed disease progression.
c: For patients of both study arms, one of the following platinum-based chemotherapies was specified before randomization: cisplatin + pemetrexed or carboplatin + pemetrexed.
d: Patients who had not progressed after completion of 4 cycles of a platinum-based combination chemotherapy had the option to receive maintenance treatment with pemetrexed.
e: Treatment could be interrupted for the following reasons: patient's decision, radiological progression or lack of clinical benefits, AEs, pregnancy, severe protocol violation, faulty initiation of the study treatment, lost to follow-up.
f: Patients of both study arms could receive the respective treatment also after progression, as long as a clinical benefit was observed in the investigator's assessment.
EGFR: epidermal growth factor receptor; n: relevant subpopulation; N: number of randomized patients; RCT: randomized controlled trial; TKI: tyrosine kinase inhibitor; AE: adverse event; vs.: versus; WHO PS: World Health Organization Performance Status

Table 7: Characteristics of the intervention – RCT, direct comparison: osimertinib versus cisplatin + pemetrexed or carboplatin + pemetrexed

Study	Intervention	Comparison
AURA3	Osimertinib 80 mg[a], orally, once daily	Comparator arm[b]: pemetrexed, 500 mg/m², i. v.+ cisplatin, 75 mg/m², i. v. or pemetrexed, 500 mg/m², i. v + carboplatin AUC 5 mg/ml/min, i. v.
	without predefined maximum treatment duration	each on day 1 of each 3-week cycle, for a maximum of 6 cycles Possibly maintenance treatment with pemetrexed, 500 mg/m², i.v.
	Concomitant treatment permitted: ▪ in the chemotherapy arm ▫ corticosteroids for 3 days, starting 1 day before the treatment with pemetrexed for the reduction of side effects on the skin ▫ folic acid and vitamin B12 for the avoidance of toxicities ▪ Leukocyte-poor blood transfusion ▪ Corticosteroids and/or bisphosphonates for the treatment of bone metastases ▪ drugs and supporting measures necessary for the patient's wellbeing **Non-permitted concomitant treatment:** ▪ Radiotherapy or other chemotherapies	

a: Dose adjustment in case of toxicity:
- Treatment interrupted in case of AEs CTCAE grade ≥ 3 or unacceptable toxicity. The treatment was resumed at AEs CTCAE grade ≤ 2, with doses of 80 mg or 40 mg. Discontinuation of the treatment if an improvement to CTCAE grade ≤ 2 failed to occur after 3 weeks.
- Treatment interrupted when QTc prolongation was > 500 msec. The treatment was resumed at QTc < 481 msec or in accordance with the baseline value in the 40 mg dose. Treatment was discontinued if signs/symptoms of a severe arrhythmia occurred.
- Discontinuation of the treatment after diagnosis of an interstitial lung disease or corneal ulceration.

b: Application, dose adjustments or treatment discontinuations according to the SPCs and guidelines.

AE: adverse event; AUC: area under the curve; CTCAE: Common Terminology Criteria for Adverse Events; i. v.: intravenous; QTc: time interval between the start of the Q wave and the end of the T wave (corrected for heart rate); RCT: randomized controlled trial; SPC: Summary of Product Characteristics; vs.: versus

The AURA3 study was a randomized, open-label, controlled study.

The study included adult patients with locally advanced or metastatic T790M mutation-positive non-small lung cancer with non-squamous histology, who had disease progression after prior first-line treatment with EGFR-TKI. The T790M status of the tumour tissue was determined in a central laboratory by means of a cobas EGFR mutation test by Roche Molecular Systems before randomization.

Patients had to be in good general condition (corresponding to a WHO PS of 0 or 1) and had to be free of uncontrolled systemic diseases such as hypertension. Moreover, patients had to

have adequate functions of the bone marrow, the kidneys and the liver. More than one previous line of treatment in the advanced disease stage was not allowed.

In this study, a total of 419 patients were randomly assigned in a ratio of 2:1, 279 of them to the osimertinib arm and 140 to the comparator arm. The participants in the comparator arm received platinum-based chemotherapy consisting of cisplatin + pemetrexed or carboplatin + pemetrexed. Before randomization, the investigator specified the platinum-based chemotherapy (cisplatin + pemetrexed or carboplatin + pemetrexed) for patients of both study arms. Stratification in the study took place according to the patients' ethnicity (Asian / non-Asian).

Patients in the osimertinib arm received 80 mg osimertinib once daily. Application of the experimental intervention corresponded to the requirements of the SPC [4].

Patients in the comparator arm received a maximum of 6 cycles of one of the two platinum-based combination chemotherapies every 3 weeks: cisplatin + pemetrexed or cisplatin + pemetrexed. The platinum-based combination chemotherapies were administered in compliance with the respective SPC [5,6]. However, carboplatin was exclusively administered in the 'area under the curve (AUC)' 5 dosage. The AUC 6 [7] dosage also stated in the Pharmaceutical Directive for off-label use was not available in the study. Underdosage can therefore not be excluded for some of the patients.

The primary outcome of the study was progression-free survival (PFS). Patient-relevant secondary outcomes were overall survival, symptoms, health status, health-related quality of life and AEs.

Treatment with the randomized study medication was continued until a criterion for discontinuation occurred, e.g. unacceptable toxicity or disease progression (see Table 6). Occurrence of disease progression was determined by means of the Response Evaluation Criteria in Solid Tumours (RECIST) Version 1.1. The patients in both treatment arms could continue to receive the randomized study medication beyond disease progression if the investigator considered the treatment to be beneficial to them. After discontinuation of the randomized study medication, subsequent therapies could be administered in both treatment arms. There was no limitation regarding subsequent therapy. In the chemotherapy arm, the patients could additionally switch to osimertinib when disease progression was confirmed. At the time point of the last study analysis available in the dossier (second data cut-off, see below), as much as 94 (67.1%) patients had switched from the comparator arm to the osimertinib arm.

Several analyses are planned for the AURA3 study: primary analysis (relevant for the outcome "PFS") and 3 interim analyses (for the outcome "overall survival"). According to amendment 3 to the study protocol of 21 March 2016, the primary analysis was to be conducted after 221 cases of disease progression. The data cut-off for this analysis was

performed on 15 April 2016 and is referred to as first data cut-off in the present benefit assessment.

The same amendment to the protocol specified that the analysis of overall survival (first interim analysis) was to be conducted approx. 4 months after the primary analysis. This data cut off took place on 2 September 2016 and was referred to as second data cut-off in the present benefit assessment. The data cut-off and the outcomes for which data were available are described in Section 2.4.1.

The AURA3 study is still ongoing. Two further analyses are to be conducted after approx. 50% (second interim analysis) or 70% of the patients (third interim analysis) have died.

Implementation of the ACT in the AURA3 study

Application of the non-approved combination of carboplatin + pemetrexed

As described above, the randomized study treatment in the comparator arm consisted of cisplatin + pemetrexed or carboplatin + pemetrexed.

Treatment with cisplatin + pemetrexed was specified before randomization for about one third of the patients (approx. 31% [n = 87] of the osimertinib arm and approx. 33% (n = 45) of the comparator arm) in case of allocation to the comparator arm, the remaining patients were to receive treatment with carboplatin + pemetrexed.

Whereas pemetrexed [5] and cisplatin [8] have been approved in the investigated therapeutic indication, carboplatin is not approved for the treatment of NSCLC [6].

According to Appendix IV to Section K of the Pharmaceutical Directive, prescription of carboplatin within this therapeutic indication is restricted to patients with an increased risk of cisplatin-induced side effects (e.g. existing neuropathy or relevant hearing impairment, particular susceptibility to nausea, renal insufficiency or cardiac failure) [7]. In the AURA3 study, treatment with carboplatin + pemetrexed was not explicitly restricted according to these criteria. Criteria for the choice between carboplatin and cisplatin were actually not outlined in the study documents.

Based on the study documents it cannot be assumed that the majority of the patients who were treated with carboplatin had an increased risk of cisplatin-induced side effects (according to the criteria of the Pharmaceutical Directive for off-label use). For instance, participation in the study was principally prohibited for patients with organ insufficiencies. In the comparator arm, the proportion of patients with hearing impairment or nausea (of any grade) was 0.7% or 7.9% at the start of the study.

Moreover, the dossier contained no data on the characteristics of those patients who had been treated with carboplatin or cisplatin; it can therefore not be understood whether certain characteristics, e.g., age or comorbidities, were decisive for the decision between carboplatin or cisplatin. However, it can be excluded that a poor general condition which in everyday

health care plays a role in the decision between carboplatin and cisplatin, counted among the decision criteria, because only patients with good general conditions (WHO PS 0-1) were included in the AURA3 study. Overall, the decision criteria for the choice between treatment with carboplatin or cisplatin remained unclear.

In the consultation with the G-BA, it was also explained that the preconditions for off-label indication of carboplatin must be demonstrated in the dossier, for instance, by stating the considerations in the decision between carboplatin and cisplatin. Moreover, it was stated that inclusion and exclusion criteria as well as other information from the study protocol might also have been suitable evidence [9]. However, in its dossier, the company neither provided corresponding information nor did it address the question whether treatment with carboplatin in the AURA3 study was in compliance with the criteria of the Pharmaceutical Directive.

Implementation of the cytotoxic chemotherapy specified by the physician

For the assessment of osimertinib, the G-BA specified a cytotoxic chemotherapy chosen by the physician as ACT. In the AURA3 study, the investigators could choose between the options cisplatin + pemetrexed or carboplatin + pemetrexed. Therefore, they could not freely choose the combination partner for the platinum derivative. Further combination partner options for the platinum derivatives have actually been approved within the therapeutic indication (e.g. docetaxel [10] or paclitaxel [11]); the cytotoxic chemotherapy specified by the physician therefore presents one choice among these several options. Moreover, the therapeutic indication permits several monotherapies (e.g. pemetrexed [5] or docetaxel [10]).

Relevant subpopulation of the study

As described above, it cannot be derived for the AURA3 study that treatment with cisplatin was actually not indicated for the majority of the patients who had been treated with carboplatin, and treatment was thus conducted in accordance with the directive for off-label use. The criteria on which the choice between carboplatin or cisplatin was based also remained unclear. Hence, the subpopulation of patients for whom treatment with cisplatin + pemetrexed had been determined before randomization corresponded to the requirements specified for the ACT by the G-BA.

Therefore, this cisplatin subpopulation is used for the benefit assessment. Since the decision as to which chemotherapy (cisplatin or carboplatin, each in combination with pemetrexed) was supposed to be administered had already been made for all patients before randomization, the randomization was also maintained for the cisplatin subpopulation.

Therefore, conclusions on the added benefit versus cisplatin + pemetrexed were drawn on the basis of the AURA3 study.

Characteristics of the study population

The characteristics of the study population were only available for the total population of the AURA3 study and are presented in Appendix B (Table 24) of the full dossier assessment. The

mean age of the patients included in the AURA3 study was 62 years, most of them were female (approx. 66%) and of Asian origin (approx. 65%). Almost all patients had metastatic disease, approx. 65% of them had brain metastases. At the start of the study, the participants were in very good or good general condition (corresponding to a World Health Organization Performance Status [WHO PS] of 0 or 1). The proportion of patients with treatment discontinuation at the second data cut-off was lower in the osimertinib arm (54.8%) than in the comparator arm (93.6%). The most common reason for treatment discontinuation in both study arms was disease progression.

Treatment duration and follow up observation

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

Table 8: Planned duration of follow-up – RCT, direct comparison: osimertinib versus cisplatin + pemetrexed or carboplatin + pemetrexed

Study **Outcome category** **Outcome**	**Planned follow-up**
AURA3	
Mortality	
Overall survival	every 6 weeks[a] after disease progression or end of treatment additionally within 2 weeks after every data cut-off for the survival time analysis
Morbidity	
Symptoms	
EORTC QLQ-C30 symptom scales	every 6 weeks[a], on treatment discontinuation and progression; recording until the end of study
EORTC QLQ-LC13:	Weekly up to and including week 3, then every 3 weeks[a] as well as on treatment discontinuation and progression; recording until the end of study
Health status (EQ-5D-5L VAS)	every 6 weeks[a], on treatment discontinuation and progression; recording until the end of study
Health-related quality of life	
EORTC QLQ-C30 functional scales	every 6 weeks[a], on treatment discontinuation and progression; recording until the end of study
Side effects	
All outcomes in the category “side effects”	until 28 days after the last dose of the study medication; then only recording of SAEs considered to be treatment-related by the investigator until disease progression[b]

a: In relation to the date of randomization.
b: For patients who discontinued the study treatment for reasons other than disease progression.
EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D-5L: European Quality of Life Questionnaire 5, Dimension 5 Level; QLQ-C30: Quality of Life Questionnaire Core-30; QLQ-LC13: Quality of Life Questionnaire-Lung Cancer 13; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

Information on the mean and median treatment duration in the study is only available for the total population and is presented in Appendix B (Table 25) of the full dossier assessment.

At the first data cut-off, median treatment duration for the total population of the study in the osimertinib arm was 8.1 months and thus twice as long as in the comparator arm (4.2 months). At the second data cut-off, the difference increased further with 11.4 versus 4.2 months. The difference in treatment durations resulted from the different treatment discontinuation rates due to disease progression as well as the different maximum treatment durations in the respective study arms (osimertinib: no restriction, comparator arm: 6 cycles [Table 7]).

For the outcomes "overall survival", "morbidity" and "health-related quality of life", the data were also recorded after the end of treatment with the randomized study medication and after a possible switch of treatment from chemotherapy to osimertinib until the end of study. The dossier contained no information on the observation period for the individual outcomes, including for the total population.

The magnitude of the different observation periods for the side effects was presumably similar to the differences in the treatment duration, because these outcomes except SAEs were recorded 28 days after the last administration of the study medication. The SAEs were recorded in addition to this observation period until disease progression if the investigator considered them to be treatment-related (see Table 8). Overall, the observation periods for the side effects were systematically shortened. To be able to draw a reliable conclusion on the total study period or the time until death of the patients, it would principally be necessary to record side effects and further relevant outcomes of the study over the total period of time.

Risk of bias at study level

Table 9 shows the risk of bias at study level.

Table 9: Risk of bias at study level – RCT, direct comparison: osimertinib versus cisplatin + pemetrexed

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patient	Treating staff			
AURA3	Yes	Yes	No	No	Yes	Yes	Low
RCT: randomized controlled trial; vs.: versus							

The risk of bias at study level was rated as low. Limitations resulting from the open-label study design are described in Section 2.4.2 with the outcome-specific risk of bias.

2.4 Results on added benefit

2.4.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.7.2.4.3 of the full dossier assessment):

- Mortality
  - overall survival
- Morbidity
  - symptoms measured with the symptom scales of the instruments EORTC QLQ-C30 and EORTC QLQ-LC13
  - health status measured with the European Quality of Life-5 Dimensions 5 Levels visual analogue scale (EQ-5D-5L VAS)
- Health-related quality of life
  - Health-related quality of life measured with the functional scales of the EORTC QLQ-C30 questionnaire
- Side effects
  - SAEs
  - discontinuation due to AEs
  - SAEs (CTCAE grade ≥ 3)
  - if applicable, further specific AEs

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4 A) (see Section 2.7.2.4.3 of the full dossier assessment).

Table 10 shows for which outcomes from which data cut-offs data were available in the study included.

Table 10: Matrix of outcomes – RCT, direct comparison: osimertinib versus cisplatin + pemetrexed

Study	Outcomes							
Data cut-off	**Overall survival**	**Symptoms [a, b] (EORTC QLQ-C30 and EORTC QLQ-LC13)**	**Health status[b] (EQ-5D-5L VAS)**	**Health-related quality of life[b, c] (EORTC QLQ-C30)**	**SAEs**	**Discontinuation due to AEs**	**Severe AEs (CTCAE grade ≥ 3)**	**Further specific AEs**
AURA3								
First data cut-off 15/04/2016	No	Yes	Yes	Yes	No	No	No	No[d]
Second data cut-off 02/09/2016	Yes	No	No	No	Yes	Yes	Yes	No[d]

a: Measured with symptom scales.
b: MMRM at week 24.
c: Measured with functional scales.
d: No data available for the relevant subpopulation.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organization for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; MMRM: mixed-effects model with repeated measures; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-LC13: Quality of Life Questionnaire-Lung Cancer 13; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

Data on the included outcomes available for the subpopulation were obtained from different data cut-offs. For the outcomes on symptoms, health status and health-related quality of life, the company presented results of the first data cut-off (15 April 2016), the results presented for overall survival and side effects originated from the second data cut-off (2 September 2016). The analysis date week 24 was used for these outcomes (for reasons, see Section 2.7.2.4.3 of the full dossier assessment). According to the study documents, all patients had already been observed for 24 weeks at the first data cut-off, there was thus no difference between the results of these outcomes in the two data cut-offs.

2.4.2 Risk of bias

Table 11 shows the risk of bias for the relevant outcomes.

Table 11: Risk of bias at study and outcome level – RCT, direct comparison: osimertinib versus cisplatin + pemetrexed

Study		Outcomes							
	Study level	Overall survival	Symptoms [a,b] (EORTC QLQ-C30, EORTC QLQ-LC13)	Health status[b] (EQ-5D-5L VAS)	Health-related quality of life[b,c] (EORTC QLQ-C30)	SAEs	discontinuation due to AEs	Severe AEs (CTCAE grade ≥ 3)	Further specific AEs
AURA3	N	H[d]	H[e,f]	H[e,f]	H[e,f]	H[g]	H[h]	H[g]	-[i]

a: Measured with symptom scales.
b: MMRM at week 24 (first data cut-off on 15 April 2016).
c: Measured with functional scales.
d: large proportion of patients who switched from treatment with chemotherapy to treatment with osimertinib (in the total population: 67.1% until the second data cut-off on 2 September 2016).
e: large proportion of patients who switched from treatment with chemotherapy to treatment with osimertinib (in the total population: 31.4% until week 24 [first data cut-off on 15 April 2016]).
f: due to incomplete blinding in the subjective recording of outcomes; large proportion of patients not included in the analysis (> 10%) or large difference between the treatment groups (> 5 percentage points); decreasing response of questionnaires in the course of the study.
g: Potentially large difference in potentially informative censorings between the treatment groups.
h: Lack of blinding in subjective recording of outcomes.
i: No data available for the relevant subpopulation.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D-5L: European Quality of Life-5 Dimension; 5: Level; H: high; MMRM: mixed-effects model repeated measures; L: low; QLQ-C30: Quality of Life Questionnaire-Core -30; QLQ-LC13: Quality of Life Questionnaire-Lung Cancer 13; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

The rating of the respective risk of bias for the relevant subpopulation (cisplatin + pemetrexed) is described hereinafter. The company conducted the assessment on the basis of the total population of the study.

The risk of bias for the outcome "overall survival" was rated as high due to the high proportion of patients in the comparator arm who switched to osimertinib following disease progression. The company also rated overall survival as having a high risk of bias (see Section 2.7.2.4.2 of the full dossier assessment).

The risk of bias for the outcomes symptoms, health status and health-related quality of life was rated as high due to the open label study design, the high proportion of patients who were not included in the analysis (approx. 18% to 26% in the osimertinib arm, approx. 7% to 20%

in the comparator arm) as well as due to the switch of treatment (see Section 2.7.2.4.2 of the full dossier assessment). The company also rated the risk of bias as high for these outcomes.

For the outcomes on side effects (SAEs and severe AEs with CTCAE grade ≥ 3), the risk of bias is assessed as high due to the large proportions of observations with potentially informative censoring (see Section 2.7.2.4.2 of the full dossier assessment). The risk of bias was also rated as high for the outcome "discontinuation due to AEs" due to the lack of blinding. The company also rated the risk of bias as high for these outcomes.

2.4.3 Results

The results on the comparison of osimertinib with cisplatin and pemetrexed in patients with locally advanced or metastatic NSCLC and a positive T790M mutation of the EGFR as well as pretreatment with an EGFR-TKI for whom cytotoxic chemotherapy is an option, are summarized in Table 12 and Table 13. The analyses on morbidity and health-related quality of life were based on the first data cut-off (15 April 2016), the analyses on overall survival and side effects were based on the second data cut-off (2 September 2016). Where necessary, the data from the company's dossier were supplemented with the Institute's calculations.

Kaplan-Meier curves on the outcomes included were not available for the relevant subpopulation. For the total population, there is only a Kaplan-Meier curve on overall survival. It is presented as additional information in Appendix D of the full dossier assessment. The other results for the total population are presented as additional information in Appendix B and Appendix C of the full dossier assessment.

Table 12: Results (mortality and side effects – time to first event) – RCT, direct comparison: osimertinib versus cisplatin + pemetrexed

Study **Outcome category**	**Osimertinib**		**Cisplatin + pemetrexed**		**Osimertinib vs. cisplatin + pemetrexed**
Outcome	**N**	**Median survival time in months [95% CI]** **Patients with event n (%)**	**N**	**Median survival time in months [95% CI]** **Patients with event n (%)**	**HR [95% CI]; p-value**
AURA3					
Mortality					
Overall survival	87	NA [NA; NA] 19 (21.8)	45	NA [17.81; NA] 10 (22.2)	0.92 [0.44; 2.07]; 0.838
Side effects					
AEs (supplementary information)	87	0.26 [ND] 86 (98.6)	45	0.10 [ND] 45 (100)	–
SAEs	87	19.81 [ND] 20 (23.0)	45	NA [ND] 12 (26.7)	0.47 [0.23; 1.00]; 0.050
Severe AEs (CTCAE grade ≥ 3)	87	19.81 [ND] 24 (27.6)	45	9.79 [ND] 22 (48.9)	0.28 [0.16; 0.51]; < 0.001
Specific AEs	Data were only available for the total population and only incomplete.				
	N	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**RR [95% CI]; p-value[a]**
Discontinuation due to AEs	87	9 (10.3)	45	7 (15.6)	0.67 [0.27; 1.67]; 0.419

a: Institute's calculation, unconditional exact test (CSZ method according to [12]).

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; ND: no data; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; vs.: versus

Table 13: Results (morbidity and health-related quality of life, MMRM) – RCT, direct comparison: osimertinib versus cisplatin + pemetrexed

Study Outcome category Outcome	Osimertinib			Cisplatin + pemetrexed			Osimertinib vs. cisplatin + pemetrexed
	N[a]	Values at start of study mean[b] (SD)	Change at end of study mean[c] (SE)	N[a]	Values at start of study mean[b] (SD)	Change at end of study mean[c] (SE)	MD [95% CI]; p-value[d]
AURA3							
Morbidity							
Symptoms (EORTC QLQ-C30 symptom scales)							
Fatigue	71	28.3 (25.60)	-6.83 (2.06)	39	28.2 (22.49)	7.95 (2.77)	-14.78 [-21.57; -8.00]; < 0.001 Hedges´g[e]: -0.85 [-1.25; -0.44]
Nausea and vomiting	71	5.4 (11.88)	-2.62 (1.21)	39	6.4 (12.46)	6.04 (1.61)	-8.66 [-12.63; -4.70]; < 0.001 Hedges´g[e]: -0.85 [-1.25; -0.44]
Pain	71	23.0 (25.88)	-11.01 (1.97)	39	23.5 (24.40)	-2.96 (2.64)	-8.05 [-14.52; -1.57]; 0.015 Hedges´g[e]: -0.48 [-0.88; -0.09]
Appetite loss	71	17.8 (26.33)	-5.53 (2.33)	39	24.8 (30.32)	5.79 (3.12)	-11.32 [-18.98; -3.65]; 0.004 Hedges´g[e]: -0.57 [-0.97; -0.17]
Diarrhoea	71	9.9 (16.32)	1.68 (1.61)	39	11.1 (20.71)	-2.63 (2.15)	4.31 [-0.97; 9.60]; 0.109
Dyspnoea	71	23.5 (26.66)	-8.98 (2.02)	39	23.1 (18.97)	2.18 (2.71)	-11.15 [-17.79; -4.51]; 0.001 Hedges´g[e]: -0.65 [-1.05; -0.25]
Insomnia	71	26.3 (29.77)	-12.47 (2.08)	39	26.5 (24.40)	1.19 (2.79)	-13.66 [-20.51; -6.80]; < 0.001 Hedges´g[e]: -0.77 [-1.18; -0.37]
Constipation	71	15.0 (23.09)	-3.96 (1.88)	39	17.1 (24.03)	3.10 (2.52)	-7.06 [-13.24; -0.88]; 0.025 Hedges´g[e]: -0.44 [-0.84; -0.05]

(continued)

Table 13: Results (morbidity and health-related quality of life, MMRM) – RCT, direct comparison: osimertinib versus cisplatin + pemetrexed (continued)

Study Outcome category Outcome	Osimertinib			Cisplatin + pemetrexed			Osimertinib vs. cisplatin + pemetrexed
	N[a]	Values at start of study mean[b] (SD)	Change at end of study mean[c] (SE)	N[a]	Values at start of study mean[b] (SD)	Change at end of study mean[c] (SE)	MD [95% CI]; p-value[d]
Symptoms (EORTC QLQ-LC13 symptom scales)							
Dysphagia	70	4.3 (11.24)	0.32 (1.18)	42	1.6 (7.18)	4.38 (1.54)	-4.06 [-7.89; -0.23]; 0.038 Hedges´g[e]: -0.40 [-0.79; -0.02]
Dyspnoea	70	19.8 (16.70)	-6.28 (1.41)	42	21.4 (20.88)	1.42 (1.83)	-7.70 [-12.23; -3.17]; < 0.001 Hedges´g[e]: -0.65 [-1.04; -0.25]
Alopecia	70	5.2 (13.47)	-1.83 (1.16)	42	5.6 (12.57)	5.34 (1.51)	-7.17 [-10.91; -3.44]; < 0.001 Hedges´g[e]: -0.73 [-1.12; -0.33]
Haemoptysis	70	4.8 (13.05)	-2.35 (0.46)	42	4.8 (17.38)	-0.86 (0.60)	-1.49 [-2.96; -0.01]; 0.048 Hedges´g[e]: -0.38 [-0.77; 0.00]
Cough	70	29.5 (25.72)	-11.46 (1.73)	42	30.2 (31.07)	-8.19 (2.25)	-3.27 [-8.85; 2.31]; 0.250
Peripheral neuropathy	70	8.1 (17.43)	-1.79 (1.44)	42	11.1 (21.67)	2.06 (1.88)	-3.84 [-8.50; 0.82]; 0.106
Pain (arm/shoulder)	70	15.7 (21.02)	-7.91 (1.53)	42	18.3 (22.33)	-0.47 (1.99)	-7.44 [-12.37; -2.51]; 0.003 Hedges´g[e]: -0.57 [-0.96; -0.18]
Pain (other)	70	19.0 (23.10)	-6.98 (1.71)	42	21.4 (27.37)	-0.57 (2.22)	-6.42 [-11.92; -0.91]; 0.022 Hedges´g[e]: -0.44 [-0.83; -0.06]
Pain (chest)	70	15.7 (23.21)	-6.48 (1.43)	42	15.9 (19.81)	0.20 (1.86)	-6.68 [-11.29; -2.07]; 0.005 Hedges´g[e]: -0.55 [-0.94; -0.16]
Sore mouth	70	3.8 (10.68)	2.02 (1.41)	42	8.7 (16.56)	7.28 (1.85)	-5.26 [-9.85; -0.68]; 0.025 Hedges´g[e]: -0.44 [-0.82; -0.05]

(continued)

Table 13: Results (morbidity and health-related quality of life, MMRM) – RCT, direct comparison: osimertinib versus cisplatin + pemetrexed (continued)

Study Outcome category Outcome	Osimertinib			Cisplatin + pemetrexed			Osimertinib vs. cisplatin + pemetrexed
	N[a]	Values at start of study mean[b] (SD)	Change at end of study mean[c] (SE)	N[a]	Values at start of study mean[b] (SD)	Change at end of study mean[c] (SE)	MD [95% CI]; p-value[d]
Health status							
EQ-5D-5L VAS	64	73.5 (19.64)	4.01 (1.81)	36	66.3 (22.21)	-2.86 (2.41)	6.94 [0.99; 12.89]; 0.022 Hedges´g[e]: 0.47 [0.06; 0.89]
EORTC QLQ-C30 functional scales							
Global health status	71	65.3 (21.78)	7.57 (1.81)	39	61.5 (24.97)	-4.30 (2.43)	11.86 [5.91; 17.82]; < 0.001 Hedges´g[e]: 0.77 [0.37; 1.18]
Physical functioning	71	81.6 (18.26)	4.52 (1.75)	39	83.8 (18.84)	-5.80 (2.36)	10.32 [4.54; 16.10]; < 0.001 Hedges´g[e]: 0.69 [0.29; 1.09]
Role functioning	71	80.8 (25.77)	4.17 (2.33)	39	79.9 (26.81)	-9.83 (3.13)	14.00 [6.33; 21.67]; < 0.001 Hedges´g[e]: 0.71 [0.31; 1.11]
Emotional functioning	71	78.5 (20.30)	9.17 (1.53)	39	72.4 (23.81)	2.26 (2.06)	6.90 [1.85; 11.95]; 0.008 Hedges´g[e]: 0.53 [0.13; 0.93]
Cognitive functioning	71	89.4 (14.97)	1.94 (1.46)	39	88.5 (14.38)	-5.30 (1.96)	7.23 [2.43; 12.04]; 0.003 Hedges´g[e]: 0.58 [0.19; 0.98]
Social functioning	71	85.9 (23.00)	5.07 (1.90)	39	82.1 (25.18)	-7.56 (2.55)	12.63 [6.37; 18.89]; < 0.001 Hedges´g[e]: 0.78 [0.38; 1.19]

a: Number of patients considered in the analysis for the calculation of the effect estimate; the values at the start of the study may be based on other patient numbers.
b: Defined as last measurement before the first administration of the study medication.
c: MMRM.
d: Institute's calculation based on effect estimate of the mean difference and CI of the MMRM from information on changes during the study.

CI: Confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D-5L: European Quality of Life Questionnaire 5, Dimension 5 Level; ITT: intention to treat; MD: mean difference; MMRM: mixed-effects model repeated measures: mean value; N: number of analysed patients; QLQ-C30: Quality of Life Questionnaire Core-30; QLQ-LC13: Quality of Life Questionnaire-Lung Cancer 13; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale; vs.: versus

On the basis of the available data, at most hints, e.g. of an added benefit, can be derived for all outcomes because of the high risk of bias.

The company assessed the added benefit of osimertinib on the basis of the total population of the AURA3 study. The company presented results for the relevant subpopulation of the present assessment in form of subgroup analyses, but derived no added benefit for this subpopulation. The extent of the deviation between the assessment of the outcomes in the present benefit assessment (on the basis of the relevant subpopulation) and the company's assessment (on the basis of the total population) is described in summary form at the end of this section.

Mortality

There was no statistically significant difference between the treatment groups for the outcome "overall survival". Hence, there was no hint of an added benefit of osimertinib in comparison with cisplatin + pemetrexed; an added benefit is therefore not proven.

Morbidity

Symptoms

Outcomes of symptoms were recorded with the symptom scales of the disease-specific instruments European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (EORTC QLQ-C30) and EORTC Quality of Life Questionnaire Lung Cancer 13 (QLQ-LC13). In the present benefit assessment, the mean change of the values at week 24 was compared with the start of the study (MMRM analysis) (see Section 2.7.2.4.3 of the full dossier assessment).

Statistically significant differences in favour of osimertinib versus cisplatin + pemetrexed were found for the outcomes fatigue, nausea and vomiting, pain, appetite loss, dyspnoea, insomnia and constipation (measured with EORTC QLQ-C30) as well as dysphagia, dyspnoea, alopecia, haemoptysis and pain (arm/shoulder), pain (other), pain (chest) and sore mouth (measured with EORTC QLQ-LC13) respectively.

For the outcomes fatigue, nausea and vomiting, insomnia and alopecia (measured with EORTC QLQ-C30) as well as dyspnoea (measured via EORTC QLQ-C30 and EORTC QLQ-LC13), the CI of Hedges' g was fully outside the irrelevance range [–0.2; 0.2]; this was interpreted to be a relevant effect. This resulted in a hint of an added benefit of osimertinib in comparison with cisplatin + pemetrexed for each of these outcomes.

For the outcomes pain, appetite loss, constipation (measured with EORTC-QLQ-C30) as well as dysphagia, haemoptysis, pain (arm/shoulder), pain (other) pain (chest) and sore mouth (measured with EORTC QLQ-LC13) the CI of Hedges' g was not fully outside the irrelevance range [−0.2; 0.2]; it can therefore not be inferred that the effect is relevant. This resulted in no hint of an added benefit of osimertinib in comparison with cisplatin + pemetrexed for these outcomes, an added benefit is therefore not proven.

No statistically significant differences between the treatment groups were shown for the further outcomes on symptoms (diarrhoea, coughing and peripheral neuropathy). This resulted in no hint of an added benefit of osimertinib in comparison with cisplatin + pemetrexed for these outcomes, an added benefit is therefore not proven for any further symptom outcome.

Health status

The outcome "health status" was recorded with the EQ-5D-5L VAS. The present benefit assessment considers the mean change of the values at week 24 compared with the start of the study (MMRM analysis) (see Section 2.7.2.4.3 of the full dossier assessment). This analysis showed a statistically significant difference in favour of osimertinib in comparison with cisplatin + pemetrexed. However, the CI of Hedges' g was not fully outside the irrelevance range [−0.2; 0.2]; it can therefore not be inferred that the effect is relevant. This resulted in no hint of an added benefit of osimertinib in comparison with cisplatin + pemetrexed for the outcome "health status", an added benefit is therefore not proven.

Health-related quality of life

Health-related quality of life was recorded with the functional scales of the disease-specific instrument EORTC QLQ-C30 questionnaire. The present benefit assessment considers the mean change of the values at week 24 compared with the start of the study (MMRM) (see Section 2.7.2.4.3 of the full dossier assessment).

There was a statistically significant difference in favour of osimertinib for all outcomes.

The CI of Hedges' g for the outcomes global health status, physical functioning, role functioning and social functioning was fully outside the irrelevance range [−0.2; 0.2]; this was interpreted to be a relevant effect. This resulted in a hint of an added benefit of osimertinib in comparison with cisplatin + pemetrexed for each of these components of health-related quality of life.

However, for the outcomes emotional functioning and cognitive functioning, in contrast, the CI of Hedges' g was not fully outside the irrelevance range [−0.2; 0.2]; it can therefore not be inferred that the effect is relevant. An added benefit for these outcomes is therefore not proven.

Side effects

SAEs, discontinuation due to AEs

There were no statistically significant differences between the treatment groups for the outcomes "SAEs" and "discontinuation due to AEs". Hence, for these outcomes, there was no hint of greater or lesser harm from osimertinib in comparison with cisplatin + pemetrexed; greater or lesser harm for these outcomes is therefore not proven.

Severe AEs (CTCAE grade ≥ 3)

There was a statistically significant difference in favour of osimertinib versus cisplatin + pemetrexed for the outcome "severe AEs (CTCAE grade ≥ 3)". This resulted in a hint of lesser harm of osimertinib in comparison with cisplatin + pemetrexed for this outcome.

Specific AEs

The dossier contained no data for the relevant subpopulation for the choice of specific AEs. The results for the total population are presented in Appendix C of the full dossier assessment. However, the available data are also incomplete for the total population (see Section 2.7.2.4.3 of the full dossier assessment)

The effects observed in the total population were mainly in favour of osimertinib. There were effects to the disadvantage of osimertinib regarding individual specific AEs (e.g., infections and diarrhoea). The effects of specific AEs in the relevant subpopulation were unclear. However, based on the information available on the total population, disadvantages of osimertinib versus the comparator therapy can in summary be excluded for the subpopulation.

Comparison with the assessment of the company

Overall survival

A statistically significant difference between the treatment arms for the outcome "overall survival" was neither observed for the relevant subpopulation nor for the total population considered by the company. Whereas the added benefit of osimertinib was not proven in the present assessment, the company derived a hint of an added benefit by adding the results of the comparison of individual arms from different studies. The company's approach was not followed (see Section 2.7.2.2 of the full dossier assessment).

Outcomes on morbidity and health-related quality of life

For all outcomes of symptoms (EORTC-QLQ-C30, EORTC-QLQ-CL13), health-related quality of life (EORTC-QLQ-C30) as well as health status (EQ-5D-5L VAS), the company presented responder analyses on the time to deterioration and on the improvement rate in addition to the MMRM analysis (see Section 2.7.2.4.3 of the full dossier assessment). It considered these analyses to be equivalent and used all of them to determine the added benefit.

The MMRM analysis is used as the relevant analysis for the present benefit assessment. Results of the analyses additionally conducted by the company are presented in Appendix A of the full dossier assessment. The result of the MMRM analysis is not called into question by the responder analyses additionally presented by the company. The results are largely consistent across the analyses. This is illustrated in the schematic overview of the results on morbidity and health-related quality of life for the relevant subpopulation (see Table 22 and Table 23 in Appendix A of the full dossier assessment).

Overall, the company derived a hint of an added benefit of osimertinib for all outcomes in the categories morbidity and health-related quality of life on the basis of the total population, while in the present benefit assessment hints of an added benefit are only derived for individual outcomes in the relevant subpopulation (see Table 14).

Outcomes on side effects

For all outcomes on side effects, the company derived an indication of an added benefit of osimertinib in comparison with a platinum-based chemotherapy on the basis of the total population. In the present benefit assessment, in contrast, an added benefit was only derived for severe AEs (CTCAE grade ≥ 3).

The dossier contained no data for the choice of specific AEs for the relevant subpopulation. The data for the total population are also incomplete in the dossier. Although the company considered several AEs to be of particular interest for the total population, it derived no greater or lesser harm for osimertinib.

2.4.4 Subgroups and other effect modifiers

There are no data on subgroup analyses for the relevant subpopulation. However, due to informative censoring and the high proportion of patients who had switched from the comparator arm to subsequent treatment with osimertinib, these subgroup analyses could not be interpreted in a reasonable way (see Section 2.7.2.2 of the full dossier assessment).

2.5 Probability and extent of added benefit

The derivation of probability and extent of added benefit for the relevant subpopulation at outcome level is presented below. The different outcome categories and the effect sizes are taken into account. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

The approach for deriving an overall conclusion on 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 data situation presented in Section 2.4 provides the following assessments of osimertinib in comparison with cisplatin and pemetrexed in patients with locally advanced or metastatic NSCLC and a positive T790M mutation of the EGFR as well as pretreatment with an EGFR-TKI, for whom cytotoxic chemotherapy is an option:

- a hint of an added benefit for each of the following outcomes: fatigue, nausea and vomiting, dyspnoea, insomnia, alopecia, global health status, physical functioning, role functioning and social functioning
- a hint of lesser harm for the outcome “severe AEs” (CTCAE grade ≥ 3).

The dossier contained no data on specific AEs for the relevant subpopulation.

Determination of the outcome category for the outcomes "symptoms"

The assessment regarding the outcome category of the individual symptoms fatigue, nausea and vomiting, dyspnoea, insomnia, alopecia of the EORTC-QLQ-C30 or the EORTC QLQ-LC13 for which an added benefit was demonstrated, depends on the severity of the respective symptom. Due to a lack of further information, the results on common AEs recorded in the AURA3 study were used by CTCAE grades to be able to assess the severity of these symptoms. Those are only available for the total population.

For the total study population, the corresponding AEs, if any, were mostly not severe (CTCAE grade 1 and 2). Correspondingly, the results of the symptoms were allocated to the outcome category "non-serious/non-severe symptoms/late complications". This classification deviated from the assessment of the company, who rated the described symptoms as being serious.

The extent of the respective added benefit at outcome level was estimated from these results (see Table 14).

Table 14: Extent of added benefit at outcome level: osimertinib versus cisplatin + pemetrexed

Outcome category **Outcome**	**Osimertinib vs. cisplatin + pemetrexed** **Median time to event** **Proportion of events or MD** **Effect estimate [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Mortality		
Overall survival	Median: NA vs. NA HR: 0.92 [0.44; 2.07]; p = 0.838	Lesser benefit/added benefit not proven
Morbidity		
Symptoms		
EORTC QLQ-C30 (symptom scales)		
Fatigue	Mean change: -6.83 vs. 7.95 MD: -14.78 [-21.57; -8.00]; p < 0.001 Hedges´gc: -0.85 [-1.25; -0.44] probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications added benefit, extent: "non-quantifiable"
Nausea and vomiting	Mean change: -2.62 vs. 6.04 MD: -8.66 [-12.63; -4.70]; p < 0.001 Hedges´g[c]: -0.85 [-1.25; -0.44] probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications added benefit, extent: "non-quantifiable"
Pain	Mean change: -11.01 vs. -2.96 MD: -8.05 [-14.52; -1.57]; p = 0.015 Hedges´g[c]: -0.48 [-0.88; -0.09]	Lesser benefit/added benefit not proven
Appetite loss	Mean change: -5.53 vs. 5.79 MD: -11.32 [-18.98; -3.65]; p = 0.004 Hedges´g[c]: -0.57 [-0.97; -0.17]	Lesser benefit/added benefit not proven
Diarrhoea	Mean change: 1.68 vs. -2.63 MD: 4.31 [-0.97; 9.60]; p = 0.109	Lesser benefit/added benefit not proven
Dyspnoea	Mean change: -8.98 vs. 2.18 MD: -11.15 [-17.79; -4.51]; p = 0.001 Hedges´g[c]: -0.65 [-1.05; -0.25] probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications added benefit, extent: "non-quantifiable"
Insomnia	Mean change: -12.47 vs. 1.19 MD: -13.66 [-20.51; -6.80]; p < 0.001 Hedges´g[c]: -0.77 [-1.18; -0.37] probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications added benefit, extent: "non-quantifiable"
Constipation	Mean change: -3.96 vs. 3.10 MD: -7.06 [-13.24; -0.88]; p = 0.025 Hedges´g[c]: -0.44 [-0.84; -0.05]	Lesser benefit/added benefit not proven

(continued)

Table 14: Extent of added benefit at outcome level: osimertinib versus cisplatin + pemetrexed (continued)

Outcome category **Outcome**	**Osimertinib vs. cisplatin + pemetrexed** **Median time to event** **Proportion of events or MD** **Effect estimate [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
EORTC QLQ-LC13 (symptom scales)		
Dysphagia	Mean change: 0.32 vs. 4.38 MD: -4.06 [-7.89; -0.23]; p = 0.038 Hedges´g[c]: -0.40 [-0.79; -0.02]	Lesser benefit/added benefit not proven
Dyspnoea	Mean change: -6.28 vs. 1.42 MD: -7.70 [-12.23; -3.17]; p < 0.001 Hedges´g[c]: -0.65 [-1.04; -0.25] probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications added benefit, extent: "non-quantifiable"
Alopecia	Mean change: -1.83 vs. 5.34 MD: -7.17 [-10.91; -3.44]; p < 0.001 Hedges´g[c]: -0.73 [-1.12; -0.33] probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications added benefit, extent: "non-quantifiable"
Haemoptysis	Mean change: -2.35 vs. -0.86 MD: -1.49 [-2.96; -0.01]; p = 0.048 Hedges´g[c]: -0.38 [-0.77; 0.00]	Lesser benefit/added benefit not proven
Cough	Mean change: -11.46 vs. -8.19 MD: -3.27 [-8.85; 2.31]; p = 0.250	Lesser benefit/added benefit not proven
Peripheral neuropathy	Mean change: -1.79 vs. 2.06 MD: -3.84 [-8.50; 0.82]; p = 0.106	Lesser benefit/added benefit not proven
Pain (arm/shoulder)	Mean change: -7.91 vs. -0.47 MD: -7.44 [-12.37; -2.51]; p = 0.003 Hedges´g[c]: -0.57 [-0.96; -0.18]	Lesser benefit/added benefit not proven
Pain (other)	Mean change: -6.98 vs. -0.57 MD: -6.42 [-11.92; -0.91]; p = 0.022 Hedges´g[c]: -0.44 [-0.83; -0.06]	Lesser benefit/added benefit not proven
Pain (chest)	Mean change: -6.48 vs. 0.20 MD: -6.68 [-11.29; -2.07]; p = 0.005 Hedges´g[c]: -0.55 [-0.94; -0.16]	Lesser benefit/added benefit not proven
Sore mouth	Mean change: 2.02 vs. 7.28 MD: -5.26 [-9.85; -0.68]; p = 0.025 Hedges´g[c]: -0.44 [-0.82; -0.05]	Lesser benefit/added benefit not proven
Health status		
EQ-5D-5L VAS	Mean change: 4.01 vs. -2.86 MD: 6.94 [0.99; 12.89]; p = 0.022 Hedges´g[c]: 0.47 [0.06; 0.89]	Lesser benefit/added benefit not proven

(continued)

Table 14: Extent of added benefit at outcome level: osimertinib versus cisplatin + pemetrexed (continued)

Outcome category **Outcome**	**Osimertinib vs. cisplatin + pemetrexed** **Median time to event** **Proportion of events or MD** **Effect estimate [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Health-related quality of life		
EORTC QLQ-C30 (functional scales)		
Global health status	Mean change: 7.57 vs. -4.30 MD: 11.86 [5.91; 17.82]; p < 0.001 Hedges´g[c]: 0.77 [0.37; 1.18] probability: "hint"	Outcome category: quality of life added benefit, extent: "non-quantifiable"
Physical functioning	Mean change: 4.52 vs. -5.80 MD: 10.32 [4.54; 16.10]; p < 0.001 Hedges´g[c]: 0.69 [0.29; 1.09] probability: "hint"	Outcome category: quality of life added benefit, extent: "non-quantifiable"
Role functioning	Mean change: 4.17 vs. -9.83 MD: 14.00 [6.33; 21.67]; p < 0.001 Hedges´g[c]: 0.71 [0.31; 1.11] probability: "hint"	Outcome category: quality of life added benefit, extent: "non-quantifiable"
Emotional functioning	Mean change: 9.17 vs. 2.26 MD: 6.90 [1.85; 11.95]; p = 0.008 Hedges´g[c]: 0.53 [0.13; 0.93]	Lesser benefit/added benefit not proven
Cognitive functioning	Mean change: 1.94 vs. -5.30 MD: 7.23 [2.43; 12.04]; p = 0.003 Hedges´g[c]: 0.58 [0.19; 0.98]	Lesser benefit/added benefit not proven
Social functioning	Mean change: 5.07 vs. -7.56 MD: 12.63 [6.37; 18.89]; p < 0.001 Hedges´g[c]: 0.78 [0.38; 1.19] probability: "hint"	Outcome category: quality of life added benefit, extent: "non-quantifiable"
Side effects		
SAEs	Median: 19.81 vs. NA HR: 0.47 [0.23; 1.00]; p = 0.050	Lesser benefit/added benefit not proven
Severe AEs (CTCAE grade ≥ 3)	Median: 19.81 vs. 9.79 HR: 0.28 [0.16; 0.51]; p < 0.001 probability: "hint"	Outcome category: serious/severe side effects CI_u < 0.75, risk ≥ 5 % lesser harm, extent: "major"
Discontinuation due to AEs	Proportion of events: 10.3 % vs. 15.6 % RR: 0.67 [0.27; 1.67]; p = 0.419	Greater/lesser harm not proven
Specific AEs	Data were only available for the total population and incomplete	

a: Probability provided if a statistically significant and relevant effect is present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
c: If the CI of Hedges' g is fully outside the irrelevance range [−0.2; 0.2], this is interpreted to be a relevant effect. In other cases, it cannot be derived that a relevant effect is present.

AE: adverse event; CI: confidence interval; CI_u: upper limit of the CI; MD: mean difference; NA: not achieved; RR: relative risk; SAE: serious adverse event; vs.: versus

2.5.2 Overall conclusion on added benefit

Table 15 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 15: Positive and negative effects from the assessment of osimertinib in comparison with cisplatin + pemetrexed

Positive effects	**Negative effects**
Non-serious/non-severe symptoms/late complications ▪ Symptoms (fatigue, nausea and vomiting, dyspnoea, insomnia, alopecia): hint of an added benefit – extent: non quantifiable	–
Health-related quality of life ▪ global health status, physical functioning, role functioning, social functioning: hint of an added benefit – extent "non quantifiable"	–
serious/severe side effects ▪ severe AEs (CTCAE grade ≥ 3): hint of lesser harm – extent: "major"	–
Data were only available for the total population and incomplete	
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; SAE: serious adverse event	

Overall, only positive effects were found. A hint to a non-quantifiable added benefit was shown for each of the symptoms fatigue, nausea and vomiting, dyspnoea, insomnia and alopecia. Moreover, there is a hint of a non-quantifiable added benefit for individual aspects of quality of life (global health status, physical functioning, role functioning and social functioning). For the outcome "severe AEs" (CTCAE grade ≥ 3), there is a hint of lesser harm of osimertinib with the extent "major".

Due to missing information on the specific AEs for the relevant subpopulations, the negative effects are subject to uncertainty. However, based on the present results it can not be assumed that the effects in the subpopulation raise doubts about the extent that are strong enough to result in only a minor added benefit of osimertinib.

The results of the assessment of the added benefit in patients with locally advanced or metastatic NSCLC and a positive T790M EGFR mutation as well as pretreatment with an EGFR-TKI, for whom cytotoxic chemotherapy is an option are summarized in comparison with the ACT Table 16.

Table 16: Osimertinib – probability and extent of added benefit

Subindication	**ACT**[a]	**Probability and extent of added benefit**
Adult patients with locally advanced or metastatic NSCLC and a positive T790M EGFR mutation as well as pretreatment with an EGFR-TKI for whom cytotoxic chemotherapy is an option	▪ physician's choice of cytotoxic chemotherapy (under consideration of the approval status together with the prescription of drugs in off-label indications in accordance with Appendix VI of the Pharmaceutical Directive) or, if applicable, ▪ BSC for patients who have already received cytotoxic chemotherapy as an alternative for further cytotoxic chemotherapy	Hint of non-quantifiable, at least considerable added benefit[b]
a: Presentation of the respective ACT specified by the G-BA. b: In the relevant subpopulation of the AURA3 study cisplatin + pemetrexed were examined in the comparator therapy. Conclusions in comparison with further therapies included in the treatment specified by the physician cannot be drawn on the basis of the study. ACT: appropriate comparator therapy; BSC: best supportive care; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer; SPC: Summary of Product Characteristics; TKI: tyrosine kinase inhibitor		

This deviates from the company's approach which derived an indication of a major added benefit of osimertinib (see Section 2.7.2.8.2 of the full dossier assessment).

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

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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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