IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Osimertinib (lung cancer) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Osimertinib (Lungenkarzinom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 10 June 2016). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BSC	best supportive care
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EGFR	epidermal growth factor receptor
EQ-5D	European Quality of Life-5 Dimensions
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HR	hazard ratio
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
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
TKI	tyrosine-kinase inhibitor
VAS	visual analogue scale
WHO	World Health Organization

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 15 March 2016.

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).

The different populations and ACTs resulted in several research questions for the assessment. Table 2 shows an overview of the research questions.

Table 2: Research questions of the benefit assessment of osimertinib

Research question	**Population**	**Appropriate comparator therapy**[a]
1	Patients with T790M mutation after pretreatment with an EGFR tyrosine kinase inhibitor	
1a	Patients for whom cytotoxic chemotherapy is an option	Physician's choice 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, best supportive care[b] for patients who have already received cytotoxic chemotherapy as an alternative for further cytotoxic chemotherapy
1b	Patients for whom cytotoxic therapy is not an option	Best supportive care[b]
2	Treatment-naive patients with *de novo* positive T790M mutation	
	Patients with activating EGFR mutations or patients with ECOG Performance Status 0, 1 or 2[c]	Gefitinib or erlotinib or afatinib or cisplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed) in accordance with the approval status or carboplatin in combination with a third-generation cytostatic agent (only for patients with increased risk of cisplatin-induced side effects in the framework of a combination therapy; see Appendix VI to Section K of the Pharmaceutical Directive)
3	Patients after pretreatment with platinum-based chemotherapy and *de novo* positive T790M mutation	
3a	Patients for whom treatment with docetaxel, pemetrexed, gefitinib, or erlotinib is indicated	Docetaxel, pemetrexed (pemetrexed: except in mainly squamous cell carcinoma histology) or gefitinib or erlotinib (only for patients with activating EGFR mutations who have not been pretreated with gefitinib or erlotinib)
3b	Patients for whom treatment with docetaxel, pemetrexed, gefitinib, or erlotinib is not indicated	Best supportive care[b]

(continued)

Table 2: Research questions of the benefit assessment of osimertinib (continued)

a: Presentation of the respective ACT specified by the G-BA. b: Best supportive care refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life. c: In patients with ECOG Performance Status 2 as an alternative to platinum-based combination treatment: monotherapy with gemcitabine or vinorelbine. ACT: appropriate comparator therapy; ECOG: Eastern Cooperative Oncology Group; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee

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

Results

Research question 1a

For research question 1a, the company identified no randomized or non-randomized studies of direct comparisons on the comparison of osimertinib with the ACT. The company therefore searched for studies for a historical comparison.

The company included 2 one-arm prospective studies (studies AURAex and AURA2) on osimertinib, which were conducted within the therapeutic indication investigated (patients with EGFR T790M mutation). The check of the completeness of the company's study pool for the historical comparison produced one additional potentially relevant (Japanese) patient cohort from the AURA study on osimertinib. Overall, the study pool of the company on the osimertinib side was therefore incomplete. The influence of the results of this cohort on the results of the company's comparisons was assessed as low, however.

For the comparator therapy physician's choice chemotherapy, the company identified individual study arms of a randomized controlled trial (RCT) sponsored by the company (IMPRESS), of another RCT (Halmos 2015), and of 7 retrospective studies (Goldberg 2013, Mariano 2014, Masuda 2015, Park 2015, Shukuya 2015, Tseng 2014, and Wu 2010). For the comparator therapy best supportive care (BSC), the company identified one study arm of an RCT (LUX-Lung 1). All studies on the comparator therapy identified by the company were not in the therapeutic indication to be assessed; in particular, the T790M mutation status was not taken into account. The T790M mutation status was investigated only in the IMPRESS study in the framework of an exploratory study objective. Based on the individual patient data of this study, the company therefore presented both an analysis of patients with positive T790M mutation and of the total population (with and without T790M mutation).

The company conducted several comparisons on the basis of the studies included, for which the 2 studies AURAex and AURA2 were the database for osimertinib. Both studies are open-label, one-arm, multicentre, ongoing approval studies on osimertinib. Adult patients with locally advanced or metastatic EGFR-mutation positive NSCLC with progression under

treatment with an EGFR tyrosine-kinase inhibitor (TKI) were included in the studies. The patients received osimertinib at a dose of 80 mg once daily.

The comparisons conducted by the company could be allocated to 3 categories:

1) comparison with the chemotherapy arm of the IMPRESS study
2) comparison with all studies on the comparator therapy physician's choice chemotherapy (study arms of 2 RCTs including IMPRESS and 7 retrospective analyses)
3) comparison with the BSC arm of the LUX-Lung 1 study

Historical comparison with the IMPRESS study on the comparator therapy physician's choice chemotherapy

The IMPRESS study was a randomized, double-blind, placebo-controlled multicentre study comparing treatment with gefitinib in combination with chemotherapy consisting of pemetrexed and cisplatin (gefitinib arm) with chemotherapy consisting of pemetrexed and cisplatin alone (chemotherapy arm). Adult patients with locally advanced or metastatic EGFR-mutation positive NSCLC with progression under first-line treatment with gefitinib (monotherapy) were included in the study. In contrast to the studies AURAex and AURA2, other previous chemotherapies or systemic treatments were not allowed. Hence the study investigated chemotherapy only as second-line treatment after EGFR-TKI pretreatment.

The company conducted 2 comparisons between the AURA studies and the subpopulation of the IMPRESS study with positive T790M mutation using propensity score matching. These comparisons differed regarding the populations considered (only second line versus all treatment lines in the AURA studies). Of these comparisons, only the comparison within the second line was potentially relevant for the reasons stated above.

Conclusions on the added benefit based on historical comparisons are only possible in the presence of very large effects (so-called dramatic effects) regarding patient-relevant outcomes. Finally, the effect estimated on the basis of the available data has to be so large that it can be excluded that it is solely caused by systematic bias due to the historical comparison. Such an effect was not achieved for any of the patient-relevant outcomes analysed by the company, neither in favour nor to the disadvantage of osimertinib.

Historical comparison with all studies on the comparator therapy physician's choice chemotherapy

The data from the company's studies on the comparator therapy were unsuitable for the benefit assessment. The T790M mutation status was not considered in any of the studies. The studies included by the company were therefore not within the therapeutic indication of osimertinib. In addition, the chemotherapy did not concur with the ACT in most studies used by the company because it did not comply with the approval for a large proportion of the patients. The corresponding information was missing for some of the studies. Finally, usable

data on patient-relevant outcomes were only available for some of the studies, and – except for the IMPRESS study – only on overall survival.

Irrespective of the missing suitability of the studies, the results on overall survival in the main analyses were not significant in any of the comparisons presented by the company. The company additionally conducted sensitivity analyses using different models, which resulted partly in statistically significant results in favour of osimertinib and partly in statistically significant results to the disadvantage of osimertinib. In none of the cases were the results in a magnitude that cannot be explained by systematic bias alone, so that neither an added benefit nor lesser benefit of osimertinib could be derived from them for the outcome "overall survival".

Historical comparison with the LUX-Lung 1 study on the comparator therapy best supportive care

The company used the control arm (placebo + BSC) of the LUX-Lung 1 study for the comparator therapy BSC. In this study, afatinib was compared with placebo, each in addition to BSC. However, the study was not conducted within the therapeutic indication of osimertinib and was therefore irrelevant for the present benefit assessment. One of the reasons was that information on the EGFR mutation status was only available for 25% of the patients (48 of 195 patients in the placebo group). Activating EGFR mutation was detectable in only 34 of these 48 patients (71%), and only 4 of these 34 patients had T790M mutation. Overall, only a very small proportion of the patients were therefore relevant for the present benefit assessment. No corresponding results on patient-relevant outcomes were available from the LUX-Lung 1 study.

Research question 1b

The company presented no data for research question 1b.

Research questions 2 and 3

For research questions 2 and 3, the company only described the results of 2 patients treated with osimertinib in the AURA study, but conducted no comparison with the ACT.

Extent and probability of added benefit, patient groups with therapeutically important added benefit[4]

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

[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].

Table 3: Osimertinib – extent and probability of added benefit

Research question	Population	Appropriate comparator therapy[a]	Extent and probability of added benefit
1	Patients with T790M mutation after pretreatment with an EGFR tyrosine kinase inhibitor		
1a	Patients for whom cytotoxic chemotherapy is an option	Physician's choice 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, best supportive care[b] for patients who have already received cytotoxic chemotherapy as an alternative for further cytotoxic chemotherapy	Added benefit not proven
1b	Patients for whom cytotoxic therapy is not an option	Best supportive care[b]	Added benefit not proven
2	Treatment-naive patients with *de novo* positive T790M mutation		
	Patients with activating EGFR mutations	Gefitinib or erlotinib or afatinib	Added benefit not proven
	or	or	
	patients with ECOG Performance Status 0, 1 or 2[c]	cisplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed) in accordance with the approval status or carboplatin in combination with a third-generation cytostatic agent (only for patients with increased risk of cisplatin-induced side effects in the framework of a combination therapy; see Appendix VI to Section K of the Pharmaceutical Directive)	Added benefit not proven

(continued)

Table 3: Osimertinib – extent and probability of added benefit (continued)

Research question	Population	Appropriate comparator therapy[a]	Extent and probability of added benefit
3	Patients after pretreatment with platinum-based chemotherapy and *de novo* positive T790M mutation		
3a	Patients for whom treatment with docetaxel, pemetrexed, gefitinib, or erlotinib is indicated	Docetaxel, pemetrexed (pemetrexed: except in mainly squamous cell carcinoma histology) or gefitinib or erlotinib (only for patients with activating EGFR mutations who have not been pretreated with gefitinib or erlotinib)	Added benefit not proven
3b	Patients for whom treatment with docetaxel, pemetrexed, gefitinib, or erlotinib is not indicated	Best supportive care[b]	Added benefit not proven

a: Presentation of the respective ACT specified by the G-BA.
b: Best supportive care refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.
c: In patients with ECOG Performance Status 2 as an alternative to platinum-based combination treatment: monotherapy with gemcitabine or vinorelbine.
ACT: appropriate comparator therapy; ECOG: Eastern Cooperative Oncology Group; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee

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 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).

The different populations and ACTs resulted in several research questions for the assessment. Table 4 shows an overview of the research questions.

Table 4: Research questions of the benefit assessment of osimertinib

Research question	Population	Appropriate comparator therapy[a]
1	Patients with T790M mutation after pretreatment with an EGFR tyrosine kinase inhibitor	
1a	Patients for whom cytotoxic chemotherapy is an option	Physician's choice 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, best supportive care[b] for patients who have already received cytotoxic chemotherapy as an alternative for further cytotoxic chemotherapy
1b	Patients for whom cytotoxic therapy is not an option	Best supportive care[b]
2	Treatment-naive patients with *de novo* positive T790M mutation	
	Patients with activating EGFR mutations or patients with ECOG Performance Status 0, 1 or 2[c]	Gefitinib or erlotinib or afatinib or cisplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed) in accordance with the approval status or carboplatin in combination with a third-generation cytostatic agent (only for patients with increased risk of cisplatin-induced side effects in the framework of a combination therapy; see Appendix VI to Section K of the Pharmaceutical Directive)
3	Patients after pretreatment with platinum-based chemotherapy and *de novo* positive T790M mutation	
3a	Patients for whom treatment with docetaxel, pemetrexed, gefitinib, or erlotinib is indicated	Docetaxel, pemetrexed (pemetrexed: except in mainly squamous cell carcinoma histology) or gefitinib or erlotinib (only for patients with activating EGFR mutations who have not been pretreated with gefitinib or erlotinib)
3b	Patients for whom treatment with docetaxel, pemetrexed, gefitinib, or erlotinib is not indicated	Best supportive care[b]

(continued)

Table 4: Research questions of the benefit assessment of osimertinib (continued)

a: Presentation of the respective ACT specified by the G-BA. b: Best supportive care refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life. c: In patients with ECOG Performance Status 2 as an alternative to platinum-based combination treatment: monotherapy with gemcitabine or vinorelbine. ACT: appropriate comparator therapy; ECOG: Eastern Cooperative Oncology Group; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee

The company used the ACT specified by the G-BA.

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

2.3 Research question 1: patients after pretreatment with an EGFR tyrosine kinase inhibitor

2.3.1 Research question 1a: patients for whom cytotoxic chemotherapy is an option

2.3.1.1 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 osimertinib (status: 19 January 2016)
- bibliographical literature search on osimertinib (last search on 16 December 2015)
- search in trial registries for studies on osimertinib (last search on 16 December 2015)
- bibliographical literature search on the ACT (last search on 16 December 2015)
- search in trial registries for studies on the ACT (last search on 16 December 2015)

To check the completeness of the study pool:

- bibliographical literature search on osimertinib (last search on 30 March 2016)
- search in trial registries for studies on osimertinib (last search on 23 March 2016)

In its information retrieval, the company identified no RCT with osimertinib. The check of completeness also produced no RCT with osimertinib.

The company therefore searched for further investigations for a historical comparison of osimertinib with the ACT. Table 5 shows the studies included by the company.

Table 5: Study pool of the company – further investigations: studies on osimertinib and on the comparator therapy; patients with T790M mutation after pretreatment with an EGFR-TKI for whom cytotoxic chemotherapy is an option

Population Study and study type	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
One-arm studies with osimertinib			
AURAex (D5160C00001)	Yes	Yes	No
AURA2 (D5160C00002)	Yes	Yes	No
Studies on the comparator therapy: physician's choice chemotherapy			
RCT			
▫ IMPRESS (D791LC0001)	No	Yes	No
▫ Halmos 2015[b]	No	No	Yes
Retrospective studies[b]			
▫ Goldberg 2013	No	No	Yes
▫ Mariano 2014	No	No	Yes
▫ Masuda 2015	No	No	Yes
▫ Park 2015	No	No	Yes
▫ Shukuya 2015	No	No	Yes
▫ Tseng 2014	No	No	Yes
▫ Wu 2010	No	No	Yes
Studies on the comparator therapy: best supportive care			
RCT			
▫ LUX-Lung 1[b]	No	No	Yes

a: Study for which the company was sponsor, or in which the company was otherwise financially involved.
b: Inclusion of the studies by the company irrespective of the T790M mutation status.
EGFR: epidermal growth factor receptor; RCT: randomized controlled trial; TKI: tyrosine kinase inhibitor; vs.: versus

The company included 2 one-arm prospective studies (studies AURAex [3-6] and AURA2 [7-9]) on osimertinib, which were conducted within the therapeutic indication investigated (patients with EGFR T790M mutation). The check of the completeness of the company's study pool for the historical comparison produced one additional potentially relevant (Japanese) patient cohort from the AURA study on osimertinib [3,6,10-13]. Overall, the study pool of the company on the osimertinib side was therefore incomplete. The influence of the results of this cohort on the results of the company's comparisons was assessed as low, however (see also Section 2.7.2.3.2 of the full dossier assessment).

For the comparator therapy physician's choice chemotherapy, the company identified individual study arms of a randomized controlled trial (RCT) sponsored by the company (IMPRESS [14-17]), of another RCT (Halmos 2015 [18]), and of 7 retrospective studies

(Goldberg 2013 [19], Mariano 2014 [20], Masuda 2015 [21], Park 2015 [22], Shukuya 2015 [23], Tseng 2014 [24], and Wu 2010 [25]). For the comparator therapy BSC, the company identified one study arm of an RCT (LUX-Lung 1) [26,27]. All studies on the comparator therapy identified by the company were not in the therapeutic indication to be assessed; in particular, the T790M mutation status was not taken into account. The T790M mutation status was investigated only in the IMPRESS study in the framework of an exploratory study objective. Based on the individual patient data of this study, the company therefore presented both an analysis of patients with positive T790M mutation and of the total population (with and without T790M mutation).

The company conducted several comparisons on the basis of the studies included, for which the 2 studies AURAex and AURA2 were the database for osimertinib. These can be allocated to 3 categories:

1) comparison with the chemotherapy arm of the IMPRESS study
2) comparison with all studies on the comparator therapy physician's choice chemotherapy (study arms of 2 RCTs including IMPRESS and 7 retrospective analyses)
3) comparison with the BSC arm of the LUX-Lung 1 study

No added benefit of osimertinib in comparison with the ACT could be derived from the comparisons presented by the company. On the one hand, the effects described by the company were not so large that they could not be caused solely by the type of comparison (historical comparison). On the other, the majority of the data presented by the company was unsuitable to answer the research question of the present benefit assessment.

Prerequisite for the derivation of an added benefit based on historical comparisons

In general, the methods used by the company for the comparison of study arms without consideration of an adequate common comparator were inadequate. This applied both to the unadjusted historical comparisons and to the historical comparison using propensity score matching in the comparison with the IMPRESS study conducted by the company (see Section 2.7.2.2 of the full dossier assessment).

Conclusions on the added benefit based on historical comparisons are only possible in the presence of very large effects (so-called dramatic effects). To derive such an effect, at first the studies for the drug under assessment and for the ACT would have to be generally suitable to provide information for the research question of the benefit assessment. Finally, the effect estimated on the basis of the available data has to be so large that it can be excluded that it is solely caused by systematic bias.

2.3.1.1.1 Description of the studies on osimertinib (AURAex and AURA2)

Tables on the characteristics of the studies AURAex and AURA2 can be found in Appendix A of the full dossier assessment.

The **AURAex** study was the extension phase of the AURA study, an open-label, one-arm, multicentre approval study of osimertinib. Adult patients with locally advanced or metastatic EGFR-mutation positive NSCLC with progression under treatment with an EGFR-TKI were included in the AURA study.

A total of 201 patients with central confirmation of T790M mutation were included in the AURAex study. Patients had to be in good general condition (corresponding to a World Health Organization Performance Status [WHO PS] of 0 or 1). There were no limitations in the study regarding the number of previous lines of treatment. The patients were stratified according to their lines of treatment (2 or ≥ 3).

The **AURA2** study was also an open-label, one-arm, multicentre study investigating a total of 210 patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC with progression after treatment with an EGFR-TKI. As in the AURAex study, only patients with a WHO PS of 0 or 1 were included in the AURA2 study.

Patients in both studies considered by the company received osimertinib at a dose of 80 mg once daily. Treatment was administered until unacceptable toxicity or progression, but could be continued if the investigator considered the treatment to be beneficial to the patient. In case of certain toxicity, the dose had to be adjusted or the treatment had to be discontinued. The follow-up observation of the study is not yet completed.

Overall, the right patient population and intervention for the present research question were investigated in the studies AURAex and AURA2.

2.3.1.1.2 Historical comparison with the IMPRESS study on the comparator therapy physician's choice chemotherapy

Description of the IMPRESS study

Tables on the characteristics of the IMPRESS study can be found in Appendix A of the full dossier assessment.

The IMPRESS study was a randomized, double-blind, placebo-controlled multicentre study comparing treatment with gefitinib in combination with chemotherapy consisting of pemetrexed and cisplatin (gefitinib arm) with chemotherapy consisting of pemetrexed and cisplatin alone (chemotherapy arm). Adult patients with locally advanced or metastatic EGFR-mutation positive NSCLC with progression under first-line treatment with gefitinib (monotherapy) were included in the study. In contrast to the studies AURAex and AURA2, other previous chemotherapies or systemic treatments were not allowed. Hence the study investigated chemotherapy only as second-line treatment after EGFR-TKI pretreatment. Patients had to be in good general condition (corresponding to a WHO PS of 0 or 1) and be suitable for treatment with cisplatin plus pemetrexed. The study documents contained no information as to when suitability for cisplatin and pemetrexed was assumed.

Overall, 265 patients were randomized in the IMPRESS study, 132 of them to the chemotherapy arm considered by the company. The patients were included in the study irrespective of their T790M mutation status, but T790M mutation was investigated in the framework of an exploratory study objective. 61 patients in the chemotherapy arm (46%) had T790M mutation.

The patients received the combination chemotherapy over a maximum of 6 cycles. The recommended dose was 75 mg/m^2 body surface area for cisplatin and 500 mg/m^2 body surface area for pemetrexed. In compliance with Summaries of Product Characteristics (SPCs) of pemetrexed [28] and cisplatin [29], no maximum number of treatment cycles was defined; the duration of the cycle can be considered adequate in the treatment situation investigated [30-32], however.

Overall, the right subpopulation of patients with positive T790M mutation for the research question was investigated in the IMPRESS study. However, since only a chemotherapy option consisting of pemetrexed and cisplatin in second-line treatment was investigated in the study, this study only provided data for patients for whom treatment with pemetrexed and cisplatin is the best treatment option – and only for patients in second-line treatment. It remains unclear, however, whether treatment with pemetrexed and cisplatin would have been the best treatment option (to date) for the patients in the studies AURAex and AURA2.

Comparisons conducted by the company partly unsuitable

The company conducted 2 comparisons between the AURA studies and the subpopulation of the IMPRESS study with positive T790M mutation. These comparisons differed regarding the populations considered (only second line versus all treatment lines in the AURA studies). Of these comparisons, only the comparison within the second line was potentially relevant for the reasons stated above.

No advantage or disadvantage of osimertinib could be derived from the magnitude of the differences

It can be assumed in a historical comparison that the study populations of the studies included differ notably. The company therefore tried to adjust for confounding variables using patient characteristics observed in the studies selected post hoc. It used propensity score matching for this. As a result, relevant proportions of patient numbers were not considered (in comparison of the second line in the osimertinib arm about 28%, and in the comparator arm of the IMPRESS study about 15% of the patients). Due to the concrete approach of the company it remains unclear whether this selection increased the certainty of results or even decreased it. Hence, the certainty of results of an RCT or of an adjusted indirect comparison based on an RCT was not achieved with this adjustment for observed patient characteristics.

As described above, conclusions on the added benefit based on historical comparisons are only possible in the presence of very large effects (so-called dramatic effects) regarding patient-relevant outcomes. Finally, the effect estimated on the basis of the available data has

to be so large that it can be excluded that it is solely caused by systematic bias due to the historical comparison.

Such an effect was not achieved for any of the patient-relevant outcomes analysed by the company. There was no statistical significance for overall survival (comparison of second line of the studies AURA versus IMPRESS: hazard ratio (HR) 1.19 [0.36; 3.91]; p = 0.775). This also applied to health status recorded with the visual analogue scale (VAS) of the European Quality of Life-5 Dimensions (EQ-5D), treatment discontinuations due to adverse events (AEs) and serious AEs (SAEs).

Statistically significant results only occurred in severe AEs Common Terminology Criteria for Adverse Events (CTCAE) grade ≥ 3 (both in total and in individual specific AEs) (e.g. overall rate of severe AEs for the comparison of second line of the studies AURA versus IMPRESS: HR 0,26 [0.13; 0.53]; p < 0.001). This difference may have been caused by systematic bias alone. It should be noted as additional information that the recording of AEs differed notably between the AURA studies and the IMPRESS study: In the AURA studies, not all AEs based on tests were recorded as such, even if they fulfilled the criteria for severe AEs CTCAE grade 3 or higher[5]. As a consequence, the results were additionally biased in favour of osimertinib.

2.3.1.1.3 Historical comparison with all studies on the comparator therapy physician's choice chemotherapy

In its dossier, the company additionally presented unadjusted historical comparisons, in which it used the chemotherapy arms of the studies IMPRESS (total population) and Halmos 2015 as well as 7 retrospective studies.

The data from the company's studies on the comparator therapy were unsuitable for the benefit assessment. Table 6 shows an overview of the reasons.

[5] "Investigators were instructed not to report laboratory abnormalities as AEs (unless they fulfilled the criteria for an SAE or resulted in discontinuation). It should be noted that there are laboratory abnormalities reported that do not fit the regulatory definition of an SAE or resulted in discontinuation." [4,8]

Table 6: Reasons for exclusion of the studies on the comparator therapy physician's choice chemotherapy presented by the company

Study	Reasons for exclusion		
	T790M mutation not considered	Chemotherapy not in compliance with approval[a]	No (usable) results on patient-relevant outcomes
Studies with physician's choice chemotherapy			
IMPRESS (total population)	●		
Halmos 2015	●	●	●
Goldberg 2013	●	○[b]	●
Mariano 2014	●	●	●
Masuda 2015	●	●	
Park 2015	●	●	
Shukuya 2015	●	●	
Tseng 2014	●	○[b]	●
Wu 2010	●	○[b]	

a: For all or most patients.
b: No sufficient information available.
●: reason for exclusion; ○: uncertainty

The T790M mutation status was not considered in any of the studies. The studies included by the company were therefore not within the therapeutic indication of osimertinib. The company provided no evidence that the results found in the studies on the basis of the mixed population with and without T790M mutation are transferable to the target population (with T790M mutation). In addition, the chemotherapy did not concur with the ACT in most studies used by the company because it did not comply with the approval for a large proportion of the patients. The corresponding information was missing for some of the studies. Finally, usable data on patient-relevant outcomes were only available for some of the studies, and – except for the IMPRESS study – only on overall survival.

Irrespective of the missing suitability of the studies, the results on overall survival in the main analyses were not statistically significant in any of the comparisons presented by the company. The company additionally conducted sensitivity analyses using different models, which resulted partly in statistically significant results in favour of osimertinib and partly in statistically significant results to the disadvantage of osimertinib. In none of the cases were the results in a magnitude that cannot be explained by systematic bias alone, so that neither an added benefit nor lesser benefit of osimertinib could be derived from them.

2.3.1.1.4 Historical comparison with the LUX-Lung 1 study on the comparator therapy best supportive care

Besides the comparisons with studies on the chemotherapy mentioned, the company also conducted a historical comparison on the comparator therapy BSC. Since for osimertinib it also used the studies AURAex and AURA2, which it had also used for the comparison with chemotherapy, this comparison referred to the group of patients who are candidates for chemotherapy, but who had already received chemotherapy and for whom therefore BSC constituted the alternative ACT.

The company used the control arm (placebo + BSC) of the LUX-Lung 1 study for the comparator therapy BSC [26,27]. In this study, afatinib was compared with placebo, each in addition to BSC. However, the study was not conducted within the therapeutic indication of osimertinib and was therefore irrelevant for the present benefit assessment. One of the reasons was that information on the EGFR mutation status was only available for 25% of the patients (48 of 195 patients in the placebo group). Activating EGFR mutation was detectable in only 34 of these 48 patients (71%). Only 4 of these 34 patients had T790M mutation. Overall, only a very small proportion of the patients were therefore relevant for the present benefit assessment. No corresponding results on patient-relevant outcomes were available from the LUX-Lung 1 study. The company itself only considered results on progression-free survival for the subgroup of the 34 EGFR-positive (but mainly T790M-negative) patients.

2.3.1.1.5 Ongoing RCT AURA3

An RCT on the direct comparison of osimertinib versus platinum-based chemotherapy in patients with locally advanced or metastatic NSCLC and positive T790M mutation is currently conducted (study AURA3 [D5160C00003] [33]). According to the company, the results of this study are expected for the end of 2016.

2.3.1.2 Results on added benefit

Based on the historical comparisons presented by the company, no added benefit of osimertinib in adult patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC who had pretreatment with an EGFR-TKI and for whom cytotoxic treatment is an option could be derived in comparison with the ACT. Hence there was no hint of an added benefit of osimertinib in comparison with the ACT. An added benefit is therefore not proven.

2.3.1.3 Extent and probability of added benefit

Based on the historical comparisons presented by the company, no added benefit of osimertinib in adult patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC who had pretreatment with an EGFR-TKI and for whom cytotoxic treatment is an option could be derived in comparison with the ACT. Hence there are also no patient groups for whom a therapeutically important added benefit can be derived.

This deviates from the company's approach, which derived an indication of a major added benefit of osimertinib for the total population of patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC.

2.3.2 Research question 1b: patients for whom cytotoxic chemotherapy is not an option

2.3.2.1 Information retrieval and study pool

Based on the G-BA's specification of the ACT, the research question of the added benefit of osimertinib versus BSC in patients with T790M mutation after pretreatment with an EGFR-TKI for whom cytotoxic chemotherapy is not an option resulted for the present benefit assessment. In the present benefit assessment, this patient group was defined as patients with an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 4, 3, and, if applicable, 2. Eligibility for treatment with chemotherapy is determined based on clinical aspects and the patient's situation.

The company presented no data for research question 1b (patients for whom cytotoxic chemotherapy is not an option). It conducted a historical comparison versus BSC (see Section 2.3.1). With its selection criteria on study inclusion (see Section 2.7.2.1 of the full dossier assessment), however, it limited its studies to patients with an ECOG PS of 0 and 1 and therefore to a subpopulation within research question 1a.

The Institute's check of completeness with a bibliographical literature search on osimertinib (last search on 30 March 2016) and a search in trial registries for studies on osimertinib (last search on 23 March 2016) produced no studies relevant for research question 1b.

Overall, no data were available for the benefit assessment of osimertinib in patients after pretreatment with an EGFR-TKI for whom cytotoxic chemotherapy is not an option.

2.3.2.2 Results on added benefit

No data were available for the assessment of the added benefit of osimertinib in patients with T790M mutation after pretreatment with an EGFR-TKI for whom cytotoxic chemotherapy is not an option. Hence there was no hint of an added benefit of osimertinib in comparison with the ACT. An added benefit of osimertinib is therefore not proven.

2.3.2.3 Extent and probability of added benefit

Since the company presented no data for the assessment of the added benefit of osimertinib in patients with T790M mutation after pretreatment with an EGFR-TKI for whom cytotoxic chemotherapy is not an option, an added benefit of osimertinib is not proven for these patients. Hence there are also no patient groups for whom a therapeutically important added benefit can be derived.

This deviates from the company's approach, which derived an indication of a major added benefit of osimertinib for the total population of patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC.

2.4 Research question 2: treatment-naive patients with *de novo* positive T790M mutation

2.4.1 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 osimertinib (status: 19 January 2016)
- bibliographical literature search on osimertinib (last search on 16 December 2015)
- search in trial registries for studies on osimertinib (last search on 16 December 2015)

To check the completeness of the study pool:

- bibliographical literature search on osimertinib (last search on 30 March 2016)
- search in trial registries for studies on osimertinib (last search on 23 March 2016)

In its information retrieval, the company identified no RCT with osimertinib. The check of completeness also produced no RCT with osimertinib.

The company described data of 4 patients with *de novo* T790M mutation from the dose expansion phase of the AURA study [11,13]. Two of these 4 patients were treatment-naive and hence did not correspond to research question 2. The company undertook no comparison with the ACT. Overall, there were therefore no relevant data for the benefit assessment of osimertinib in treatment-naive patients with *de novo* T790M mutation.

2.4.1.1 Ongoing RCT FLAURA

An RCT on the direct comparison of osimertinib versus EGFR-TKI monotherapy in patients with locally advanced or metastatic NSCLC, which includes patients both with and without T790M mutation, is currently conducted (study FLAURA [D5160C00007][34]). According to trial registry ClinicalTrials.gov, the results of this study are expected for October 2018.

2.4.2 Results on added benefit

No data were available for the assessment of the added benefit of osimertinib in treatment-naive patients with *de novo* T790M mutation. Hence there was no hint of an added benefit of osimertinib in comparison with the ACT. An added benefit of osimertinib is therefore not proven.

2.4.3 Extent and probability of added benefit

Since the company presented no data for the assessment of the added benefit of osimertinib in treatment-naive patients with *de novo* T790M mutation, an added benefit of osimertinib for these patients is not proven. Hence there are also no patient groups for whom a therapeutically important added benefit can be derived.

This deviates from the company's approach, which derived a non-quantifiable added benefit for patients with *de novo* T790M mutation irrespective of the line of treatment on the basis of the molecular mechanism of action, a postulated superiority over chemotherapy, and "supporting data" from the AURA study.

2.5 Research question 3: patients after pretreatment with platinum-based chemotherapy and *de novo* positive T790M mutation

2.5.1 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 osimertinib (status: 19 January 2016)
- bibliographical literature search on osimertinib (last search on 16 December 2015)
- search in trial registries for studies on osimertinib (last search on 16 December 2015)

To check the completeness of the study pool:

- bibliographical literature search on osimertinib (last search on 30 March 2016)
- search in trial registries for studies on osimertinib (last search on 23 March 2016)

In its information retrieval, the company identified no RCT with osimertinib. The check of completeness also produced no RCT with osimertinib.

The company described data of 4 patients with *de novo* T790M mutation from the dose expansion phase of the AURA study [11,13]. Two of these 4 patients were pretreated with platinum-based chemotherapy and hence corresponded to research question 3. The company undertook no comparison with the ACT. Overall, there were therefore no relevant data for the benefit assessment of osimertinib in pretreated patients with *de novo* T790M mutation.

2.5.2 Results on added benefit

No data were available for the assessment of the added benefit of osimertinib in pretreated patients with *de novo* T790M mutation. Hence there was no hint of an added benefit of osimertinib in comparison with the ACT. An added benefit of osimertinib is therefore not proven.

2.5.3 Extent and probability of added benefit

Since the company presented no data for the assessment of the added benefit of osimertinib in pretreated patients with *de novo* T790M mutation, an added benefit of osimertinib for these patients is not proven. Hence there are also no patient groups for whom a therapeutically important added benefit can be derived.

This deviates from the company's approach, which derived a non-quantifiable added benefit for patients with *de novo* T790M mutation irrespective of the line of treatment on the basis of the molecular mechanism of action, a postulated superiority over chemotherapy, and "supporting data" from the AURA study.

2.6 Extent and probability of added benefit – summary

The result of the assessment of the added benefit of osimertinib in comparison with the ACT is summarized in Table 7.

Table 7: Osimertinib – extent and probability of added benefit

Research question	Population	Appropriate comparator therapy[a]	Extent and probability of added benefit
1	Patients with T790M mutation after pretreatment with an EGFR tyrosine kinase inhibitor		
1a	Patients for whom cytotoxic chemotherapy is an option	Physician's choice 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, best supportive care[b] for patients who have already received cytotoxic chemotherapy as an alternative for further cytotoxic chemotherapy	Added benefit not proven
1b	Patients for whom cytotoxic therapy is not an option	Best supportive care[b]	Added benefit not proven
2	Treatment-naive patients with *de novo* positive T790M mutation		
	Patients with activating EGFR mutations	Gefitinib or erlotinib or afatinib	Added benefit not proven
	or	or	
	patients with ECOG Performance Status 0, 1 or 2[c]	cisplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed) in accordance with the approval status or carboplatin in combination with a third-generation cytostatic agent (only for patients with increased risk of cisplatin-induced side effects in the framework of a combination therapy; see Appendix VI to Section K of the Pharmaceutical Directive)	Added benefit not proven

(continued)

Table 7: Osimertinib – extent and probability of added benefit (continued)

Research question	Population	Appropriate comparator therapy[a]	Extent and probability of added benefit
3	Patients after pretreatment with platinum-based chemotherapy and *de novo* positive T790M mutation		
3a	Patients for whom treatment with docetaxel, pemetrexed, gefitinib, or erlotinib is indicated	Docetaxel, pemetrexed (pemetrexed: except in mainly squamous cell carcinoma histology) or gefitinib or erlotinib (only for patients with activating EGFR mutations who have not been pretreated with gefitinib or erlotinib)	Added benefit not proven
3b	Patients for whom treatment with docetaxel, pemetrexed, gefitinib, or erlotinib is not indicated	Best supportive care[b]	Added benefit not proven

a: Presentation of the respective ACT specified by the G-BA.
b: Best supportive care refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.
c: In patients with ECOG Performance Status 2 as an alternative to platinum-based combination treatment: monotherapy with gemcitabine or vinorelbine.
ACT: appropriate comparator therapy; ECOG: Eastern Cooperative Oncology Group; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee

The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

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