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Osimertinib (NSCLC, adjuvant) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Osimertinib (NSCLC, adjuvant) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 29 September 2021). 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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Address of publisher
Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

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

Medical and scientific advice

- Ingo Schmidt-Wolf, University Hospital Bonn, Germany

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

IQWiG employees involved in the dossier assessment

- Anna-Katharina Barnert
- Lars Beckmann
- Tatjana Hermanns
- Kirsten Janke
- Michaela Florina Kerekes
- Dominik Schierbaum
- Sonja Schiller
- Volker Vervölgyi

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[2] 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
AJCC	American Joint Committee on Cancer
EGFR	epidermal growth factor receptor
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
ILD	interstitial lung disease
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MCS	mental component summary
NSCLC	non-small cell lung cancer
PCS	physical component summary
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SF-36v2	Short Form (36) – version 2 Health Survey
SGB	Sozialgesetzbuch (Social Code Book)
SMQ	standardized MedDRA query
SPC	Summary of Product Characteristics
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 is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 23 June 2021.

Research question

Aim of the present report is the assessment of the added benefit of osimertinib in comparison with the appropriate comparator therapy (ACT) for the adjuvant treatment of patients with stage IB to IIIA non-small cell lung cancer (NSCLC) after complete tumour resection whose tumours have mutations of the epidermal growth factor receptor (EGFR) in the form of exon 19 deletion or exon 21 substitution mutation (L858R).

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

Table 2: Research questions of the benefit assessment of osimertinib

Research question	Therapeutic indication	ACT[a]
1	Adjuvant treatment of adult patients with stage IB to IIIA[b] NSCLC with exon 19 deletion or exon 21 substitution mutation (L858R) of the EGFR, after complete tumour resection, without prior adjuvant platinum-based chemotherapy	Stage IB: ▪ watchful waiting or ▪ systemic antineoplastic drug treatment of physician's choice ▪ stages II and IIIA: ▪ systemic antineoplastic drug treatment of physician's choice
2	Adjuvant treatment of adult patients with stage IB to IIIA[b] NSCLC with exon 19 deletion or exon 21 substitution mutation (L858R) of the EGFR, after complete tumour resection, after prior adjuvant platinum-based chemotherapy or for whom this therapy is not suitable	Watchful waiting

a. Presentation of the respective ACT specified by the G-BA.
b. For the present therapeutic indication, the G-BA assumes that patients in stage IIIA3/IIIA4 and patients with Pancoast tumours were not included.

ACT: appropriate comparator therapy; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer

In the present assessment, the following terms are used for the patient populations of the 2 research questions:

- Research question 1: patients without prior adjuvant platinum-based chemotherapy
- Research question 2: patients after prior adjuvant platinum-based chemotherapy or for whom this therapy is not suitable

The company initially followed the ACT specified by the G-BA for the two research questions. However, the company said it assumed that all patients for whom adjuvant platinum-based chemotherapy was suitable would receive it in accordance with the recommendations of the guidelines and the Summary of Product Characteristics (SPC). Thus, the company considered patients who had not yet received adjuvant platinum-based chemotherapy, but for whom this was suitable, only eligible for treatment with osimertinib in rare cases or not at all. For its benefit assessment, the company searched for studies for both research questions and included a study for the patient population on research question 2. However, it derived the added benefit on the basis of the available evidence for the entire therapeutic indication of osimertinib.

Deviating from the company's approach, the present benefit assessment was conducted separately for the two research questions.

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

Research question 1: patients without prior adjuvant platinum-based chemotherapy

Results

In its dossier, the company presented no data for the assessment of the added benefit of osimertinib versus the ACT for patients without prior adjuvant platinum-based chemotherapy. This resulted in no hint of an added benefit of osimertinib in comparison with the ACT; an added benefit is therefore not proven for this research question.

Research question 2: patients after prior adjuvant platinum-based chemotherapy or for whom this therapy is not suitable

Study pool and study design

The study pool for the benefit assessment of osimertinib in comparison with the ACT consists of the RCT ADAURA.

The ADAURA study is an ongoing, double-blind, randomized multicentre study for the comparison of osimertinib with placebo. The study included adult patients with stage IB-IIIA NSCLC (classification according to the 7th edition of the American Joint Committee on Cancer [AJCC]) after complete tumour resection whose tumours had EGFR mutations in the form of exon 19 deletion or exon 21 substitution mutation (L858R).

The ADAURA study included a total of 682 patients who were randomly assigned to treatment with osimertinib or placebo in a 1:1 ratio. Randomization was stratified according to the disease

stage (IB vs. II vs. IIIA), the EGFR mutation status (deletion in exon 19 vs. substitution mutation in exon 21 [L858R]) and family origin (Asian vs. non-Asian).

Treatment with osimertinib according to the specifications of the SPC was performed until occurrence of a recurrence, unacceptable toxicity, decision of the patient or until the regular end of the study treatment after 3 years.

Primary outcome of the study was disease-free survival. Patient-relevant secondary outcomes were outcomes on mortality, morbidity, health-related quality of life and adverse events (AEs).

Suitability of the patient population of the ADAURA study for research question 2

The ADAURA study included patients with and without adjuvant platinum-based chemotherapy. Based on the information provided by the company, it remains unclear whether patients who had not received prior adjuvant chemotherapy would have been suitable for this. Such patients should have been assigned to research question 1 of the benefit assessment. In the ADAURA study, only about a quarter of the patients in disease stage IB and three quarters of the patients in disease stages II and IIIA had received adjuvant chemotherapy before study inclusion. It is not clear from the dossier why adjuvant chemotherapy was not suitable for the remaining patients. For patients in disease stages II and IIIA, the assignment to research question 1 would result in a different ACT, a systemic antineoplastic therapy according to physician's choice instead of watchful waiting.

Overall, on the basis of the available data, it remains unclear whether the patient population of the ADAURA study can be completely assigned to research question 2 of the present benefit assessment, or whether the study also included patients for whom adjuvant chemotherapy would have been a suitable option, but who did not receive it, and would thus have to be assigned to research question 1. However, this uncertainty did not result in an exclusion of the study. It was assumed that conclusions on the added benefit of osimertinib in comparison with the ACT can be drawn for the present research question on the basis of the study results. The uncertainties described were considered in the assessment of the certainty of conclusions of the results, however.

Implementation of the ACT

The G-BA specified watchful waiting as ACT for patients after prior adjuvant platinum-based chemotherapy or for whom this therapy was not suitable.

ADAURA used placebo as comparator therapy. The study was not designed for a comparison with watchful waiting, but is nonetheless suitable for such a comparison.

Although the investigations carried out in the study do not fully encompass the recommendations of the S3 guideline, the study regimen in the ADAURA study as a whole is considered to be a sufficient approximation to the ACT “watchful waiting” for the present benefit assessment.

Risk of bias and certainty of conclusions

The risk of bias across outcomes was rated as low for the ADAURA study. The risk of bias for the results on the outcomes "overall survival" and “recurrence” was rated as low. For the outcome “health-related quality of life”, recorded using the Short Form (36) – version 2 Health Survey (SF-36v2), as well as for the outcomes of the category “side effects”, with the exception of the outcome “discontinuation due to AEs”, there is a high risk of bias of the results.

Taking into account the uncertainty with regard to the included patient population, at most hints, for example of an added benefit, can be determined for all outcomes for the present research question on the basis of the ADAURA study.

Results

Mortality

Overall survival

No statistically significant difference between the treatment groups was shown for the outcome "overall survival". This resulted in no hint of an added benefit of osimertinib in comparison with watchful waiting; an added benefit is therefore not proven.

Morbidity

Recurrence

For the outcome “recurrence” (operationalized as recurrence rate and disease-free survival), a statistically significant difference in favour of osimertinib in comparison with placebo was shown for both operationalizations. This resulted in a hint of an added benefit of osimertinib versus watchful waiting.

Health-related quality of life

SF-36v2 – Physical and Mental Component Summary

For the mental component summary (MCS) of the SF-36v2, there was no statistically significant difference between the treatment groups on the basis of the responder analysis on the time to confirmed deterioration. This resulted in no hint of an added benefit of osimertinib in comparison with watchful waiting; an added benefit is therefore not proven.

For the physical component summary (PCS) of the SF-36v2, there was a statistically significant difference to the disadvantage of osimertinib in comparison with placebo on the basis of the responder analysis on the time to confirmed deterioration. However, there was an effect modification by the characteristic “disease stage”. This resulted in a hint of lesser benefit of osimertinib in comparison with watchful waiting for patients with stage II and IIIA disease. This resulted in no hint of an added benefit of osimertinib in comparison with watchful waiting for patients with stage IB disease; an added benefit is therefore not proven.

Side effects

Serious adverse events (SAEs)

No statistically significant difference between the treatment groups was shown for the outcome "SAEs". This resulted in no hint of greater or lesser harm from osimertinib in comparison with watchful waiting; greater or lesser harm is therefore not proven.

Severe AEs and discontinuation due to AEs

A statistically significant difference to the disadvantage of osimertinib in comparison with placebo was shown for each of the outcomes “severe AEs” and "discontinuation due to AEs". In each case, this resulted in a hint of greater harm from osimertinib versus watchful waiting.

Skin and subcutaneous tissue disorders (AEs)

There was a statistically significant difference to the disadvantage of osimertinib in comparison with placebo for the outcome "skin and subcutaneous tissue disorders” (AEs). This resulted in a hint of greater harm from osimertinib versus watchful waiting.

Interstitial lung disease (ILD) and pneumonitis (SAEs) and cardiac events (severe AEs)

There was no statistically significant difference between the treatment groups for each of the outcomes "ILD" and "pneumonitis” (SAEs) and “cardiac events” (severe AEs). In each case, this resulted in no hint of greater or lesser harm from osimertinib in comparison with watchful waiting; greater or lesser harm is therefore not proven.

Further specific AEs

Gastrointestinal disorders (AEs) (including diarrhoea [AEs], mouth ulceration [AEs], stomatitis [AEs]), gastrointestinal disorders (severe AEs), paronychia (AEs), decreased appetite (AEs)

A statistically significant difference to the disadvantage of osimertinib in comparison with placebo was shown for each of the specific AEs “gastrointestinal disorders (AEs) (including diarrhoea [AEs], mouth ulceration [AEs], stomatitis [AEs]), gastrointestinal disorders (severe AEs), paronychia (AEs) and decreased appetite (AEs). In each case, this resulted in a hint of greater harm from osimertinib versus watchful waiting.

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

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

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the

Research question 1: patients without prior adjuvant platinum-based chemotherapy

The company presented no data for the assessment of the added benefit of osimertinib versus the ACT in patients without prior adjuvant platinum-based chemotherapy. An added benefit of osimertinib versus the ACT is therefore not proven for research question 1.

Research question 2: patients after prior adjuvant platinum-based chemotherapy or for whom this therapy is not suitable

Overall, one positive and several negative effects of different extents were shown, each with the probability "hint".

A positive effect of osimertinib in comparison with watchful waiting with the extent "major" was shown for the outcome "recurrence". In contrast, there were negative effects for osimertinib in comparison with watchful waiting, especially in the outcome category "side effects". Negative effects in serious/severe side effects were shown for the superordinate outcome of severe AEs with the extent "minor" and for gastrointestinal disorders (severe AEs) with the extent "major". Among the non-serious/non-severe side effects, there were several specific AEs with the extent "considerable" to the disadvantage of osimertinib. In the outcome category "health-related quality of life", there is a negative effect of osimertinib with the extent "major" in the PCS of the SF-36v2 compared to watchful waiting for patients in disease stages II and IIIA. However, these negative effects do not completely challenge the positive effect with the extent "major" for the outcome "recurrence".

In summary, there is a hint of considerable added benefit of osimertinib versus the ACT "watchful waiting" for patients after prior adjuvant platinum-based chemotherapy or for whom this therapy it is not suitable.

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

first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

Table 3: Osimertinib – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Adjuvant treatment of adult patients with stage IB to IIIA[b] NSCLC with exon 19 deletion or exon 21 substitution mutation (L858R) of the EGFR, after complete tumour resection, without prior adjuvant platinum-based chemotherapy	Stage IB: ▪ watchful waiting or ▪ systemic antineoplastic drug treatment of physician's choice stages II and IIIA: ▪ systemic antineoplastic drug treatment of physician's choice	Added benefit not proven
2	Adjuvant treatment of adult patients with stage IB to IIIA[b] NSCLC with exon 19 deletion or exon 21 substitution mutation (L858R) of the EGFR, after complete tumour resection, after prior adjuvant platinum-based chemotherapy or for whom this therapy it is not suitable	Watchful waiting	Hint of considerable added benefit[c]

a. Presentation of the respective ACT specified by the G-BA.
b. For the present therapeutic indication, the G-BA assumes that patients in stage $IIIA_3$/$IIIA_4$ and patients with Pancoast tumours were not included.
c. Only patients with a WHO PS of 0 or 1 were included in the ADAURA study. It remains unclear whether the observed effects are transferable to patients with a WHO PS ≥ 2.

ACT: appropriate comparator therapy; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer; WHO PS: World Health Organization Performance Status

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

2.2 Research question

Aim of the present report is the assessment of the added benefit of osimertinib in comparison with the ACT for the adjuvant treatment of patients with stage IB to IIIA NSCLC after complete tumour resection whose tumours have mutations of the EGFR in the form of exon 19 deletion or exon 21 substitution mutation (L858R).

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

Table 4: Research questions of the benefit assessment of osimertinib

Research question	Therapeutic indication	ACT[a]
1	Adjuvant treatment of adult patients with stage IB to IIIA[b] NSCLC with exon 19 deletion or exon 21 substitution mutation (L858R) of the EGFR, after complete tumour resection, without prior adjuvant platinum-based chemotherapy	Stage IB: ▪ watchful waiting or ▪ systemic antineoplastic drug treatment of physician's choice ▪ stages II and IIIA: ▪ systemic antineoplastic drug treatment of physician's choice
2	Adjuvant treatment of adult patients with stage IB to IIIA[b] NSCLC with exon 19 deletion or exon 21 substitution mutation (L858R) of the EGFR, after complete tumour resection, after prior adjuvant platinum-based chemotherapy or for whom this therapy it is not suitable	Watchful waiting

a. Presentation of the respective ACT specified by the G-BA.
b. For the present therapeutic indication, the G-BA assumes that patients in stage IIIA3/IIIA4 and patients with Pancoast tumours were not included.

ACT: appropriate comparator therapy; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer

In the present assessment, the following terms are used for the patient populations of the 2 research questions:

- Research question 1: patients without prior adjuvant platinum-based chemotherapy
- Research question 2: patients after prior adjuvant platinum-based chemotherapy or for whom this therapy is not suitable

Initially, the company followed the ACT specified by the G-BA for the two research questions. However, in Module 1, the company states to assume that all patients for whom adjuvant platinum-based chemotherapy was suitable would receive it according to the recommendations of the guidelines and the SPC. Thus, the company considered patients who had not yet received adjuvant platinum-based chemotherapy, but for whom this was suitable, only eligible for treatment with osimertinib in rare cases or not at all. For its benefit assessment, the company searched for studies for both research questions and included a study for the patient population on research question 2. However, in Section 4.4.3 of Module 4 A of the dossier, it derived the added benefit on the basis of the evidence available for the entire therapeutic indication of osimertinib, whereas in other sections it derived the added benefit only for the patient population of research question 2 (e.g. in Module 1, Section 1.5).

The approach of the company was not appropriate. According to the SPC, osimertinib can be administered irrespective of whether adjuvant chemotherapy is a treatment option for patients

in the present therapeutic indication or not [3]. Moreover, the S3 guideline on the prevention, diagnosis, treatment and follow-up of lung cancer [4] describes that the effectiveness of adjuvant chemotherapy has not been clarified for patients with stage IB disease. According to the guideline, individual treatment decisions under consideration of comorbidity, age and cardiopulmonary function are recommended for this patient population. A decision against adjuvant chemotherapy can thus also be made irrespective of whether this treatment is suitable for the patient. Therefore, the present benefit assessment was conducted separately for the research questions listed in Table 4.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs were used for the derivation of the added benefit. This concurs with the company's inclusion criteria.

2.3 Research question 1: patients without prior adjuvant platinum-based chemotherapy

2.3.1 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: 16 April 2021)
- bibliographical literature search on osimertinib (last search on 16 April 2021)
- search in trial registries/trial results databases for studies on osimertinib (last search on 20 April 2021)
- search on the G-BA website for osimertinib (last search on 20 April 2021)

To check the completeness of the study pool:

- search in trial registries for studies on osimertinib (last search on 28 June 2021); for search strategies, see Appendix A of the full dossier assessment.

No relevant study was identified from the check. The company also identified no suitable studies.

2.3.2 Results on added benefit

In its dossier, the company presented no data for the assessment of the added benefit of osimertinib versus the ACT for patients without prior adjuvant platinum-based chemotherapy. This resulted in no hint of an added benefit of osimertinib in comparison with the ACT; an added benefit is therefore not proven for this research question.

2.3.3 Probability and extent of added benefit

The company presented no data for the assessment of the added benefit of osimertinib versus the ACT in patients without prior adjuvant platinum-based chemotherapy. An added benefit of osimertinib versus the ACT is therefore not proven for research question 1.

This deviates from the company's assessment, which did not assess the added benefit for research question 1 in its dossier. The company assumed that patients of research question 1 were only eligible for treatment with osimertinib in rate cases or not at all (see Section 2.2 for explanation).

2.4 Research question 2: patients with prior adjuvant platinum-based chemotherapy or for whom this therapy is not suitable

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: 16 April 2021)
- bibliographical literature search on osimertinib (last search on 16 April 2021)
- search in trial registries/trial results databases for studies on osimertinib (last search on 20 April 2021)
- search on the G-BA website for osimertinib (last search on 20 April 2021)

To check the completeness of the study pool:

- search in trial registries for studies on osimertinib (last search on 28 June 2021); for search strategies, see Appendix A of the full dossier assessment

The check did not identify any additional relevant study.

2.4.1.1 Studies included

The study presented in the following Table 5 was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: osimertinib vs. placebo

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication and other sources[c] yes/no [citation])
D5164C00001 (ADAURA[d])	Yes	Yes	No	Yes [5]	Yes [6,7]	Yes [8-10]

a. Study for which the company was sponsor.
b. Citation of the study registry entries and, if available, of the reports on study design and/or results listed in the study registries.
c. Other sources: documents from the search on the G-BA website and other publicly available sources.
d. In the following tables, the study is referred to with this abbreviated form.

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

The ADAURA study was used for the benefit assessment. The study pool generally concurred with that of the company. Deviating from the company, whose approach for the separate derivation of the added benefit is inconsistent for the two research questions in the dossier, the study for the present benefit assessment is used to assess the added benefit on research question 2 (see Section 2.2 for explanation).

2.4.1.2 Study characteristics

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

Table 6: Characteristics of the study included – RCT, direct comparison: osimertinib vs. placebo

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
ADAURA	RCT, double-blind, parallel	Adult patients (≥ 18 years [≥ 20 years in Japan and Taiwan]) ▪ with histologically confirmed stage IB, II or IIIA NSCLC[b] ▪ with activating EGFR mutation (deletion in exon 19 or substitution mutation in exon 21 [L858R])[c] ▪ after complete tumour resection with or without subsequent adjuvant platinum-based chemotherapy[d] ▪ WHO-PS 0 or 1	Osimertinib (n = 339) placebo (N = 343)	Screening: up to 28 days before start of treatment treatment: until recurrence, unacceptable toxicity or decision of the patient, at most 3 years observation[e]: outcome-specific, at most until death or end of study	185 study centres in: Australia, Belgium, Brazil, Canada, China, France, Germany, Hong Kong, Hungary, Israel, Italy, Japan, Poland, Romania, Russia, South Korea, Spain, Sweden, Taiwan, Thailand, Turkey, Ukraine, USA, Vietnam 10/2015–ongoing data cut-off: 17 January 2020 (primary analysis)[f]	Primary: disease-free survival secondary: overall survival, morbidity, health-related quality of life, AEs

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b. Patients should primarily have adenocarcinomas.
c. The mutation could occur alone or in combination with other EGFR mutations, including the T790M mutation.
d. Start of treatment 4 weeks after surgery at the earliest. For patients without adjuvant chemotherapy, a maximum of ten weeks were allowed to elapse between surgery and randomization, for patients with adjuvant chemotherapy a maximum of 26 weeks.
e. Outcome-specific information is described in Table 8.
f. The primary analysis of disease-free survival was originally intended to be carried out after 247 events in the subpopulation of stage II-IIIA patients. Following the recommendation of the IDMC, this was brought forward.

AE: adverse event; EGFR: epidermal growth factor receptor; IDMC: Independent Data Monitoring Committee, N: number of randomized patients; NSCLC: non-small cell lung cancer; RCT: randomized controlled trial; WHO PS: World Health Organization Performance Status

Table 7: Characteristics of the intervention – RCT, direct comparison: osimertinib vs. placebo

Study	Intervention	Comparison
ADAURA	Osimertinib: 80 mg once daily, orally	Placebo once daily, orally
	dose adjustment: ▪ interruption in case of AEs with CTCAE grade ≥ 3; resumption at full or reduced dose (40 mg/day) ▪ interruption if symptoms of an interstitial lung disease (ILD) occur (treatment discontinuation after confirmed diagnosis) ▪ treatment discontinuation, if the toxicity has not improved to grade ≤ 2[a] after 3 weeks	
	Permitted pretreatment ▪ complete surgical resection of the NSCLC ≥ 4 weeks and ≤ 10 weeks[b] before randomization ▪ postoperative (adjuvant) platinum-based chemotherapy ≥ 2 weeks and ≤ 10 weeks before randomization **non-permitted pretreatment** ▪ preoperative, postoperative or planned radiotherapy of the lungs ▪ preoperative (neoadjuvant) platinum-based chemotherapy or other chemotherapies ▪ any prior anticancer therapy (including test therapies) for the treatment of NSCLC, with the exception of postoperative adjuvant platinum-based chemotherapy ▪ neoadjuvant or adjuvant EGFR-TKI **non-permitted concomitant treatment** ▪ other anticancer therapies including radiotherapy and investigational products ▪ CYP3A4 inducers ≤ 3 weeks before the first study medication and during the study ▪ drugs that can trigger QT time prolongation should be avoided as far as possible	

a. Improvement to CTCAE grade 1 in case of a QT time prolongation.
b. For adjuvant platinum-based chemotherapy ≤ 26 weeks, where chemotherapy had to start ≤ 8 weeks after surgery.

CTCAE: Common Terminology Criteria for Adverse Events; CYP: cytochrome P450; EGFR: epidermal growth factor receptor; ILD: interstitial lung disease; NSCLC: non-small cell lung cancer; QT time: measured variable in the evaluation of the electrocardiogram; RCT: randomized controlled trial; TKI: tyrosine kinase inhibitor

The ADAURA study is an ongoing, double-blind, randomized multicentre study for the comparison of osimertinib with placebo. The study included adult patients with stage IB-IIIA NSCLC (classification according to the 7th edition of the AJCC after complete tumour resection whose tumours had EGFR mutations in the form of exon 19 deletion or exon 21 substitution mutation (L858R). The presence of EGFR mutations was determined by a central laboratory using the Cobas test. Patients had to be in good general condition (World Health Organization Performance Status [WHO PS] ≤ 1). Patients with a WHO PS > 1 were excluded from the study participation.

The ADAURA study included a total of 682 patients who were randomly assigned to treatment with osimertinib (N = 339) or placebo (N = 343) in a 1:1 ratio. Randomization was stratified according to the disease stage (IB vs. II vs. IIIA), the EGFR mutation status (deletion in exon 19 vs. substitution mutation in exon 21 [L858R]) and family origin (Asian vs. non-Asian).

Treatment with osimertinib in the intervention arm was in compliance with the specifications of the SPC [3]. Dose adjustment was possible if AEs occurred.

Treatment of the study population was performed until occurrence of a recurrence, unacceptable toxicity, decision of the patient or until the regular end of the study treatment after 3 years.

Primary outcome of the study was disease-free survival. Patient-relevant secondary outcomes were outcomes on mortality, morbidity, health-related quality of life and AEs.

Suitability of the patient population of the ADAURA study for research question 2

The study included patients with and without adjuvant platinum-based chemotherapy. At the time of randomization, wound healing after surgery for complete surgical resection of NSCLC had to be completely finished. Patients without adjuvant chemotherapy could be randomized 4 weeks and at the latest 10 weeks after surgery at the earliest. For patients with adjuvant chemotherapy, it was recommended according to the study planning that this be started no later than 8 weeks after surgery. This is in line with the recommendation of the S3 guideline stating that adjuvant chemotherapy should start within 60 days after resection [4]. Patients with adjuvant chemotherapy could be randomized 2 weeks after the last dose of chemotherapy and at the latest 26 weeks after surgery at the earliest.

According to the information provided by the company in Module 4A of its dossier, the decision as to whether the patients should receive adjuvant platinum-based chemotherapy was made by the investigator before randomization. However, it is not clear from the dossier what criteria were used to make this decision. According to the S3 guidelines, adjuvant chemotherapy after complete tumour resection is recommended for patients in disease stages II and IIIA who have a good general condition [4]. In the ADAURA study, all patients had a good general condition (WHO PS $\leq$ 1), however, only 76% of the patient population in stages II and IIIA received adjuvant chemotherapy (see Table 9). According to the S3 guideline, individual treatment decisions under consideration of comorbidity, age and cardiopulmonary function are recommended for patients in disease stage IB [4]. In the ADAURA study, 26% of the patients with disease stage IB received adjuvant chemotherapy (see Table 9). The company provided no information on why adjuvant chemotherapy was not suitable for the remaining patients for any of these patient groups.

The company only described in general terms that the ADAURA study includes patients who have already received all indicated adjuvant treatment options or for whom these were not suitable. According to the company, the latter applied if adjuvant chemotherapy was unsuitable due to patient-specific factors or was not indicated due to the stage of the disease. For the latter group, it remains unclear whether the company also included patients in stage IB for whom adjuvant chemotherapy would basically have been suitable. Such patients should be assigned to research question 1 of the present benefit assessment. The same applies to patients in disease stages II and IIIA, if adjuvant chemotherapy was an option for them. Moreover, the assignment

to research question 1 would result in a different ACT for these patients, i.e. a systemic antineoplastic therapy according to physician's choice instead of watchful waiting.

Overall, on the basis of the available data, it remains unclear whether the patient population of the ADAURA study can be completely assigned to research question 2 of the present benefit assessment, or whether the study also included a relevant proportion of patients for whom adjuvant chemotherapy would have been suitable but who did not receive it, and would thus have to be assigned to research question 1. However, this uncertainty did not result in an exclusion of the study. It was assumed that conclusions on the added benefit of osimertinib in comparison with the ACT can be drawn for the present research question on the basis of the study results. However, the uncertainties described were considered in the assessment of the certainty of conclusions of the results (see Section 2.4.2.2).

Implementation of the ACT

The G-BA specified watchful waiting as ACT for patients after prior adjuvant platinum-based chemotherapy or for whom this therapy it was not suitable.

ADAURA used placebo as comparator therapy. The study was not designed for a comparison with watchful waiting, but is nonetheless suitable for such a comparison. This is explained below.

The following examinations were performed for the assessment of the health status or the detection of recurrences in the ADAURA study:

- Imaging (computed tomography or magnetic resonance imaging) of the chest and the abdomen including liver and adrenal glands after 12 and 24 weeks, then every 24 weeks for up to 5 years, from year 5 onwards annually.
- Physical examination after 2, 4 and 12 weeks, then every 12 weeks until year 3, thereafter every 24 weeks until year 5.

According to the S3 guideline [4], there is still no optimal follow-up concept for patients with stage IB-IIIA NSCLC after complete tumour resection. The guideline recommends quarterly examinations for the first 2 years, then every six months and annually from 5 years onwards. The examination should comprise a dedicated anamnesis, a physical examination and suitable imaging techniques. According to the European guideline, semi-annual examinations using imaging techniques are recommended in the first 2 years, followed by annual imaging examinations [11].

Despite the deviations in the recommended time intervals of the imaging procedures according to the S3 guideline, the study regimen in the ADAURA study as a whole is considered to be a sufficient approximation to the ACT “watchful waiting” for the present benefit assessment.

Data cut-offs

Analyses on the first data cut-off of 17 January 2020 are available for the ongoing ADAURA study. This data cut-off for the primary analysis was originally planned after 247 events in "disease-free survival" in the subpopulation of patients with stage II-IIIA disease. Following the recommendation of an independent data monitoring committee as part of regular efficacy and safety assessments, the data cut-off was brought forward by 2 years and was conducted on 17 January 2020 after 156 events in "disease-free survival" in the subpopulation of patients with stage II-IIIA disease. This data cut-off was used for the present benefit assessment.

Final analyses of the ADAURA study

Originally, the final analysis of overall survival was to take place approx. 1 year after the primarily planned analysis (after the occurrence of 247 events in disease-free survival). However, this timing was adjusted following unblinding of the study as recommended by the independent data monitoring committee and in consultation with the responsible health authority. The final analysis of overall survival will now take place when 94 events in the outcome "overall survival" are reached in the patient population with stage II and IIIA disease.

The final analysis of disease-free survival is now planned to take place when 247 events in the outcome "disease-free survival" are reached in the patient population with stage II and IIIA disease. However, if there are significantly fewer than 70 events in the patient population with stage IB disease at the time of this analysis, a further analysis shall be performed when this number of events is reached (analysis IB).

According to information in the assessment report of the European Medicines Agency, the study report for the final analysis of the ADAURA study is expected for the second quarter of 2024.

Follow-up observation

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

Table 8: Planned duration of follow-up observation – RCT, direct comparison: osimertinib vs. placebo

Study **outcome category** **outcome**	**Planned follow-up observation**
ADAURA	
Mortality	
Overall survival	Until death or end of study[a]
Morbidity	
Recurrence	Until recurrence or planned final analysis[b], whichever occurred first
Health-related quality of life (SF-36v2)	Until recurrence, last dose of the study medication, or study discontinuation, whichever occurred first
Side effects	
All outcomes in the category of side effects	Up to 28 days after the last dose of the study medication

a. The end of the study is planned when 94 events in the outcome "overall survival" are reached in the patient population with stage II and IIIA disease.
b. The final analysis is planned to be performed when 247 events in "disease-free survival" have occurred in the patient population with stage II and IIIA disease. If there are significantly fewer than 70 events in disease-free survival in the patient population with stage IB disease at the time of this analysis, all patients should continue to be observed until this number of events is reached, and a further analysis should be carried out when this number of events is reached (analysis IB).

RCT: randomized controlled trial; SF-36v2: Short Form (36) – version 2 Health Survey

The observation periods for the outcomes of the categories "health-related quality of life" and "side effects" were systematically shortened because they were only recorded for the time period of treatment with the study medication (plus 28 days for AEs). To be able to draw a reliable conclusion on the total study period or the time until death of the patients, it would be necessary, however, to record these outcomes over the total period of time, as was the case for survival.

Characteristics of the study population

Table 9 shows the characteristics of the patients in the study included.

Table 9: Characteristics of the study population – RCT, direct comparison: osimertinib vs. placebo (multipage table)

Study characteristic category	Osimertinib N[a] = 339	Placebo N[a] = 343
ADAURA		
Age [years], mean (SD)	63 (10)	62 (10)
Sex [F/M], %	68/32	72/28
Family origin, n (%)		
Caucasian	122 (36)	122 (36)
Asian	216 (64)	218 (64)
Other	1 (0.3)	2 (1)
Missing	0 (0)	1 (0.3)
AJCC stage at diagnosis[b], n (%)		
IB	107 (32)	109 (32)
Non-IB	232 (68)	234 (68)
IIA	86 (25)	90 (26)
IIB	29 (9)	26 (8)
IIIA	117 (35)	118 (34)
Prior adjuvant chemotherapy, n (%)	202 (60)	207 (60)
IB[c]	27 (25)	30 (28)
Non-IB[c]	175 (75)	177 (76)
IIA[c]	60 (70)	65 (72)
IIB[c]	20 (69)	20 (77)
IIIA[c]	95 (81)	92 (78)
Smoking status, n (%)		
Never smoker	231 (68)	257 (75)
Current smoker	4 (1)	3 (1)
Ex-smoker	104 (31)	83 (24)
WHO Performance Status, n (%)		
0	216 (64)	218 (64)
1	123 (36)	125 (36)
EGFR mutation[d, e], n (%)		
Exon 19 deletion	185 (55)	188 (55)
Exon 21 substitution mutation (L858R)	153 (45)	155 (45)
Type of resection, n (%)		
Lobectomy	328 (97)	322 (94)
Cuff resection	1 (0.3)	3 (1)
Bilobectomy	7 (2)	8 (2)
Pneumonectomy	3 (1)	10 (3)
Treatment discontinuation, n (%)	92 (27)	174 (51)
Study discontinuation, n (%)	30 (9)[f]	36 (11)[f]

Table 9: Characteristics of the study population – RCT, direct comparison: osimertinib vs. placebo (multipage table)

Study characteristic category	Osimertinib N[a] = 339	Placebo N[a] = 343

a. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. Classification according to the 7th edition of the AJCC.
c. The percentages refer to the number of patients in the respective AJCC stage.
d. Patients can have more than one EGRF mutation.
e. Testing for mutation-positive EGFR variants took place in a central laboratory.
f. Study discontinuation due to death affected 8 (2.4%) patients in the osimertinib arm and 20 (5.8%) patients in the placebo arm.

AJCC: American Joint Committee on Cancer; EGFR: epidermal growth factor receptor; F: female; M: male; n: number of patients in the category; N: number of randomized patients; RCT: randomized controlled trial; SD: standard deviation; WHO: World Health Organization

The patient characteristics were largely balanced between the study arms. The mean age of the patients was about 62 years, and the proportion of female and male patients was comparable in both study arms. 64% of the patients had a WHO PS of 0. With 68%, the larger proportion of patients had disease stages II-IIIA, 32% of patients had stage IB disease. With 55%, an exon 19 deletion mutation was slightly more common in both study arms compared to an L858R mutation in exon 21 (45%).

Approx. 75% of the patients with stage II-IIIA disease and 26% patients with stage IB received prior adjuvant chemotherapy.

Compared to the intervention arm, almost twice as many patients in the comparator arm discontinued therapy. In the intervention arm, the main reasons for treatment discontinuation were the occurrence of AEs (10.7%) and the decision of the patient (8.9%). In the comparator arm, 43.1% of the patients discontinued treatment due to disease recurrence.

Information on the course of the study

Table 10 shows the median treatment duration of the patients and the median observation period for individual outcomes.

Table 10: Information on the course of the study – RCT, direct comparison: osimertinib vs. placebo

Study **duration of the study phase** **outcome category**	**Osimertinib** **N = 339**	**Placebo** **N = 343**
ADAURA		
Treatment duration [months][a]		
Median [min; max]	22.5 [0; 38]	18.7 [0; 36]
Observation period [months]		
Overall survival [b]		
Median [min; max]	26.1 [ND]	26.5 [ND]
Morbidity		
Recurrence[c]		
Median [min; max]	22.1 [ND]	16.6 [ND]
Health-related quality of life		
Median [min; max]	22.1 [ND]	16.6 [ND]
Side effects[a]		
Median [min; max]	23.3 [ND]	19.2 [ND]

a. The data refer to patients who received at least one dose of the study medication (osimertinib: N = 337, placebo: N = 343).
b. The observation period is calculated on the basis of the observed time until censoring of all non-deceased patients.
c. Calculated as median time from randomization until event or censoring.

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

With 22.5 months, the median treatment duration was slightly longer in the osimertinib arm in comparison with the placebo arm with 18.7 months.

Information on subsequent therapies

Table 11 shows, which subsequent therapies patients received after discontinuation of the study medication.

Table 11: Information on subsequent antineoplastic therapies (≥ 1% of the patients in ≥ 1 treatment arm) – RCT, direct comparison: osimertinib vs. placebo

Study drug	Patients with subsequent therapy n (%)	
	osimertinib N = 339	placebo N = 343
ADAURA		
First subsequent therapy	30 (8.8)	125 (36.4)
Afatinib	1 (0.3)	11 (3.2)
Erlotinib	1 (0.3)	8 (2.3)
Erlotinib hydrochloride	1 (0.3)	6 (1.7)
Gefitinib	8 (2.4)	34 (9.9)
Icotinib hydrochloride	1 (0.3)	7 (2.0)
Osimertinib	0 (0)	10 (2.9)
Osimertinib mesylate	3 (0.9)	9 (2.6)
Radiotherapy	4 (1.2)	19 (5.5)
Second subsequent therapy	9 (2.7)	42 (12.2)
Gefitinib	1 (0.3)	4 (1.2)
Osimertinib	0 (0)	5 (1.5)
Osimertinib mesylate	0 (0)	5 (1.5)
Radiotherapy	2 (0.6)	7 (2.0)

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

Subsequent therapies after recurrence of the disease were allowed without restrictions for patients in both study arms. Overall, 8.8% of the patients in the intervention arm and 36.4% of the patients in the comparator arm were receiving subsequent antineoplastic therapy at the present data cut-off. 2.7% or 12.2% of the patients received a second subsequent therapy.

In both study arms, the most frequent first subsequent antineoplastic therapy was the administration of the EGFR inhibitor gefitinib. Osimertinib was also frequently used as first subsequent therapy in the comparator arm. Both gefitinib and osimertinib are approved for the treatment of locally advanced or metastatic NSCLC with activating EGFR mutations [3,12].

Risk of bias across outcomes (study level)

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

Table 12: Risk of bias across outcomes (study level) – RCT, direct comparison: osimertinib vs. placebo

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

The risk of bias across outcomes was rated as low for the ADAURA study. This concurs with the company's assessment.

Transferability of the study results to the German health care context

Due to the sufficient comparability of selected patient characteristics of the study population with patients in Germany, the company assumed that the observed clinical effects of the ADAURA study also occur in the German target population in health care under everyday conditions. It pointed out that the ADAURA study is being conducted in 185 study centres and 24 countries worldwide, and that 36% of the patients are of Caucasian origin. In addition, the company also addressed the characteristics "age", "sex" and "disease stage".

With regard to pretreatment with adjuvant chemotherapy, the company described that a similar rate as in everyday health care in Germany was observed in the ADAURA study. In this context, the company referred to a retrospective observational study on treatment protocols, which showed that the proportion of German patients in stage IB-IIIA with adjuvant systemic therapy after tumour resection was 51.9% [13]. According to the company, in relation to all patients in Germany in the respective stage of disease, 17.1% of patients in stage IB, 59.6% of patients in stage IIA, 60.9% of patients in stage IIB and 66.7% of patients in stage IIIA received adjuvant chemotherapy.

2.4.2 Results on added benefit

2.4.2.1 Outcomes included

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

- Mortality
  - overall survival
- Morbidity
  - recurrence

- Health-related quality of life
  - measured using the SF-36v2
- Side effects
  - SAEs
  - severe AEs (CTCAE grade ≥ 3)
  - discontinuation due to AEs
  - skin and subcutaneous tissue disorders (System Organ Class [SOC], AEs)
  - ILD and pneumonitis (company's Preferred Term [PT] collection, SAEs)
  - cardiac events (standardized MedDRA query [SMQ] heart failure and SMQ cardiomyopathy, severe AEs)
  - further specific AEs, if any

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

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

Table 13: Matrix of outcomes – RCT, direct comparison: osimertinib vs. placebo

Study	Outcomes									
	Overall survival	Recurrence[a]	Health-related quality of life (SF-36v2)	SAEs	Severe AEs[b]	Discontinuation due to AEs	Skin and subcutaneous tissue disorders (SOC, AEs)	ILD and pneumonitis[c] (PT, SAEs)	Cardiac events[d] (severe AEs[b])	Further specific AEs[e]
ADAURA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a. Presented based on the recurrence rate and disease-free survival, includes the events of local/regional recurrence, distant recurrence with CNS recurrence and death from any cause.
b. Operationalized as CTCAE grade ≥ 3.
c. PT collection of the company (PTs included: interstitial lung disease, pneumonitis, acute interstitial pneumonitis, alveolitis, diffuse alveolar damage, idiopathic pulmonary fibrosis, lung disease, pulmonary toxicity and pulmonary fibrosis).
d. Operationalized using the SMQ "heart failure" and the SMQ "cardiomyopathy".
e. The following events (MedDRA coding) were considered: "gastrointestinal disorders" (SOC, AEs), "diarrhoea" (PT, AEs), "mouth ulceration" (PT, AEs), "stomatitis" (PT, AEs), "gastrointestinal disorders" (SOC, severe AEs), "paronychia" (PT, AEs), "reduced appetite" (PT, AEs).

AE: adverse event; CNS: central nervous system; CTCAE: Common Terminology Criteria for Adverse Events; ILD: interstitial lung disease, MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SF-36v2: Short Form (36) – version 2 Health Survey; SMQ: standardized MedDRA query; SOC: System Organ Class

For the outcome "progression-free survival (PFS)", the company also provided information on the proportion of patients in the study arms who experienced symptomatic progression. However, it is not clear from the available data how symptomatic progression was recorded or whether the survey recorded whether symptoms were present for all progression events. Moreover, the company did not present any event time analyses on symptomatic progression. Due to the lack of analyses and the lack of information on operationalization, the results on symptomatic progression cannot be used for the present benefit assessment.

2.4.2.2 Risk of bias

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

Table 14: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: osimertinib vs. placebo

Study	Study level	Outcomes									
		Overall survival	Recurrence[a]	Health-related quality of life (SF-36v2)	SAEs	Severe AEs[b]	Discontinuation due to AEs	Skin and subcutaneous tissue disorders (SOC, AEs)	ILD and pneumonitis[c] (PT, SAEs)	Cardiac events[d] (severe AEs[b])	Further specific AEs[e]
ADAURA	N	N	N	H[f]	H[g]	H[g]	L[h]	H[g]	H[g]	H[g]	H[g]

a. Presented based on the recurrence rate and disease-free survival, includes the events of local/regional recurrence, distant recurrence with CNS recurrence and death from any cause.
b. Operationalized as CTCAE grade ≥ 3.
c. PT collection of the company (PTs included: interstitial lung disease, pneumonitis, acute interstitial pneumonitis, alveolitis, diffuse alveolar damage, idiopathic pulmonary fibrosis, lung disease, pulmonary toxicity and pulmonary fibrosis).
d. Operationalized using the SMQ "heart failure" and the SMQ "cardiomyopathy".
e. The following events (MedDRA coding) were considered: "gastrointestinal disorders" (SOC, AEs), "diarrhoea" (PT, AEs), "mouth ulceration" (PT, AEs), "stomatitis" (PT, AEs), "gastrointestinal disorders" (SOC, severe AEs), "paronychia" (PT, AEs), "reduced appetite" (PT, AEs).
f. Strongly decreasing and highly differential returns; large intervals between the documentation times.
g. Large difference in observation periods between the treatment arms; potentially informative censorings.
h. Despite the low risk of bias, the certainty of results for the outcome "discontinuation due to AEs" was assumed to be limited (see running text).

AE: adverse event; CNS: central nervous system; CTCAE: Common Terminology Criteria for Adverse Events; H: high; ILD: interstitial lung disease, L: low; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SF-36v2: Short Form (36) – version 2 Health Survey; SMQ: standardized MedDRA query; SOC: System Organ Class

The risk of bias for the results on the outcomes "overall survival" and "recurrence" was rated as low. This concurs with the company's assessment.

For the outcome "health-related quality of life", recorded using the SF-36v2, the risk of bias of the results was assessed as high due to a strong decrease and large differences in response. In addition, there are large time gaps (24 weeks) between the recordings, which must be taken into account for the operationalization of the time to confirmed deterioration. In the case of different observation times between the study arms, the large time interval between the recordings can lead to a higher probability that a deterioration in the shorter observed arm can no longer be confirmed.

This deviates from the assessment of the company, which assumed a low risk of bias for the results on the outcome "health-related quality of life" recorded with the SF 36v2.

With the exception of the outcome “discontinuation due to AEs”, there is a high risk of bias of the results due to incomplete observations for potentially informative reasons for outcomes of the category “side effects”. Planned observation until the end of treatment (plus 28 days) for these outcomes resulted in significant differences in median observation duration between the treatment groups (23.3 vs. 19.2 months). The observation period was thus determined by the reasons for treatment discontinuation (mainly by the recurrence of the disease), which clearly differed between the treatment arms. A total of 27.3% of the patients in the intervention arm and 50.7% in the comparator arm discontinued treatment. In 26.1% or 85.1% of patients who discontinued treatment, the reason for the discontinuation was a recurrence, and in 39.1% or 5.7% an AE.

The certainty of results for the outcome “discontinuation due to AEs” was restricted despite a low risk of bias. Premature treatment discontinuation for reasons other than AEs is a competing event for the outcome “discontinuation due to AEs” to be recorded. This means that, after discontinuation for other reasons, AEs that would have led to treatment discontinuation may have occurred, but that the criterion "discontinuation" can no longer be applied to them. It cannot be estimated how many AEs this concerns.

This assessment deviates from that of the company, which assumed a low risk of bias for the results on outcomes of the category “side effects”.

Overall assessment of the certainty of conclusions

Taking into account the uncertainty with regard to the included patient population, at most hints, for example of an added benefit, can be determined for all outcomes for the present research question on the basis of the ADAURA study (see Section 2.4.1.2 for explanation).

2.4.2.3 Results

Table 15 summarizes the results for the comparison of osimertinib with placebo in patients after prior adjuvant platinum-based chemotherapy or for whom this therapy was not suitable. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company’s dossier.

Kaplan-Meier curves on the presented event time analyses can be found in Appendix B of the full dossier assessment. The results on common AEs, SAEs, severe AEs and discontinuations due to AEs are presented in Appendix C of the full dossier assessment.

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: osimertinib vs. placebo (multipage table)

Study outcome category outcome	Osimertinib N	Osimertinib median time to event in months [95% CI] patients with event n (%)	Placebo N	Placebo median time to event in months [95% CI] patients with event n (%)	Osimertinib vs. placebo HR [95% CI]; p-value
ADAURA					
Mortality					
Overall survival	339	NA 9 (2.7)	343	–[a] 20 (5.8)	0.48 [0.23; 1.02]; 0.055[b]
Morbidity					
Recurrence					
Recurrence rate[c]	339	– 37 (10.9)	343	– 159 (46.4)	RR: 0.24 [0.17; 0.32]; < 0.001[d]
Local/regional	339	– 23 (6.8)	343	– 61 (17.8)	–
Distant recurrence	339	– 10 (2.9)	343	– 78 (22.7)	–
CNS recurrences	339	– 4 (1.2)	343	– 33 (9.6)	–
Local/regional and distant recurrence	339	– 4 (1.2)	343	– 18 (5.2)	–
Death	339	– 0 (0)	343	– 2 (0.6)	–
Disease-free survival[e]	339	NA 37 (10.9)	343	27.5 [22.0; 35.0] 159 (46.4)	0.20 [0.15; 0.27]; < 0.001[f]
Health-related quality of life					
SF-36v2					
Physical Component Summary (PCS)[g]	339	NA 19 (5.6)	343	NA 8 (2.3)	2.21 [1.04; 4.70]; 0.040[b]
Mental Component Summary (MCS)[h]	339	NA 30 (8.8)	343	NA 27 (7.9)	1.02 [0.60; 1.71]; 0.950[b]
Side effects					
AEs (supplementary information)	337	0.4 [0.3; 0.5] 329 (97.6)	343	1.0 [0.7; 1.1] 306 (89.2)	
SAEs	337	NA 54 (16.0)	343	NA 42 (12.2)	1.21 [0.81; 1.81]; 0.343[b]
Severe AEs[i]	337	NA 68 (20.2)	343	NA 46 (13.4)	1.46 [1.01; 2.10]; 0.045[b]
Discontinuation due to AEs	337	NA 37 (11.0)	343	NA 10 (2.9)	3.08 [1.73; 5.45]; < 0.001[b]
Skin and subcutaneous tissue disorders (SOC, AEs)	337	2.8 [1.9; 5.3] 238 (70.6)	343	NA 122 (35.6)	2.72 [2.20; 3.36]; < 0.001[b]

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: osimertinib vs. placebo (multipage table)

Study outcome category outcome	Osimertinib N	Osimertinib median time to event in months [95% CI] patients with event n (%)	Placebo N	Placebo median time to event in months [95% CI] patients with event n (%)	Osimertinib vs. placebo HR [95% CI]; p-value
ILD and pneumonitis[j] (PT, SAEs)	337	NA 1 (0.3)	343	NA 0 (0)	ND
Cardiac events[k] (severe AEs[i])	337	NA 3 (0.9)	343	NA 1 (0.3)	2.53 [0.35; 18.05] 0.355[b]
Gastrointestinal disorders (SOC, AEs)	337	1.9 [1.1; 2.6] 239 (70.9)	343	26.9 [19.2; NC] 149 (43.4)	2.29 [1.87; 2.81]; < 0.001[b]
Including:					
Diarrhoea (PT, AEs)	337	34.9 [14.3; NC] 156 (46.3)	343	NA 68 (19.8)	2.69 [2.07; 3.50]; < 0.001[b]
Mouth ulceration (PT, AEs)	337	NA 39 (11.6)	343	NA 8 (2.3)	3.88 [2.19; 6.88]; < 0.001[b]
Stomatitis (PT, AEs)	337	NA 59 (17.5)	343	NA 14 (4.1)	3.73 [2.36; 5.90]; < 0.001[b]
Gastrointestinal disorders (SOC, severe AEs)	337	NA 17 (5.0)	343	NA 3 (0.9)	4.12 [1.71; 9.90]; 0.002[b]
Paronychia (PT, AEs)	337	NA 85 (25.2)	343	NA 5 (1.5)	6.79 [4.49; 10.27]; < 0.001[b]
Decreased appetite (PT, AEs)	337	NA 44 (13.1)	343	NA 13 (3.8)	3.12 [1.85; 5.24]; < 0.001[b]

a. Median not meaningfully interpretable.
b. Effect estimation and 95% CI by means of U and V statistics from unstratified log-rank test; p-value via unstratified log-rank test.
c. Proportion of patients, individual components are presented in the lines below.
d. Effect estimation and 95% CI by means of log-binomial model.
e. Operationalized as time from the day of randomization to the first occurrence of an event, for individual components see recurrence rate.
f. Effect estimation and 95% CI by means of U and V statistics from stratified log-rank test; p-value via stratified log-rank test; stratification variables: stage (IB vs. II vs. IIIA), EGFR mutation status (exon 19 deletion vs. exon 21 substitution mutation [L858R], either alone or in combination with other EGFR mutations) and origin (Asian versus non-Asian).
g. Analyses on the time to confirmed deterioration by ≥ 9.4 points (corresponds to 15% of the scale range; normalized scale with a minimum of approx. 7 and a maximum of approx. 70).
h. Analyses on the time to confirmed deterioration by ≥ 9.6 points (corresponds to 15% of the scale range; normalized scale with a minimum of approx. 6 and a maximum of approx. 70).
i. Operationalized as CTCAE grade ≥ 3.
j. PT collection of the company (PTs included: interstitial lung disease, pneumonitis, acute interstitial pneumonitis, alveolitis, diffuse alveolar damage, idiopathic pulmonary fibrosis, lung disease, pulmonary toxicity and pulmonary fibrosis).
k. Operationalized using the SMQ “heart failure” and the SMQ “cardiomyopathy”.

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: osimertinib vs. placebo (multipage table)

Study outcome category outcome	Osimertinib N	Osimertinib median time to event in months [95% CI] patients with event n (%)	Placebo N	Placebo median time to event in months [95% CI] patients with event n (%)	Osimertinib vs. placebo HR [95% CI]; p-value
AE: adverse event; CI: confidence interval; CNS: central nervous system; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; ILD: interstitial lung disease; MCS: Mental Component Summary; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; PT: Preferred Term; PCS: Physical Component Summary; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SF-36v2: Short Form (36) – version 2 Health Survey; SMQ: standardized MedDRA query; SOC: System Organ Class					

On the basis of the available data, no more than hints, e.g. of an added benefit, can be determined for all outcomes (see Section 2.4.2.2).

Mortality

Overall survival

No statistically significant difference between the treatment groups was shown for the outcome "overall survival". This resulted in no hint of an added benefit of osimertinib in comparison with watchful waiting; an added benefit is therefore not proven.

This deviates from the assessment of the company, which, in addition to analyses on the total study population, also considered analyses of patients in disease stages II and IIIA, and on this basis overall derived an indication of an added benefit.

Morbidity

Recurrence

Operationalization

For the present benefit assessment, the proportion of patients with recurrence and, additionally, the time to recurrence of the disease were used for the outcome “recurrence”.

Result

For the outcome “recurrence” (operationalized as recurrence rate and disease-free survival), a statistically significant difference in favour of osimertinib in comparison with placebo was shown for both operationalizations. This resulted in a hint of an added benefit of osimertinib versus watchful waiting.

This deviates from the assessment of the company insofar as the company overall derived an indication of an added benefit for the outcome category “morbidity”. The company did not make a separate assessment for the outcome “recurrence”.

Health-related quality of life

SF-36v2 – PCS and MCS

Operationalization

Besides analyses based on mean differences for the PCS and MCS of the SF-36v2, the company also presented responder analyses on the time to confirmed deterioration in the dossier. According to the study planning, the time to confirmed deterioration corresponds to the predefined operationalization for the SF-36v2. A deterioration was considered confirmed if a deterioration of ≥ 9.4 points for the PCS or of ≥ 9.6 points for the MCS was shown over 2 consecutive measurements. For the questionnaire version used in the study with a recall time of 4 weeks, this corresponds to a deterioration by ≥ 15% of the scale range (normalized scale with a minimum of approx. 7 [PCS] or 6 [MCS] and a maximum of approx. 70 in each case; for the derivation of the response criteria, see Appendix E of the full dossier assessment). Patients without any values at baseline or at subsequent visits were censored on day 1. Patients with deterioration or death after at least 2 missed visits were censored on the last available visit before the missed ones. The available data show that such censoring occurred only for a small proportion of patients in both study arms. Therefore, the responder analyses on the time to confirmed deterioration were used for the present benefit assessment. Uncertainties resulting from the decreasing response rates over time with clear differences between the study arms as well as the relatively large time span of 24 weeks between the recordings of the SF-36v2 are taken into account in the risk of bias (see Section 2.4.2.2). This deviates from the company's approach insofar as the company used analyses on the basis of mean differences for its assessment.

Result

For the PCS of the SF-36v2, there was a statistically significant difference to the disadvantage of osimertinib in comparison with placebo on the basis of the responder analysis on the time to confirmed deterioration. However, there was an effect modification by the characteristic "disease stage". This resulted in a hint of lesser benefit of osimertinib in comparison with watchful waiting for patients with stage II and IIIA disease. However, no hint of an added benefit of osimertinib in comparison with watchful waiting was shown for patients with stage IB disease; an added benefit is therefore not proven (see Section 2.4.2.4).

For the MCS of the SF-36v2, there was no statistically significant difference between the treatment groups on the basis of the responder analysis on the time to confirmed deterioration. This resulted in no hint of an added benefit of osimertinib in comparison with watchful waiting; an added benefit is therefore not proven.

This deviates from the assessment of the company, which used analyses on the basis of mean differences for its assessment and considered an added benefit for health-related quality of life as not proven on the basis of these analyses.

Side effects

Overall, the company derived a disadvantage of osimertinib versus watchful waiting for the outcome category “side effects”. The company makes this assessment based on the results for the superordinate outcome “SAEs”, “severe AEs”, “discontinuation due to AEs” and the specific AEs “ILD” and “pneumonitis”. It drew no conclusion on individual outcomes. The company also drew no separate conclusion on the added benefit for further specific AEs. For these reasons, a description of the extent to which the statement on the added benefit differs from the assessment of the company is omitted for the following outcomes on side effects.

SAEs

No statistically significant difference between the treatment groups was shown for the outcome "SAEs". This resulted in no hint of greater or lesser harm from osimertinib in comparison with watchful waiting; greater or lesser harm is therefore not proven.

Severe AEs and discontinuation due to AEs

A statistically significant difference to the disadvantage of osimertinib in comparison with placebo was shown for each of the outcomes “severe AEs” and "discontinuation due to AEs". In each case, this resulted in a hint of greater harm from osimertinib versus watchful waiting.

Skin and subcutaneous tissue disorders (AEs)

There was a statistically significant difference to the disadvantage of osimertinib in comparison with placebo for the outcome "skin and subcutaneous tissue disorders (AEs)”. This resulted in a hint of greater harm from osimertinib versus watchful waiting.

ILD and pneumonitis (SAEs) and cardiac events (severe AEs)

There was no statistically significant difference between the treatment groups for each of the outcomes "ILD" and "pneumonitis” (SAEs) and “cardiac events” (severe AEs). In each case, this resulted in no hint of greater or lesser harm from osimertinib in comparison with watchful waiting; greater or lesser harm is therefore not proven.

Further specific AEs

Gastrointestinal disorders (AEs) (including diarrhoea [AEs], mouth ulceration [AEs], stomatitis [AEs]), gastrointestinal disorders (severe AEs), paronychia (AEs), decreased appetite (AEs)

A statistically significant difference to the disadvantage of osimertinib in comparison with placebo was shown for each of the specific AEs “gastrointestinal disorders (AEs)” (including diarrhoea [AEs], mouth ulceration [AEs], stomatitis [AEs]), “gastrointestinal disorders (severe AEs)”, “paronychia (AEs)” and “decreased appetite (AEs)”. In each case, this resulted in a hint of greater harm from osimertinib versus watchful waiting.

2.4.2.4 Subgroups and other effect modifiers

The following potential effect modifiers were considered in the present assessment:

- Age (< 65 years vs. ≥ 65 years)
- Sex (men vs. women)
- Disease stage (IB vs. II vs. IIIA)

The mentioned characteristics were defined a priori. In the ADAURA study, subgroup analyses were only prespecified for disease-free survival. In the dossier, the company presented subgroup analyses for all outcomes of the present benefit assessment.

Interaction tests were performed when at least 10 patients per subgroup were included in the analysis. Moreover, for binary data, there had to be at least 10 events in at least one subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are only presented if there is a statistically significant and relevant effect in at least one subgroup.

Table 16 summarizes the subgroup results for the comparison of osimertinib with placebo in patients after prior adjuvant platinum-based chemotherapy or for whom this therapy was not suitable. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

Kaplan-Meier curves on the presented event time analyses can be found in Appendix B of the full dossier assessment.

Table 16: Subgroups (morbidity, health-related quality of life) – RCT, direct comparison: osimertinib vs. placebo

Study outcome characteristic subgroup	Osimertinib N	Osimertinib median time to event in months [95% CI] patients with event n (%)	Placebo N	Placebo median time to event in months [95% CI] patients with event n (%)	Osimertinib vs. placebo HR [95% CI]	Osimertinib vs. placebo p-value
ADAURA						
Morbidity						
Recurrence						
Recurrence rate						
Disease stage						
IB	106	– 11 (10.4)	106	– 29 (27.4)	RR: 0.38 [0.19; 0.70]	0.001
II	118	– 11 (9.3)	118	– 52 (44.1)	RR: 0.21 [0.11; 0.37]	< 0.001
IIIA	115	– 15 (13.0)	119	– 78 (65.5)	RR: 0.20 [0.12; 0.31]	< 0.001
Total					Interaction:	0.282
Disease-free survival						
Disease stage						
IB	106	NA 11 (10.4)	106	–[a] 29 (27.4)	0.39 [0.18; 0.76]	0.005
II	118	NA 11 (9.3)	118	28.1 [20.4; NC] 52 (44.1)	0.17 [0.08; 0.31]	< 0.001
IIIA	115	38.8 [34.3; NC] 15 (13.0)	119	12.7 [11.0; 18.3] 78 (65.5)	0.12 [0.07; 0.20]	< 0.001
Total					Interaction:	0.041
Health-related quality of life						
SF-36v2						
PCS						
Disease stage						
IB	106	NA 2 (1.9)	106	NA 5 (4.7)	0.43 [0.06; 2.00]	0.291
II	118	NA 8 (6.8)	118	NA 2 (1.7)	3.93 [0.98; 26.03]	0.053
IIIA	115	NA 9 (7.8)	119	NA 1 (0.8)	7.98 [1.50; 147.36]	0.011
Total					Interaction:	0.030

Table 16: Subgroups (morbidity, health-related quality of life) – RCT, direct comparison: osimertinib vs. placebo

Study outcome characteristic subgroup	Osimertinib N	Osimertinib median time to event in months [95% CI] patients with event n (%)	Placebo N	Placebo median time to event in months [95% CI] patients with event n (%)	Osimertinib vs. placebo HR [95% CI]	Osimertinib vs. placebo p-value
Health-related quality of life						
SF-36v2						
PCS						
Disease stage						
IB	106	NA 2 (1.9)	106	NA 5 (4.7)	RR: 0.40 [0.08; 2.02][b]	0.284[c]
II and IIIA	233	– 17 (7.3)	237	– 3 (1.3)	RR: 5.75 [1.71; 19.33][d]	0.005[d]
II	*118*	*NA* *8 (6.8)*	*118*	*NA* *2 (1.7)*	*RR: 4.00 [0.87; 18.44][b]*	*0.059[c]*
IIIA	*115*	*NA* *9 (7.8)*	*119*	*NA* *1 (0.8)*	*RR: 9.31 [1.20; 72.34][b]*	*0.008[c]*
Total					Interaction	0.010[e]

a. Median not meaningfully interpretable.
b. Institute's calculation.
c. Institute's calculation, unconditional exact test (CSZ method according to [14]).
d. Institute's calculation, meta-analysis with fixed effect, Mantel/Haenszel method.
e. Institute's calculation, p-value from Q test for heterogeneity, relating to the two subgroups "IB" and "IIIA".

CI: confidence interval; HR: hazard ratio; n: number of patients with event; N: number of analysed patients; NA: not achieved; NC: not calculable; PCS: Physical Component Summary; RCT: randomized controlled trial; RR: relative risk; SF-36v2: Short Form (36) – version 2 Health Survey

Notes on the event time analyses presented by the company

The event time analyses are based on log-rank test statistics. However, the calculation of the related 95% confidence intervals is not comprehensible. For the Institute's calculations, it is necessary to calculate a standard error from the width of the confidence intervals. This is not possible in the present case because the confidence intervals on the logarithmic scale are not symmetrical. Therefore, calculations by the Institute cannot be conducted on the basis of the estimations of the company. This concerns the pooling of the subgroups into disease stages II and IIIA for the PCS of the SF-36v2. For the Institute's calculations on the PCS, the RR is therefore used as an effect measure as an approximation.

Morbidity

Recurrence

For the outcome "recurrence", there is an effect modification by the characteristic "disease stage" for the results of the operationalization "disease-free survival". For this

operationalization, a statistically significant difference in favour of osimertinib in comparison with placebo was shown for patients in all three stages. However, the effect modification for the characteristic "disease stage" does not show up for the recurrence rate, and is thus not consistent for the results of both operationalizations. Therefore, the effect modification is not assumed to be relevant for the outcome "recurrence". The derivation of the added benefit for the outcome "recurrence" was therefore based on the total population.

This concurs with the assessment of the company insofar as the company did not consider the effect modification for disease-free survival for its assessment. It justified this with the argument that no noticeable increase of effects in the same direction could be found for the characteristic "disease stage" across a sufficient number of outcomes.

Health-related quality of life

SF-36v2 – PCS

There is an effect modification by the characteristic "disease stage" for the PCS of the SF-36v2.

The present data situation suggests that the results between stages II and IIIA are sufficiently homogeneous and can be pooled. For the event time analyses, the company presented no summarizing analysis for disease stages II and IIIA. Therefore, as an approximation, a pooled effect estimation of stages II and IIIA was made via the calculation of the RR (see Appendix D of the full dossier assessment). In the following, the derivation of the added benefit for the PCS of the SF-36v2 was based on the results of the Institute's calculations.

There was a statistically significant difference to the disadvantage of osimertinib in comparison with placebo for the pooled analysis of disease stages II and IIIA. This resulted in a hint of lesser benefit of osimertinib in comparison with watchful waiting for patients with stage II and IIIA disease. In contrast, no statistically significant difference between the treatment groups was shown for patients with stage IB disease; an added benefit for these patients is therefore not proven.

This deviates from the approach of the company, which did not consider the effect modification for the PCS in its assessment. Analogous to disease-free survival, it justified this with the argument that no noticeable increase of effects in the same direction could be found for the characteristic "disease stage" across a sufficient number of outcomes.

2.4.3 Probability and extent of added benefit

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

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

2.4.3.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Section 2.4.2 (see Table 17).

Determination of the outcome category for outcomes on morbidity and side effects

It cannot be inferred from the dossier for the outcomes "recurrence" and "discontinuation due to AEs" whether they are serious/severe or non-serious/non-severe. The classification was justified for these outcomes.

The outcome "recurrence" is considered to be serious/severe. On the one hand, recurrence of the cancer can be life-threatening, or rather a recurrence shows that the attempt to cure a potentially life-threatening disease with the curative therapy approach was not successful. On the other hand, the event "death from any cause" is a component of the outcome "recurrence".

The outcome "discontinuation due to AEs" was assigned to the outcome category of non-serious/non-severe side effects because no information was available on the severity of the AEs that led to discontinuation of at least one treatment component.

Table 17; Extent of added benefit at outcome level: osimertinib vs. watchful waiting (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Osimertinib vs. placebo** **median time to event (months)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival	NA vs. –[c] HR: 0.48 [0.23; 1.02]; p = 0.055	Lesser benefit/added benefit not proven
Morbidity		
Recurrence		Outcome category: serious/severe symptoms/late complications $CI_u < 0.75$, risk ≥ 5% added benefit, extent: “major”
Recurrence rate	Proportion of events (%): 10.9% vs. 46.4% RR: 0.24 [0.17; 0.32]; p < 0.001 probability: "hint"	
Disease-free survival	NA vs. 27.5 HR: 0.20 [0.15; 0.27] p < 0.001 probability: "hint"	
Health-related quality of life		
SF-36v2		
PCS[d]		
Disease stage		
IB	Proportion of events (%): 1.9% vs. 5.7% RR: 0.40 [0.08; 2.02] p = 0.284	Lesser benefit/added benefit not proven
II and IIIA	Proportion of events (%): 7.3% vs. 1.3% RR: 5.75 [1.71; 19.33] RR: 0.17 [0.05; 0.58][e] p = 0.001 probability: "hint"	Outcome category: health-related quality of life $CI_u < 0.75$, risk ≥ 5% lesser benefit, extent: "major"
MCS	NA vs. NA HR: 1.02 [0.60; 1.71] p = 0.950	Lesser benefit/added benefit not proven
Side effects		
SAEs	NA vs. NA HR: 1.21 [0.81; 1.81] p = 0.343	Greater/lesser harm not proven
Severe AEs	NA vs. NA HR: 1.46 [1.01; 2.10] HR: 0.68 [0.48; 0.99][e] p = 0.045 probability: "hint"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ greater harm, extent: “minor”

Table 17; Extent of added benefit at outcome level: osimertinib vs. watchful waiting (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Osimertinib vs. placebo** **median time to event (months)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Discontinuation due to AEs	NA vs. NA HR: 3.08 [1.73; 5.45] HR: 0.32 [0.18; 0.58][e] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects CI_u < 0.80 greater harm, extent: “considerable”
Skin and subcutaneous tissue disorders (AEs)	2.8 vs. NA HR: 2.72 [2.20; 3.36] HR: 0.37 [0.30; 0.45][e] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects CI_u < 0.80 greater harm, extent: “considerable”
ILD and pneumonitis (SAEs)	NA vs. NA. HR: ND p = ND	Greater/lesser harm not proven
Cardiac events (severe AEs)	NA vs. NA HR: 2.53 [0.35; 18.05] p = 0.355	Greater/lesser harm not proven
Gastrointestinal disorders (AEs)	1.9 vs. 26.9 HR: 2.29 [1.87; 2.81] HR: 0.44 [0.36; 0.53][e] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects CI_u < 0.80 greater harm, extent: “considerable”
Including:		
Diarrhoea (AEs)	34.9 vs. NA HR: 2.69 [2.07; 3.50] HR: 0.37 [0.29; 0.48][e] p < 0.001 probability: "hint"	
Mouth ulceration (AEs)	NA vs. NA HR: 3.88 [2.19; 6.88] HR: 0.26 [0.15; 0.46][e] p < 0.001 probability: "hint"	
Stomatitis (AEs)	NA vs. NA HR: 3.73 [2.36; 5.90] HR: 0.27 [0.17; 0.42][e] p < 0.001 probability: "hint"	
Gastrointestinal disorders (severe AEs)	NA vs. NA HR: 4.12 [1.71; 9.90] HR: 0.24 [0.10; 0.58][e] p < 0.002 probability: "hint"	Outcome category: serious/severe side effects CI_u < 0.75, risk ≥ 5% greater harm, extent: “major”

Table 17; Extent of added benefit at outcome level: osimertinib vs. watchful waiting (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Osimertinib vs. placebo** **median time to event (months)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Paronychia (AEs)	NA vs. NA HR: 6.79 [4.49; 10.27] HR: 0.15 [0.1; 0.22][e] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: “considerable”
Decreased appetite (AEs)	NA vs. NA HR: 3.12 [1.85; 5.24] HR: 0.32 [0.19; 0.54][e] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: “considerable”

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u).
c. Median not meaningfully interpretable.
d. The derivation of the added benefit was based on the effect estimation of the RR, which was used as an approximation for the Physical Component Summary (see Section 2.4.2.4).
e. Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit.

AE: adverse event; CI: confidence interval; CI_u: upper limit of the confidence interval; HR: hazard ratio; ILD: interstitial lung disease; MCS: Mental Component Summary; NA: not achieved; PCS: Physical Component Summary; RR: relative risk; SAE: serious adverse event; SF-36v2: Short Form (36) – version 2 Health Survey

2.4.3.2 Overall conclusion on added benefit

Table 18 summarizes the results considered in the overall conclusion on the extent of added benefit.

Table 18: Positive and negative effects from the assessment of osimertinib in comparison with watchful waiting

Positive effects	**Negative effects**
Morbidity serious/severe symptoms/late complications ▪ recurrence: hint of an added benefit – extent: "major"	Health-related quality of life ▪ PCS ▫ disease stages (II and IIIA) hint of lesser benefit – extent: "major"
▪ –	Serious/severe side effects ▪ severe AEs: hint of greater harm – extent: “minor” ▪ gastrointestinal disorders (severe AEs): hint of greater harm – extent: "major"
▪ –	Non-serious/non-severe side effects ▪ discontinuation due to AEs ▪ skin and subcutaneous tissue disorders (AEs) ▪ gastrointestinal disorders (AEs, including: diarrhoea [AEs], mouth ulceration [AEs], stomatitis [AEs]) ▪ paronychia (AEs) ▪ decreased appetite (AEs) in each case: hint of greater harm – extent: "considerable"
AEs: adverse events; PCS: Physical Component Summary	

Overall, one positive and several negative effects of different extents were shown, each with the probability “hint”.

A positive effect of osimertinib in comparison with watchful waiting with the extent “major” was shown for the outcome “recurrence”. In contrast, there were negative effects for osimertinib in comparison with watchful waiting, especially in the outcome category “side effects”. Negative effects in serious/severe side effects were shown for the superordinate outcome of severe AEs with the extent "minor" and for gastrointestinal disorders (severe AEs) with the extent "major". Among the non-serious/non-severe side effects, there were several specific AEs with the extent “considerable” to the disadvantage of osimertinib. In the outcome category “health-related quality of life”, there is a negative effect of osimertinib with the extent “major” in the PCS of the SF-36v2 compared to watchful waiting for patients in disease stages II and IIIA . However, these negative effects do not completely challenge the positive effect with the extent “major” for the outcome “recurrence”.

In summary, there is a hint of considerable added benefit of osimertinib versus the ACT “watchful waiting” for patients after prior adjuvant platinum-based chemotherapy or for whom this therapy it is not suitable.

The assessment described above deviates from that of the company, which, based on the results of the ADAURA study derived an indication of a considerable added benefit for osimertinib compared to the ACT observational waiting for patients after previous adjuvant platinum-based

chemotherapy or for whom this is not suitable. In part, the company refers this added benefit to the entire therapeutic indication of osimertinib, although its approach in the dossier is not consistent in this respect (for explanation see Section 2.2).

2.5 Probability and extent of added benefit – summary

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

Table 19: Osimertinib – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Adjuvant treatment of adult patients with stage IB to IIIA[b] NSCLC with exon 19 deletion or exon 21 substitution mutation (L858R) of the EGFR, after complete tumour resection, without prior adjuvant platinum-based chemotherapy	Stage IB: ▪ watchful waiting or ▪ systemic antineoplastic drug treatment of physician's choice stages II and IIIA: ▪ systemic antineoplastic drug treatment of physician's choice	Added benefit not proven
2	Adjuvant treatment of adult patients with stage IB to IIIA[b] NSCLC with exon 19 deletion or exon 21 substitution mutation (L858R) of the EGFR, after complete tumour resection, after prior adjuvant platinum-based chemotherapy or for whom this is not suitable	Watchful waiting	Hint of considerable added benefit[c]

a. Presentation of the respective ACT specified by the G-BA.
b. For the present therapeutic indication, the G-BA assumes that patients in stage $IIIA_3$/$IIIA_4$ and patients with Pancoast tumours were not included.
c. Only patients with an WHO PS of 0 or 1 were included in the ADAURA study. It remains unclear whether the observed effects are transferable to patients with an WHO PS ≥ 2.

ACT: appropriate comparator therapy; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer; WHO PS: World Health Organization Performance Status

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

References for English extract

Please see full dossier assessment for full reference list.

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

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