Osimertinib (NSCLC, adjuvant)

Benefit assessment according to §35a SGB V[1] (expiry of the decision)

EXTRACT

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

Patient and family involvement

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

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Part I: Benefit assessment

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

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DFS	disease-free survival
ECOG PS	Eastern Cooperative Oncology Group Performance Status
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)
MRI	magnetic resonance imaging
NSCLC	non-small cell lung cancer
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
SPC	Summary of Product Characteristics
TKI	tyrosine kinase inhibitor
WHO PS	World Health Organization Performance Status

I 1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) has 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 28 June 2024.

The company had already submitted a dossier for a previous benefit assessment of the drug to be assessed. The dossier was sent to IQWiG on 23 June 2021. In this procedure, by decision of 16 December 2021, the G-BA limited its decision until 01 July 2024. The main reason for the time limit was that further results on overall survival and relapses were expected from the ADAURA study.

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 adult 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 presented in Table 2 result from the ACT specified by the G-BA.

Table 2: Research questions of the benefit assessment of osimertinib

Research question	**Therapeutic indication**	**ACT[a, b]**
1	Adjuvant treatment after complete tumour resection in adult patients with stage IB to IIIA NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations and for whom adjuvant platinum-based chemotherapy is an option	Individualized treatment[c, d] choosing from ▪ watchful waiting (only for patients in stage IB) and ▪ postoperative (adjuvant) systemic chemotherapy choosing from ▫ cisplatin in combination with vinorelbine and ▫ cisplatin in combination with paclitaxel (only for patients in the advanced stage) taking into account the stage of the tumour
2	Adjuvant treatment after complete tumour resection in adult patients with stage IB to IIIA NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations, after previous adjuvant platinum-based chemotherapy or for whom this is not suitable	Watchful waiting

a. Presented is the respective ACT specified by the G-BA.
b. For stages IB to IIIA, the ACT was determined according to UICC 8.
c. The patient population in this therapeutic indication, particularly within stage IIIA, is considered to be very heterogeneous. After R0 resection, patients with stage IIIA1 and IIIA2 mediastinal lymph node involvement have the option of postoperative mediastinal radiotherapy in addition to adjuvant chemotherapy. According to current guidelines, the indication should be checked individually, but not recommended routinely. Due to the unclear data situation, adjuvant chemotherapy followed by radiotherapy is not defined as an ACT.
d. For the implementation of individualized therapy in a study of direct comparison, the investigator is expected to have a selection of several treatment options at disposal to permit an individualized treatment decision taking into account the listed criteria (multicomparator study). A rationale must be provided for the choice and any limitation of treatment options.

ACT: appropriate comparator therapy; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer; UICC: Union for International Cancer Control

The company basically follows the ACT specified by the G-BA, but in general assigns patients in stage IB to research question 2 of the G-BA (referred to by the company as subpopulation 1). The company justified its approach by stating that, according to current guidelines and clinical practice, there is generally no medical indication for chemotherapy in these patients.

The approach of the company is not appropriate. The G-BA subdivides the research questions of the benefit assessment depending on whether adjuvant chemotherapy is suitable for the patients or not. The second question also includes patients who have already received adjuvant chemotherapy. Therefore, the present benefit assessment was conducted in accordance with the research questions listed in Table 2.

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

Research question 1: patients for whom adjuvant platinum-based chemotherapy is suitable

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 for whom adjuvant platinum-based chemotherapy is suitable. There is no hint of an added benefit of osimertinib in comparison with the ACT; an added benefit is therefore not proven.

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

Study pool and study design

The ADAURA study was included in the benefit assessment.

The ADAURA study is a completed, double-blind, randomized multicentre study for the comparison of osimertinib with placebo. The study included adult patients with stage IB-IIIA NSCLC after complete tumour resection whose tumours had EGFR mutations in the form of exon 19 deletion or exon 21 substitution mutation (L858R). Staging at the start of the study was based on the classification of the 7th edition of the UICC. Pretreatment with a platinum-based chemotherapy was allowed. Patients had to be in good general condition (World Health Organization Performance Status [WHO PS] ≤ 1).

A total of 682 patients were included in the ADAURA study and randomly assigned to the treatment arms in a 1:1 ratio. A total of 339 patients were randomized to the intervention arm and 343 patients to the comparator arm. Randomization was stratified according to the disease stage (IB vs. II vs. IIIA, classified in accordance with the 7th edition of the UICC), 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 SPC. Treatment 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 ADAURA study was disease-free survival (DFS). Patient-relevant secondary outcomes were overall survival, outcomes on 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. The proportion of patients without prior adjuvant platinum-based chemotherapy was 40%. However, the company provided no reasons why patients did not receive adjuvant platinum-based chemotherapy. It is therefore unclear whether all patients who have not yet received adjuvant platinum-based chemotherapy are to be assigned to research question 2 (chemotherapy not suitable), or at least in part to research question 1, as adjuvant platinum-based chemotherapy would be (medically) suitable for them, but they have not yet received it or it would not be indicated due to the tumour stage.

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 results. The described uncertainties were taken into account in the assessment of the certainty of conclusions.

Implementation of the ACT

The G-BA specified watchful waiting as the ACT. ADAURA used placebo as comparator therapy. The study was not designed for a comparison with watchful waiting. Despite deviations from the guidelines regarding the recommended time intervals when performing the imaging procedures, the 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.

Shortcomings in the subsequent therapies used

The guideline recommendations for the advanced therapy stage of NSCLC are decisive for the assessment of the administered subsequent therapies after relapse. According to the guidelines, patients with advanced or metastatic NSCLC and the presence of a typical activating EGFR mutation and ECOG PS (Eastern Cooperative Oncology Group Performance Status) 0 to 2 should receive an EGFR-tyrosine kinase inhibitor (TKI) in first-line therapy. Patients with tumours with exon 19 deletion should preferably receive osimertinib in first-line therapy.

At the time of the final DFS analysis, 172 patients in the comparator arm, i.e. 84% of patients with recurrence in this arm, were receiving antineoplastic follow-up therapy. Only 114 (56%) patients with recurrence in the comparator arm received a first systemic subsequent therapy with an approved TKI (afatinib, erlotinib, gefitinib, osimertinib). Among these, the use of osimertinib as a subsequent therapy was low. Thus, only 36 (18%) of the 205 relapsing patients from the comparator arm received osimertinib as their first systemic follow-up therapy. Due to the lack of information on patients with recurrence at this data cut-off, it is unclear how these proportions present themselves at the 3rd data cut-off.

Based on the available data, it is assumed that the subsequent therapies administered in the comparator arm do not adequately reflect the current standard of care after recurrence. The important deficiencies with regard to the follow-up therapies used are taken into account for the outcome of overall survival when assessing the risk of bias and determining the extent.

Data cut-offs

In the present benefit assessment, the results of the 3rd data cut-off from 27 January 2023 (final analysis of overall survival) are used for the outcome "overall survival". The results of the 2nd data cut-off from 11 April 2022 (final analysis on DFS) are used for all other relevant outcomes, as recurrences as well as the outcomes on health-related quality of life and side effects were no longer recorded after the 2nd data cut-off.

Risk of bias

The risk of bias across outcomes is rated as low for the ADAURA study. The risk of bias for the outcomes of recurrences and discontinuation due to AEs was also rated as low.

The risk of bias of the results on the outcome "overall survival" is high due to great uncertainties in the subsequent therapies administered. The risk of bias for the health-related quality of life outcomes, recorded using the SF-36v2, is rated as high due to a strong decrease and large differences in the response to the questionnaires. There is a high risk of bias for the results on the outcomes in the side effects category due to strongly differing observation durations for potentially informative reasons. Although the risk of bias is low for the results on the outcome of discontinuation due to AEs, the certainty of results is reduced for this outcome. Premature treatment discontinuation for reasons other than AEs represents a competing event for the outcome to be recorded, discontinuation due to AEs. This means that, after discontinuation for other reasons, AEs which would have led to treatment discontinuation may have occurred, but that the criterion "discontinuation" can no longer be applied to them. It is impossible to estimate how many AEs are affected by this issue.

Irrespective of the aspects described for the risk of bias, the certainty of conclusions of the study results is reduced. This is due to the uncertainties regarding the allocation of patients from the study population to research question 2. For the outcome "recurrence", the certainty of conclusions is also reduced due to the premature termination of the recording of this outcome. Due to these uncertainties, overall, at most hints, e.g. of an added benefit, can be determined for all outcomes.

Results

Mortality

Overall survival

For the outcome of overall survival, a statistically significant difference was found in favour of pembrolizumab in comparison with placebo. There is a hint of an added benefit of osimertinib in comparison with watchful waiting for the outcome of overall survival.

Morbidity

Recurrence

For the outcome “recurrence” (operationalized as recurrence rate and DFS), a statistically significant difference in favour of osimertinib over placebo was shown. There is a hint of an added benefit of osimertinib in comparison with watchful waiting for this outcome.

Health-related quality of life

Health-related quality of life outcomes were recorded using the SF-36v2.

For the outcome “Physical Component Summary (PCS)”, measured using the SF-36v2, the analysis of the time to first deterioration showed no statistically significant difference between the treatment arms. There is no hint of an added benefit of osimertinib in comparison with watchful waiting; an added benefit is therefore not proven.

The analysis on the time to first deterioration showed no statistically significant difference between the treatment groups for the outcome “Mental Component Summary (MCS)”, recorded using the SF-36v2. There is no hint of an added benefit of osimertinib in comparison with watchful waiting; an added benefit is therefore not proven.

Side effects

SAEs

There was no statistically significant difference between the treatment arms for the outcome of SAEs. There is 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” (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)” and "discontinuation due to AEs". In each case, there was a hint of greater harm from osimertinib in comparison with watchful waiting.

Specific AEs

Skin and subcutaneous tissue disorders (System Organ Class [SOC], AEs)

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

Interstitial Lung Disease (ILD) and pneumonitis (PTs, SAEs) and cardiac events (severe AEs)

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

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

For the specific AEs of gastrointestinal disorders (SOC, AEs, including: diarrhoea [PT, AEs], mouth ulceration [PT, AEs], stomatitis [PT, AEs]), paronychia (PT, AEs), decreased appetite (PT, AEs), gastrointestinal disorders (SOC, severe AEs) and examinations (SOC, severe AEs), there was a statistically significant difference in favour of osimertinib compared to placebo in each case. 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:

Research question 1: patients for whom adjuvant platinum-based chemotherapy is suitable

Because no relevant study is available for answering the present research question, there is no hint of added benefit of osimertinib in comparison with the ACT; an added benefit is therefore not proven.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

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

The overall assessment shows both positive and negative effects with different extents for osimertinib compared with watchful waiting.

On the side of positive effects, there is a hint of a non-quantifiable added benefit for the outcome of overall survival, and a hint of major added benefit for the outcome of recurrence.

On the other hand, there are hints of greater harm with different, in some cases major extent for numerous outcomes in the side effects category.

The negative effects in the side effects do not completely challenge the positive effects in the outcomes of overall survival and recurrences.

In summary, for patients with stage IB-IIIA NSCLC after complete tumour resection with exon 19 deletion or exon 21 substitution mutation (L858R) of the EGFR, after prior adjuvant platinum-based chemotherapy or for whom this is not suitable, there is a hint of considerable added benefit of osimertinib compared with the ACT of watchful waiting.

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

Table 3: Osimertinib – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Adjuvant treatment after complete tumour resection in adult patients with stage IB to IIIA NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations and for whom adjuvant platinum-based chemotherapy is an option	Individualized treatment[b, c] choosing from: ▪ watchful waiting (only for patients in stage IB) and ▪ postoperative (adjuvant) systemic chemotherapy choosing from ▫ cisplatin in combination with vinorelbine and ▫ cisplatin in combination with paclitaxel (only for patients in the advanced stage) taking into account the stage of the tumour	Added benefit not proven
2	Adjuvant treatment after complete tumour resection in adult patients with stage IB to IIIA NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations, after previous adjuvant platinum-based chemotherapy or for whom this is not suitable	Watchful waiting	Hint of considerable added benefit[d]

a. Presented is the respective ACT specified by the G-BA. b. For stages IB to IIIA, these were determined according to UICC 8.
b. The patient population in this therapeutic indication, particularly within stage IIIA, is considered to be very heterogeneous. After R0 resection, patients with stage IIIA1 and IIIA2 mediastinal lymph node involvement have the option of postoperative mediastinal radiotherapy in addition to adjuvant chemotherapy. According to current guidelines, the indication should be checked individually, but not recommended routinely. Due to the unclear data situation, adjuvant chemotherapy followed by radiotherapy is not defined as an ACT.
c. For the implementation of individualized therapy in a study of direct comparison, the investigator is expected to have a selection of several treatment options at disposal to permit an individualized treatment decision taking into account the listed criteria (multicomparator study). A rationale must be provided for the choice and any limitation of treatment options.
d. The ADAURA study included only patients with an WHO PS of 0 or 1. 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; UICC: Union for International Cancer Control

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

I 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 adult 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 presented in Table 4 result from the ACT specified by the G-BA.

Table 4: Research questions of the benefit assessment of osimertinib

Research question	Therapeutic indication	ACT[a, b]
1	Adjuvant treatment after complete tumour resection in adult patients with stage IB to IIIA NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations and for whom adjuvant platinum-based chemotherapy is an option	Individualized treatment[c, d] choosing from ▪ watchful waiting (only for patients in stage IB) ▪ and ▪ postoperative (adjuvant) systemic chemotherapy choosing from ▫ cisplatin in combination with vinorelbine ▫ and ▫ cisplatin in combination with paclitaxel (only for patients in the advanced stage) taking into account the stage of the tumour
2	Adjuvant treatment after complete tumour resection in adult patients with stage IB to IIIA NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations, after previous adjuvant platinum-based chemotherapy or for whom this is not suitable	Watchful waiting

a. Presented is the respective ACT specified by the G-BA.
b. For stages IB to IIIA, the ACT was determined according to UICC 8.
c. The patient population in this therapeutic indication, particularly within stage IIIA, is considered to be very heterogeneous. After R0 resection, patients with stage IIIA1 and IIIA2 mediastinal lymph node involvement have the option of postoperative mediastinal radiotherapy in addition to adjuvant chemotherapy. According to current guidelines, the indication should be checked individually, but not recommended routinely. Due to the unclear data situation, adjuvant chemotherapy followed by radiotherapy is not defined as an ACT.
d. For the implementation of individualized therapy in a study of direct comparison, the investigator is expected to have a selection of several treatment options at disposal to permit an individualized treatment decision taking into account the listed criteria (multicomparator study). A rationale must be provided for the choice and any limitation of treatment options.

ACT: appropriate comparator therapy; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer; UICC: Union for International Cancer Control

The company basically follows the ACT specified by the G-BA, but in general assigns patients in stage IB to research question 2 of the G-BA (referred to by the company as subpopulation 1).

The company justified its approach by stating that, according to the current guidelines [3,4] and clinical practice, there is generally no therapeutic indication for chemotherapy for these patients.

The approach of the company is not appropriate. The G-BA subdivides the research questions of the benefit assessment depending on whether chemotherapy is suitable for the patients or not. The second question also includes patients who have already received adjuvant chemotherapy. The minutes of the consultation also state that research question 1 covers patients for whom adjuvant platinum-based chemotherapy is (medically) suitable [5]. In research question 1, watchful waiting also represents a choice for patients in stage IB in the patient-specific therapy defined by the G-BA as an ACT. Therefore, the present benefit assessment was conducted in accordance with the research questions listed in Table 4.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs are used to derive added benefit. This concurs with the company's inclusion criteria.

I 3 Research question 1: patients for whom adjuvant platinum-based chemotherapy is suitable

I 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 2024)
- bibliographical literature search on osimertinib (last search on 16 April 2024)
- search in trial registries/trial results databases for studies on osimertinib (last search on 16 April 2024)
- search on the G-BA website for osimertinib (last search on 17 April 2024)

To check the completeness of the study pool:

- search in trial registries for studies on osimertinib (last search on 11 July 2024); for search strategies, see I Appendix A of the full dossier assessment

No relevant study was identified from the check. The company likewise did not identify any suitable studies.

I 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 for whom adjuvant platinum-based chemotherapy is suitable. There is no hint of an added benefit of osimertinib in comparison with the ACT; an added benefit is therefore not proven for research question 1.

I 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 for whom adjuvant platinum-based chemotherapy was suitable. An added benefit of osimertinib versus the ACT is therefore not proven for research question 1.

This concurs with the company’s assessment.

I 4 Research question 2: patients with prior adjuvant platinum-based chemotherapy or for whom this therapy is not suitable

I 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 2024)
- bibliographical literature search on osimertinib (last search on 16 April 2024)
- search in trial registries/trial results databases for studies on osimertinib (last search on 16 April 2024)
- search on the G-BA website for osimertinib (last search on 17 April 2024)

To check the completeness of the study pool:

- search in trial registries for studies on osimertinib (last search on 11 July 2024); for search strategies, see I Appendix A of the full dossier assessment

The check did not identify any additional relevant study.

I 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. watchful waiting

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 (yes/no [citation])
D5164C00001 (ADAURA[c])	Yes	Yes	No	Yes [6-8]	Yes [9,10]	Yes [11-17]

a. Study sponsored by the company.
b. Citation of the trial registry entries and, if available, of the reports on study design and/or results listed in the trial registries.
c. In the tables below, the study will be referred to using this acronym.

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

For the benefit assessment of osimertinib, the procedure in the placebo-controlled ADAURA study was rated as sufficient implementation of the ACT (see Section I 4.1.2) and the ADAURA study was included. Accordingly, the study pool is consistent with that selected by the company.

I 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 (multipage table)

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[e] ▪ WHO PS 0 or 1	Osimertinib (n = 339) placebo (N = 343)	Screening: up to 28 days before start of treatment treatment: until recurrence[f], unacceptable toxicity or decision of the patient, at most 3 years observation[g]: 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 10/2015–01/2023 ▪ data cut-offs: ▪ 17 January 2020 (interim analysis DFS)h ▪ 11 April 2022 (final DFS analysis)i ▪ 27 January 2023 (final analysis overall survival)[j]	Primary: disease-free survival secondary: overall survival, morbidity, health-related quality of life, AEs

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

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]

a. Primary outcomes include information without taking into account the relevance for this benefit assessment. Secondary outcomes include only information on relevant available outcomes for this benefit assessment.
b. Patients should primarily have adenocarcinomas.
c. Postoperative classification into stages IB, II or IIIA based on pathological criteria. The study was categorized and analysed according to the TNM classification for lung cancer of the 7th edition of the UICC. In protocol amendment 3 of 1 August 2019 it was supplemented that patients were also classified according to the 8th edition of the UICC.
d. The mutation could occur alone or in combination with other EGFR mutations, including the T790M mutation.
e. 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.
f. Protocol amendment 4 of 2 July 2020 introduced the option for patients to switch to unblinded administration of osimertinib after a relapse and in the presence of a locally advanced (no longer curatively treatable) or metastatic stage in accordance with the approval. According to protocol amendment 5 (25 January 2021), osimertinib treatment had to have been started before the data cut-off for the final analysis of overall survival.
g. Outcome-specific information is provided in Table 8.
h. The primary DFS analysis 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. The patients and the treating physicians remained blinded to the assigned treatment during the further course of the study.
i. According to the originally planned primary analysis, the final DFS analysis was planned to be performed after 247 DFS events in the subpopulation of stage II-IIIA patients.
j. The final analysis of overall survival was planned after approximately 94 deaths in stage II-IIIA patients.

AE: adverse event; AJCC: American Joint Committee on Cancer; DFS: disease-free survival; EGFR: epidermal growth factor receptor; IDMC: Independent Data Monitoring Committee, N: number of randomized patients; RCT: randomized controlled trial; AE: adverse event; UICC: Union for International Cancer Control; WHO PS: World Health Organization Performance Status

Table 7: Characteristics of the intervention – RCT, direct comparison: osimertinib versus 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 (in case of unacceptable toxicity also with CTCAE grade < 3a); resumption at full or reduced dose (40 mg/day) ▪ interruption if symptoms of an interstitial lung disease (ILD) occur with treatment discontinuation after confirmed diagnosis ▪ treatment discontinuation, if the toxicity has not improved to grade ≤ 2[b] after 3 weeks	
	Permitted pretreatment ▪ complete surgical resection of the NSCLC ≥ 4 weeks and ≤ 10 weeksc before randomization ▪ postoperative (adjuvant) platinum-based chemotherapy ≥ 2 weeks and ≤ 10 weeks before randomization **non-permitted pretreatment** ▪ preoperative or postoperative 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. AEs that were independent of the underlying disease and disease-related procedures and which, according to the investigator's assessment, were related to the dosage of the study medication.
b. Improvement to CTCAE grade 1 in case of a QT time prolongation.
c. For adjuvant platinum-based chemotherapy ≤ 26 weeks, where chemotherapy was to start ≤ 8 weeks after surgery.

AE: adverse event; 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 a completed, double-blind, randomized multicentre study for the comparison of osimertinib with placebo. The study included adult patients with stage IB-IIIA NSCLC 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. Staging at the start of the study was based on the classification of the 7th edition of the UICC. Even though the study should be analysed according to the 7th edition of the UICC, all randomized patients should also be classified in accordance with the 8th edition of the UICCC. Pretreatment with a platinum-based chemotherapy was allowed. Patients had to be in good general condition (WHO PS ≤ 1).

A total of 682 patients were included in the ADAURA study and randomly assigned to the treatment arms in a 1:1 ratio. A total of 339 patients were randomized to the intervention arm and 343 patients to the comparator arm. Randomization was stratified according to the disease stage (IB vs. II vs. IIIA, classified in accordance with the 7th edition of the UICC), 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 Summary of Product Characteristics (SPC) [18].

Treatment 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. From protocol amendment 4 of 2 July 2020 patients were allowed to switch to unblinded administration of osimertinib after a relapse and in the presence of an advanced (no longer curatively treatable) or metastatic stage.

The primary outcome of the ADAURA study was DFS. Patient-relevant secondary outcomes were overall survival, outcomes on morbidity, health-related quality of life and AEs.

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

UICC classification

Inclusion of the patients in the ADAURA study was based on the 7th edition of the TNM classification according to UICC. In Module 4A, in order to describe the patient characteristics, the company explains how patients are staged according to the currently valid 8th edition of the UICC classification. According to the staging according to the 8th edition of the UICC classification, there are mainly shifts within stages IIA and IIB (see also Table 9). In the superordinate stages IA, II and IIIA, there are no relevant changes in the proportions of patients. However, pursuant to the new staging according to the 8th edition of the UICC classification, 3.8% of patients in the total population are in a stage that is outside the therapeutic indication to be assessed or for which no information is available. Nevertheless, the company included these patients in the analyses of the ADAURA study presented. Due to the small proportion of patients outside the therapeutic indication to be assessed, this has no consequences for the benefit assessment.

Uncertainties for the subgroup of patients without prior adjuvant chemotherapy

The study included patients with and without prior 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 platinum-based chemotherapy, the study planning recommended that this be

started no later than 8 weeks after surgery. This corresponds to the recommendation of the S3 guideline, according to which adjuvant platinum-based chemotherapy should be started within 60 days of tumour resection. Patients with adjuvant platinum-based chemotherapy could be randomized 2 weeks after the last chemotherapy at the earliest, and 26 weeks after surgery at the latest.

In the ADAURA study, 40% of the patients included had not received any prior adjuvant platinum-based chemotherapy, with the proportion differing depending on the tumour stage (in stage IB, around three quarters of patients and in stages II and IIIA around one quarter had not received any adjuvant chemotherapy [see also Table 9]). In Module 4A, the company states that the decision for or against adjuvant platinum-based chemotherapy after complete tumour resection was made by the investigator before study inclusion. However, the company provided no reasons why patients did not receive adjuvant platinum-based chemotherapy. It is therefore unclear whether all patients who have not yet received adjuvant platinum-based chemotherapy are to be assigned to research question 2 (chemotherapy not suitable), or at least in part to research question 1, as adjuvant platinum-based chemotherapy would be (medically) suitable for them, but they have not yet received it or it would not be indicated due to the tumour stage.

In Module 4A, the company presents subgroup analyses on the characteristic of prior adjuvant platinum-based chemotherapy (yes/no) (see also supplementary information in I Appendix D). Although these analyses provide results for the patient group with prior adjuvant platinum-based chemotherapy for patients who can be safely assigned to research question 2, they cannot address the uncertainties that exist for the patient group without prior adjuvant chemotherapy.

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 results. This approach is supported by the largely consistent results between the subgroups of patients with versus without prior adjuvant chemotherapy and these subgroups compared to the total population (see also I Appendix D). The described uncertainties were taken into account in the assessment of the certainty of conclusions (see Section I 4.2.2).

Exclusion of patients with cerebral metastases

To exclude cerebral metastasis, both a magnetic resonance imaging (MRI) scan and a computed tomography (CT) scan were accepted in the ADAURA study. According to the guideline recommendation, however, a CT scan to exclude brain metastases should only be performed if there is a contraindication to an MRI scan [3]. The sole examination by means of CT is not suitable to exclude patients with cerebral metastases with certainty. It is therefore possible that patients with brain metastases were included in the study who were not covered by the therapeutic indication. The company did not present information on the use of CT and MRI scans of the cranium. The supplement to the autumn 2023 publication [17] shows that the distribution of examinations performed was similar in both treatment arms; overall, 51% of patients were examined by MRI and 49% by CT.

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. However, the study is 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 (primarily contrast-enhanced CT or MRI) 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 and once a year from Year 5.

According to the current S3 Guideline on the Prevention, Diagnosis, Treatment and Follow-up of Lung Cancer [3] no optimal follow-up care concept is yet in place for patients with NSCLC following complete tumour resection. The guideline recommends a quarterly examination in the first 2 years, followed by a semi-annual examination and inclusion in a lung cancer screening program after 5 years. The examination should comprise a dedicated anamnesis, a physical examination and suitable imaging techniques. According to the European guideline for the treatment of early and locally advanced NSCLC, semi-annual and then annual examinations using imaging techniques are recommended in the first 2 years [19,20].

Despite the deviations from the above mentioned guidelines regarding the recommended time intervals when performing the imaging procedures specified, 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

Three data cut-offs are available for the ADAURA study:

- 1st data cut-off from 17 January 2020 (DFS interim analysis)
- 2nd data cut-off from 11 April 2022 (final DFS analysis after 247 DFS events in the subpopulation of patients in stage II-IIIA, according to originally planned primary analysis)
- 3rd data cut-off from 27 January 2023 (pre-specified final analysis of overall survival after approx. 94 events in stage II-IIIA patients)

In Module 4A, the company presented results based on the 2nd data cut-off from 11 April 2022 for the outcome "recurrence" and for the outcomes of health-related quality of life and side effects. For the outcome of overall survival, the company presented results based on the 3rd data cut-off of 27 January 2023. This approach is appropriate because relapses as well as the outcomes on health-related quality of life and side effects were no longer recorded after the second data cut-off (at which time, according to the company, no patient in the intervention arm was still under treatment).

In the present benefit assessment, the results of the 3rd data cut-off from 27 January 2023 were used for the outcome of overall survival in accordance with the company's procedure. For all other relevant outcomes, the results of the 2nd data cut-off of 11 April 2022 were used.

Planned duration of follow-up observation

Table 8 shows the planned duration of patient follow-up observation 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, death 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 side effects category	Up to 28 days after the last dose of the study medication

a. The end of the study was planned when 94 events in the outcome "overall survival" were reached in the patient population with stage II and IIIA disease.
b. Final DFS analysis after 247 DFS events in the subpopulation of patients in stage II-IIIA.

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

In the ADAURA study, only overall survival was recorded until study end.

The observation periods for the other relevant outcomes are shortened to varying degrees. Thus, the observation for the outcome of recurrence ended with the final DFS analysis, planned after 247 recurrence events in the subpopulation of patients in stage II-IIIA. This 2nd data cut-off was performed on 11 April 2022 (after having reached 242 recurrence events). 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). Drawing a reliable conclusion on the total study period or the time to patient death, however, would require surveying these outcomes for the total period, as was done for survival.

Patient characteristics

Table 9 shows the patient characteristics of the included study.

Table 9: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: osimertinib versus 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 (%)		
White	122 (36)	122 (36)
Asian	216 (64)	218 (64)
Other	1 (< 1)	2 (< 1)
Missing	0 (0)	1 (< 1)
UICC 7 stage at diagnosis, n (%)		
IB	107 (32)	108 (31)
IIA	85 (25)	90 (26)
IIB	28 (8)	26 (8)
IIIA	119 (35)	119 (35)
UICC 8 stage at diagnosis, n (%)		
IA2	1 (< 1)	0 (0)
IA3	1 (< 1)	1 (< 1)
IB	101 (30)	98 (29)
IIA	19 (6)	28 (8)
IIB	94 (28)	91 (27)
IIIA	110 (32)	115 (34)
IIIB	11 (3)	7 (2)
IVA	0 (0)	1 (< 1)
Unknown	2 (< 1)	2 (< 1)
Prior adjuvant chemotherapy, n (%)	202[b] (60)	207 (60)
IB[c]	25 (25)	25 (26)
II[c]	78 (69)	83 (70)
IIIA[c]	90 (82)	92 (80)
Unknown or other[c]	9 (3)	7 (2)
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	215 (63)	218 (64)
1	124 (37)	125 (36)

Table 9: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: osimertinib versus placebo (multipage table)

Study characteristic category	**Osimertinib N[a] = 339**	**Placebo N[a] = 343**
EGFR mutation[d, e], n (%)		
Exon 19 deletion	185 (55)	188 (55)
L858R	153 (45)	155 (45)
Missing	1 (< 1)	0 (0)
Type of resection, n (%)		
Lobectomy	328 (97)	322 (94)
Cuff resection	1 (< 1)	3 (< 1)
Bilobectomy	7 (2)	8 (2)
Pneumonectomy	3 (< 1)	10 (3)
Treatment discontinuation, n (%)[f]	114 (34)	204 (59)
Study discontinuation, n (%)[g]	75 (22)	107 (31)

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. In the results, the number of patients with prior adjuvant chemotherapy in the intervention arm is reported as 203 patients.
c. The percentages refer to the number of patients in the respective stage classified in accordance with UICC 8.
d. Patients can have more than one EGRF mutation.
e. Results of testing for mutation-positive EGFR variants confirmed in a central laboratory.
f. Common reasons for treatment discontinuation in the intervention vs. the control arm were (percentages based on randomized patients): recurrence of disease (10% versus 50%), treatment discontinuation due to AEs (13% vs. 3%), patient's decision (10% vs. 3%). 2 patients in the intervention arm never started treatment. At the time of the present data cut-off, 66% vs. 41% of patients had completed treatment as planned.
g. Common reasons for study discontinuation in the intervention arm vs. control arm were death (12% vs. 24%), withdrawal of consent (7% vs. 6%) and other reasons (3% vs. 0%).

AE: adverse event; EGFR: epidermal growth factor receptor; f: female; m: male; n: number of patients in the category; N: number of randomized (or included) patients; RCT: randomized controlled trial; SD: standard deviation; UICC: Union for International Cancer Control; WHO: World Health Organization

Patient characteristics are largely balanced between the two treatment arms of the ADAURA study. The mean age of the patients was 63 and 62 years, most of them were female (68% and 72%) and the majority were of Asian family origin. 63% of patients in the intervention arm and 64% of the patients in the comparator arm had a WHO PS of 0. About one third of the patients included were in stage IB, about two thirds in stages II-IIIA (according to both the 7th and 8th edition of the UICC classification). With 55%, an exon 19 deletion mutation was slightly more common in both study arms compared to an L858R mutation in exon 21 (45%).

Around one quarter of patients had received prior adjuvant chemotherapy in stage IB, and around three quarters (69% to 82%) in stages II and IIIA.

Treatment was discontinued more frequently in the comparator arm (59%) than in the intervention arm (34%). The main reasons for premature treatment discontinuation were AEs in the intervention arm and recurrence of the disease in the comparator arm.

Course of the study

Table 10 shows the mean and median treatment durations of the patients and the median observation periods 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/outcome**	**Osimertinib** **N = 339**	**Placebo** **N = 343**
ADAURA		
Treatment duration [months][a]		
Median [min; max]	35.8 [0; 38]	25.1 [0; 39]
Mean (SD)	28.4 (12.4)	22.7 (13.2)
Observation period [months]		
Overall survival [b]		
Median [min; max]	61.5 [ND]	61.5 [ND]
Morbidity		
Recurrence[c]		
Median [min; max]	47.2 [ND]	49.7 [ND]
Health-related quality of life[d]		
Median [min; max]	35.8 [0.0; 38.8]	22.1 [0.0; 37.7]
Side effects[a, e]		
Median [min; max]	36.8 [0.2; 38.9]	26.1 [1.0; 40.0]

a. The data refer to patients who received at least one dose of the study medication (osimertinib: N = 337, placebo: N = 343).
b. Calculated on the basis of the observed time to the censoring of all non-deceased patients.
c. Calculated on the basis of the observed time to censoring of all patients without event.
d. Defined as the time from randomization to the earliest date of the last assessment of the SF-36v2 questionnaire, death or date of data cut-off. If no survey was carried out at the start of the study or during its course, censoring took place on Day 1.
e. Defined as the period from the first dose of study medication to the earliest of the following time points: data cut-off, 28 days after discontinuation of study treatment, date of initiation of subsequent anticancer therapy, or date of death.

max: maximum; min: minimum; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation

In the AUDAURA study, the median treatment duration (approx. 36 months) was about 11 months longer in the intervention arm than in the comparator arm (about 25 months).

At the time of the final analysis of overall survival (3rd data cut-off of 27 January 2023), the median observation period for the outcome of overall survival was identical between the two treatment arms (61.5 months).

The median observation duration for the outcome of recurrence specified by the company is 47.2 months in the intervention arm and 49.7 months in the comparator arm. Compared to the outcome of overall survival, the observation period is shortened, as the observation for this outcome ended at the time of the 2nd data cut-off (11 April 2022) (see also Section I 4.2.1).

Due to the different median treatment durations between the treatment arms, the median observation periods for the outcomes of the health-related quality of life and side effect categories differ accordingly, as these outcomes should only be observed up to the last dose of the study medication (or up to 28 days afterwards for AEs). Compared to overall survival, the observation period for these outcomes is systematically shortened with approx. 36 months in the intervention arm and approx. 24 months in the comparator arm.

Table 11 shows the subsequent therapies patients received after discontinuing the study medication.

Table 11: Information on subsequent antineoplastic therapiesa (≥ 1% of the patients in ≥ 1 treatment arm) in the entire study population – RCT, direct comparison: osimertinib vs. placebo (ADAURA study) (multipage table)

Study drug class drug	Patients with subsequent therapy, n (%)	
	osimertinib N = 339	placebo N = 343
ADAURA		
Patients with recurrence[b]		
Data cut-off: 27 January 2023	ND	ND
Data cut-off: 11 April 2022	93 (27.4)	205 (59.8)
Patients with at least one subsequent therapy (data cut-off: 27 January 2023)	76 (22.4[c])	184 (53.6[c])
First subsequent therapy		
EGFR tyrosine kinase inhibitors	53 (15.6[c])	154 (44.9[c])
Afatinib	3 (0.9[c])	25 (7.3[c])
Erlotinib	6 (1.8[c])	21 (6.1[c])
Gefitinib	11 (3.2[c])	53 (15.5[c])
Icotinib hydrochloride	2 (0.6[c])	13 (3.8[c])
Osimertinib	31 (9.1[c])	50 (14.6[c])
Folic acid analogues	10 (2.9[c])	8 (2.3[c])
Pemetrexed	10 (2.9[c])	8 (2.3[c])
Radiotherapy	28 (8.3[c])	47 (13.7[c])
Platinum-containing compounds	17 (5.0[c])	18 (5.2[c])
Carboplatin	13 (3.8[c])	10 (2.9[c])
Cisplatin	3 (0.9[c])	7 (2.0[c])
Taxanes	5 (1.5[c])	7 (2.0[c])
Paclitaxel	4 (1.2[c])	5 (1.5[c])
VEGF/VEGFR inhibitors	5 (1.5[c])	7 (2.0[c])
Bevacizumab	5 (1.5[c])	7 (2.0[c])
Any subsequent therapy[d]		
EGFR tyrosine kinase inhibitors	58 (17.1[c])	162 (47.2[c])
Afatinib	7 (2.1[c])	30 (8.7[c])
Erlotinib	6 (1.8[c])	24 (7.0[c])
Gefitinib	13 (3.8[c])	55 (16.0[c])
Icotinib hydrochloride	2 (0.6[c])	15 (4.4[c])
Osimertinib	31 (9.1[c])	79 (23.0[c])
Folic acid analogues	13 (3.8[c])	27 (7.9[c])
Pemetrexed	13 (3.8[c])	27 (7.9[c])
Radiotherapy	30 (8.9[c])	53 (15.5[c])
Other protein kinase inhibitors	1 (0.3[c])	4 (1.2[c])
PD-1/PDL-1 inhibitors	4 (1.2[c])	6 (1.7[c])

Table 11: Information on subsequent antineoplastic therapiesa (≥ 1% of the patients in ≥ 1 treatment arm) in the entire study population – RCT, direct comparison: osimertinib vs. placebo (ADAURA study) (multipage table)

Study drug class drug	Patients with subsequent therapy, n (%)	
	osimertinib N = 339	placebo N = 343
Platinum-containing compounds	20 (5.9[c])	43 (12.5[c])
Carboplatin	16 (4.7[c])	31 (9.0[c])
Cisplatin	3 (0.9[c])	10 (2.9[c])
Pyrimidine analogues	4 (1.2[c])	9 (2.6[c])
Gemcitabine	1 (0.3[c])	4 (1.2[c])
Gimeracil; oteracil; tegafur	2 (0.6[c])	4 (1.2[c])
Taxanes	8 (2.4[c])	20 (5.8[c])
Docetaxel	3 (0.9[c])	9 (2.6[c])
Paclitaxel	6 (1.8[c])	13 (3.8[c])
VEGF/VEGFR inhibitors	5 (1.5[c])	18 (5.2[c])
Bevacizumab	5 (1.5[c])	17 (5.0[c])
Vinca alkaloids and analogues	1 (0.3[c])	6 (1.7[c])
Vinorelbine	1 (0.3[c])	5 (1.5[c])

a. Subsequent antineoplastic therapies from the time of the last dose of study medication until study discontinuation; without antineoplastic therapies with start date after the end of the study.
b. The data refer to recurrences without taking deaths into account. Recurrences were no longer recorded after the final DFS data cut of 11 April 2022.
c. Institute's calculation; related to the number of randomized patients.
d. Includes all subsequent therapies up to the time of the data cut-off of 27 January 2023.

EGFR: epidermal growth factor receptor; n: number of patients with subsequent therapy; N: number of analysed patients; PD-1: programmed cell death receptor 1; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; VEGF: vascular endothelial growth factor; VEGFR: vascular endothelial growth factor receptor

In the ADAURA study, subsequent therapies were allowed without restrictions after disease recurrence. From protocol amendment 4 of 2 July 2020 patients were allowed to switch to unblinded administration of osimertinib after a relapse and in the presence of an advanced (no longer curatively treatable) or metastatic stage.

At the time of the final analysis of the outcome “overall survival” (27 January 2023), 22% of patients in the intervention arm and 54% of patients in the comparator arm had received at least 1 subsequent antineoplastic therapy.

In both treatment arms, an EGFR-TKI was the most common first subsequent therapy, in the intervention arm primarily osimertinib (9.1%), in the comparator arm gefitinib (15.5%) and osimertinib (14.6%).

To assess whether the antineoplastic follow-up therapies documented in the ADAURA study suggest adequate follow-up treatment of the patients, information on the proportion of patients with recurrence is indispensable. These are not available at the time of the final analysis of the outcome “overall survival”, as recurrences were only recorded up to the final DFS data cut-off (see also Section I 4.2.1). The documented subsequent therapies for the final DFS analysis (data cut-off of 11 April 2022) are therefore also used for the assessment (see I Appendix E).

The guideline recommendations for the advanced therapy stage of NSCLC are decisive for the assessment of the administered subsequent therapies after relapse. According to the S3 guideline on the Prevention, Diagnosis, Treatment and Follow-up of Lung Cancer [3] and the guideline of the German Society for Haematology and Medical Oncology [4], patients with advanced or metastatic NSCLC and the presence of a typical activating EGFR mutation and ECOG PS 0 to 2 were to receive an EGFR-TKI in first-line therapy. Patients with tumours with exon 19 deletion should preferably receive osimertinib in the first-line therapy [3].

In the ADAURA study, 211 patients in the comparator arm had a recurrence event at the time of the final DFS analysis, with 6 patients having died without a previous recurrence. This means that 205 (60%) patients in the comparator arm had a potential need for a subsequent therapy. The company did not provide any precise information on the tumour stages of the patients after recurrence. Within the comparator arm, 107 patients had a distant recurrence, a further 20 patients had a locoregional recurrence and a distant recurrence (see also Table 15). It should also be noted that according to current guidelines, molecular pathological examinations should be initiated for patients in advanced stages of NSCLC for all therapeutically relevant molecular changes (according to the current status prior to first-line therapy, EGFR mutations in exons 18-21, BRAF V600 mutations, ALK fusions, ROS1 fusions, RET fusions and NTRK1-3 fusions as a minimum requirement) [3].

The study documents of the ADAURA study show that re-biopsy after recurrence was only performed on an optional basis. Related results are lacking.

At the time of the final DFS analysis, 172 patients in the comparator arm, i.e. 84% of patients with recurrence in this arm, were receiving subsequent antineoplastic therapy (radiotherapy and subsequent systemic therapies). Information on subsequent oncological surgeries is not available. Only 114 (56%) patients with recurrence in the comparator arm received a first subsequent systemic therapy with an approved TKI (afatinib, erlotinib, gefitinib, osimertinib) (see I Appendix E). Among these, the use of osimertinib as a subsequent therapy was low. Thus, only 36 (18%) of the 205 relapsing patients from the comparator arm received osimertinib as their first systemic follow-up therapy. The company provided no further information on why the proportion of patients with subsequent osimertinib therapy was so

small, although according to the protocol amendment of 2 July 2020, treatment with osimertinib was to be made available to all patients with recurrence and in the presence of an advanced (no longer curatively treatable) or metastatic stage. Due to the lack of data because of survey shortcomings on patients with recurrence at this data cut-off, it is unclear how these proportions present themselves at the 3rd data cut-off.

According to the guideline recommendations cited above, it can be assumed that subsequent therapy using a TKI would have been indicated for almost all patients with recurrence in the comparator arm, especially for patients with distant recurrence. Subsequent therapy with osimertinib would be preferable for patients with tumours with exon 19 deletion, who make up 55% of the total population. Based on the available data, it is assumed that the subsequent therapies administered in the comparator arm do not adequately reflect the current standard of care after recurrence.

Overall, the described deficiencies in the subsequent therapies administered in the ADAURA study are considered to be serious. The important deficiencies with regard to the subsequent therapies used are taken into account for the outcome of overall survival when assessing the risk of bias and determining the extent (see I 4.2.2 and Section I 4.2.1).

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	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes is rated as low for the ADAURA study.

Transferability of the study results to the German health care context

The company stated that due to the sufficient comparability of selected patient characteristics of the study population with patients in Germany, the observed clinical effects of the ADAURA study also occur in the German target population in health care under everyday conditions.

Regarding the distribution of disease stages according to the 8th edition of the UICC classification, the company describes that this corresponds to the German healthcare context

with around one third per stage (IB vs. II vs. IIIA). The company also points out that the proportion of patients who received adjuvant platinum-based chemotherapy per stage is similar to the rate observed in everyday health care in Germany. The company referred to a retrospective observational study that showed that the proportion of German patients in stage IB-IIIA with adjuvant systemic therapy after tumour resection was 51.9%. 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.

The company did not provide any further information on the transferability of the study results to the German health care context.

I 4.2 Results on added benefit

I 4.2.1 Outcomes included

The following patient-relevant outcomes were to be included 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 (SOC, AEs)
  - ILD and pneumonitis (company's Preferred Term [PT] collection, SAEs)
  - Cardiac events (SMQ heart failure and SMQ cardiomyopathy, severe AEs)
  - Other specific AEs, if any

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

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

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

Study	Outcomes									
	Overall survival	Recurrences[a]	Health-related quality of life (SF-36v2)	SAEs[b]	Severe AEs[b, c]	Discontinuation due to AEs[b]	Skin and subcutaneous tissue disorders (SOC, AEs)	ILD and pneumonitis[d] (PT, SAEs)	Cardiac events[e] (severe AEs[c])	Other specific Aesc,[c, f]
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. According to the study protocol, progression-related events were not recorded as AEs.
c. Severe AEs are operationalized as CTCAE grade ≥ 3.
d. 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).
e. Operationalized using the SMQ "heart failure" and the SMQ "cardiomyopathy".
f. The following events (MedDRA coding) were considered: "gastrointestinal disorders" (SOC, AEs), "diarrhoea" (PT, AEs), "mouth ulceration" (PT, AEs), "stomatitis" (PT, AEs), paronychia" (PT, AEs), "reduced appetite" (PT, AEs) "gastrointestinal disorders" (SOC, severe AEs), examinations (SOC, severe 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

Overall survival

The overall survival of patients in the present therapeutic indication is composed of a phase of DFS until recurrence and the subsequent stage of advanced and/or metastatic NSCLC.

An observed effect in the outcome "overall survival" is not only influenced by the initial study treatment, but also by the subsequent antineoplastic therapies used after disease progression or recurrence [21,22]. In order for an observed effect in the outcome of overall survival to be interpreted meaningfully, adequate guideline-compliant subsequent treatment of patients after progression or recurrence of the disease is therefore necessary, especially in the adjuvant therapy situation.

As described in Section I 4.1.2, the ADAURA study is considered to have serious shortcomings with regard to the subsequent therapies used in the comparator arm. Due to the size of the effect for the outcome of overall survival, it is nevertheless considered to be interpretable to

a limited extent, even if the extent is considered as non-quantifiable due to the uncertainties described.

Recurrence

Operationalization

The outcome of recurrence is a composite outcome and comprises the components death (without previous recurrence), local or regional recurrence and distant recurrence.

For the outcome of recurrence, the results of the operationalizations are presented as the proportion of patients with recurrence ("recurrence rate") and as DFS. The patients considered in the present stage of the disease are a group of patients who were treated with a curative treatment approach. The occurrence of a recurrence in this situation means that the attempt at cure by the curative treatment approach was not successful.

Shortened follow-up

At the time point of the data cut-off of 11 April 2022 used for the benefit assessment, the median observation period for the outcome "recurrence" was about 47 months in the intervention arm and 50 months in the comparator arm (see Table 10). Due to the planned premature termination of the recording of the outcome "recurrence", namely at the time of the final DFS analysis, which was planned after 247 events in the stage II-IIIA subpopulation (2nd data cut-off of 11 April 2022), the observation period does not cover the entire course of the study. This results in an uncertainty as to the extent to which the effects observed for this outcome can be transferred to the entire study period.

Particularly for the intervention arm, in which the median duration of treatment with osimertinib is 36 months, the question arises as to what extent relapses are actually prevented even after discontinuation of treatment and not only occur with a delay. The Kaplan-Meier curve for DFS in the intervention arm (see Figure 2) shows that there is no plateau after 36 months (which would suggest that no or at least hardly any further events occur after this period), but that patients still under observation in the intervention arm actually experience slightly more events. However, the information in the study report shows that the majority of patients in the intervention arm were followed up for at least 1 year after the planned end of treatment for the outcome of recurrence. Against this background, the observed effect is considered interpretable in the present data constellation. Overall, the described uncertainty due to the lack of further observation is taken into account in the certainty of conclusions of the outcome, so that for this reason alone at most a hint, e.g. of an added benefit, can be derived.

Health-related quality of life

SF-36v2 – PCS and MCS

Health-related quality of life outcomes were recorded using the SF-36v2. In Module 4A, the company presents analyses on the time to first deterioration of the PCS and the MCS. It was not necessary to confirm the deterioration at the subsequent visit. A decrease by ≥ 9.423 (PCS) or ≥ 9.618 points (MCS) was considered a deterioration. This corresponds to a deterioration by ≥ 15% of the scale range (standardized scale with a minimum of approx. 7 [PCS] or 6 [MCS] and a maximum of approx. 70 in each case). As explained in the IQWiG *General Methods* [1], for a response criterion to reflect with sufficient certainty a patient-noticeable change, it should correspond to at least 15% of the scale range of an instrument if prespecified (and exactly 15% of the scale range in post-hoc analyses). Accordingly, the above-mentioned responder analyses can be used to derive the added benefit for the outcomes of the SF-36v2.

I 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	Recurrences[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[d] (PT, SAEs)[c]	Cardiac events[d] (severe AEs[b])	Further specific AEs[b, e]
ADAURA	L	H[f]	L	H[g]	H[h]	H[h]	L[i]	H[h]	H[h]	H[h]	H[h]

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. Severe AEs are 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), paronychia" (PT, AEs), "reduced appetite" (PT, AEs) "gastrointestinal disorders" (SOC, severe AEs), examinations (SOC, severe AEs).
f. Due to uncertainties in the use of adequate subsequent therapies.
g. Strongly decreasing and strongly differential responses and censoring of patients with event if at least 2 study visits were previously missing.
h. Large difference in observation period between the treatment arms; potentially informative censorings.
i. 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 Health Survey Version 2; SMQ: standardized MedDRA query; SOC: System Organ Class

The risk of bias was rated as high for the results of the outcome "overall survival". Large uncertainties in the subsequent therapies administered in the comparator arm (see subsequent therapies in Section I 4.1.2) are decisive for the high risk of bias in the results.

The outcome-specific risk of bias of the outcome "recurrence" was rated as low. The list of important protocol deviations shows striking differences for the category "lack of adherence to the examination plan with effects on the recording of recurrences" (31.0% in the intervention arm vs. 21.9% in the comparator arm). The study report describes that these were visits that were postponed for a few days on the one hand and completely missed visits

on the other. The latter was the main reason for the described protocol deviations during the COVID-19 pandemic (11.2% vs. 5.8%). Nevertheless, a low risk of bias is assumed for the outcome "recurrence", as the available information does not suggest any relevant bias. In addition, the company states that patients who showed a recurrence of the disease or died after at least 2 missing study visits were censored at the time of the last assessment before the missing study visits. The available data show that such censoring was only performed for 2 (0.6%) patients in the intervention arm and 5 (1.5%) patients in the control arm.

For the results of health-related quality of life and for the outcomes in the side effects category (with the exception of the outcome discontinuation due to AEs, see below), the risk of bias is rated as high. For the results on health-related quality of life, this is due to clearly decreasing and differential questionnaire return rates. Moreover, in the intervention arm, several patients with an analysable visit or death after at least 2 missed visits were censored. This applied to approx. 6% of the patients in the intervention arm and approx. 10% of the patients in the comparator arm. For each of the results on side effects, the reason for the high risk of bias is the incomplete observation for potentially informative reasons. 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 (36.8 vs. 26.1 months). The observation period was thus determined by the reasons for treatment discontinuation (mainly by the recurrence of the disease or AEs), which clearly differed between the treatment arms. A total of 34% of the patients in the intervention arm and 59% in the comparator arm discontinued treatment. In 10% or 50% of patients who discontinued treatment, the reason for the discontinuation was a recurrence, and in 13% or 3% an AE.

Although the risk of bias is low for the outcome of discontinuation due to AEs, the certainty of results for this outcome is reduced. Premature treatment discontinuation for reasons other than AEs represents a competing event for the outcome to be recorded, discontinuation due to AEs. This means that, after discontinuation for other reasons, AEs which would have led to treatment discontinuation may have occurred, but that the criterion "discontinuation" can no longer be applied to them. It is impossible to estimate how many AEs are affected by this issue.

Summary assessment of the certainty of conclusions

Irrespective of the aspects described for the risk of bias, the certainty of conclusions of the study results is reduced. This is due to the uncertainties described in Section I 4.1.2. regarding the allocation of patients from the study population to research question 2. For the outcome "recurrence", the certainty of conclusions is also reduced due to the premature termination of the recording of this outcome described in Section I 4.1.2.

Due to these uncertainties, overall, at most hints, e.g. of an added benefit, can be determined for all outcomes.

I 4.2.3 Results

Table 15 summarizes the results on the comparison of osimertinib with placebo in patients with stage IB-IIIA NSCLC after complete tumour resection with exon 19 deletion or exon 21 substitution mutation (L858R) of the EGFR, after prior adjuvant platinum-based chemotherapy or for whom this therapy is not suitable. Where necessary, IQWiG calculations are provided to supplement the data from the company's dossier.

The Kaplan-Meier curves for the time-to-event analyses of the outcomes in the ADAURA study are shown in I Appendix B. The results on common AEs, SAEs, severe AEs and discontinuations due to AEs can be found in I 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 (data cut-off) 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 (27 January 2023)					
Overall survival	339	NA 42 (12.4)	343	NA 82 (23.9)	0.49 [0.34; 0.70]; < 0.001[a]
Morbidity (11 April 2022)					
Recurrence					
Recurrence rate[b]	339	94 (27.7)	343	211 (61.5)	RR: 0.45 [0.37; 0.54]; < 0.001[c]
Local/regional	339	42 (12.4)	343	78 (22.7)	
Distant recurrence	339	45 (13.3)	343	107 (31.2)	
CNS recurrences	339	20 (5.9)	343	38 (11.1)	
Local/regional and distant recurrence	339	6 (1.8)	343	20 (5.8)	
Death	339	1 (0.3)	343	6 (1.7)	
Disease-free survival[d]	339	65.8 [61.7; NC] 94 (27.7)	343	28.1 [22.1; 35.0] 211 (61.5)	0.27 [0.21; 0.34]; < 0.001[a]
Health-related quality of life (11 April 2022)					
SF-36v2 – time to first deterioration					
Physical Component Summary (PCS)[e]	339	NA 57 (16.8)	343	NA 53 (15.5)	0.99 [0.68;1.44]; 0.944[f]
Mental Component Summary (MCS)[g]	339	NA 98 (28.9)	343	NA 89 (25.9)	1.01 [0.76;1.35]; 0.928[f]

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

Study outcome category (data cut-off) 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
Side effects (11 April 2022)					
AEs (supplementary information)	337	0.4 [0.3; 0.5] 330 (97.9)	343	1.0 [0.7; 1.0] 309 (90.1)	–
SAEs	337	NA 68 (20.2)	343	NA 47 (13.7)	1.28 [0.88;1.84]; 0.193[f]
Severe AEs[h]	337	NA 79 (23.4)	343	NA 48 (14.0)	1.55 [1.09;2.19]; 0.014[f]
Discontinuation due to AEs	337	NA 43 (12.8)	343	NA 9 (2.6)	3.44 [1.99; 5.93]; < 0.001[f]
Skin and subcutaneous tissue disorders (SOC, AEs)	337	2.7 [1.8; 4.8] 249 (73.9)	343	NA 130 (37.9)	2.71 [2.21; 3.33]; < 0.001[f]
ILD and pneumonitis[i] (PT, SAEs)	337	NA 2 (0.6)	343	NA 0 (0.0)	ND; 0.198[f]
Cardiac events[i] severe AEs[h])	337	NA 4 (1.2)	343	NA 1 (0.3)	2.98 [0.51;17.30]; 0.224[f]
Gastrointestinal disorders (SOC, AEs) including:	337	1.9 [1.1; 2.5] 243 (72.1)	343	25.0 [19.2; NC] 157 (45.8)	2.23 [1.82; 2.72]; < 0.001[f]
Diarrhoea (PT, AEs)	337	NA 159 (47.2)	343	NA 70 (20.4)	2.64 [2.04; 3.43]; < 0.001[f]
Mouth ulceration (PT, AEs)	337	NA 39 (11.6)	343	NA 10 (2.9)	3.35 [1.91; 5.87]; < 0.001[f]
Stomatitis (PT, AEs)	337	NA 59 (17.5)	343	NA 15 (4.4)	3.55 [2.25; 5.60]; < 0.001[f]
Paronychia (PT, AEs)	337	NA 92 (27.3)	343	NA 5 (1.5)	6.84 [4.59; 10.19]; < 0.001[f]
Decreased appetite (PT, AEs)	337	NA 48 (14.2)	343	NA 13 (3.8)	3.26 [1.97; 5.39]; < 0.001[f]
Gastrointestinal disorders (SOC, severe AEs[h])	337	NA 21 (6.2)	343	NA 3 (0.9)	4.27 [1.91; 9.54]; < 0.001[f]
Investigations (SOC, severe AEs[h])	337	NA 14 (4.2)	343	NA 4 (1.2)	2.62 [1.03;6.64]; 0.042[f]

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

Study	Osimertinib		Placebo		Osimertinib vs. placebo
outcome category (data cut-off) outcome	N	Median time to event in months [95% CI] patients with event n (%)	N	Median time to event in months [95% CI] patients with event n (%)	HR [95% CI]; p-value

a. 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 family origin (Asian versus non-Asian).
b. Proportion of patients, individual components are presented in the lines below.
c. Effect estimate, 95% CI and p-value using the log-binomial model.
d. Operationalized as time from the day of randomization to the first occurrence of an event, for individual components see recurrence rate.
e. A (PCS) score decrease by ≥ 9.4 points from baseline is considered a clinically relevant deterioration (range of the standardized scale: approx. 7 to approx. 70).
f. Effect estimation and 95% CI by means of U and V statistics from unstratified log-rank test; p-value via unstratified log-rank test.
g. A (MCS) score decrease by ≥ 9.6 points from baseline is considered a clinically relevant deterioration (range of the standardized scale: approx. 6 to approx. 70).
h. Operationalized as CTCAE grade ≥ 3.
i. PT collection of the company. In the intervention arm, interstitial lung disease occurred in 1 patient and pneumonitis occurred in 1 patient.
j. Operationalized using the SMQ “heart failure” and the SMQ “cardiomyopathy”.

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; ND: no data; 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

As described in Section I 4.1.2, there are uncertainties that affect the certainty of results. On the basis of the available information, no more than hints, e.g. of an added benefit, can be determined for all outcomes.

Mortality

Overall survival

For the outcome of overall survival, a statistically significant difference was found in favour of pembrolizumab in comparison with placebo. There is a hint of an added benefit of osimertinib in comparison with watchful waiting for the outcome of overall survival.

Morbidity

Recurrence

For the outcome “recurrence” (operationalized as recurrence rate and DFS), a statistically significant difference in favour of osimertinib over placebo was shown. There is a hint of an added benefit of osimertinib in comparison with watchful waiting for this outcome.

Health-related quality of life

SF-36v2 – PCS and MCS

Health-related quality of life outcomes were recorded using the SF-36v2.

For the outcome “PCS”, measured using the SF-36v2, the analysis of the time to first deterioration showed no statistically significant difference between the treatment arms. There is no hint of an added benefit of osimertinib in comparison with watchful waiting; an added benefit is therefore not proven.

The analysis on the time to first deterioration showed no statistically significant difference between the treatment groups for the outcome “MCS”, recorded using the SF-36v2. There is no hint of an added benefit of osimertinib in comparison with watchful waiting; an added benefit is therefore not proven.

Side effects

SAEs

There was no statistically significant difference between the treatment arms for the outcome of SAEs. There is 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” (CTCAE grade ≥ 3)” and "discontinuation due to AEs". In each case, there was a hint of greater harm from osimertinib in comparison with watchful waiting.

Specific AEs

Skin and subcutaneous tissue disorders (SOC, AEs)

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

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

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

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

For the specific AEs of gastrointestinal disorders (SOC, AEs, including: diarrhoea [PT, AEs], mouth ulceration [PT, AEs], stomatitis [PT, AEs]), paronychia (PT, AEs), decreased appetite (PT, AEs), gastrointestinal disorders (SOC, severe AEs) and examinations (SOC, severe AEs), there was a statistically significant difference in favour of osimertinib compared to placebo in each case. In each case, this resulted in a hint of greater harm from osimertinib versus watchful waiting.

I 4.2.4 Subgroups and other effect modifiers

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

- Age (< 65 years versus ≥ 65 years)
- sex (male versus female)
- Disease stage (IB vs. II vs. IIIA, according to UICC 8)

The subgroup characteristics of age and sex selected in the present benefit assessment had been defined a priori, but only for the outcome of DFS. The subgroup characteristic "disease stage" was also predefined, but only according to UICC Edition 7. In the dossier, the company presented subgroup analyses on all outcomes of the present benefit assessment.

Interaction tests are performed when at least 10 patients per subgroup are included in the analysis. For binary data, there must also 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 presented only if there is a statistically significant and relevant effect in at least one subgroup. Subgroup results where the extent does not differ between subgroups are not presented.

Applying the methods described above, there were no effect modifications for the characteristics considered.

I 4.3 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *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.

I 4.3.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section I 4.2 (see Table 16).

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

It cannot be inferred from the dossier for the outcomes of recurrence and discontinuation due to AEs whether they are serious/severe or non-serious/non-severe. Reasoning is provided for the classification of these outcomes.

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

The outcome of discontinuation due to AEs was allocated to the outcome category of non-serious/non-severe side effects because no information was available on the severity of the AEs which led to discontinuation of therapy.

Table 16: 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]
Outcomes with observation over the entire study duration		
Mortality		
Overall survival	NA vs. NA HR: 0.49 [0.34; 0.70]; p < 0.001 probability: “hint”	Outcome category: mortality added benefit, extent: "non-quantifiable"[c]
Outcomes with shortened observation period		
Morbidity		
Recurrence Recurrence rate	Proportion of events (%): 27.7 vs. 61.5 RR: 0.45 [0.37; 0.54]; p < 0.001 probability: “hint”	Outcome category: serious/severe symptoms/late complications CI_u < 0.75, risk ≥ 5% added benefit, extent: “major”
Disease-free survival	65.8 vs. 28.1 HR: 0.27 [0.21; 0.34]; p < 0.001 probability: “hint”	
Health-related quality of life		
SF-36v2		
Physical Component Summary (PCS)	NA vs. NA HR: 0.99 [0.68; 1.44]; p = 0.944	Lesser added benefit/added benefit not proven
Mental Component Summary (MCS)	NA vs. NA HR: 1.01 [0.76; 1.35]; p = 0.928	Lesser added benefit/added benefit not proven
Side effects		
SAEs	NA vs. NA HR: 1.28 [0.88; 1.84]; p = 0.193	Greater/lesser harm not proven
Severe AEs	NA vs. NA HR: 1.55 [1.09; 2.19] HR: 0.65 [0.46; 0.92][d]; p = 0.014 probability: “hint”	Outcome category: serious/severe side effects 0.90 ≤ CI_u < 1.00 greater harm, extent: “minor”

Table 16: 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: 3.44 [1.99; 5.93] HR: 0.29 [0.17; 0.50][d]; 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 (SOC, AEs)	2.7 vs. NA HR: 2.71 [2.21; 3.33] HR: 0.37 [0.30; 0.45][d]; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects CI_u < 0.80 greater harm; extent: "considerable"
ILD and pneumonitis (PT, SAEs)	NA vs. NA HR: ND; p = 0.198	greater/lesser harm not proven
Cardiac events (severe AEs)	NA vs. NA HR: 2.98 [0.51; 17.30]; p = 0.224	greater/lesser harm not proven
Gastrointestinal disorders (SOC, AEs) including:	1.9 vs. 25.0 HR: 2.23 [1.82; 2.72] HR: 0.45 [0.37; 0.55][d]; p < 0.001 probability: "hint"	outcome category: non-serious/non-severe side effects CI_u < 0.80 greater harm; extent: "considerable"
Diarrhoea (PT, AEs)	NA vs. NA HR: 2.64 [2.04; 3.43] HR: 0.38 [0.29; 0.49][d]; p < 0.001 probability: "hint"	
Mouth ulceration (PT, AEs)	NA vs. NA HR: 3.35 [1.91; 5.87] HR: 0.30 [0.17; 0.52][d]; p < 0.001 probability: "hint"	
Stomatitis (PT, AEs)	NA vs. NA HR: 3.55 [2.25; 5.60] HR: 0.28 [0.18; 0.44][d]; p < 0.001 probability: "hint"	

Table 16: 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 (PT, AEs)	NA vs. NA HR: 6.84 [4.59; 10.19] HR: 0.15 [0.09; 0.22][d]; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm; extent: "considerable"
Decreased appetite (PT, AEs)	NA vs. NA HR: 3.26 [1.97; 5.39] HR: 0.31 [0.19; 0.51][d]; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm; extent: "considerable"
Gastrointestinal disorders (SOC, severe AEs)	NA vs. NA HR: 4.27 [1.91; 9.54] HR: 0.23 [0.10; 0.52][d]; p < 0.001 probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% greater harm, extent: "major"
Investigations (SOC, severe AEs)	NA vs. NA HR: 2.62 [1.03; 6.64] HR: 0.38 [0.15; 0.97][d]; p = 0.042 probability: "hint"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ greater harm, extent: "minor"

a. Probability provided if there is a statistically significant and relevant effect.
b. The effect size is estimated depending on the outcome category and with different limits based on the upper limit of the confidence interval (CI_u).
c. See Section I 4.1.2 and Section I 4.2.2 for a rationale.
d. Institute's calculation; reversed direction of effect to enable the use of limits to derive the extent of 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; ND: no data; PCS: Physical Component Summary; PT: Preferred Term; RR: relative risk; SAE: serious adverse event; SF-36v2: Short Form (36) – version 2 Health Survey; SOC: System Organ Class

I 4.3.2 Overall conclusion on added benefit

Table 17 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 17: Positive and negative effects from the assessment of osimertinib in comparison with watchful waiting

Positive effects	Negative effects
Outcomes with observation over the entire study duration	
Mortality overall survival: hint of added benefit – extent: “non-quantifiable”	–
Outcomes with shortened observation period	
Morbidity serious/severe symptoms/late complications recurrence: hint of an added 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" ▪ examinations (severe AEs): hint of greater harm – extent: “minor”
–	Non-serious/non-severe side effects ▪ discontinuation due to AEs: hint of greater harm – extent: “considerable” ▪ diseases of the skin and subcutaneous tissue (AEs): hint of greater harm – extent: considerable ▪ gastrointestinal disorders (AEs, including: diarrhoea [AEs], mouth ulceration [AEs], stomatitis [AEs]): Hint of greater harm - extent: “considerable” ▪ paronychia (AEs): hint of greater harm - extent: “considerable” ▪ decreased appetite (AEs): hint of greater harm – extent: "considerable"
AE: adverse event; SAE: serious adverse event	

The overall assessment shows both positive and negative effects with different extents for osimertinib compared with watchful waiting.

On the side of positive effects, there is a hint of a non-quantifiable added benefit for the outcome of overall survival, and a hint of major added benefit for the outcome of recurrence.

On the other hand, there are hints of greater harm with different, in some cases major extent for numerous outcomes in the side effects category.

The negative effects in the side effects do not completely challenge the positive effects in the outcomes of overall survival and recurrences.

In summary, for patients with stage IB-IIIA NSCLC after complete tumour resection with exon 19 deletion or exon 21 substitution mutation (L858R) of the EGFR, after prior adjuvant platinum-based chemotherapy or for whom this is not suitable, there is a hint of considerable added benefit of osimertinib compared with the ACT of watchful waiting.

The assessment described above deviates from that by the company, which derived an indication of major added benefit of osimertinib in comparison with the ACT for these patients.

I 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 18.

Table 18: Osimertinib – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Adjuvant treatment after complete tumour resection in adult patients with stage IB to IIIA NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations and for whom adjuvant platinum-based chemotherapy is an option	Individualized treatment[b, c] choosing from: ▪ watchful waiting (only for patients in stage IB) ▪ and ▪ postoperative (adjuvant) systemic chemotherapy choosing from ▫ cisplatin in combination with vinorelbine ▫ and ▫ cisplatin in combination with paclitaxel (only for patients in the advanced stage) ▫ taking into account the stage of the tumour	Added benefit not proven
2	Adjuvant treatment after complete tumour resection in adult patients with stage IB to IIIA NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations, after previous adjuvant platinum-based chemotherapy or for whom this is not suitable	Watchful waiting	Hint of considerable added benefit[d]

a. Presented is the respective ACT specified by the G-BA. b. For stages IB to IIIA, these were determined according to UICC 8.
b. The patient population in this therapeutic indication, particularly within stage IIIA, is considered to be very heterogeneous. After R0 resection, patients with stage IIIA1 and IIIA2 mediastinal lymph node involvement have the option of postoperative mediastinal radiotherapy in addition to adjuvant chemotherapy. According to current guidelines, the indication should be checked individually, but not recommended routinely. Due to the unclear data situation, adjuvant chemotherapy with subsequent radiotherapy is not defined as an ACT.
c. For the implementation of individualized therapy in a study of direct comparison, the investigator is expected to have a selection of several treatment options at disposal to permit an individualized treatment decision taking into account the listed criteria (multicomparator study). A rationale must be provided for the choice and any limitation of treatment options.
d. The ADAURA study included only patients with an WHO PS of 0 or 1. 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; UICC: Union for International Cancer Control

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

I 6 References

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

Please see full dossier assessment for full reference list.

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