Osimertinib
(locally advanced, unresectable NSCLC)

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

EXTRACT

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Medical and scientific advice

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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
BICR	blinded independent central review
BSC	best supportive care
EGFR	epidermal growth factor receptor
FDG-PET	18F-fluorodeoxyglucose positron emission tomography
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IASLC	International Association for the Study of Lung Cancer
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
NSCLC	non-small cell lung cancer
PD-L1	programmed cell death ligand 1
PFS	progression-free survival
RCT	randomized controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
WHO PS	World Health Organization Performance Status

I 1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug osimertinib. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 13 January 2025.

Research question

The aim of this report is to assess the added benefit of osimertinib compared with the appropriate comparator therapy (ACT) in patients with locally advanced, unresectable non-small cell lung cancer (NSCLC) whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations and whose disease has not progressed during or following platinum-based chemoradiation therapy.

The research questions presented in Table 2 were defined in accordance with the ACT specified by the G-BA.

Table 2: Research questions for the benefit assessment of osimertinib

Research question	Therapeutic indication	ACT[a]
1	Adults with locally advanced, unresectable NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations, whose disease has not progressed during or following platinum-based chemoradiation therapy, and whose tumours express PD-L1 in ≥ 1% of tumour cells	Durvalumab
2	Adults with locally advanced, unresectable NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations, whose disease has not progressed during or following platinum-based chemoradiation therapy, and whose tumours express PD-L1 in < 1% of tumour cells	BSC[b]

a. Presented is the respective ACT specified by the G-BA.
b. BSC refers to the therapy that provides the patient with the best possible, individually optimized supportive treatment to alleviate symptoms and improve quality of life.

ACT: appropriate comparator therapy; BSC: best supportive care; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer; PD-L1: programmed cell death ligand 1

The company followed the specified ACT for both research questions.

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

Results

Consistent with the findings of the company, a review of the completeness of the study pool identified no relevant studies for the direct comparison of osimertinib with the ACT for either of the research questions.

Due to a lack of suitable data, in Module 4 A of its dossier the company presented the results of the pivotal RCT LAURA (D5160C0048), but did not use these results to derive an added benefit.

In agreement with the company's assessment, the LAURA study is not suitable for deriving conclusions on the added benefit of osimertinib in comparison with the ACT for either of the 2 research questions. The reasons for this are provided below.

Evidence presented by the company

LAURA

The LAURA study is an ongoing, double-blind RCT comparing osimertinib with placebo.

Included in the study were adult patients with locally advanced, unresectable NSCLC (stage III) of predominantly non-squamous pathology (according to version 8 of the International Association for the Study of Lung Cancer [IASLC] Staging Manual in Thoracic Oncology) whose disease had not progressed during or following definitive platinum-based chemoradiation therapy (concurrent or sequential) completed ≤ 6 weeks prior to randomization. Only patients with a proven mutation of the EGFR gene in the form of an exon 19 deletion or an exon 21 (L858R) substitution mutation, either alone or in combination with other EGFR mutations, were included.

The LAURA study included a total of 216 patients, randomized in a 2:1 ratio to treatment with either osimertinib (N = 143) or placebo (N = 73).

Treatment was continued until objective radiological disease progression according to Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 was confirmed by a blinded independent central review (BICR) prior to analysis of the primary outcome of progression-free survival (PFS), or until other discontinuation criteria were met, such as toxicity or patient's decision. As of protocol amendment 1 dated 28 February 2020, following disease progression patients were able to continue or initiate treatment with osimertinib (open-label) in the intervention and comparator arms respectively, as long as no other anticancer therapy was administered after discontinuation of the study medication (with the exception of palliative radiotherapy). Open-label treatment with osimertinib could be continued until, based on the physician's assessment, there was no longer any clinical benefit for the patient.

The primary outcome of the LAURA study is PFS assessed by BICR. Further outcomes were recorded in the categories of mortality, morbidity, health-related quality of life, and side effects.

LAURA study presented by the company is unsuitable for the benefit assessment

No recording of PD-L1 status in the LAURA study

Two research questions, which differ with regards to the programmed cell death ligand 1 (PD-L1) status of the patients, were defined in accordance with the ACT specified by the G-BA. However, the PD-L1 status was not recorded as part of the LAURA study. Consequently, it is not possible to assign the study population to the research questions to be evaluated (patients whose tumours express PD-L1 in either ≥ 1% or < 1% of tumour cells).

Implementation of the ACT

The G-BA defined durvalumab as the ACT for patients whose tumours express PD-L1 in ≥ 1% of tumour cells (research question 1). The placebo-controlled LAURA study does not allow a comparison of osimertinib with durvalumab. Thus, in Module 4 A, regardless of the unknown PD-L1 status of the study population, no suitable data were provided for the benefit assessment of osimertinib in comparison with the ACT for research question 1.

The G-BA defined best supportive care (BSC) as the ACT for patients whose tumours express PD-L1 in < 1% of tumour cells (research question 2). Irrespective of the unknown PD-L1 status of the study population, on the basis of the available documentation it remains unclear whether the ACT in terms of BSC was adequately implemented in the LAURA study.

Results on added benefit

Since no suitable data are available for either research question of the benefit assessment, there is no hint of an added benefit of osimertinib in comparison with the ACT in either case; an added benefit is therefore not proven.

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

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

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

Table 3: Osimertinib – probability and extent of added benefit

Research question	**Therapeutic indication**	**ACT**[a]	**Probability and extent of added benefit**
1	Adults with locally advanced, unresectable NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations, whose disease has not progressed during or following platinum-based chemoradiation therapy, and whose tumours express PD-L1 in ≥ 1% of tumour cells	Durvalumab	Added benefit not proven
2	Adults with locally advanced, unresectable NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations, whose disease has not progressed during or following platinum-based chemoradiation therapy, and whose tumours express PD-L1 in < 1% of tumour cells	BSC[b]	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. BSC refers to the therapy that provides the patient with the best possible, individually optimized supportive treatment to alleviate symptoms and improve quality of life.

ACT: appropriate comparator therapy; BSC: best supportive care; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer; PD-L1: programmed cell death ligand 1

The G-BA decides on the added benefit.

I 2 Research question

The aim of this report is to assess the added benefit of osimertinib compared with the ACT in patients with locally advanced, unresectable NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations and whose disease has not progressed during or following platinum-based chemoradiation therapy.

The research questions presented in Table 4 were defined in accordance with the ACT specified by the G-BA.

Table 4: Research questions for the benefit assessment of osimertinib

Research question	Therapeutic indication	ACT[a]
1	Adults with locally advanced, unresectable NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations, whose disease has not progressed during or following platinum-based chemoradiation therapy, and whose tumours express PD-L1 in ≥ 1% of tumour cells	Durvalumab
2	Adults with locally advanced, unresectable NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations, whose disease has not progressed during or following platinum-based chemoradiation therapy, and whose tumours express PD-L1 in < 1% of tumour cells	BSC[b]

a. Presented is the respective ACT specified by the G-BA.
b. BSC refers to the therapy that provides the patient with the best possible, individually optimized supportive treatment to alleviate symptoms and improve quality of life.

ACT: appropriate comparator therapy; BSC: best supportive care; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer; PD-L1: programmed cell death ligand 1

For the present assessment, the following descriptions were used for the patient populations of the 2 research questions:

- Research question 1: Patients whose tumours express PD-L1 in ≥ 1% of tumour cells
- Research question 2: Patients whose tumours express PD-L1 in < 1% of tumour cells

The company followed the specified ACT for both research questions.

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

I 3 Information retrieval and study pool

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

Sources used by the company in the dossier:

- Study list on osimertinib (status: 19 November 2024)
- Bibliographical literature search on osimertinib (last search on 18 November 2024)
- Search of trial registries/trial results databases for studies on osimertinib (last search on 25 November 2024)
- Search on the G-BA website for osimertinib (last search on 26 November 2024)

To check the completeness of the study pool:

- Search of trial registries for studies on osimertinib (last search on 23 January 2025); for search strategies, see I Appendix A of the full dossier assessment

Consistent with the findings of the company, the review of the completeness of the study pool identified no relevant studies for the direct comparison of osimertinib with the ACT for either of the research questions.

Due to a lack of suitable data, in Module 4 A of its dossier the company presented the results of the RCT LAURA (D5160C0048) [3], on which the approval was based, but did not use these results to derive an added benefit.

In agreement with the company's assessment, the LAURA study is not suitable for deriving conclusions on the added benefit of osimertinib in comparison with the ACT for either of the 2 research questions. The reasons for this are provided below.

Evidence presented by the company

LAURA

The LAURA study is an ongoing, double-blind RCT comparing osimertinib with placebo.

Included in the study were adult patients with locally advanced, unresectable NSCLC (stage III) of predominantly non-squamous pathology (according to version 8 of the IASLC Staging Manual in Thoracic Oncology) whose disease had not progressed during or following definitive platinum-based chemoradiation therapy (concurrent or sequential) completed ≤ 6 weeks prior to randomization. The inclusion criteria specified that NSCLC must be histologically documented. Staging using imaging techniques such as whole-body 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) in clinical stages IB to IIIB, which is recommended by the S3 guideline on lung cancer [4], was not mandatory for inclusion in the study. Only

patients with a proven mutation of the EGFR gene in the form of an exon 19 deletion or an exon 21 (L858R) substitution mutation, either alone or in combination with other EGFR mutations, were included. For patients with an existing local EGFR mutation-positive test result, EGFR mutations were detected using a tissue-based CDx test (cobas EGFR Mutation Test v2 or Foundation One CDx Test); for patients without a local EGFR mutation test result, detection was via centralized testing (cobas EGFR Mutation Test v2). In addition, patients were to be in good general health, corresponding to a World Health Organization Performance Status (WHO PS) of 0 or 1, and have a life expectancy of > 12 weeks.The LAURA study included a total of 216 patients, randomized in a 2:1 ratio to treatment with either osimertinib (N = 143) or placebo (N = 73). Randomization was stratified according to the following characteristics: prior chemoradiation therapy strategy (concurrent versus sequential); disease stage prior to chemoradiation therapy (IIIA versus IIIB/IIIC); and China cohort (patients enrolled at a Chinese site and self-identifying as being of Chinese family origin versus patients enrolled at a non-Chinese site or self-identifying as being of non-Chinese family origin).Treatment with osimertinib in the intervention arm was largely in compliance with the Summary of Product Characteristics (SPC) [5]. Other anticancer therapies, investigational products and radiotherapies were not permitted during study treatment, and strong CYP3A4 inducers were to be avoided. Apart from this, any concomitant medication that was considered necessary for the treatment of a patient was permitted in both study arms (for further restrictions on concomitant therapy, see also the section *Implementation of the ACT*).

Treatment was continued until objective radiological disease progression according to RECIST 1.1 criteria was confirmed by a BICR prior to analysis of the primary outcome of PFS, or until other discontinuation criteria were met, such as toxicity or patient's decision. After analysing the primary outcome PFS, disease progression was assessed by the investigator. As of protocol amendment 1 dated 28 February 2020, following disease progression patients were able to continue or initiate treatment with osimertinib (open-label) in the intervention and comparator arms respectively, as long as no other anticancer therapy was administered after discontinuation of the study medication (with the exception of palliative radiotherapy). Open-label treatment with osimertinib could be continued until, based on the physician's assessment, there was no longer any clinical benefit for the patient.

The primary outcome of the LAURA study is PFS assessed by BICR. Further outcomes were recorded in the categories of mortality, morbidity, health-related quality of life, and side effects.

LAURA study presented by the company is unsuitable for the benefit assessment

No recording of PD-L1 status in the LAURA study

Two research questions, which differ with regards to the PD-L1 status of the patients, were defined in accordance with the ACT specified by the G-BA. However, the PD-L1 status was not

recorded as part of the LAURA study. Consequently, it is not possible to assign the study population to the research questions to be evaluated (patients whose tumours express PD-L1 in either ≥ 1% or < 1% of tumour cells). Determination of PD-L1 status in this therapeutic indication is recommended in the guidelines as part of primary diagnostics [4], and described as indispensable for further therapy stratification [6]. It is therefore a standard diagnostic procedure. The company did not address the possibility of a retrospective follow-up assessment of the PD-L1 status (which was used, for example, for the benefit assessment procedure of the same company on durvalumab [7]) in the context of the present benefit assessment on osimertinib.

Implementation of the ACT

Research question 1: Patients whose tumours express PD-L1 in ≥ 1% of tumour cells

The G-BA specified durvalumab as the ACT for patients whose tumours express PD-L1 in ≥ 1% of tumour cells. The placebo-controlled LAURA study does not allow a comparison of osimertinib with durvalumab. Thus, in Module 4 A, regardless of the unknown PD-L1 status of the study population, no suitable data were provided for the benefit assessment of osimertinib in comparison with the ACT for research question 1.

Research question 2: Patients whose tumours express PD-L1 in < 1% of tumour cells

The G-BA specified BSC as the ACT for patients whose tumours express PD-L1 in < 1% of tumour cells. BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.

In the placebo-controlled LAURA study, any concomitant medication deemed necessary for the treatment of patients was permitted in accordance with the study protocol. However, if medically possible, regular use of concomitant medication (with the exception of strong CYP3A4 inducers) should be maintained throughout the entire study period. In addition, the use of radiotherapy, among other things, was not permitted in the context of the study treatment. The extent to which this results in restrictions in terms of the best possible, individually optimized treatment for each patient is questionable. Overall, regardless of the unknown PD-L1 status of the study population, it remains unclear on the basis of the available documentation whether the ACT in terms of BSC was adequately implemented in the LAURA study.

I 4 Results on added benefit

For the assessment of the added benefit of osimertinib compared with the ACT in patients with locally advanced, unresectable NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations and whose disease has not progressed during or following platinum-based chemoradiation therapy, no suitable data are available. There is no hint of an added benefit of osimertinib in comparison with the ACT for either research question; an added benefit is therefore not proven for either of them.

I 5 Probability and extent of added benefit

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

Table 5: Osimertinib – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Adults with locally advanced, unresectable NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations, whose disease has not progressed during or following platinum-based chemoradiation therapy, and whose tumours express PD-L1 in ≥ 1% of tumour cells	Durvalumab	Added benefit not proven
2	Adults with locally advanced, unresectable NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations, whose disease has not progressed during or following platinum-based chemoradiation therapy, and whose tumours express PD-L1 in < 1% of tumour cells	BSC[b]	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. BSC refers to the therapy that provides the patient with the best possible, individually optimized supportive treatment to alleviate symptoms and improve quality of life.

ACT: appropriate comparator therapy; BSC: best supportive care; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer; PD-L1: programmed cell death ligand 1

The assessment described above concurs with that by the company.

The G-BA decides on the added benefit.

I 6 References for English extract

Please see full dossier assessment for full reference list.

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

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