# Osimertinib (NSCLC, combination with pemetrexed and platinum-based chemotherapy)

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

**EXTRACT**

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

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# Part I: Benefit assessment

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# I List of abbreviations

| Abbreviation | Meaning |
|---|---|
| ACT | appropriate comparator therapy |
| AE | adverse event |
| CI | confidence interval |
| CNS | central nervous system |
| CTCAE | Common Terminology Criteria for Adverse Events |
| EORTC QLQ-C30 | European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 |
| EORTC QLQ-LC13 | European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer 13 |
| EGFR | epidermal growth factor receptor |
| EMA | European Medicines Agency |
| G-BA | Gemeinsamer Bundesausschuss (Federal Joint Committee) |
| IASLC | International Association for the Study of Lung Cancer |
| ILD | interstitial lung disease |
| IQWiG | Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care) |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MMRM | mixed-effects model with repeated measures |
| NSAID | non-steroidal anti-inflammatory drug |
| NSCLC | non-small cell lung cancer |
| PD-1 | programmed cell death protein 1 |
| PD-L1 | programmed cell death ligand 1 |
| PFS | progression-free survival |
| PGIS | Patient Global Impression of Severity |
| PT | Preferred Term |
| RCT | randomized controlled trial |
| SAE | serious adverse event |
| SGB | Sozialgesetzbuch (Social Code Book) |
| SMD | statistical mean difference |
| SMQ | standardized MedDRA query |
| SOC | System Organ Class |
| SPC | Summary of Product Characteristics |
| TKI | tyrosine kinase inhibitor |

| Abbreviation | Meaning |
|---|---|
| VAS | visual analogue scale |
| VEGF | vascular endothelial growth factor |
| 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) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug osimertinib (in combination with pemetrexed and platinum-based chemotherapy). 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 30 July 2024.

### Research question

The aim of the present report is to assess the added benefit of osimertinib in combination with pemetrexed and platinum-based chemotherapy (hereinafter referred to as osimertinib + pemetrexed + platinum-based chemotherapy) in comparison with the appropriate comparator therapy (ACT) for the first-line treatment of adult patients with advanced non-small cell lung cancer (NSCLC) whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations.

The research question presented in Table 2 results from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of osimertinib in combination with pemetrexed and platinum-based chemotherapy

| **Therapeutic indication** | **ACT**[a, b, c] |
|---|---|
| Adult patients with advanced NSCLC whose tumours have epidermal growth factor receptor exon 19 deletions or exon 21 (L858R) substitution mutations; first-line treatment | ▪ Afatinib (only for patients with the activating EGFR mutation deletion in exon 19)<br>or<br>▪ Osimertinib |
| a. Presented is the ACT specified by the G-BA.<br>b. In terms of therapeutic indication, it is assumed that neither definitive radiochemotherapy nor definitive local therapy are indicated. In addition, it is assumed that molecularly stratified therapy (directed against ALK, BRAF, Exon 20, KRAS G12C, METex14, RET, or ROS1) is not an option for the patients at the time of treatment with osimertinib.<br>c. The ACT specified here comprises several alternative treatment options. However, individual treatment options only represent a comparator therapy for those members of the patient population who have the patient and disease characteristics shown in brackets. The alternative treatment options are only to be regarded as equally appropriate in the area in which the patient populations have the same characteristics.<br>ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; BRAF: rapidly accelerated fibrosarcoma isoform B; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; KRAS: Kirsten Rat Sarcoma Viral Oncogene Homologue; METex14: Exon 14 of the mesenchymal epithelial transition factor gene; NSCLC: non-small cell lung cancer; RET: Rearranged during Transfection; ROS1: C-ros Oncogene 1 | |

The company did not follow the G-BA's specification of the ACT, as in the company's view only osimertinib represents the ACT. It justified this with the preferred use of osimertinib over

afatinib also in patients with activating EGFR mutation deletion in exon 19. However, this is of no consequence for the benefit assessment, as osimertinib is also included in the G-BA's ACT and the company presented evidence in relation to this option. The present benefit assessment was conducted in comparison with the ACT specified by the G-BA.

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.

**Study pool and study design**

The FLAURA-2 study was included for the benefit assessment.

The FLAURA-2 study is an ongoing, open-label RCT comparing osimertinib + pemetrexed + platinum-based chemotherapy vs. osimertinib. It included adult patients with newly diagnosed locally advanced or metastatic stage IIIB to IV NSCLC or recurrent non-squamous NSCLC whose tumours have proven EGFR exon 19 deletions or exon 21 (L858R) substitution mutations. Furthermore, patients had to be non-amenable to curative surgery or radiotherapy, and they were to be in good general health in accordance with Eastern Cooperative Oncology Group – Performance Status (WHO PS) 0 or 1. Patients were not allowed to have received any prior therapy for the advanced disease. Adjuvant or neoadjuvant therapies were allowed if they had been completed at least 12 months before recurrence occurred. Pretreatment with an EGFR tyrosine kinase inhibitor (TKI) was generally ruled out.

Overall, 557 patients were enrolled and randomly allocated in a 1:1 ratio to either treatment with osimertinib + pemetrexed + platinum-based chemotherapy (N = 279) or to osimertinib (N = 278). The choice of platinum component (cisplatin or carboplatin) was made by the investigator before randomization.

Treatment with osimertinib + pemetrexed + platinum-based chemotherapy in the intervention arm and osimertinib in the comparator arm was largely carried out according to the Summary of Product Characteristics (SPC). Contrary to the recommendation in the SPC, continuation of study treatment with osimertinib was also possible after disease progression if, in the opinion of the investigator, there was still a clinical benefit and no discontinuation criteria were present.

The primary outcome of the FLAURA-2 study is progression-free survival (PFS). Further outcomes were recorded in the categories of mortality, morbidity, health-related quality of life, and side effects.

***Data cut-offs***

The present benefit assessment uses the results from the prespecified 2nd data cut-off on 3 April 2023 for all outcomes.

***Subsequent therapies***

In the FLAURA-2 study, subsequent antineoplastic therapies were permitted without restrictions in both study arms. Based on the available data, it can be assumed that the subsequent therapies after disease progression in the FLAURA-2 study were not adequate for a relevant proportion of patients:

- Continued treatment with osimertinib beyond disease progression was given to approximately 85% of patients with disease progression and is not recommended by either the SPC or the guidelines. Such continued treatment potentially leads to a delay in starting subsequent therapy in line with the guidelines.
- Information is missing as to why approximately 40% of patients with progression did not receive subsequent therapy. According to the guideline, patients without treatable genetic alterations should be offered chemoimmunotherapy following treatment with osimertinib in the same way as first-line treatment in patients without mutations. This is particularly relevant for patients in the comparator arm, who – unlike those in the intervention arm – have not yet received chemotherapy. It is highly likely that patients who did not receive subsequent therapy were instead given continued treatment with osimertinib, which is not recommended (see above).
- A relevant proportion of patients received treatment with an EGFR-TKI as part of a subsequent therapy, which is not in line with the recommendations of the guideline. A re-biopsy to test for resistance mutations (which is recommended according to the guideline for further treatment selection) was also only optional in the FLAURA-2 study. The study documents do not show how many patients underwent this procedure.

The described deficiencies in the subsequent therapies used are taken into account in the assessment of the outcome-specific risk of bias.

**Risk of bias**

The risk of bias across outcomes was rated as low for the FLAURA-2 study. There is a high risk of bias in the results for the outcome "overall survival" due to the deficiencies in the subsequent therapies used. For the results on morbidity and health-related quality of life, the risk of bias is rated as high, primarily due to the lack of blinding with subjective recording of outcomes and strongly decreasing questionnaire return rates in the course of the study, which differed between the treatment arms.

The risk of bias is high for the results on the outcome “discontinuation due to adverse events” (AEs), as the unblinded study design results in a subjective decision to discontinue treatment. Due to incomplete observations for potentially informative reasons, the risk of bias for the results on the outcomes “serious adverse events” (SAEs) and “severe AEs” was rated as high. Furthermore, for the non-serious/non-severe AEs, the risk of bias is additionally increased due to lack of blinding in the presence of subjective outcome recording.

On the basis of the available information, no more than hints, e.g. of an added benefit, can be determined for all outcomes.

**Results**

***Mortality***

*Overall survival*

There was no statistically significant difference between the treatment arms for the outcome "overall survival". This results in no hint of an added benefit of osimertinib + pemetrexed + platinum-based chemotherapy in comparison with osimertinib; an added benefit is therefore not proven.

***Morbidity***

*Symptoms (surveyed with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; [EORTC QLQ-C30])*

On the basis of the mean difference, the analyses showed no statistically significant difference between the treatment arms for each of the following outcomes: pain, dyspnoea, insomnia, and diarrhoea. This results in no hint of an added benefit of osimertinib + pemetrexed + platinum-based chemotherapy in comparison with osimertinib in each case; an added benefit is therefore not proven.

On the basis of the mean difference, the analyses showed a statistically significant difference between the treatment arms for each of the following outcomes: fatigue, nausea and vomiting, appetite loss, and constipation. The SMD is analysed to examine the relevance of the results. The 95% CI of the SMD is not fully outside the irrelevance range of −0.2 to 0.2. It can therefore not be inferred that the effects are relevant. This results in no hint of an added benefit of osimertinib + pemetrexed + platinum-based chemotherapy in comparison with osimertinib in each case; an added benefit is therefore not proven.

*Symptoms (surveyed with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer 13; [EORTC QLQ-LC13])*

On the basis of the mean difference, the analyses showed a statistically significant difference between treatment arms for the outcome of cough. The SMD is analysed to examine the relevance of the results. The 95% CI of the SMD is not fully outside the irrelevance range of

−0.2 to 0.2. It can therefore not be inferred that the effects are relevant. However, there is an effect modification by the characteristic of CNS metastases at baseline. For patients with CNS metastases at baseline, there is a hint of an added benefit from osimertinib + pemetrexed + platinum-based chemotherapy in comparison with osimertinib. For patients without CNS metastases at baseline, there is no hint of an added benefit of osimertinib + pemetrexed + platinum-based chemotherapy in comparison with osimertinib; an added benefit is therefore not proven.

On the basis of the mean difference, the analyses showed no statistically significant difference between the treatment arms for each of the following outcomes: haemoptysis, dysphagia, pain (arm/shoulder), pain (chest), dyspnoea, peripheral neuropathy, and alopecia. This results in no hint of an added benefit of osimertinib + pemetrexed + platinum-based chemotherapy in comparison with osimertinib in each case; an added benefit is therefore not proven.

On the basis of the mean difference, the analyses showed a statistically significant difference between treatment arms for the outcome of pain (other body parts). However, there was an effect modification by the characteristic of age. For patients < 65 years, there is a hint of lesser benefit from osimertinib + pemetrexed + platinum-based chemotherapy in comparison with osimertinib. For patients ≥ 65 years, there is no hint of an added benefit of osimertinib + pemetrexed + platinum-based chemotherapy in comparison with osimertinib; an added benefit is therefore not proven.

On the basis of the mean difference, the analyses showed a statistically significant difference between treatment arms for the outcome of sore mouth. The statistical mean difference (SMD) was analysed to examine the relevance of the results. The 95% CI of the SMD is not fully outside the irrelevance range of −0.2 to 0.2. It can therefore not be inferred that the effects are relevant. This results in no hint of an added benefit of osimertinib + pemetrexed + platinum-based chemotherapy in comparison with osimertinib; an added benefit is therefore not proven.

*Symptoms surveyed using Patient Global Impression of Severity (PGIS)*

On the basis of mean difference, the analysis showed no statistically significant difference between treatment groups for the outcome of symptoms (recorded using the PGIS). This results in no hint of an added benefit of osimertinib + pemetrexed + platinum-based chemotherapy in comparison with osimertinib; an added benefit is therefore not proven.

*Health status (surveyed using the EQ-5D visual analogue scale [VAS])*

On the basis of the mean difference, no statistically significant difference between treatment arms was found for the outcome “health status” (recorded using the EQ-5D VAS). This results in no hint of an added benefit of osimertinib + pemetrexed + platinum-based chemotherapy in comparison with osimertinib; an added benefit is therefore not proven.

*Health-related quality of life (recorded using EORTC QLQ-C30)*

On the basis of the mean difference, the analyses showed a statistically significant difference between the treatment arms for each of the following outcomes: physical functioning, social functioning, and global health status. The SMD is analysed to examine the relevance of the results. In each case, the 95% CI of the SMD is not fully outside the irrelevance range of −0.2 to 0.2. It can therefore not be inferred that the effects are relevant. This results in no hint of an added benefit of osimertinib + pemetrexed + platinum-based chemotherapy in comparison with osimertinib in each case; an added benefit is therefore not proven.

On the basis of the mean difference, the analyses showed no statistically significant difference between the treatment arms for each of the following outcomes: role functioning and emotional functioning. This results in no hint of an added benefit of osimertinib + pemetrexed + platinum-based chemotherapy in comparison with osimertinib in each case; an added benefit is therefore not proven.

***Side effects***

*SAEs*

For the outcome of SAEs, a statistically significant difference was found to the disadvantage of osimertinib + pemetrexed + platinum-based chemotherapy in comparison with osimertinib. However, there was an effect modification by the characteristic of age. For patients < 65 years, there is a hint of greater harm from osimertinib + pemetrexed + platinum-based chemotherapy in comparison with osimertinib. For patients ≥ 65 years, there is no hint of greater or lesser harm from osimertinib + pemetrexed + platinum-based chemotherapy in comparison with osimertinib; greater or lesser harm is therefore not proven.

*Severe AEs (CTCAE grade ≥ 3)*

For the outcome of severe AEs (CTCAE grade ≥ 3), a statistically significant difference was found to the disadvantage of osimertinib + pemetrexed + platinum-based chemotherapy in comparison with osimertinib. There is a hint of greater harm from osimertinib + pemetrexed + platinum-based chemotherapy in comparison with osimertinib.

*Discontinuation due to AEs*

For the outcome of discontinuation due to AEs, a statistically significant difference was found to the disadvantage of osimertinib + pemetrexed + platinum-based chemotherapy in comparison with osimertinib. There is a hint of greater harm from osimertinib + pemetrexed + platinum-based chemotherapy in comparison with osimertinib.

*PRO-CTCAE*

There are no suitable data in the dossier for the outcome of Patient-Reported Outcomes of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). There is no hint of greater

or lesser harm from osimertinib + pemetrexed + platinum-based chemotherapy in comparison with osimertinib; greater or lesser harm is therefore not proven.

*Skin and subcutaneous tissue disorders (AEs) and interstitial lung disease [ILD] and pneumonitis (severe AEs)*

For the outcomes of skin and subcutaneous tissue disorders (AEs) and ILD and pneumonitis (severe AEs), no statistically significant difference between the treatment arms is shown. There is no hint of greater or lesser harm from osimertinib + pemetrexed + platinum-based chemotherapy in comparison with osimertinib in each case; greater or lesser harm is therefore not proven.

*Cardiac effects (severe AEs)*

For the outcome of cardiac effects (severe AEs) a statistically significant difference was found to the disadvantage of osimertinib + pemetrexed + platinum-based chemotherapy in comparison with osimertinib. There is a hint of greater harm from osimertinib + pemetrexed + platinum-based chemotherapy in comparison with osimertinib.

*Other specific AEs*

For the outcomes of decreased appetite (AEs), general disorders and administration site conditions (severe AEs), blood and lymphatic system disorders (SAEs), gastrointestinal disorders (severe AEs) and investigations (SAEs), there is a statistically significant difference to the disadvantage of osimertinib + pemetrexed + platinum-based chemotherapy in comparison with osimertinib. In each case, there is a hint of greater harm from osimertinib + pemetrexed + platinum-based chemotherapy in comparison with osimertinib.

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

On the basis of the results presented, the probability and extent of added benefit of the drug combination osimertinib + pemetrexed + platinum-based chemotherapy in comparison with osimertinib are assessed as follows:

Overall, one favourable and several unfavourable effects of osimertinib + pemetrexed + platinum-based chemotherapy were found in comparison with 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].

For the outcome “cough” in patients with CNS metastases at baseline, there is a hint of a minor added benefit from osimertinib + pemetrexed + platinum-based chemotherapy in comparison with osimertinib.

On the other hand, for the outcome “pain (other body parts)” in patients < 65 years, there is a hint of lesser benefit from osimertinib + pemetrexed + platinum-based chemotherapy in comparison with osimertinib. Furthermore, there are hints of greater harm with different, in some cases major extent for numerous outcomes in the side effects category.

The negative effects, some of which are of major extent, clearly outweigh the positive effects, which are of minor extent. In summary, there is therefore a hint of lesser benefit from osimertinib in combination with pemetrexed and platinum-based chemotherapy versus osimertinib for the first-line treatment of adult patients with advanced NSCLC, whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations.

Table 3 shows a summary of the probability and extent of added benefit of osimertinib + pemetrexed + platinum-based chemotherapy.

Table 3: Osimertinib + pemetrexed + platinum-based chemotherapy – probability and extent of added benefit

| **Therapeutic indication** | **ACT**[a, b, c] | **Probability and extent of added benefit** |
|---|---|---|
| Adult patients with advanced NSCLC whose tumours have epidermal growth factor receptor exon 19 deletions or exon 21 (L858R) substitution mutations; first-line treatment | ▪ Afatinib (only for patients with the activating EGFR mutation deletion in exon 19)<br>or<br>▪ Osimertinib | Hint of lesser benefit[d] |

a. Presented is the ACT specified by the G-BA.
b. In terms of therapeutic indication, it is assumed that neither definitive radiochemotherapy nor definitive local therapy are indicated. In addition, it is assumed that molecularly stratified therapy (directed against ALK, BRAF, Exon 20, KRAS G12C, METex14, RET, or ROS1) is not an option for the patients at the time of treatment with osimertinib.
c. The ACT specified here comprises several alternative treatment options. However, individual treatment options only represent a comparator therapy for those members of the patient population who have the patient and disease characteristics shown in brackets. The alternative treatment options are only to be regarded as equally appropriate in the area in which the patient populations have the same characteristics.
d. Only patients with an WHO PS of 0 or 1 were included in the FLAURA-2 study. It remains unclear whether the observed effects are transferable to patients with an WHO PS ≥ 2.

ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; BRAF: rapidly accelerated fibrosarcoma isoform B; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; KRAS: Kirsten Rat Sarcoma Viral Oncogene Homologue; METex14: Exon 14 of the mesenchymal epithelial transition factor gene; NSCLC: non-small cell lung cancer; RET: Rearranged during Transfection; ROS1: C-ros Oncogene 1 WHO PS: World Health Organization – Performance Status

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

The aim of the present report is to assess the added benefit of osimertinib in combination with pemetrexed and platinum-based chemotherapy (hereinafter referred to as osimertinib + pemetrexed + platinum-based chemotherapy) in comparison with the ACT for the first-line treatment of adult patients with advanced NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations.

The research question presented in Table 4 results from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of osimertinib in combination with pemetrexed and platinum-based chemotherapy

| **Therapeutic indication** | **ACT**[a, b, c] |
|---|---|
| Adult patients with advanced NSCLC whose tumours have estimated glomerular filtration rate exon 19 deletions or exon 21 (L858R) substitution mutations; first-line treatment | ▪ Afatinib (only for patients with the activating EGFR mutation deletion in exon 19)<br>or<br>▪ Osimertinib |
| a. Presented is the ACT specified by the G-BA.<br>b. In terms of therapeutic indication, it is assumed that neither definitive radiochemotherapy nor definitive local therapy are indicated. In addition, it is assumed that molecularly stratified therapy (directed against ALK, BRAF, Exon 20, KRAS G12C, METex14, RET, or ROS1) is not an option for the patients at the time of treatment with osimertinib.<br>c. The ACT specified here comprises several alternative treatment options. However, individual treatment options only represent a comparator therapy for those members of the patient population who have the patient and disease characteristics shown in brackets. The alternative treatment options are only to be regarded as equally appropriate in the area in which the patient populations have the same characteristics.<br>ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; BRAF: rapidly accelerated fibrosarcoma isoform B; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; KRAS: Kirsten Rat Sarcoma Viral Oncogene Homologue; METex14: Exon 14 of the mesenchymal epithelial transition factor gene; NSCLC: non-small cell lung cancer; RET: Rearranged during Transfection; ROS1: C-ros Oncogene 1 | |

The company did not follow the G-BA's specification of the ACT, as in the company's view only osimertinib represents the ACT. It justified this with the preferred use of osimertinib over afatinib also in patients with activating EGFR mutation deletion in exon 19. However, this is of no consequence for the benefit assessment, as osimertinib is also included in the G-BA's ACT and the company presented evidence in relation to this option (see Section I 3.1). The present benefit assessment was conducted in comparison with the ACT specified by the G-BA.

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. This concurs with the company’s inclusion criteria.

## I 3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on osimertinib (status: 16 May 2024)
- bibliographical literature search on osimertinib (last search on 16 May 2024)
- search in trial registries/trial results databases for studies on osimertinib (last search on 16 May 2024)
- search on the G-BA website for osimertinib (last search on 16 May 2024)

To check the completeness of the study pool:

- search in trial registries for studies on osimertinib (last search on 08 August 2024); for search strategies, see I Appendix A of the full dossier assessment

The check did not identify any additional relevant study.

### I 3.1 Studies included

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

Table 5: Study pool – RCT, direct comparison: osimertinib + pemetrexed + platinum-based chemotherapy[a] vs. osimertinib

| Study | Study category | | | Available sources | | |
|---|---|---|---|---|---|---|
| | Study for the approval of the drug to be assessed (yes/no) | Sponsored study[b] (yes/no) | Third-party study (yes/no) | CSR (yes/no [citation]) | Registry entries[c] (yes/no [citation]) | Publication (yes/no [citation]) |
| D5169C00001 (FLAURA-2[d]) | Yes | Yes | No | Yes [3] | Yes [4,5] | Yes [6-8] |

a. Cisplatin/carboplatin.
b. Study for which the company was sponsor.
c. Citation of the trial registry entries and, if available, of the reports on study design and/or results listed in the trial registries.
d. In the following tables, the study is referred to by this acronym.
CSR: clinical study report; RCT: randomized controlled trial

### I 3.2 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 + pemetrexed + platinum-based chemotherapy[a] vs. osimertinib (multipage table)

| Study | Study design | Population | Interventions (number of randomized patients) | Study duration | Location and period of study | Primary outcome; secondary outcomes[b] |
|---|---|---|---|---|---|---|
| FLAURA-2[c] | RCT, open-label, parallel | Adult[d] patients with<br>▪ Newly diagnosed locally advanced or metastatic, or recurring NSCLC[e] with EGFR mutation (Ex19del and/or L858R)<br>▪ Without prior treatment for advanced disease[f]<br>▪ WHO-PS 0 or 1 | ▪ Osimertinib + pemetrexed + cisplatin/carboplatin (N = 279)<br>▪ Osimertinib (n = 278) | ▪ Screening: 28 days<br>▪ Treatment:<br>until disease progression (RECIST 1.1)[g], unacceptable toxicity, treatment discontinuation as decided by the investigator or the patient<br>▪ Observation[h]:<br>outcome-specific, at most until death, withdrawal of consent or final analysis of overall survival[i] | 151 centres in Argentina, Australia, Brazil, Canada, Chile, China, Czech Republic, France, India, Japan, Korea, Peru, Philippines, Russia, Slovakia, South Africa, Taiwan, Thailand, United States, United Kingdom, Vietnam<br><br>15 May 2020–ongoing<br><br>Data cut-offs:<br>22 September 2021[j]<br>3 April 2023[k]<br>8 January 2024[l] | Primary: PFS<br>Secondary: overall survival, morbidity, health-related quality of life, AEs |

Table 6: Characteristics of the study included – RCT, direct comparison: osimertinib + pemetrexed + platinum-based chemotherapy[a] vs. osimertinib (multipage table)

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

a. Cisplatin/carboplatin.
b. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes include only information on relevant available outcomes for this benefit assessment.
c. The FLAURA-2 study was conducted in 2 separate parts: Part 1 – safety run-in phase; followed by Part 2 – randomized, open-label, sponsor-blinded phase 3 study. The information in this dossier assessment refers only to the randomized study phase.
d. Patients from Japan had to be at least 20 years old.
e. Pathologically confirmed, non-squamous NSCLC (NSCLC with mixed histology was permitted).
f. Previous adjuvant and neoadjuvant therapies or definitive radiotherapy (chemotherapy) were permitted if the treatment had been completed at least 12 months before the recurrence of the disease. Adjuvant treatment with an EGFR TKI was an exception; this was ruled out.
g. Continuation of study treatment with osimertinib was also possible after disease progression if, in the opinion of the investigator, there was still a clinical benefit and no discontinuation criteria were present.
h. Outcome-specific information is described in Table 8.
i. Fnal analysis of overall survival planned after reaching approximately 334 death events.
j. Prespecified interim futility analysis after reaching approximately 83 events in the primary outcome of PFS.
k. Prespecified interim analysis after reaching approximately 278 events in the primary outcome of PFS and at least 16 months follow-up after the last patient started the study.
l. According to the company, data cut-off on overall survival requested by the EMA.

AE: adverse event; EGFR: epidermal growth factor receptor; EMA: European Medicines Agency; Ex19del: exon 19 deletion; L858R: amino acid substitution at position 858 in exon 21 of EGFR, from a leucine to an arginine; N: number of randomized patients; NSCLC: non-small cell lung cancer; PFS: progression-free survival; RCT: randomized controlled trial; RECIST: Response Evaluation Criteria in Solid Tumours; TKI: tyrosine kinase inhibitor; WHO PS: World Health Organization - Performance Status

Table 7: Characteristics of the intervention – RCT, direct comparison: osimertinib + pemetrexed + platinum-based chemotherapy[a] vs. osimertinib (multipage table)

| Study | Intervention | Comparison |
|---|---|---|
| FLAURA-2 | Cycles 1–4 (21 days each):<br>▪ Osimertinib 80 mg orally once daily<br>▪ Day 1 of each cycle:<br>o Pemetrexed 500 mg/m$^2$, BSA, IV<br>o Cisplatin 75 mg/m$^2$ BSA IV or carboplatin 5 mg/mL/min (AUC 5) IV[b, c]<br>Followed by maintenance therapy:<br>▪ Osimertinib 80 mg orally once daily<br>▪ Pemetrexed 500 mg/m$^2$, BSA, IV, every 3 weeks | Osimertinib 80 mg orally once daily |
| | **Dose adjustment:**<br>▪ Dose adjustments and delays permitted in the event of severe AEs (CTCAE ≥ 3) and/or unacceptable toxicity<br>▪ Treatment interruption permitted for a maximum of 3 weeks<br>▪ Resumption of treatment if improvement to CTCAE ≤ 1 with the starting dose or dose reduction, re-escalation after dose adjustment was not permitted<br>▪ Osimertinib: 1 dose reduction to 40 mg permitted<br>▪ Pemetrexed: 1st dose reduction to 375 mg/m22, 2nd dose reduction to 250 mg/m2<br>▪ Cisplatin: 1st dose reduction to 56 mg/m2, 2nd dose reduction to 38 mg/m2<br>▪ Carboplatin: 1st dose reduction to 3.75 mg/mL/min, 2nd dose reduction to 2.5 mg/mL/min<br>▪ Further dose reductions were not permitted and led to the discontinuation of the respective drug.<br>▪ If one or more drugs were discontinued, treatment could be continued with the remaining study medication. | |
| | **Non-permitted pretreatment**<br>▪ Systemic cancer therapies for the treatment of advanced NSCLC that cannot be treated with curative surgery or radiotherapy<br>▪ Adjuvant and neoadjuvant therapies or definitive radiotherapy (chemotherapy), with or without treatments including immunotherapy, biological therapy, investigational medicinal products, which were completed less than 12 months before recurrence occurred<br>▪ EGFR tyrosine kinase inhibitors<br>▪ Radiotherapy of ≥ 30% of the bone marrow, or wide-field radiotherapy within 4 weeks of the start of study treatment | |

Table 7: Characteristics of the intervention – RCT, direct comparison: osimertinib + pemetrexed + platinum-based chemotherapy[a] vs. osimertinib (multipage table)

| Study | Intervention | Comparison |
|---|---|---|
| | **Concomitant treatment**<br>▪ Pemetrexed:<br>o Folic acid or multivitamin preparation with folic acid (350–1000 µg daily) orally, for the entire duration of treatment, as well as at least 5 doses in the 7 days before the start of treatment, and for a further 21 days after the administration of the last dose<br>o Vitamin $B_{12}$ injection (1000 µg) i.m. in the week before starting treatment, and then once every 3 cycles<br>o Corticosteroids (equivalent to 4 mg dexamethasone) orally, twice daily, 1 day before to 1 day after pemetrexed administration<br>▪ Cisplatin: hydration immediately before and after treatment<br>▪ Antiemetic therapy according to local standards<br><br>**Non-permitted concomitant treatment**<br>▪ Other cancer medications (incl. immuno-oncological therapies), investigational products, non-palliative radiotherapies<br>▪ Strong CYP3A4 inducers: 3 weeks before the start of treatment until 3 weeks after the last dose of osimertinib (except for the treatment of AEs)<br>▪ NSAIDs: 2 days before to 2 days after administration of pemetrexed (NSAIDs with a long half-life: 5 days before to 2 days after administration of pemetrexed)<br>▪ G-CSF: prophylactic use during cycle 1 | |

a. Cisplatin/carboplatin.
b. The selection of the platinum component was made by the investigator prior to randomization.
c. Patients in the intervention arm who discontinued treatment with the platinum component only were able to continue treatment with the alternative platinum component for the remaining time of the platinum combination cycles (maximum 4 cycles) upon the investigator's discretion.

AE: adverse event; AUC: area under the curve; CTCAE: Common Terminology Criteria for Adverse Events; CYP: cytochrome P450; EGFR: epidermal growth factor receptor; G-CSF: granulocyte colony-stimulating factor; IM: intramuscular; IV: intravenous; BSA: body surface area; NSAID: non-steroidal anti-inflammatory drug; NSCLC: non-small cell lung cancer; P.O.: peroral; RCT: randomized controlled trial

## Study design

The FLAURA-2 study is an ongoing, open-label RCT comparing osimertinib + pemetrexed + platinum-based chemotherapy vs. osimertinib. It included adult patients with newly diagnosed locally advanced or metastatic stage IIIB to IV NSCLC or recurrent non-squamous NSCLC (according to Version 8 of the International Association for the Study of Lung Cancer [IASLC] Staging Manual in Thoracic Oncology), whose tumours have proven EGFR exon 19 deletions or exon 21 (L858R) substitution mutations. The EGFR mutation was detected either by a local tissue test or by a central laboratory using Cobas tests. Furthermore, patients had to be non-amenable to curative surgery or radiotherapy, and they were to be in good general health in accordance with Eastern Cooperative Oncology Group – Performance Status (WHO PS) 0 or 1. Patients were not allowed to have received any prior therapy for the advanced disease. Adjuvant or neoadjuvant therapies were allowed if they had been completed at least 12 months before recurrence occurred. Pretreatment with an EGFR

tyrosine kinase inhibitor (TKI) was generally ruled out. This means that all patients who have received adjuvant therapy with osimertinib after complete resection and adjuvant chemotherapy in stage II NSCLC with activating EGFR mutation (only exon 19 deletion and exon 21 L858R substitution mutation) according to the S3 guideline [9] are excluded from the study. It is unclear how this restriction of prior therapy in the FLAURA-2 study can be transferred to the current situation in everyday health care. This remains of no consequence for the benefit assessment, however.

Overall, 557 patients were enrolled and randomly allocated in a 1:1 ratio to either treatment with osimertinib + pemetrexed + platinum-based chemotherapy (N = 279) or to osimertinib (N = 278). Randomisation was stratified by family origin (Chinese/Asian vs. non-Chinese/Asian vs. non-Asian), WHO PS (0 vs. 1) and tissue testing method (central vs. local). The choice of platinum component (cisplatin or carboplatin) was made by the investigator before randomization.

Treatment with osimertinib + pemetrexed + platinum-based chemotherapy in the intervention arm and osimertinib in the comparator arm was largely carried out according to the SPC [10-12]. Contrary to the recommendation in the SPC, continuation of study treatment with osimertinib was also possible after disease progression if, in the opinion of the investigator, there was still a clinical benefit and no discontinuation criteria were present (see details in the section on subsequent therapies below).

The primary outcome of the FLAURA-2 study is progression-free survival (PFS). Further outcomes were recorded in the categories of mortality, morbidity, health-related quality of life, and side effects.

**Data cut-offs**

The FLAURA-2 study is an ongoing study. So far, 3 data cut-offs are available:

- 1st data cut-off (22 September 2021): prespecified interim futility analysis after reaching approximately 83 events in the primary outcome of PFS
- 2nd data cut-off (3 April 2023): primary PFS data cut-off: prespecified interim analysis after reaching approximately 278 events in the primary outcome of PFS and at least 16 months follow-up after the last patient started the study
- 3rd data cut-off (8 January 2024): According to the information provided by the company in Module 4 A, this data cut-off with analyses on overall survival was requested by the European Medicines Agency (EMA) to support the approval procedure.

In Module 4 A, the company presented analyses on the 2nd data cut-off for all outcomes relevant to the present benefit assessment, with the exception of the outcome of overall

survival. For that outcome, the company presented analyses on the 3rd data cut-off in Module 4 A. Results on that outcome for the 2nd data cut-off are only available exclusively in Module 5.

The approach of the company is not appropriate. On the one hand, it cannot be verified on the basis of the information presented by the company whether the 3rd data cut-off, as stated by the company, was prepared at the request of the EMA and is therefore suitable for the benefit assessment. On the other hand, the analyses presented in Module 4 A on the 3rd data cut-off are incomplete. Only results on overall survival are available for the 3rd data cut-off. However, these cannot be interpreted due to a lack of information on subsequent therapies, regardless of whether the 3rd data cut-off is essentially suitable or not. Analyses of outcomes in the morbidity and side effects category are completely missing for the 3rd data cut-off. For the outcomes related to morbidity, this is of minor importance, as no follow-up observation was planned beyond the 2nd data cut-off for these outcomes. For the outcomes of the side effects category, however, observation up to 28 days after the end of treatment with the study medication was planned (see Table 8). According to the information in Module 4 A, around 50% of patients were still being treated with the study medication at the 2nd data cut-off and were therefore still being monitored for the outcomes in the side effects category. Consequently, a relevant number of events in the side effects category could potentially still be added between the 2nd and 3rd data cut-offs.

Therefore, for the present benefit assessment (in deviation from the approach of the company), only the results of the 2nd data cut-off of 3 April 2023 are considered, since that data cut-off date was prespecified and is the only one for which complete analyses are available.

**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 + pemetrexed + platinum-based chemotherapy[a] vs. osimertinib

| **Study**<br>**Outcome category**<br>**Outcome** | **Planned follow-up observation** |
|---|---|
| **FLAURA-2** | |
| Mortality | |
| Overall survival | Until death, withdrawal of informed consent or the time of the final analysis of overall survival |
| Morbidity | |
| Symptoms (EORTC QLQ-C30, EORTC QLQ-LC13, PGIS) | Until the 2nd disease progression (PFS2) or the primary PFS data cut-off[b], whichever occurs first |
| Health status (EQ-5D VAS) | |
| Health-related quality of life | |
| EORTC QLQ-C30 | Until the 2nd disease progression (PFS2) or the primary PFS data cut-off[b], whichever occurs first |
| Side effects | |
| All outcomes of the side effects category (except PRO-CTCAE) | Until 28 days after the end of the study treatment or the start of a subsequent cancer therapy[c] |
| PRO-CTCAE | Until the 2nd disease progression (PFS2) or the primary PFS data cut-off[b], whichever occurs first |

a. Cisplatin/carboplatin.
b. 2nd data cut-off from 3 April 2023.
c. SAEs that were considered to be related to the study treatment were recorded until the end of the study.
EORTC: European Organisation for Research and Treatment of Cancer; PFS: progression-free survival; PGIS: Patient Global Impression of Change; PRO-CTCAE: Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events; QLQ-C30: Quality of Life Questionnaire – Core 30; QLQ-LC13: Quality of Life Questionnaire – Lung Cancer 13; RCT: randomised controlled trial; SAE: serious adverse event; VAS: visual analogue scale

For the outcomes on morbidity and health-related quality of life, a follow-up observation until the 2nd disease progression or the primary PFS data cut-off (2nd data cut-off on 3 April 2023) was planned. Thus, while the observation periods are shortened and do not cover the entire study period, it is positive to note that the collection of patient-reported outcomes was continued at least until the 2nd disease progression or the primary PFS data cut-off.

The observation periods for the outcomes on side effects were systematically shortened because they were only recorded for the time period of treatment with the study medication (plus 28 days). Only SAEs that were considered to be related to the study treatment were to be recorded until the end of the study.

In order to be able to draw a reliable conclusion about the entire study period or about the time until patient death, it would be necessary for these outcomes – such as overall survival – to be recorded over the entire period.

### Patient characteristics

Table 9 shows the patient characteristics of the included study.

Table 9: Characteristics of the study population and study/treatment discontinuation – RCT, direct comparison: osimertinib + pemetrexed + platinum-based chemotherapy[a] vs. osimertinib (multipage table)

| **Study**<br>**Characteristic**<br>**Category** | **Osimertinib + pemetrexed + platinum-based chemotherapy**<br>**N[b] = 279** | **Osimertinib**<br>**N[b] = 278** |
|---|---|---|
| **FLAURA-2** | | |
| Age [years], mean (SD) | 61 (10) | 61 (11) |
| Sex [F/M], % | 62/38 | 61/39 |
| Family origin, n (%) | | |
| Asian/Chinese | 71 (26) | 69 (25) |
| Asian/Non-Chinese | 107 (38) | 107 (38) |
| Non-Asian | 101 (36) | 102 (37) |
| WHO PS, n (%) | | |
| 0 | 104 (37) | 102 (37) |
| 1 | 174 (62) | 176 (63) |
| 2 | 1 (< 1) | 0 (0) |
| Disease stage at diagnosis[c], n (%) | | |
| IIIB | 9 (3) | 4 (1) |
| IIIC | 4 (1) | 3 (1) |
| IVA | 98 (35) | 104 (37) |
| IVB | 168 (60) | 167 (60) |
| Patients with metastases, n (%) | | |
| CNS | 116 (42) | 110 (40) |
| Liver | 43 (15) | 66 (24) |
| Lung/pleura | 196 (70) | 216 (78) |
| Lymph nodes | 160 (57) | 170 (61) |
| Bones and musculoskeletal system | 132 (47) | 142 (51) |
| Extrathoracic | 147 (53) | 149 (54) |
| Other | 64 (23) | 58 (21) |

Table 9: Characteristics of the study population and study/treatment discontinuation – RCT, direct comparison: osimertinib + pemetrexed + platinum-based chemotherapy[a] vs. osimertinib (multipage table)

| **Study**<br>**Characteristic**<br>**Category** | **Osimertinib + pemetrexed + platinum-based chemotherapy**<br>**N[b] = 279** | **Osimertinib**<br>**N[b] = 278** |
|---|---|---|
| Histology type, n (%) | | |
| Adenocarcinoma[d] | 275 (99) | 275 (99) |
| Carcinoma, adenosquamous | 2 (< 1) | 0 (0) |
| Other | 2 (< 1) | 3 (1) |
| Disease duration: time from first diagnosis to first dose [months], mean (SD) | 3.6 (12.0) | 3.6 (16.2) |
| EGFR mutation at the time of randomization, n (%)[e] | | |
| Ex19del | 169 (61) | 168 (60) |
| L858R | 106 (38) | 107 (38) |
| Ex19del and L858R | 3 (1) | 1 (< 1) |
| EGFRm unknown/not detected | 1 (< 1) | 2 (< 1) |
| Smoking status, n (%) | | |
| Never smoker | 188 (67) | 181 (65) |
| Smoker | 91 (33) | 97 (35) |
| Current smoker | 4 (1) | 4 (1) |
| Ex-smoker | 87 (31) | 93 (34) |
| Treatment discontinuation, n (%)[f, g, h] | 122 (44) | 152 (55) |
| Study discontinuation, n (%)[i] | 82 (29) | 87 (31) |

a. Cisplatin/carboplatin.
b. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
c. Classification according to the 8th edition of the UICC.
d. Represents a combination of the following adenocarcinoma categories: NOS, acinar, papillary, bronchiolo-alveolar, and solid adenocarcinomas with mucus formation.
e. Testing of the EGFR mutation type was based on central or local tissue tests.
f. Percentages refer to the number of randomized patients in the intervention vs. control arm who have received at least 1 dose of the study treatment (276 vs. 275 patients). One patient was randomized to the intervention arm, but was only treated with osimertinib.
g. Discontinuation of all drugs.
h. Common reasons for treatment discontinuation of osimertinib in the intervention vs. control arm were: disease progression (68 [24%] vs. 118 [42%]), adverse event (30 [11%] vs. 17 [6%]), patient's decision (8 [3%] vs. 6 [2%]). The most common reason for the discontinuation of chemotherapy components in the intervention arm were adverse events (119 [43%] for pemetrexed, 47 [17%] for the platinum component).
i. Reasons for study discontinuation in the intervention vs. control arm were: withdrawal of consent (11 [4%] vs. 9 [3%]) and screening failure (1 [< 1%] vs. 1 [< 1%]). The data also include patients who have died during the course of the study (intervention arm: 70 [25%] vs. control arm: 77 [28%]).

Table 9: Characteristics of the study population and study/treatment discontinuation – RCT, direct comparison: osimertinib + pemetrexed + platinum-based chemotherapy[a] vs. osimertinib (multipage table)

| Study Characteristic Category | Osimertinib + pemetrexed + platinum-based chemotherapy N[b] = 279 | Osimertinib N[b] = 278 |
|---|---|---|

CNS: central nervous system; ctDNA: circulating tumour DNA; EGFRm: epidermal growth factor receptor mutation; Ex19del: exon 19 deletion; L858R: amino acid substitution at position 858 in exon 21 of the EGFR; L861Q: amino acid substitution at position 861 in exon 21 of the EGFR; m: male; n: number of patients in the category; N: number of randomized patients; NOS: not otherwise specified; RCT: randomized controlled trial; SD: standard deviation; UICC: Union for International Cancer Control; f: female; WHO PS: World Health Organization –Performance Status

The demographic and clinical characteristics of the patients were largely balanced between the two study arms of FLAURA-2. The mean patient age was 61 years; most of them were female (62% versus 61%) and primarily of Asian ancestry (64% versus 63%). The majority of the patient population had a WHO PS of 1 (62% vs. 63%) and were in stage IV disease (95% vs. 97%). Adenocarcinoma was present in 99% of patients, predominantly with an exon 19 deletion (61% vs. 60%). The subgroup analyses in Module 4 A show that in individual patients (< 5% in the intervention and comparator arm) whose EGFR mutation was detected by a local tissue test, the test result was not confirmed by central testing. Due to the small proportion, this had no consequence for the benefit assessment.

The proportion of patients who discontinued treatment was slightly lower in the intervention arm than in the comparator arm (44% versus 55%). In the intervention arm, the treatment with pemetrexed was most frequently discontinued. The main reason for treatment discontinuation in the intervention arm (at least one component) was the occurrence of AEs, whereas in the comparator arm it was disease progression. The number of patients who discontinued the study differed only slightly between the intervention and comparator arm (29% vs. 31%).

**Information on the 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 + pemetrexed + platinum-based chemotherapy[a] vs. osimertinib (multipage table)

| **Study**<br>**Duration of the study phase**<br>**Outcome category/outcome** | | **Osimertinib + pemetrexed + platinum-based chemotherapy**<br>**N[b] = 279** | **Osimertinib**<br>**N[b] = 278** |
|---|---|---|---|
| **FLAURA-2** | | | |
| Treatment duration[c] [months] | | | |
| Median [min; max] | Osimertinib | 22.3 [0.1; 33.8] | 19.3 [0.1; 33.8] |
| | Carboplatin/cisplatin | 2.8 [0.7; 4.1] | – |
| | Pemetrexed | 8.3 [0.7; 33.8] | – |
| Mean (SD) | Osimertinib | 19.7 (9.1) | 18.1 (8.9) |
| | Carboplatin/cisplatin | 2.6 (0.7) | – |
| | Pemetrexed | 12.1 (9.8) | – |
| Observation period [months] | | | |
| Overall survival[d] | | | |
| Median [min; max] | | 25.0 [0.2; 34.1] | 25.1 [0.1; 33.9] |
| Mean (SD) | | ND | ND |
| Morbidity[e] | | | |
| EORTC QLQ-C30 | | | |
| Median [min; max] | | 21.3 [0.0; 33.1] | 17.3 [0.0; 32.5] |
| Mean (SD) | | ND | ND |
| EORTC QLQ-LC13 | | | |
| Median [min; max] | | 21.4 [0.0; 33.8] | 17.7 [0.0; 33.2] |
| Mean (SD) | | ND | ND |
| PGIS | | | |
| Median [min; max] | | 20.3 [0.0; 33.8] | 17.3 [0.0; 32.5] |
| Mean (SD) | | ND | ND |
| EQ-5D VAS | | | |
| Median [min; max] | | 20.7 [0.0; 33.8] | 17.3 [0.0; 32.5] |
| Mean (SD) | | ND | ND |
| Side effects | | | |
| PRO-CTCAE[e] | | | |
| Median [min; max] | | 18.4 [0.0; 33.8] | 15.6 [0.0; 33.2] |
| Mean (SD) | | ND | ND |
| AEs/SAEs/severe AEs[f] | | | |
| Median [min; max] | | 22.5 [0.1; 33.8] | 19.3 [1.0; 33.8] |
| Mean (SD) | | ND | ND |

Table 10: Information on the course of the study – RCT, direct comparison: osimertinib + pemetrexed + platinum-based chemotherapy[a] vs. osimertinib (multipage table)

| **Study**<br>**Duration of the study phase**<br>**Outcome category/outcome** | **Osimertinib + pemetrexed + platinum-based chemotherapy**<br>**N[b] = 279** | **Osimertinib**<br>**N[b] = 278** |
|---|---|---|
| a. Cisplatin/carboplatin.<br>b. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.<br>c. Treatment durations refer to the number of randomized patients in the intervention vs. control arm who have received at least 1 dose of the study treatment (276 vs. 275 patients).<br>d. The observation period is calculated on the basis of the observed time until censoring of all non-deceased patients.<br>e. The observation period for PROs is defined as the time from randomization to the earliest date of the last assessment of the questionnaire prior to 2nd disease progression, death, or date of data cut-off. Patients without baseline or post-baseline measurements are summarized with a duration of 1 day.<br>f. Operationalized as CTCAE grade ≥ 3.<br>AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; max: maximum; min: mimum; N: number of analysed patients; ND: no data; PGIS: Patient Global Impression of Severity; PRO: patient-reported outcome; PRO-CTCAE: Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events; QLQ-C30: Quality of Life Questionnaire – Core 30; QLQ-LC13: Quality of Life Questionnaire – Lung Cancer 13; RCT: randomized controlled trial; SAE: serious adverse event; SD: standard deviation; VAS: visual analogue scale | | |

The median treatment duration for osimertinib differed only slightly between the study arms (approx. 22 months vs. approx. 19 months). The median treatment duration for carboplatin or cisplatin in the intervention arm was approximately 3 months and thus corresponds approximately to the planned total duration of 4 cycles. For pemetrexed, a maintenance treatment along with osimertinib was planned in the intervention arm, however, the median treatment duration for pemetrexed was about 8 months, significantly shorter than for osimertinib. Accordingly, some of the patients in the intervention arm received only osimertinib monotherapy in the further course of the study, as in the comparator arm.

The median observation periods were sufficiently comparable between the 2 study arms. Compared to the outcome of overall survival, however, all other outcomes have a shortened median observation period. This is noticeable for the outcomes on morbidity and health-related quality of life, which according to the study protocol should be followed up until the 2nd disease progression (which had occurred only in < 50% of the patients at the time of the present data cut-off) or the primary PFS data cut-off.

**Subsequent therapies**

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

Table 11: Information on subsequent antineoplastic therapies (≥ 2% of the patients in ≥ 1 treatment arm) – RCT, direct comparison: osimertinib + pemetrexed + platinum-based chemotherapy vs. osimertinib (multipage table)[a]

| **Study** | **Patients with subsequent therapy n (%)[b]** | |
|---|---|---|
| **Subsequent therapy**<br>**Drug class**<br>**Drug** | **Osimertinib + pemetrexed + platinum-based chemotherapy N = 279** | **Osimertinib N = 278** |
| **FLAURA-2 (data cut-off from 3 April 2023)** | | |
| Patients with at least one subsequent therapy | 57 (20.4) | 91 (32.7) |
| **First subsequent therapy** | | |
| Cytotoxic chemotherapy | 37 (13.3) | 75 (27.0) |
| Platinum-containing compounds | 17 (6.1) | 71 (25.5) |
| Folic acid analogues (pemetrexed) | 7 (2.5) | 43 (15.5) |
| Taxanes | 22 (7.9) | 24 (8.6) |
| EGFR-TKI | 12 (4.3) | 13 (4.7) |
| First or second generation EGFR-TKI | 9 (3.2) | 5 (1.8) |
| Third-generation EGFR-TKI | 3 (1.1) | 8 (2.9) |
| Osimertinib | 3 (1.1) | 7 (2.5) |
| VEGF Inhibitors – monoclonal antibodies | 12 (4.3) | 32 (11.5) |
| PD-1/PD-L1 inhibitors | 7 (2.5) | 17 (6.1) |
| Investigational preparations | 7 (2.5) | 13 (4.7) |
| Targeted therapy | 6 (2.2) | 9 (3.2) |
| Radiotherapy | ND | ND |
| **Any subsequent therapy** | | |
| Cytotoxic chemotherapy | 41 (14.7) | 81 (29.1) |
| Platinum-containing compounds | 19 (6.8) | 78 (28.1) |
| Folic acid analogues (pemetrexed) | 8 (2.9) | 55 (19.8) |
| Taxanes | 26 (9.3) | 39 (14.0) |
| Pyrimidine analogues | 8 (2.9) | 9 (3.2) |
| Vinca alkaloids and analogues | 5 (1.8) | 6 (2.2) |
| EGFR-TKI | 18 (6.5) | 39 (14.0) |
| First or second generation EGFR-TKI | 12 (4.3) | 22 (7.9) |
| Erlotinib | 5 (1.8) | 11 (4.0) |
| Afatinib | 4 (1.4) | 6 (2.2) |
| Third-generation EGFR-TKI | 6 (2.2) | 22 (7.9) |
| Osimertinib | 6 (2.2) | 19 (6.8) |
| VEGF Inhibitors – monoclonal antibodies | 14 (5.0) | 38 (13.7) |
| PD-1/PD-L1 inhibitors | 10 (3.6) | 22 (7.9) |
| Investigational preparations | 10 (3.6) | 19 (6.8) |
| Targeted therapy | 8 (2.9) | 17 (6.1) |
| Radiotherapy | 13 (4.7) | 30 (10.8) |

Table 11: Information on subsequent antineoplastic therapies (≥ 2% of the patients in ≥ 1 treatment arm) – RCT, direct comparison: osimertinib + pemetrexed + platinum-based chemotherapy vs. osimertinib (multipage table)[a]

| Study | Patients with subsequent therapy n (%)[b] | |
|---|---|---|
| Subsequent therapy<br>Drug class<br>Drug | Osimertinib + pemetrexed + platinum-based chemotherapy<br>N = 279 | Osimertinib<br>N = 278 |

a. In Module 5, the company presented various tables with discrepant information on individual follow-up therapies. The data presented correspond to the information in the main part of the clinical study report.
b. The percentages refer to the proportion of all patients analysed.

EGFR: epidermal growth factor receptor; n: number of patients with subsequent therapy; N: number of analysed patients; ND: no data; PD-1: programmed cell death protein 1; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; TKI: tyrosine kinase inhibitor; VEGF: vascular endothelial growth factor

In the FLAURA-2 study, subsequent antineoplastic therapies were permitted without restrictions in both study arms. The choice of subsequent therapy was at the discretion of the investigator and was carried out according to local standards.

The company did not provide any information on subsequent therapies in Module 4 A. However, the study documents show that a total of 20% of all randomized patients in the intervention arm and 33% in the comparator arm received at least 1 follow-up therapy. Therefore, with regard to patients with objective disease progression (95 vs. 158 patients in the intervention and comparator arms), about 60% received follow-up therapy. The most common subsequent therapy was a cytotoxic chemotherapy, some patients were also treated with vascular endothelial growth factor (VEGF) inhibitors and/or with immunotherapies (inhibitors of programmed cell death protein 1 [PD-1] or programmed cell death ligand 1 [PD-L1]). Furthermore, some patients received an EGFR-TKI (21% of patients with subsequent therapy in the intervention arm and 14% in the comparator arm). It is not clear from the data in which combinations the individual drugs were given. The CSR also indicates that a significant proportion of all randomized patients in the intervention and comparator arms (81 [29%] vs. 133 [48%]) continued to be treated with osimertinib beyond the 1st disease progression (at a median of about 2 months each). In terms of patients with objective disease progression, this corresponds to a proportion of approx. 85% in both study arms. This treatment was not documented as a subsequent therapy, but as a continuation of the first-line treatment.

Based on the available data, it can be assumed that the subsequent therapies after disease progression in the FLAURA-2 study were not adequate for a relevant proportion of patients:

- Continued treatment with osimertinib beyond disease progression is not recommended by either the SPC or the guidelines [9,10]. Such continued treatment potentially leads to a delay in starting subsequent therapy in line with the guidelines.

- Information is missing as to why approximately 40% of patients with progression did not receive subsequent therapy. According to the guideline, patients without treatable genetic alterations should be offered chemoimmunotherapy following treatment with osimertinib in the same way as first-line treatment in patients without mutations. This is particularly relevant for patients in the comparator arm, who – unlike those in the intervention arm – have not yet received chemotherapy. It is highly likely that patients who did not receive subsequent therapy were instead given continued treatment with osimertinib, which is not recommended (see above).
- A relevant proportion of patients received treatment with an EGFR-TKI as part of a subsequent therapy, which is not in line with the recommendations of the guideline. A re-biopsy to test for resistance mutations (which is recommended according to the guideline for further treatment selection) was also only optional in the FLAURA-2 study. The study documents do not show how many patients underwent this procedure. The only data available are those presented in a conference abstract, which show that, as of 15 December 2022, liquid biopsies had been performed in about 50% of patients [13].

The described deficiencies in the follow-up therapies used are taken into account in the assessment of the outcome-specific risk of bias (see Section I 4.2).

**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 + pemetrexed + platinum-based chemotherapy[a] vs. osimertinib

| Study | 1 Adequate random sequence generation | 2 Allocation concealment | Blinding | | 3 Reporting independent of the results | 4 No additional aspects | 5 Risk of bias at study level |
|---|---|---|---|---|---|---|---|
| | | | 6 Patients | 7 Treating staff | | | |
| FLAURA-2 | Yes | No | No | No | Yes | No | Low |

a. Cisplatin/carboplatin.
RCT: randomized controlled trial

The risk of bias across outcomes was rated as low for the FLAURA-2 study.

Limitations resulting from the open-label study design are described in Section I 4.2 on outcome-specific risk of bias.

**Transferability of the study results to the German health care context**

In the company's opinion, the results of the FLAURA-2 study are transferable to the German health care context. The study was conducted in 21 countries worldwide and there was no indication of clinically significant differences between population groups and geographical regions within the study. The median age and the disease-specific patient characteristics of the study population are comparable to the German target population [14-16]. The higher proportion of central nervous system (CNS) metastases compared to previous studies is consistent with findings from real-world care [15,17]. In addition, the study is comparable to other TKI studies in terms of demographics and disease characteristics.

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

## I 4 Results on added benefit

### I 4.1 Outcomes included

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

- Mortality
  - Overall survival
- Morbidity
  - Symptoms
    - recorded using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; (EORTC QLQ-C30)
    - recorded using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer 13; (EORTC QLQ-LC13)
    - recorded using the Patient Global Impression of Severity (PGIS)
  - Health status recorded using the EQ-5D VAS
- Health-related quality of life
  - recorded using the EORTC QLQ-C30
- Side effects
  - SAEs
  - Severe adverse events (AEs) (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)
  - Discontinuation due to AEs
  - Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE)
  - Skin and subcutaneous tissue disorders (System Organ Class [SOC], AEs)
  - Interstitial lung disease (ILD) and pneumonitis (company's Preferred Term [PT] collection, severe AEs)
  - Cardiac effects (standardized MedDRA query [SMQ] "heart failure" and SMQ "cardiomyopathy", severe AEs)
  - Other specific AEs

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

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

Table 13: Matrix of outcomes – RCT, direct comparison: osimertinib + pemetrexed + platinum-based chemotherapy[a] vs. osimertinib

| Study | Outcomes | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 8 Overall survival | 9 Symptoms (EORTC QLQ-C30, EORTC QLQ-LC13, PGIS) | 10 Health status (EQ-5D VAS) | 11 Health-related quality of life (EORTC QLQ-C30) | 12 SAEs[b] | 13 Severe AEs[b, c] | 14 Discontinuation due to AEs[b] | 15 PRO-CTCAE | 16 Skin and subcutaneous tissue disorders (SOC, AEs) | 17 ILD and pneumonitis[d] (PT, severe AEs[c]) | 18 Cardiac effects[e] (SMQs, severe AEs[c]) | 19 Other specific AEs[c, f] |
| FLAURA-2 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No[g] | Yes | Yes | Yes | Yes |

a. Cisplatin/carboplatin.
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: acute interstitial pneumonitis, alveolitis, diffuse alveolar damage, idiopathic pulmonary fibrosis, interstitial lung disease, lung disease, organising pneumonia, pneumonitis, pulmonary toxicity and pulmonary fibrosis).
e. Cardiac effects are operationalized using the SMQs "heart failure" and "cardiomyopathy".
f. The following events (MedDRA coding) are considered: decreased appetite (PT, AEs), general disorders and administration site conditions (SOC, severe AEs), blood and lymphatic system disorders (SOC, SAEs), gastrointestinal disorders (SOC, severe AEs), and investigations (SOC, SAEs).
g. No suitable data available; see the following text section for reasons.
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; ILD: interstitial lung disease; MedDRA: Medical Dictionary for Regulatory Activities; PGIS: Patient Global Impression of Severity; PRO-CTCAE: Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire – Core 30; QLQ-LC13: Quality of Life Questionnaire – Lung Cancer 13; RCT: randomized controlled trial; SMQ: Standardized MedDRA Query; SOC: System Organ Class; SAE: serious adverse event; VAS: visual analogue scale

**Notes on the included outcomes**

***Overall survival***

The effects on the outcome of overall survival are influenced not only by the initial study treatment, but also by the subsequent therapies used after treatment discontinuation. In order for an observed effect in the outcome of overall survival to be interpreted meaningfully, adequate subsequent treatment of patients after progression or recurrence of the disease is therefore necessary.

This is not guaranteed in the FLAURA-2 study as described in Section I 3.2. This aspect is taken into account when assessing the outcome-specific risk of bias (see Section I 4.2). Since there was no statistically significant difference between the treatment groups for the outcome "overall survival" at the 2nd data cut-off (3 April 2023) used for the present benefit assessment, the shortcomings described in Section I 3.2 regarding the subsequent therapies in the present data constellation have no consequences for the benefit assessment.

***EORTC QLQ-C30 and EORTC QLQ-LC13***

For the outcomes “symptoms” and “health-related quality of life”, recorded using the EORTC QLQ-C30 and EORTC QLQ-LC13, the company presented analyses in Module 4 A on the mean change from baseline using a mixed-effects model with repeated measures (MMRM) over the course of the study at all data collection points up to and including week 100 (includes all visits with at least 25% non-missing data in both treatment arms). In addition, various responder analyses were planned in the study protocol for these outcomes (time to confirmed deterioration and time to permanent deterioration). For this operationalization, the company did not present any results in Module 4 A.

The responder analyses available in the study documents in Module 5 on confirmed or permanent deterioration are not usable in the present data constellation. Although the reported median observation times in the intervention and comparator arms are sufficiently comparable, there is a continuous decline in the proportion of completed questionnaires over the course of the study, which differs between the study arms (Institute's calculations). This differential decrease cannot be explained solely by the patients who died during the observation period (see Kaplan-Meier curves in I Appendix B). After just one year, the response rate of the EORTC QLQ-C30 in the comparator arm is already more than 10 percentage points lower than in the intervention arm. Therefore, it cannot be assumed with certainty that the observation periods are sufficiently equal over the course of the study. In addition, according to the data in Module 4 A, the median time to disease progression differs between the intervention and comparator arm by around 9 months. The survey frequency of the questionnaires was reduced to 8 weeks after disease progression (compared to survey intervals of 1 to 6 weeks during treatment). This means that a different number of surveys can be expected between the study arms.

Overall, the analyses on the time to confirmed or persistent deterioration can therefore not be used in the present data situation. Analyses for the time to first deterioration would be the adequate operationalization. Since the company did not present these for this procedure (in contrast to the recently presented dossier on osimertinib in the adjuvant treatment of NSCLC [18]), the MMRM analyses presented in Module 4 A were considered for the benefit assessment.

***PGIS***

In addition to the EORTC QLQ-C30 and the EORTC QLQ-LC13, the PGIS was also used to assess symptoms. It consists of a single question that asks patients to rate the severity of their symptoms on the day of the survey on a scale of 0 (no symptoms) to 5 (very severe symptoms).

The MMRM analyses presented by the company (data on all data collection points up to and including week 100, see section on EORTC QLQ-C30 and EORTC QLQ-LC13) are suitable for the benefit assessment and are used to assess the symptoms.

***Side effects***

*AEs, SAEs, and severe AEs*

In the analysis of side effects, the number of patients in whom an event occurred is primarily relevant. However, when analysing the time until occurrence of the event, effects may also result from an earlier or later occurrence of the event rather than on the basis of the proportions. Time-to-event analyses are of particular relevance in between-group comparisons with different mean observation periods [1]. The company presented time-to-event analyses for all side effects outcomes. In the present situation, however, the mean observation periods between the treatment arms are sufficiently similar (see Table 10) to use the relative risk as an effect measure to derive the added benefit for all outcomes in the side effects category.

*PRO-CTCAE*

In the FLAURA-2 study, side effects were also recorded with the PRO-CTCAE instrument. Overall, this instrument is a valuable addition to the usual recording and analysis of AEs. It comprises a total of 78 symptomatic AEs of the CTCAE system, which are compiled into a questionnaire adapted to the respective study situation. The selection of the individual patient-reported symptomatic AEs was to be prespecified and plausible in the study protocol, e.g. to ensure the recording of all important potential AEs of the drugs used in the intervention and comparator arms. For a detailed description of the PRO-CTCAE instrument, see the corresponding explanations in dossier assessment A20-87 [19].

The following 9 symptoms were prespecified in the FLAURA-2 study protocol:

- Sores in the mouth or throat
- Nausea
- Vomiting
- Loose or watery stools
- Pain in the lower abdomen

- Loss of control over bowel movements
- Dry skin
- Hair loss
- Numbness or tingling in the hands and feet

The available documents do not show on what basis the events from the PRO-CTCAE system were selected. The company does not provide more detailed information on its approach – e.g. on its search. On the basis of the information provided by the company, it is thus impossible to determine whether the company implemented the approaches described in A20-87 [19] for a selection of items as per Tolstrup [20] or Taarnhøj [21]. It is also impossible to determine whether the side effects of osimertinib, pemetrexed, carboplatin, and cisplatin have been mapped adequately. For example, it is unclear why symptoms such as rash or lack of appetite were not included in the questionnaire, even though these are mentioned as very common side effects in the SPC for osimertinib [10]. Overall, the data for the PRO-CTCAE outcome are not suitable for benefit assessment due to the lack of transparency in the selection process and because the selection of items for mapping symptomatic AEs is not comprehensible.

### I 4.2 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 + pemetrexed + platinum-based chemotherapy[a] vs. osimertinib

| Study | Outcomes | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 20 Study level | 21 Overall survival | 22 Symptoms (EORTC QLQ-C30, EORTC QLQ-LC13, PGIS) | 23 Health status (EQ-5D VAS) | 24 Health-related quality of life (EORTC QLQ-C30) | 25 SAEs[b] | 26 Severe AEs[b, c] | 27 Discontinuation due to AEs[b] | 28 PRO-CTCAE | 29 Skin and subcutaneous tissue disorders (SOC, AEs) | 30 ILD and pneumonitis[d] (PT, severe AEs[c]) | 31 Cardiac effects[e] (SMQs, severe AEs[c]) | 32 Other specific AEs[c, f] |
| FLAURA-2 | L | H[g] | H[g, h, i, j] | H[g, h, i, j] | H[g, h, i, j] | H[i] | H[i] | H[k] | –[l] | H[h, i] | H[i] | H[i] | H[h, i] |

a. Cisplatin/carboplatin.
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: acute interstitial pneumonitis, alveolitis, diffuse alveolar damage, idiopathic pulmonary fibrosis, interstitial lung disease, lung disease, organising pneumonia, pneumonitis, pulmonary toxicity and pulmonary fibrosis).
e. Cardiac effects are operationalized using the SMQs “heart failure” and “cardiomyopathy”.
f. The following events (MedDRA coding) are considered: decreased appetite (PT, AEs), general disorders and administration site conditions (SOC, severe AEs), blood and lymphatic system disorders (SOC, SAEs), gastrointestinal disorders (SOC, severe AEs), and investigations (SOC, SAEs).
g. Due to uncertainties in the use of adequate subsequent therapies.
h. Lack of blinding in subjective outcome recording; applies to the following specific AEs for the following PT: decreased appetite
i. Incomplete observations for potentially informative reasons.
j. Marked decrease in questionnaire return rates in the course of the study, which differed between treatment arms.
k. Lack of blinding in the presence of subjective decision on treatment discontinuation.
l. No usable data available; see Section I 4.1 for reasons.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; H: high; ILD: interstitial lung disease; L: low; MedDRA: Medical Dictionary for Regulatory Activities; PGIS: Patient Global Impression of Severity; PRO-CTCAE: Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire – Core 30; QLQ-LC13: Quality of Life Questionnaire – Lung Cancer 13; RCT: randomized controlled trial; SMQ: Standardized MedDRA Query; SOC: System Organ Class; SAE: serious adverse event; VAS: visual analogue scale

For the outcome "overall survival", the risk of bias is high due to the deficiencies in the subsequent therapies used (see Section I 3.2). Due to the differences in the median time to 1st disease progression (25.5 months in the intervention arm vs. 16.7 months in the

comparator arm), these had a significantly earlier impact on overall survival in the comparator arm than in the intervention arm.

The results on morbidity and health-related quality of life, recorded using the EORTC QLQ-C30, EORTC QLQ-LC13, PGIS and EQ-5D VAS instruments, also have a high risk of bias. One reason is the lack of blinding, as the outcomes are subjectively recorded by the patients. Furthermore, the proportion of estimated missing questionnaires rose sharply over the course of the study and differed between the treatment arms, particularly clearly from 12 months after the start of observation. These shortened observations may have potentially informative reasons, partly caused by the linking of the questionnaire survey to the 2nd disease progression (see Table 8). However, since the 2nd disease progression is observed after a median of 30.6 months (intervention arm) or 27.8 months (comparator arm), it is assumed that the distorting effect due to the linking of the surveys to the 2nd disease progression has only a minor influence, since the results of the outcomes relate to the period between baseline and week 100 (23 months). The results of these outcomes are also influenced by the deficiencies or uncertainties in the use of adequate subsequent therapies, as they were recorded beyond the 1st disease progression.

The risk of bias is high for the results on the outcome “discontinuation due to AEs”, as the unblinded study design results in a subjective decision to discontinue treatment. The certainty of results is further limited by the fact that treatment can also be discontinued for reasons other than AEs. These reasons represent a competing event for the outcome "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.

Regarding the results of the outcome category “side effects”, the high risk of bias is due to the shortened observations for potentially informative reasons. These result from the fact that the recording of side effects is linked to the end of the study treatment (see Table 8). In addition, the unblinded study design leads to a high risk of bias in the non-serious/non-serious side effects due to subjective outcome recording.

### I 4.3 Results

Table 15 and Table 16 summarize the results comparing osimertinib + pemetrexed + platinum-based chemotherapy with osimertinib for the first-line treatment of adult patients with advanced NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations. Where necessary, IQWiG calculations are provided to supplement the data from the company’s dossier. For assessing clinical relevance, the standardized mean difference (SMD) is used, provided the mean difference is statistically significant.

The Kaplan-Meier curves on the time-to-event analysis for the outcome of overall survival are presented in I Appendix B of the full dossier assessment, and 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, side effects) – RCT, direct comparison: osimertinib + pemetrexed + platinum-based chemotherapy[a] vs. osimertinib (multipage table)

| **Study**<br>**Outcome category**<br>**Outcome** | **Osimertinib + pemetrexed + platinum-based chemotherapy** | | **Osimertinib** | | **Osimertinib + pemetrexed + platinum-based chemotherapy vs. osimertinib** |
|---|---|---|---|---|---|
| | **N[b]** | **Median time to event in months [95% CI]**<br>**Patients with event n (%)** | **N[b]** | **Median time to event in months [95% CI]**<br>**Patients with event n (%)** | **RR [95% CI]; p-value[c]** |
| **FLAURA-2 (data cut-off from 3 April 2023)** | | | | | |
| **Mortality** | | | | | |
| Overall survival | 279 | NA [31.9; NC]<br>71 (25.4) | 278 | NA<br>78 (28.1) | HR: 0.90 [0.65; 1.24]; 0.524[d] |
| **Side effects** | | | | | |
| AEs (supplementary information) | 276 | –<br>276 (100) | 275 | –<br>268 (97.5) | – |
| SAEs | 276 | –<br>104 (37.7) | 275 | –<br>53 (19.3) | 1,96 [1,47; 2,60]; < 0,001 |
| Severe AEs[e] | 276 | –<br>176 (63.8) | 275 | –<br>75 (27.3) | 2.34 [1.89; 2.89]; < 0.001 |
| Discontinuation due to AEs[f] | 276 | –<br>132 (47.8) | 275 | –<br>17 (6.2) | 7.74 [4,80; 12.46]; < 0.001 |
| PRO-CTCAE | | | | No suitable data[g] | |
| Skin and subcutaneous tissue disorders (SOC, AEs) | 276 | –<br>191 (69.2) | 275 | –<br>184 (66.9) | 1.03 [0.92; 1.16]; 0.602 |
| ILD and pneumonitis[h] (PT, severe AEs[e]) | 276 | –<br>2 (0.7) | 275 | –<br>5 (1.8) | 0.40 [0.08; 2.04]; 0.268 |
| Cardiac effects[i] (SMQs, severe AEs[e]) | 276 | –<br>12 (4.3) | 275 | –<br>3 (1.1) | 3.99 [1.14; 13.97]; 0.020 |
| Decreased appetite (PT, AEs) | 276 | –<br>85 (30.8) | 275 | –<br>26 (9.5) | 3.26 [2.17; 4.89]; < 0.001 |

Table 15: Results (mortality, side effects) – RCT, direct comparison: osimertinib + pemetrexed + platinum-based chemotherapy[a] vs. osimertinib (multipage table)

| Study<br>Outcome category<br>Outcome | Osimertinib + pemetrexed + platinum-based chemotherapy | | Osimertinib | | Osimertinib + pemetrexed + platinum-based chemotherapy vs. osimertinib |
|---|---|---|---|---|---|
| | N[b] | Median time to event in months [95% CI]<br>Patients with event n (%) | N[b] | Median time to event in months [95% CI]<br>Patients with event n (%) | RR [95% CI]; p-value[c] |
| General disorders and administration site conditions (SOC, severe AEs[e]) | 276 | –<br>10 (3.6) | 275 | –<br>2 (0.7) | 4.98 [1.10; 22.53]; 0.021 |
| Blood and lymphatic system disorders (SOC, SAEs) | 276 | –<br>18 (6.5) | 275 | –<br>0 (0.0) | 36.87 [2.23; 608.72]; < 0.001 |
| Gastrointestinal disorders (SOC, severe AEs[e]) | 276 | –<br>20 (7.2) | 275 | –<br>4 (1.5) | 4.98 [1.73; 14.39]; < 0.001 |
| Investigations (SOC, SAEs) | 276 | –<br>10 (3.6) | 275 | –<br>1 (0.4) | 9.96 [1.28; 77.31]; 0.006 |

a. Cisplatin/carboplatin.
b. Mortality data refer to the number of randomized patients. Data on side effects refer to the number of randomized patients in the intervention vs. control arm who have received at least 1 dose of the study treatment (276 vs. 275 patients).
c. For outcomes of the side effects category: Institute's calculation of RR, 95% CI and p-value (unconditional exact test, CSZ method according to [22]).
d. Analysis using log-rank test, stratified by family origin (Chinese/Asian vs. non-Chinese/Asian vs. non-Asian), WHO PS (0 vs. 1) and tissue testing method (central vs. local).
e. Operationalized as CTCAE grade ≥ 3.
f. Discontinuation of 1 or more components.
g. For an explanation, see Section I 4.1.
h. PT collection of the company (PTs included: acute interstitial pneumonitis, alveolitis, diffuse alveolar damage, idiopathic pulmonary fibrosis, interstitial lung disease, lung disease, organising pneumonia, pneumonitis, pulmonary toxicity and pulmonary fibrosis); of these, the following PTs occurred: interstitial lung disease, pneumonitis, organising pneumonia).
i. Operationalized using the SMQs “heart failure” and “cardiomyopathy”.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; ILD: interstitial lung disease; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least 1) event; N: number of analysed patients; NC: not calculable; NR: not reached; PRO-CTCAE: Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events; RCT: randomized controlled trial; RR: relative risk; SMQ: Standardized MedDRA Query; SOC: System Organ Class; SAE: serious adverse event; WHO-PS: World Health Organization – Performance Status

Table 16: Results (morbidity, health-related quality of life) – RCT, direct comparison: osimertinib + pemetrexed + platinum-based chemotherapy[a] vs. osimertinib (multipage table)

| Study<br>Outcome category<br>Outcome | Osimertinib + pemetrexed + platinum-based chemotherapy | | | Osimertinib | | | Osimertinib + pemetrexed + platinum-based chemotherapy vs. osimertinib |
|---|---|---|---|---|---|---|---|
| | N[b] | Values at baseline mean (SD) | Mean change in the course of the study mean[c] (SE) | N[b] | Values at baseline mean (SD) | Mean change in the course of the study mean[c] (SE) | MWD [95% CI]; p-value[c] |
| **FLAURA-2 (data cut-off from 3 April 2023)** | | | | | | | |
| **Morbidity** | | | | | | | |
| Symptoms (EORTC QLQ-C30)[d] | | | | | | | |
| Fatigue | 253 | 29.60 (21.33) | 0.13 (0.89) | 253 | 34.12 (26.73) | -4.28 (0.90) | 4.40 [1.91; 6.89]; 0.001e<br>SMD: 0.31 [0.13; 0.48] |
| Pain | 253 | 26.28 (24.26) | -7.97 (0.87) | 253 | 29.78 (28.80) | -8.78 (0.88) | 0.81 [-1.61; 3.23]; 0.511 |
| Nausea and vomiting | 253 | 6.19 (12.56) | 1.45 (0.50) | 253 | 5.99 (14.86) | -0.94 (0.51) | 2.40 [1.00; 3.80]; 0.001e<br>SMD: 0.30 [0.12; 0.47] |
| Dyspnoea | 253 | 24.64 (25.96) | -6.88 (0.92) | 253 | 29.64 (28.86) | -8.68 (0.93) | 1.79 [-0.77; 4.36]; 0.170 |
| Insomnia | 253 | 29.91 (25.31) | -8.98 (0.91) | 253 | 31.49 (31.79) | -10.92 (0.92) | 1.94 [-0.59; 4.48]; 0.133 |
| Appetite loss | 253 | 20.95 (26.98) | 2.01 (0.99) | 253 | 21.87 (29.63) | -3.02 (1.00) | 5.04 [2.27; 7.81]; 0.001e<br>SMD: 0.32 [0.14; 0.49] |
| Constipation | 253 | 14.76 (23.04) | -0.13 (0.80) | 253 | 14.49 (24.32) | -3.04 (0.81) | 2.91 [0.67; 5.15]; 0.011<br>SMD: 0.23 [0.05; 0.40] |
| Diarrhoea | 253 | 5.01 (12.30) | 9.51 (0.85) | 253 | 6.59 (15.45) | 11.00 (0.86) | -1.49 [-3.86; 0.88]; 0.219 |
| Symptoms (EORTC QLQ-LC13)[d] | | | | | | | |
| Cough | 253 | 32.41 (27.44) | -12.66 (0.83) | 251 | 31.34 (28.61) | -10.04 (0.84) | -2.62 [-4.94; -0.31]; 0.027<br>SMD: -0.20 [-0.37; -0.02] |
| Haemoptysis | 253 | 2.11 (8.66) | -1.94 (0.20) | 251 | 5.58 (16.99) | -1.94 (0.21) | 0.00 [-0.57; 0.58]; 0.988 |
| Dysphagia | 253 | 5.53 (15.00) | 3.07 (0.63) | 251 | 4.78 (14.43) | 2.16 (0.64) | 0.91 [-0.85; 2.68]; 0.310 |
| Pain in arm or shoulder | 253 | 17.79 (22.12) | -3.61 (0.80) | 251 | 18.86 (24.92) | -2.86 (0.81) | -0.75 [-2.99; 1.49]; 0.510 |
| Pain (other body parts) | 253 | 21.87 (23.67) | -2.47 (0.83) | 251 | 27.09 (29.68) | -3.80 (0.84) | 1.34 [-0.98; 3.65]; 0.258 |

Table 16: Results (morbidity, health-related quality of life) – RCT, direct comparison: osimertinib + pemetrexed + platinum-based chemotherapy[a] vs. osimertinib (multipage table)

| Study<br>Outcome category<br>Outcome | Osimertinib + pemetrexed + platinum-based chemotherapy | | | Osimertinib | | | Osimertinib + pemetrexed + platinum-based chemotherapy vs. osimertinib |
|---|---|---|---|---|---|---|---|
| | N[b] | Values at baseline mean (SD) | Mean change in the course of the study mean[c] (SE) | N[b] | Values at baseline mean (SD) | Mean change in the course of the study mean[c] (SE) | MWD [95% CI]; p-value[c] |
| Pain (chest) | 253 | 16.86 (20.49) | -5.82 (0.69) | 251 | 21.25 (25.47) | -5.80 (0.69) | -0.02 [-1.94; 1.90]; 0.980 |
| sore mouth | 253 | 3.82 (12.19) | 11.12 (0.84) | 251 | 4.78 (14.73) | 8.74 (0.84) | 2.38 [0.06; 4.71]; 0.045<br>SMD:<br>0.18 [0.00; 0.35] |
| Dyspnoea | 253 | 23.54 (20.58) | -2.52 (0.81) | 251 | 26.69 (24.25) | -4.42 (0.82) | 1.90 [-0.36; 4.16]; 0.099 |
| Peripheral neuropathy | 253 | 7.77 (16.70) | 9.08 (0.84) | 251 | 7.17 (16.65) | 7.84 (0.85) | 1.24 [-1.11; 3.58]; 0.301 |
| Alopecia | 253 | 5.67 (16.76) | 6.63 (0.84) | 251 | 9.96 (23.53) | 6.44 (0.85) | 0.19 [-2.17; 2.55]; 0.874 |
| Symptoms (PGIS)[d] | 242 | 1.58 (1.40) | -0.16 (0.05) | 248 | 1.75 (1.47) | -0.24 (0.05) | 0.09 [-0.06; 0.23]; 0.230 |
| Health status (EQ-5D VAS)[e] | 246 | 71.94 (18.26) | 1.26 (0.79) | 249 | 71.28 (19.47) | 2.49 (0.79) | -1.23 [-3.42; 0.96]; 0.272 |
| **Health-related quality of life** | | | | | | | |
| EORTC QLQ-C30[e] | | | | | | | |
| Physical functioning | 253 | 78.66 (20.30) | 1.91 (0.80) | 253 | 75.97 (23.07) | 4.62 (0.81) | -2.71 [-4.94; -0.47]; 0.018<br>SMD:<br>-0.21 [-0.39; -0.04] |
| Role functioning | 253 | 76.94 (25.93) | 1.09 (1.06) | 253 | 72.86 (30.01) | 3.98 (1.07) | -2.89 [-5.86; 0.08]; 0.056 |
| Cognitive functioning | 253 | 85.64 (16.20) | -2.75 (0.72) | 253 | 85.51 (19.88) | -0.43 (0.72) | -2.32 [-4.31; -0.32]; 0.023<br>SMD:<br>-0.20 [-0.38; -0.03] |
| Emotional functioning | 253 | 74.60 (20.40) | 6.22 (0.78) | 253 | 74.47 (21.90) | 7.45 (0.79) | -1.23 [-3.42; 0.95]; 0.268 |
| Social functioning | 253 | 75.69 (23.50) | 0.09 (1.01) | 253 | 74.18 (27.87) | 5.40 (1.01) | -5.31 [-8.12; -2.51]; 0.001<br>SMD:<br>-0.33 [-0.51; -0.16] |
| Global health status | 253 | 65.91 (19.45) | 3.04 (0.80) | 253 | 63.77 (21.56) | 5.51 (0.80) | -2.47 [-4.69; -0.25]; 0.029<br>SMD:<br>-0.19 [-0.37; -0.02] |

Table 16: Results (morbidity, health-related quality of life) – RCT, direct comparison: osimertinib + pemetrexed + platinum-based chemotherapy[a] vs. osimertinib (multipage table)

| Study<br>Outcome category<br>Outcome | Osimertinib + pemetrexed + platinum-based chemotherapy | | | Osimertinib | | | Osimertinib + pemetrexed + platinum-based chemotherapy vs. osimertinib |
|---|---|---|---|---|---|---|---|
| | N[b] | Values at baseline mean (SD) | Mean change in the course of the study mean[c] (SE) | N[b] | Values at baseline mean (SD) | Mean change in the course of the study mean[c] (SE) | MWD [95% CI]; p-value[c] |

a. Cisplatin/carboplatin.
b. Number of patients taken into account in the analysis for calculating the effect estimation; baseline values may rest on different patient numbers.
c. MMRM (contains data for all survey time points up to and including week 100) with treatment, visit and interaction from treatment and visit as fixed effects as well as baseline value as covariate and interaction between baseline and visit.
d. Lower (decreasing) values indicate improved symptoms; negative effects (intervention minus comparison) indicate an advantage for the intervention (scale range: 0 to 100).
e. Higher (increasing) values indicate better health status/health-related quality of life; positive effects (intervention minus comparison) indicate an advantage for the intervention (scale range: 0 to 100).

CI: confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; MMRM: mixed-effects model with repeated measures; MD: mean difference; N: number of analysed patients; PGIS: Patient Global Impression of Severity; QLQ-C30: Quality of Life Questionnaire – Core 30; QLQ-LC13: Quality of Life Questionnaire – Lung Cancer 13; RCT: randomized controlled trial; SE: standard error; SMD: standardized mean difference; VAS: visual analogue scale

On the basis of the available information, no more than hints, e.g. of an added benefit, can be determined for all outcomes due to the high outcome-specific risk of bias.

### Mortality

#### *Overall survival*

There was no statistically significant difference between the treatment arms for the outcome "overall survival". This results in no hint of an added benefit of osimertinib + pemetrexed + platinum-based chemotherapy in comparison with osimertinib; an added benefit is therefore not proven.

### Morbidity

#### *Symptoms (recorded with the EORTC QLQ-C30)*

On the basis of the mean difference, the analyses showed no statistically significant difference between the treatment arms for each of the following outcomes: pain, dyspnoea, insomnia, and diarrhoea. This results in no hint of an added benefit of osimertinib + pemetrexed + platinum-based chemotherapy in comparison with osimertinib in each case; an added benefit is therefore not proven.

On the basis of the mean difference, the analyses showed a statistically significant difference between the treatment arms for each of the following outcomes: fatigue, nausea and vomiting, appetite loss, and constipation. The SMD is analysed to examine the relevance of the results. The 95% CI of the SMD is not fully outside the irrelevance range of −0.2 to 0.2. It can therefore not be inferred that the effects are relevant. This results in no hint of an added benefit of osimertinib + pemetrexed + platinum-based chemotherapy in comparison with osimertinib in each case; an added benefit is therefore not proven.

***Symptoms (recorded with the EORTC QLQ-LC13)***

On the basis of the mean difference, the analyses showed a statistically significant difference between treatment arms for the outcome of cough. The SMD is analysed to examine the relevance of the results. The 95% CI of the SMD is not fully outside the irrelevance range of −0.2 to 0.2. It can therefore not be inferred that the effects are relevant. There is an effect modification by the characteristic of CNS metastases at baseline, however (see Section I 4.4). For patients with CNS metastases at baseline, there is a hint of an added benefit from osimertinib + pemetrexed + platinum-based chemotherapy in comparison with osimertinib. For patients without CNS metastases at baseline, there is no hint of an added benefit of osimertinib + pemetrexed + platinum-based chemotherapy in comparison with osimertinib; an added benefit is therefore not proven.

On the basis of the mean difference, the analyses showed no statistically significant difference between the treatment arms for each of the following outcomes: haemoptysis, dysphagia, pain (arm/shoulder), pain (chest), dyspnoea, peripheral neuropathy, and alopecia. This results in no hint of an added benefit of osimertinib + pemetrexed + platinum-based chemotherapy in comparison with osimertinib in each case; an added benefit is therefore not proven.

On the basis of the mean difference, the analyses showed a statistically significant difference between treatment arms for the outcome of pain (other body parts). There is an effect modification by the characteristic of age, however (see Section I 4.4). For patients < 65 years, there is a hint of lesser benefit from osimertinib + pemetrexed + platinum-based chemotherapy in comparison with osimertinib. For patients ≥ 65 years, there is no hint of an added benefit of osimertinib + pemetrexed + platinum-based chemotherapy in comparison with osimertinib; an added benefit is therefore not proven.

On the basis of the mean difference, the analyses showed a statistically significant difference between treatment arms for the outcome of sore mouth. The statistical mean difference (SMD) was analysed to examine the relevance of the results. The 95% CI of the SMD is not fully outside the irrelevance range of −0.2 to 0.2. It can therefore not be inferred that the effects are relevant. This results in no hint of an added benefit of osimertinib + pemetrexed +

platinum-based chemotherapy in comparison with osimertinib; an added benefit is therefore not proven.

***Symptoms (recorded with the PGIS)***

On the basis of mean difference, the analysis showed no statistically significant difference between treatment groups for the outcome of symptoms (recorded using the PGIS). This results in no hint of an added benefit of osimertinib + pemetrexed + platinum-based chemotherapy in comparison with osimertinib; an added benefit is therefore not proven.

***Health status (recorded with the EQ-5D VAS)***

On the basis of the mean difference, no statistically significant difference between treatment arms was found for the outcome "health status" (recorded using the EQ-5D VAS). This results in no hint of an added benefit of osimertinib + pemetrexed + platinum-based chemotherapy in comparison with osimertinib; an added benefit is therefore not proven.

***Health-related quality of life (recorded using EORTC QLQ-C30)***

On the basis of the mean difference, the analyses showed a statistically significant difference between the treatment arms for each of the following outcomes: physical functioning, social functioning, and global health status. The SMD is analysed to examine the relevance of the results. In each case, the 95% CI of the SMD is not fully outside the irrelevance range of −0.2 to 0.2. It can therefore not be inferred that the effects are relevant. This results in no hint of an added benefit of osimertinib + pemetrexed + platinum-based chemotherapy in comparison with osimertinib in each case; an added benefit is therefore not proven.

On the basis of the mean difference, the analyses showed no statistically significant difference between the treatment arms for each of the following outcomes: role functioning and emotional functioning. This results in no hint of an added benefit of osimertinib + pemetrexed + platinum-based chemotherapy in comparison with osimertinib in each case; an added benefit is therefore not proven.

**Side effects**

***SAEs***

For the outcome of SAEs, a statistically significant difference was found to the disadvantage of osimertinib + pemetrexed + platinum-based chemotherapy in comparison with osimertinib. However, there was an effect modification by the characteristic of age. For patients < 65 years, there is a hint of greater harm from osimertinib + pemetrexed + platinum-based chemotherapy in comparison with osimertinib. For patients ≥ 65 years, there is no hint of greater or lesser harm from osimertinib + pemetrexed + platinum-based chemotherapy in comparison with osimertinib; greater or lesser harm is therefore not proven (see Section I 4.4).

***Severe AEs (CTCAE grade ≥ 3)***

For the outcome of severe AEs (CTCAE grade ≥ 3), a statistically significant difference was found to the disadvantage of osimertinib + pemetrexed + platinum-based chemotherapy in comparison with osimertinib. There is a hint of greater harm from osimertinib + pemetrexed + platinum-based chemotherapy in comparison with osimertinib.

***Discontinuation due to AEs***

For the outcome of discontinuation due to AEs, a statistically significant difference was found to the disadvantage of osimertinib + pemetrexed + platinum-based chemotherapy in comparison with osimertinib. There is a hint of greater harm from osimertinib + pemetrexed + platinum-based chemotherapy in comparison with osimertinib.

***PRO-CTCAE***

No suitable data are available for the outcome of PRO-CTCAE (see Section I 4.1 for reasons). There is no hint of greater or lesser harm from osimertinib + pemetrexed + platinum-based chemotherapy in comparison with osimertinib; greater or lesser harm is therefore not proven.

***Skin and subcutaneous tissue disorders (AEs) and ILD and pneumonitis (severe AEs)***

For the outcomes of skin and subcutaneous tissue disorders (AEs) and ILD and pneumonitis (severe AEs), no statistically significant difference between the treatment arms is shown. There is no hint of greater or lesser harm from osimertinib + pemetrexed + platinum-based chemotherapy in comparison with osimertinib in each case; greater or lesser harm is therefore not proven.

***Cardiac effects (severe AEs)***

For the outcome of cardiac effects (severe AEs) a statistically significant difference was found to the disadvantage of osimertinib + pemetrexed + platinum-based chemotherapy in comparison with osimertinib. There is a hint of greater harm from osimertinib + pemetrexed + platinum-based chemotherapy in comparison with osimertinib.

***Other specific AEs***

For the outcomes of decreased appetite (AEs), general disorders and administration site conditions (severe AEs), blood and lymphatic system disorders (SAEs), gastrointestinal disorders (severe AEs) and investigations (SAEs), there is a statistically significant difference to the disadvantage of osimertinib + pemetrexed + platinum-based chemotherapy in comparison with osimertinib. In each case, there is a hint of greater harm from osimertinib + pemetrexed + platinum-based chemotherapy in comparison with osimertinib.

### I 4.4 Subgroups and other effect modifiers

The following subgroup characteristics were considered in the present benefit assessment:

- Age (< 65 years versus ≥ 65 years)
- Sex (male versus female)
- CNS metastases at baseline (yes versus no)

The subgroup characteristics mentioned were predefined in the FLAURA-2 study for the PFS outcome. In Module 4 A, the company presented subgroup analyses for all outcomes presented, but not for the outcome "overall survival" for the 2nd data cut-off from 3 April 2023 relevant for the present benefit assessment. These subgroup analyses are missing.

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

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are 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.

The results are presented in Table 17 and Table 18. Forest plots for the Institute's calculations of subgroup analyses that meet the criteria mentioned for the presentation of the benefit assessment can be found in I Appendix D.

Table 17: Subgroups (side effects) – RCT, direct comparison: osimertinib + pemetrexed + platinum-based chemotherapy[a] vs. osimertinib

| Study<br>Outcome<br>Characteristic<br>Subgroup | Osimertinib + pemetrexed + platinum-based chemotherapy | | Osimertinib | | Osimertinib + pemetrexed + platinum-based chemotherapy vs. osimertinib | |
|---|---|---|---|---|---|---|
| | N[b] | Patients with event<br>n (%) | N[b] | Patients with event<br>n (%) | RR [95% CI][c] | p-value[c] |
| **FLAURA-2 (data cut-off from 3 April 2023)** | | | | | | |
| **Side effects** | | | | | | |
| SAEs | | | | | | |
| Age | | | | | | |
| < 65 years | 172 | 64 (37.2) | 164 | 23 (14.0) | 2.65 [1.73; 4.06] | < 0.001 |
| ≥ 65 years | 104 | 40 (38.5) | 111 | 30 (27.0) | 1.42 [0.96; 2.10] | 0.080 |
| Total | | | | | Interaction: | 0.033[d] |

a. Cisplatin/carboplatin.
b. The data refer to the number of randomized patients in the respective subgroup.
c. Institute's calculation of RR, 95% CI and p-value (unconditional exact test, CSZ method according to [22]) for the side effects.
d. Institute's calculation: Q test for heterogeneity.
CI: confidence interval; CNS: central nervous system; n: number of patients with (at least 1) event; N: number of analysed patients; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event

Table 18: Subgroups (morbidity) – RCT, direct comparison: osimertinib + pemetrexed + platinum-based chemotherapy[a] vs. osimertinib

| Study<br>Outcome<br>Characteristic<br>Subgroup | Osimertinib + pemetrexed + platinum-based chemotherapy | | | Osimertinib | | | Osimertinib + pemetrexed + platinum-based chemotherapy vs. osimertinib |
|---|---|---|---|---|---|---|---|
| | N[b] | Values at baseline mean (SD) | Mean change in the course of the study mean[c] (SE) | N[b] | Values at baseline mean (SD) | Mean change in the course of the study mean[c] (SE) | MWD [95% CI]; p-value |
| **FLAURA-2 (data cut-off from 3 April 2023)** | | | | | | | |
| **Morbidity** | | | | | | | |
| Cough (EORTC QLQ-LC13)[d] | | | | | | | |
| CNS metastases at baseline | | | | | | | |
| Yes | 103 | 39.16 (27.39) | -18.55 (0.70) | 101 | 35.97 (28.94) | -14.24 (0.78) | -4.31 [-6.38; -2.25]; < 0.001<br>SMD: -0.57 [-0.85; -0.29] |
| No | 150 | 27.78 (26.59) | -9.74 (0.62) | 150 | 28.22 (28.05) | -8.64 (0.61) | -1.11 [-2.82; 0.60]; 0.203 |
| Total | | | | | | Interaction: | p-value = 0.021 |
| Pain, other body parts (EORTC QLQ-LC13)[d] | | | | | | | |
| Age | | | | | | | |
| < 65 years | 158 | 23.21 (24.30) | -3.14 (0.54) | 150 | 27.78 (28.49) | -6.88 (0.58) | 3.74 [2.18; 5.30]; < 0.001<br>SMD: 0.54 [0.31; 0.76] |
| ≥ 65 years | 95 | 19.65 (22.54) | -1.76 (0.74) | 101 | 26.07 (31.48) | 0.50 (0.72) | -2.26 [-4.29; -0.22]; 0.030<br>SMD: -0.31 [-0.59; -0.03] |
| Total | | | | | | Interaction: | p-value < 0.001 |

a. Cisplatin/carboplatin.
b. Number of patients taken into account in the effect estimation; baseline values may rest on different patient numbers.
c. MMRM (contains data for all survey time points up to and including week 100) with treatment, visit and interaction from treatment and visit as fixed effects as well as baseline value as covariate and interaction between baseline and visit.
d. Lower (decreasing) values indicate improved symptoms; negative effects (intervention minus comparison) indicate an advantage for the intervention (scale range: 0 to 100).

CI: confidence interval; CNS: central nervous system; EORTC: European Organisation for Research and Treatment of Cancer; MMRM: mixed-effects model with repeated measures; MD: mean difference; N: number of analysed patients; QLQ-LC13: Quality of Life Questionnaire – Lung Cancer 13; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; SMD: standardized mean difference

**Morbidity**

***Cough (recorded with the EORTC QLQ-LC13)***

For the outcome of cough, the analyses on the basis of the mean difference show a statistically significant effect modification by the characteristic CNS metastases at baseline. For patients with CNS metastases at baseline, there is a statistically significant difference in favour of osimertinib + pemetrexed + platinum-based chemotherapy in comparison with osimertinib. The SMD is analysed to examine the relevance of the results. The 95% CI of the SMD lies fully outside the irrelevance range of -0.2 to 0.2. This was interpreted to be a relevant effect. For patients with CNS metastases at baseline, there is a hint of an added benefit from osimertinib + pemetrexed + platinum-based chemotherapy in comparison with osimertinib. However, for patients without CNS metastases at baseline, there was no statistically significant difference between the treatment arms. This results in no hint of an added benefit of osimertinib + pemetrexed + platinum-based chemotherapy in comparison with osimertinib in this subgroup; an added benefit is therefore not proven.

***Pain, other body parts (recorded with EORTC QLQ-LC13)***

On the basis of the mean difference, the analyses showed a statistically significant difference effect modification by the characteristic of age for the outcome of pain (other body parts). For patients < 65 years, a statistically significant difference was found to the disadvantage of osimertinib + pemetrexed + platinum-based chemotherapy in comparison with osimertinib. The SMD is analysed to examine the relevance of the results. The 95% CI of the SMD lies fully outside the irrelevance range of -0.2 to 0.2. This was interpreted to be a relevant effect. For patients < 65 years, there is a hint of lesser benefit from osimertinib + pemetrexed + platinum-based chemotherapy in comparison with osimertinib. For patients ≥ 65 years, however, a statistically significant difference was found in favour of osimertinib + pemetrexed + platinum-based chemotherapy in comparison with osimertinib. The SMD is analysed to examine the relevance of the results. The 95% confidence interval (CI) of the SMD was not completely outside the irrelevance range of −0.2 to 0.2. The effect can therefore not be inferred to be relevant. This results in no hint of an added benefit of osimertinib + pemetrexed + platinum-based chemotherapy in comparison with osimertinib in this subgroup; an added benefit is therefore not proven.

**Side effects**

***SAEs***

There was a statistically significant effect modification by the characteristic "age" for the outcome "SAEs". For patients < 65 years, a statistically significant difference was found to the disadvantage of osimertinib + pemetrexed + platinum-based chemotherapy in comparison with osimertinib. For patients < 65 years, there is a hint of greater harm from osimertinib + pemetrexed + platinum-based chemotherapy in comparison with osimertinib. For patients

≥ 65 years, there is no hint of greater or lesser harm from osimertinib + pemetrexed + platinum-based chemotherapy in comparison with osimertinib; greater or lesser harm is therefore not proven.

## I 5 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 IQWiG *General Methods* [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 5.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Chapter I 4 (see Table 19).

**Determination of the outcome category for outcomes on symptoms and side effects**

***Symptoms***

For the outcomes of cough and pain (other body parts) recorded with EORTC QLQ-C30, insufficient information is available to classify the severity category as serious/severe. The outcomes were therefore assigned to the outcome category of non-serious/non-severe symptoms/late complications.

***Side effects***

For the outcome of discontinuation due to AEs, the available severity data are also insufficient for a classification as serious/severe. The outcome of discontinuation due to AEs was therefore assigned to the outcome category of non-serious/non-severe side effects.

Table 19: Extent of added benefit at outcome level: osimertinib + pemetrexed + platinum-based chemotherapy[a] vs. osimertinib (multipage table)

| **Observation period**<br>**Outcome category**<br>**Outcome**<br>**Effect modifier**<br>**Subgroup** | **Osimertinib + pemetrexed + platinum-based chemotherapy vs. osimertinib**<br>**Median time to event (months) or proportion of events (%) or mean change in the course of the study**<br>**Effect estimation [95% CI];**<br>**p-value**<br>**Probability[b]** | **Derivation of extent[c]** |
|---|---|---|
| **Outcomes with observation over the entire study duration** | | |
| **Mortality** | | |
| Overall survival | Median: NA vs. NA<br>HR: 0.90 [0.65; 1.24]<br>p = 0.524 | Lesser/added benefit not proven |
| **Outcomes with shortened observation period** | | |
| **Morbidity** | | |
| Symptoms (EORTC QLQ-C30) | | |
| Fatigue | 0.13 vs. -4.28<br>MD: 4.40 [1.91; 6.89]<br>p < 0.001<br>SMD: 0.31 [0.13; 0.48][d] | Lesser/added benefit not proven |
| Pain | -7.97 vs. -8.78<br>MD: 0.81 [-1.61; 3.23]<br>p = 0.511 | Lesser/added benefit not proven |
| Nausea and vomiting | 1.45 vs. -0.94<br>MD: 2.40 [1.00; 3.80]<br>p < 0.001<br>SMD: 0.30 [0.12; 0.47][d] | Lesser/added benefit not proven |
| Dyspnoea | -6.88 vs. -8.68<br>MD: 1.79 [-0.77; 4.36]<br>p = 0.170 | Lesser/added benefit not proven |
| Insomnia | -8.98 vs. -10.92<br>MD: 1.94 [-0.59; 4.48]<br>p = 0.133 | Lesser/added benefit not proven |
| Appetite loss | 2.01 vs. -3.02<br>MD: 5.04 [2.27; 7.81]<br>p < 0.001<br>SMD: 0.32 [0.14; 0.49][d] | Lesser/added benefit not proven |
| Constipation | -0.13 vs. -3.04<br>MD: 2.91 [0.67; 5.15]<br>p = 0.011<br>SMD: 0.23 [0.05; 0.40][d] | Lesser/added benefit not proven |
| Diarrhoea | 9.51 vs. 11.00<br>MD: -1.49 [-3.86; 0.88]<br>p = 0.219 | Lesser/added benefit not proven |

Table 19: Extent of added benefit at outcome level: osimertinib + pemetrexed + platinum-based chemotherapy[a] vs. osimertinib (multipage table)

| **Observation period**<br>**Outcome category**<br>**Outcome**<br>**Effect modifier**<br>**Subgroup** | **Osimertinib + pemetrexed + platinum-based chemotherapy vs. osimertinib**<br>**Median time to event (months) or proportion of events (%) or mean change in the course of the study**<br>**Effect estimation [95% CI];**<br>**p-value**<br>**Probability[b]** | **Derivation of extent[c]** |
|---|---|---|
| Symptoms (EORTC QLQ-LC13) | | |
| Cough | | |
| CNS metastases at baseline | | |
| Yes | -18.55 vs. -14.24<br>MD: -4.31 [-6.38; -2.25]<br>p < 0.001<br>SMD: -0.57 [-0.85; -0.29][d]<br>SMD: 0.57 [0.29; 0.85][e]<br>Probability: hint | Outcome category: non-serious/non-severe symptoms/late complications<br>$0.2 < CI_L < 0.40$<br>added benefit, extent "minor" |
| No | -9.74 vs. -8.64<br>MD: -1.11 [-2.82; 0.60]<br>p = 0.203 | Lesser/added benefit not proven |
| Haemoptysis | -1.94 vs. -1.94<br>MD: 0.00 [-0.57; 0.58]<br>p = 0.988 | Lesser/added benefit not proven |
| Dysphagia | 3.07 vs. 2.16<br>MD: 0.91 [-0.85; 2.68]<br>p = 0.310 | Lesser/added benefit not proven |
| Pain in arm or shoulder | -3.61 vs. -2.86<br>MD: -0.75 [-2.99; 1.49]<br>p = 0.510 | Lesser/added benefit not proven |
| Pain<br>(other body parts) | | |
| Age | | |
| < 65 years | -3.14 vs. -6.88<br>MD: 3.74 [2.18; 5.30]<br>p < 0.001<br>SMD: 0.54 [0.31; 0.76][d]<br>Probability: “hint” | Outcome category: non-serious/non-severe symptoms/late complications<br>$0.2 \leq CI_L < 0.40$<br>Lesser benefit, extent: “minor” |
| ≥ 65 years | -1.76 vs. 0.50<br>MD: -2.26 [-4.29; -0.22]<br>p = 0.030<br>SMD: -0.31 [-0.59; -0.03][d] | Lesser/added benefit not proven |
| Pain (chest) | -5.82 vs. -5.80<br>MD: -0.02 [-1.94; 1.90]<br>p = 0.980 | Lesser/added benefit not proven |

Table 19: Extent of added benefit at outcome level: osimertinib + pemetrexed + platinum-based chemotherapy[a] vs. osimertinib (multipage table)

| **Observation period**<br>**Outcome category**<br>**Outcome**<br>**Effect modifier**<br>**Subgroup** | **Osimertinib + pemetrexed + platinum-based chemotherapy vs. osimertinib**<br>**Median time to event (months) or proportion of events (%) or mean change in the course of the study**<br>**Effect estimation [95% CI];**<br>**p-value**<br>**Probability[b]** | **Derivation of extent[c]** |
|---|---|---|
| sore mouth | 11.12 vs. 8.74<br>MD: 2.38 [0.06; 4.71]<br>p = 0.045<br>SMD: 0.18 [0.00; 0.35][d] | Lesser/added benefit not proven |
| Dyspnoea | -2.52 vs. -4.42<br>MD: 1.90 [-0.36; 4.16]<br>p = 0.099 | Lesser/added benefit not proven |
| Peripheral neuropathy | 9.08 vs. 7.84<br>MD: 1.24 [-1.11; 3.58]<br>p = 0.301 | Lesser/added benefit not proven |
| Alopecia | 6.63 vs. 6.44<br>MD: 0.19 [-2.17; 2.55]<br>p = 0.874 | Lesser/added benefit not proven |
| Symptoms | | |
| PGIS | -0.16 vs. -0.24<br>MD: 0.09 [-0.06; 0.23]<br>p = 0.230 | Lesser/added benefit not proven |
| Health status | | |
| EQ-5D VAS | 1.26 vs. 2.49<br>MD: -1.23 [-3.42; 0.96]<br>p = 0.272 | Lesser/added benefit not proven |
| **Health-related quality of life** | | |
| EORTC QLQ-C30 | | |
| Physical functioning | 1.91 vs. 4.62<br>MD: -2.71 [-4.94; -0.47]<br>p = 0.018<br>SMD: -0.21 [-0.39; -0.04][d] | Lesser/added benefit not proven |
| Role functioning | 1.09 vs. 3.98<br>MD: -2.89 [-5.86; 0.08]<br>p = 0.056 | Lesser/added benefit not proven |
| Cognitive functioning | -2.75 vs. -0.43<br>MD: -2.32 [-4.31; -0.32]<br>p = 0.023<br>SMD: -0.20 [-0.38; -0.03][d] | Lesser/added benefit not proven |
| Emotional functioning | 6.22 vs. 7.45<br>MD: -1.23 [-3.42; 0.95]<br>p = 0.268 | Lesser/added benefit not proven |

Table 19: Extent of added benefit at outcome level: osimertinib + pemetrexed + platinum-based chemotherapy[a] vs. osimertinib (multipage table)

| **Observation period**<br>**Outcome category**<br>**Outcome**<br>**Effect modifier**<br>**Subgroup** | **Osimertinib + pemetrexed + platinum-based chemotherapy vs. osimertinib**<br>**Median time to event (months) or proportion of events (%) or mean change in the course of the study**<br>**Effect estimation [95% CI];**<br>**p-value**<br>**Probability[b]** | **Derivation of extent[c]** |
|---|---|---|
| Social functioning | 0.09 vs. 5.40<br>MD: -5.31 [-8.12; -2.51]<br>p < 0.001<br>SMD: -0.33 [-0.51; -0.16][d] | Lesser/added benefit not proven |
| Health status | 3.04 vs. 5.51<br>MD: -2.47 [-4.69; -0.25]<br>p = 0.029<br>SMD: -0.19 [-0.37; -0.02][d] | Lesser/added benefit not proven |
| **Side effects** | | |
| SAEs<br>Age<br>< 65 years | 37.2% vs. 14.0%<br>RR: 2.65 [1.73; 4.06]<br>RR: 0.38 [0.25; 0.58][e]<br>p < 0.001<br>Probability: "hint" | Outcome category: serious/severe side effects<br>$CI_u$ < 0.75, risk ≥ 5%<br>Greater harm, extent: “major” |
| ≥ 65 years | 38.5% vs. 27.0%<br>RR: 1.42 [0.96; 2.10];<br>p = 0.080 | Greater/lesser harm not proven |
| Severe AEs | 63.8% vs. 27.3%<br>RR: 2.34 [1.89; 2.89]<br>RR: 0.43 [0.35; 0.53][e]<br>p < 0.001<br>Probability: "hint" | Outcome category: serious/severe side effects<br>$CI_u$ < 0.75; risk ≥ 5%<br>Greater harm, extent: “major” |
| Discontinuation due to AEs | 47.8 % vs. 6.2 %<br>RR: 7.74 [4.80; 12.46]<br>RR: 0.13 [0.08; 0.21][e]<br>p < 0.001<br>Probability: "hint" | Outcome category: non-serious/non-severe side effects<br>$CI_u$ < 0.80<br>Greater harm; extent: “considerable” |
| PRO-CTCAE | No suitable data[f] | Greater/lesser harm not proven |
| Skin and subcutaneous tissue disorders (AEs) | 69.2% vs. 66.9%<br>RR: 1.03 [0.92; 1.16];<br>p = 0.602 | Greater/lesser harm not proven |
| ILD and pneumonitish (severe AEs) | 0.7% vs. 1.8%<br>RR: 0.40 [0.08; 2.04];<br>p = 0.268 | Greater/lesser harm not proven |

Table 19: Extent of added benefit at outcome level: osimertinib + pemetrexed + platinum-based chemotherapy[a] vs. osimertinib (multipage table)

| **Observation period**<br>**Outcome category**<br>**Outcome**<br>**Effect modifier**<br>**Subgroup** | **Osimertinib + pemetrexed + platinum-based chemotherapy vs. osimertinib**<br>**Median time to event (months) or proportion of events (%) or mean change in the course of the study**<br>**Effect estimation [95% CI];**<br>**p-value**<br>**Probability[b]** | **Derivation of extent[c]** |
|---|---|---|
| Cardiac effects<br>(severe AEs) | 4.3% vs. 1.1%<br>RR: 3.99 [1.14; 13.97]<br>RR: 0.25 [0.07; 0.88][e]<br>p = 0.020<br>Probability: "hint" | Outcome category: serious/severe side effects<br>$0.75 < CI_u < 0.90$<br>Greater harm; extent: “considerable” |
| Decreased appetite<br>(AEs) | 30.8% vs. 9.5%<br>RR: 3.26 [2.17; 4.89]<br>RR: 0.31 [0.20; 0.46][e]<br>p < 0.001<br>Probability: "hint" | Outcome category "non-serious/non-severe AEs"<br>$CI_u < 0.80$<br>Greater harm; extent: “considerable” |
| General disorders and administration site conditions<br>(severe AEs) | 3.6% vs. 0.7%<br>RR: 4.98 [1.10; 22.53]<br>RR: 0.20 [0.04; 0.91][e]<br>p = 0.021<br>Probability: "hint" | Outcome category: serious/severe side effects<br>$0.90 \leq CI_u < 1.00$<br>greater harm, extent: minor |
| Blood and lymphatic system disorders<br>(SAEs) | 6.5% vs. 0.0%<br>RR: 36.87 [2.23; 608.72]<br>RR: 0.03 [0.00; 0.45][e]<br>p < 0.001<br>Probability: "hint" | Outcome category: serious/severe side effects<br>$CI_u < 0.75$; risk ≥ 5%<br>Greater harm, extent: “major” |
| Gastrointestinal disorders<br>(severe AEs) | 7.2% vs. 1.5%<br>RR: 4.98 [1.73; 14.39]<br>RR: 0.20 [0.07; 0.58][e]<br>p < 0.001<br>Probability: "hint" | Outcome category: serious/severe side effects<br>$CI_u < 0.75$; risk ≥ 5%<br>Greater harm, extent: “major” |
| Investigations<br>(SAEs) | 3.6% vs. 0.4%<br>RR: 9.96 [1.28; 77.31]<br>RR: 0.10 [0.01; 0.78][e]<br>p = 0.006<br>Probability: "hint" | Outcome category: serious/severe side effects<br>$0.75 \leq CI_u < 0.90$<br>Greater harm; extent: “considerable” |

a. Cisplatin/carboplatin.
b. Probability provided if a statistically significant and relevant effect is present.
c. Depending on the outcome category and the scale of the outcome, effect size is estimated with different limits based on the upper or lower limit of the confidence interval ($CI_u$ or $CI_L$).
d. If the CI for the SMD is fully outside the irrelevance range [-0.2; 0.2], this is interpreted to be a relevant effect. In other cases, the presence of a relevant effect cannot be derived.
e. Institute’s calculation; inverse direction of effect to enable use of limits to derive the extent of the added benefit.
f. For an explanation, see Section I 4.1.

Table 19: Extent of added benefit at outcome level: osimertinib + pemetrexed + platinum-based chemotherapy[a] vs. osimertinib (multipage table)

| **Observation period**<br>**Outcome category**<br>**Outcome**<br>**Effect modifier**<br>**Subgroup** | **Osimertinib + pemetrexed + platinum-based chemotherapy vs. osimertinib**<br>**Median time to event (months) or proportion of events (%) or mean change in the course of the study**<br>**Effect estimation [95% CI];**<br>**p-value**<br>**Probability[b]** | **Derivation of extent[c]** |
|---|---|---|
| AE: adverse event; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; ILD: interstitial lung disease; ND no data; CI: confidence interval; $CI_U$: upper limit of confidence interval; $CI_L$: lower limit of confidence interval; MD: mean difference; NR: not reached; PGIS: Patient Global Impression of Severity; PRO-CTCAE: Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events; QLQ-C30: Quality of Life Questionnaire – Core 30; QLQ-LC13: Quality of Life Questionnaire – Lung Cancer 13; RR: relatives Risiko; SMD: standardized mean difference; SAE: serious adverse event; VAS: visual analogue scale; CNS: central nervous system | | |

## I 5.2 Overall conclusion on added benefit

Table 20 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 20: Positive and negative effects from the assessment of osimertinib + pemetrexed + platinum-based chemotherapy[a] in comparison with osimertinib

| Positive effects | Negative effects |
|---|---|
| **Outcomes with shortened observation period** | |
| Non-serious/non-severe symptoms/late complications<br>Cough:<br>CNS metastases at baseline: hint of an added benefit – extent: "minor" | Non-serious/non-severe symptoms/late complications<br>Pain (other body parts):<br>Age, < 65 years: hint of lesser benefit – extent: "minor" |
| – | Serious/severe side effects<br>SAEs:<br>Age, < 65 years): hint of greater harm – extent: "major"<br>Severe AEs: hint of greater harm – extent: “major”<br>Cardiac effects (severe AEs): hint of greater harm – extent "considerable"<br>General disorders and administration site conditions (severe AEs): hint of greater harm – extent: "minor"<br>Blood and lymphatic system disorders (SAEs): hint of greater harm – extent: "major"<br>Gastrointestinal disorders (severe AEs): hint of greater harm – extent: "major"<br>Investigations (SAEs): hint of greater harm, extent: "considerable" |
| – | Non-serious/non-severe side effects<br>Discontinuation due to AEs: hint of greater harm – extent "considerable"<br>Decreased appetite (AEs): hint of greater harm – extent: "considerable" |
| a. Cisplatin/carboplatin.<br>AE: adverse event; CNS: central nervous system; SAE: serious adverse event | |

Overall, one favourable and several unfavourable effects of osimertinib + pemetrexed + platinum-based chemotherapy were found in comparison with osimertinib.

For the outcome “cough” in patients with CNS metastases at baseline, there is a hint of a minor added benefit from osimertinib + pemetrexed + platinum-based chemotherapy in comparison with osimertinib.

On the other hand, for the outcome “pain (other body parts)” in patients < 65 years, there is a hint of lesser benefit from osimertinib + pemetrexed + platinum-based chemotherapy in comparison with osimertinib. Furthermore, there are hints of greater harm for numerous outcomes in the category of side effects, including the overall rates for SAEs (for the subgroup < 65 years), severe AEs and discontinuation due to AEs, with varying, sometimes major, extent.

The negative effects, some of which are of major extent, clearly outweigh the positive effects, which are of minor extent. In summary, there is therefore a hint of lesser benefit from osimertinib in combination with pemetrexed and platinum-based chemotherapy versus osimertinib for the first-line treatment of adult patients with advanced NSCLC, whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations.

The result of the assessment of the added benefit of osimertinib + pemetrexed + platinum-based chemotherapy in comparison with osimertinib is summarized in Table 21.

Table 21: Osimertinib + pemetrexed + platinum-based chemotherapy – probability and extent of added benefit

| **Therapeutic indication** | **ACT**[a, b, c] | **Probability and extent of added benefit** |
|---|---|---|
| Adult patients with advanced NSCLC whose tumours have epidermal growth factor receptor exon 19 deletions or exon 21 (L858R) substitution mutations; first-line treatment | ▪ Afatinib (only for patients with the activating EGFR mutation deletion in exon 19)<br>or<br>▪ Osimertinib | Hint of lesser benefit[d] |

a. Presented is the ACT specified by the G-BA.
b. In terms of therapeutic indication, it is assumed that neither definitive radiochemotherapy nor definitive local therapy are indicated. In addition, it is assumed that molecularly stratified therapy (directed against ALK, BRAF, Exon 20, KRAS G12C, METex14, RET, or ROS1) is not an option for the patients at the time of treatment with osimertinib.
c. The ACT specified here comprises several alternative treatment options. However, individual treatment options only represent a comparator therapy for those members of the patient population who have the patient and disease characteristics shown in brackets. The alternative treatment options are only to be regarded as equally appropriate in the area in which the patient populations have the same characteristics.
d. Only patients with an WHO PS of 0 or 1 were included in the FLAURA-2 study. It remains unclear whether the observed effects are transferable to patients with an WHO PS ≥ 2.

ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; BRAF: rapidly accelerated fibrosarcoma isoform B; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; KRAS: Kirsten Rat Sarcoma Viral Oncogene Homologue; METex14: Exon 14 of the mesenchymal epithelial transition factor gene; NSCLC: non-small cell lung cancer; RET: Rearranged during Transfection; ROS1: C-ros Oncogene 1 WHO PS: World Health Organization – Performance Status

The assessment described above deviates from that by the company, which derived an indication of considerable added benefit.

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 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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