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

Addendum to Project A24-77 (dossier assessment)[1]

ADDENDUM

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
NSCLC	non-small cell lung cancer
PFS	progression-free survival
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)

1 Background

On 10 December 2024, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A24-77 (Osimertinib – Benefit assessment according to §35a Social Code Book V) [1].

The commission comprises the assessment of the analyses of the 3rd data cut-off of the FLAURA-2 study dated 8 January 2024 presented by the pharmaceutical company (hereinafter referred to as “the company”) in the commenting procedure [2], taking into account the information provided in the dossier [3].

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

The randomized controlled trial (RCT) FLAURA-2 was included for the benefit assessment 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. A detailed description of the FLAURA-2 study can be found in dossier assessment A24-77 [1].

Analyses on 3 data cut-offs are available for the FLAURA-2 study:

- 1st data cut-off (22 September 2021): prespecified interim futility analysis after reaching approximately 83 events in the primary outcome of progression-free survival (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 of follow-up after the last patient started the study
- 3rd data cut-off (8 January 2024): data cut-off requested by the European Medicines Agency (EMA) to support the approval procedure. For this data cut-off, the company presented exclusively analyses for the outcome of overall survival.

The 3rd data cut-off from 8 January 2024 was not used for benefit assessment A24-77 [1] because it was unclear whether it had been requested by the EMA. Besides, only analyses on the outcome of overall survival were available. This does not meet the requirements of a complete analysis of all recorded relevant outcomes according to the dossier template [4]. In particular, there were no analyses on the outcomes in the side effects category, in which a relevant number of events could still occur between the 2nd and 3rd data cut-offs (for details see A24-77 [1]). Therefore, the analyses of the prespecified 2nd data cut-off from 3 April 2023, which were completely available in the company's dossier, were used for the benefit assessment and taken into account in the derivation of the added benefit.

In the commenting procedure [2], the company submitted documents [5] showing that the 3rd data cut-off from 8 January 2024 was requested by the EMA. However, it did not present any analyses of outcomes in the side effects category for the 3rd data cut-off in the context of the commenting procedure either. In addition, as already noted in the dossier assessment, information on subsequent therapies for the 3rd data cut-off from 8 January 2024 is missing, which would be necessary for an interpretation of the results on overall survival at this data cut-off. At the 2nd data cut-off on 3 April 2023, around 40% of patients with disease progression had not received any subsequent therapy. Even after the commenting procedure, it remains unclear why a relevant proportion of patients did not receive any subsequent

therapy after disease progression. Patients in the comparator arm in particular who – in contrast to the intervention arm – had not yet received any chemotherapy might have benefited from guideline-compliant subsequent therapy after disease progression. The uncertainty described in benefit assessment A24-77 regarding the results on overall survival thus remains.

In summary, the available analyses of the 3rd data cut-off from 8 January 2024 are still not suitable for the benefit assessment. Although the data cut-off was requested by the EMA, the analyses are still incomplete and therefore do not meet the requirements of the dossier template.

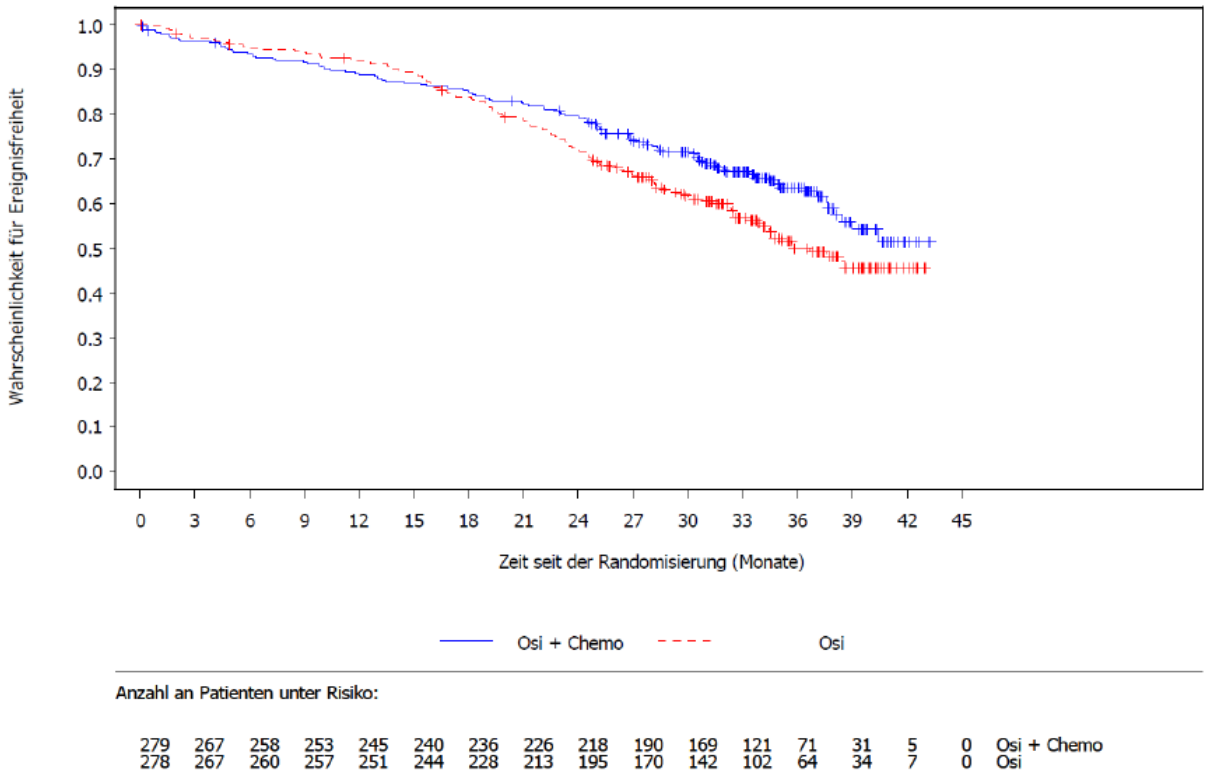
Regardless of this, there is a statistically significant difference in overall survival at the 3rd data cut-off in favour of osimertinib + pemetrexed + platinum-based chemotherapy (see Table 1 and Figure 1). This result must be interpreted against the background of the uncertainty described above regarding the subsequent therapies administered (missing data at the 3rd data cut-off; high proportion of patients without subsequent therapy in the comparator arm at the 2nd data cut-off). Assuming that the observed statistically significant effect is not solely due to inadequate subsequent therapies and that no further adverse events occurred to a relevant extent between the 2nd and 3rd data cut-offs, an advantage in the outcome of overall survival would be offset by disadvantages, in some cases to a major extent, in the outcome category of side effects. Overall, no advantage or disadvantage of 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 could be derived in this data situation.

Table 1: Results (mortality) – RCT, direct comparison: osimertinib + pemetrexed + platinum-based chemotherapy[a] vs. osimertinib

Study Outcome category Outcome	Osimertinib + pemetrexed + platinum-based chemotherapy		Osimertinib		Osimertinib + pemetrexed + platinum-based chemotherapy vs. osimertinib
	N[b]	Median time to event in months [95% CI] Patients with event n (%)	N[b]	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[c]
FLAURA-2 (data cut-off from 8 January 2024)					
Mortality					
Overall survival	279	NA 100 (35.8)	278	36.7 [33.2; NC] 126 (45.3)	0.75 [0.57; 0.97]; 0.028

a. Cisplatin/carboplatin.
b. Data refer to the number of randomized patients.
c. Using U- and V- statistics from stratified log-rank test, stratified by family origin (Chinese/Asian vs. non-Chinese/Asian vs. non-Asian), WHO PS (0 vs. 1), and method of tissue testing (central vs. local).

CI: confidence interval; HR: hazard ratio; n: number of patients with event; N: number of analysed patients; NA: not achieved; NC: not calculable; RCT: randomized controlled trial



Wahrscheinlichkeit für Ereignisfreiheit – Probability of overall survival
Zeit seit der Randomisierung (Monate) – Time from randomization (months)
Anzahl an Patienten unter Risiko – Number of patients at risk

Figure 1: Kaplan-Meier curves for the outcome of overall survival in the FLAURA-2 study, 3rd data cut-off (8 January 2024)

Subgroups and other effect modifiers

The following potential effect modifiers were considered for the present addendum:

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

The methods described in Section I 4.4 of dossier assessment A24-77 are used.

Irrespective of the lack of suitability of the results of the 3rd data cut-off for the benefit assessment described above, no relevant effect modifications were shown for the outcome of overall survival for the 3rd data cut-off.

3 References

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5. European Medicines Agency. Extension of indication variation assessment report (Request for Supplementary Information); Procedure No. EMEA/H/C/004124/II/0053; Invented name: TAGRISSO [unpublished]. 2023.