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Osimertinib (non-small cell lung cancer) –

Addendum to Commission A17-20[1]

Addendum

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List of abbreviations

Abbreviation	Meaning
AE	adverse event
CTCAE	Common Terminology Criteria for Adverse Events
EGFR	epidermal growth factor receptor
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
PT	Preferred Term
SOC	System Organ Class
TKI	tyrosine kinase inhibitor

1 Background

On 12 September 2017, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A17-20 (Osimertinib – Benefit assessment according to §35a Social Code Book V [1]).

In its dossier [2], the pharmaceutical company (hereinafter referred to as "the company") had presented results from the AURA3 study to prove the added benefit of osimertinib. A subpopulation of the study was used for the benefit assessment, namely patients for whom treatment with cisplatin was determined before randomization (cisplatin population). The results of the total population were presented as additional information [1].

With its comment, the company submitted supplementary information on adverse events (AEs), which went beyond the information provided in the dossier [3]. The G-BA commissioned IQWiG with the assessment of the analyses presented by the company on AEs at System Organ Class (SOC) level and at Preferred Term (PT) level and under consideration of the information in the dossier. The assessment was to be conducted both for the subpopulation of patients for whom treatment with cisplatin was determined before randomization, and for the total population of the AURA3 study.

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

2.1 Data availability on specific adverse events of the AURA3 study

The company presented the AURA3 study for the benefit assessment of osimertinib. This study was a randomized, open-label, active-controlled study on the comparison of osimertinib with a platinum-based chemotherapy consisting of cisplatin + pemetrexed or carboplatin + pemetrexed. In the study, treatment with carboplatin-based chemotherapy was not explicitly limited according to the criteria of the Pharmaceutical Directive for the off-label indication of carboplatin [4]. For this reason, only a subpopulation of patients (cisplatin population) was used for the benefit assessment [1].

No information was provided on specific AEs for the relevant subpopulation of the study. In its original dossier [2], the company had presented survival time analyses for specific AEs, which, in addition, were only selective, only for the total population of the AURA3 study. This choice included predefined AEs (referred to by the company as "AEs of special interest"), common severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3) and common AEs. For common AEs and common severe AEs, the company presented analyses only at Medical Dictionary for Regulatory Activities (MedDRA) PT level; analyses at SOC level were missing.

With its comment, the company presented survival time analyses for the SOC level of AEs and severe AEs (CTCAE grade ≥ 3) both for the cisplatin population and for the total population of the AURA3 study [3]. However, the company still did not present any analyses for the events at PT level and the predefined AEs for the relevant cisplatin population with the comment. Hence, the information base for the outcomes on side effects for the cisplatin population was still incomplete.

The following Table 1 provides an overview of the survival time analyses on common AEs, severe AEs, and "AEs of special interest" available in the dossier and subsequently submitted by the company with the comment.

Table 1: Overview of the survival time analyses on adverse events for the AURA3 study

Outcome **MedDRA level**	**Cisplatin population**	**Total population**
Common AEs		
SOC	Subsequently submitted	Subsequently submitted
PT	Analyses missing	Available in the dossier
Common severe AEs (CTCAE grade ≥ 3)		
SOC	Subsequently submitted	Subsequently submitted
PT	Analyses missing	Available in the dossier
AEs predefined in the CSR, which consist of different PTs[a]	Analyses missing	Available in the dossier

a: Referred to by the company as "AEs of special interest".

AE: adverse event; CSR: clinical study report; CTCAE: Common Terminology Criteria for Adverse Events; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; SOC: System Organ Class

2.2 Results

Table 2 compiles the results on specific AEs for osimertinib. The data subsequently submitted by the company for the cisplatin population (proportions of patients with at least 1 event) on common AEs and severe AEs (CTCAE grade ≥ 3) are presented in Appendix A.

Table 2: Results (specific AEs, time to first event) – RCT, direct comparison: osimertinib vs. cisplatin + pemetrexed and (as additional information) osimertinib vs. cisplatin + pemetrexed or cisplatin + pemetrexed

Study Outcome category Outcome	Osimertinib		Cisplatin + pemetrexed		Osimertinib vs. cisplatin + pemetrexed	Osimertinib		Carboplatin + pemetrexed or carboplatin + pemetrexed		Osimertinib vs. cisplatin + pemetrexed or carboplatin + pemetrexed
	N	Median survival time in months [95% CI] Patients with event n (%)	N	Median survival time in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value	N	Median survival time in months [95% CI] Patients with event n (%)	N	Median survival time in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value
AURA3										
Specific AEs										
Diarrhoea (PT)	87	ND ND	45	ND ND	ND	279	NA 115 (41.2)	136	NA 15 (11.0)	3.67 [2.21; 6.56]; < 0.001
Constipation (PT)	87	ND ND	45	ND ND	ND	279	NA 43 (15.4)	136	NA 47 (34.6)	0.24 [0.16; 0.38]; < 0.001
Nausea (PT)	87	ND ND	45	ND ND	ND	279	NA 56 (20.1)	136	3.94 [NC] 67 (49.3)	0.20 [0.14; 0.30]; < 0.001
Vomiting (PT)	87	ND ND	45	ND ND	ND	279	NA 36 (12.9)	136	NA 28 (20.6)	0.39 [0.23; 0.65]; < 0.001
General disorders and administration site conditions (SOC)[a]	87	ND [6.18; ND] 38 (43.7)	45	2.07 [0.85; ND] 27 (60.0)	0.47 [0.29; 0.78]; 0.004	279	19.61 [13.37; NC] 117 (41.9)	136	1.31 [0.76; 2.30] 88 (64.7)	0.36 [0.27; 0.48]; < 0.001

(continued)

Table 2: Results (specific AEs, time to first event) – RCT, direct comparison: osimertinib vs. cisplatin + pemetrexed and (as additional information) osimertinib vs. cisplatin + pemetrexed or cisplatin + pemetrexed (continued)

Study Outcome category Outcome	Osimertinib		Cisplatin + pemetrexed		Osimertinib vs. cisplatin + pemetrexed	Osimertinib		Carboplatin + pemetrexed or carboplatin + pemetrexed		Osimertinib vs. cisplatin + pemetrexed or carboplatin + pemetrexed
	N	Median survival time in months [95% CI] Patients with event n (%)	N	Median survival time in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value	N	Median survival time in months [95% CI] Patients with event n (%)	N	Median survival time in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value
AURA3										
Specific AEs										
Nail effects (AESI)		ND		ND	ND	279	NA 68 (24.4)	136	NA 2 (1.5)	12.24 [3.83; 74.61]; < 0.001
Skin effects (AESI)		ND		ND	ND	279	6.97 [NC] 146 (52.3)	136	NA 22 (16.2)	3.40 [2.22; 5.48]; < 0.001
Skin and subcutaneous tissue disorders (SOC)	87	2.46 [0.76; ND] 51 (58.6)	45	NA [14.52; ND] 9 (20.0)	3.57 [1.85; 7.78]; < 0.001	279	2.83 [2.00; 6.87] 166 (59.5)	136	14.52 [14.52; NC] 37 (27.2)	2.28 [1.61; 3.30]; < 0.001
Blood and lymphatic system disorders (SOC, severe AEs of CTCAE grade ≥ 3)	87	NC 0 (0)	45	NC [ND] 4 (8.9)	0.00 [ND; 0.23]; 0.001	279	NA 5 (1.8)	136	NA 21 (15.4)	0.07 [0.02; 0.18]; < 0.001

a: The most common PTs in the total population are asthenia and fatigue.

AE: adverse event; AESI: AE of special interest; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; n: number of patients with (at least 1) event; N: number of analysed patients; NA: not achieved; NC: not calculable; ND: no data; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus

In the total population, negative effects of osimertinib were shown in diarrhoea, nail effects and side effects of the skin (skin effects and SOC skin and subcutaneous tissue disorders). An advantage of osimertinib was shown for each of the following specific AEs: constipation, nausea, vomiting, general disorders and administration site conditions, and blood and lymphatic system disorders.

Under consideration of the information on the proportion of patients with at least 1 common AE subsequently submitted with the comment (see Appendix A), there were overall no indications that there are other specific severe or serious side effects of osimertinib for the cisplatin population than in the total population. The results of the total population could therefore be used to estimate the potential influence of the negative effects in individual specific AEs on the positive overall result (see dossier assessment A17-20 [1]) for osimertinib. Overall, it was not assumed that negative effects in the subpopulation could call into question the positive effects of osimertinib regarding severe AEs (CTCAE grade ≥ 3), health-related quality of life and symptoms to such an extent that this would overall result in a minor added benefit of osimertinib. The estimation of the added benefit of osimertinib has therefore not changed in comparison with the assessment.

In summary, there is still a hint of a non-quantifiable, at least considerable added benefit of osimertinib in comparison with cisplatin + pemetrexed for patients with locally advanced or metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer (NSCLC) who have been pretreated with an EGFR tyrosine kinase inhibitor (TKI) and for whom cytotoxic chemotherapy is an option. A more specific quantification is not possible due to the missing data on specific AEs at PT level for the relevant subpopulation.

The results of the assessment of the added benefit of osimertinib compared with the appropriate comparator therapy in patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC who have received prior EGFR-TKI therapy for whom cytotoxic chemotherapy is an option are shown in Table 3.

Table 3: Osimertinib – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with locally advanced or metastatic NSCLC and a positive T790M EGFR mutation as well as pretreatment with an EGFR-TKI for whom cytotoxic chemotherapy is an option	▪ Pysician's choice of cytotoxic chemotherapy (under consideration of the approval status together with the prescription of drugs in off-label indications in accordance with Appendix VI of the Pharmaceutical Directive) or, if applicable, ▪ best supportive care for patients who have already received cytotoxic chemotherapy as an alternative for further cytotoxic chemotherapy	Hint of non-quantifiable, at least considerable added benefit[b]
a: Presentation of the respective ACT specified by the G-BA. b: In the relevant subpopulation of the AURA3 study cisplatin + pemetrexed were examined in the comparator therapy. Conclusions in comparison with further therapies included in the treatment specified by the physician cannot be drawn on the basis of the study. ACT: appropriate comparator therapy; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer; TKI: tyrosine kinase inhibitor		

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

3 References

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Appendix A – Results on side effects for the cisplatin population of the AURA3 study

Table 4: Common AEs – RCT, direct comparison: osimertinib vs. cisplatin + pemetrexed

Study	Patients with event n (%)	
SOC[a] **PT[a]**	**Osimertinib** **N = 87**	**Cisplatin + pemetrexed** **N = 45**
AURA3		
Overall rate of AEs	86 (98.9)	45 (100)
Infections and infestations	55 (63.2)	15 (33.3)
PT	ND	ND
Blood and lymphatic system disorders	18 (20.7)	18 (40.0)
PT	ND	ND
Metabolism and nutrition disorders	24 (27.6)	25 (55.6)
PT	ND	ND
Psychiatric disorders	14 (16.1)	8 (17.8)
PT	ND	ND
Nervous system disorders	22 (25.3)	17 (37.8)
PT	ND	ND
Eye disorders	12 (13.8)	9 (20.0)
PT	ND	ND
Ear and labyrinth disorders	5 (5.7)	9 (20.0)
PT	ND	ND
Vascular disorders	8 (9.2)	9 (20.0)
PT	ND	ND
Respiratory, thoracic and mediastinal disorders	42 (48.3)	15 (33.3)
PT	ND	ND
Gastrointestinal disorders	61 (70.1)	38 (84.4)
PT	ND	ND
Skin and subcutaneous tissue disorders	51 (58.6)	9 (20.0)
PT	ND	ND
Musculoskeletal and connective tissue disorders	35 (40.2)	13 (28.9)
PT	ND	ND
General disorders and administration site conditions	38 (43.7)	27 (60.0)
PT	ND	ND

(continued)

Table 4: Common AEs – RCT, direct comparison: osimertinib vs. cisplatin + pemetrexed (continued)

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**Osimertinib** **N = 87**	**Cisplatin + pemetrexed** **N = 45**
Investigations	33 (37.9)	20 (44.4)
PT	ND	ND
Injury, poisoning and procedural complications	4 (4.6)	3 (6.7)
PT	ND	ND

a: MedDRA version 19.0.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least 1) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus

Table 5: Common severe AEs (CTCAE grade ≥ 3) – RCT, direct comparison: osimertinib vs. cisplatin + pemetrexed

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**Osimertinib** **N = 87**	**Cisplatin + pemetrexed** **N = 45**
AURA3		
Overall rate of CTCAE grade ≥ 3 AEs	24 (27.6)	22 (48.9)
Infections and infestations	2 (2.3)	2 (4.4)
PT	ND	ND
Blood and lymphatic system disorders	0 (0.0)	4 (8.9)
PT	ND	ND
Metabolism and nutrition disorders	6 (6.9)	7 (15.6)
PT	ND	ND
Nervous system disorders	2 (2.3)	2 (4.4)
PT	ND	ND
Vascular disorders	0 (0.0)	2 (4.4)
PT	ND	ND
Respiratory, thoracic and mediastinal disorders	5 (5.7)	2 (4.4)
PT	ND	ND
Gastrointestinal disorders	1 (1.1)	3 (6.7)
PT	ND	ND
General disorders and administration site conditions	1 (1.1)	3 (6.7)
PT	ND	ND
Investigations	6 (6.9)	8 (17.8)
PT	ND	ND

a: MedDRA version 19.0.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least 1) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus