IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Alectinib (non-small cell lung cancer) –

Addendum to Commission A17-67[1]

Addendum

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
CNS	central nervous system
CSR	clinical study report
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HGG	high-grade glioma
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
RANO	Response Assessment in Neuro-Oncology
RECIST	Response Evaluation Criteria in Solid Tumors
SGB	Sozialgesetzbuch (Social Code Book)

1 Background

On 8 May 2018, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A17-67 (Alectinib – 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 of the ALEX study on the comparison of alectinib with the appropriate comparator therapy (ACT) crizotinib. Among other aspects, the ALEX study investigated central nervous system (CNS) response and CNS progression. For reasons relating to content and methods, the respective data presented in the dossier were unsuitable for the derivation of an added benefit of alectinib [1]. After the oral hearing, the company submitted further analyses on these outcomes.

The G-BA commissioned IQWiG with the analysis of the data on the outcomes "time to CNS progression" and "CNS response".

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 Analyses presented by the company

Analyses on the outcome "time to CNS progression"

In its dossier, the company had presented different analyses on the outcome "time to CNS progression", both assessed according to RECIST[2] and assessed according to RANO-HGG[3]. Dossier assessment A17-67 described that the underlying RECIST and RANO-HGG criteria do not guarantee patient relevance of the outcomes in the present therapeutic indication [1]. In addition, it was explained in dossier assessment A17-67 that the analyses presented by the company were unsuitable also for methodological reasons as the patients were censored after non-CNS progression [1]. Hence, the analyses presented by the company in the dossier only recorded part of the CNS events, i. e. those events that had occurred before non-CNS disease progression. This aspect was also discussed in the oral hearing on alectinib. After the oral hearing, the company therefore subsequently submitted analyses without censoring after non-CNS progression [3]. However, it could be inferred from these documents subsequently submitted that no systematic follow-up observation of CNS progression was conducted after the end of treatment. Hence, irrespective of the analysis, CNS progression was not completely recorded due to the design of the ALEX study.

For the assessment of CNS progression according to RANO-HGG, the documents subsequently submitted [3] only contained analyses for the subpopulation with CNS metastases at baseline. The company justified this by claiming that an assessment of CNS metastases according to RANO-HGG was only conducted for the population with CNS metastases at baseline. It explained that, according to the study protocol, the parameters "corticosteroid use" and "clinical neurological status", which are relevant for the assessment according to RANO-HGG, were only recorded for patients with CNS metastases at baseline. However, the study protocol mandated the recording of corticosteroid use and clinical neurological status in general in patients with known CNS metastases, and not explicitly only in CNS metastases at baseline. This would therefore also include patients with new metastases. Correspondingly, the clinical study report (CSR) contained analyses of the time to CNS progression according to RANO-HGG (with censoring of patients with non-CNS disease progression or death) for the total population of the study. The company's justification for not presenting these data with changed censoring for the total population after the oral hearing is therefore not comprehensible.

The available data for the time to CNS progression are presented in the following Table 1. The corresponding Kaplan-Meier curves and cumulative incidence curves can be found in Appendix A.

[2] RECIST: Response Evaluation Criteria in Solid Tumors Version 1.1

[3] RANO-HGG: Response Assessment in Neuro-Oncology criteria for high-grade gliomas

Table 1: Results (morbidity, time to CNS progression) – RCT, direct comparison: alectinib vs. crizotinib

Study Outcome category Outcome Operationalization	Alectinib N	Alectinib Median time to event in months [95% CI] Patients with event n (%)	Crizotinib N	Crizotinib Median time to event in months [95% CI] Patients with event n (%)	Alectinib vs. crizotinib HR [95% CI][a]; p-value[b]
ALEX					
Morbidity					
Time to CNS progression[c]					
with complete follow-up observation of the CNS					
according to RANO-HGG		ND		ND	ND
according to RECIST		ND		ND	ND
without censoring due to non-CNS progression, but observation only until treatment discontinuation					
according to RANO-HGG		ND		ND	ND
according to RECIST		NA 22 (14.5)		14.6 [9.4; 21.9] 71 (47.0)	0.21 [0.13; 0.35]; < 0.001
with censoring due to non-CNS progression, observation only until treatment discontinuation					
according to RANO-HGG	152	ND 16 (10.5)	151	ND 54 (35.8)	0.18 [0.10; 0.33][d]; < 0.001
according to RECIST	152	ND 18 (11.8)	151	ND 68 (45.0)	0.16 [0.10; 0.28][d]; < 0.001

a: Stratified Cox model with the following stratification factors: ethnicity (Asian/non-Asian) and CNS metastases at baseline according to the IRC (yes/no).
b: Stratified log-rank test with the following stratification factors: ethnicity (Asian/non-Asian) and CNS metastases at baseline according to the IRC (yes/no).
c: Data cut-off 9 February 2017.
d: Cause-specific HR, competing risk analysis of CNS progression, non-CNS progression, and death as competing events.
CI: confidence interval; CNS: central nervous system; HR: hazard ratio; IRC: independent review committee; n: number of patients with event; N: number of analysed patients; NA: not achieved, ND: no data; RANO-HGG: Response Assessment in Neuro-Oncology criteria for high-grade gliomas; RCT: randomized controlled trial; RECIST: Response Evaluation Criteria in Solid Tumours; vs.: versus

There were statistically significant differences between the treatment groups in favour of alectinib for the outcome "time to CNS progression" for both analyses (with and without censoring due to non-CNS progression). This applied to both operationalizations, RECIST and RANO-HGG. On the one hand, this effect was visible at an early time point (see figures in Appendix A). On the other, the difference in CNS progressions (according to RECIST) between crizotinib and alectinib was notably higher (50 events) than the number of non-CNS progressions under alectinib (36 events). The lack of systematic follow-up observation after the

end of treatment therefore did not raise doubts about the positive effect of alectinib on CNS progressions; the magnitude of the effect was unclear, however.

This positive effect on CNS progressions was only partly reflected in the patient-relevant outcomes recorded in the ALEX study, namely in the symptoms "nausea and vomiting". It is unclear, however, whether this was primarily caused by the higher rate of CNS progressions under crizotinib or by crizotinib side effects. Further symptoms associated with CNS metastases, e.g. headache, hemiparesis or psychiatric disorders, were not more common under crizotinib than under alectinib [1]. Also regarding health-related quality of life, no advantage of alectinib was shown, despite lesser CNS progression [1].

Analyses on CNS response

In its dossier, the company also presented analyses on CNS response (operationalized as "objective response rate" using RECIST or RANO-HGG) and duration of CNS response. Consistent differences in favour of alectinib were shown; depending on the operationalization, the results were statistically significant [2]. In contrast to CNS progression, however, the company presented no time-adjusted analysis for CNS response, but only corresponding event rates and their relative risk. As described above, systematic investigations of the CNS were only conducted until treatment discontinuation (or until 4 weeks afterwards), however. Since treatment duration was markedly longer under alectinib than under crizotinib (median: 17.9 versus 10.7 months, data cut off on 9 February 2017), CNS response could be recorded for a substantially longer period of time under alectinib than under crizotinib. The event rates and the corresponding relative risk are therefore not meaningfully interpretable, irrespective of the question whether the used criteria according to RECIST or RANO-HGG were suitable with regard to content. The same therefore applies to analyses on the duration of CNS response.

Further analyses subsequently submitted by the company

Besides the analysis on the time to CNS progression described above, in which patients were censored in the event of death, the company also subsequently submitted analyses on the composite outcome "CNS progression or death". Irrespective of the question whether this analysis is meaningful with regard to content, it is not meaningful in the present data constellation as it constitutes a combination of outcomes with different observation periods. The reason is that patients who discontinued treatment before CNS progression were followed up regarding survival, but not regarding CNS progression. The observation of the composite outcome was therefore incomplete. Hence, the outcome is not meaningfully interpretable in the present data constellation.

3 References

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Alectinib (nicht kleinzelliges Lungenkarzinom): Nutzenbewertung gemäß § 35a SGB V (neues Anwendungsgebiet); Dossierbewertung; Auftrag A17-67 [online]. 28.03.2018 [Accessed 25.04.2018]. (IQWiG-Berichte; Volume 612). URL: https://www.iqwig.de/download/A17-67_Alectinib_Nutzenbewertung-35a-SGB-V_V1-0.pdf.

2. Roche Pharma. Alectinib (Alecensa): Dossier zur Nutzenbewertung gemäß § 35a SGB V [online]. 21.12.2017 [Accessed: 04.04.2018]. URL: https://www.g-ba.de/informationen/nutzenbewertung/339/#tab/dossier.

3. Roche Pharma. Randomized, multicenter, phase III, open-label study of alectinib versus crizotinib in treatment-naive anaplastic lymphoma kinase-positive advanced non−small cell lung cancer: study BO28984; Zusatzanalysen [unpublished]. 2018.

Appendix A – Kaplan-Meier curves, cumulative incidence curves

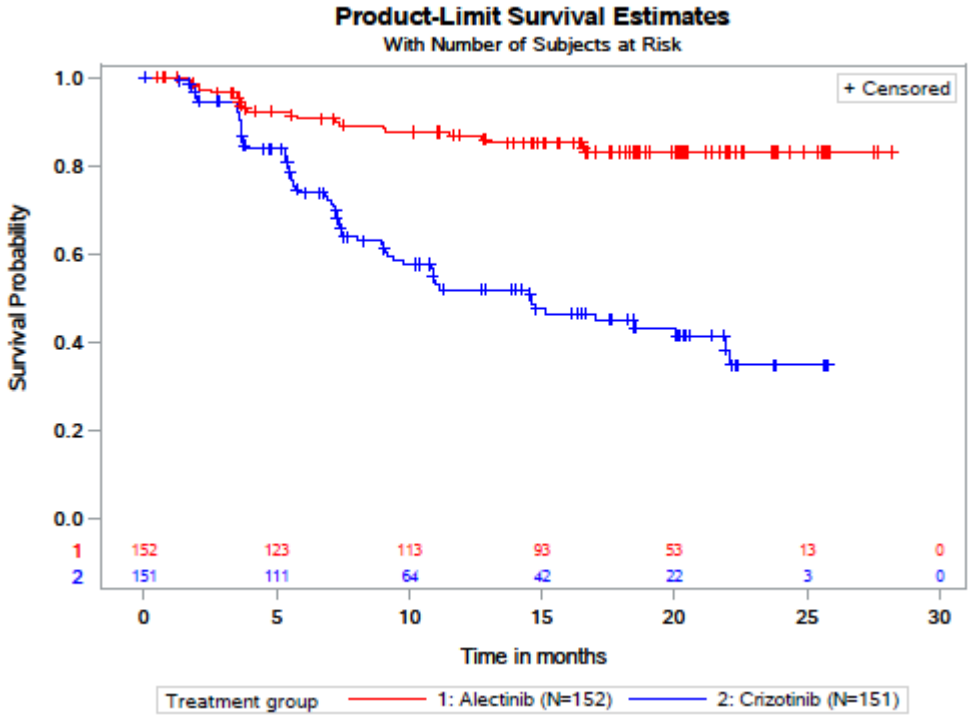

Figure 1: Kaplan-Meier curve on the time to CNS progression (without censoring due to non-CNS progression, according to RECIST, total population) – RCT, direct comparison: alectinib vs. crizotinib

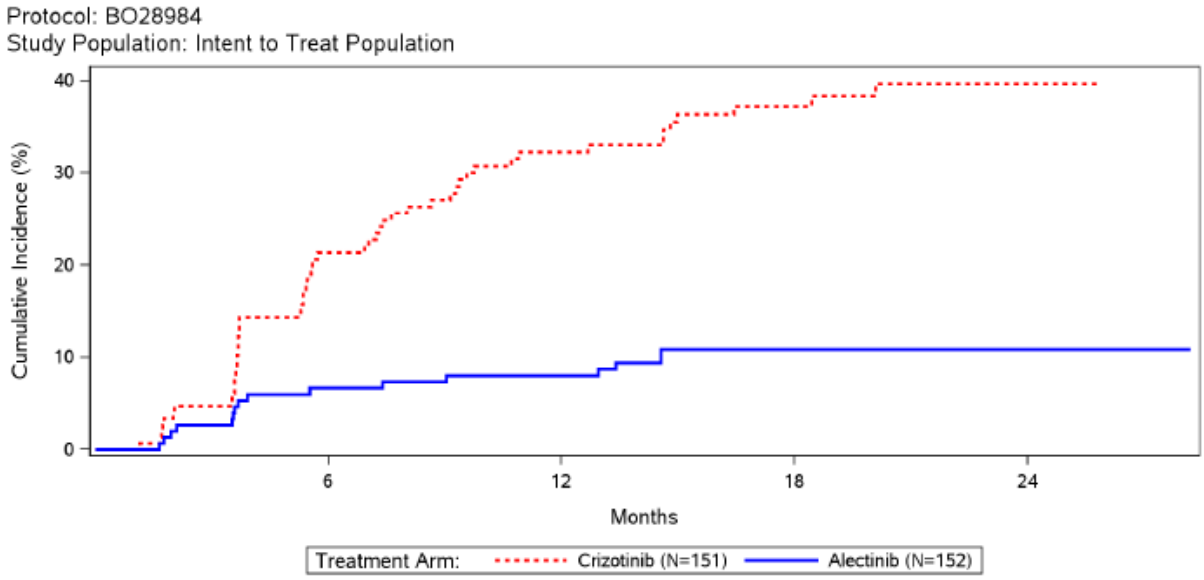

Figure 2: Cumulative incidence curve on the time to CNS progression (with censoring due to non-CNS progression, according to RANO-HGG, total population) – RCT, direct comparison: alectinib vs. crizotinib

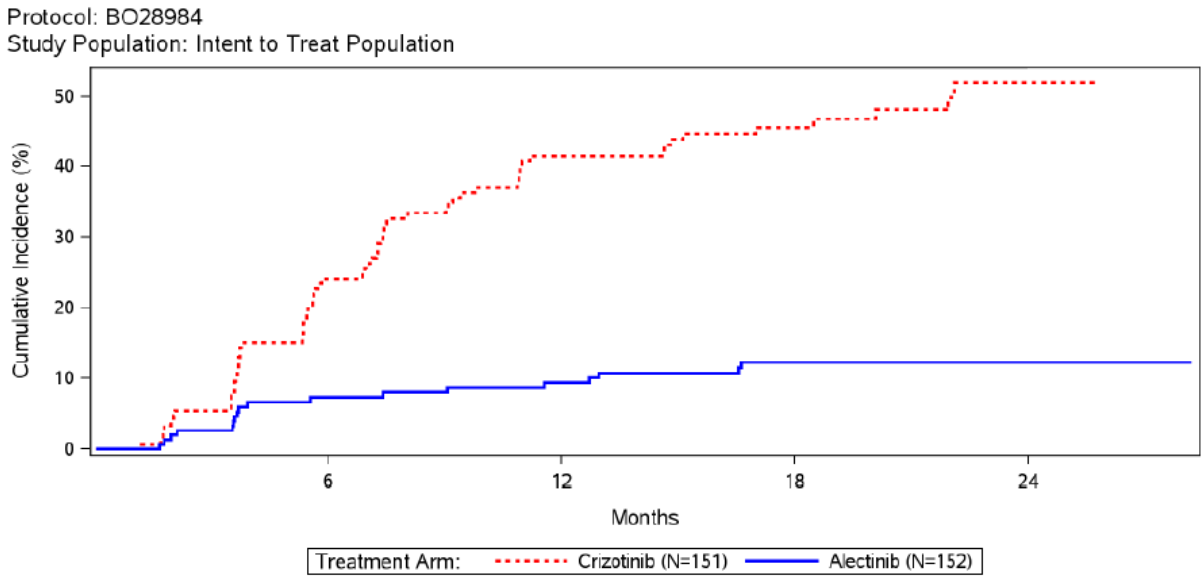

Figure 3: Cumulative incidence curve on the time to CNS progression (with censoring due to non-CNS progression, according to RECIST, total population) – RCT, direct comparison: alectinib vs. crizotinib