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Entrectinib (NSCLC) –

Addendum to Commission A20-75[1]

Addendum

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
ECOD	enrolment cut-off date
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IPTW	inverse probability of treatment weighting
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MAIC	matching-adjusted indirect comparison
NC	Not calculable
NSCLC	non-small cell lung cancer
PFS	progression-free survival
ROS1	C-ros oncogene-1
SGB	Sozialgesetzbuch (Social Code Book)

1 Background

On 13 January 2021, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A20-75 (Entrectinib – Benefit assessment according to §35a Social Code Book V) [1].

In its dossier [2], the pharmaceutical company (hereinafter referred to as "the company") used analyses on the subpopulation of adult patients with C-ros oncogene-1 (ROS1)-positive, advanced non-small cell lung cancer (NSCLC) previously not treated with an ROS1 inhibitors (hereinafter referred to as the ROS1 population) from the uncontrolled STARTRK-2 study. For this purpose, it presented different analysis populations for the benefit and harm outcomes. To compare entrectinib with the appropriate comparator therapy (ACT) crizotinib, the company presented comparisons of analysis population 1 at the data cut-off of 1 May 2019 (N = 78) of the STARTRK study-2 with a cohort treated with crizotinib from a US cancer database (Flatiron Health Database) (N = 69) and with patients from the EUCROSS study (N = 30) for the outcomes "overall survival" and "progression-free survival (PFS)". Analysis population 1 of the STARTRK-2 study used by the company for both comparisons includes clearly fewer patients than would have been possible at the time of the dossier submission (analysis population 2 also at the data cut-off of 1 May 2019, N = 145). Moreover, there were uncertainties regarding the exact composition of the analysis populations formed by the company [1].

In the commenting procedure, the company presented comparisons of entrectinib versus crizotinib for the outcome "overall survival" that were based on the larger analysis population of the STARTRK-2 study (analysis population 2) and the Flatiron Health Database or the EUCROSS study [3] in addition to clarifying information on the analysis populations of the ROS1 population of STARTRK-2.

The G-BA commissioned IQWiG with the assessment of the analyses on the comparisons of entrectinib with data from the Flatiron Health Database and the EUCROSS study on the outcome "overall survival" presented in the commenting procedure under consideration of the information provided in the dossier.

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 Composition of the evaluation populations

In the dossier, the company presented different analysis populations for the benefit and harm outcomes of the ROS1 population of the STARTRK-2 study. Moreover, the number of considered patients varied depending on the data cut-off and the time by which patients were included in the analysis population (enrolment cut-off date [ECOD]). An overview of the different analysis populations can be found in Table 3 of dossier assessment A20-75 [1]. The exact composition particularly of the most recent analysis populations for the benefit outcomes (analysis population 2, data cut-off of 1 May 2019, ECOD 31 October 2018) could not be derived from the information provided by the company in the dossier. Moreover, based on the information provided by the company in the dossier, it was assumed that only patients with a follow-up period of ≥ 6 months after initial response were included in the analysis populations for the benefit outcomes. This would mean that unresponsive patients would not be considered in the analyses.

In its comments [3], the company clarified that the analysis populations for the benefit outcomes considered all patients included by the respective ECOD, irrespective of whether the patients responded to treatment with entrectinib, discontinued the study, had progressed or died. The company justified the exclusion of patients who had only been included after the ECOD with a sufficient follow-up period for the analysis of the primary outcome "objective response rate". Moreover, the company clarified the reasons for exclusion in the formation of the analysis populations providing corresponding data on the number of patients who were consequentially excluded with the information on the patient flow at the data cut-off of 1 May 2019 (EMA-D194) submitted with the comments. With the information subsequently submitted with the comments, the composition of the analysis population is thus sufficiently comprehensible. However, it should be noted that regardless of whether the restriction of the analysis population is adequate for the primary outcome, the exclusion of patients for other benefit outcomes such as "overall survival" is not appropriate.

2.2 Comparisons of individual arms from different studies

With the comments [3], the company again presented comparisons of individual arms from different studies on entrectinib and crizotinib. In doing so, the company compared the results of analysis population 2 of the ROS1 population of the STARTRK-2 study at the data cut-off of 1 May 2019 (EMA-D194-ROS1 efficacy, N = 145) with the data on crizotinib already submitted with the dossier, the Flatiron Health Database (N = 69) and the EUCROSS study (N = 30) on the outcome "overall survival".

Dossier assessment A20-75 [1] includes a description of the STARTRK-2 on entrectinib, the cohort of the Flatiron Health Database and the EUCROSS study.

For the comparison of analysis population 2 of the ROS1 population of the STARTRK-2 study with the Flatiron Health Database based on individual data, the company conducted a

propensity score analysis using inverse probability of treatment weighting (IPTW). The company compared the aggregated data of the EUCROSS study with the individual data of analysis population 2 of the STARTRK-2 study using the matching-adjusted indirect comparison (MAIC) method. The company thus used the same methods as in the comparisons with analysis population 1 (N = 78) of the STARTRK-2 study presented in the dossier. The potentially relevant effect modifiers or prognostic factors also correspond to those considered by the company in the analyses presented with the dossier. As a sensitivity analysis, the company additionally presented the results of a comparison of the arms without adjustment for both comparisons. The points of criticism already addressed in dossier assessment A20-75 regarding the comparability of the patient populations for entrectinib and crizotinib [1] also apply to the present addendum.

In the IPTW comparison versus the Flatiron Health Database, there was a statistically significant difference in favour of entrectinib versus crizotinib for the outcome "overall survival" (median survival [95% confidence interval [95% CI]] in months: 30.75 [28.32; not calculated [NC]] vs. 15.82 [15.36; 19.87]; hazard ratio [95% CI]: 0.50 [0.34; 0.75]; p = 0.016). In the weighted comparison versus the EUCROSS study using the MAIC method, the survival advantage of entrectinib was not statistically significant (median survival [95% CI] in months: 30.75 [28.32; NC] vs. NA [21.6; NC]; hazard ratio [95% CI]: 0.85 [0.54; 1.22]). The results of the sensitivity analyses without adjustment confirm the respective result from the IPTW comparison or the MAIC.

Although an adjustment was made in the analysis with regard to potentially relevant effect modifiers or prognostic factors, the results from the two comparisons of individual arms from different studies are subject to inherent uncertainty due to the lack of randomization, so an added benefit can only be derived if the effects are sufficiently large. For both comparisons on overall survival presented by the company, the observed effects were not large enough that they could not be caused by systematic bias alone. That there could be a systematic bias in the results is also shown by the fact that the survival time analyses (analogous to the analyses with analysis population 1 presented with the dossier) of patients differed notably between the Flatiron Health Database and the EUCROSS study. For example, patients from the Flatiron Health Database have a significantly worse prognosis under treatment with crizotinib than patients treated with crizotinib in the EUCROSS study.

2.3 Summary

The data subsequently submitted by the company in the commenting procedure have not changed the conclusion on the added benefit of entrectinib from dossier assessment A20-75.

The following Table 1 shows the result of the benefit assessment of entrectinib under consideration of dossier assessment A20-75 and the present addendum.

Table 1: Entrectinib – probability and extent of added benefit:

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adult patients with ROS1-positive advanced NSCLC previously not treated with a ROS1 inhibitor[b]	Crizotinib	Added benefit not proven
a. Presentation of the ACT specified by the G-BA. b. For the present therapeutic indication, it is assumed that patients have no medical indication for definitive local therapy. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer; ROS1: c-ros oncogene 1		

The G-BA decides on the added benefit.

3 References

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

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3. Roche Pharma. Stellungnahme zum IQWiG-Bericht Nr. 1003; Entrectinib (NSCLC); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A20-75. 2020: [Soon available under https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/587/#beschluesse in the document "Zusammenfassende Dokumentation"].

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