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Entrectinib (solid tumours with neurotrophic tyrosine receptor kinase (NTRK) gene fusion) –

Addendum to Commission A20-74[1]

Addendum

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Abbreviation	Meaning
ACT	appropriate comparator therapy
ALK	anaplastic lymphoma kinase
CI	confidence interval
ECOD	enrolment cut-off date
EE	efficacy evaluable
EPAR	European Public Assessment Report
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
NC	Not calculable
NSCLC	non-small cell lung cancer
NTRK	neurotrophic tyrosine receptor kinase
ROS1	C-ros oncogene-1
SE	safety evaluable
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics

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 A20-74 (Entrectinib – Benefit assessment according to §35a Social Code Book (SGB) V) [1].

In its dossier [2], the pharmaceutical company (hereinafter referred to as "the company") presented analyses of the subpopulation of patients with locally advanced or metastatic solid tumours with neurotrophic tyrosine receptor kinase (NTRK) gene fusion from the uncontrolled basket study STARTRK-2. Moreover, the company presented comparative data exclusively for the two tumour entities "non-small cell lung cancer (NSCLC)" and "soft tissue sarcoma" with the approach for the search and selection of the studies remaining unclear. The data presented by the company are insufficient in the preparation presented with the dossier and are not suitable for the benefit assessment of entrectinib versus the appropriate comparator therapy (ACT) in adult and paediatric patients from 12 years of age with solid tumours that display a NTRK gene fusion, who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity and who have not yet received an NTRK inhibitor and who have no satisfactory treatment options. Data for paediatric patients from 12 years of age and older who were also covered by the therapeutic indication of entrectinib are not available [1].

With the commenting procedure, the company presented a comparison of individual arms of different studies for the outcome "overall survival" using data of the Flatiron Health Database and analyses on paediatric patients [3].

The G-BA commissioned IQWiG with the assessment of the analyses on the comparison of entrectinib with data of the Flatiron Health Database for the outcome "overall survival" presented in the commenting procedure, taking into account the information subsequently submitted on the patient flow of the analysis populations and on analyses on paediatric patients, each under consideration of the data 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 Notes on the data subsequently submitted with the comments

It is not ensured that the analysis populations of the company represent the relevant patient population according to the approval

In its dossier, the company presented analyses of a subpopulation of the uncontrolled basket study STARTRK-2. This subpopulation included patients with locally advanced or metastatic solid tumours with NTRK gene fusion. According to the Summary of Product Characteristics (SPC), entrectinib is only approved for patients with NTRK gene fusion who have no satisfactory treatment options. The data in the dossier provide no information on the extent to which the presented analysis populations correspond to the population relevant to the research question. A corresponding operationalization is neither found in the inclusion criteria of the STARTRK-2 study nor in the criteria for the formation of the analysis populations specified by the company. However, in its comments, the company also submitted no new data confirming that the company's analysis population reflects the relevant patient population according to the approval.

Formation of the NTRK efficacy evaluable (EE) analysis population in the STARTRK-2 study for the patient-relevant outcomes

In its dossier, the company presented analyses separated by benefit and harm outcomes. In doing so, it provided a different analysis population for benefit outcomes (NTRK EE, data cut-off of 31 October 2018: n = 71) than for harm outcomes (NTRK safety evaluable [SE], data cut-off of 31 October 2018: n = 108). The exclusion criteria applied by the company and thus the composition of the NTRK EE analysis population at the data cut-off of 31 October 2018 were not comprehensible on the basis of the data provided by the company in the dossier. The information subsequently submitted by the company in the comments has shown (i) that, contrary to the information provided by the company in the dossier, the NTRK EE analysis population did not include patients with a follow-up ≥ 6 months after initial response, but patients who were enrolled in the study until 30 April 2018 (enrolment cut-off date [ECOD]), namely 6 months before the data cut-off of 31 October 2018, and (ii) which patients were excluded when forming the NTRK EE analysis population. 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". Irrespective of the comprehensibility of the restriction of the analysis population for the primary outcome, the exclusion of patients for other benefit outcomes such as "overall survival" is not appropriate in view of the already small number of cases.

Results separated by tumour entity are incomplete

In the present therapeutic indication, consideration of the results separated by tumour entity is useful and necessary (a detailed justification can be found in dossier assessment A20-74 [1]). In its benefit assessment, the company only presented results for 3 entities: "soft tissue sarcoma", "NSCLC" and "secretory salivary gland cancer". Results for other entities were not presented in the comments. The comparison of individual arms of different studies presented

in the comments (see the following Section 2.2) was also not carried out separated by tumour entity.

2.2 Comparison of individual arms of different studies on the outcome "overall survival"

In its comments, the company presented a comparison between i) adult patients in the STARTRK-1, STARTRK-2 and ALKA372-001 studies with locally advanced or metastatic solid tumours with an NTRK gene fusion, who received a dosage ≥ 600 mg entrectinib and ii) adult patients with advanced or metastatic solid tumours that displayed an NTRK gene fusion who, according to the company, received individual therapy, excluding an NTRK inhibitor, and for whom the company had individual data from the Flatiron Health Database [3,4]. The Flatiron Health Database contains data from electronic patient records of cancer patients of oncology clinics in the USA. For the comparison, the company conducted a propensity score analysis taking into account the factors "tumour type", "age", "time from the initial diagnosis until the index date" (start of the therapy in the entrectinib arm or presence of an NTRK-positive test result in the Flatiron Health Database), "stage at initial diagnosis" and "number of prior lines of therapy since advanced disease". As a sensitivity analysis, the company additionally presented results of a comparison without adjustment. The company only presented an analysis on the outcome "overall survival" and independently of the tumour histology. As already explained in the dossier assessment, consideration separated by tumour entities is necessary in the present field of application. Therefore, the comparative data presented by the company are unusable for the benefit assessment of entrectinib in comparison with the ACT.

Irrespective of the lack of usability of the data, the comparison across tumour entities under consideration of the propensity score for the outcome "overall survival" shows no statistically significant difference between entrectinib and an individual therapy as stated by the company (median survival (95% confidence interval [CI]) in months: 20.9 [16.03; not calculabe [NC]] vs. 6.77 [3.68; NC]; hazard ratio [95% CI]: 0.44 [0.15; 1.30; p = 0.056]. The comparison without adjustment showed a statistically significant difference in favour of entrectinib versus an individual therapy according to the information provided by the company (median survival [95% CI] in months: 20.9 [16.03; NC] vs. 11.0 [3.81; NC]; hazard ratio [95% CI]: 0.44 [0.21; 0.90]; p = 0.032). Thus, regardless of the statistical significance, the observed effects were not large enough that they could not be caused by systematic bias alone in this comparison of individual arms of different studies. Moreover, the analysis included patients who received a dosage > 600 mg, which was not in compliance with the approval. Information on the treatment of patients in the Flatiron Health Database is not available.

2.3 Analyses on paediatric patients

In its comments, the company presented 2 figures on the tumour response in paediatric patients of the STARTRK-NG study [5]. STARTRK-NG is a dose escalation study with subsequent dose extension in paediatric and adult patients (according to the European public Assessment Report (EPAR) up to 22 years of age [6]) with relapsed or refractory solid extracranial tumours

or primary tumours of the central nervous system with or without NTRK, C-ros oncogene-1 (ROS1) or anaplastic lymphoma kinase (ALK) fusions. Following dose escalation, the patients received entrectinib in doses between 250 and 750 mg/m^2 body surface area. Neither in the dossier nor in the comments does the company provide information on the number of paediatric patients aged ≥ 12 years with NTRK gene fusion according to the therapeutic indication for whom data are available in the STARTRK-NG study. According to the EPAR, 29 patients were included until 31 October 2018, of whom 7 patients had NTRK gene fusion. According to the EPAR [6], these 7 patients were aged between 4 months and 9 years. Thus, the STARTRK-NG study did not include any patients in the present therapeutic indication until 31 October 2018. The company's comments state that analyses for the STARTRK-NG study are available for the data cut-offs of 1 July 2019 [7] and 5 November 2019 [3]. It is unclear whether these analyses include data of individual patients corresponding to the therapeutic indication (NTRK gene fusion, age ≥ 12 years). Irrespective of this, information is only available for the outcome "tumour response", but not for patient-relevant outcomes such as "overall survival".

The data on paediatric patients submitted by the company with the commenting procedure are unsuitable for the assessment of the added benefit in the present therapeutic indication.

2.4 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 A20-74.

The following Table 1 shows the result of the benefit assessment of entrectinib under consideration of dossier assessment A20-74 and the present addendum.

Table 1: Entrectinib – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult and paediatric patients from 12 years of age with solid tumours that display an NTRK gene fusion, ▪ who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and ▪ who have not yet received an NTRK inhibitor and ▪ who have no satisfactory treatment options	Individual treatment choosing from ▪ BSC[b] and ▪ surgical resection, which is likely to result in severe morbidity, for whom a clinical benefit is to be expected for individual patients	Added benefit not proven
a. Presentation of the ACT specified by the G-BA. b. BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life. ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee; NTRK: neurotrophic tyrosine receptor kinase		

The G-BA decides on the added benefit.

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