IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Crizotinib (non-small cell lung cancer) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Crizotinib (nicht kleinzelliges Lungenkarzinom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 22 December 2016). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
ALK	anaplastic lymphoma kinase
BSC	best supportive care
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
Module 4 AB	Module 4 A and 4 B
NSCLC	non-small cell lung cancer
RCT	randomized controlled trial
ROS1	c-ros oncogene 1
SGB	Sozialgesetzbuch (Social Code Book)

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug crizotinib. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 20 September 2016.

Research question

The aim of this report was to assess the added benefit of crizotinib in comparison with the appropriate comparator therapy (ACT) specified by the G-BA in adult patients with c-ros oncogene 1 (ROS1)-positive advanced non-small cell lung cancer (NSCLC).

Three research questions resulted from the ACT specified by the G-BA for the present benefit assessment (see Table 2).

Table 2: Research questions of the benefit assessment of crizotinib

Research question	Therapeutic indication	ACT[a]
Treatment-naive patients[b] with ROS1-positive advanced NSCLC		
1	Patients with ECOG Performance Status 0, 1 or 2	**Cisplatin in combination with a third-generation cytostatic agent** (vinorelbine or gemcitabine or docetaxel or paclitaxel or **pemetrexed**) in accordance with the approval status or **carboplatin in combination with a third-generation cytostatic agent**[c] (only for patients with increased risk of cisplatin-induced side effects in the framework of a combination therapy; see Appendix VI to Section K of the Pharmaceutical Directive)
	Patients with ECOG Performance Status 2	As an alternative to the platinum-based combination therapy: monotherapy with gemcitabine or vinorelbine
Pretreated patients[b] with ROS1-positive advanced NSCLC		
2a	Patients for whom treatment with docetaxel or pemetrexed is an option (hereinafter referred to as "chemotherapy population")	Docetaxel or pemetrexed
2b	Patients for whom treatment with docetaxel or pemetrexed is not an option (hereinafter referred to as "BSC population")	Best supportive care

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold.
b: It is assumed that the NSCLC patients have stage IIIB to IV disease (staging according to IASLC, UICC), without indication for curative resection, radiotherapy or radiochemotherapy. Treatment is palliative.
c: The company chose pemetrexed as combination partner also in this case.
ACT: appropriate comparator therapy; BSC: best supportive care; ECOG: Eastern Cooperative Oncology Group; G-BA: Federal Joint Committee; IASLC: International Association for the Study of Lung Cancer; NSCLC: non-small cell lung cancer; ROS1: c-ros oncogene 1; UICC: Union for International Cancer Control

In its choice of the ACT, the company followed the G-BA's specification for all 3 research questions. However, it presented no data for the patients in the best supportive care (BSC) population (research question 2b) because, according to the company, treatment with crizotinib is usually not intended for these patients.

Deviating from the company, the benefit assessment was conducted for all 3 research questions.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

Results on research questions 1 and 2a (treatment-naive patients and chemotherapy population of pretreated patients)

Concurring with the company, the check of the completeness of the study pool produced no randomized controlled trials (RCTs) with patients with ROS1-positive advanced NSCLC on the direct comparison of crizotinib versus the ACT or on a corresponding indirect comparison based on RCTs.

Since no studies of direct comparisons were available, the company conducted a search on further investigations with crizotinib. In this search, it identified 8 single-arm studies on crizotinib in patients with ROS1-positive advanced NSCLC, which constituted the company's study pool. These 8 studies were heterogeneous because they included both prospective intervention studies and retrospective case series, some of which only included very few patients. Only 32 patients of the 281 patients in total were treatment-naive.

Furthermore, the company used additional evidence outside its study pool for the derivation of the added benefit. It assumed that results from studies with patients with anaplastic lymphoma kinase (ALK)-positive advanced NSCLC can be transferred to patients with ROS1-positive advanced NSCLC.

Hence the derivation of the added benefit by the company was based on

- the results of 8 single-arm crizotinib studies with patients with ROS1-positive advanced NSCLC
- transferability of results from 2 RCTs (PROFILE 1007 and PROFILE 1014) with patients with ALK-positive advanced NSCLC to patients with ROS1-positive advanced NSCLC (both RCTs compared crizotinib with chemotherapy in treatment-naive [PROFILE 1014] and pretreated [PROFILE 1007] patients with ALK-positive advanced NSCLC and were already assessed for these patients)
- a comparison of individual arms from these studies (referred to by the company as "unadjusted indirect comparison"). The study arms on the ACT were only from the studies mentioned above (PROFILE 1007 and PROFILE 1014), which investigated patients with ALK-positive advanced NSCLC. The arms on the crizotinib side, in contrast, were data from the single-arm studies in patients with ROS1-positive advanced NSCLC.

Hence the company's comparison on the ACT side was based only on data with ALK-positive advanced NSCLC and not on data for the patients of interest, i.e. patients with ROS1-positive advanced NSCLC. The company assumed transferability of the treatment results between both patient populations. The company's considerations on transferability were not followed. Hence no relevant data for the derivation of an added benefit were available. This is explained below.

Comparability of both patient groups and transferability of the treatment results

For the company, the comparability of both patient groups, on the one hand, resulted from the similarity of the ALK and ROS1 receptors and the comparable binding affinity of crizotinib to ALK and ROS1 receptors. On the other hand, the company saw comparability due to the similarity of the patient characteristics and the similarity of the "natural course", which it understood to mean the "prognosis of affected patients when treated with standard chemotherapies".

Since the company's considerations on transferability were not sufficiently based on data, a simplified search was conducted for studies containing information on patient characteristics and the course of treatment under chemotherapy for patients with ROS1-positive tumour and ALK-positive tumour. Only sources reporting the data of both patient groups were used to reduce potential differences caused by patient recruitment and setting of the studies. The identified studies showed – as the studies presented by the company – a number of limitations regarding their informative value. For example, they were mostly patient groups analysed retrospectively with incomplete reporting of data.

Comparability of patients with ALK-positive and ROS1-positive tumour

From the company's point of view, the patient characteristics of the patients with ALK-positive tumour and the patients with ROS1-positive tumour are largely comparable because, for example, they are younger and more often never or non-smokers than the total population of NSCLC patients. It mainly used one study and one review to support this view. These 2 publications showed no relevant differences regarding patient characteristics between patients with ROS1-positive NSCLC and those with ALK-positive NSCLC. The reported data were incomplete, however, because data beyond age and sex were partly not recorded or reported at all or recorded or reported incompletely.

The patient characteristics from the studies additionally identified in the simplified search also showed no consistent picture. Overall, the data on the patient characteristics of the patients with ROS1-positive and ALK1-positive NSCLC were heterogeneous or inadequately described. Hence no conclusion can be drawn on the question whether patients with ROS1-positive NSCLC and patients with ALK-positive NSCLC have similar characteristics or show differences. Hence the company's assumption that treatment results of patients with ALK-positive NSCLC are transferable to patients with ROS1-positive NSCLC due to the similarity of the patient populations is not sufficiently supported by data.

Prognosis under chemotherapy (and other treatments)

The central argument in the company's approach is the transferability of the treatment results from patients with ALK-positive NSCLC to those with ROS1-positive NSCLC. The company stated that the prognosis of both patient groups under treatment with standard chemotherapy is comparable. In contrast to the patient characteristics, it cited no sources for this.

The considered sources of the simplified search often describe the prognosis under chemotherapy (and other treatments) inadequately. In addition, important information on the patients included and on the conduct of the study, for example time since (first) diagnosis, treatment duration or prohibited concomitant treatment, was lacking to be able to interpret the data in a meaningful way.

Overall, the identified studies provided no sufficient support for the company's assumption of transferability. At first sight, some studies even showed signs for the assumption that the prognosis of patients with ROS1-positive NSCLC and ALK-positive NSCLC under chemotherapy differs. This concerned both overall survival and treatment effects that are based mostly on imaging techniques (objective response, progression-free survival). Hence the company's assumption that treatment results of patients with ALK-positive NSCLC are transferable to patients with ROS1-positive NSCLC due to the similarity of the patient populations regarding their prognosis under chemotherapy is also not sufficiently supported by data. The company itself neither searched for data nor presented data to support its assumption.

Further limitations of the evidence presented by the company

In addition, the evidence presented by the company had further limitations.

In particular, the company conducted no search for non-randomized studies on the ACT in patients with ROS1-positive advanced NSCLC to enable a comparison versus the ACT outside RCTs.

In addition, there was no systematic search or processing of the data used by the company in addition to its study pool for the derivation of the added benefit.

Conclusion

The company's approach that the results from the RCTs with patients with ALK-positive advanced NSCLC can be transferred to patients with ROS1-positive advanced NSCLC for the present research question of the added benefit versus the ACT was not followed. This also concerned the comparison of individual arms from different studies because the data on the ACT used by the company were also from the RCTs in patients with ALK-positive NSCLC. Hence there were no data that allow an assessment of the added benefit of crizotinib versus the ACT.

Results on research question 2b (BSC population of pretreated patients)

According to the company, the patients in the BSC population do not belong to the target population of crizotinib (research question 2b) because treatment with crizotinib is not intended for these patients. Hence it conducted no information retrieval for research question 2b and presented no data.

Since the company presented no data for the assessment of the added benefit of crizotinib in the BSC population in the dossier, there was no hint of an added benefit of crizotinib in comparison with the ACT; an added benefit is therefore not proven.

Extent and probability of added benefit, patient groups with therapeutically important added benefit[4]

Table 3 presents a summary of the extent and probability of the added benefit of crizotinib.

[4] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, no added benefit, or less benefit). For further details see [1,2].

Table 3: Crizotinib – extent and probability of added benefit

Research question	Therapeutic indication	ACT[a]	Extent and probability of added benefit
Treatment-naive patients[b] with ROS1-positive advanced NSCLC			
1	Patients with ECOG Performance Status 0, 1 or 2	**Cisplatin in combination with a third-generation cytostatic agent** (vinorelbine or gemcitabine or docetaxel or paclitaxel or **pemetrexed**) in accordance with the approval status or **carboplatin in combination with a third-generation cytostatic agent**[c] (only for patients with increased risk of cisplatin-induced side effects in the framework of a combination therapy; see Appendix VI to Section K of the Pharmaceutical Directive)	Added benefit not proven
	Patients with ECOG Performance Status 2	As an alternative to the platinum-based combination therapy: monotherapy with gemcitabine or vinorelbine	Added benefit not proven
Pretreated patients[b] with ROS1-positive advanced NSCLC			
2a	Patients for whom treatment with docetaxel or pemetrexed is an option	Docetaxel or pemetrexed	Added benefit not proven
2b	Patients for whom treatment with docetaxel or pemetrexed is not an option	Best supportive care	Added benefit not proven

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold.
b: It is assumed that the NSCLC patients have stage IIIB to IV disease (staging according to IASLC, UICC), without indication for curative resection, radiotherapy or radiochemotherapy. Treatment is palliative.
c: The company chose pemetrexed as combination partner also in this case.
ACT: appropriate comparator therapy; ECOG: Eastern Cooperative Oncology Group; G-BA: Federal Joint Committee; IASLC: International Association for the Study of Lung Cancer; NSCLC: non-small cell lung cancer; ROS1: c-ros oncogene 1; UICC: Union for International Cancer Control

The G-BA decides on the added benefit.

2.2 Research question

The aim of this report was to assess the added benefit of crizotinib in comparison with the ACT specified by the G-BA in adult patients with ROS1-positive advanced NSCLC.

Three research questions resulted from the ACT specified by the G-BA for the present benefit assessment (see Table 4).

Table 4: Research questions of the benefit assessment of crizotinib

Research question	Therapeutic indication	ACT[a]
Treatment-naive patients[b] with ROS1-positive advanced NSCLC		
1	Patients with ECOG Performance Status 0, 1 or 2	**Cisplatin in combination with a third-generation cytostatic agent** (vinorelbine or gemcitabine or docetaxel or paclitaxel or **pemetrexed**) in accordance with the approval status or **carboplatin in combination with a third-generation cytostatic agent**[c] (only for patients with increased risk of cisplatin-induced side effects in the framework of a combination therapy; see Appendix VI to Section K of the Pharmaceutical Directive)
	Patients with ECOG Performance Status 2	As an alternative to the platinum-based combination therapy: monotherapy with gemcitabine or vinorelbine
Pretreated patients[b] with ROS1-positive advanced NSCLC		
2a	Patients for whom treatment with docetaxel or pemetrexed is an option (hereinafter referred to as "chemotherapy population")	Docetaxel or pemetrexed
2b	Patients for whom treatment with docetaxel or pemetrexed is not an option (hereinafter referred to as "BSC population")	Best supportive care

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold.
b: It is assumed that the NSCLC patients have stage IIIB to IV disease (staging according to IASLC, UICC), without indication for curative resection, radiotherapy or radiochemotherapy. Treatment is palliative.
c: The company chose pemetrexed as combination partner also in this case.
ACT: appropriate comparator therapy; BSC: best supportive care; ECOG: Eastern Cooperative Oncology Group; G-BA: Federal Joint Committee; IASLC: International Association for the Study of Lung Cancer; NSCLC: non-small cell lung cancer; ROS1: c-ros oncogene 1; UICC: Union for International Cancer Control

In its choice of the ACT, the company followed the G-BA's specification for all 3 research questions. However, it presented no data for the patients in the BSC population (research question 2b) because, according to the company, treatment with crizotinib is usually not intended for these patients.

Deviating from the company, the benefit assessment was conducted for all 3 research questions.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

2.3 Information retrieval and study pool

2.3.1 Research questions 1 and 2a (treatment-naive patients and chemotherapy population of pretreated patients)

The research questions 1 and 2a are investigated jointly. This corresponds to the approach of the company, which investigated both research questions jointly in its dossier in Module 4 A and 4 B (hereinafter referred to as "Module 4 AB") because of the available evidence base.

For both research questions, the study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on crizotinib (status: 1 August 2016)
- bibliographical literature search on crizotinib (last search on 1 August 2016)
- search in trial registries for studies on crizotinib (last search on 1 August 2016)

To check the completeness of the study pool:

- search in trial registries for studies on crizotinib (last search on 10 October 2016)

Concurring with the company, the check of the completeness of the study pool produced no RCTs with patients with ROS1-positive advanced NSCLC on the direct comparison of crizotinib versus the ACT or on a corresponding indirect comparison based on RCTs.

Since no studies of direct comparisons were available, the company conducted a search on further investigations with crizotinib. In this search, it identified 8 single-arm studies on crizotinib in patients with ROS1-positive advanced NSCLC, which constituted the company's study pool. These 8 studies were heterogeneous because they included both prospective intervention studies and retrospective case series, some of which only included very few patients. The largest study (OO12-01 [3,4], N = 129; in accordance with the company hereinafter referred to as „Goto 2016") only included patients from South East Asia, whereas the company's approval study (PROFILE 1001 [5], N = 53; referred to by the company as „A8081001" in Module 4 AB) included patients from Australia, South Korea and the USA. The remaining 6 studies were conducted in Europe and Turkey, but included fewer patients overall (N = 99) than the 2 largest studies. Only 32 patients of the 281 patients in total were treatment-naive. A description of the study characteristics, the intervention and the patient

characteristics can be found in Table 11 to Table 16 in Appendix A of the full dossier assessment.

Furthermore, the company used additional evidence outside its study pool for the derivation of the added benefit. It assumed that results from studies with patients with ALK-positive advanced NSCLC can be transferred to patients with ROS1-positive advanced NSCLC.

Hence the derivation of the added benefit by the company was based on

- the results of 8 single-arm crizotinib studies with patients with ROS1-positive advanced NSCLC
- transferability of results from 2 RCTs (PROFILE 1007 and PROFILE 1014) with patients with ALK-positive advanced NSCLC to patients with ROS1-positive advanced NSCLC (both RCTs compared crizotinib with chemotherapy in treatment-naive [PROFILE 1014] and pretreated [PROFILE 1007] patients with ALK-positive advanced NSCLC and were already assessed for these patients [6-10])
- a comparison of individual arms from these studies (referred to by the company as "unadjusted indirect comparison"). The study arms on the ACT were only from the studies mentioned above (PROFILE 1007 and PROFILE 1014), which investigated patients with ALK-positive advanced NSCLC. The arms on the crizotinib side, in contrast, were data from the single-arm studies in patients with ROS1-positive advanced NSCLC.

Hence the company's comparison on the ACT side was based only on data with ALK-positive advanced NSCLC and not on data for the patients of interest, i.e. patients with ROS1-positive advanced NSCLC. The company assumed transferability of the treatment results between both patient populations. It provided no adequate justification for this assumption. Instead, studies from a simplified search showed that the data on the prognosis under chemotherapy raise doubts about the assumption of transferability. The company's considerations on transferability were therefore not followed. Hence no relevant data for the derivation of an added benefit were available. This is explained in detail below.

Comparability of both patient groups and transferability of the treatment results

For the company, the comparability of both patient groups, on the one hand, resulted from the similarity of the ALK and ROS1 receptors and the comparable binding affinity of crizotinib to ALK and ROS1 receptors. On the other hand, the company saw comparability due to the similarity of the patient characteristics and the similarity of the "natural course", which it understood to mean the "prognosis of affected patients when treated with standard chemotherapies".

Simplified search on possible transferability

Since the company's considerations on transferability were not sufficiently based on data, a simplified search was conducted for studies containing information on patient characteristics

and the course of treatment under chemotherapy for patients with ROS1-positive tumour and ALK-positive tumour. Only sources reporting the data of both patient groups were used to reduce potential differences caused by patient recruitment and setting of the studies. The identified studies showed – as the studies presented by the company – a number of limitations regarding their informative value. For example, they were mostly patient groups analysed retrospectively with incomplete reporting of data.

Comparability of patients with ALK-positive and ROS1-positive tumour

Regarding the patient characteristics, the company noted that the characteristics of the patients with ALK-positive tumour and the patients with ROS1-positive tumour are largely comparable because, for example, they are younger and more often never or non-smokers than the total population of NSCLC patients. It mainly used the study Bergethon 2012 [11] and the review by Gainor 2013 [12] for this.

The information on the comparability of both patient groups in Bergethon 2012 was only interpretable to a limited extent because the proportion of missing values was partly very large (e.g. 45% for the smoking status of the patients with ALK-positive NSCLC). From the 11 sources on the prevalence of ROS1 mutation in NSCLC cited in Gainor 2013, only Bergethon 2012 (see above) and Takeuchi 2012 [13] showed data on patients with ROS1-positive NSCLC and on patients with ALK-positive NSCLC. Both publications showed no relevant differences regarding patient characteristics between patients with ROS1-positive NSCLC and those with ALK-positive NSCLC. The reported data were incomplete, however, because data beyond age and sex were partly not recorded or reported at all or recorded or reported incompletely (see Table 5).

The studies additionally identified in the simplified search [5,14-18] also showed no consistent picture (see Table 5). For example, some studies showed a similar mean age of both patient groups, whereas in other studies it differed notably. Overall, the data on the patient characteristics of the patients with ROS1-positive and ALK1-positive NSCLC were heterogeneous or inadequately described. Hence no conclusion can be drawn on the question whether patients with ROS1-positive NSCLC and patients with ALK-positive NSCLC have similar characteristics or show differences. Hence the company’s assumption that treatment results of patients with ALK-positive NSCLC are transferable to patients with ROS1-positive NSCLC due to the similarity of the patient populations is not sufficiently supported by data.

Table 5: Patient characteristics, comparison ROS1-positive NSCLC vs. ALK-positive NSCLC, simplified search

Source	Study design/ patients	Tumour mutation status	N	Age (years) median [min; max][a]	Sex (M/F) (%)	Never smoker n (%)	Patients with systemic chemotherapy n (%)	Stage I/II/IIIa/IIIb/IV (%)[a]
Bergethon 2012 [11]	Retrospective analysis of 1073 patients with NSCLC from 3 clinics in the USA and 1 clinic in China	ROS1-positive	18	49.8 [32; 79]	39/61	14 (82)[b]	ND	11[c]/6/11/11/61
		ALK-positive	31	51.6 [29; 73]	55/45	13 (76)[b]	ND	8/13/21/8/50[b]
Takeuchi 2012 [13]	Retrospective analysis of 1529 operated patients with lung cancer in a clinic in Japan, period: 1995 until 2009	ROS1-positive	13	57 [36; 79]	38/62	8 (62)	ND	69/15/0/8/8[c]
		ALK-positive	44	59 [26; 84]	43/57	29 (66)	ND	48/18/14/18/2[c]
Scheffler 2015 [16]	Retrospective analysis of 1137 patients with NSCLC for ROS1 mutation of the tumour control group: search for adequate controls with ALK- and other tumour mutations and the same smoking habits as in the ROS1 group who were pretreated with TKI patients from Germany and Spain	ROS1-positive	19	60 [26; 82]	53/47	13 (68)	16 (84)[c]	11/0/5[c]/11[c]/74[d]
		ALK-positive	13	42 [28; 70]	ND	ND	ND	ND

(continued)

Table 5: Patient characteristics, comparison ROS1-positive NSCLC vs. ALK-positive NSCLC, simplified search (continued)

Source	Study design/ patients	Tumour mutation status	N	Age (years) median [min; max][a]	Sex (M/F) (%)	Never smoker n (%)	Patients with systemic chemotherapy n (%)	Stage I/II/IIIa/IIIb/IV (%)[a]
Chen 2014 [17]	Prospective determination of the mutation status of 492 consecutive lung adenocarcinoma patients with surgical resection or pleuracentesis after malignant pleural effusion one clinic in Taiwan	ROS1-positive	12	45.0 [32; 71]	50/50	6 (50)[e]	≥ 6/7 (≥ 86)[f]	41.7 (I to IIIa)/58.3 (IV)
		ALK-positive	60	60.2 [27; 85]	50/50	37 (62)[e]	≥ 32/49 (≥ 65)[f]	18.3 (I to IIIa)/81.7 (IV)
Chen 2016 [18][g]	Retrospective determination of the mutation status of 253 patients with advanced lung adenocarcinoma and treatment with pemetrexed one clinic in Taiwan	ROS1-positive	19	43.8 [30; 75]	47/53	13 (68)[e]	19 (100)	ND
		ALK-positive	32	55.7 [31; 84]	56/44	20 (63)[e]	32 (100)	ND
Kim 2013 [14]	Retrospective 208 consecutive never smokers with lung adenocarcinoma in one clinic in South Korea, including analysis of the tumour mutation status Period: 1/2005 until 2/2012	ROS1-positive	7	55 [30; 68]	14/86	7 (100)	5 (71[c])	29/0/14/14/43
		ALK-positive	15	58 [34; 78]	13/87	15 (100)	13 (87[c])	20/20/20/7/33

(continued)

Table 5: Patient characteristics, comparison ROS1-positive NSCLC vs. ALK-positive NSCLC, simplified search (continued)

Source	Study design/ patients	Tumour mutation status	N	Age (years) median [min; max][a]	Sex (M/F) (%)	Never smoker n (%)	Patients with systemic chemotherapy n (%)	Stage I/II/IIIa/IIIb/IV (%)[a]
PROFILE 1001 [5][h]	Uncontrolled, open-label intervention study 8 centres in Australia, South Korea and USA inclusion criteria of an intervention study recruitment: 10/2010 until 8/2013, data recording ongoing	ROS1-positive	53	55 [25; 81]	43/57	40 (75)	46 (87)	4 (III)/2 (IIIa)/2 (IIIb)/91[c] (IV)[j]
PROFILE 1001 [19]	Uncontrolled, open-label intervention study Australia, South Korea and USA inclusion criteria of an intervention study recruitment: 8/2008 until 6/2011 status unclear	ALK-positive	149	52 [21; 86]	49/51	106 (71)	125 (84[c])	100 (III, IIIa, IIIb or IV)
Song 2016 [15]	Retrospective determination of the mutation status of 1750 consecutive NSCLC patients in 2 clinics in China Period: 1/2010 until 12/2014	ROS1-positive	34	n < 60 years: 19 [56%[c]]	47/53[c]	29 (85[c])	≥ 23 (≥ 68[c])	56[c] (I to IIIa) 44[c] (IIIb or IV)
		ALK-positive	46	n < 60 years: 28 [61%[c]]	46/54[c]	35 (76[c])	≥ 27 (≥ 59[c])	59 (I to IIIa) 41 (IIIb or IV)

(continued)

Table 5: Patient characteristics, comparison ROS1-positive NSCLC vs. ALK-positive NSCLC, simplified search (continued)

a: Deviations from this form are mentioned in the cell.
b: (Large) proportion of missing values; therefore Institute's calculation based on the number of patients with data (17 patients for never smokers and 24 patients for the tumour stage).
c: Institute's calculation.
d: Deviation of more than 100% due to rounding.
e: Calculation from the difference of the group size minus the number of smokers in the group.
f: The information was only available for the 7 and 49 patients in stage IV.
g: The retrospective recording of the data was conducted in the same clinic as for Chen et al. 2014. It is therefore unclear whether the data are overlapping.
h: See also patient characteristics in Table 15 of the full dossier assessment.
j: The sum is < 100%, because the stage of one patient is unknown.

ALK: anaplastic lymphoma kinase; F: female; M: male; max: maximum; min: minimum; n: number of patients with characteristic; N: number of patients included; ND: no data; NSCLC: non-small cell lung cancer; ROS1: c-ros oncogene 1; vs.: versus

Prognosis under chemotherapy (and other treatments)

The central argument in the company's approach is the transferability of the treatment results from patients with ALK-positive NSCLC to those with ROS1-positive NSCLC. The company stated that the prognosis of both patient groups under treatment with standard chemotherapy is comparable. In contrast to the patient characteristics, it cited no sources for this.

The considered sources of the simplified search often describe the prognosis under chemotherapy (and other treatments) inadequately (see Table 6). In addition, important information on the patients included and on the conduct of the study, for example time since (first) diagnosis, treatment duration or prohibited concomitant treatment, was lacking to be able to interpret the data in a meaningful way.

Overall, the identified studies provided no sufficient support for the company's assumption of transferability. At first sight, some studies even showed signs for the assumption that the prognosis of patients with ROS1-positive NSCLC and ALK-positive NSCLC under chemotherapy differs. This concerned both overall survival [16] and treatment effects that are based mostly on imaging techniques (objective response, progression-free survival) [14,18]. The available results are presented in Table 6. Hence the company's assumption that treatment results of patients with ALK-positive NSCLC are transferable to patients with ROS1-positive NSCLC due to the similarity of the patient populations regarding their prognosis under chemotherapy is also not sufficiently supported by data. The company itself neither searched for data nor presented data to support its assumption.

Table 6: Course under chemotherapy (and other treatments), comparison ROS1-positive NSCLC vs. ALK-positive NSCLC, simplified search

Source	Mutation status	N	Treatment n (%)	Treatment duration	Overall survival	Result according to imaging techniques
Scheffler 2015 [16]	ROS1-positive	9[a]	CT	ND	Time from first diagnosis of NSCLC until death median: 36.7 months	ND
		5[a]	Crizotinib	ND	Time from first diagnosis of NSCLC until death median: not achieved	ND
	ALK-positive	13[a]	Crizotinib and/or ceritinib	ND	Time from first diagnosis of NSCLC until death median: 23.9 months	ND
Chen 2014 [17]	ROS1-positive	7[a]	≥ 6 (≥ 86) CT[b] 3 (43) EGFR-TKI	ND	Time from first systemic treatment until death 11.9 months	ND
	ALK-positive	49[a]	≥ 32 (≥ 65) CT[b] 35 (71) EGFR-TKI 10 (20) crizotinib	ND	12.5 months	ND
Chen 2016 [18]	ROS1-positive	19	19 (100) CT[c] 11 (58) TKI 5 (26) crizotinib	ND	ND	Median PFS [95% CI]: 7.5 [0.6; 14.3] months ORR[d]: 11 (58%) patients
	ALK-positive	32	32 (100) CT[c] 19 (59) TKI 14 (44) crizotinib	ND	ND	Median PFS [95% CI]: 5.4 [2.7; 8.2] months ORR[d]: 9 (28%) patients

(continued)

Table 6: Course under chemotherapy (and other treatments), comparison ROS1-positive NSCLC vs. ALK-positive NSCLC, simplified search (continued)

Source	Mutation status	N	Treatment n (%)	Treatment duration	Overall survival	Result according to imaging techniques
Kim 2013 [14]	ROS1-positive	5[e]	5 (100) platinum CT (all first-line)	ND	Diagnosis of the metastatic disease until death ND	Median PFS: 8.4 months ORR[d,f]: 2 (40%)
			5 (100) pemetrexed (2 second-line, 3 third-line)			Median PFS: not achieved ORR[d,f]: 3 (60%)
			3 (60) TKI (all second-line)			Median PFS: 2.5 months ORR[d,f]: 0 (0%)
	ALK-positive	13[e]	9 (69) platinum CT (all first-line)	ND	ND	Median PFS: 5.0 months ORR[d,f]: 0 (0%)
			6 (46) pemetrexed (2 second-line, 4 third-line)			Median PFS: 11.5 months ORR[d,f]: 2 (33%)
			8 (62) TKI (1 first-line, 7 second-line)			Median PFS: 2.1 months ORR[d,f]: 0 (0%)
PROFILE 1001[g] [5,20]	ROS1-positive	46[a,h]	≥ 38 (83) CT[i]	ND	Unsuitable	BOR[d] after first-line treatment: 10/46 (22)[j] BOR[d] after second-line treatment: 4/24 (17)[j] BOR[d] after third-line treatment and later: 0/12 (0)[j]
PROFILE 1001[g] [19,21]	ALK-positive	125[a, h]	125 (100) CT ≥ 64 (51) TKI	ND	Unsuitable	ND
Song 2016 [15]	ROS1-positive	23	12 (52) platinum/ pemetrexed first-line	ND	ND	Median PFS: 6.8 months
			11 (48) other first-line			Median PFS: 5.0 months
	ALK-positive	27	27 (100) platinum/ pemetrexed first-line	ND	ND	Median PFS: 6.7 months

(continued)

Table 6: Course under chemotherapy (and other treatments), comparison ROS1-positive NSCLC vs. ALK-positive NSCLC, simplified search (continued)

a: Only patients under CT in stage IV.
b: Includes monotherapy or dual combination with pemetrexed, and platinum-based dual combination.
c: All patients received pemetrexed-based treatment; the sequence of the treatments is unclear.
d: Complete response or partial response.
e: Only patients with metastatic NSCLC who received chemotherapy.
f: Best response in the respective regimen.
g: The information refers to the data before study inclusion.
h: Only pretreated patients.
i: The proportion of patients with chemotherapy was not provided. This information was inferred from the information on BOR under pemetrexed.
j: There was no information whether these are different patients.

ALK: anaplastic lymphoma kinase; BOR: best overall response; CI: confidence interval; CT: chemotherapy; EGFR: epidermal growth factor receptor; n: number of patients with characteristic; N: number of patients included; ND: no data; NSCLC: non-small cell lung cancer; ORR: overall response rate; PFS: progression-free survival; ROS1: c-ros oncogene 1; TKI: tyrosine kinase inhibitor; vs.: versus

Conclusion – assumption of transferability not followed

The studies found in the simplified search raised doubts concerning the comparability of the prognosis under chemotherapy and therefore concerning the comparability of both patient groups postulated by the company. Hence the company's approach that the results from the RCTs with patients with ALK-positive advanced NSCLC can be transferred to patients with ROS1-positive advanced NSCLC for the present research question of the added benefit versus the ACT was not followed. This also concerned the comparison of individual arms from different studies because the data on the ACT used by the company were also from the RCTs in patients with ALK-positive NSCLC. Hence there were no data that allow an assessment of the added benefit of crizotinib versus the ACT.

Further limitations of the evidence presented by the company

Missing search for further investigations with the ACT

In addition, under "further investigations", the company conducted no search for non-randomized studies on the ACT in patients with ROS1-positive advanced NSCLC to enable a comparison versus the ACT outside RCTs. However, the company itself presented studies on chemotherapy in patients with ROS1-positive NSCLC to the European Medicines Agency in the framework of the approval, e.g. the studies Scheffler 2015 [16] and Mazières 2015 [22] (see European Public Assessment Report [23] of the European Medicines Agency). Due to the missing search for studies with the ACT, the content of the company's dossier was potentially incomplete regarding non-randomized studies. Because of the low certainty of results, a comparison of individual arms from different studies would only be relevant for the derivation of an added benefit, however, if there were dramatic effects for patient-relevant outcomes [1].

Missing search regarding further evidence used

As explained above, the company assumed transferability of the results of patients with ALK-positive advanced NSCLC to patients with ROS1-positive advanced NSCLC. Referring to the previous early benefit assessments on crizotinib based on its 2 RCTs of direct comparisons with patients with ALK-positive advanced NSCLC, it derived the added benefit from this. It did not check, however, whether new studies with patients with ALK-positive advanced NSCLC have become available since the previous early benefit assessments. Hence its dossier is potentially incomplete with regard to content. Since the data presented by the company were unsuitable for the derivation of an added benefit versus the ACT, this potential incompleteness of the dossier with regard to content had no consequences for the present benefit assessment. Systematic searches by the company to support its assumptions on the transferability of the effects between patients with ALK-positive and ROS1-positive tumour with data (such as the comparability of the patient characteristics or the prognosis under chemotherapy) were also lacking.

Missing examination of similarity for the comparison of arms from different studies

The company did not conduct the comparison of individual arms from different studies on the basis of the 8 single-arm studies (crizotinib side) and both RCTs (ACT side) consistently

because it did not examine the prerequisite for such a comparison, i.e. the similarity of the studies. This would have been important because, as the comparison of the information provided by the company [11,12] showed, patient populations differ notably depending on setting and inclusion criteria, which may limit the informative value based on comparisons of individual arms from different studies.

The presentation of the patient characteristics for both RCTs was also missing. Since, as described above, the company's considerations regarding transferability were not followed, this had no further consequences for the present benefit assessment.

Limited informative value of the single-arm studies

Finally, the 8 single-arm studies on crizotinib in patients with ROS1-positive NSCLC presented by the company were lacking important amounts of data (see Appendix A of the full dossier assessment). Hence the interpretability of a comparison on the basis of these single-arm studies would have been questionable also for reasons of content.

Conclusion from the further limitations

The further limitations described also resulted in the conclusion that the data presented by the company were unsuitable for the derivation of an added benefit of crizotinib versus the ACT.

2.3.2 Research question 2b (BSC population of pretreated patients)

According to the company, the patients in the BSC population do not belong to the target population of crizotinib (research question 2b) because treatment with crizotinib is not intended for these patients. Hence it conducted no information retrieval for research question 2b and presented no data.

The Institute's check of completeness on the basis of the company's study list on crizotinib (status: 1 August 2016) and the search in trial registries on crizotinib (last search on 10 October 2016) identified no studies relevant for research question 2b.

2.4 Results on added benefit

In the dossier, the company presented no suitable data for the assessment of the added benefit of crizotinib versus the ACT for any of the 3 research questions. This resulted in no hint of an added benefit of crizotinib in comparison with the ACT; an added benefit is therefore not proven.

2.5 Extent and probability of added benefit

Since the company presented no suitable data for the assessment of the added benefit of crizotinib for any of the 3 research questions in the dossier, an added benefit of crizotinib is not proven.

This result deviates from the assessment of the company, which derived a non-quantifiable added benefit on the basis of the data presented by the company, but made no statement on the probability of the added benefit.

The result of the assessment of the added benefit of crizotinib in comparison with the ACT is summarized in Table 7.

Table 7: Crizotinib – extent and probability of added benefit

Research question	Therapeutic indication	ACT[a]	Extent and probability of added benefit
Treatment-naive patients[b] with ROS1-positive advanced NSCLC			
1	Patients with ECOG Performance Status 0, 1 or 2	**Cisplatin in combination with a third-generation cytostatic agent** (vinorelbine or gemcitabine or docetaxel or paclitaxel or **pemetrexed**) in accordance with the approval status or **carboplatin in combination with a third-generation cytostatic agent**[c] (only for patients with increased risk of cisplatin-induced side effects in the framework of a combination therapy; see Appendix VI to Section K of the Pharmaceutical Directive)	Added benefit not proven
	Patients with ECOG Performance Status 2	As an alternative to the platinum-based combination therapy: monotherapy with gemcitabine or vinorelbine	Added benefit not proven
Pretreated patients[b] with ROS1-positive advanced NSCLC			
2a	Patients for whom treatment with docetaxel or pemetrexed is an option	Docetaxel or pemetrexed	Added benefit not proven
2b	Patients for whom treatment with docetaxel or pemetrexed is not an option	Best supportive care	Added benefit not proven

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold.
b: It is assumed that the NSCLC patients have stage IIIB to IV disease (staging according to IASLC, UICC), without indication for curative resection, radiotherapy or radiochemotherapy. Treatment is palliative.
c: The company chose pemetrexed as combination partner also in this case.

ACT: appropriate comparator therapy; ECOG: Eastern Cooperative Oncology Group; G-BA: Federal Joint Committee; IASLC: International Association for the Study of Lung Cancer; NSCLC: non-small cell lung cancer; ROS1: c-ros oncogene 1; UICC: Union for International Cancer Control

The G-BA decides on the added benefit.

2.6 List of included studies

Not applicable as the company presented no relevant data for the benefit assessment.

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Please see full dossier assessment for full reference list.

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The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a16-59-crizotinib-lung-cancer-benefit-assessment-according-to-35a-social-code-book-v.7635.html.