IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. A16-41

Crizotinib (NSCLC) –

Benefit assessment according to §35a Social Code Book V[1] (expiry of the decision)

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Crizotinib (NSCLC) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 27 September 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.

Publishing details

Publisher:
Institute for Quality and Efficiency in Health Care

Topic:
Crizotinib (NSCLC) – Benefit assessment according to §35a Social Code Book V

Commissioning agency:
Federal Joint Committee

Commission awarded on:
30 June 2016

Internal Commission No.:
A16-41

Address of publisher:
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Keywords: crizotinib, carcinoma – non-small-cell lung, benefit assessment

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[3] Table numbers start with "2" as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
ALK	anaplastic lymphoma kinase
BSC	best supportive care
CSR	clinical study report
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
ITT	intention to treat
NSCLC	non-small cell lung cancer
PFS	progression-free survival
RCT	randomized controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
RPSFTM	rank preserving structural failure time model
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 30 June 2016.

On 15 November 2012, the company submitted a first dossier for the early benefit assessment of the drug to be evaluated in the treatment of anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC). In this procedure, by decision of 2 May 2013, the G-BA limited its decision until 2 May 2015, which it extended, by decision of 16 April 2015, until 1 April 2016, and, by decision of 7 January 2016, until 1 July 2016.

Research question

The aim of this report was to assess the added benefit of crizotinib in comparison with the appropriate comparator therapy (ACT) in patients with previously treated ALK-positive advanced NSCLC.

Two 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	Subindication	ACT[a]
1	Patients in whom chemotherapy is indicated (in particular, these can be patients with ECOG Performance Status 0, 1, and, if applicable, 2) (hereinafter referred to as "chemotherapy population")	Docetaxel or pemetrexed
2	Patients in whom chemotherapy is not indicated (in particular, these can be patients with ECOG Performance Status 4, 3, and, if applicable, 2) (hereinafter referred to as "BSC population")	BSC
a: Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; BSC: best supportive care; ECOG: Eastern Cooperative Oncology Group; G-BA: Federal Joint Committee		

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

Deviating from the company's approach, the benefit assessment was conducted for both research questions.

The assessment was conducted based on patient-relevant outcomes and on the data provided by the company in the dossier.

Results on research question 1 (chemotherapy population)

As in the first assessment, the PROFILE 1007 study was included for research question 1.

Study characteristics

The PROFILE 1007 study was an open-label, randomized controlled, multicentre approval study on the comparison of crizotinib versus pemetrexed or docetaxel. It included pretreated patients with ALK-positive advanced NSCLC. A total of 347 patients were randomly assigned in a ratio of 1:1.

Treatment with the randomized study medication was continued until a criterion for discontinuation occurred. One of the criteria for discontinuation was occurrence of progression determined with an independent review according to the Response Evaluation Criteria in Solid Tumours (RECIST) Version 1.1. On progression, the patients in the chemotherapy arm could switch to treatment with crizotinib on an individual basis (treatment switching). This treatment was not conducted in the randomized controlled trial (RCT) PROFILE 1007, but in the one-arm study A8081005.

Duration of follow-up

Except for overall survival, the duration of follow-up in the PROFILE 1007 study was attached to the end of the randomized study treatment. The data on morbidity and on health-related quality of life were to be recorded at most until the day of the last administration of the randomized study treatment, whereas the outcomes on side effects were to be documented until 28 days after the last administration of the randomized study medication. Due to the individual treatment switching, this approach had a huge influence on the follow-up period of these outcomes.

Newly submitted data the PROFILE 1007 study

Analyses on 2 data cut offs were available for the PROFILE 1007 study.

For the first assessment, the company presented the data of the first data cut-off (30 March 2012). This was the data cut-off of the final analysis of the outcome "progression-free survival (PFS)" and the interim analysis for the outcome "overall survival". This data cut-off provided the data for the first assessment of crizotinib for all patient-relevant outcomes.

For the present assessment, the company presented data from the second data cut-off (31 August 2015). This was the data cut-off of the final analysis of the outcome "overall survival". The data presented by the company on the basis of the second data cut-off only

included results on the outcome "overall survival" and on the outcomes of side effects. For the outcomes on morbidity and on health-related quality of life, the company presented the results of the first data cut-off again.

Interpretability of the second data cut-off severely limited

The data of the second data cut-off presented by the company were not informative. The reason for this is that the interpretability of the second data cut-off was subject to notable further limitations in comparison with the first data cut-off because of the higher proportion of patients with treatment switching.

The treatment switching caused a general problem for overall survival because it remained unclear how long the patients in the chemotherapy arm after progression would have lived with a subsequent antineoplastic treatment other than crizotinib (or, following an individual decision, without subsequent antineoplastic treatment). This problem was aggravated in the course of the PROFILE 1007 study because the proportion of patients with treatment switching increased from 62% in the first data cut-off to 87% in the second data cut-off. For the results of the outcome "overall survival", this means that, with such a high proportion of patients with treatment switching, the available result of the intention-to-treat (ITT) analysis on overall survival does not represent the treatment effect of interest of crizotinib in comparison with pemetrexed or docetaxel without treatment switching.

For the outcomes of side effects, the discontinuation of the randomized study treatment by treatment switching additionally resulted in an increasing difference in the observation period between the treatment arms because, with the treatment switching, treatment and observation of the patients in the chemotherapy arm were transferred from the PROFILE 1007 study to the one-arm study A8081005. The patients in the crizotinib arm, in contrast, continued treatment in the PROFILE 1007 study and were observed for all outcomes including side effects.

The limitations of interpretability of the results on side effects resulting from the study design were already present at the first data cut-off, but had increased further at the time of the second data cut-off. With such a high proportion of patients with treatment switching (87%), the study after the second data cut-off practically only consisted of one (intervention) arm, which alone contributed data on side effects. This was shown accordingly in the data on the treatment duration. Whereas the median treatment duration in the crizotinib arm between the first and the second data cut-off increased from 31 to 48 weeks, it increased from 12.3 to only 13 weeks in the chemotherapy arm. Only very few additional patients in the chemotherapy arm had an adverse event (AE) after the first data cut-off, which primarily reflects the short observation period of few patients in this arm. In the crizotinib arm, where the observation period was longer, an AE occurred in substantially more additional patients.

In the situation described, the analyses on side effects from the second data cut-off presented by the company were not meaningfully interpretable. They provided no new findings compared with the results of the first data cut-off.

Additional comment on morbidity and health-related quality of life

The company's dossier provided no data on morbidity and health-related quality of life for the second data cut-off, although they were still recorded between the first and the second data cut-off, according to the study documents. This lack of data had no consequences for the present assessment because these data would have had the same limitations of interpretability as the data on side effects.

Extent and probability of added benefit (research question 1)

As shown above, the data from the second data cut-off were notably more uncertain than the ones from the first data cut-off because of the treatment switching and the substantial difference in observation periods between the treatment arms. As a result, the data of the second data cut-off were not informative. The results of the second data cut-off were therefore not used for the derivation of the added benefit.

The available data provided no new findings on the added benefit in comparison with the first assessment.

This deviates from the company's approach, which used the results of the second data cut-off for the derivation of the added benefit for overall survival and side effects. For the outcomes on morbidity and on health-related quality of life, the company considered the results of the first data cut-off. The company claimed an indication of major added benefit under inclusion of the outcome "PFS" and a hint of considerable added benefit without inclusion of the outcome "PFS".

Results on research question 2 (BSC population)

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

For research question 1, the results of the second data cut-off presented for the assessment after expiry of the decision were unsuitable to derive a conclusion on the added benefit of crizotinib in comparison with docetaxel or pemetrexed. The company presented no data for research question 2 (as in the first assessment). Hence there are no new findings in comparison with the conclusions on the added benefit from the first assessment (A12-15 and A13-13).

The G-BA decides on the added benefit.

[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].

2.2 Research question

The aim of this report was to assess the added benefit of crizotinib in comparison with the ACT in patients with previously treated ALK-positive advanced NSCLC.

Two research questions resulted from the ACT specified by the G-BA for the present benefit assessment (see Table 3).

Table 3: Research questions of the benefit assessment of crizotinib

Research question	**Subindication**	**ACT[a]**
1	Patients in whom chemotherapy is indicated (in particular, these can be patients with ECOG Performance Status 0, 1, and, if applicable, 2) (hereinafter referred to as "chemotherapy population")	Docetaxel or pemetrexed
2	Patients in whom chemotherapy is not indicated (in particular, these can be patients with ECOG Performance Status 4, 3, and, if applicable, 2) (hereinafter referred to as "BSC population")	BSC
a: Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; BSC: best supportive care; ECOG: Eastern Cooperative Oncology Group; G-BA: Federal Joint Committee		

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

Deviating from the company's approach, the benefit assessment was conducted for both research questions.

The assessment was conducted based on patient-relevant outcomes and on the data provided by the company in the dossier.

2.3 Research question 1 (chemotherapy population)

2.3.1 Information retrieval and study pool (research question 1)

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: 12 April 2016)
- bibliographical literature search on crizotinib (last search on 12 April 2016)
- search in trial registries for studies on crizotinib (last search on 12 April 2016)

To check the completeness of the study pool:

- search in trial registries for studies on crizotinib (last search on 6 July 2016)

No additional relevant study was identified from the check.

2.3.1.1 Studies included

As in the first assessment [3], study A8081005 – hereinafter referred to as "PROFILE 1007" – was included for research question 1.

Section 2.3.4 contains a reference list for the study included.

2.3.1.2 Study characteristics

The study characteristics, the characteristics of the interventions and the patient characteristics of study PROFILE 1007 were already described in the first assessment [3].

The PROFILE 1007 study was an open-label, randomized controlled, multicentre approval study on the comparison of crizotinib in the intervention arm versus pemetrexed or docetaxel in the control arm. It included pretreated patients with ALK-positive advanced NSCLC. A total of 347 patients were randomized, of which 173 patients were allocated to the intervention arm and 174 patients to the control arm.

Treatment with the randomized study medication was continued until a criterion for discontinuation occurred. Criteria for discontinuation included, for example, withdrawal of consent, unacceptable toxicity and occurrence of progression. Occurrence of progression was determined with an independent review according to RECIST Version 1.1 [4]. The patients in both arms could continue to receive the randomized study medication beyond progression if the investigator considered the treatment to be beneficial to them. Finally, on progression, the patients in the chemotherapy arm could switch to treatment with crizotinib on an individual basis (treatment switching). This treatment was not conducted in the RCT PROFILE 1007, but in the one-arm study A8081005 [5,6].

Duration of follow-up

Table 4 shows the planned duration of follow-up for each outcome in the PROFILE 1007 study.

Table 4: Planned duration of follow-up – RCT, direct comparison: crizotinib vs. pemetrexed or docetaxel, chemotherapy population

Study **Outcome category** **Outcome**	**Planned follow-up**
PROFILE 1007	
Mortality	
Overall survival	Every 2 months until death, until reaching the number of deaths required for the final analysis of overall survival, until withdrawal of consent or until the patients were lost to follow-up
Morbidity	
Symptoms (EORTC QLQ-C30, QLQ-LC13)	Until the end of the randomized study treatment if not documented in the last 4 weeks under treatment, or until reaching the number of deaths for the final analysis
Health status (EQ-5D VAS)	Until the end of the randomized study treatment if not documented in the last 4 weeks under treatment, or until reaching the number of deaths for the final analysis
Health-related quality of life	
Functional scales (EORTC QLQ-C30 and QLQ-LC13)	Until the end of the randomized study treatment if not documented in the last 4 weeks under treatment, or until reaching the number of deaths for the final analysis
Side effects	
All outcomes in the category “side effects”	Until 28 days after the end of the randomized study treatment

EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; QLQ-C30: Quality of Life Questionnaire Core-30; QLQ-LC13: Quality of Life Questionnaire-Lung Cancer-13; RCT: randomized controlled trial; VAS: visual analogue scale; vs.: versus

Except for overall survival, the duration of follow-up in the PROFILE 1007 study was attached to the end of the randomized study treatment. The data on morbidity and on health-related quality of life were to be recorded at most until the day of the last administration of the randomized study treatment, whereas the outcomes on side effects were to be documented until 28 days after the last administration of the randomized study medication. Due to the individual treatment switching, this approach had a huge influence on the follow-up period of these outcomes, which was confirmed by the data (see Section 2.3.2.2).

The data after the end of the randomized study medication and, if applicable, after the treatment switching were also used for the analysis of overall survival.

2.3.2 Results on added benefit (research question 1)

The data of the second data cut-off presented by the company were not informative. The reason for this is that the interpretability of the second data cut-off was subject to notable further limitations in comparison with the first data cut-off because of the higher proportion of patients with treatment switching. For all outcomes except overall survival, the discontinuation of the randomized study treatment by treatment switching resulted in discontinuation of the observation in the control arm and therefore to an increasing difference in observation period between the treatment arms. For the outcomes on side effects presented by the company, this means that the increase in data between the first and the second data cut-off was notably lower in the control arm of the study than in the crizotinib arm because of the missing follow-up. As a result, the changes of data between the first and the second data cut-off were largely based on the crizotinib arm and were therefore not meaningfully interpretable. Hence the first data cut-off was still decisive for the assessment of the added benefit of crizotinib.

The informative value of the results of the second data cut-off is described below.

2.3.2.1 Newly submitted data the PROFILE 1007 study

Analyses on 2 data cut offs were available for the PROFILE 1007 study.

For the first assessment, the company presented the data of the first data cut-off (30 March 2012). This was the data cut-off of the final analysis of the outcome “PFS” and the interim analysis for the outcome “overall survival”. This data cut-off provided the data for the first assessment of crizotinib for all patient-relevant outcomes. According to Amendment 13 to study A8081005 (26 April 2012), to which the patients in the chemotherapy arm of study PROFILE 1007 could switch, with the availability of the results on the primary outcome (PFS), treatment switching from study PROFILE 1007 to study A8081005 [7] was also possible without presence of progression.

For the present assessment, the company presented data from the second data cut-off (31 August 2015). This was the data cut-off of the final analysis of the outcome “overall survival”. The data presented by the company on the basis of the second data cut-off only included results on the outcome “overall survival” and on the outcomes of side effects. For the outcomes on morbidity and health-related quality of life, the company presented the results of the first data cut-off again, although these outcomes were recorded until the final analysis for overall survival, according to the study documents.

According to the company, the recording of the data ended with the visit of the last patient on 5 January 2016, and the study had the status “completed”. The data documented between 31 August 2015 and 5 January 2016 were to be described in an additional clinical study report (CSR), which, according to the company, will not be submitted to the regulatory authorities,

however. As shown in Section 2.6.2.4.3 of the full dossier assessment, the data from this time period are not needed for the derivation of the added benefit.

2.3.2.2 Interpretability of the second data cut-off severely limited

It was already discussed in the first assessment of crizotinib that a large proportion of patients with treatment switching (i.e. an allowed change of treatment from the control arm to treatment with crizotinib) (62%)[5] can have an important influence on the effect estimates of all outcomes investigated ([3], Section 2.7.2.4.2 of the full dossier assessment). The interpretability of the results of the second data cut-off was limited further by the even higher proportion of patients with treatment switching (87%) compared with the first data cut-off. For all outcomes except overall survival, the increased treatment switching resulted in an even greater difference in observation period between the treatment arms, which additionally decreased the interpretability of the results.

Results on the outcome "overall survival"

The treatment switching caused a general problem for overall survival because it remained unclear how long the patients in the chemotherapy arm after progression would have lived with a subsequent antineoplastic treatment other than crizotinib (or, following an individual decision, without subsequent antineoplastic treatment). This problem was aggravated in the course of the PROFILE 1007 study because the proportion of patients with treatment switching increased from 62% in the first data cut-off to 87% in the second data cut-off.

For the results of the outcome "overall survival", this means that, with such a high proportion of patients with treatment switching, the available result of the ITT analysis on overall survival (see Table 9 and Figure 1 in Appendix A of the full dossier assessment) does not represent the treatment effect of interest of crizotinib in comparison with pemetrexed or docetaxel without treatment switching. The sensitivity analysis conducted by the company with the rank preserving structural failure time model (RPSFTM) [8] could not dispel this uncertainty. Latimer et al. [9] showed in simulations that the proportion of patients with treatment switching had an important influence on the size of the bias.

In summary, the interpretability of the data of overall survival was limited more severely at the second data cut-off than at the first data cut-off.

Results on side effects

The problems of the high proportion of patients with treatment switching in the PROFILE 1007 study and of the different observation periods are closely connected. With the

[5] This proportion resulted from the information of the company for the first assessment (108 of 174 patients with treatment switching) and referred to the patients who were included in the one-arm study A8081005 after switching to crizotinib treatment. According to the study documents of the current assessment 107 of 174 patients (61%) had treatment switching. In addition, 5 patients received subsequent treatment with crizotinib outside study A8081005. Hence 112 (64%) of the patients had treatment switching from chemotherapy to crizotinib.

treatment switching, treatment and observation of the patients in the chemotherapy arm were transferred from the PROFILE 1007 study to the one-arm study A8081005, where all patients received crizotinib. The patients in the crizotinib arm, in contrast, continued treatment in the PROFILE 1007 study and were observed for all outcomes including side effects. The resulting limitations of interpretability of the results on side effects were already present at the first data cut-off, but had increased notably at the time of the second data cut-off. This is explained below.

At the time point of the first data cut-off, 85 (49.1%) of the patients in the crizotinib arm were receiving treatment with crizotinib, whereas only 28 (16.1%) of the patients in the chemotherapy arm were receiving treatment with chemotherapy.

The study documents showed that over 80% of the patients remaining in the chemotherapy arm were switched to treatment with crizotinib. With such a high proportion of patients with treatment switching, particularly when they were switched soon after the first data cut-off, this means that the study practically only consisted of one (intervention) arm, which alone contributed data on side effects.

The switching of patients from the control arm of the PROFILE 1007 study to the one-arm study A8081005 is also shown in the data on treatment duration. Table 5 shows the treatment duration in the PROFILE 1007 study at the time point of the first and the second data cut-off.

Table 5: Course of the study per data cut-off – RCT, direct comparison: crizotinib vs. pemetrexed or docetaxel, chemotherapy population

Study **Duration of the study phase** **Outcome category**	**Crizotinib** **N = 173**		**Pemetrexed or docetaxel** **N = 174**	
PROFILE 1007	**Data cut-off**			
	30 Mar 2012	31 Aug 2015	30 Mar 2012	31 Aug 2015
Treatment duration [weeks][a]				
Median [min; max]	31.0 [1.3; 110.1]	48.0 [1.3; 262.6]	12.3 [3.0; 90.0]	13.0 [3; 162]
Mean (SD)	36.5 (25.9)	71.2 (64.8)	18.6 (17.9)	22 (27.4)
Observation duration				
Overall survival, morbidity, health-related quality of life, side effects	ND	ND	ND	ND

a: 1 (0.6%) vs. 3 (1.7%) patients were randomized, but not treated. This was not considered in the estimation of the treatment duration.

max: maximum; min: minimum; N: number of randomized patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

Whereas the median treatment duration in the crizotinib arm between the first and the second data cut-off increased from 31 to 48 weeks, it increased from 12.3 to only 13 weeks in the

chemotherapy arm. This shows that treatment and observation in the PROFILE 1007 study after the first data cut-off was largely limited to patients in the crizotinib arm.

Consequently, the ratio of the observation periods for side effects between the treatment arms was less favourable in the second data cut-off than in the first data cut-off. The median treatment duration in the second data cut-off was 48 weeks in the crizotinib arm and 13 weeks in the chemotherapy arm, whereas in the first data cut-off it had been 31 versus 12.3 weeks. Since the dossier contained no information on the duration of follow-up, it was estimated on the basis of the information provided on the treatment duration.

Since the outcomes on side effects were recorded at most 28 days after the end of the randomized study medication, 4 weeks were added to the median treatment duration to estimate the median observation period. For the outcomes of side effects, this resulted in an estimated median observation period of 52 versus 17 weeks in the second data cut-off (in the control arm 33% of the estimated observation period of the crizotinib arm), whereas this was 35 versus 16.3 weeks in the first data cut-off (in the control arm 47% of the estimated observation period of the crizotinib arm). The potential bias associated with the different observation periods was more pronounced in the second data cut-off than in the first data cut-off because of the greater differences in observation periods.

For the PROFILE 1007 study, this situation was reflected in the proportions of patients with at least 1 AE (see Table 6).

Table 6: Influence of missing observation on AEs in the control arm – RCT, direct comparison: crizotinib vs. pemetrexed or docetaxel, chemotherapy population

Study	**Crizotinib N = 172[a]**		**Pemetrexed or docetaxel N = 171[a]**	
PROFILE 1007	**Data cut-off**			
	30 Mar 2012	31 Aug 2015	30 Mar 2012	31 Aug 2015
Number of AEs	2085	2734	1358	1430
n (%) patients with AEs	172 (100.0)	172 (100.0)	168 (98.2)	169 (98.8)
n (%) patients with SAEs	64 (37.2)	80 (46.5)	40 (23.4)	42 (24.6)
n (%) patients with severe AEs (CTCAE grade 3 or 4)	97 (56.4)	111 (64.5)	78 (45.6)	82 (48.0)
n (%) patients with fatal AEs (CTCAE grade 5)	25 (14.5)	30 (17.4)	7 (4.1)	7 (4.1)
n (%) patients with discontinuation due to AEs	30 (17.4)	30 (17.4)	23 (13.5)	34 (19.9)

a: In addition, 1 (0.6%) vs. 3 (1.7%) patients were randomized, but not treated.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; n: number of patients with (at least one) event; N: number of treated patients; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

It was shown in the second data cut-off in the chemotherapy arm of the study that only very few additional patients had an AE after the first data cut-off. This result primarily reflects the short observation period of few patients in this arm. In the crizotinib arm, where the observation period was longer, an AE occurred in substantially more additional patients.

In this situation, the data of the second data cut-off cannot be meaningfully interpreted. This also concerned the survival time analyses presented by the company for the second data cut-off, which, due to the problems described, were largely based on the same events as the analyses based on the first data cut-off.

In summary, the analyses on side effects from the second data cut-off presented by the company were not meaningfully interpretable. They provided no new findings compared with the results of the first data cut-off.

Additional comment on morbidity and health-related quality of life

The company's dossier provided no data on morbidity and health-related quality of life for the second data cut-off, although they were still recorded between the first and the second data cut-off, according to the study documents. It remained unclear why the company did not present the data; no justification was provided in the dossier. This lack of data had no consequences for the present assessment because, due to the problems described above for side effects, these data would have had the same limitations of interpretability as the data on side effects.

2.3.2.3 Subgroups and other effect modifiers

Due to the substantial limitations of the interpretability of the data of the second data cut-off, subgroups and other effect modifiers were not considered.

2.3.3 Extent and probability of added benefit (research question 1)

As shown in Section 2.3.2, the data from the second data cut-off were notably more uncertain than the ones from the first data cut-off because of the treatment switching and the substantial difference in observation periods between the treatment arms. As a result, the data of the second data cut-off were not informative. The results of the second data cut-off were therefore not used for the derivation of the added benefit.

The available data provided no new findings on the added benefit in comparison with the first assessment [3,10].

This deviates from the company's approach, which used the results of the second data cut-off for the derivation of the added benefit for overall survival and side effects. For the outcomes on morbidity and on health-related quality of life, the company considered the results of the first data cut-off. The company claimed an indication of major added benefit under inclusion of the outcome "PFS" and a hint of considerable added benefit without inclusion of the outcome "PFS".

2.3.4 List of included studies (research question 1)

PROFILE 1007

Blackhall F, Kim DW, Besse B, Nokihara H, Han JY, Wilner KD et al. Patient-reported outcomes and quality of life in PROFILE 1007: a randomized trial of crizotinib compared with chemotherapy in previously treated patients with ALK-positive advanced non-small-cell lung cancer. J Thorac Oncol 2014; 9(11): 1625-1633.

Blackhall F, Kim DW, Besse B, Nokihara H, Han JY, Wilner K et al. Erratum: "Patient-reported outcomes and quality of life in PROFILE 1007: a randomized trial of crizotinib compared with chemotherapy in previously treated patients with ALK-positive advanced non-small-cell lung cancer" (J Thorac Oncol 2014; 9(11): 1625-1633). J Thorac Oncol 2015; 10(11): 1657.

Pfizer. Phase 3, randomized, open-label study of the efficacy and safety of PF-02341066 Versus Standard Of Care Chemotherapy (Pemetrexed Or Docetaxel) In Patients With Advanced Non-Small Cell Lung Cancer (Nsclc) harboring a translocation or inversion event involving the anaplastic lymphoma kinase (Alk) gene locus [online]. In: PharmNet.Bund Klinische Prüfungen. [Accessed: 06.05.2016]. URL: https://www.pharmnet-bund.de/dynamic/de/klinische-pruefungen/index.html.

Pfizer. Phase 3, randomized, open-label study of the efficacy and safety of PF 02341066 versus standard of care chemotherapy (pemetrexed or docetaxel) in patients with advanced non-small cell lung cancer (NSCLC) harboring a translocation or inversion event involving the anaplastic lymphoma kinase (ALK) gene locus [online]. In: EU Clinical Trials Register. [Accessed: 06.05.2016]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2009-012595-27.

Pfizer. Phase 3, randomized, open-label study of the efficacy and safety of PF-02341066 versus standard of care chemotherapy (pemetrexed or docetaxel) in patients with advanced non-small cell lung cancer (NSCLC) harboring a translocation or inversion involving the anaplastic lymphoma kinase (ALK) gene locus: study A8081007; preliminary clinical study report [unpublished]. 2012.

Pfizer. An investigational drug, PF-02341066 is being studied versus standard of care in patients with advanced non-small cell lung cancer with a specific gene profile involving the anaplastic lymphoma kinase (ALK) gene: full text view [online]. In: ClinicalTrials.gov. 11.04.2016 [Accessed: 06.05.2016]. URL: https://ClinicalTrials.gov/show/NCT00932893.

Pfizer. Phase 3, randomized, open-label study of the efficacy and safety of PF-02341066 versus standard of care chemotherapy (pemetrexed or docetaxel) in patients with advanced non-small cell lung cancer (NSCLC) harboring a translocation or inversion involving the anaplastic lymphoma kinase (ALK) gene locus: study A8081007; preliminary clinical study report [unpublished]. 2015.

Pfizer. Phase 3, randomized, open-label study of the efficacy and safety of PF-02341066 versus standard-of-care chemotherapy (pemetrexed or docetaxel) in patients with advanced non-small cell lung cancer (NSCLC) harboring a translocation or inversion event involving the anaplastic lymphoma kinase (ALK) gene locus: study A8081007 (PROFILE 1007); Zusatzanalysen [unpublished]. 2016.

Pfizer. Phase 3, randomized, open-label study of the efficacy and safety of PF-02341066 versus standard of care chemotherapy (pemetrexed or docetaxel) in patients with advanced non-small cell lung cancer (NSCLC) harboring a translocation or inversion involving the anaplastic lymphoma kinase (ALK) gene locus: study A8081007; clinical study report [unpublished]. 2016.

Shaw AT, Kim DW, Nakagawa K, Seto T, Crino L, Ahn MJ et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. N Engl J Med 2013; 368(25): 2385-2394.

2.4 Research question 2 (BSC population)

2.4.1 Information retrieval and study pool (research question 2)

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

The Institute's check of completeness on the basis of the company's study list on crizotinib (status: 12 April 2016) and the search in trial registries on crizotinib (last search on 6 July 2016) identified no studies relevant for research question 2.

2.4.2 Results on added benefit (research question 2)

The company presented no data for the assessment of the added benefit of crizotinib in the BSC population in the dossier. This resulted in no hint of an added benefit of crizotinib in comparison with the ACT; an added benefit is therefore not proven.

2.4.3 Extent and probability of added benefit (research question 2)

Since the company presented no data for the assessment of the added benefit of crizotinib in the BSC population in the dossier, an added benefit of crizotinib is not proven.

This result concurs with the assessment of the company.

2.4.4 List of included studies (research question 2)

Not applicable as no studies were included in the benefit assessment.

2.5 Extent and probability of added benefit – summary

For research question 1, the results of the second data cut-off presented for the assessment after expiry of the decision were unsuitable to derive a conclusion on the added benefit of crizotinib in comparison with docetaxel or pemetrexed. The company presented no data for research question 2 (as in the first assessment). Hence there are no new findings in comparison with the conclusions on the added benefit from the first assessment [3,10].

The G-BA decides on the added benefit.

References for English extract

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/a16-41-crizotinib-new-therapeutic-indication-benefit-assessment-according-to-35a-sgb-v.7571.html.