IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Crizotinib –

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 – Nutzenbewertung gemäß § 35a SGB V" (Version 1.0; Status: 13.02.2013). 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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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. Individual sections and conclusions in the dossier assessment therefore do not necessarily reflect his opinion.

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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
CTCAE	Common Terminology Criteria for Adverse Events
CI	confidence interval
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D	European Quality of Life-5 Dimensions
G-BA	*Gemeinsamer Bundesausschuss* (Federal Joint Committee)
IQWiG	*Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen* (Institute for Quality and Efficiency in Health Care)
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PFS	progression-free survival
QLQ-C30	Quality of Life Questionnaire-Core 30
QLQ-LC13	Quality of Life Questionnaire-Lung Cancer 13
RCT	randomized controlled trial
SAE	serious adverse event
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 abbreviated to "the company"). The dossier was sent to IQWiG on 15.11.2012.

Research question

The aim of this report is to assess the added benefit of crizotinib in patients with previously treated anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC)

- in whom chemotherapy is indicated (in particular, these can be patients with Eastern Cooperative Oncology Group [ECOG] performance status 0, 1, and, if applicable, 2), in comparison with chemotherapy (docetaxel/pemetrexed) as appropriate comparator therapy (ACT) (chemotherapy population).
- in whom chemotherapy is not indicated (in particular, these can be patients with ECOG performance status 4, 3, and, if applicable, 2), in comparison with best supportive care (BSC) as ACT (BSC population).

The assessment was conducted based on patient-relevant outcomes. Direct comparative randomized controlled trials (RCTs) were included in the assessment.

Results on the chemotherapy population

One relevant study (PROFILE 1007) was included in the benefit assessment for the chemotherapy population. This is an approval study of crizotinib, an open-label RCT. The risk of bias was rated as high both at study level and at outcome level. This was mainly due to the facts that the study was unblinded and that a high proportion of the patients in the control group (62%) switched to the crizotinib treatment during the course of the study (crossover).

Moreover, the company also presented results on non-randomized comparative and non-comparative studies, which on the basis of their study population should have been used for the research question on the chemotherapy population. As there already was an RCT on the chemotherapy population and the studies did not contain any information beyond those contained in the RCT, they were not included in the dossier assessment.

Overall survival

There was no statistically significant difference between crizotinib and chemotherapy in this outcome for the chemotherapy population.

An added benefit of crizotinib in comparison with chemotherapy (docetaxel/pemetrexed) for overall survival (OS) is not proven.

Morbidity

In the study, data on symptoms were collected using the questionnaires "European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30" (EORTC QLQ-C30) and "EORTC QLQ-Lung Cancer 13" (LC13). However, the company did not present any assessable evaluations on symptoms in its dossier.

An added benefit of crizotinib in comparison with chemotherapy (docetaxel/pemetrexed) for morbidity (symptoms) is not proven.

Health-related quality of life

The dossier did not contain any results on health-related quality of life recorded with the instrument "European Quality of Life-5 Dimensions" (EQ-5D) for the chemotherapy population, although this questionnaire was used in the study. Results on quality of life recorded with the disease-specific instrument EORTC QLQ-C30 showed a statistically significant difference between the treatment groups for 5 of 6 subscales. However, the 95% confidence intervals (CIs) of the corresponding effect estimators were only fully above the irrelevance threshold for 2 of these 5 subscales (global health status/health-related quality of life and physical functioning).

In summary, considering the high risk of bias, there is a hint of an added benefit of crizotinib in comparison with chemotherapy (docetaxel/pemetrexed) for health-related quality of life (disease-specific instrument EORTC QLQ-C30).

Adverse events

The analysis of the overall rate of adverse events (AEs) showed that an AE was observed in almost all patients in the course of the study. There was no statistically significant difference in the overall rate of AEs between crizotinib and chemotherapy.

Vision disorders were more common in the patients treated with crizotinib than in the chemotherapy arm. Each of the individual events "diarrhoea", "nausea", "vomiting", and "constipation" was also observed more frequently in the patients treated with crizotinib than in the chemotherapy arm (these individual events are summarized as "gastrointestinal AEs"). The group difference was statistically significant in all cases. Considering the high risk of bias, there is a hint of a greater harm from crizotinib for these events.

The proportion of patients with severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] Grade 3 and 4) was not statistically significantly different between the treatment groups. There was also no statistically significant difference in the overall rate of treatment discontinuations due to AEs between crizotinib and chemotherapy. A lesser/greater harm from crizotinib in comparison with chemotherapy is not proven for these outcomes.

Serious adverse events (SAEs) were more common in patients treated with crizotinib than in patients receiving chemotherapy. The difference was statistically significant. The risk of bias at study and outcome level was rated as high. Hence there is a hint of a greater harm from crizotinib in the chemotherapy population for this outcome.

Relevant subgroups

Although subgroup analyses for age and sex were planned in the included study, the company did not present any subgroup analyses on patient-relevant outcomes, but only on surrogates.

Results on the BSC population

There were no results on the BSC population in the dossier.

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

The overall conclusion on the extent of the added benefit will be presented separately for the chemotherapy population and the BSC population. On the basis of the results presented, the extent and probability of the added benefit of the drug crizotinib compared with the ACT is assessed as follows:

For adult patients with previously treated ALK-positive advanced NSCLC, **for whom chemotherapy is indicated (chemotherapy population)**, positive and negative effects remain. On the positive side, in the category "health-related quality of life", there is an added benefit of crizotinib with the probability "hint" and the extent "minor".

On the negative side, there is greater harm from crizotinib with the probability "hint" and the extent "considerable" in the category "non-serious/non-severe AEs" for 2 outcomes (vision disorders, gastrointestinal events). There is also a "hint" of greater harm from crizotinib in the category "serious/severe AEs" for the outcome "SAEs" with the extent "non-quantifiable".

For an overall conclusion, the added benefit regarding health-related quality of life has to be contrasted with the greater harm from crizotinib. It cannot be finally assessed on the basis of the available information whether the greater harm, which reaches a considerable or non-quantifiable extent respectively, outweighs the positive effect regarding health-related quality of life so that lesser benefit of crizotinib in comparison with chemotherapy would have to be assumed. On the whole, the added benefit of crizotinib for adult patients with previously

[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 1-3 cannot be drawn from the available data), see [1]. 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), see [2].

treated ALK-positive advanced NSCLC **for whom chemotherapy is indicated (chemotherapy population)** is not proven.

For adult patients with previously treated ALK-positive advanced NSCLC **for whom chemotherapy is not indicated (BSC population)**, there were no data for a comparison of crizotinib with BSC in the dossier (see Section 2.3.1). Hence the added benefit of crizotinib in the BSC population is not proven.

Table 2 summarizes the extent and probability of the added benefit for the different therapeutic situations of crizotinib in comparison with the ACT.

Table 2: Crizotinib: extent and probability of added benefit

Therapeutic situation	**ACT**	**Extent and probability of added benefit**
Treatment of previously treated ALK-positive advanced NSCLC in patients for whom chemotherapy is indicated (chemotherapy population)	Chemotherapy (docetaxel or pemetrexed)	Added benefit not proven
Treatment of previously treated ALK-positive advanced NSCLC in patients for whom chemotherapy is not indicated (BSC population)	Best supportive care	Added benefit not proven
ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; BSC: best supportive care; NSCLC: non-small cell lung cancer		

In summary, an added benefit for adult patients with previously treated ALK-positive advanced NSCLC is not proven. The overall conclusion on the added benefit is based on the aggregation of the extent of the added benefit derived at outcome level in the subpopulations resulting from the ACT.

The approach for deriving an overall conclusion on added benefit is a proposal by IQWiG. The decision on added benefit is made by the G-BA.

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. The benefit assessment was conducted according to the Summary of Product Characteristics (SPC) [3] for adult patients.

The company cited the following ACTs for the treatment of previously treated ALK-positive advanced NSCLC:

- for patients in whom chemotherapy is indicated (in particular, these can be patients with ECOG performance status 0, 1, and, if applicable, 2), docetaxel or pemetrexed, adhering to the respective approved therapeutic indication.
- for patients in whom chemotherapy is not indicated (in particular, these can be patients with ECOG performance status 4, 3, and, if applicable, 2), BSC. BSC means the best possible supportive therapy, optimized for the individual patient, for alleviation of symptoms and improvement in the quality of life.

Table 3 shows the ACT specified by the G-BA.

Table 3: Therapeutic situation and ACT specified by the G-BA

Therapeutic situation	**ACT**
Treatment of previously treated ALK-positive advanced NSCLC in patients in whom chemotherapy is indicated (in particular, these can be patients with ECOG performance status 0, 1, and, if applicable, 2) (chemotherapy population)	docetaxel or pemetrexed
Treatment of previously treated ALK-positive advanced NSCLC in patients in whom chemotherapy is not indicated (in particular, these can be patients with ECOG performance status 4, 3, and, if applicable, 2) (BSC population)	best supportive care
ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; BSC: best supportive care; NSCLC: non-small cell lung cancer	

The ACT of the company corresponded with the GBA's specification. It was also used for this assessment.

The assessment was conducted based on patient-relevant outcomes. Only direct comparative RCTs were included in the assessment.

Further information on the research question can be found in Module 3, Section 3.1 and in Module 4, Section 4.2.1 of the dossier and in Sections 2.7.1 and 2.7.2.1 of the full dossier assessment.

2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

- Studies on crizotinib completed by the company up to 15.08.2012 (study list of the company)
- Results of a search in bibliographical databases and trial registries for studies on crizotinib (last search 05.11.2012 in bibliographical databases and 28.09.2012 in trial registries, searches by the company)

- A search by the Institute in trial registries and in the bibliographical database Pubmed for studies on crizotinib to check the search results of the company up to 28.11.2012. The check produced no deviations from the study pool presented in the company's dossier.

The resulting study pool of RCTs corresponded to that of the company. The study pool of non-RCTs was not checked because these studies were not included in the benefit assessment (see Section 2.7.2.3.2 of the full dossier assessment).

Further information on the inclusion criteria for studies in this benefit assessment and the methods of information retrieval can be found in Module 4, Sections 4.2.2 and 4.2.3 of the dossier and in Sections 2.7.2.1 and 2.7.2.3 of the full dossier assessment.

2.3.1 Studies included

The study listed in the following table was included in the benefit assessment.

Table 4: Study pool – RCT, direct comparison – crizotinib vs. chemotherapy, chemotherapy population

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored studya (yes/no)	Third-party study (yes/no)
PROFILE 1007	yes	yes	no
a: study for which the company was sponsor, or in which the company was otherwise financially involved RCT: randomized controlled trial; vs.: versus			

The study PROFILE 1007 was included in the assessment of the added benefit to answer the research question on the chemotherapy population. In addition, the company presented 2 non-randomized, retrospective comparative studies and 2 non-comparative studies. These were not included in the study pool for the dossier assessment as they addressed the same question as the RCT, but did not offer any additional information. See Section 2.7.2.3.2 of the full dossier assessment for more details.

The company did not submit any studies to answer the research question on the BSC population.

Section 2.6 contains a list of the data sources cited by the company for the studies included by the Institute.

According to the company, there was no final study report of the study PROFILE 1007 yet at the time of the dossier compilation and market access. The company presented a selection of the planned analyses of the study in form of a summary as source of the information in Module 4. A presentation enclosed also contained information on the methods and results of the study.

Further information on the results of the information retrieval and the study pool derived from it can be found in Module 4, Sections 4.3.1.1 and 4.3.2.1.1 of the dossier and in Sections 2.7.2.3.1 and 2.7.2.3.2 of the full dossier assessment.

2.3.2 Study characteristics

Table 5 and Table 6 describe the study used for the benefit assessment in the chemotherapy population. This is the approval study PROFILE 1007 on crizotinib.

The study PROFILE 1007 is an open-label, parallel-group RCT. It was declared as an ongoing study in the dossier. It is a multicentre study and is being conducted in Western industrial nations as well as in countries in Asia and Latin America. It included patients with advanced ALK-positive NSCLC after previous treatment. Crizotinib is compared with a chemotherapy with docetaxel and pemetrexed. The patients were stratified according to ECOG performance status, brain metastases (present versus absent) and to pre-treatment with an epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TK1). Patients were randomized 1:1 to crizotinib or chemotherapy (docetaxel or pemetrexed). A total of 347 patients were randomized to crizotinib (n = 173) or chemotherapy (n = 174).

At the time of this benefit assessment, observation of the patients in the study was not yet completed. The analysis of the primary outcome "progression-free survival" (PFS) was planned for the time at which 217 patients had shown progression of the disease or had died. Data cut-off for all outcomes presented was 30.03.2012. At this time only 40% of all deaths had occurred that had been envisaged for the final analysis of the outcome OS.

Crizotinib as well as pemetrexed and docetaxel were administered according to their current approval status. The intervention consisted of 250 mg crizotinib twice daily. In the control arm, patients were either given pemetrexed 500 mg/m^2 or docetaxel 75 mg/m^2. Predefined concomitant therapies and supportive interventions were possible.

Patients in the control arm of the study could change to crizotinib treatment if a progression had occurred (i.e. after event in the primary outcome). These patients were continued to be analysed in the study PROFILE 1005, however, information on these patients was included in the analyses of OS also after their crossover to crizotinib treatment. Only the period up to the change of treatment of a patient was considered for the health-related quality of life and non-serious adverse events. For SAEs, this period was prolonged up to 28 days after the change of treatment.

Table 5: Characteristics of the studies included – RCT, direct comparison – crizotinib vs. chemotherapy, chemotherapy population

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
PROFILE 1007	RCT, open-label, parallel	Adult patients with proven translocation or inversion in the ALK locus and locally advanced or metastatic NSCLC. The disease had to be progressive after only one prior platinum-based combination chemotherapy, which could include maintenance therapy.	Crizotinib (n = 173) chemotherapy (n = 174) Of which: pemetrexed (n = 99) docetaxel (n = 72)	Approximately 42 months[b] Treatment: until first occurrence of progression, unacceptable toxicity, treatment pause of more than 6 weeks or deterioration of general disease symptoms	21 Western industrial countries and countries in Asia and South America Ongoing study; accrual February 2010 – February 2012, planned end of study: March 2013[b] Analyses of data cut-off 30.03.2012	Primary: progression-free survival Secondary: overall survival; symptoms; health-related quality of life; adverse events

a: Primary outcomes contain information without consideration of the relevance for the present benefit assessment. Secondary outcomes contain exclusively information on relevant available outcomes for the present benefit assessment.
b: Information from the company in Module 4, the study duration did not correspond with the planned duration of the study (from beginning of accrual until the planned end of study: 38 months). This discrepancy could not be resolved on the basis of the dossier.
ALK: anaplastic lymphoma kinase; n: relevant subpopulation; NSCLC: non-small cell lung cancer; RCT: randomized controlled trial; vs.: versus

Table 6: Characteristics of the interventions – RCT, direct comparison – crizotinib vs. chemotherapy, chemotherapy population

Study **Study arm**	**Study treatment**	**Concomitant medication: dexamethasone**	**Other concomitant medication**	**Supportive intervention**
PROFILE 1007				
Crizotinib	Crizotinib orally 500 mg/day			Antiemetics; haematopoietic growth factors, anti-inflammatories, analgesics and opioids, bisphosphonates and hormone replacement therapies, and palliative radiotherapy or surgery and megestrol acetate in anorexia
Chemotherapy	Pemetrexed 500 mg/m^2 i.v.[a]	Dexamethasone 8 mg/day orally[b]	Folic acid orally 350 – 1000 µg/day Vitamin B12 1000 µg i.m.[c]	
	Docetaxel 75 mg/m^2 i.v.[a]	Dexamethasone 8 mg/day orally[b]		

a: administration on day 1 of a 21-day cycle
b: administration on the day before and on the day of the administration of pemetrexed and on the following day
c: administration 1 – 2 weeks before pemetrexed, and then every 9 weeks
i.m.: intramuscular; i.v.: intravenous; RCT: randomized controlled trial; vs.: versus

Table 7 shows the characteristics of the patients in the study included.

Table 7: Characteristics of the study populations – RCT, direct comparison – crizotinib vs. chemotherapy, chemotherapy population

Characteristics **Category**	**Crizotinib** **N = 173**	**Chemotherapy** **N = 174**
Age [years]: median (min, max)	51 (22, 81)	49 (24, 85)
Sex [f/m], %	56.6 / 43.4	55.2 / 44.8
Ethnic origin, n (%)		
white	90 (52.0)	91 (52.3)
Asian	79 (45.7)	78 (44.8)
ECOG performance status, n (%)		
0 or 1	156 (90.2)	160 (92)
2	16 (9.2)	14 (8.0)
Proportion of patients with adenocarcinoma, n (%)	163 (94.2)	160 (92.0)
Smoking status, n (%)		
never smoker	108 (62.4)	111 (63.8)
ex-smoker	59 (34.1)	54 (31.0)
smoker	5 (2.9)	9 (5.2)
discontinuations[a], n (%)	no data[b]	no data[b]

a: discontinuations at the time of the analysis
b: Based on information on patients who died and patients who changed treatment it could be reconstructed that the number of discontinuations was 39 (22.5%) in the crizotinib group, and between 22 (13.2%) and 38 (21.8%) in the chemotherapy group. In addition, 108 patients under chemotherapy changed to crizotinib treatment. There is a discrepancy between the number of patients in the documents and in the modules of the dossier (n = 108 vs. 111).
ECOG: Eastern Cooperative Oncology Group; f: female; m: male; max: maximum; min: minimum; N: number of randomized patients; n: number of patients in the category; RCT: randomized controlled trial; vs.: versus

Due to the stratified randomization, the ECOG performance status was mainly equally distributed. Over 90% of the patients were assigned an ECOG performance status 0 or 1, i.e. they were still physically active or restricted to some degree but were able to carry out light activities themselves. The distribution of other characteristics was also balanced in both arms.

Over 90% of the patients in both study arms had NSCLC with the histology of an adenocarcinoma. This corresponds to the typical histology of ALK-positive NSCLC.

It is also known that smoking is not the primary risk factor for this form of non-small cell lung cancer. This is reflected by the high proportion of never smokers in the patient population of the study.

The overall rate of study discontinuations remained unclear. The dossier only contained information on the number of patients who discontinued treatment because of an adverse event, changed treatment, or died.

About 45% of the study population were patients of Asian ethnicity. The European Medicines Agency (EMA) advises that ethnic origin might be an effect modifier [3]. This question could not be examined in the dossier assessment, as the company did not give any information about it and did not present any subgroup analyses which might have answered this question.

Table 8 shows the risk of bias at study level.

Table 8: Risk of bias at study level – RCT, direct comparison – crizotinib vs. chemotherapy, chemotherapy population

Study	Adequate random sequence generation	Allocation concealment	Blinding		Potential selective reporting	Other factors influencing risk of bias	Risk of bias at study level
			Patient	Treating staff			
PROFILE 1007	yes	yes	no	no	yes[a]	yes[b]	high[a, b, c]

a: The results reported by the company are based on an evaluation that only contained selected outcomes or analyses, without reasons being presented for this selection.
b: high proportion (62%) of patients in the control group who changed to crizotinib treatment during the course of the study (crossover patients)
c: unblinded study (lack of blinding of patient and treating staff)
RCT: randomized controlled trial; vs.: versus

The risk of bias at study level is rated as high in the PROFILE 1007 study. This is due to the lack of blinding of treating staff and patients, to the potentially selective reporting, and to the high proportion of patients in the control group who changed to the crizotinib arm of another study. The effects of the crossover are different for the outcomes included, and are therefore described in the risk of bias at outcome level (see Sections 2.7.2.4.2 and 2.7.2.4.3 of the full dossier assessment).

This contradicts the company's assessment, which rated the risk of bias at study level as low.

Further information on study design, study populations and the risk of bias at study level can be found in Module 4, Sections 4.3.1.2.1, 4.3.1.2.2 and 4.3.2.1.2, and also in Appendix 4-G of the dossier and in Sections 2.7.2.4.1 and 2.7.2.4.2 of the full dossier assessment.

2.4 Results on added benefit

The following patient-relevant outcomes were considered in this assessment (for reasons, see Section 2.7.2.4.3 of the full dossier assessment):

- Mortality (overall survival)
- Morbidity: symptoms (recorded with the symptom scales of disease-specific instruments [EORTC QLQ-C30 and QLQ-LC13])
- Health-related quality of life: generic instrument (EQ-5D) and disease-specific instrument (EORTC QLQ-C30)
- Adverse events
  - overall rate of AEs
  - severe AEs (CTCAE Grade 3 and 4)
  - severe AEs that lead to death (CTCAE Grade 5)
  - serious AEs (SAEs)
  - treatment discontinuations due to AEs
  - vision disorders
  - diarrhoea
  - nausea
  - vomiting
  - constipation
  - skin and subcutaneous tissue disorders

The Institute's choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4). In particular, the outcomes PFS and objective response rate (ORR) were not used for this assessment since neither the patient relevance postulated in the dossier (in this study, PFS and ORR were exclusively recorded using imaging methods) nor the validity of a surrogate characteristic for these outcomes was presented. However, additional outcomes were used for this assessment. See Section 2.7.2.4.3 of the full dossier assessment for reasons for the choice of outcomes.

Table 9 shows for which outcomes data were available in the studies included. Table 10 describes the risk of bias for these outcomes.

Table 9: Matrix of outcomes – RCT, direct comparison – crizotinib vs. chemotherapy, chemotherapy population

Study	Outcomes														
	Overall survival	Symptoms[a]	Health-related quality of life (disease-specific instrument)[b]	Health-related quality of life (generic instrument)[c]	Overall rate of AEs	Severe AEs (CTCAE Grade 3 and 4)	Fatal AEs (CTCAE Grade 5)	SAEs	Treatment discontinuations due to AEs	Vision disorders	Diarrhoea	Nausea	Vomiting	Constipation	Skin and subcutaneous tissue disorders
PROFILE 1007	yes	no	yes	no	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	no

a: recorded with the symptom scales of disease-specific instruments [EORTC QLQ-C30 and QLQ-LC13), no adequate analysis presented
b: recorded with EORTC QLQ C-30
c: recorded with EQ-5D, no data presented

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events, EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D: European Quality of Life-5 Dimensions; QLQ-LC13: Quality of Life Questionnaire-LC 13; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

Table 10: Risk of bias at study and outcome level – RCT, direct comparison – crizotinib vs. chemotherapy, chemotherapy population

Study		Outcomes														
	Study level	Overall survival	Symptoms[b]	Health-related quality of life (disease-specific instrument)[d]	Health-related quality of life (generic instrument EQ-5D)	Overall rate of AEs	Severe AEs (CTCAE Grade 3 and 4)	Fatal AEs (CTCAE Grade 5)	SAEs	Treatment discontinuations due to AEs	Vision disorders	Diarrhoea	Nausea	Vomiting	Constipation	Skin and subcutaneous tissue disorders[e]
PROFILE 1007	h	h[a]	-[c]	h[a, f]	-[c]	h[a]	h[a]	h[a]	h[a]	h[a]	h[a]	h[a]	h[a]	h[a]	h[a]	-[c]

a: risk of bias already high at study level
b: recorded with the symptom scales of disease-specific instruments (EORTC QLQ-C30 and QLQ-LC13)
c: risk of bias not assessed because no adequately operationalized assessments and therefore no usable results were available (see Section 2.7.2.4.3 of the full dossier assessment)
d: recorded with EORTC QLQ-C30
e: The dossier contained study data on skin events. However, these were operationalized using the MedDRA PT "rash", and therefore did not represent the relevant event. Thus, there were no usable data.
f: number of patients in the evaluation population unclear

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events, EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D: European Quality of Life-5 Dimensions; MedDRA: Medical Dictionary for Regulatory Activities; PT: preferred term; QLQ-LC13: Quality of Life Questionnaire-LC 13; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

The risk of bias was rated as high for all outcomes for which results were presented in the dossier. The main reason for this rating is the open-label study design and the high proportion of patients (62%) who changed from the control arm of the study to crizotinib treatment. After the change to crizotinib treatment, information on these patients was included in the analyses of OS. Only the period up to the change of treatment of a patient was considered for the health-related quality of life and non-serious adverse events. For serious adverse events, this period was prolonged up to 28 days after the change of treatment (see Sections 2.7.2.4.2 and 2.7.2.4.3 of the full dossier assessment).

For the outcomes OS and AEs, this corresponds to the company's assessment. In contrast, the company rated the health-related quality of life (recorded with the disease-specific instrument EORTC QLQ-C30) as having a low risk of bias. Module 4 did not contain any evaluable results on the outcomes "symptoms" (recorded with the symptom scales of EORTC QLQ-C30 and QLQ-LC13), "health-related quality of life" (recorded with the generic instrument

EQ-5D), and "skin and subcutaneous tissue disorders". Therefore no outcome-specific assessment of the risk of bias was conducted.

Further information on the choice of outcomes and risk of bias at outcome level can be found in Module 4, Sections 4.3.1.2.2, 4.3.1.3 and 4.3.2.1.3 of the dossier and in Sections 2.7.2.4.2 and 2.7.2.4.3 of the full dossier assessment.

Table 11, Table 12 and Table 13 summarize the results on the comparison of crizotinib versus chemotherapy (docetaxel or pemetrexed) in patients with ALK-positive NSCLC for the chemotherapy population. The data from the company's dossier were supplemented, where necessary, by the Institute's calculations.

Table 11: Results on mortality and morbidity – RCT, direct comparison – crizotinib vs. chemotherapy, chemotherapy population

Outcome category **Outcome** **Study**	**Crizotinib**			**Chemotherapy**			**crizotinib vs. chemotherapy**
	N	**Patients with event n (%)**	**Median survival time in months [95% CI]**	**N**	**Patients with event n (%)**	**Median survival time in months [95% CI]**	**HR [95% CI] p-value**
PROFILE 1007							
Mortality							
Overall survival	173	49 (28)	20.3 [18.1; n. c.]	174	47 (27)	22.8 [18.6; n. c.]	1.02 [0.68; 1.54]; 0.539
Morbidity							
Symptoms[a]	no results available[b]						

a: recorded with the symptom scales of disease-specific instruments (EORTC QLQ-C30 and QLQ-LC13)

b: The dossier did not contain any results on symptoms with sufficient information or plausible operationalization (see Section 2.7.2.4.3 of the full dossier assessment).

CI: confidence interval; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C 30; QLQ-LC13: Quality of Life Questionnaire-LC 13; HR: hazard ratio; N: number of analysed patients; n: number of patients with event; n. c.: not calculable; RCT: randomized controlled trial; vs.: versus

Table 12: Results on health-related quality of life – RCT, direct comparison – crizotinib vs. chemotherapy, chemotherapy population

Outcome category Outcome Study	Crizotinib			Chemotherapy			Crizotinib vs. chemotherapy	
	N[a]	Values at the start of the study mean (SD)	Values at the end of the study mean[b] (SD)	N[a]	Values at the start of the study mean (SD)	Values at the end of the study mean[b] (SD)	Estimated mean difference [95% CI]; p-value	Hedges' g[b] [95% CI] p-value
PROFILE 1007								
Health-related quality of life								
Disease-specific instrument (EORTC QLQ-C30)								
global health status/health-related quality of life	162	no data	no data	151[c]	no data	no data	9.84 [5.39; 14.28]; no data	0.49 [0.26; 0.71]; p < 0.001
physical functioning	162	no data	no data	151[c]	no data	no data	10.11 [6.12; 14.10]; no data	0.56 [0.33; 0.79]; p < 0.001
role functioning	162	no data	no data	151[c]	no data	no data	8.75 [3.57; 13.92]; no data	0.37 [0.15; 0.60]; p = 0.001
emotional functioning	162	no data	no data	151[c]	no data	no data	5.06 [1.06; 9.06]; no data	0.28 [0.06; 0.50]; p = 0.014
cognitive functioning	162	no data	no data	151[c]	no data	no data	3.67 [-0.16; 7.49]; no data	n. c.[d]
social functioning	162	no data	no data	151[c]	no data	no data	8.76 [3.40; 14.12]; no data	0.36 [0.14; 0.58]; p = 0.002
generic instrument (EQ-5D)								
No results available[e]								

a: number of patients in the analysis at the end of the study, the values at the beginning of the study (at other times, if applicable) may be based on other patient numbers.
b: Institute's calculation
c: The exact number of patients evaluated is unclear: based on the Institute's calculation, the numbers of 162 (CRI) vs. 162 (CHE) patients could be deduced from the data in the dossier. In further documents of the manufacturer (Module 5), 162 vs. 151 patients were reported in the more extensive reporting of the outcomes TTD and quality of life.
d: Hedges' g not calculated as the effect estimator was not significant.
e: The dossier did not contain any results on this outcome (see Section 2.7.2.4.3 of the full dossier assessment).
CHE: chemotherapy; CI: confidence interval; CRI: crizotinib; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D: European Quality of Life-5 Dimensions; N: number of analysed patients; n. c.: not calculated; RCT: randomized controlled trial; SD: standard deviation; TTD: time to deterioration; vs.: versus

Table 13: Results on adverse events – RCT, direct comparison – crizotinib vs. chemotherapy, chemotherapy population

Outcome Study	Crizotinib		Chemotherapy		Crizotinib vs. chemotherapy
Operationalization	**N**	**Patients with events n (%)**	**N**	**Patients with events n (%)**	**RR [95% CI][a]; p-value[b]**
PROFILE 1007					
Adverse events					
Total	172	172 (100)	171	168 (98.2)	1.02 [1.00; 1.04]; p = 0.084
Selection of frequent AEs[c]					
vision disorders	172	103 (59.9)	171	16 (9.4)	6.40 [3.95; 10.37]; p < 0.001
diarrhoea	172	103 (59.9)	171	33 (19.3)	3.10 [2.23; 4.32]; p < 0.001
nausea	172	94 (54.7)	171	64 (37.4)	1.46 [1.15; 1.85]; p = 0.001
vomiting	172	80 (46.5)	171	30 (17.5)	2.65 [1.85; 3.81]; p < 0.001
constipation	172	73 (42.4)	171	39 (22.8)	1.86 [1.34; 2.58]; p < 0.001
skin and subcutaneous tissue disorders	No results available[d]				
Serious adverse events					
Total	172	64 (37.2)	171	40 (23.4)	1.59 [1.14; 2.22]; p = 0.005
Severe adverse events (CTCAE 3 and 4)					
Total	172	76 (44.2)	171	72 (42.1)	1.05 [0.82; 1.34]; p = 0.761
Severe adverse events that result in death (CTCAE 5)					
Total	172	25 (14.5)	171	7 (4.1)	3.55 [1.58; 7.99]; p < 0.001
Treatment discontinuations due to AEs					
Total	172	30 (17)	171	23 (14)	1.30 [0.79; 2.14]; p = 0.331

a: Institute's calculation (asymptotic)
b: Institute's calculation, unconditional exact test (CSZ method according to [4])
c: events that occurred in ≥ 15% of patients in one of the treatment arms, operationalized using MedDRA PT and chosen according to relevance, see Section 2.7.2.4.3 of the full dossier assessment.
d: skin events in the PROFILE 1007 study were operationalized using the PT "rash" so that adverse events to be represented were rated as non-representable in this analysis (see Section 2.7.2.4.3 of the full dossier assessment).
AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; CSZ: convexity, symmetry, z score; N: number of analysed patients; n: number of patients with event; MedDRA: Medical Dictionary for Regulatory Activities; PT: preferred term; RCT: randomized controlled trial; RR: relative risk; vs.: versus

Table 14: Results on adverse events – RCT, direct comparison – crizotinib vs. chemotherapy, chemotherapy population; most frequent severe adverse events (CTCAE Grade 3 and 4)

Outcome	Crizotinib		Chemotherapy	
Study	**N**	**Patients with events n (%)**	**N**	**Patients with events n (%)**
PROFILE 1007				
Transaminase elevation	172	27 (15.7)	171	4 (2.3)
Neutropenia	172	23 (13.4)	171	33 (19.3)
Pulmonary embolism	172	9 (5.2)	171	3 (1.8)
Dyspnoea	172	7 (4.1)	171	5 (2.9)
Anaemia	172	4 (2.3)	171	9 (5.3)
Fatigue	172	4 (2.3)	171	7 (4.1)
Lowered white blood cell count	172	2 (1.2)	171	8 (4.7)
CTCAE: Common Terminology Criteria for Adverse Events; N: number of analysed patients; n: number of patients with event; RCT: randomized controlled trial; vs.: versus				

Since only one study was available, no more than “indications”, for example of an added benefit, could be derived, provided outcome-specific aspects did not weaken the informative value.

Mortality

Overall survival

There was no statistically significant difference between crizotinib and chemotherapy in this outcome for the chemotherapy population.

An added benefit of crizotinib in comparison with chemotherapy (docetaxel/pemetrexed) for OS is not proven.

Morbidity

In the study, data on symptoms were collected using the questionnaires EORTC QLQ-C30 and EORTC QLQ-LC13. However, the company did not present any assessable evaluations on symptoms in its dossier.

An added benefit of crizotinib in comparison with chemotherapy (docetaxel/pemetrexed) for morbidity (symptoms) is not proven.

Health-related quality of life: generic instrument (EQ-5D)

There were no results for health-related quality of life measured with EQ-5D for the chemotherapy population.

Health-related quality of life: disease-specific instrument (EORTC QLQ-C30)

EORTC QLQ-C30 is an instrument developed for cancer patients, which contains 6 subscales on quality of life. These are analysed separately. Therefore, results on quality of life that were recorded with the disease-specific instrument will first be described separately below. They are interpreted in the overall results of the individual scales, however.

- Global health status/health-related quality of life and physical functioning

Mean improvement in the subscales on global health status/health-related quality of life and physical functioning is higher in the crizotinib group than in patients in the chemotherapy arm. Both differences between the treatment arms are statistically significant and not irrelevant (the 95% confidence interval for the standardized mean difference was fully above the irrelevance threshold of 0.2).

- Role functioning, emotional, cognitive and social functioning

In cognitive functioning, the effect was not statistically significantly different between crizotinib and chemotherapy. In the remaining 3 subscales role functioning, emotional and social functioning, there was a statistically significant group difference, the confidence intervals were not fully above the irrelevance threshold, however.

The fact that a treatment effect cannot be comprehensively assessed because of a lack of data on the baseline level of health-related quality of life and on change in the treatment arms, makes the interpretation of the results on health-related quality of life difficult (see Section 2.7.2.4.3 of the full dossier assessment). Furthermore, in the dossier, there were no responder analyses, which would have facilitated an interpretation of the results.

In summary, considering the high risk of bias, there is a hint of an added benefit of crizotinib in comparison with chemotherapy (docetaxel/pemetrexed) for health-related quality of life (disease-specific instrument EORTC QLQ-C30). No effects with confidence intervals that were above the irrelevance threshold were observed in 4 of the total of 6 subscales. However, in 2 subscales (global health status/health-related quality of life and physical functioning) effects were recorded that were not irrelevant. Furthermore, the results of the individual scales are consistent in so far as that a statistically significant result was observed in favour of crizotinib in 5 subscales.

Adverse events

Overall rate of adverse events

The analysis of the overall rate of AEs showed that an AE was observed in almost all patients in the course of the study. For the chemotherapy population, there was no statistically significant difference between crizotinib and chemotherapy in the overall rate of AEs.

A lesser/greater harm from crizotinib in comparison with chemotherapy is not proven for this outcome. This corresponds with the company's assessment.

Frequent adverse events

Some individual events were identified as relevant for this assessment (see Section 2.7.2.4.3 of the full dossier assessment) and assessed using the information on frequent AEs (proportion of patients of a study arm with event ≥ 15%) in the dossier.

- Vision disorders

The company summarized a number of MedDRA preferred terms under the term "vision disorders" (see Section 2.7.2.4.3 of the full dossier assessment). Vision disorders were more common in the patients treated with crizotinib than in the chemotherapy arm. The difference was statistically significant. The high risk of bias at study and outcome level led to downgrading an "indication" to a "hint" of a greater harm from crizotinib in the chemotherapy population.

- Frequent gastrointestinal adverse events: diarrhoea, nausea, vomiting and constipation

Each of the individual events "diarrhoea", "nausea", "vomiting", and "constipation" was more frequent in patients treated with crizotinib than in the chemotherapy arm. The differences were statistically significant. These individual events, summarized as "gastrointestinal adverse events", are described below. The high risk of bias at study and outcome level led to downgrading an "indication" to a "hint" of a greater harm from crizotinib in the chemotherapy population.

- Skin and subcutaneous tissue disorders

No evaluable results were available for this outcome. A lesser/greater harm from crizotinib in comparison with chemotherapy is not proven for this outcome.

Severe and serious adverse events

The proportion of patients with severe AEs (CTCAE Grade 3 and 4) was not statistically significantly different between the treatment groups. For information about the type of severe AEs, Table 14 shows the AEs with CTCAE Grade 3 and 4 that were documented in more than 4% of the patients in one of the treatment groups.

Severe AEs that resulted in death (CTCAE Grade 5) were more common in patients treated with crizotinib than in patients receiving chemotherapy. The difference was statistically significant. The outcome of severe AEs of CTCAE Grade 5 was potentially highly biased (see Section 2.7.2.4.3 of the full dossier assessment). This possible bias was caused by the way the AEs were documented after crossover and by different observation periods in the treatment groups, among other things. Furthermore, deaths were completely contained in the outcome "overall survival". Severe AEs with CTCAE Grade 5 are therefore not considered separately.

Serious adverse events (SAEs) were observed more frequently in patients treated with crizotinib than in patients receiving chemotherapy. The difference was statistically significant. Deaths after progression of the disease were also included in the analysis of SAEs (crizotinib 13 [7.6%]; chemotherapy 3 [1.8%]). The most common individual events in the SAEs were, besides progression of the disease (that resulted in death), were neutropenia (1.7% under crizotinib versus 8.2% under chemotherapy), dyspnoea and lung diseases (e.g. events that were summarized as "pulmonary embolism": 3.5% versus 1.8%, pneumonia: 4.1% versus 1.8%, and interstitial lung disease: 2.9% versus 0%, each for crizotinib versus chemotherapy group).

The analysis of SAEs is also potentially highly biased (see Section 2.7.2.4.3 of the full dossier assessment). In the Institute's sensitivity analysis it was assessed if an effect on SAEs also exists if patients with fatal progression are not considered in the operationalization. According to the company's statement, SAE due to fatal progression occurred in 13 (crizotinib) versus 3 (chemotherapy) patients. If these patients are excluded, 51 (crizotinib) versus 37 (chemotherapy) patients with event remain in the analysis. Since it was unclear whether these excluded patients might not have to be included due to a different SAE, the reliability of results of this analysis also remains restricted. The relative risk in this scenario was 1.37 (95% CI [0.95; 1.98]), p = 0.093. An effect on SAEs would therefore not have been proven.

The company did not present further analyses and information on the duration of treatment, continued treatment of patients after progression or at the time AEs occurred that would allow a general estimation of the influence of the bias on the analysis of AEs. Due to the high uncertainty of the results on SAEs there is a hint of a greater harm from crizotinib in the chemotherapy population.

Treatment discontinuation due to adverse events

For the chemotherapy population, there was no statistically significant difference in the overall rate of treatment discontinuations due to AEs between crizotinib and chemotherapy.

A lesser/greater harm from crizotinib in comparison with chemotherapy is not proven for this outcome.

Relevant subgroups

Although subgroup analyses for age and sex were planned in the included study, the company did not present any corresponding subgroup analyses on patient-relevant outcomes (see Section 2.7.2.4.3 of the full dossier assessment). Therefore no conclusions on effect modification are possible.

Further information on the choice of outcomes, on risk of bias at outcome level, and on outcome results can be found in Module 4, Sections 4.3.1.2.2, 4.3.1.3 and 4.3.2.1.3 of the dossier and in Sections 2.7.2.4.2 and 2.7.2.4.3 of the full dossier assessment.

2.5 Extent and probability of added benefit

The derivation of extent and probability of added benefit is presented below for each subquestion/subpopulation at outcome level, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in Appendix A of Benefit Assessment A11-02 [2].

The procedure for deriving an overall conclusion on added benefit based on the aggregation of the conclusions derived at outcome level is a proposal from IQWiG. The decision on added benefit is made by the G-BA.

2.5.1 Evaluation of added benefit at outcome level

The assessment of the added benefit is based on the data presented in Section 2.4.

For adult patients with previously treated ALK-positive advanced NSCLC for whom chemotherapy is indicated (chemotherapy population), the assessment provided a hint of an added benefit for health-related quality of life. In contrast, there was a hint of a greater harm regarding vision disorders and gastrointestinal events, as well as regarding SAEs. The extent of the respective added benefit at outcome level was estimated from these results (see Table 15).

For adult patients with previously treated ALK-positive advanced NSCLC form whom chemotherapy is not indicated (BSC population), the company did not present any data.

Table 15: Crizotinib vs. chemotherapy – extent of added benefit at outcome level, chemotherapy population

Outcome	**Effect estimator [95% CI] / proportion of events crizotinib vs. chemotherapy / p-value / probability[a]**	**Derivation of extent[b]**
Mortality		
Overall survival	HR: 1.02 [0.68; 1.54] p = 0.539	lesser benefit/added benefit not proven
Morbidity		
no evaluable analysis available		
Health-related quality of life		
Disease-specific instrument (EORTC QLQ-C30)		
▫ Global health status/health-related quality of life	SMD: 9.84 [5.39; 14.28] no data Hedges' g[c]: 0.49 [0.26; 0.71]; CI_l > 0.2 p < 0.001	Outcome category: health-related quality of life: Added benefit, extent: “minor”
▫ Physical functioning	SMD: 10.11 [6.12; 14.10] no data Hedges' g[c]: 0.56 [0.33; 0.79]; CI_l > 0.2 p < 0.001	
▫ Role functioning	SMD: 8.75 [3.57; 13.92] no data Hedges' g[c]: 0.37 [0.15; 0.60] p = 0.001	
▫ Emotional functioning	SMD: 5.06 [1.06; 9.06] no data Hedges' g[c]: 0.28 [0.06; 0.50] p = 0.014	

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Table 15: Crizotinib vs. chemotherapy – extent of added benefit at outcome level, chemotherapy population (continued)

Outcome	**Effect estimator [95% CI] / proportion of events crizotinib vs. chemotherapy / p-value / probability[a]**	**Derivation of extent[b]**
▫ Cognitive functioning	SMD: 3.67 [-0.16; 7.49] no data Hedges' g: not calculated as effect estimator was not statistically significant	
▫ Social functioning	SMD: 8.76 [3.40; 14.12] no data Hedges' g[c]: 0.36 [0.14; 0.58] p = 0.002 Probability: "hint"	
Generic instrument (EQ-5D)	no results available	lesser benefit/added benefit not proven
Adverse events		
Total AEs	RR[f]: 1.02 [1.00; 1.04] 100% vs. 98.2% p = 0.084[h]	lesser/greater harm not proven
Further adverse events		
▫ Vision disorders	RR[f]: 6.40 [3.95; 10.37] RR[g]: 0.16 [0.10; 0.25] 59.9% vs. 9.4% p < 0.001[h] Probability: "hint"	Outcome category: non-severe/non-serious adverse events CI_o < 0.80 greater harm, extent: "considerable"
▫ Diarrhoea[d]	RR[f]: 3.10 [2.23; 4.32] RR[g]: 0.32 [0.23; 0.45] 59.9% vs. 19.3% p < 0.001[h] Probability: "hint"	Outcome category: non-severe/non-serious adverse events CI_o < 0.80 greater harm, extent: "considerable"
▫ Nausea[d]	RR[f]: 1.46 [1.15; 1.85] RR[g]: 0.68 [0.54; 0.87] 54.7% vs. 37.4% p = 0.001[h] Probability: "hint"	Outcome category: non-severe/non-serious adverse events CI_o < 0.90 greater harm, extent: "minor"

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Table 15: Crizotinib vs. chemotherapy – extent of added benefit at outcome level, chemotherapy population (continued)

Outcome	**Effect estimator [95% CI] / proportion of events crizotinib vs. chemotherapy / p-value / probability[a]**	**Derivation of extent[b]**
▫ Vomiting[d]	RR[f]: 2.65 [1.85; 3.81] RR[g]: 0.38 [0.26; 0.54] 46.5% vs. 17.5% $p < 0.001$[h] Probability: "hint"	Outcome category: non-severe/non-serious adverse events $CI_o < 0.80$ greater harm, extent: "considerable"
▫ Constipation[d]	RR[f]: 1.86 [1.34; 2.58] RR[g]: 0.54 [0.39; 0.74] 42.4% vs. 22.8% $p < 0.001$[i] Probability: "hint"	Outcome category: non-severe/non-serious adverse events $CI_o < 0.80$ greater harm, extent: "considerable"
▫ Skin and subcutaneous tissue disorders	no results available[e]	lesser benefit/added benefit not proven
SAEs	RR[g]: 1.59 [1.14; 2.22] RR[h]: 0.63 [0.45; 0.88] 37.2% vs. 23.4% $p < 0.005$[i] Sensitivity analysis[i]: RR[g]: 1.37 [0.95; 1.98] 29.7 % vs. 21.6 % $p < 0.093$[i] Probability: "hint"	Outcome category: serious/severe adverse events greater harm, extent: "non-quantifiable"
Severe AEs (CTCAE Grade 3 and 4)	RR[g]: 1.05 [0.82; 1.34] 44.2 % vs. 42.1 % $p = 0.761$[h]	lesser benefit/added benefit not proven
Treatment discontinuations due to AEs	RR[g]: 1.30 [0.79; 2.14] 17% vs. 14% $p = 0.331$[h]	greater/lesser harm not proven

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Table 15: Crizotinib vs. chemotherapy – extent of added benefit at outcome level, chemotherapy population (continued)

a: probability of added benefit provided if statistically significant differences were present. b: Estimations of effect size are made depending on the outcome category with different limits based on the upper limit of the confidence interval (CI_o). c: SMD in the form of Hedges' g for assessing the relevance of the statistically significant group difference, Institute's calculation. If the 95% CI for the SMD was not fully above the irrelevance threshold of 0.2, the effect was considered as not relevant. d: The outcomes "diarrhoea", "nausea", "vomiting", and "constipation" can be considered as representations of gastrointestinal events, and are summarized for the overall results. e: The dossier contained study data on skin events in an operationalization that did not represent the relevant event (see Section 2.7.2.4.3 of the full dossier assessment). f: Institute's calculation (asymptotic), proportion of events crizotinib vs. chemotherapy. g: Institute's calculation (asymptotic), proportion of events chemotherapy vs. crizotinib (reversed direction of effect to derive the extent of added benefit). h: Institute's calculation, unconditional exact test (CSZ method according to [4]). i: analysis without patients for whom AEs were documented due to progression of disease (see Section 2.7.2.4.3 of the full dossier assessment). AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; CI: confidence interval; CI_o: upper limit of confidence interval; CI_l :lower limit of confidence interval; CSZ: convexity, symmetry, z score; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C 30; EQ-5D: EuroQol-5D; HR: hazard ratio; RR: relative risk; SAE: serious adverse event; SMD: standardized mean difference; vs.: versus

2.5.2 Overall conclusion on added benefit

The overall conclusion on the extent of the added benefit will be presented separately for the chemotherapy population and the BSC population. Table 16 summarizes the results that were considered in the overall conclusion on the extent of added benefit for the chemotherapy population.

Table 16: Positive and negative effects from the assessment of crizotinib compared with chemotherapy (docetaxel or pemetrexed), chemotherapy population

Positive effects	**Negative effects**
Hint of an added benefit – extent: "minor" (health-related quality of life [disease-specific instrument EORTC QLQ-C30])	Hint of greater harm – extent: "considerable" (non-serious/non-severe adverse events: vision disorders, gastrointestinal events[a])
	Hint of greater harm – extent: "non-quantifiable" (serious/severe adverse events: SAEs)
a: Gastrointestinal events include the outcomes "diarrhoea", "nausea", "vomiting", and "constipation" (see Section 2.4). AE: adverse event; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30; SAE: serious adverse event	

Overall, positive and negative effects remain. On the positive side, in the category "health-related quality of life", there is an added benefit of crizotinib with the probability "hint". Five of the 6 subscales of the questionnaire showed statistically significant results, however, only

the results of 2 subscales were certainly not irrelevant. In summary, the extent of added benefit for health-related quality of life is rated as "minor".

On the negative side, there is greater harm from crizotinib in the category "non-serious/non-severe AEs" for 2 outcomes. In the gastrointestinal events, the individual events "diarrhoea", "nausea", "vomiting", and "constipation" led to 3 negative effects with the extent "considerable" and one negative effect with the extent "minor". Summarized as gastrointestinal events, these effects are assessed with the extent "considerable". Therefore for both outcomes of this category, there is greater harm from crizotinib with the probability "hint", and the extent "considerable". Moreover, there is a hint of greater harm from crizotinib in the category "serious/severe adverse events", the extent of which was rated as "non-quantifiable", as the effect size could not be limited, even after conducting a sensitivity analysis.

For an overall conclusion, the added benefit regarding health-related quality of life has to be contrasted with the greater harm from crizotinib. It cannot be finally assessed on the basis of the available information whether the greater harm, which reaches a considerable or non-quantifiable extent respectively, outweighs the positive effect regarding health-related quality of life so that lesser benefit of crizotinib in comparison with chemotherapy would have to be assumed. On the whole, the added benefit of crizotinib for adult patients with previously treated ALK-positive advanced NSCLC **for whom chemotherapy is indicated (chemotherapy population)** is not proven.

For adult patients with previously treated ALK-positive advanced NSCLC **for whom chemotherapy is not indicated (BSC population)**, there were no data for a comparison of crizotinib with BSC in the dossier (see Section 2.3.1). Hence the added benefit of crizotinib in the BSC population is not proven.

2.5.3 Extent and probability of added benefit – summary

An overview of the extent and probability of added benefit for the various therapeutic situations of crizotinib compared with the ACT is given below (see Table 17):

Table 17: Crizotinib: extent and probability of added benefit – summary

Therapeutic situation	ACT	Extent and probability of added benefit
Treatment of previously treated ALK-positive advanced NSCLC in patients for whom chemotherapy is indicated (chemotherapy population)	Chemotherapy (docetaxel or pemetrexed)	Added benefit not proven
Treatment of previously treated ALK-positive advanced NSCLC in patients for whom chemotherapy is not indicated (BSC population)	Best supportive care	Added benefit not proven
ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; BSC: best supportive care; NSCLC: non-small cell lung cancer		

The overall assessment deviates substantially from that of the company, which claimed an indication of a considerable added benefit for both populations.

Further information on the extent and probability of the added benefit can be found in Module 4, Section 4.4 of the dossier and in Section 2.7.2.8 of the full dossier assessment.

2.6 List of included studies

PROFILE 1007

Pfizer. A phase 3, randomized, open-label study of the efficacy and safety of PF-02341066 (crizotinib) vs. standard of care chemotherapy (pemetrexed or docetaxel) in patients with previously treated advanced NSCLC whose tumors harbor gene rearrangements: study A8081007; top-line-summary [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. 22.05.2012 [accessed 04.06.2012]. URL: http://clinicaltrials.gov/ct2/show/study/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 event involving the anaplastic lymphoma kinase (ALK) gene locus: study A8081007; clinical protocol; amendment 10 [unpublished]. 2011.

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; statistical analysis plan [unpublished]. 2012.

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