IQWiG Reports – Commission No. A16-26

Crizotinib – Addendum to Commission A15-59[1]

Addendum

Commission: A16-26
Version: 1.0
Status: 27 May 2016

[1] Translation of addendum A16-26 *Crizotinib – Addendum zum Auftrag A15-59* (Version 1.0; Status: 27 May 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 – Addendum to Commission A15-59

Commissioning agency:
Federal Joint Committee

Commission awarded on:
9 May 2016

Internal Commission No.:
A16-26

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

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
ALK	anaplastic lymphoma kinase
CTCAE	Common Terminology Criteria for Adverse Events
EORTC	European Organisation for Research and Treatment of Cancer
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
QLQ-C30	Quality of Life Questionnaire-Core-30
QLQ-LC13	Quality of Life Questionnaire-Lung Cancer 13
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)

1 Background

On 9 May 2016, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A15-59 (Crizotinib – Benefit assessment according to §35a Social Code Book (SGB) V [1]).

The pharmaceutical company (hereinafter referred to as "the company") had presented the PROFILE 1014 study in its dossier on crizotinib [2]. Based on the information provided in the dossier, the study was assessed as unsuitable in dossier assessment A15-59 for answering the research question of the benefit assessment of crizotinib. The reason was that a large proportion of the patients (46%) in the control arm of the study received carboplatin. Carboplatin is not approved for the treatment of non-small cell lung cancer (NSCLC). For patients at an increased risk of cisplatin-induced side effects in the framework of a combination therapy, however, according to Appendix VI to Section K of the Pharmaceutical Directive, carboplatin can be prescribed in the combination therapy for palliative treatment of NSCLC in this unapproved therapeutic indication (off-label use) [3]. Therefore, the G-BA, besides cisplatin, also specified carboplatin as appropriate comparator therapy (ACT), but only for patients at increased risk of cisplatin-induced side effects. It was not clear from the company's dossier that the patients in the PROFILE study had an increased risk of cisplatin-induced side effects. On the contrary, various exclusion criteria prevented participation of these patients in the study.

In its comment, the company presented supplementary information to prove the added benefit. To be able to make a decision on the added benefit, the G-BA commissioned IQWiG with the analysis of the PROFILE 1014 study on the basis of the data in the dossier and of the information presented in the commenting procedure.

The responsibility for the present assessment and the results of the assessment lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment of the study PROFILE 1014

In accordance with the commission, the PROFILE 1014 study is assessed in the following sections [4,5]. The company used the PROFILE 1014 study in its dossier [2] to assess the added benefit of crizotinib in comparison with a platinum-based combination therapy with pemetrexed in first-line treatment of anaplastic lymphoma kinase (ALK)-positive advanced NSCLC.

2.1 Study design and study characteristics

A detailed description of the study and tables presenting the study characteristics and the interventions can be found in dossier assessment A15-59 [1]. The characteristics of the patients, the planned duration of follow-up, and the information on the course of the study are presented in the following tables Table 1, Table 2, and Table 3 as supplementary information.

Table 1: Characteristics of the study population – RCT, direct comparison: crizotinib vs. chemotherapy (cisplatin + pemetrexed or carboplatin + pemetrexed)

Study **Characteristics** **Category**	**Crizotinib**	**Chemotherapy** **Cisplatin + pemetrexed** **Carboplatin + pemetrexed**
PROFILE 1014	N[a] = 172	N[a,b] = 171
Age [years]: median (min; max)	52 (22; 76)	54 (19; 78)
Sex [F/M], %	60.5/39.5	63.2/36.8
Ethnicity, n (%)		
White	91 (52.9)	85 (49.7)
Black	0	4 (2.3)
Asian	77 (44.8)	80 (46.8)
Other	4 (2.3)	2 (1.2)
ECOG PS, n (%)		
0	58 (33.7)	47 (27.5)
1	105 (61.0)	117 (68.4)
2	9 (5.2)	7 (4.1)
Disease duration[c] [years], median (min; max)	0.1 (0.0; 9.5)	0.1 (0.0; 7.8)
Smoking status, n (%)		
Never-smoker	106 (61.6)	112 (65.5)
Ex-smoker	56 (32.6)	54 (31.6)
Smoker	10 (5.8)	5 (2.9)
Histology, n (%)		
Adenocarcinoma	158 (91.9)	159 (93.0)
Large-cell carcinoma	3 (1.7)	8 (4.7)
Adenosquamous carcinoma	5 (2.9)	1 (< 1.0)
Other	6 (3.5)	3 (1.8)
Disease stage at baseline, n (%)		
Locally advanced NSCLC	4 (2.3)	3 (1.8)
Metastatic NSCLC	168 (97.7)	168 (98.2)
Brain metastases, n (%)		
Yes	45 (26.2)	47 (27.5)
No	127 (73.8)	124 (72.5)
Treatment discontinuation, n (%)	92 (53.8)	61 (36.1)[d,e]
Study discontinuation, n (%)[f]	52 (30.2)	54 (31.6)

a: Number of randomized patients.
b: Allocation to cisplatin or carboplatin by the investigator after randomization.
c: Time from first diagnosis to randomization.
d: Institute's calculation.
e: Proportion of patients who did not receive all 6 cycles of the chemotherapy (based on pemetrexed). No patient was treated with chemotherapy anymore at the time point of the data cut-off.
f: Including deaths.
ECOG PS: Eastern Cooperative Oncology Group Performance Status, F: female; M: male; max: maximum; min: minimum , n: number of patients in the category; N: number of randomized patients; NSCLC: non-small cell lung cancer; RCT: randomized controlled trial; vs.: versus

Table 2: Planned duration of follow-up – RCT, direct comparison: crizotinib vs. chemotherapy (cisplatin + pemetrexed or carboplatin + pemetrexed)

Study **Outcome category** **Outcome**	**Planned follow-up**
PROFILE 1014	
Mortality	
All-cause mortality	Every 2 months until death, withdrawal of consent, or until 18 months after the last patient was randomized to the study
Morbidity	
EORTC QLQ-C30 (symptoms) EORTC QLQ-LC13	Weekly during the first treatment cycle, then once per cycle until the end of the study treatment
Health-related quality of life	
EORTC QLQ-C30 (functional scales)	Weekly during the first treatment cycle, then once per cycle until the end of the study treatment
Side effects	Starting with the first administration of the study medication continuously until 28 days after the last treatment with the study medication
EORTC: European Organisation for Research and Treatment of Cancer; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-LC13: Quality of Life Questionnaire-Lung Cancer 13; RCT: randomized controlled trial; vs.: versus	

Table 3: Information on the course of the study – RCT, direct comparison: crizotinib vs. chemotherapy (cisplatin + pemetrexed or carboplatin + pemetrexed)

Study Characteristics Category	Crizotinib N = 172	Chemotherapy N = 171
PROFILE 1014		
Treatment duration [months][a]:		
Median [min; max]	10.9 [0.4; 34.2]	4.1 [0.7; 6.2]
Observation period [months]:		
Overall survival		
Median [min; max]	17.4 [15.7; 19.3]	16.7 [14.9; 19.8]
Side effects	ND	ND
Further outcomes	ND	ND

a: Information was only available for the safety population (171 vs. 169 patients) and not for the ITT population.
ITT: intention to treat; max: maximum; min: minimum; N: number of randomized patients; ND: no data; RCT: randomized controlled trial; vs.: versus

The distribution of the patient characteristics was largely balanced between the study arms. The mean age of the patients was just over 50 years. About 60% of patients were men. Half of the study population were white, about 45% were Asian.

2.2 Results

2.2.1 Outcomes included

The following patient-relevant outcomes were to be considered:

- Mortality
  - overall survival
- Morbidity
  - symptoms recorded with the symptom scales of the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core-30 (QLQ-C30)
  - symptoms recorded with the EORTC Quality of Life Questionnaire-Lung Cancer 13 (QLQ-LC13)
- Health-related quality of life
  - health-related quality of life recorded with the EORTC QLQ-C30 functional scales
- Side effects

Table 4 shows for which outcomes results were available in the PROFILE 1014 study.

Table 4: Matrix of outcomes – RCT, direct comparison: crizotinib vs. chemotherapy (cisplatin + pemetrexed or carboplatin + pemetrexed)

Study	Outcomes							
	All-cause mortality	Symptoms (EORTC QLQ-C30)[a]	Symptoms (EORTC QLQ-LC13)[b]	Health-related quality of life (EORTC QLQ-C30)[c]	SAEs	Discontinuation due to AEs	Severe AEs (CTCAE grade 3 and 4)	Specific AEs[d]
Study PROFILE 1014	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a: Recorded with the symptom scales of the EORTC QLQ-C30 version 3.0.
b: Recorded with the symptom scales of the EORTC QLQ-LC13.
c: Recorded with the functional scales of the EORTC QLQ-C30 version 3.0.
d: The company presented results on a number of specific AEs in its dossier. Presentation of patient-relevant specific AEs in which there was a statistically significant difference between the treatment groups and in which events occurred in ≥ 10% of the patients in one study arm.
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; 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; vs.: versus

2.2.2 Risk of bias

The risk of bias at the study level was rated as low for the PROFILE 1014 study, but there was a high risk of outcome-specific bias for all outcomes. The risk of bias of the outcome "all-cause mortality" was rated as high because of the large proportion (> 70%) of patients who switched from the control arm to treatment with crizotinib. The risk of bias of the patient-reported outcomes on symptoms, health-related quality of life, discontinuation due to adverse events (AEs), and specific AEs was rated as high because of the open-label study design and the large differences in treatment duration (10.9 months in the crizotinib arm versus 4.1 months in the control arm). The risk of bias of the outcomes "serious AEs (SAEs)" and "severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade 3 and 4)" was also rated as high because of the large differences in treatment duration.

2.2.3 Results

Due to the large differences in treatment duration between the study arms, only analyses using survival time analyses were used.

Table 5 shows the results of the PROFILE 1014 study.

Table 5: Results of the total population – RCT, direct comparison: crizotinib vs. chemotherapy (cisplatin + pemetrexed or carboplatin + pemetrexed)

Study Outcome category Outcome Subscale	Crizotinib		Chemotherapy Cisplatin + pemetrexed Carboplatin + pemetrexed		Crizotinib vs. chemotherapy
	N	Median survival time in months [95% CI] Patients with event n (%)	N	Median survival time in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value
PROFILE 1014					
Mortality					
Overall survival	172	NA [NA; NA] 44 (25.6)	171	NA [NA; NA] 46 (26.9)	0.82 [0.54; 1.26]; 0.180[a]
Morbidity					
EORTC QLQ-C30 symptom scales – time to deterioration of symptoms[b]					
Dyspnoea	164	NA [16.1; NA] 55 (33.5)	163	8.7 [4.7; 8.7] 64 (39.3)	0.54 [0.36; 0.80]; 0.002
Fatigue	166	1.5 [0.8; 3.5] 103 (62.0)	163	0.4 [0.3; 0.6] 122 [74.8]	0.58 [0.44; 0.76]; < 0.001
Insomnia	166	13.9 [7.0; NA] 75 (45.2)	163	3.6 [1.5; 8.7] 82 (50.3)	0.60 [0.43; 0.84]; 0.003
Pain	166	10.4 [5.0; 19.4] 84 (50.6)	163	2.2 [1.3; 4.3] 89 (54.6)	0.58 [0.42; 0.80]; < 0.001
Appetite loss	165	10.9 [2.1; NA] 83 (50.3)	163	1.4 [0.5; 2.9] 96 (58.9)	0.66 [0.49; 0.89]; 0.009
Diarrhoea	166	0.6 [0.5; 0.8] 125 (75.3)	162	6.5 [3.7; 22.3] 69 (42.6)	2.23 [1.65; 3.00]; < 0.001
Nausea and vomiting	166	0.5 [0.3; 0.8] 124 (74.7)	163	0.5 [0.4; 0.7] 115 (70.6)	1.04 [0.80; 1.34]; 0.825
Constipation	166	0.8 [0.6; 1.5] 124 (74.7)	162	1.2 [0.5; 2.9] 95 (58.6)	1.13 [0.86; 1.48]; 0.376
EORTC QLQ-LC13 symptom scales – time to deterioration of symptoms[b]					
Haemoptysis	166	NA [NA; NA]; 14 (8.4)	162	NA [NA; NA]; 17 (10.5)	0.56 [0.26; 1.20]; 0.131
Dyspnoea	165	7.6 [4.0; 16.1]; 88 (53.3)	162	1.4 [0.6; 2.1]; 98 (60.5)	0.55 [0.40; 0.74]; < 0.001
Alopecia	166	NA [15.9; NA]; 53 (31.9)	163	3.5 [2.1; 4.7] 85 (52.1)	0.29 [0.19; 0.42]; < 0.001
Cough	166	21.4 [17.9; NA] 52 (31.3)	163	NA [5.2; NA] 52 (31.9)	0.57 [0.37; 0.87]; 0.009
Sore mouth	166	NA [9.7; NA] 67 (40.4)	163	4.4 [2.9; 6.5] 78 (47.9)	0.63 [0.45; 0.88]; 0.007

(continued)

Table 5: Results of the total population – RCT, direct comparison: crizotinib vs. chemotherapy (cisplatin + pemetrexed or carboplatin + pemetrexed) (continued)

Study Outcome category Outcome Subscale	Crizotinib		Chemotherapy Cisplatin + pemetrexed Carboplatin + pemetrexed		Crizotinib vs. chemotherapy
	N	Median survival time in months [95% CI] Patients with event n (%)	N	Median survival time in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value
Peripheral neuropathy	166	6.2 [2.8; 10.9] 94 (56.6)	163	4.9 [3.5; 22.3] 74 (45.4)	0.98 [0.71; 1.35]; 0.904
Dysphagia	165	NA [11.1; NA] 66 (40.0)	163	8.7 [5.7; NA] 47 (28.8)	1.19 [0.81; 1.76]; 0.383
Pain (arm/shoulder)	166	NA [15.7; NA] 60 (36.1)	162	8.7 [6.5; NA] 48 (29.6)	0.88 [0.59; 1.31]; 0.543
Pain (thorax)	166	NA [NA; NA] 54 (32.5)	163	6.5 [6.5; NA] 59 (36.2)	0.65 [0.44; 0.96]; 0.029
Pain (other parts)	164	7.7 [4.0; 20.8] 82 (50.0)	160	6.5 [4.2; NA] 66 (41.3)	0.91 [0.65; 1.28]; 0.612
EORTC QLQ-C30 functional scales – time to deterioration of health-related quality of life[c]					
Global health status	166	9.4 [2.8; NA] 83 (50.0)	163	0.7 [0.4; 1.4] 113 (69.3)	0.48 [0.36; 0.65]; < 0.001
Physical functioning	166	24.9 [16.1; NA] 63 (38.0)	163	3.7 [1.4; NA] 83 (50.9)	0.46 [0.32; 0.66]; < 0.001
Role functioning	166	7.5 [2.1; NA] 84 (50.6)	163	0.5 [0.4; 1.4] 102 (62.6)	0.56 [0.42; 0.76]; < 0.001
Emotional functioning	166	NA [17.3; NA] 61 (36.7)	163	3.5 [2.6; NA] 77 (47.2)	0.56 [0.39; 0.79]; 0.001
Cognitive functioning	166	4.5 [2.2; 8.6] 96 (57.8)	163	2.0 [0.8; 4.2] 96 (58.9)	0.71 [0.53; 0.95]; 0.023
Social functioning	165	6.7 [2.1; NA] 85 (51.5)	162	1.0 [0.5; 3.1] 94 (58.0)	0.71 [0.52; 0.95]; 0.027
Adverse events[d]					
AEs (supplementary information)	171	ND 170 (99.4)	169	ND 168 (99.4)	–
SAEs	171	NA [16.9; NA] 58 (33.9)	169	6.9 [6.6; 9.3] 47 (27.8)	0.70 [0.46; 1.07]; 0.098
Discontinuation due to AEs	171	NA [NA; NA] 21 (12.3)	169	NA [NA; NA] 24 (14.2)	0.43 [0.21; 0.86]; 0.017
AEs CTCAE grade 3 or 4	171	7.3 [4.9; 12.6] 97 (56.7)	169	4.0 [2.6; 7.0] 87 (51.5)	0.68 [0.50; 0.93]; 0.015

(continued)

Table 5: Results of the total population – RCT, direct comparison: crizotinib vs. chemotherapy (cisplatin + pemetrexed or carboplatin + pemetrexed) (continued)

Study Outcome category Outcome Subscale	Crizotinib		Chemotherapy Cisplatin + pemetrexed Carboplatin + pemetrexed		Crizotinib vs. chemotherapy
	N	Median survival time in months [95% CI] Patients with event n (%)	N	Median survival time in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value
Alopecia[e]	171	NA [NA; NA] 12 (7.0)	169	10.6 [5.9; 12.2] 17 (10.1)	0.18 [0.06; 0.50]; 0.001
Appetite loss[e]	171	NA [25.7; NA] 51 (29.8)	169	8.2 [8.2; 14.4] 57 (33.7)	0.56 [0.37; 0.85]; 0.006
Asthenia[e]	171	NA [NA; NA] 22 (12.9)	169	8.2 [8.1; 9.2] 41 (24.3)	0.31 [0.17; 0.55]; < 0.001
Bradycardia[f]	171	NA [NA; NA] 23 (13.5)	169	NA [NA; NA] 1 (0.6)	18.57 [2.49; 138.74]; 0.004
Diarrhoea[e]	171	2.2 [0.9; 5.4] 105 (61.4)	169	NA [NA; NA] 22 (13.0)	5.71 [3.59; 9.08]; < 0.001
Tiredness[e]	171	NA [NA; NA] 49 (28.7)	169	7.8 [4.9; 7.8] 65 (38.5)	0.52 [0.35; 0.78]; 0.001
Neuropathy[f]	171	NA [NA; NA] 35 (20.5)	169	6.1 [5.6; 6.6] 38 (22.5)	0.26 [0.15; 0.48]; < 0.001
Oedema[f]	171	12.2 [6.5; 20.6] 83 (48.5)	169	6.7 [6.7; 9.2] 21 (12.4)	2.79 [1.69; 4.59]; < 0.001
Dysphagia[e]	171	NA [NA; NA] 45 (26.3)	169	NA [NA; NA] 9 (5.3)	5.25 [2.56; 10.77]; < 0.001
Vision disorder[f]	171	0.5 [0.3; 0.7] 122 (71.3)	169	7.1 [NA; NA] 16 (9.5)	12.65 [7.49; 21.36]; < 0.001
Stomatitis[f]	171	NA [NA; NA] 24 (14.0)	169	9.2 [5.7; 9.2] 34 [20.1]	0.36 [0.20; 0.66]; 0.001

a: One-sided p-value from stratified log-rank test.

b: Time to increase in score by at least 10 points versus the baseline value.
c: Time to decrease in score by at least 10 points versus the baseline value.
d: Institute's calculation of months from days.
e: PT coded according to MedDRA 16.1.
f: Clustered Term coded according to MedDRA 16.1.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; PT: Preferred Term; 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; vs.: versus

The company's dossier contained Kaplan-Meier curves on the outcomes presented [2].

Mortality

All-cause mortality

There was no statistically significant difference between the treatment groups for the outcome "all-cause mortality".

Morbidity

Symptoms (EORTC QLQ-C30)

For each of the outcomes **"dyspnoea", "fatigue"** and **"pain"**, there was a statistically significant effect in favour of crizotinib.

No statistically significant difference between the treatment groups was shown for the outcomes **"nausea/vomiting"** and **"constipation"**.

For the outcome **"diarrhoea"**, there was a statistically significant effect to the disadvantage of crizotinib.

For the outcomes **"insomnia"** and **"appetite loss"**, there was a statistically significant effect in favour of crizotinib. In addition, there was proof of an effect modification by the characteristic "brain metastases" for both outcomes. Additional separate consideration of the results in patients with and without brain metastases was therefore meaningful (see Section 2.2.4). For patients with brain metastases, no statistically significant difference between the treatment groups was shown for the outcomes **"appetite loss"** and **"insomnia"**. For patients without brain metastases, there was a statistically significant difference in favour of crizotinib for the outcomes **"appetite loss"** and **"insomnia"**.

Symptoms (EORTC QLQ-LC13)

For each of the outcomes **"dyspnoea", "cough"**, **"sore mouth"**, and **"pain (thorax)"**, there was a statistically significant effect in favour of crizotinib.

There was no statistically significant difference between the treatment groups for each of the outcomes **"haemoptysis", "dysphagia", "pain (arm/shoulder)"** and **"pain (other)"**.

For the outcome **"alopecia"**, there was a statistically significant effect in favour of crizotinib. In addition, there was proof of an effect modification by the characteristic "brain metastases" for the outcome. Additional separate consideration of the results in patients with and without brain metastases was therefore meaningful (see Section 2.2.4). For patients with brain metastases, there was no statistically significant difference between the treatment groups for the outcome **"alopecia"**. For patients without brain metastases, there was a statistically significant difference in favour of crizotinib for the outcome **"alopecia"**.

There was no statistically significant difference between the treatment groups for the outcome **"peripheral neuropathy"**. In addition, there was proof of an effect modification by the characteristic "region" for the outcome (see Section 2.2.4). Separate consideration of the

results in patients from Europe was therefore meaningful for the present report. For patients from Europe, there was a statistically significant difference to the disadvantage of crizotinib for the outcome **"peripheral neuropathy"**.

Health-related quality of life

Health-related quality of life (EORTC QLQ-LC13)

For each of the outcomes **"physical functioning", "role functioning", "emotional functioning"**, and **"social functioning"**, there was a statistically significant effect in favour of crizotinib.

For the outcome **"global health status"**, there was a statistically significant effect in favour of crizotinib. In addition, there was proof of an effect modification by the characteristic "brain metastases" for the outcome. Additional separate consideration of the results in patients with and without brain metastases was therefore meaningful (see Section 2.2.4). For patients with brain metastases, there was no statistically significant difference between the treatment groups for the outcome **"global health status"**. For patients without brain metastases, there was a statistically significant difference in favour of crizotinib for the outcome **"global health status"**.

For the outcome **"cognitive functioning"**, there was a statistically significant effect in favour of crizotinib. In addition, there was proof of an effect modification by the characteristic "sex" for the outcome. Additional separate consideration of the results in men and women was therefore meaningful (see Section 2.2.4). For women, there was no statistically significant difference between the treatment groups for the outcome **"cognitive functioning"**. For men, there was a statistically significant difference in favour of crizotinib for the outcome **"cognitive functioning"**.

Side effects

Severe adverse events

There was no statistically significant difference between the treatment groups for the outcome "SAEs".

Discontinuation due to adverse events and adverse events CTCAE grade 3 or 4

There was a statistically significant effect in favour of crizotinib for each of the outcomes "discontinuation due to AEs" and "severe AEs CTCAE grade 3 and 4".

Specific adverse events

For each of the outcomes **"alopecia", "appetite loss", "asthenia", "tiredness", "neuropathy",** and **"stomatitis"**, there was a statistically significant effect in favour of crizotinib.

For each of the outcomes **"bradycardia", "diarrhoea", "oedema", "dysphagia"**, and **"vision disorder"**, there was a statistically significant effect to the disadvantage of crizotinib.

2.2.4 Subgroups and other effect modifiers

In order to uncover possible effect differences between patient groups, the following subgroup characteristics were investigated:

- age (< 65/≥ 65 years)
- brain metastases (yes/no)
- region (Europe/North America/Asia/other)
- sex

No subgroup analyses were considered for the outcome "overall survival". Due to the large proportion of patients who switched from treatment in the control group to the crizotinib arm, the analyses were not conclusive.

The results on subgroups with at least proof of an effect modification and, additionally, statistically significant results in at least one subgroup are presented below for the outcomes "symptoms", "health-related quality of life", and "side effects" (except specific AEs). The prerequisite for proof of differing effects is a statistically significant homogeneity and/or interaction test ($p < 0.05$).

Table 6 shows the results of the subgroup analyses.

Table 6: Results of the subgroups – RCT, direct comparison: crizotinib vs. chemotherapy (cisplatin + pemetrexed or carboplatin + pemetrexed)

Study Outcome category Outcome Characteristic Subgroup	Crizotinib		Chemotherapy Cisplatin + pemetrexed Carboplatin + pemetrexed		Crizotinib vs. chemotherapy	
	N	Median survival time in months [95% CI] Patients with event n (%)	N	Median survival time in months [95% CI] Patients with event n (%)	HR [95% CI]	p-value
PROFILE 1014						
EORTC QLQ-C30 symptom scales – time to deterioration of symptoms[c]						
Appetite loss						
Brain metastases						
Yes	41	1.4 [0.4; 2.1] 30 (73.2)	41	2.0 [0.3; 8.7] 25 (61.0)	1.08 [0.63; 1.86]	0.774[d]
No	124	NA [11.1; NA] 53 (42.7)	122	1.4 [0.4; 3.5] 71 (58.2)	0.55 [0.38; 0.79]	0.002[d]
Total					Interaction[b]:	0.029
Insomnia						
Brain metastases						
Yes	41	6.3 [1.4; NA] 22 (53.7)	41	8.7 [1.5; 8.7] 16 (39.0)	1.19 [0.61; 2.33]	0.629[d]
No	125	NA [8.3; NA] 53 (42.4)	122	2.1 [1.4; 6.5] 66 (54.1)	0.49 [0.33; 0.72]	< 0.001[d]
Total					Interaction[b]:	0.019
EORTC QLQ-LC13 symptom scales – time to deterioration of symptoms[c]						
Alopecia						
Brain metastases						
Yes	41	12.4 [8.3; NA] 18 (43.9)	41	NA [3.0; NA] 16 (39.0)	0.51 [0.23; 1.12]	0.087[d]
No	125	NA [NA; NA] 35 (28.0)	122	2.8 [1.5; 4.3] 69 (56.6)	0.24 [0.16; 0.38]	< 0.001[d]
Total					Interaction[b]:	0.019

(continued)

Table 6: Results of the subgroups – RCT, direct comparison: crizotinib vs. chemotherapy (cisplatin + pemetrexed or carboplatin + pemetrexed) (continued)

Study **Outcome category** **Outcome** **Characteristic** **Subgroup**	**Crizotinib**		**Chemotherapy** **Cisplatin + pemetrexed** **Carboplatin + pemetrexed**		**Crizotinib vs. chemotherapy**	
	N	**Median survival time in months [95% CI]** **Patients with event n (%)**	**N**	**Median survival time in months [95% CI]** **Patients with event n (%)**	**HR [95% CI]**	**p-value**
Peripheral neuropathy						
Region						
Europe	57	1.5 [0.8; 3.4] 41 (71.9)	62	4.9 [3.5; 22.3] 25 (40.3)	1.85 [1.11; 3.06]	0.018[d]
North America	18	9.0 [3.5; NA] 8 (44.4)	13	NA [1.5; NA] 5 (38.5)	0.79 [0.24; 2.58]	0.685[d]
Asia	72	12.1 [6.9; NA] 37 (51.4)	71	2.8 [1.7; NA] 39 (54.9)	0.59 [0.37; 0.97]	0.034[d]
Other	19	NA [1.7; NA] 8 (42.1)	17	NA [2.9; NA] 5 (29.4)	1.32 [0.42; 4.15]	0.639[d]
Total					Interaction[b]:	0.010
Pain (other)						
Region						
Europe	55	5.6 [2.1; NA] 29 (52.7)	60	8.7 [3.5; NA] 21 (35.0)	1.24 [0.70; 2.20]	0.464[d]
North America	18	2.9 [0.6; 8.3] 12 (66.7)	12	NA [NA; NA] 1 (8.3)	9.92 [1.27; 77.56]	0.008[d]
Asia	72	16.1 [7.3; NA] 32 (44.4)	71	4.2 [2.0; NA] 36 (50.7)	0.54 [0.32; 0.90]	0.017[d]
Other	19	9.4 [1.4; NA] 9 (47.4)	17	4.2 [0.8; NA] 8 (47.1)	0.86 [0.32; 2.28]	0.754[d]
Total					Interaction[b]:	0.019

(continued)

Table 6: Results of the subgroups – RCT, direct comparison: crizotinib vs. chemotherapy (cisplatin + pemetrexed or carboplatin + pemetrexed) (continued)

Study Outcome category Outcome Characteristic Subgroup	Crizotinib		Chemotherapy Cisplatin + pemetrexed Carboplatin + pemetrexed		Crizotinib vs. chemotherapy	
	N	Median survival time in months [95% CI] Patients with event n (%)	N	Median survival time in months [95% CI] Patients with event n (%)	HR [95% CI]	p-value
EORTC QLQ-C30 functional scales – time to deterioration of health-related quality of life[e]						
Global health status						
Brain metastases						
Yes	41	1.4 [0.6; NA] 24 (58.5)	41	2.7 [0.3; 8.7] 23 (56.1)	0.84 [0.46; 1.52]	0.577[d]
No	125	12.5 [4.2; NA] 59 (47.2)	122	0.5 [0.3; 1.2] 90 (73.8)	0.40 [0.28; 0.57]	< 0.001[d]
Total					Interaction[b]:	0.025
Cognitive functioning						
Sex						
Men	65	10.1 [5.6; NA] 32 (49.2)	61	1.5 [0.6; 4.7] 39 (63.9)	0.43 [0.26; 0.72]	0.001[d]
Women	101	2.8 [1.4; 5.1] 64 (63.4)	102	2.1 [1.2; 4.9] 57 (55.9)	0.94 [0.65; 1.35]	0.725[d]
Total					Interaction[b]:	0.046

a: One-sided unstratified log-rank test.
b: Cox model with interaction term.
c: Time to increase in score by at least 10 points versus the baseline value.
d: Two-sided unstratified log-rank test.
e: Time to decrease in score by at least 10 points versus the baseline value.

CI: confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-LC13: Quality of Life Questionnaire-Lung Cancer 13; RCT: randomized controlled trial; vs.: versus

Morbidity

Symptoms (EORTC QLQ-C30)

There was proof of an effect modification by the characteristic "brain metastases" for the outcomes **"appetite loss"** and **"insomnia"** (interaction tests: insomnia p = 0.019; appetite loss p = 0.029). For patients with brain metastases, no statistically significant difference between the treatment groups was shown for the outcomes **"appetite loss"** and **"insomnia"**.

For patients without brain metastases, there was a statistically significant difference in favour of crizotinib for the outcomes **"appetite loss"** and **"insomnia"**.

Symptoms (EORTC QLQ-LC13)

There was proof of an effect modification by the characteristic "brain metastases" for the outcome **"alopecia"** (interaction test: p = 0.019). For patients with brain metastases, there was no statistically significant difference between the treatment groups for the outcome **"alopecia"**. For patients without brain metastases, there was a statistically significant difference in favour of crizotinib for the outcome **"alopecia"**.

There was proof of an effect modification by the characteristic "region" for the outcome **"peripheral neuropathy"** (interaction test: p = 0.010). For patients from Asia, there was a statistically significant difference in favour of crizotinib for the outcome **"peripheral neuropathy"**. For patients from North America and other countries, there was no statistically significant difference between the treatment groups. For patients from Europe, there was a statistically significant difference to the disadvantage of crizotinib for the outcome **"peripheral neuropathy"**.

There was proof of an effect modification by the characteristic "region" for the outcome **"pain (other)"** (interaction test: p = 0.019). For patients from Asia, there was a statistically significant difference in favour of crizotinib for the outcome **"pain (other)"**. For patients from Europe and other countries, there was no statistically significant difference between the treatment groups for the outcome **"pain (other)"**. For patients from North America, there was a statistically significant difference to the disadvantage of crizotinib for the outcome **"pain (other)"**.

Health-related quality of life

EORTC QLQ-C30

There was proof of an effect modification by the characteristic "brain metastases" for the outcome **"global health status"** (interaction p = 0.025). For patients with brain metastases, there was no statistically significant difference between the treatment groups for the outcome **"global health status"**. For patients without brain metastases, there was a statistically significant difference in favour of crizotinib for the outcome **"global health status"**.

There was proof of an effect modification by the characteristic "sex" for the outcome **"cognitive functioning"** (interaction p = 0.046). For women, there was no statistically significant difference between the treatment groups for the outcome **"cognitive functioning"**. For men, there was a statistically significant difference in favour of crizotinib for the outcome **"cognitive functioning"**.

2.2.5 Summary of positive and negative effects

The following Table 7 shows an overview of the positive and negative effects resulting from the PROFILE 1014 study for crizotinib in comparison with chemotherapy (cisplatin + pemetrexed or carboplatin + pemetrexed).

Table 7: Positive and negative effects of crizotinib in comparison with chemotherapy (cisplatin + pemetrexed or carboplatin + pemetrexed) – study PROFILE 1014

Positive effects	Negative effects
Morbidity (non-serious/non-severe symptoms) ▪ EORTC QLQ-C30: ▫ dyspnoea, fatigue, pain ▫ patients without brain metastases: appetite loss, insomnia ▪ EORTC QLQ-LC13: ▫ dyspnoea, cough, sore mouth, pain (thorax) ▫ patients without brain metastases: alopecia Health-related quality of life ▪ EORTC QLQ-C30: ▫ physical functioning, role functioning, emotional functioning, and social functioning ▫ patients without brain metastases: global health status ▫ men: cognitive functioning Serious/severe side effects ▪ severe AEs (CTCAE grade 3 and 4) Non-serious/non-severe side effects ▪ discontinuation due to AEs ▪ specific AEs: alopecia, appetite loss, asthenia, tiredness, neuropathy, stomatitis	Morbidity (non-serious/non-severe symptoms) ▪ EORTCQLQ-C30: ▫ diarrhoea ▪ EORTC QLQ-LC13: ▫ patients from Europe: peripheral neuropathy Non-serious/non-severe side effects ▪ specific AEs: bradycardia, diarrhoea, oedema, dysphagia, vision disorder

In the overall consideration, there is an advantage of crizotinib in comparison with chemotherapy (cisplatin + pemetrexed or carboplatin + pemetrexed).

It remains unclear, however, in how far the patients in the control arm were undertreated because the patients in the control arm were not allowed to receive maintenance treatment after the 6 cycles of chemotherapy. Moreover it is unclear in how far the patients in the control arm who were receiving carboplatin would have benefitted from treatment with cisplatin.

2.2.6 Data additionally presented by the company

In the commenting procedure, the company presented analyses on the following comparisons:

- all patients in the crizotinib arm versus patients in the control arm who received cisplatin

- all patients in the crizotinib arm versus patients in the control arm who received carboplatin
- patients in the control arm who received cisplatin versus patients in the control arm who received carboplatin

These analyses were based on non-randomized comparisons and were therefore not informative. They were therefore not considered.

It could be inferred from the company's comment that 32 of the 100 centres in the study were only using cisplatin (for a total of 74 patients) in the comparator arm, and 29 centres were only using carboplatin (for 61 patients). Conclusive randomized comparisons between crizotinib and cisplatin + pemetrexed would have been possible on the basis of those study centres that only administered cisplatin in the control arm. However, the company presented no separate analysis of these centres.

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