IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. A16-62

Ceritinib (non-small cell lung cancer) –

Addendum to Commission A16-62[1]

Addendum

Commission: A17-05
Version: 1.1
Status: 1 March 2017

[1] Translation of addendum A17-05 *Ceritinib (nicht kleinzelliges Lungenkarzinom) – Addendum zum Auftrag A16-62* (Version 1.1; Status: 1 March 2017). 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:
Ceritinib (non-small cell lung cancer) – Addendum to Commission A16-62

Commissioning agency:
Federal Joint Committee

Commission awarded on:
6 February 2017

Internal Commission No.:
A17-05

Address of publisher:
Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

IQWiG employees involved in the addendum[2]:

- Gregor Moritz
- Lars Beckmann
- Katharina Biester
- Thomas Kaiser

Keywords: ceritinib, carcinoma – non-small-cell lung, benefit assessment

[2] Due to legal data protection regulations, employees have the right not to be named.

Table of contents

List of tables

Page

List of figures

Page

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
ALK	anaplastic lymphoma kinase
ASBI	average symptom burden index
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
QLQ-C30	Quality of Life Questionnaire-Core 30
QLQ-LC13	Quality of Life Questionnaire-Lung Cancer 13
SAE	serious adverse event
SOC	System Organ Class
VAS	visual analogue scale

1 Background

On 6 February 2017, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A16-62 (Ceritinib – Benefit assessment according to §35a Social Code Book V).

In its dossier, the pharmaceutical (hereinafter referred to as "the company") presented results from the ASCEND-5 study [1-4] to prove the added benefit of ceritinib. These results included analyses on morbidity, health-related quality of life and specific adverse events (AEs). These analyses were not usable, however, because the company had not appropriately analysed the data [5].

In the oral hearing, the company presented modified analyses on symptoms, health status, health-related quality of life and AEs [6,7]. The G-BA commissioned IQWiG to assess these analyses.

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.

Changes in comparison with Version 1.0

The present Version 1.1 of 1 March 2017 replaces Version 1.0 of the addendum to commission A16-62 of 23 February 2017. The following change is contained in Version 1.1 compared with Version 1.0:

- Table 2 additionally shows the results on the outcomes "general disorders and administration site conditions" and "nervous system disorders". Both outcomes were already included in Version 1.0 both in Table 1 and in Table 3.

The result of the assessment was not affected by the change.

2 Assessment

2.1 Data availability

New analyses on research question 1 of the dossier assessment (study ASCEND-5)

For the benefit assessment of ceritinib in comparison with the appropriate comparator therapy (ACT) docetaxel or pemetrexed, the company had presented the ASCEND-5 study , which was assessed in dossier assessment A16-62 [5,8]. The study was an open-label, randomized controlled, multicentre study on the comparison of ceritinib with chemotherapy consisting of docetaxel or pemetrexed. 231 adult patients with advanced anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC) were included in the study (ceritinib: N = 115; chemotherapy: N = 116). The ASCEND-5 study was relevant for research question 1 of the dossier assessment (crizotinib-pretreated adult patients with advanced ALK-positive NSCLC for whom treatment with docetaxel or pemetrexed is an option).

Responder analyses on morbidity and health-related quality of life

In the ASCEND-5 study, symptoms were recorded with the symptom scales of the instruments European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30), Quality of Life Questionnaire-Lung Cancer 13 (QLQ-LC13) and Lung Cancer Symptom Scale (LCSS). Health status was recorded with the visual analogue scale (VAS) of the European Quality of Life-5 Dimensions (EQ-5D) questionnaire and health-related quality of life with the EORTC QLQ-C30 functional scales. In its dossier on the current assessment procedure, the company had presented responder analyses for the time to definitive deterioration by a validated threshold value versus the baseline value as response criterion. These analyses were not meaningfully interpretable and therefore not usable for the benefit assessment, however. Due to the design of the ASCEND-5 study it could be assumed that, particularly in the comparator therapy arm, single deteriorations were often also declared as definitive because most patients in the comparator arm were not followed-up due to progression. It could therefore not be excluded that the investigation did not target the comparison of the time to definitive deterioration, which was the comparison aimed at, but rather a comparison between the time to definitive deterioration (ceritinib arm) and the time to a single or temporary deterioration (chemotherapy arm). More details can be found in dossier assessment A16-62.

In the oral hearing on the current assessment procedure, the company presented responder analyses for the time to first deterioration by a validated threshold value in comparison with the baseline value as response criterion for the outcomes on morbidity and on health-related quality of life.

Analyses on specific adverse event outcomes

In its dossier, the company had only selectively presented analyses on specific adverse events (AEs) (individual System Organ Classes [SOCs]). There were no corresponding analyses for all SOCs on severe AEs, serious adverse events (SAEs) and discontinuation due to AEs. The

company subsequently submitted such analyses in the oral hearing. These analyses subsequently submitted were usable for the benefit assessment.

2.2 Results on added benefit

2.2.1 Risk of bias

The analyses subsequently submitted by the company on morbidity (symptoms and health status), health-related quality of life and AEs had a high risk of bias.

The outcomes "symptoms", "health status" and "health-related quality of life" were only recorded until progression, the AE outcomes were recorded until 30 days after progression or until switching from the chemotherapy arm to ceritinib.

Since the observation period was linked to progression, there were notable differences in observation period between the treatment arms. All outcomes had a high risk of bias due to potentially informative censoring (see dossier assessment A16-62 for a detailed description). A further aspect of bias was the lack of blinding in subjective recording of outcomes.

2.2.2 Results

The results on the comparison of ceritinib with chemotherapy (docetaxel or pemetrexed) subsequently submitted by the company are summarized in Table 1.

If available, Kaplan-Meier curves on the outcomes included with statistically significant differences between the treatment groups are presented in Appendix A. The results for the outcome "overall survival" and further outcomes of the category "side effects" can be found in dossier assessment A16-62.

Table 1: Results – RCT, direct comparison: ceritinib vs. chemotherapy (docetaxel or pemetrexed)

Study Outcome category Outcome	Ceritinib N	Ceritinib Median time to event in months [95% CI] Patients with event n (%)	Chemotherapy N	Chemotherapy Median time to event in months [95% CI] Patients with event n (%)	Ceritinib vs. chemotherapy HR [95% CI]; p-value
ASCEND-5					
Morbidity					
Symptoms					
EORTC QLQ-C30 (symptom scales) – time to first deterioration[a]					
Dyspnoea	115	11.0 [4.4; NC] 45 (39.1)	116	4.1 [1.7; NC] 27 (23.3)	0.70 [0.43; 1.15] 0.158
Fatigue	115	1.5 [1.4; 2.8] 73 (63.5)	116	1.0 [0.8; 2.1] 50 (43.1)	0.77 [0.53; 1.11] 0.150
Insomnia	115	7.2 [2.8; NC] 51 (44.3)	116	4.1 [2.8; 12.5] 30 (25.9)	0.88 [0.55; 1.41] 0.621
Pain	115	2.8 [1.5; 7.1] 64 (55.7)	116	3.1 [1.2; 6.9] 38 (32.8)	0.82 [0.54; 1.24] 0.355
Appetite loss	115	1.5 [1.1; 2.8] 74 (64.3)	116	3.7 [1.6; NC] 29 (25.0)	1.60 [1.03; 2.47] 0.040
Diarrhoea	115	0.9 [0.9; 1.4] 82 (71.3)	116	8.3 [5.7; NC] 20 (17.2)	3.57 [2.18; 5.84] < 0.001
Nausea/vomiting	115	0.9 [0.8; 1.4] 82 (71.3)	116	5.6 [2.4; NC] 28 (24.1)	2.48 [1.61; 3.81] < 0.001
Constipation	115	NA [5.8; NC] 40 (34.8)	116	7.0 [3.6; NC] 24 (20.7)	0.75 [0.44; 1.28] 0.280
EORTC QLQ-LC13 (symptom scales) – time to first deterioration[a]					
Dyspnoea	115	4.2 [1.5; 7.1] 61 (53.0)	116	2.1 [1.0; 5.5] 41 (35.3)	0.76 [0.50; 1.14] 0.183
Pain in chest	115	18.0 [7.0; NC] 39 (33.9)	116	7.1 [4.2; NC] 20 (17.2)	0.99 [0.57; 1.72] 0.972
Pain in arm or shoulder	115	NA [13.6; NC] 32 (27.8)	116	5.6 [3.6; NC] 26 (22.4)	0.56 [0.33; 0.95] 0.030
Pain in other parts	115	5.6 [3.1; 19.7] 51 (44.3)	116	2.1 [1.0; 5.7] 42 (36.2)	0.52 [0.34; 0.80] 0.003
Cough	115	NA [9.1; NC] 35 (30.4)	116	5.7 [2.8; NC] 25 (21.6)	0.50 [0.29; 0.86] 0.011
Haemoptysis	115	NA 4 (3,5)	116	NA [8.6; NC] 4 (3.4)	0.30 [0.06; 1.42] 0.111

(continued)

Table 1: Results – RCT, direct comparison: ceritinib vs. chemotherapy (docetaxel or pemetrexed) (continued)

Study Outcome category Outcome	Ceritinib N	Ceritinib Median time to event in months [95% CI] Patients with event n (%)	Chemotherapy N	Chemotherapy Median time to event in months [95% CI] Patients with event n (%)	Ceritinib vs. chemotherapy HR [95% CI]; p-value
ASCEND-5					
Alopecia	115	NA 19 (16,5)	116	1.0 [0.8; 1.4] 55 (47.4)	0.12 [0.06; 0.20] < 0.001
Dysphagia	115	NA 27 (23,5)	116	6.8 [3.3; NC] 22 (19.0)	0.60 [0.34; 1.07] 0.077
Sore mouth	115	NA [11.0; NC] 30 (26.1)	116	5.6 [2.8; NC] 27 (23.3)	0.42 [0.25; 0.73] 0.002
Peripheral neuropathy	115	NA [7.2; NC] 35 (30.4)	116	2.9 [1.7; 9.0] 35 (30.2)	0.32 [0.19; 0.54] < 0.001
LCSS (symptom scales) – time to first deterioration[b]					
ASBI[c]	115	20.0 [11.1; NC] 33 (28.7)	116	8.5 [2.9; NC] 20 (17.2)	0.69 [0.38; 1.22] 0.200
Health status					
EQ-5D VAS – time to first deterioration					
MID 7 points			No data		
MID 10 points	115	2.9 [1.6; 12.4] 59 (51.3)	116	2.9 [1.0; 5.6] 41 (35.3)	0.82 [0.54; 1.24] 0.342
Health-related quality of life					
EORTC QLQ-C30 (functional scales) – time to first deterioration[a]					
Global health status	115	3.0 [1.5; 11.0] 62 (53.9)	116	6.2 [1.1; 11.1] 35 (30.2)	0.95 [0.62; 1.46] 0.811
Emotional functioning	115	NA [11.0; NC] 36 (31.3)	116	7.0 [3.6; NC] 20 (17.2)	0.81 [0.46; 1.42] 0.461
Cognitive functioning	115	4.4 [2.8; 9.5] 59 (51.3)	116	NA [1.8; NC] 27 (23.3)	0.96 [0.60; 1.55] 0.871
Physical functioning	115	9.9 [4.2; NC] 51 (44.3)	116	2.9 [1.5; 7.0] 37 (31.9)	0.60 [0.38; 0.93] 0.022
Role functioning	115	5.6 [1.8; 8.5] 59 (51.3)	116	1.7 [0.9; 3.3] 43 (37.1)	0.62 [0.41; 0.93] 0.020
Social functioning	115	2.8 [1.4; 8.3] 67 (58.3)	116	1.4 [0.9; 5.5] 46 (39.7)	0.66 [0.45; 0.98] 0.036

(continued)

Table 1: Results – RCT, direct comparison: ceritinib vs. chemotherapy (docetaxel or pemetrexed) (continued)

Study Outcome category	Ceritinib		Chemotherapy		Ceritinib vs. chemotherapy
Outcome	**N**	**Median time to event in months [95% CI] Patients with event n (%)**	**N**	**Median time to event in months [95% CI] Patients with event n (%)**	**HR [95% CI]; p-value**
ASCEND-5					
Side effects					
Specific adverse events					
General disorders and administration site conditions	115	2.3 [1.4; 8.5] 71 (61.7)	113	0.9 [0.4; 2.1] 71 (62.8)	0.59 [0.41; 0.83] 0.003
Nervous system disorders	115	11.3 [8.9; 26.9] 45 (39.1)	113	4.9 [2.6; 8.3] 45 (39.8)	0.46 [0.29; 0.72] < 0.001
Respiratory, thoracic and mediastinal disorders	115	19.1 [6.6; 22.1] 48 (41.7)	113	2.1 [1.2; 5.5] 60 (53.1)	0.42 [0.28; 0.62] < 0.001
Gastrointestinal disorders	115	0.1 [0.1; 0.3] 108 (93.9)	113	1.5 [0.7; 3.2] 65 (57.5)	3.00 [2.17; 4.14] < 0.001
Blood and lymphatic system disorders (CTCAE grade 3 or 4)	115	NA 1 (0,9)	113	NA 28 (24,8)	0.03 [0.00; 0.20] < 0.001
Investigations (CTCAE grade 3 or 4)	115	10.3 [4.9; NA] 50 (43.5)	113	NA [7.7; NA] 19 (16.8)	1.78 [1.04; 3.06] 0.034
Musculoskeletal and connective tissue disorders (CTCAE grade 3 or 4)[d]	115	NA 5 (4,3)	113	NA 9 (8,0)	0.25 [0.07; 0.84] 0.018
Psychiatric disorders	115	NA 16 (13,9)	113	NA [7.0; NA] 23 (20.4)	0.37 [0.19; 0.73] 0.003

(continued)

Table 1: Results – RCT, direct comparison: ceritinib vs. chemotherapy (docetaxel or pemetrexed) (continued)

a: Time to deterioration by at least 10 points.
b: Time to deterioration by at least 15 points.
c: Mean of the 6 LCSS symptom scales (loss of appetite, fatigue, cough, dyspnoea, haemoptysis, pain).
d: A statistically significant result was available also for the analysis of all CTCAE grades: ceritinib: n = 50 (43.5%), chemotherapy: n = 47 (41.6%), HR = 0.64 [0.42; 0.97]; p = 0.035.
AE: adverse event; ASBI: average symptom burden index; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; LCSS: Lung Cancer Symptom Scale; MID: minimally important difference; n: number of patients with event; N: number of analysed patients; NA: not achieved; NC: not calculable; 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; SOC: System Organ Class according to Medical Dictionary for Regulatory Activities; VAS: visual analogue scale; vs.: versus

On the basis of the available data, at most hints, e.g. of an added benefit, can be derived for all outcomes because of the high risk of bias (see Section 2.2.1).

The analyses subsequently submitted by the company on the time to first deterioration confirmed that the analyses on definitive deterioration submitted with the dossier were unsuitable. Whereas with the new analysis notably more events were recorded in the ceritinib arm, this was not the case or not as pronounced in the comparator arm (e.g. for the symptom "nausea and vomiting" of the EORTC QLQ-C30: 71.3% first deterioration versus 33.0% definitive deterioration under ceritinib and 24.1% versus 21.6% in the comparator arm).

Morbidity

Symptoms

Outcomes of symptoms were recorded with the symptom scales of the disease-specific instruments EORTC QLQ-C30, EORTC QLQ-LC13 and LCSS.

Appetite loss, diarrhoea, nausea and vomiting

Statistically significant differences to the disadvantage of ceritinib in comparison with docetaxel or pemetrexed were shown for the outcomes "appetite loss", "diarrhoea" and "nausea and vomiting". This led to a hint of lesser benefit of ceritinib for all 3 outcomes.

Pain in arm or shoulder, pain in other parts, cough, alopecia, sore mouth, peripheral neuropathy

Statistically significant differences in favour of ceritinib versus docetaxel or pemetrexed were shown for each of the outcomes "pain in arm or shoulder", "pain in other parts", "cough", "alopecia", "sore mouth" and "peripheral neuropathy". This led to a hint of an added benefit of ceritinib for these outcomes.

Further outcomes on symptoms

No statistically significant differences between the treatment groups were shown for any further outcomes on symptoms (including the analysis on the LCSS [average symptom burden index, ASBI]). This led to a hint of an added benefit of ceritinib in comparison with docetaxel or pemetrexed for the further symptom outcomes; an added benefit is therefore not proven.

Health status

In its dossier, the company presented an analysis of the time to definitive deterioration by a threshold value of 10 points for the outcome "health status". There was no such analysis for the threshold value of 7 points.

The analyses on the time to definitive deterioration were not meaningfully interpretable for the reasons described in dossier assessment A16-62. In its data subsequently submitted, the company presented an analysis of the time to first deterioration for the threshold value of 10 points. It also subsequently submitted an analysis for the threshold value of 7 points, but only for the time to definitive deterioration. This analysis was therefore not usable.

Since the literature specifies a range of 7 to 10 points [9], analyses of the time to first deterioration would have been desirable for the interpretation of the result for both threshold values. The result on the upper threshold value (10 points) was not statistically significant.

In summary, there was no hint of an added benefit of ceritinib in comparison with docetaxel or pemetrexed for the outcome "health status"; an added benefit is therefore not proven.

Health-related quality of life

Health-related quality of life was recorded with the functional scales and with the scale for the recording of the global health status of the disease-specific instrument EORTC-QLQ-C30.

Physical functioning, role functioning, social functioning

Statistically significant differences in favour of ceritinib in comparison with docetaxel or pemetrexed were shown for the outcomes "physical functioning", "role functioning" and "social functioning". This resulted in a hint of an added benefit of ceritinib in comparison with docetaxel or pemetrexed for each of the 3 outcomes.

Further outcomes on health-related quality of life

No statistically significant differences between the treatment groups were shown for any further outcomes on health-related quality of life. This led to a hint of an added benefit of ceritinib in comparison with docetaxel or pemetrexed for the further outcomes on health-related quality of life; an added benefit is therefore not proven.

Side effects

Specific adverse events

The choice of specific AEs was based on the frequency of the events occurred in the relevant study, the survival time analyses submitted by the company, statistically significant group differences and under consideration of patient relevance. The AE outcomes cited below were chosen based on these aspects.

Statistically significant differences in favour of ceritinib versus docetaxel or pemetrexed were shown for each of the following AE outcomes: general disorders and administration site conditions; nervous system disorders, respiratory, thoracic and mediastinal disorders, blood and lymphatic system disorders (CTCAE grade 3 or 4), musculoskeletal and connective tissue disorders (CTCAE grade 3 or 4) and psychiatric disorders. This resulted in a hint of lesser harm of ceritinib in comparison with docetaxel or pemetrexed for each of these outcomes.

Statistically significant differences to the disadvantage of ceritinib in comparison with docetaxel or pemetrexed were shown for the AE outcomes "gastrointestinal disorders" and "investigations" (CTCAE grade 3 or 4). This resulted in a hint of greater harm of ceritinib in comparison with docetaxel or pemetrexed for each of these 2 outcomes.

2.2.3 Extent and probability of added benefit at outcome level

Hereinafter, the derivation of extent and probability of the added benefit is presented at outcome level under consideration of the present addendum and dossier assessment A16-62, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [10].

It could not be inferred from the dossier for all outcomes considered in the present benefit assessment whether they were non-severe/non-serious or severe/serious. Since it was not clear from the dossier or from the data subsequently submitted by the company that the outcomes on symptoms and on health-related quality of life were severe or serious symptoms, these outcomes were allocated to non-serious/non-severe symptoms/late complications.

The extent of the respective added benefit at outcome level was estimated from these results (see Table 2).

Table 2: Extent of added benefit at outcome level: ceritinib vs. chemotherapy (docetaxel or pemetrexed)

Outcome category **Outcome**	**Ceritinib vs. chemotherapy** **Median time to event** **Effect estimate [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival	Median: 18.1 vs. 20.1 months HR: 1.00 [0.67; 1.49] p = 0.496	Lesser benefit/added benefit not proven
Morbidity		
Symptoms		
EORTC QLQ-C30 (symptom scales) – time to first deterioration[c]		
Dyspnoea	Median: 11.0 vs. 4.1 months HR: 0.70 [0.43; 1.15] p = 0.158	Lesser benefit/added benefit not proven
Fatigue	Median: 1.5 vs. 1.0 months HR: 0.77 [0.53; 1.11] p = 0.150	Lesser benefit/added benefit not proven
Insomnia	Median: 7.2 vs. 4.1 months HR: 0.88 [0.55; 1.41] p = 0.621	Lesser benefit/added benefit not proven
Pain	Median: 2.8 vs. 3.1 months HR: 0.82 [0.54; 1.24] p = 0.355	Lesser benefit/added benefit not proven
Appetite loss	Median: 1.5 vs. 3.7 months HR: 1.60 [1.03; 2.47] HR: 0.63 [0.40; 0.97][d] p = 0.040[e]	Lesser benefit/added benefit not proven
Diarrhoea	Median: 0.9 vs. 8.3 months HR: 3.57 [2.18; 5.84] HR: 0.28 [0.17; 0.46][d] p < 0.001 probability: “hint”	Outcome category: non-serious/non-severe symptoms/late complications CI_u < 0.80 lesser benefit, extent: “considerable”
Nausea/vomiting	Median: 0.9 vs. 5.6 months HR: 2.48 [1.61; 3.81] HR: 0.40 [0.26; 0.62][d] p < 0.001 probability: “hint”	Outcome category: non-serious/non-severe symptoms/late complications CI_u < 0.80 lesser benefit, extent: “considerable”
Constipation	Median: NA vs. 7.0 months HR: 0.75 [0.44; 1.28] p = 0.280	Lesser benefit/added benefit not proven

(continued)

Table 2: Extent of added benefit at outcome level: ceritinib vs. chemotherapy (docetaxel or pemetrexed) (continued)

Outcome category **Outcome**	**Ceritinib vs. chemotherapy** **Median time to event** **Effect estimate [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
EORTC QLQ-LC13 (symptom scales) – time to first deterioration[c]		
Dyspnoea	Median: 4.2 vs. 2.1 months HR: 0.76 [0.50; 1.14] p = 0.183	Lesser benefit/added benefit not proven
Pain in chest	Median: 18.0 vs. 7.1 months HR: 0.99 [0.57; 1.72] p = 0.972	Lesser benefit/added benefit not proven
Pain in arm or shoulder	Median: NA vs. 5.6 months HR: 0.56 [0.33; 0.95] p = 0.030[e]	Lesser benefit/added benefit not proven
Pain in other parts	Median: 5.6 vs. 2.1 months HR: 0.52 [0.34; 0.80] p = 0.003 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $0.80 \leq CI_u < 0.90$ added benefit, extent: "minor"
Cough	Median: NA vs. 5.7 months HR: 0.50 [0.29; 0.86] p = 0.011 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $0.80 \leq CI_u < 0.90$ added benefit, extent: "minor"
Haemoptysis	Median: NA vs. NA months HR: 0.30 [0.06; 1.42] p = 0.111	Lesser benefit/added benefit not proven
Alopecia	Median: NA vs. 1.0 months HR: 0.12 [0.06; 0.20] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $CI_u < 0.80$ added benefit, extent: "considerable"
Dysphagia	Median: NA vs. 6.8 months HR: 0.60 [0.34; 1.07] p = 0.077	Lesser benefit/added benefit not proven
Sore mouth	Median: NA vs. 5.6 months HR: 0.42 [0.25; 0.73] p = 0.002 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $CI_u < 0.80$ added benefit, extent: "considerable"

(continued)

Table 2: Extent of added benefit at outcome level: ceritinib vs. chemotherapy (docetaxel or pemetrexed) (continued)

Outcome category **Outcome**	**Ceritinib vs. chemotherapy** **Median time to event** **Effect estimate [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Peripheral neuropathy	Median: NA vs. 2.9 months HR: 0.32 [0.19; 0.54] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $CI_u < 0.80$ added benefit, extent: "considerable"
LCSS (symptom scales) – time to first deterioration[f]		
ASBI[g]	Median: 20.0 vs. 8.5 months HR: 0.69 [0.38; 1.22] p = 0.200	Lesser benefit/added benefit not proven
Health status		
EQ-5D VAS – time to first deterioration		
MID 7 points	No data	Lesser benefit/added benefit not proven
MID 10 points	Median: 2.9 vs. 2.9 months HR: 0.82 [0.54; 1.24] p = 0.342	
Health-related quality of life		
EORTC QLQ-C30 (functional scales) – time to first deterioration[c]		
Global health status	Median: 3.0 vs. 6.2 months HR: 0.95 [0.62; 1.46] p = 0.811	Lesser benefit/added benefit not proven
Emotional functioning	Median: NA vs. 7.0 months HR: 0.81 [0.46; 1.42] p = 0.461	Lesser benefit/added benefit not proven
Cognitive functioning	Median: 4.4 vs. NA months HR: 0.96 [0.60; 1.55] p = 0.871	Lesser benefit/added benefit not proven
Physical functioning	Median: 9.9 vs. 2.9 months HR: 0.60 [0.38; 0.93] p = 0.022 probability: "hint"	Outcome category: Health-related quality of life $0.90 \leq CI_u < 1.00$ added benefit, extent: "minor"
Role functioning	Median: 5.6 vs. 1.7 months HR: 0.62 [0.41; 0.93] p = 0.020 probability: "hint"	Outcome category: Health-related quality of life $0.90 \leq CI_u < 1.00$ added benefit, extent: "minor"

(continued)

Table 2: Extent of added benefit at outcome level: ceritinib vs. chemotherapy (docetaxel or pemetrexed) (continued)

Outcome category **Outcome**	**Ceritinib vs. chemotherapy** **Median time to event** **Effect estimate [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Social functioning	Median: 2.8 vs. 1.4 months HR: 0.66 [0.45; 0.98] p = 0.036 probability: "hint"	Outcome category: Health-related quality of life $0.90 \leq CI_u < 1.00$ added benefit, extent: "minor"
Side effects		
SAEs	Median: 11.9 vs. 10.1 months HR: 0.69 [0.43; 1.08] p = 0.104	Lesser benefit/added benefit not proven
Severe AEs (CTCAE grade 3 or 4)	Median: 2.1 vs. 1.1 months HR: 0.79 [0.57; 1.08] p = 0.133	Lesser benefit/added benefit not proven
Discontinuation due to AEs	Median: NA vs. NA HR: 0.89 [0.41; 1.94] p = 0.763	Lesser benefit/added benefit not proven
Specific adverse events		
General disorders and administration site conditions	Median: 2.3 vs. 0.9 months HR: 0.59 [0.41; 0.83] p = 0.003 probability: "hint"	Outcome category: non-serious/non-severe side effects $0.80 \leq CI_u < 0.90$ lesser harm, extent: "minor"
Nervous system disorders	Median: 11.3 vs. 4.9 months HR: 0.46 [0.29; 0.72] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ lesser harm, extent: "considerable"
Respiratory, thoracic and mediastinal disorders	Median: 19.1 vs. 2.1 months HR: 0.42 [0.28; 0.62] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ lesser harm, extent: "considerable"
Gastrointestinal disorders	Median: 0.1 vs. 1.5 months HR: 3.00 [2.17; 4.14] HR: 0.33 [0.24; 0.46][d] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: "considerable"

(continued)

Table 2: Extent of added benefit at outcome level: ceritinib vs. chemotherapy (docetaxel or pemetrexed) (continued)

Outcome category **Outcome**	**Ceritinib vs. chemotherapy** **Median time to event** **Effect estimate [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Blood and lymphatic system disorders (CTCAE grade 3 or 4)	Median: NA vs. NA months HR: 0.03 [0.00; 0.20] p < 0.001 probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$; risk ≥ 5% lesser harm, extent: "major"
Investigations (CTCAE grade 3 or 4)	Median: 10.3 vs. NA months HR: 1.78 [1.04; 3.06] HR: 0.56 [0.33; 0.96][d] p = 0.034 probability: "hint"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ greater harm, extent: "minor"
Musculoskeletal and connective tissue disorders (CTCAE grade 3 or 4)	Median: NA vs. NA months HR: 0.25 [0.07; 0.84] p = 0.018 probability: "hint"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ lesser harm, extent: "considerable"
Psychiatric disorders	Median: NA vs. NA months HR: 0.37 [0.19; 0.73] p = 0.003 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ lesser harm, extent: "considerable"

a: Probability provided if statistically significant differences are present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CIu.
c: Time to deterioration by at least 10 points.
d: Institute's calculation, reversed direction of effect to enable use of limits to derive the extent of the added benefit.
e: Greater/lesser harm is not proven because the effect size is only marginal. Outcome category "non-serious/non-severe symptoms/late complications" 0.90 ≤ CIu < 1.00
f: Time to deterioration by at least 15 points.
g: Mean of the 6 LCSS symptom scales (loss of appetite, fatigue, cough, dyspnoea, haemoptysis, pain).
AE: adverse event; ASBI: average symptom burden index; CI: confidence interval; CIu: upper limit of confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; LCSS: Lung Cancer Symptom Scale; MID: minimally important difference; NA: not achieved; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-LC13: Quality of Life Questionnaire-Lung Cancer 13; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

Due to the documents subsequently submitted, results on morbidity, health-related quality of life and specific AEs were now available in comparison with dossier assessment A16-62.

2.2.4 Overall conclusion on added benefit

Table 3 summarizes the results considered in the overall conclusion about the extent of added benefit.

Table 3: Positive and negative effects from the assessment of ceritinib compared with chemotherapy (docetaxel or pemetrexed)

Positive effects	**Negative effects**
▪ Non-serious/non-severe symptoms/late complications ▫ symptoms: hint of an added benefit – extent: "considerable" (including alopecia, sore mouth, peripheral neuropathy – extent: in each case "considerable"; pain in other parts, cough – extent: in each case "minor")	▪ Non-serious/non-severe symptoms/late complications ▫ symptoms: hint of lesser benefit – extent: "considerable" (including: diarrhoea and nausea and vomiting)
▪ Health-related quality of life ▫ hint of an added benefit – extent: "minor" (including physical functioning, role functioning, social functioning)	-
▪ Non-serious/non-severe side effects ▫ specific AEs: hint of lesser harm – extent: "considerable" (including nervous system disorders, respiratory, thoracic and mediastinal disorders and psychiatric disorders – extent: "considerable"; general disorders and administration site conditions – extent: "minor")	▪ Non-serious/non-severe side effects ▫ specific AEs: hint of greater harm – extent "considerable" (gastrointestinal disorders)
▪ Severe/serious side effects ▫ specific AEs: hint of lesser harm – extent: "major" (including: blood and lymphatic system disorders [CTCAE grade 3 or 4] – extent: "major"; musculoskeletal and connective tissue disorders [CTCAE grade 3 or 4] – extent: "considerable")	▪ Severe/serious side effects ▫ specific AEs: hint of greater harm – extent: "minor" (investigations [CTCAE grade 3 or 4])
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events	

Overall, there were positive and negative effects of ceritinib.

On the positive side, there was a hint of an added benefit with the extent "minor" or "considerable" for several symptoms (e.g. peripheral neuropathy, cough, pain). There were also several hints of lesser harm in the area of side effects, mostly regarding non-severe AEs (extent "minor" to "considerable"), but also regarding individual severe AEs (extent "considerable" to "major"). Finally, there was a hint of an added benefit for several dimensions of health-related quality of life (extent in each case "minor").

The positive effects were accompanied by negative effects, particularly in outcomes on the gastrointestinal tract (recorded as symptoms and side effects). There were hints of lesser benefit or of greater harm with the extent "considerable".

Overall, the positive effects of ceritinib notably outweigh the negative effects. Hence there is a hint of considerable added benefit of ceritinib for crizotinib-pretreated adult patients with advanced ALK-positive NSCLC for whom treatment with docetaxel or pemetrexed is an option.

The company also derived considerable added benefit, but determined a high certainty of conclusions.

This procedure for deriving an overall conclusion on added benefit on the basis of the aggregation of the conclusions deduced at the outcome level represents a suggestion by IQWiG. The G-BA decides on the added benefit.

3 References

1. Novartis. A phase III, multicenter, randomized, open-label study of oral LDK378 versus standard chemotherapy in adult patients with ALK-rearranged (ALK-positive) advanced non-small cell lung cancer who have been treated previously with chemotherapy (platinum doublet) and crizotinib: study CLDK378A2303; Zusatzanalysen [unpublished]. 2016.

2. Novartis. A phase III, multicenter, randomized, open-label study of oral LDK378 versus standard chemotherapy in adult patients with ALK-rearranged (ALK-positive) advanced non-small cell lung cancer who have been treated previously with chemotherapy (platinum doublet) and crizotinib: study CLDK378A2303; clinical study report [unpublished]. 2016.

3. Novartis Pharma Services. A phase III, multicenter, randomized, open-label study of oral LDK378 versus standard chemotherapy in adult patients with ALK-rearranged (ALK-positive) advanced non-small cell lung cancer who have been treated previously with chemotherapy (platinum doublet) and crizotinib [online]. In: EU Clinical Trials Register. [Accessed: 25.07.2016]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2012-005637-36.

4. Novartis Pharmaceuticals. LDK378 versus chemotherapy in ALK rearranged (ALK positive) patients previously treated with chemotherapy (platinum doublet) and crizotinib: full text view [online]. In: ClinicalTrials.gov. 25.04.2016 [Accessed: 25.07.2016]. URL: https://clinicaltrials.gov/ct2/show/NCT01828112.

5. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Ceritinib (nicht kleinzelliges Lungenkarzinom): Nutzenbewertung gemäß § 35a SGB V (Ablauf Befristung); Dossierbewertung; Auftrag A16-62 [online]. 22.12.2016 [Accessed: 23.01.2017]. (IQWiG-Berichte; Volume 471). URL: https://www.iqwig.de/download/A16-62_Ceritinib_Nutzenbewertung-%C2%A735a-SGB-V.pdf.

6. Novartis Pharma. Stellungnahme zum IQWiG-Bericht Nr. 471: Ceritinib (nicht kleinzelliges Lungenkarzinom); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A16-62. [Soon available under https://www.g-ba.de/informationen/nutzenbewertung/264/#tab/ in the document "Zusammenfassende Dokumentation"].

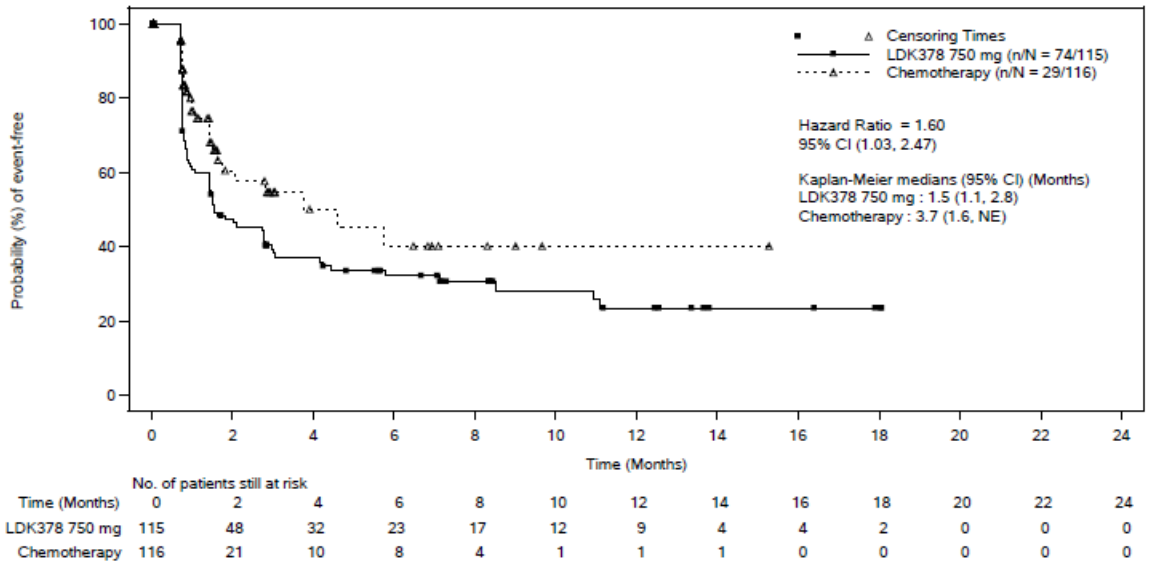
7. Novartis. A phase III, multicenter, randomized, open-label study of oral LDK378 versus standard chemotherapy in adult patients with ALK-rearranged (ALK-positive) advanced non-small cell lung cancer who have been treated previously with chemotherapy (platinum doublet) and crizotinib: study CLDK378A2303; Zusatzanalysen [unpublished]. 2017.

8. Novartis Pharma. Ceritinib (Zykadia): Dossier zur Nutzenbewertung gemäß § 35a SGB V; Modul 4 A; Behandlung des Crizotinib-vorbehandelten, fortgeschrittenen, ALK-positiven, nicht-kleinzelligen Lungenkarzinoms (NSCLC); medizinischer Nutzen und medizinischer Zusatznutzen, Patientengruppen mit therapeutisch bedeutsamem Zusatznutzen [online]. 27.09.2019 [Accessed: 13.02.2017]. URL: https://www.g-ba.de/downloads/92-975-1687/2016-09-27_Modul4A_Ceritinib.pdf.

9. Pickard AS, Neary MP, Cella D. Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. Health Qual Life Outcomes 2007; 5: 70.

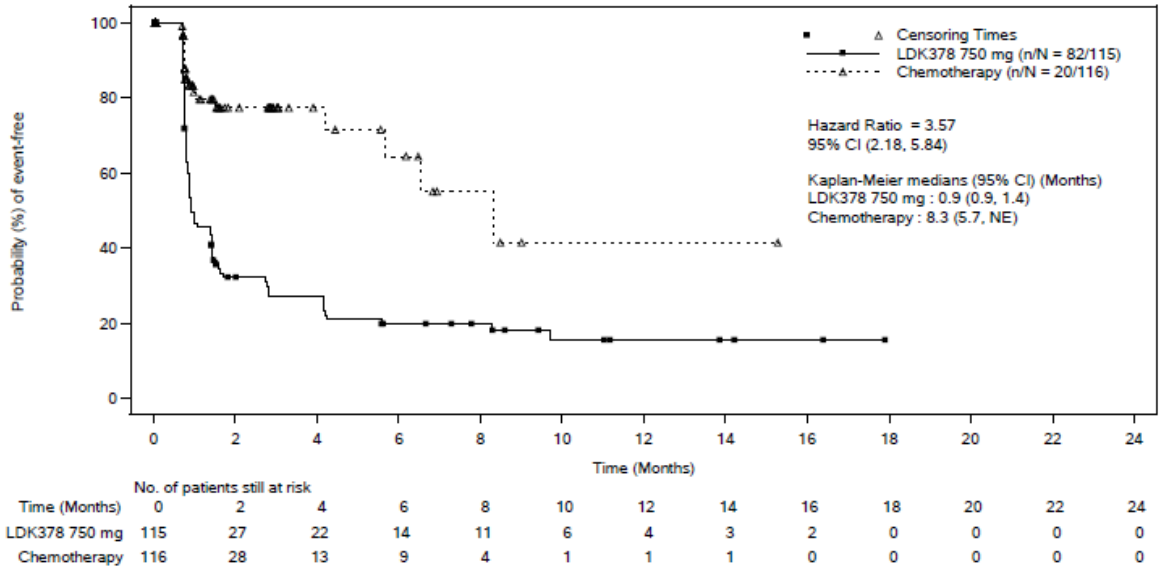
10. Institute for Quality and Efficiency in Health Care. General Methods: version 4.2 [online]. 22.04.2015 [Accessed: 01.06.2016]. URL: https://www.iqwig.de/download/IQWiG_General_Methods_Version_%204-2.pdf.

Appendix A– Kaplan-Meier curves on results of the ASCEND-5 study



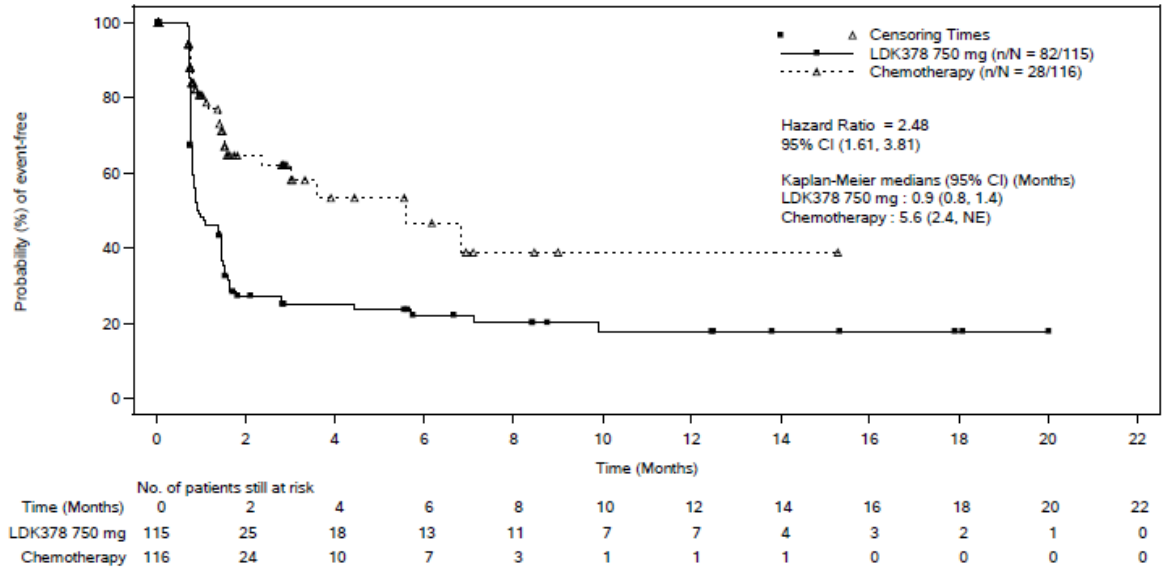
Time (Months)	0	2	4	6	8	10	12	14	16	18	20	22	24
LDK378 750 mg	115	48	32	23	17	12	9	4	4	2	0	0	0
Chemotherapy	116	21	10	8	4	1	1	1	0	0	0	0	0

Figure 1: Kaplan-Meier curve for the time to first deterioration: appetite loss (EORTC QLQ-C30) – RCT, direct comparison: ceritinib versus chemotherapy (docetaxel or pemetrexed)



Time (Months)	0	2	4	6	8	10	12	14	16	18	20	22	24
LDK378 750 mg	115	27	22	14	11	6	4	3	2	0	0	0	0
Chemotherapy	116	28	13	9	4	1	1	1	0	0	0	0	0

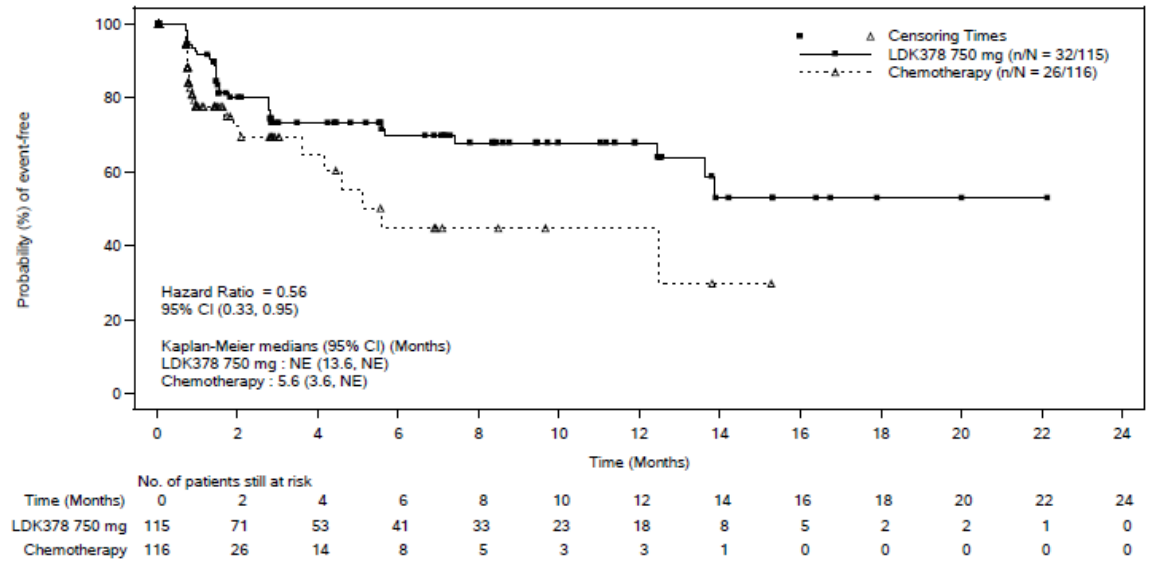
Figure 2: Kaplan-Meier curve for the time to first deterioration: diarrhoea (EORTC QLQ-C30) – RCT, direct comparison: ceritinib versus chemotherapy (docetaxel or pemetrexed)



No. of patients still at risk

Time (Months)	0	2	4	6	8	10	12	14	16	18	20	22
LDK378 750 mg	115	25	18	13	11	7	7	4	3	2	1	0
Chemotherapy	116	24	10	7	3	1	1	1	0	0	0	0

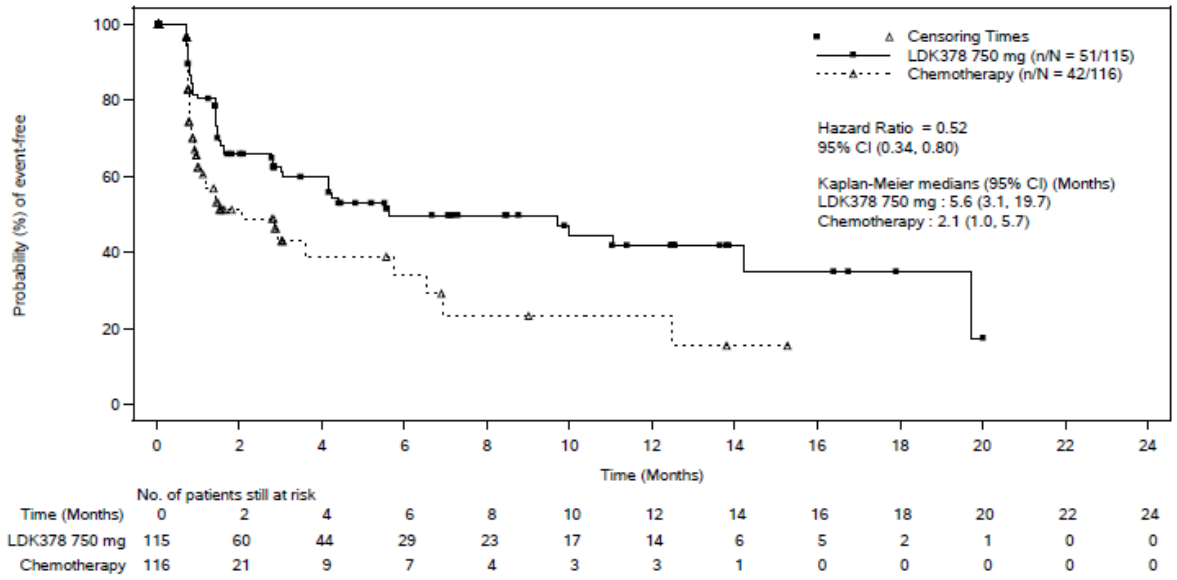
Figure 3: Kaplan-Meier curve for the time to first deterioration: nausea and vomiting (EORTC QLQ-C30) – RCT, direct comparison: ceritinib versus chemotherapy (docetaxel or pemetrexed)



No. of patients still at risk

Time (Months)	0	2	4	6	8	10	12	14	16	18	20	22	24
LDK378 750 mg	115	71	53	41	33	23	18	8	5	2	2	1	0
Chemotherapy	116	26	14	8	5	3	3	1	0	0	0	0	0

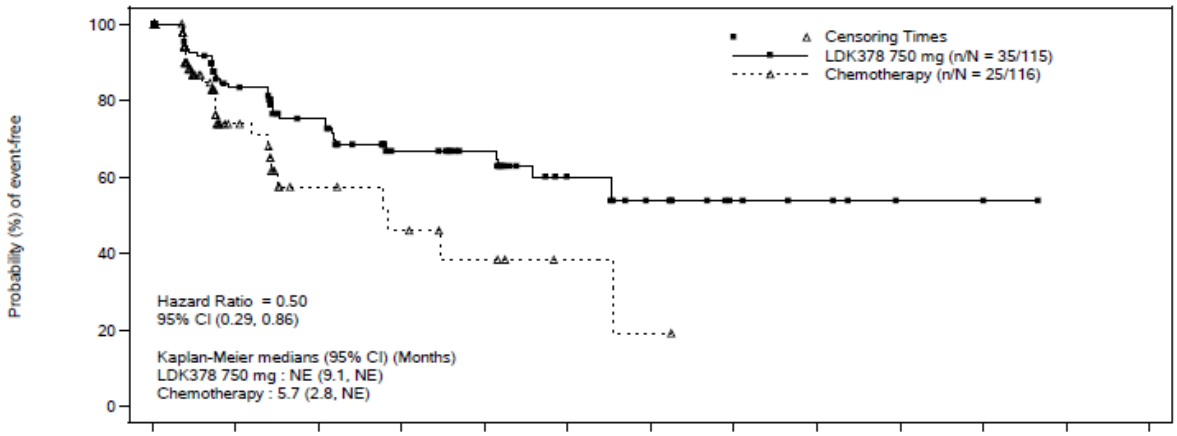
Figure 4: Kaplan-Meier curve for the time to first deterioration: pain in arm or shoulder (EORTC QLQ-LC13) – RCT, direct comparison: ceritinib versus chemotherapy (docetaxel or pemetrexed)



No. of patients still at risk

Time (Months)	0	2	4	6	8	10	12	14	16	18	20	22	24
LDK378 750 mg	115	60	44	29	23	17	14	6	5	2	1	0	0
Chemotherapy	116	21	9	7	4	3	3	1	0	0	0	0	0

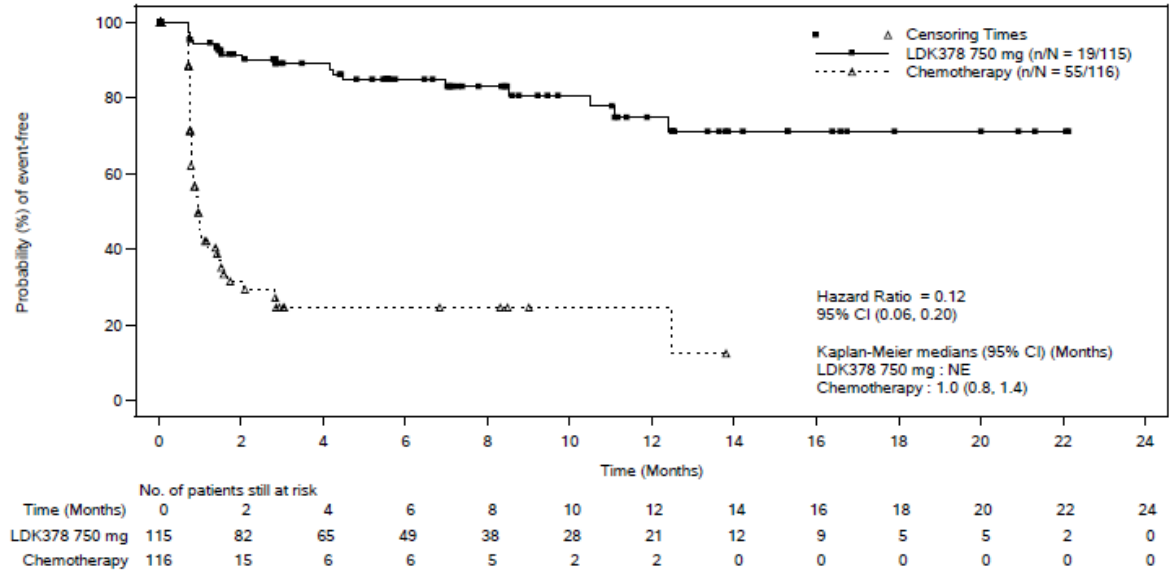
Figure 5: Kaplan-Meier curve for the time to first deterioration: pain in other parts (EORTC QLQ-LC13) – RCT, direct comparison: ceritinib versus chemotherapy (docetaxel or pemetrexed)



No. of patients still at risk

Time (Months)	0	2	4	6	8	10	12	14	16	18	20	22	24
LDK378 750 mg	115	78	57	39	33	19	13	7	5	2	2	0	0
Chemotherapy	116	26	11	8	5	2	1	0	0	0	0	0	0

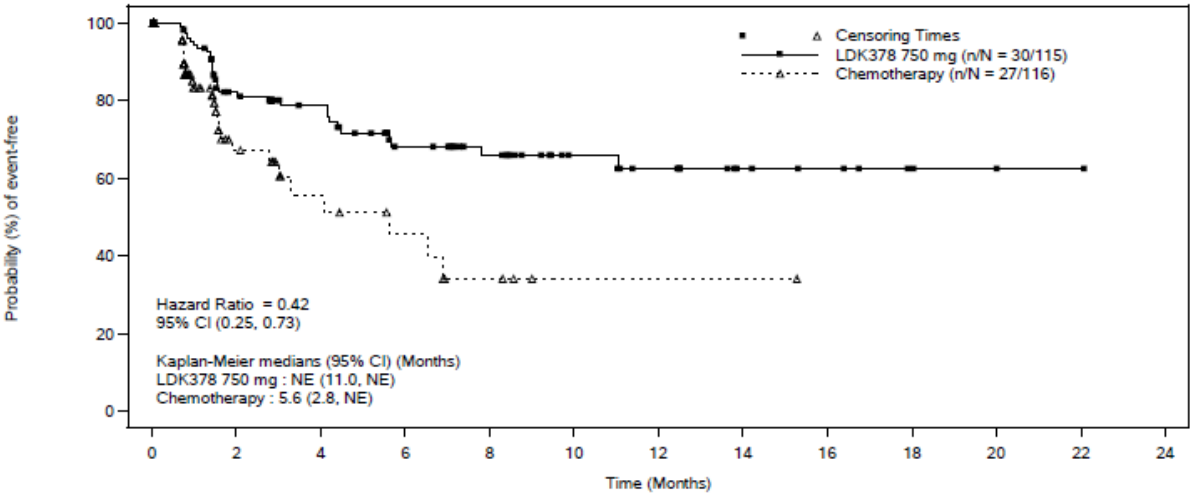
Figure 6: Kaplan-Meier curve for the time to first deterioration: cough (EORTC QLQ-LC13) – RCT, direct comparison: ceritinib versus chemotherapy (docetaxel or pemetrexed)



No. of patients still at risk

Time (Months)	0	2	4	6	8	10	12	14	16	18	20	22	24
LDK378 750 mg	115	82	65	49	38	28	21	12	9	5	5	2	0
Chemotherapy	116	15	6	6	5	2	2	0	0	0	0	0	0

Figure 7: Kaplan-Meier curve for the time to first deterioration: alopecia (EORTC QLQ-LC13) – RCT, direct comparison: ceritinib versus chemotherapy (docetaxel or pemetrexed)



No. of patients still at risk

Time (Months)	0	2	4	6	8	10	12	14	16	18	20	22	24
LDK378 750 mg	115	75	56	38	30	19	15	8	6	3	2	1	0
Chemotherapy	116	24	12	8	4	1	1	1	0	0	0	0	0

Figure 8: Kaplan-Meier curve for the time to first deterioration: sore mouth (EORTC QLQ-LC13) – RCT, direct comparison: ceritinib versus chemotherapy (docetaxel or pemetrexed)

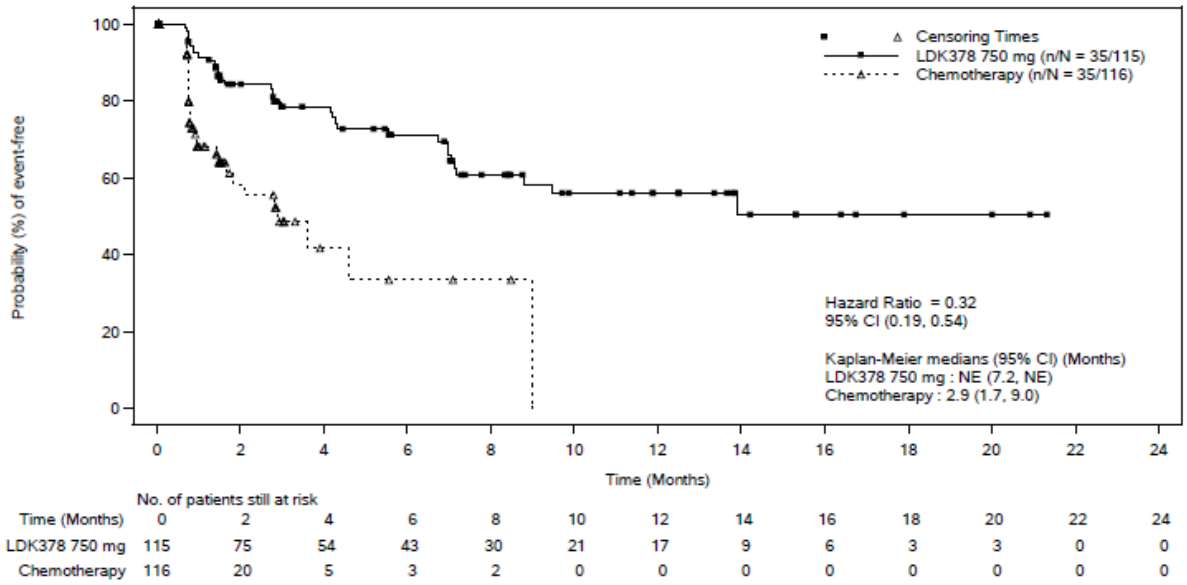


Figure 9: Kaplan-Meier curve for the time to first deterioration: peripheral neuropathy (EORTC QLQ-LC13) – RCT, direct comparison: ceritinib versus chemotherapy (docetaxel or pemetrexed)

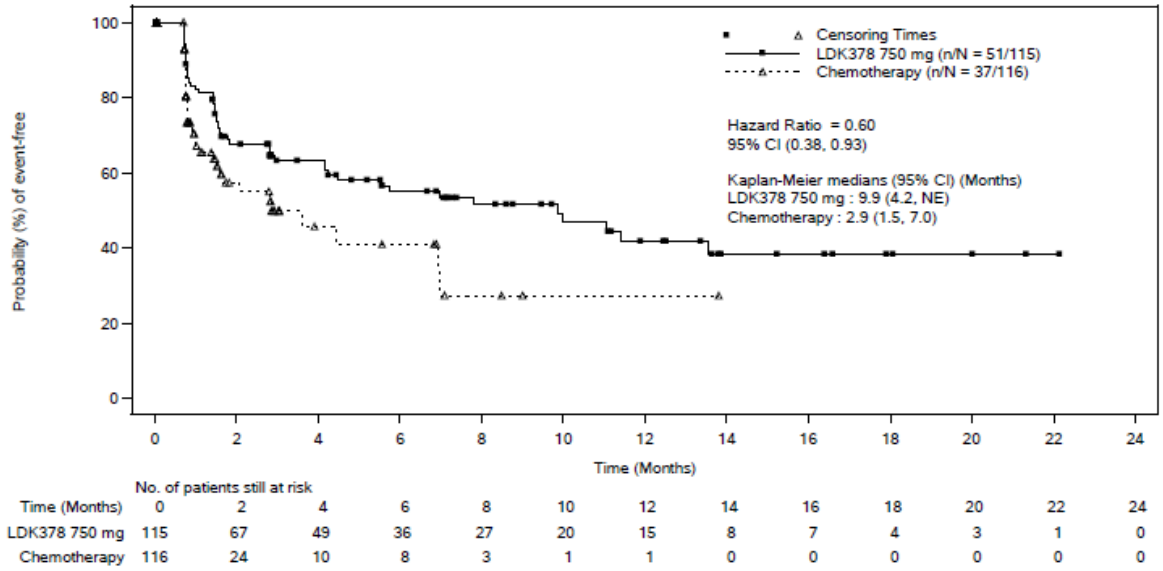
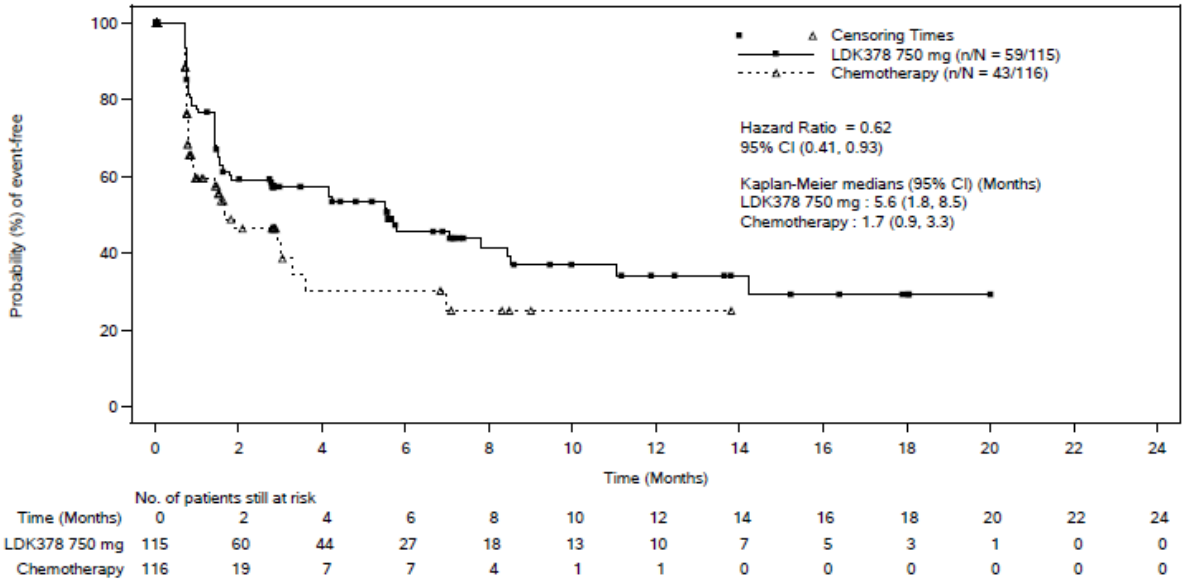


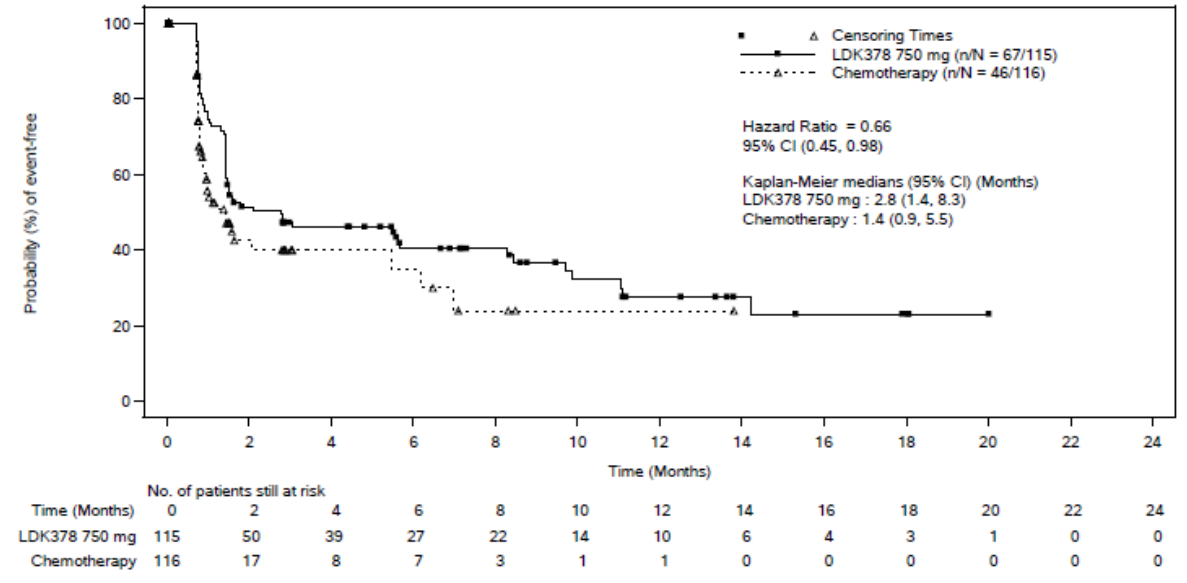
Figure 10: Kaplan-Meier curve for the time to first deterioration: physical functioning (EORTC QLQ-C30) – RCT, direct comparison: ceritinib versus chemotherapy (docetaxel or pemetrexed)



No. of patients still at risk

Time (Months)	0	2	4	6	8	10	12	14	16	18	20	22	24
LDK378 750 mg	115	60	44	27	18	13	10	7	5	3	1	0	0
Chemotherapy	116	19	7	7	4	1	1	0	0	0	0	0	0

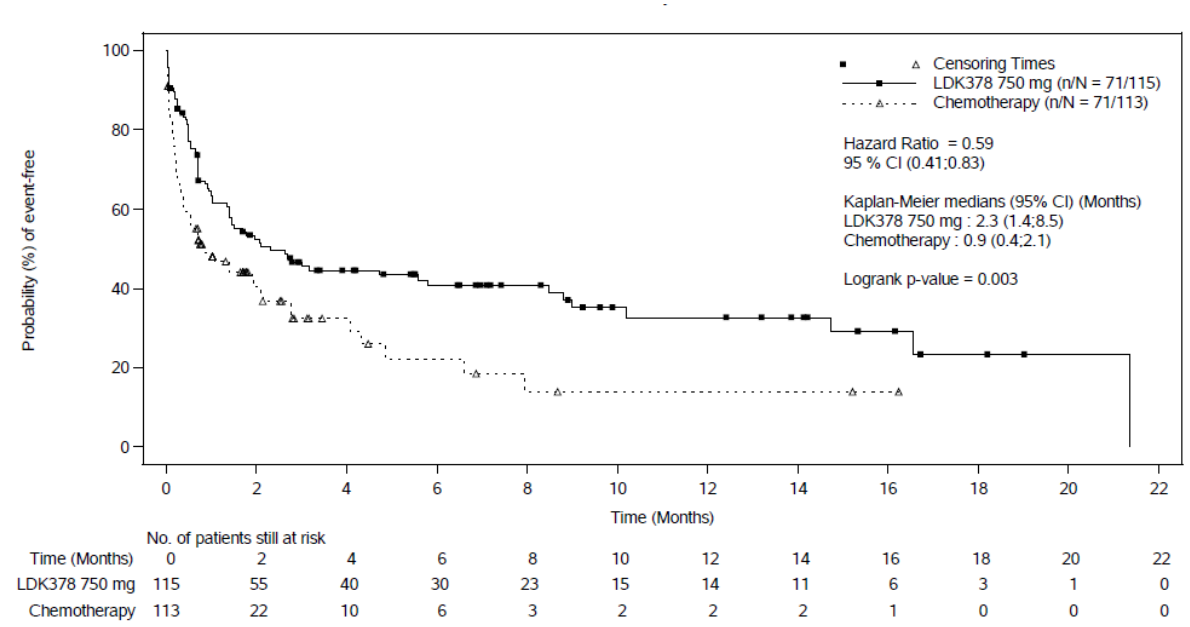
Figure 11: Kaplan-Meier curve for the time to first deterioration: role functioning (EORTC QLQ-C30) – RCT, direct comparison: ceritinib versus chemotherapy (docetaxel or pemetrexed)



No. of patients still at risk

Time (Months)	0	2	4	6	8	10	12	14	16	18	20	22	24
LDK378 750 mg	115	50	39	27	22	14	10	6	4	3	1	0	0
Chemotherapy	116	17	8	7	3	1	1	0	0	0	0	0	0

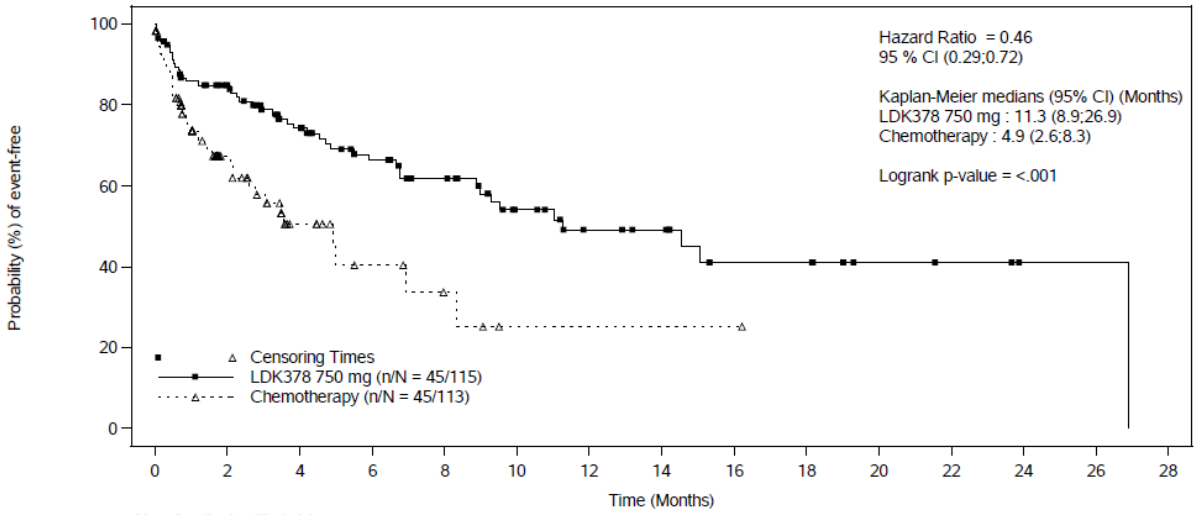
Figure 12: Kaplan-Meier curve for the time to first deterioration: social functioning (EORTC QLQ-C30) – RCT, direct comparison: ceritinib versus chemotherapy (docetaxel or pemetrexed)



No. of patients still at risk

Time (Months)	0	2	4	6	8	10	12	14	16	18	20	22
LDK378 750 mg	115	55	40	30	23	15	14	11	6	3	1	0
Chemotherapy	113	22	10	6	3	2	2	2	1	0	0	0

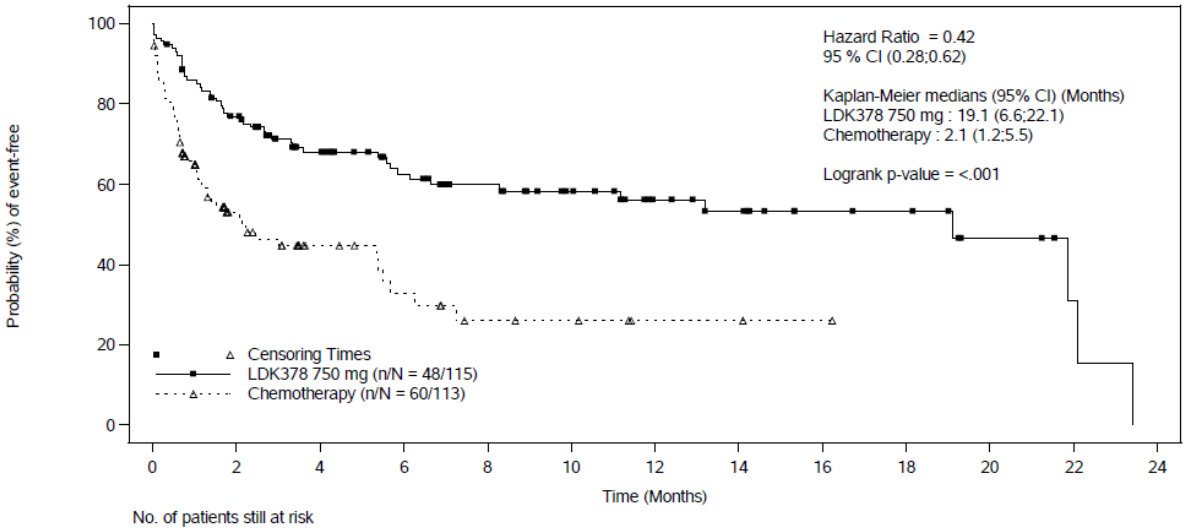
Figure 13: Kaplan-Meier curve for AEs for the SOC "general disorders and administration site conditions" – RCT, direct comparison: ceritinib versus chemotherapy (docetaxel or pemetrexed)



No. of patients still at risk

Time (Months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28
LDK378 750 mg	115	86	63	47	38	24	17	15	8	8	4	3	1	1	0
Chemotherapy	113	37	14	7	4	1	1	1	1	0	0	0	0	0	0

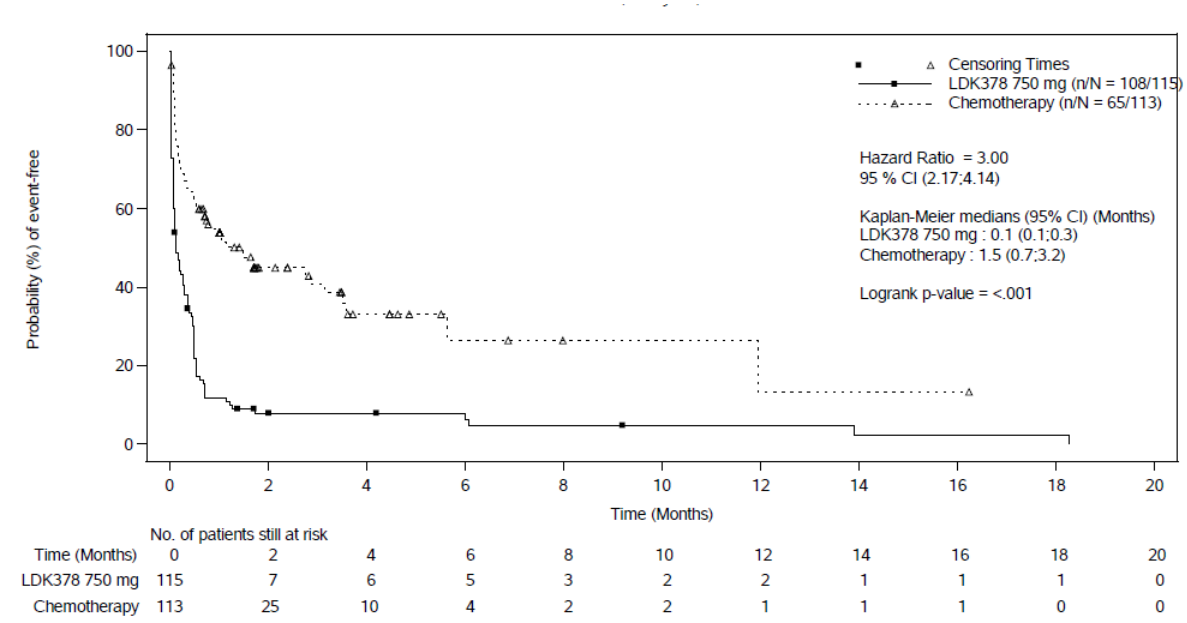
Figure 14: Kaplan-Meier curve for AEs for the SOC "nervous system disorders" – RCT, direct comparison: ceritinib versus chemotherapy (docetaxel or pemetrexed)



No. of patients still at risk

Time (Months)	0	2	4	6	8	10	12	14	16	18	20	22	24
LDK378 750 mg	115	84	61	46	38	30	21	17	11	10	5	2	0
Chemotherapy	113	33	17	11	6	5	2	2	1	0	0	0	0

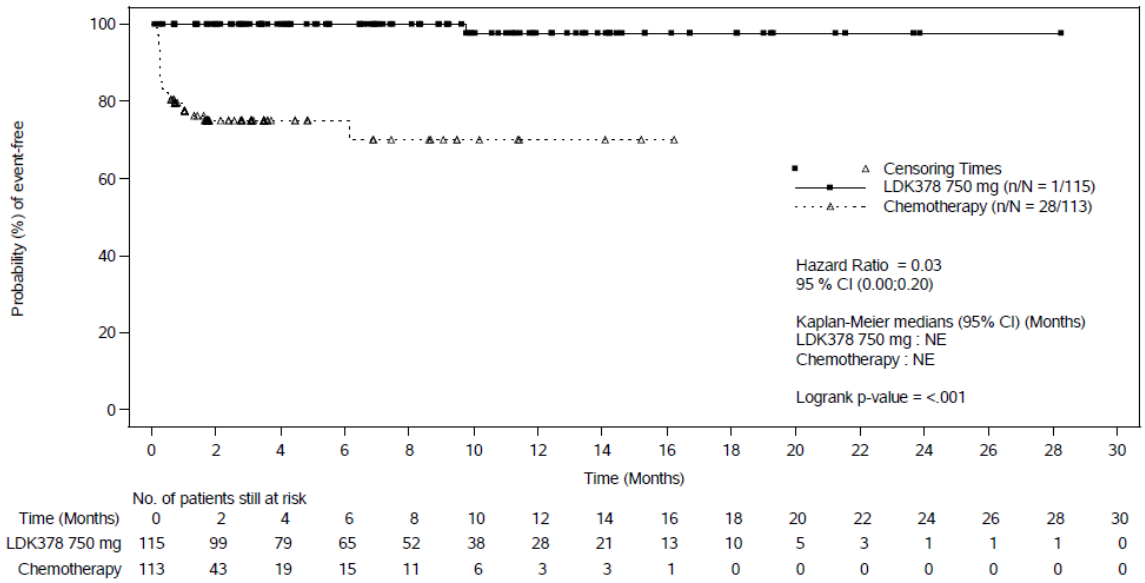
Figure 15: Kaplan-Meier curve for AEs for the SOC "respiratory, thoracic and mediastinal disorders" – RCT, direct comparison: ceritinib versus chemotherapy (docetaxel or pemetrexed)



No. of patients still at risk

Time (Months)	0	2	4	6	8	10	12	14	16	18	20
LDK378 750 mg	115	7	6	5	3	2	2	1	1	1	0
Chemotherapy	113	25	10	4	2	2	1	1	1	0	0

Figure 16: Kaplan-Meier curve for AEs for the SOC "gastrointestinal disorders" – RCT, direct comparison: ceritinib versus chemotherapy (docetaxel or pemetrexed)



No. of patients still at risk

Time (Months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30
LDK378 750 mg	115	99	79	65	52	38	28	21	13	10	5	3	1	1	1	0
Chemotherapy	113	43	19	15	11	6	3	3	1	0	0	0	0	0	0	0

Figure 17: Kaplan-Meier curve for severe AEs (CTCAE grade 3 or 4) for the SOC "blood and lymphatic system disorders" – RCT, direct comparison: ceritinib versus chemotherapy (docetaxel or pemetrexed)