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Brigatinib (non-small cell lung cancer) –

Addendum to Commission A20-42[1]

Addendum

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List of abbreviations

Abbreviation	Meaning
ALK	anaplastic lymphoma kinase
CNS	central nervous system
EORTC QLQ-LC13	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Lung Cancer 13
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
RECIST	Response Evaluation Criteria in Solid Tumours
SPC	Summary of Product Characteristics

1 Background

On 8 September 2020, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A20-42 (Brigatinib – Benefit assessment according to §35a Social Code Book V) [1].

In its dossier [2], the pharmaceutical company (hereinafter referred to as "the company") presented results of the ALTA-1L study on the comparison of brigatinib with crizotinib in patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously not treated with an ALK inhibitor. Besides other outcomes, the time to central nervous system (CNS) progression was investigated as an outcome in the ALTA-1L study. For reasons relating to content and methods, the respective data presented in the dossier were unsuitable for the derivation of an added benefit of brigatinib [1]. In the framework of the commenting procedure, the company presented further analyses on the outcome "time to CNS progression". In addition, the company presented data on subsequent therapies as well as analyses on the symptom scales of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Lung Cancer 13 (EORTC QLQ-LC13) [3,4].

The G-BA commissioned IQWiG with the assessment of the analyses on the EORTC QLQ-LC13, on subsequent antineoplastic therapies and on the outcome "time to CNS progression" presented in the commenting procedure, as well as the assessment of the corresponding subgroup analyses (specifically patients with and without brain metastases at baseline) under consideration of the information provided in the dossier.

In addition to the information provided in Modules 1 to 4 and the data subsequently submitted in the commenting procedure, it was necessary to use information from Module 5 of the company's dossier for the present addendum. This was information on study methods and study results. The respective information was included in the present addendum.

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

2 Assessment

2.1 Information on subsequent therapies

With the comments, the company subsequently submitted information on subsequent therapies. Table 1 shows the subsequent therapies of the patients in the ALTA-1L study.

Table 1: Information on subsequent antineoplastic therapies – RCT, direct comparison: brigatinib vs. crizotinib

Study	**Patients with subsequent therapy n (%)**	
Drug class **Drug**	**Brigatinib** **N = 137**	**Crizotinib** **N = 138**
ALTA-1L (data cut-off 28 June 2019)		
Total	ND	ND
Surgery	0 (0)	2 (1.5)
Radiotherapy	1 (0.7)	10 (7.3)
Systemic therapy	35 (25.7)	97 (70.8)
ALK inhibitor	31 (22.8)	93 (67.9)
Alectinib	10 (7.4)	24 (17.5)
Brigatinib	1 (0.7)	73 (53.3)
Ceritinib	4 (2.9)	5 (3.6)
Crizotinib	11 (8.1)	5 (3.6)
Lorlatinib	14 (10.3)	12 (8.8)
Chemotherapy	15 (11.0)	16 (11.7)
Carboplatin	7 (5.1)	10 (7.3)
Cisplatin	6 (4.4)	4 (2.9)
Docetaxel	3 (2.2)	0 (0)
Erlotinib	1 (0.7)	0 (0)
Etoposide	1 (0.7)	0 (0)
Gemcitabine	2 (1.5)	4 (2.9)
Paclitaxel	1 (0.7)	1 (0.7)
Pemetrexed	11 (8.1)	11 (8.0)
Vinorelbine	0 (0)	1 (0.7)

n: number of patients with subsequent therapy; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; vs.: versus

The most common subsequent therapies in the brigatinib arm were lorlatinib, crizotinib and pemetrexed. The most common subsequent therapies in the crizotinib arm were brigatinib, alectinib and lorlatinib. The treatment of patients with brigatinib after previous treatment with crizotinib is approved according to the Summary of Product Characteristics (SPC) [5] and constitutes a therapeutic option according to guidelines [6,7].

2.2 Analyses of the EORTC QLQ-LC13 symptom scales

In accordance with the protocol change of 21 September 2016, data on symptoms were also recorded with the EORTC QLQ-LC13 instrument in the ALTA-1L study. This recording started about 4 months after inclusion of the first patient. At this time point, 134 of the total of 275 patients (48.9%) had already been randomized. In Module 4 B of the dossier, the company did not present any results for the EORTC QLQ-LC13 and justified this with the fact that the responses, in relation to the total study population, were markedly below 70% and that therefore a relevant proportion of the study population was not included in the recording. As explained in the dossier assessment, the 141 patients who were included after the introduction of the EORTC QLQ-LC13 were a random and representative subpopulation, and no additional aspects against the usability of the data resulted from the company's information in the dossier [1]. With the comments, the company presented the analyses of the EORTC QLQ-LC13.

Risk of bias

The risk of bias of the results was rated as high. The reasons for this were the lack of blinding in subjective recording of outcomes as well as the strong decrease in response rates to questionnaires in the course of the study that differed between the treatment arms. Furthermore, there was selective follow-up observation of the patients in the control arm. After progression, the patients in the crizotinib arm could receive brigatinib as subsequent therapy at the physician's discretion, and observation was continued also during this treatment. For patients who did not receive brigatinib as subsequent therapy, the observation ended 30 days after the last dose of the study medication.

Results

Morbidity

Symptoms (EORTC QLQ-LC13 – symptom scales)

Table 2 shows the results of the comparison of brigatinib with crizotinib in patients with ALK-positive advanced NSCLC previously not treated with an ALK inhibitor for the EORTC QLQ-LC13 symptom scales.

Table 2: Results (morbidity, EORTC QLQ-LC13) – RCT, direct comparison: brigatinib vs. crizotinib

Study Outcome category Outcome	Brigatinib N[a] Median time to event in months [95% CI] Patients with event n (%)	Crizotinib N[a] Median time to event in months [95% CI] Patients with event n (%)	Brigatinib vs. crizotinib HR [95% CI]; p-value[b]
ALTA-1L (data cut-off 28 June 2019)			
Morbidity			
Symptoms			
EORTC QLQ-LC13 (symptom scales) – time to first deterioration by ≥ 10 points			
Dyspnoea	63 24.0 [7.4; NA] 27 (42.9)[c]	78 8.3 [4.5; 19.3] 42 (53.8)[c]	0.64 [0.39; 1.05]; 0.076
Pain (chest)	63 NA [15.8; NA] 23 (36.5)[c]	78 13.9 [7.7; NA] 31 (39.7)[c]	0.77 [0.44; 1.32]; 0.307
Pain (arm/shoulder)	63 NA [13.9; NA] 21 (33.3)[c]	78 12.1 [6.5; 16.7] 38 (48.7)[c]	0.51 [0.30; 0.88]; 0.011
Pain (other)	63 15.9 [2.9; NA] 29 (46.0)[c]	78 11.5 [4.7; 27.8] 37 (47.4)[c]	0.88 [0.54; 1.45]; 0.620
Cough	63 NA [7.4; NA] 25 (39.7)[c]	78 24.2 [11.8; NA] 29 (37.2)[c]	0.97 [0.57; 1.67]; 0.971
Haemoptysis	63 NA 8 (12.7)[c]	78 NA 6 (7.7)[c]	1.45 [0.50; 4.20]; 0.507
Alopecia	63 NA [18.5; NA] 19 (30.2)[c]	78 NA [9.5; NA] 25 (32.1)[c]	0.76 [0.42; 1.39]; 0.452
Dysphagia	63 24.9 [12.9; NA] 26 (41.3)[c]	78 22.1 [13.9; NA] 27 (34.6)[c]	0.98 [0.57; 1.69]; 0.873
Sore mouth	63 8.3 [3.1; NA] 32 (50.8)[c]	78 14.8 [5.5; NA] 35 (44.9)[c]	1.14 [0.70; 1.84]; 0.624
Peripheral neuropathy	63 NA [8.3; NA] 24 (38.1)[c]	78 7.4 [3.7; 14.8] 43 (55.1)[c]	0.53 [0.32; 0.89]; 0.017

a. The recording of the EORTC QLQ-LC13 started about 4 months after inclusion of the first patient. At this time point, 134 of the total of 275 patients (48.9%) had already been randomized.
b. HR and 95% CI calculated using Cox regression model with the stratification parameters (presence of CNS metastases at baseline and prior chemotherapy for the treatment of advanced or metastatic disease) as covariates; p-value calculated using log-rank test, stratified by the stratification parameters mentioned above.
c. Institute's calculation.

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

A statistically significant difference in favour of brigatinib in comparison with crizotinib was shown for each of the scales "pain (arm/shoulder)" and "peripheral neuropathy". This resulted in a hint of an added benefit of brigatinib in comparison with crizotinib for each of the 2 outcomes.

No statistically significant difference between the treatment groups was shown for any of the following scales: dyspnoea, pain (chest), pain (other), cough, haemoptysis, alopecia, dysphagia and sore mouth. This resulted in no hint of an added benefit of brigatinib in comparison with crizotinib for each of these outcomes; an added benefit is therefore not proven.

The Kaplan-Meier curves for the EORTC QLQ-LC13 symptom scales are presented in Appendix A.

Subgroups

Concurring with the approach used in the benefit assessment, the following subgroup characteristics were used for the present addendum: sex (female versus male), age (< 65 years versus ≥ 65 years), and brain metastases at baseline (yes versus no). No statistically significant interaction between treatment and the subgroup characteristics used was shown for any of the EORTC QLQ-LC13 symptom scales.

2.3 Analyses on the outcome "time to CNS progression"

In its dossier, the company had presented analyses on the outcome "time to CNS progression", assessed by a blinded independent committee based on Response Evaluation Criteria in Solid Tumours (RECIST). CNS progression was defined by progression of brain metastases already present at baseline and/or development of new brain metastases. Dossier assessment A20-42 described that the underlying RECIST criteria did not guarantee the patient relevance of the outcome [1]. It also explained that, regardless of the patient relevance, the analyses presented by the company were unsuitable also for methodological reasons, as patients were censored after non-CNS progression [1]. Hence, the analyses presented by the company in the dossier only considered part of the CNS progressions, i.e. only those progressions that had occurred before non-CNS disease progression. In the commenting procedure, the company subsequently submitted analyses in which patients were not censored after non-CNS progression [3,4]. In accordance with the study protocol, however, follow-up observation of CNS progression was only conducted until the last dose of the study medication, until disease progression or the start of a new systemic anticancer therapy. Hence, irrespective of the analysis, CNS progression was not completely recorded due to the design of the ALTA-1L study.

Thus, as a result of the analyses subsequently submitted by the company, possible CNS progression also after non-CNS progression in certain situations could be considered in the analysis only for a selective proportion of the randomized patients. According to the information provided by the company, this concerned the following patients:

- patients who could continue their treatment at the investigator's discretion after systemic progression under brigatinib, and
- patients of both treatment arms who continued treatment until notification of systemic progression (in accordance with blinding independent committee) if the investigator had not determined progression.

In addition, in accordance with the study protocol, patients in the crizotinib arm who, after disease progression, received brigatinib as subsequent therapy at the investigator's discretion, also had follow-up observation until the last dose of brigatinib. According to the information in the additional analyses in the framework of the comments [4], the follow-up observation of these patients was not completely taken into account in the analysis subsequently submitted, as these patients were censored at the first dose of brigatinib.

Overall, the analyses subsequently submitted also comprise only part of the CNS progression events, as these had no systematic follow-up observation after the end of therapy.

Regardless of the incomplete recording of CNS progression events, their assessment was based exclusively on imaging techniques and did not consider any symptoms noticeable by the patients. As described in the dossier assessment of brigatinib, the operationalization of the outcome is therefore not directly patient-relevant. The outcome "time to CNS progression" was therefore not used for the derivation of an added benefit. In addition, patient-relevant outcomes on symptoms and health-related quality of life reported by the patient are available in the ALTA-1L study.

Results

The analyses of the time to CNS progression provided by the company in the dossier and in the comments are presented in Table 3. The corresponding Kaplan-Meier curves and cumulative incidence curves are presented in Appendix A.

Table 3: Results (morbidity, time to CNS progression) – RCT, direct comparison: brigatinib vs. crizotinib

Study Outcome category Outcome	Brigatinib N	Brigatinib Median time to event in months [95% CI] Patients with event n (%)	Crizotinib N	Crizotinib Median time to event in months [95% CI] Patients with event n (%)	Brigatinib vs. crizotinib HR [95% CI]; p-value[a]
ALTA-1L (data cut-off 28 June 2019)					
Morbidity					
Time to CNS progression					
With complete follow-up observation of CNS progression				No data	
Without censoring due to non-CNS progression[b], incomplete observation of CNS progression[c]	137	32.29 [ND] 30 (21.9)	138	NA 42 (30.4)	0.34 [0.21; 0.56]; < 0.001
With censoring due to non-CNS progression, incomplete observation of CNS progression[c]	137	ND 22 (16.1)	138	ND 36 (26.1)	0.30 [0.17; 0.53][d]; < 0.001

a. HR and 95% CI calculated using Cox regression model with the stratification parameters (presence of CNS metastases at baseline and prior chemotherapy for the treatment of advanced or metastatic disease) as covariates; p-value calculated using log-rank test, stratified by the stratification parameters mentioned above.
b. For the following patients, data regarding CNS progression were considered in the analysis also after non-CNS progression: 1) patients who could continue their treatment at the investigator's discretion after systemic progression under brigatinib, 2) patients of both treatment arms who continued treatment until notification of systemic progression (in accordance with blinding independent committee) if the investigator had not determined progression, and 3) patients in the crizotinib arm who, after disease progression, received brigatinib as subsequent therapy at the investigator's discretion, but only until the first dose of brigatinib.
c. In accordance with the study protocol, systematic follow-up observation of CNS progression was only conducted until the last dose of the study medication, until disease progression or the start of a new systemic anticancer therapy.
d. Competing risk analysis with non-CNS progression, CNS progression and death as competing events.

CI: confidence interval; CNS: central nervous system; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; ND: no data; RCT: randomized controlled trial; vs.: versus

Both analyses (with and without censoring due to non-CNS progression) showed statistically significant differences between the treatment groups in favour of brigatinib for the outcome "time to CNS progression".

Subgroups

The company did not present any subgroup analyses for the analyses on CNS progression subsequently submitted with the comments. Subgroup analyses by sex, age, and brain

metastases at baseline are therefore only available for the original analysis with censoring due to non-CNS progression [8]. These analyses showed no statistically significant interaction between treatment and the subgroup characteristics used in the assessment for the outcome "time to CNS progression". Table 4 presents the subgroup results for the subgroup characteristic "brain metastases at baseline" irrespective of the missing statistically significant interaction. The cumulative incidence curves for the subgroup analysis are presented in Appendix A.

Table 4: Subgroups (time to CNS progression) – RCT, direct comparison: brigatinib vs. crizotinib

Study Outcome Characteristic Subgroup	Brigatinib N	Brigatinib Median time to event in months [95% CI] Patients with event n (%)	Crizotinib N	Crizotinib Median time to event in months [95% CI] Patients with event n (%)	Brigatinib vs. crizotinib HR [95% CI][a]	 p-value[b]
ALTA-1L (data cut-off 28 June 2019)						
Time to CNS progression						
With complete follow-up observation of CNS progression				No data		
Without censoring due to non-CNS progression, incomplete observation of CNS progression[c]				No data		
With censoring due to non-CNS progression, incomplete observation of CNS progression[c]						
Brain metastases at baseline						
Yes	41	ND 17 (41.5)	40	ND 20 (50.0)	0.27 [0.13; 0.57][d]	< 0.001
No	96	ND 5 (5.2)	98	ND 16 (16.3)	0.26 [0.09; 0.71][d]	0.007
Total					Interaction:	0.792[e]

a. HR and 95% CI from a Cox proportional hazards model with stratification parameters as covariates.
b. p-value for the individual subgroups from a stratified log-rank test; stratification variables: presence of CNS metastases at baseline and prior chemotherapy for the treatment of advanced or metastatic disease.
c. In accordance with the study protocol, systematic follow-up observation of CNS progression was only conducted until the last dose of the study medication, until disease progression or the start of a new systemic anticancer therapy.
d. Competing risk analysis with non-CNS progression, CNS progression and death as competing events.
e. p-value for the interaction: calculated using a Cox proportional hazards model.

CI: confidence interval; CNS: central nervous system; HR: hazard ratio; n: number of patients with event; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; vs.: versus

2.4 Probability and extent of added benefit

Table 5 shows the probability and the extent of added benefit for the EORTC QLQ-LC13 symptom scales under consideration of the data subsequently submitted.

The company's dossier and the analyses subsequently submitted in the comments did not provide any information on the assignment of the severity grade for the outcomes (symptom scales) of the EORTC QLQ-LC13. Therefore, the outcomes were assigned to the outcome category of non-serious/non-severe symptoms/late complications.

Table 5: Extent of added benefit for the symptom scales of the EORTC QLQ-LC13: brigatinib vs. crizotinib

Outcome category **Outcome**	**Brigatinib vs. crizotinib** **median time to event (months)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Morbidity		
Symptoms (EORTC QLQ-LC13 symptom scales – deterioration by ≥ 10 points)		
Dyspnoea	Median: 24.0 vs. 8.3 HR: 0.64 [0.39; 1.05]; p = 0.076	Lesser benefit/added benefit not proven
Pain (chest)	Median: NA vs. 13.9 HR: 0.77 [0.44; 1.32]; p = 0.307	Lesser benefit/added benefit not proven
Pain (arm/shoulder)	Median: NA vs. 12.1 HR: 0.51 [0.30; 0.88]; 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"
Pain (other)	Median: 15.90 vs. 11.5 HR: 0.88 [0.54; 1.45]; p = 0.620	Lesser benefit/added benefit not proven
Cough	Median: NA vs. 24.2 HR: 0.97 [0.57; 1.67]; p = 0.971	Lesser benefit/added benefit not proven
Haemoptysis	Median: NA vs. NA HR: 1.45 [0.50; 4.20]; p = 0.507	Lesser benefit/added benefit not proven
Alopecia	Median: NA vs. NA HR: 0.76 [0.42; 1.39]; p = 0.452	Lesser benefit/added benefit not proven
Dysphagia	Median: 24.9 vs. 22.1 HR: 0.98 [0.57; 1.69]; p = 0.873	Lesser benefit/added benefit not proven
Sore mouth	Median: 8.3 vs. 14.8 HR: 1.14 [0.70; 1.84]; p = 0.624	Lesser benefit/added benefit not proven
Peripheral neuropathy	Median: NA vs. 7.4 0.53 [0.32; 0.89]; p = 0.017 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $0.80 \leq CI_u < 0.90$ added benefit, extent: "minor"

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u).

CI: confidence interval; CI_u: upper limit of confidence interval; EORTC QLQ-LC13: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Lung Cancer 13; HR: hazard ratio; NA: not achieved; vs.: versus

2.5 Overall conclusion on added benefit

Table 6 summarizes the results considered in the overall conclusion about the extent of added benefit.

Table 6: Positive and negative effects from the assessment of brigatinib in comparison with crizotinib

Positive effects	**Negative effects**
Mortality ▪ Overall survival ▫ brain metastases at baseline (yes) indication of an added benefit – extent: "minor"	–
Non-serious/non-severe symptoms/late complications ▪ Nausea and vomiting, constipation, **pain (arm/shoulder), peripheral neuropathy**: hint of an added benefit – extent: **"minor" (pain [arm/shoulder], peripheral neuropathy)** and "considerable" (nausea and vomiting, constipation) ▪ Pain: ▫ sex (women) hint of an added benefit – extent: "minor"	–
Health-related quality of life ▪ Global health status and emotional functioning: hint of an added benefit – extent: "minor" (global health status) and "considerable" (emotional functioning) ▪ Role functioning, social functioning ▫ sex (women) hint of an added benefit – extent: "considerable" (role functioning) and "major" (social functioning)	–
Non-serious/non-severe side effects ▪ Eye disorders (SOC, AEs), gastrointestinal disorders (SOC, AEs), peripheral oedema (PT, AEs): hint of lesser harm – extent: "considerable" Serious/severe side effects ▪ SAEs ▫ age (< 65 years): hint of lesser harm – extent: "minor"	Non-serious/non-severe side effects ▪ Skin and subcutaneous tissue disorders (SOC, AEs) ▫ age (≥ 65 years): hint of greater harm – extent "considerable" Serious/severe side effects ▪ Creatine phosphokinase increased (PT, severe AEs [CTCAE grade ≥ 3]): indication of greater harm – extent: "major" ▪ Hypertension (PT, severe AEs [CTCAE grade ≥ 3]): hint of greater harm – extent: "major"
The results presented in **bold** result from the analyses subsequently submitted by the company with its written comments. AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; PT: Preferred Term; SAE: serious adverse event; SOC: System Organ Class	

Under consideration of the data subsequently submitted in the comments, there are 2 additional positive effects in comparison with dossier assessment A20-42 in the category of non-serious/severe symptoms/late complications for the outcomes "pain (arm/shoulder)" and "peripheral neuropathy", each with minor extent. As already described in dossier assessment

A20-42, there are both positive and negative effects of brigatinib in comparison with crizotinib. The positive effect in overall survival was only shown in patients with brain metastases at baseline. For this reason, positive and negative effects are assessed separately for patients with and without brain metastases at baseline.

Overall, the positive effects still outweigh the negative effects, and, as was the case already in dossier assessment A20-42, there is an indication of a minor added benefit of brigatinib in comparison with crizotinib for patients with brain metastases at baseline, and a hint of a minor added benefit for patients without brain metastases at baseline.

2.6 Summary

The data subsequently submitted by the company in the commenting procedure have not changed the conclusion on the added benefit of brigatinib from dossier assessment A20-42.

The following Table 7 shows the result of the benefit assessment of brigatinib under consideration of dossier assessment A20-42 and the present addendum.

Table 7: Brigatinib – probability and extent of added benefit

Subindication	**ACT**[a]	**Probability and extent of added benefit**
Adult patients with ALK-positive advanced NSCLC previously not treated with an ALK inhibitor	Alectinib or **crizotinib**	▪ Patients with brain metastases[b]: indication of a minor added benefit ▪ Patients without brain metastases[b]: hint of a minor added benefit
a. Presentation of the ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**. b. Referring to the start of treatment. ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer		

The G-BA decides on the added benefit.

3 References

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Appendix A – Kaplan-Meier curves, cumulative incidence curves

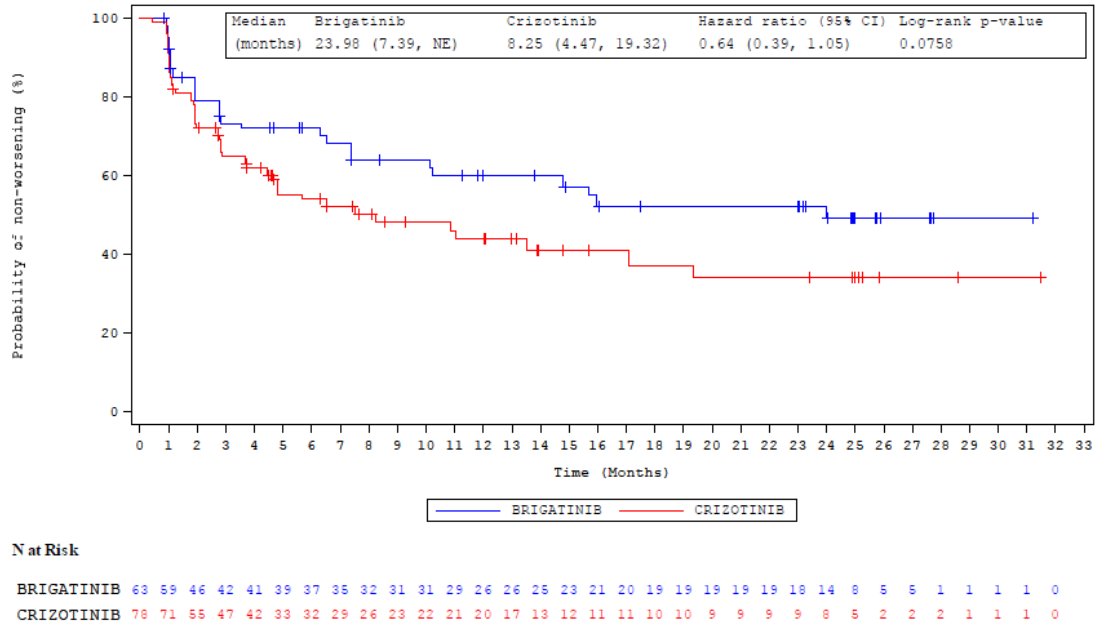


Figure 1: Kaplan-Meier curves on the outcome "dyspnoea" (EORTC QLQ-LC13), deterioration by ≥ 10 points, total population (study ALTA-1L, data cut-off 28 June 2019)

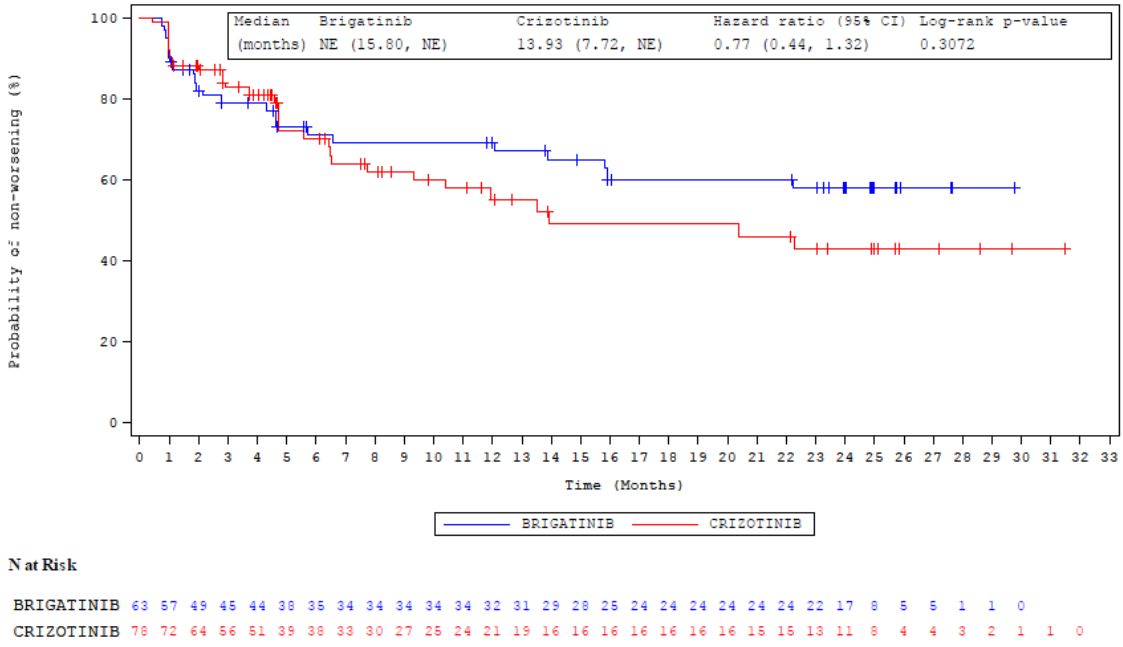


Figure 2: Kaplan-Meier curves on the outcome "pain (chest)" (EORTC QLQ-LC13), deterioration by ≥ 10 points, total population (study ALTA-1L, data cut-off 28 June 2019)

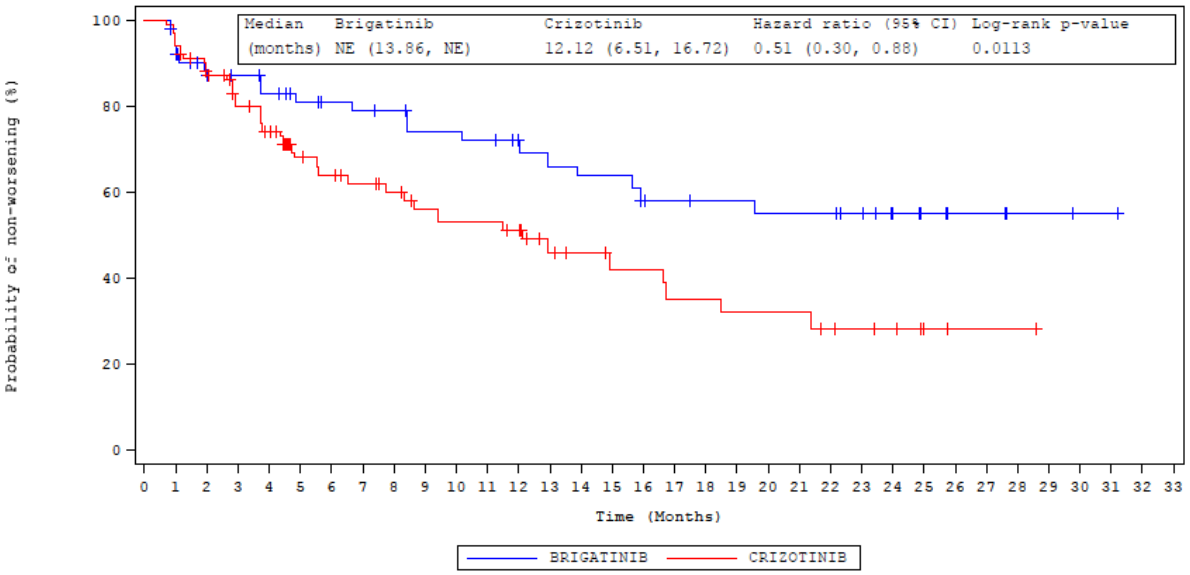


Figure 3: Kaplan-Meier curves on the outcome "pain (arm/shoulder)" (EORTC QLQ-LC13), deterioration by ≥ 10 points, total population (study ALTA-1L, data cut-off 28 June 2019)

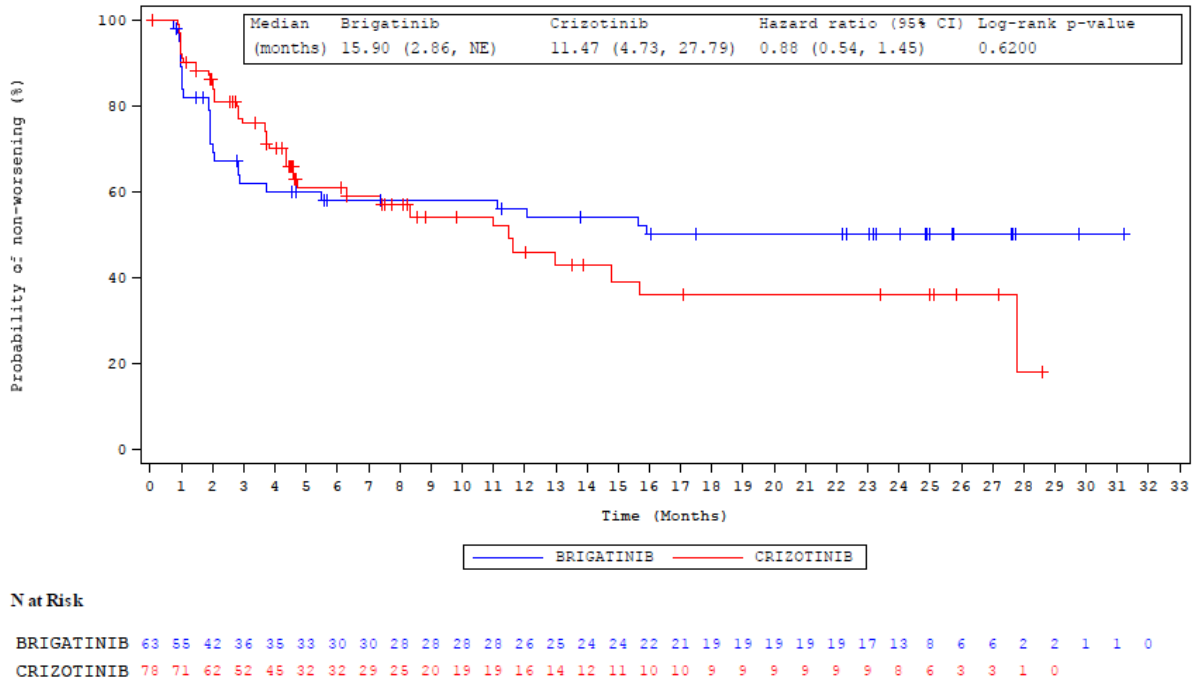


Figure 4: Kaplan-Meier curves on the outcome "pain (other)" (EORTC QLQ-LC13), deterioration by ≥ 10 points, total population (study ALTA-1L, data cut-off 28 June 2019)

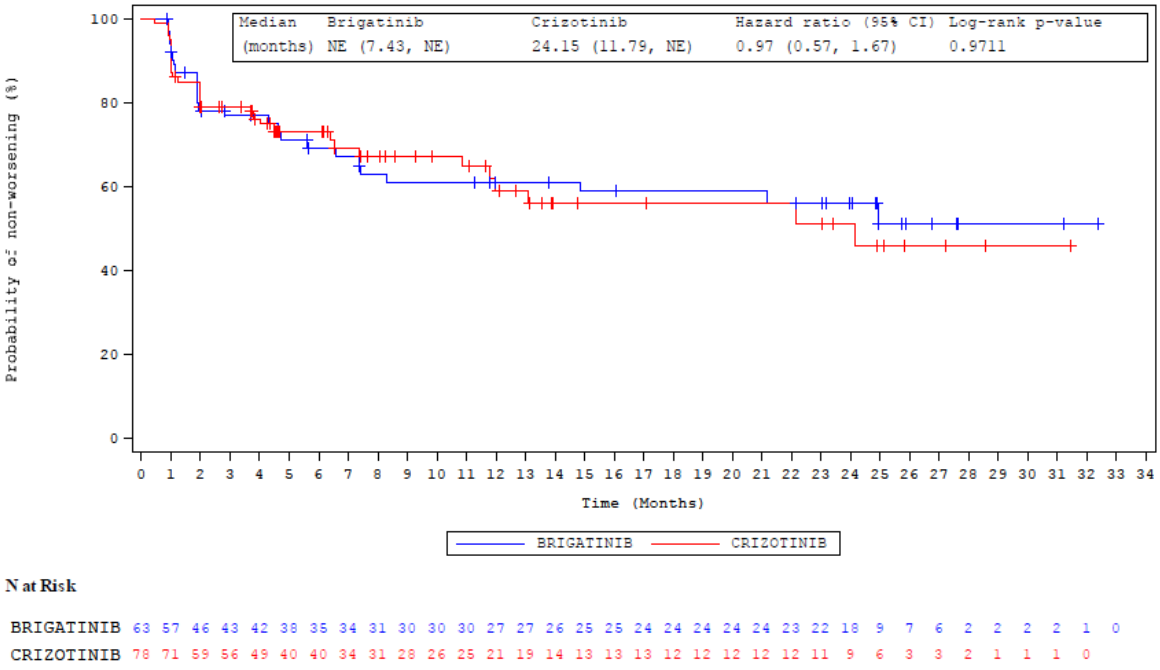


Figure 5: Kaplan-Meier curves on the outcome "cough" (EORTC QLQ-LC13), deterioration by ≥ 10 points, total population (study ALTA-1L, data cut-off 28 June 2019)

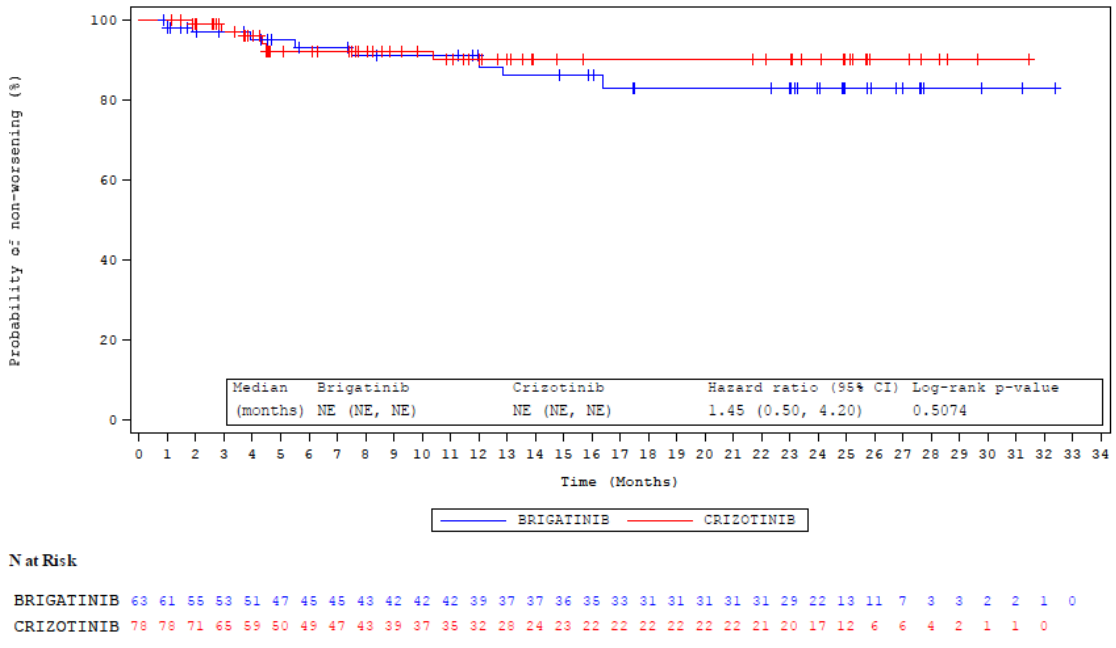
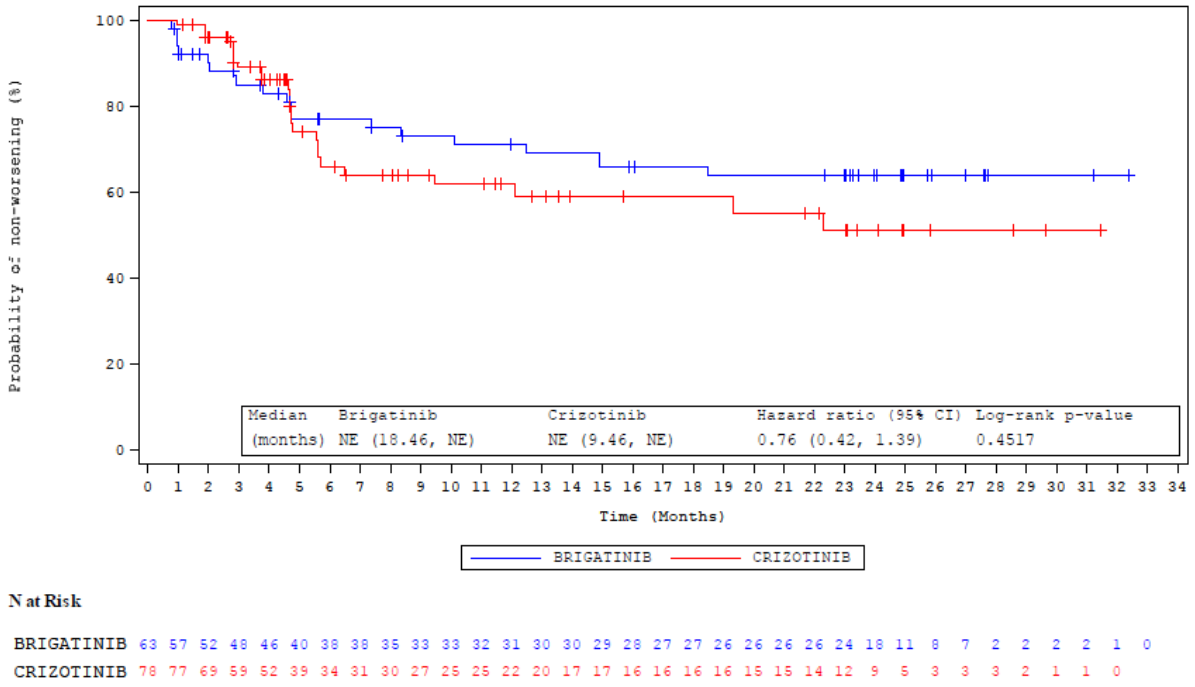


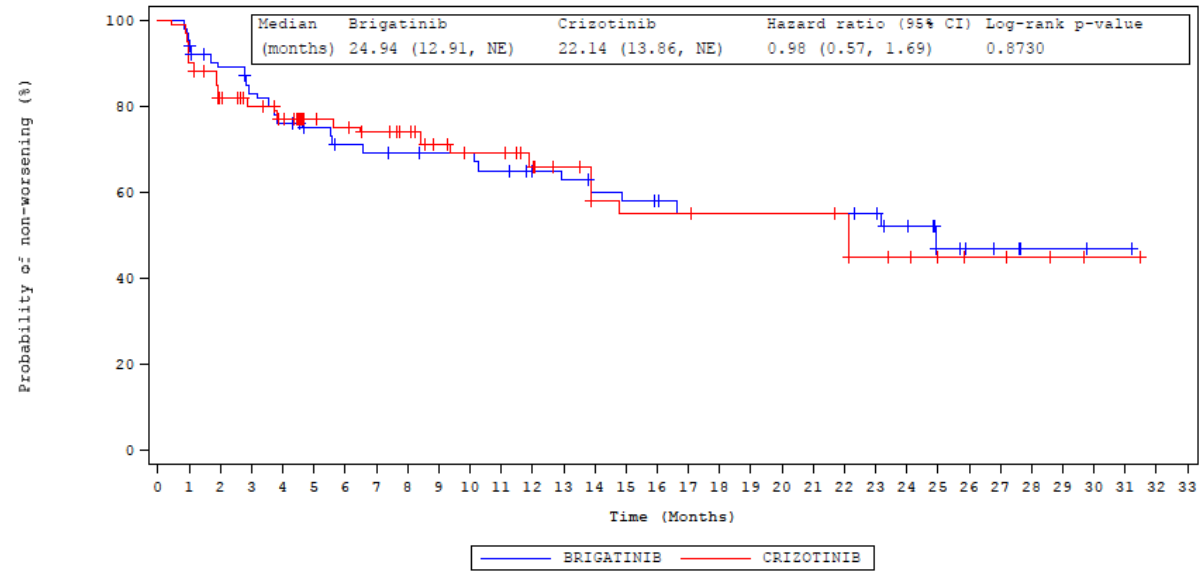
Figure 6: Kaplan-Meier curves on the outcome "haemoptysis" (EORTC QLQ-LC13), deterioration by ≥ 10 points, total population (study ALTA-1L, data cut-off 28 June 2019)



N at Risk

BRIGATINIB	63	57	52	48	46	40	38	38	35	33	33	32	31	30	30	29	28	27	27	26	26	26	26	24	18	11	8	7	2	2	2	2	1	0
CRIZOTINIB	78	77	69	59	52	39	34	31	30	27	25	25	22	20	17	17	16	16	16	16	15	15	14	12	9	5	3	3	3	2	1	1	0	

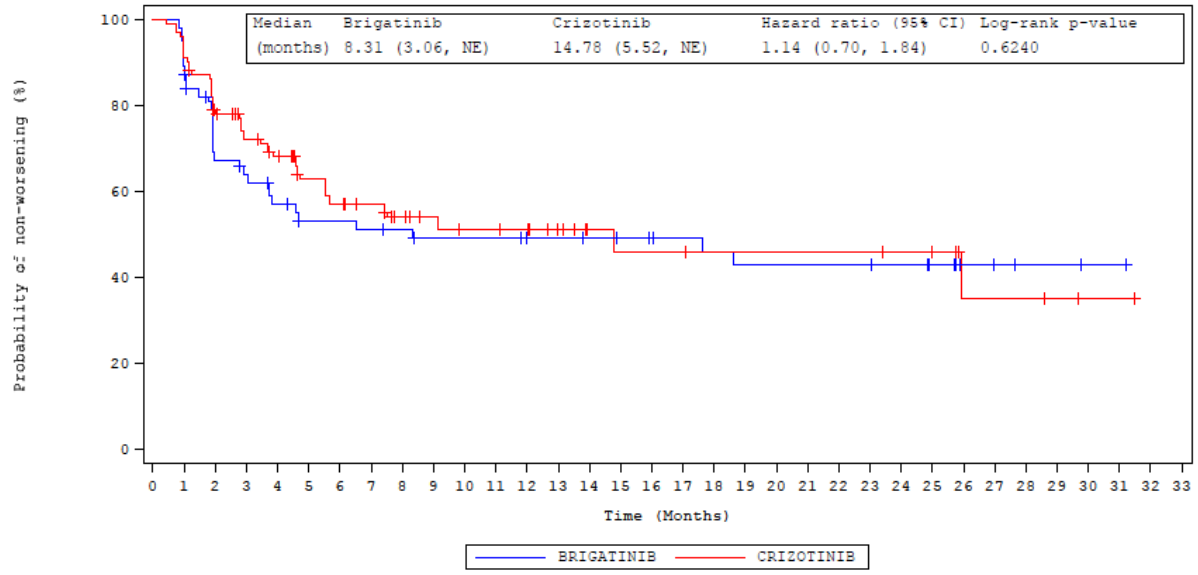
Figure 7: Kaplan-Meier curves on the outcome “alopecia” (EORTC QLQ-LC13), deterioration by ≥ 10 points, total population (study ALTA-1L, data cut-off 28 June 2019)



N at Risk

BRIGATINIB	63	60	52	48	44	40	37	36	34	33	33	31	28	27	25	24	23	21	21	21	21	21	21	20	15	8	6	5	2	2	1	1	0	
CRIZOTINIB	78	70	60	55	50	42	40	37	34	29	26	26	22	19	15	14	14	14	13	13	13	13	12	9	8	5	4	4	3	2	1	1	0	

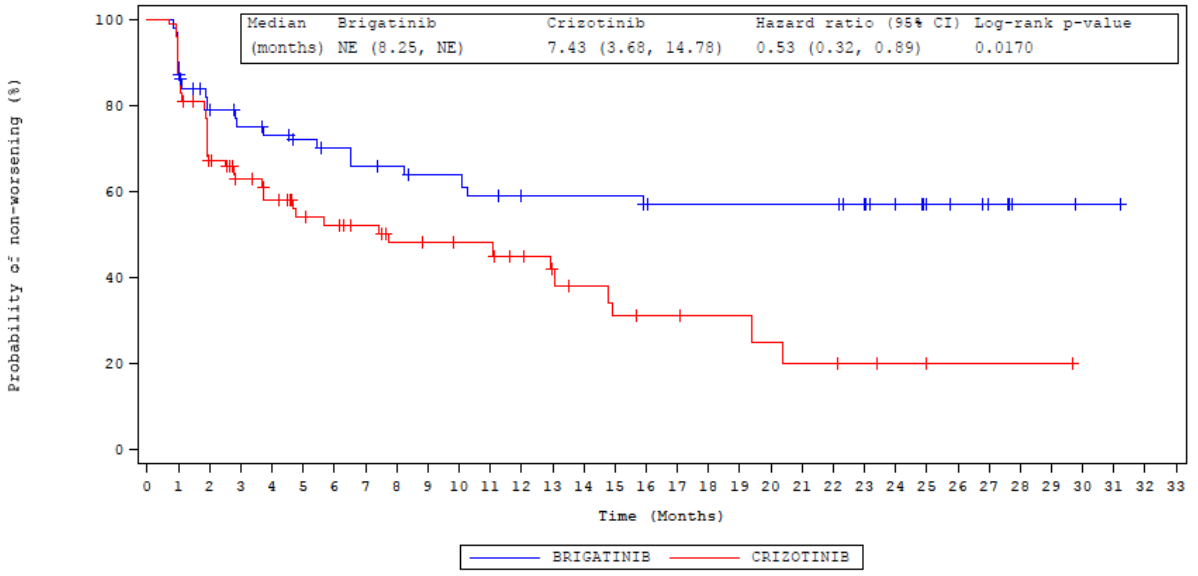
Figure 8: Kaplan-Meier curves on the outcome “dysphagia” (EORTC QLQ-LC13), deterioration by ≥ 10 points, total population (study ALTA-1L, data cut-off 28 June 2019)



N at Risk

BRIGATINIB	63	56	40	37	32	27	27	26	25	23	23	23	21	21	20	19	18	17	16	15	15	15	15	15	12	8	5	4	2	2	1	1	0
CRIZOTINIB	78	71	59	50	44	36	33	30	25	22	20	20	19	15	11	10	10	10	9	9	9	9	9	8	7	3	3	3	2	1	1	0	

Figure 9: Kaplan-Meier curves on the outcome "sore mouth" (EORTC QLQ-LC13), deterioration by ≥ 10 points, total population (study ALTA-1L, data cut-off 28 June 2019)



N at Risk

BRIGATINIB	63	57	46	42	40	37	35	33	31	29	29	27	25	25	25	25	23	22	22	22	22	22	22	19	15	11	10	6	2	2	1	1	0
CRIZOTINIB	78	68	48	40	35	29	27	24	20	19	18	18	15	12	10	8	7	7	6	6	5	4	4	3	2	1	1	1	1	1	0		

Figure 10: Kaplan-Meier curves on the outcome "peripheral neuropathy" (EORTC QLQ-LC13), deterioration by ≥ 10 points, total population (study ALTA-1L, data cut-off 28 June 2019)

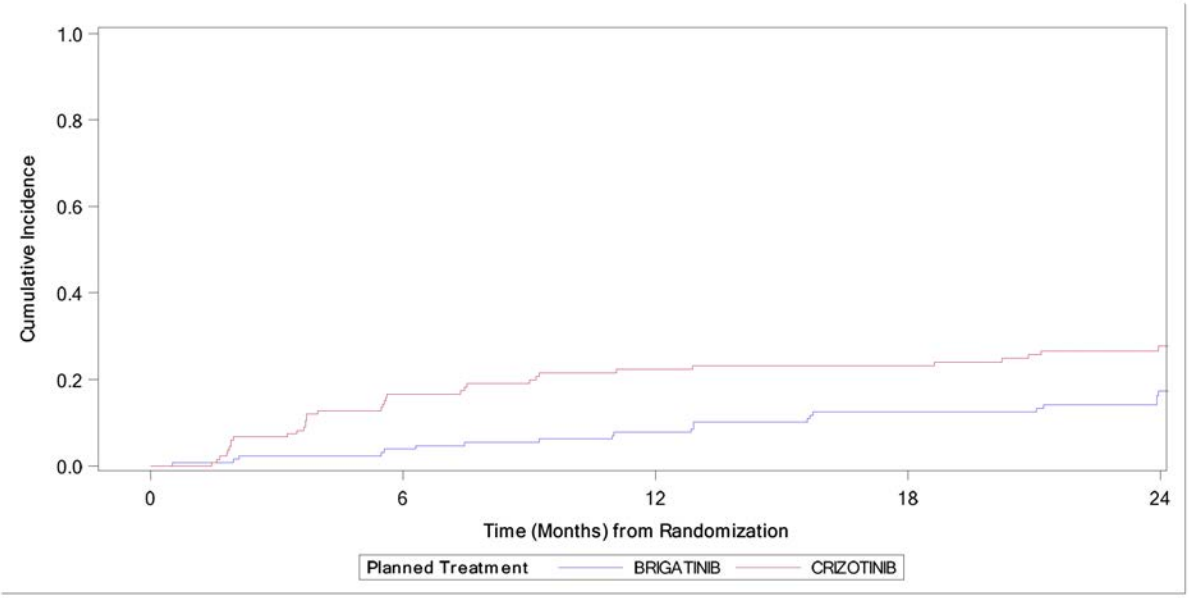


Figure 11: Cumulative incidence curves on the outcome "time to CNS progression" according to RECIST (with censoring due to non-CNS progression, no complete follow-up observation of CNS progression), total population (study ALTA-1L, data cut-off 28 June 2019)

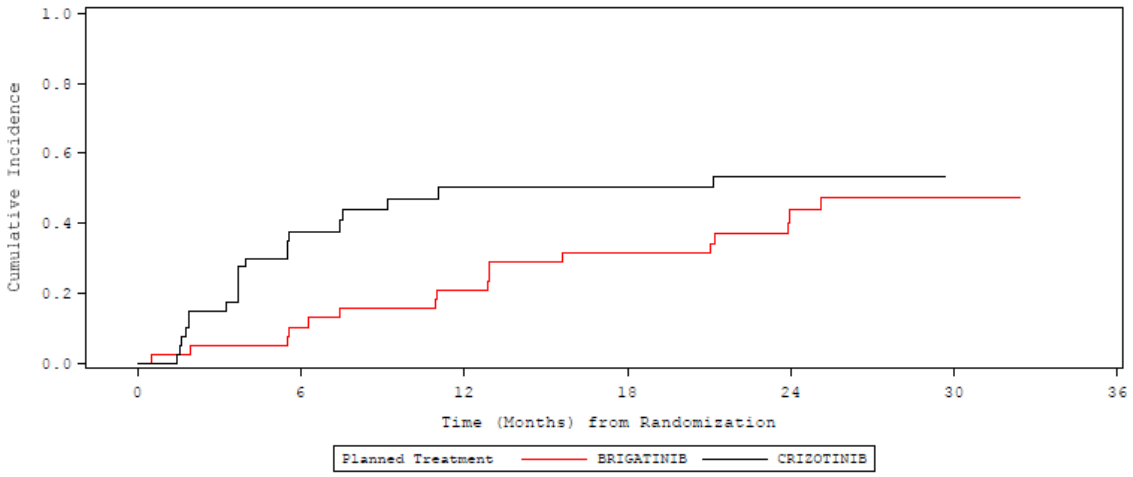


Figure 12: Cumulative incidence curves on the outcome "time to CNS progression" according to RECIST (with censoring due to non-CNS progression, no complete follow-up observation of CNS progression), patients with brain metastases at baseline (study ALTA-1L, data cut-off 28 June 2019)

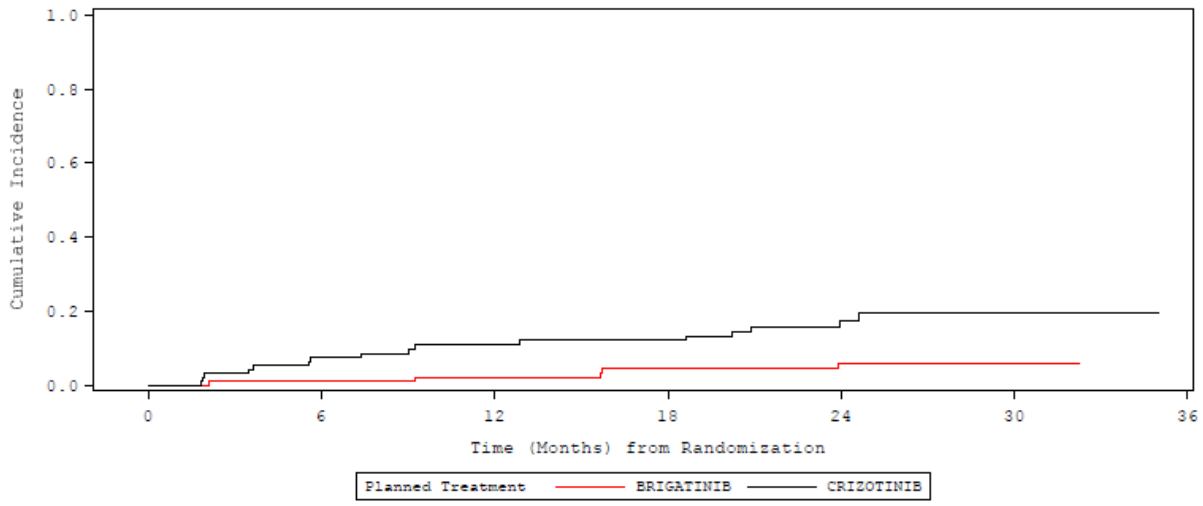


Figure 13: Cumulative incidence curves on the outcome "time to CNS progression" according to RECIST (with censoring due to non-CNS progression, no complete follow-up observation of CNS progression), patients without brain metastases at baseline (study ALTA-1L, data cut-off 28 June 2019)

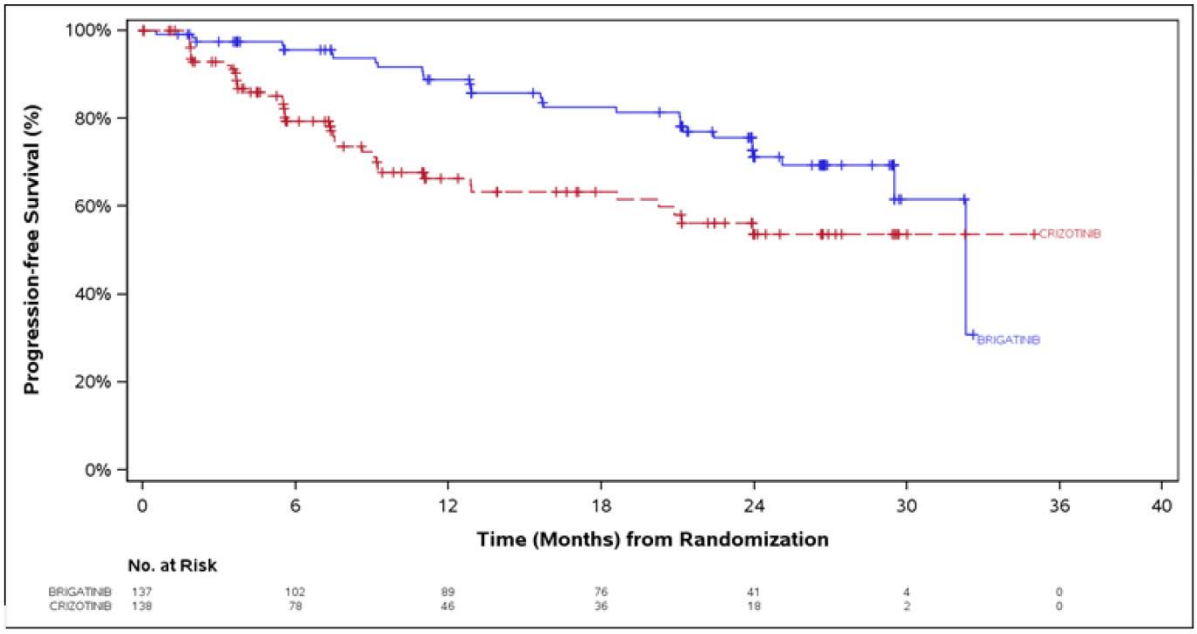


Figure 14: Kaplan-Meier curves on the outcome "time to CNS progression" (without censoring due to non-CNS progression, no complete follow-up observation of CNS progression), total population (study ALTA-1L, data cut-off 28 June 2019)