Das treibermutierte Lungenkarzinom: Testverhalten und -methoden, Daten und Behandlungsoptionen (mit dem Fokus auf ALK+ NSCLC und Brigatinib)

Dialog mit der Pharmaindustrie

Takeda: Überblick Geschichte weltweit

Gründung von Takeda durch Chobei Takeda

1781

Takeda erwirbt Millennium Pharmaceuticals

2008

Takeda erwirbt Nycomed

2011

Gründung der Oncology Business Unit

2014

1962-1997

Takeda expandiert: Asien, USA und Europa

2011

Takeda feiert 230-jähriges Jubiläum

2011

Eröffnung Shonan Research Center

2017

Takeda erwirbt Ariad

2019

Takeda erwirbt Shire

Vertrauliche Informationen!
Nicht zur Weitergabe an Dritte!

Takeda in Zahlen – weltweit

>54.000

Mitarbeiter weltweit

Top 10

Globales pharmazeutisches Unternehmen

4

Fokus-Therapiegebiete:
Onkologie, Gastroenterologie, Neurologie, Seltene Erkrankungen

>80

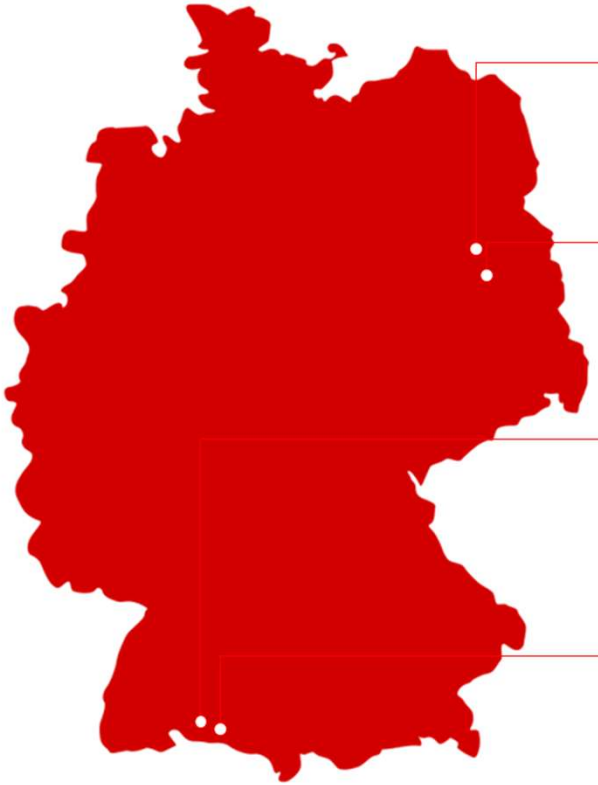
Länder und Regionen, in denen Takeda Produkte verfügbar sind

3

Spezialisierte Business Units: Impfstoffe, plasmabasierte Therapien, Onkologie

Vertrauliche Informationen!
Nicht zur Weitergabe an Dritte!

Takeda in Deutschland (mit Shire)



ORANIENBURG

BERLIN

SINGEN

KONSTANZ

PRODUKTION

VERTRIEB TAKEDA & SHIRE

PRODUKTION

VERWALTUNG

Seit **1981** in Deutschland

~63 Produkte in Deutschland verfügbar

Mehr als **2.300** Mitarbeiter

8 Therapiebereiche

- Gastroenterologie
- Onkologie
- Hämatologie
- Immunologie/hereditäres Angioödem, HAE
- Genetic Disease
- Neurowissenschaften
- Innere Medizin
- Etablierte Produkte

#1 bei seltenen Erkrankungen

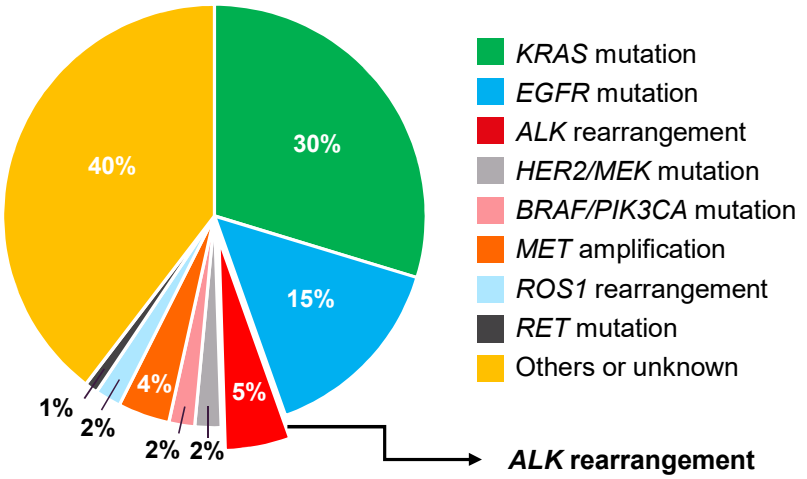
Vertrauliche Informationen!
Nicht zur Weitergabe an Dritte!

ALK+ NSCLC

ALK is a validated target expressed in about 3% to 5% of NSCLC[1-4]

- *ALK* rearrangement, *ALK* fusion, ALK+
  - All mean the same thing
- The most common *ALK* fusion partner in NSCLC is *EML4*[4]
  - EML4-ALK accounts for ≈30% of all ALK fusion proteins[4]
- *ALK* rearrangements are usually mutually exclusive with *EGFR*, *KRAS* mutations, or *ROS1* rearrangements[4-6]

Mutations in NSCLC (adenocarcinoma)[5]



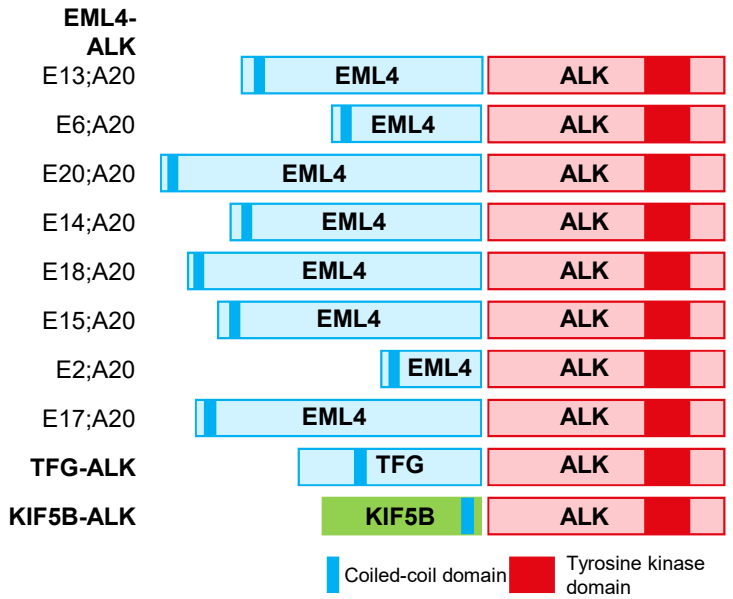
ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; EML4, echinoderm microtubule-associated protein-like 4; EML4-ALK, echinoderm microtubule-associated protein-like 4–anaplastic lymphoma kinase; HER2, human epidermal growth factor receptor 2; MEK, mitogen-activated protein kinase (MAPK) kinase; NSCLC, non–small cell lung cancer; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit α; RET, rearranged during transfection.

1. Gainor JF, et al. *Clin Cancer Res*. 2013;19:4273-4281. 2. Wong DW, et al. *Cancer*. 2009;115:1723-1733. 3. Koivunen JP, et al. *Clin Cancer Res*. 2008;14:4275-4283. 4. Chia PL, et al. *Clin Epidemiol*. 2014;6:423-432. 5. Chan BA, Hughes BGM. *Transl Lung Cancer Res*. 2015;4:36-54. 6. Lin JJ, et al. *J Thorac Oncol*. 2017;12:872-877.

ALK rearrangements in NSCLC

- Patients with ALK+ NSCLC
  - Typically have adenocarcinoma histology[1]
  - Typically (but not always!) never smokers or light former smokers[1,2]
- Detection methods[2,3]
  - FISH
  - IHC
  - NGS
- Multiple studies have now shown that tumors harboring *ALK* rearrangement are sensitive to ALK inhibition[2,4]

Schematic representation of *ALK* rearrangements found in lung cancer[2]



Modified from a presentation slide by CM Lovly at ASCO 2018 with associated abstract Yu HA, et al. *Am Soc Clin Oncol Educ Book*. 2018;38:726-739.
ALK, anaplastic lymphoma kinase; EML4, echinoderm microtubule-associated protein-like 4; FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; NGS, next-generation sequencing; NSCLC, non–small cell lung cancer. 1. Shaw AT, et al. *J Clin Oncol*. 2009:4247-4253. 2. Reprinted from Sasaki T, et al. *Eur J Cancer*. 2010;46:1772-1780. The biology and treatment of EML4-ALK non-small cell lung cancer. Copyright 2010, with permission from Elsevier. 3. Ali SM, et al. *Oncologist*. 2016;21:762-770. 4. Soda M, et al. *Nature*. 2007;4848:561-566.

Brigatinib vs crizotinib in patients with ALK inhibitor-naive advanced ALK+ NSCLC: Updated results from the phase III ALTA-1L trial

R. Camidge, H.R. Kim, M. Ahn, J.C. Yang, J. Han, M.J. Hochmair, K.H. Lee, A. Delmonte, M.R. Garcia Campelo, D. Kim, F. Griesinger, E. Felip, R. Califano, A. Spira, S. Gettinger, M. Tiseo, Q. Ni, P. Zhang, S. Popat

Presidential Session
ESMO ASIA 2019

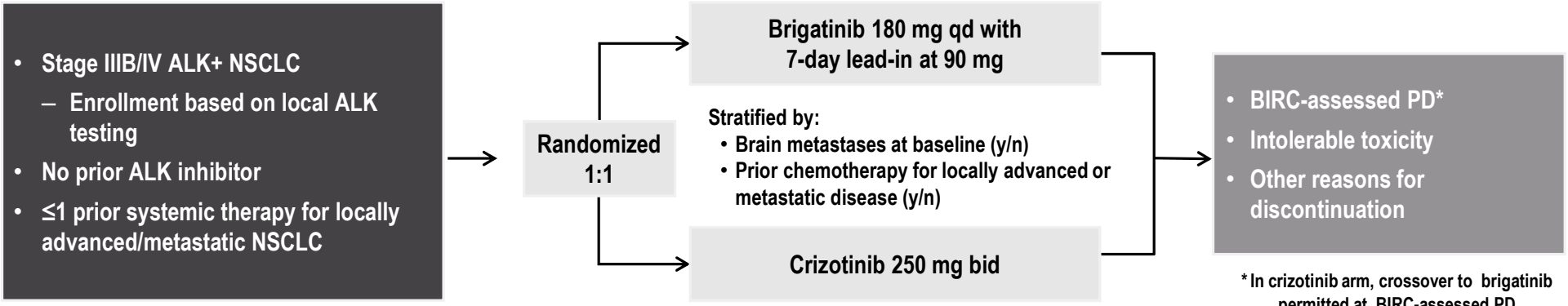
Zulassungsstatus von Brigatinib

- Brigatinib ist als Monotherapie bei erwachsenen Patienten mit anaplastischer-Lymphomkinase (ALK)-positivem, fortgeschrittenem, nicht-kleinzelligem Lungenkarzinom (NSCLC) angezeigt, **die zuvor nicht mit einem ALK-Inhibitor behandelt wurden.**

- Brigatinib ist als Monotherapie bei erwachsenen Patienten mit ALK-positivem, fortgeschrittenem NSCLC angezeigt, **die zuvor mit Crizotinib behandelt wurden.**

Aktuelle Fachinformation Alunbrig®

ALTA-1L: Phase 3, Open-label, Randomized, Multicenter Study (NCT02737501); Second Interim Analysis



- **Primary endpoint**[a]: Blinded independent review committee (BIRC)–assessed PFS per RECIST v1.1
- **Key secondary endpoints**: Confirmed ORR, confirmed intracranial ORR, intracranial PFS, OS, safety, and tolerability
- **Statistical considerations**: ≈270 total patients (198 events); 135 in each arm to detect a 6-month improvement in PFS (HR=0.625), assuming:
  - 10-month PFS in crizotinib arm
  - 2 planned interim analyses at 99 (50%) and 149 (75%) total expected events

Trial fully accrued in August 2017 (N=275)

[a] *Statistical significance for the primary endpoint was achieved at the first interim analysis*

Camidge, R, Annals of Oncology (2019) 30 (suppl_9): ix183-ix202. 10.1093/annonc/mdz446 (ESMO Asia 2019)

Demographics and baseline characteristics reflect a real-world setting and included patients with prior chemotherapy and allowed local testing

		Brigatinib n=137	Crizotinib n=138	Total N=275
Median age, y (range)		58 (27–86)	60 (29–89)	59 (27–89)
Sex, %	Female	50	59	55
Race, %	White, Asian, unknown	55, 43, 1	62, 36, 1	59, 39, 1
ECOG performance status, %	0, 1, 2	39, 55, 5	38, 57, 5	39, 56, 5
Stage of disease at study entry, %	IIIB, IV	6, 94	9, 91	7, 93
Median time since advanced/metastatic NSCLC diagnosis, mo (range)		3.2 (0.3–73.2)	3.5 (0.4–86.0)	3.5 (0.3–86.0)
ALK status assessed locally by FDA-approved test, %[a]		90	81	86
Brain metastases at baseline, %[b]		29	30	29
Prior radiotherapy to the brain, %	WBRT, SRS	11, 3	9, 6	10, 4
Prior chemotherapy in the locally advanced or metastatic setting, %[c]		26	27	27

[a] Patients whose ALK+ status was confirmed locally by Vysis FISH or Ventana IHC. [b] As assessed by the investigator. [c] Prior chemotherapy was defined as completion of at least 1 full cycle of chemotherapy in the locally advanced or metastatic setting. SRS, stereotactic radiosurgery; WBRT, whole brain radiotherapy

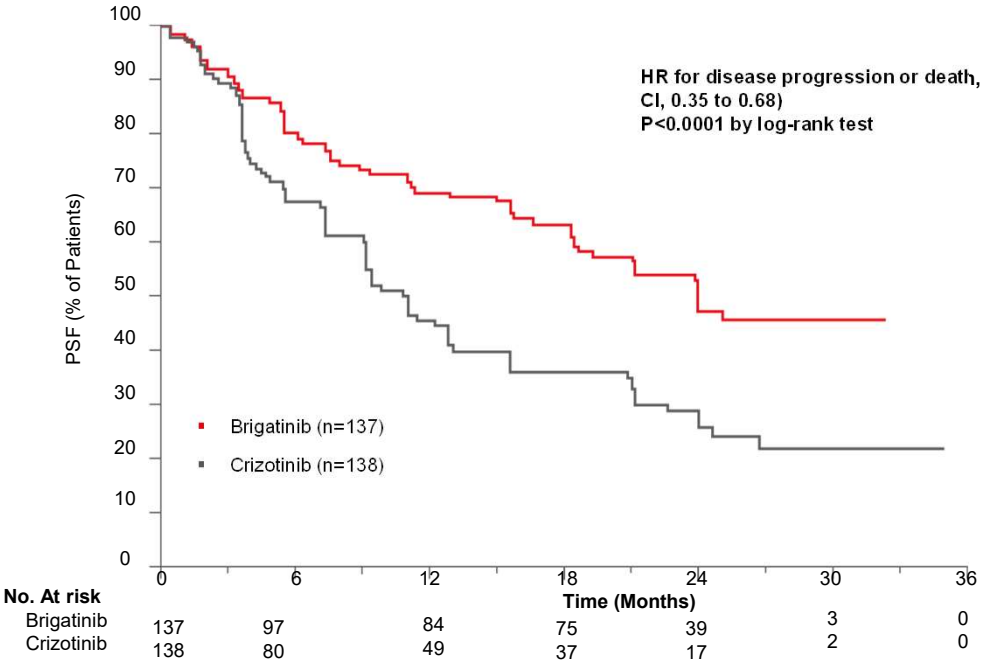
As of the second interim analysis (data cutoff: June 28, 2019):

- 75 patients (55%) in the brigatinib arm and 23 (17%) in the crizotinib arm remained on study treatment
- Median (range) follow-up: brigatinib, 24.9 (0–34.1) months; crizotinib, 15.2 (0.1–36.0) months
- 61 patients (44%) discontinued crizotinib and crossed over to receive brigatinib study drug according to the protocol

Camidge, R, Annals of Oncology (2019) 30 (suppl_9): ix183-ix202. 10.1093/annonc/mdz446 (ESMO Asia 2019)

Brigatinib significantly reduced the risk of progression or death by 51% vs crizotinib by BIRC respectively

Primary Endpoint: BIRC-Assessed PFS

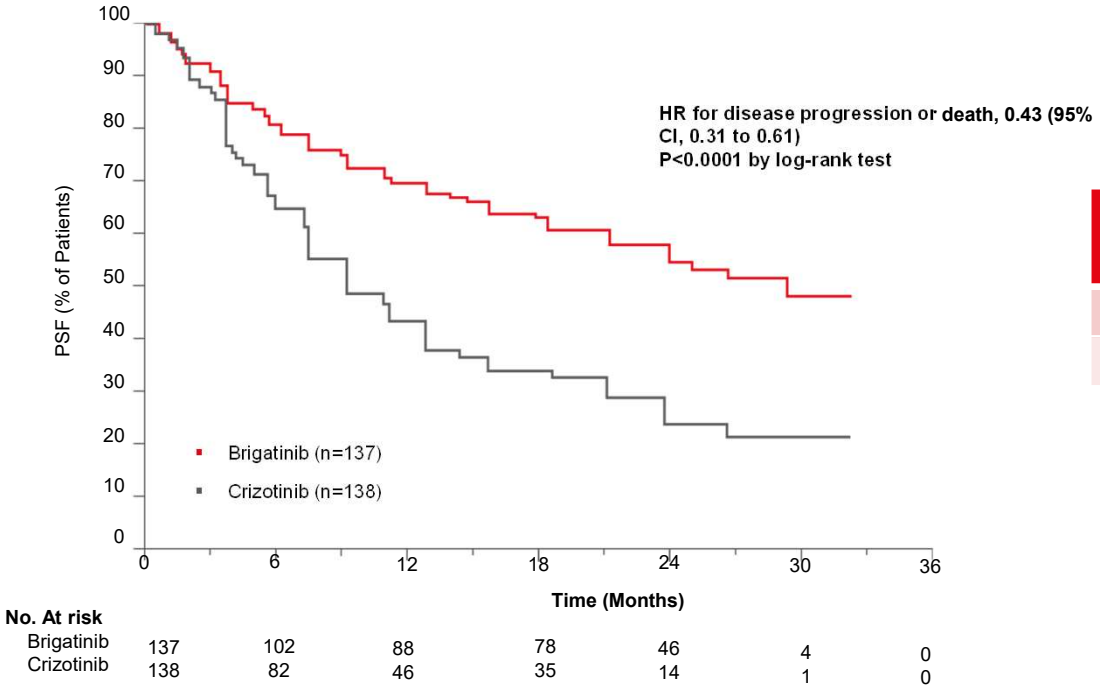


Treatment	No. (%) of Patients With Events	Median PFS (95% CI)	2-Year PFS, % (95% CI)
Brigatinib (n=137)	63 (46)	24.0 mo (18.5–NR)	48 (39–57)
Crizotinib (n=138)	87 (63)	11.0 mo (9.2–12.9)	26 (18–35)

Camidge, R, Annals of Oncology (2019) 30 (suppl_9): ix183-ix202. 10.1093/annonc/mdz446 (ESMO Asia 2019)

Brigatinib significantly reduced the risk of progression or death by 57% vs crizotinib, by INV respectively

Investigator-Assessed PFS

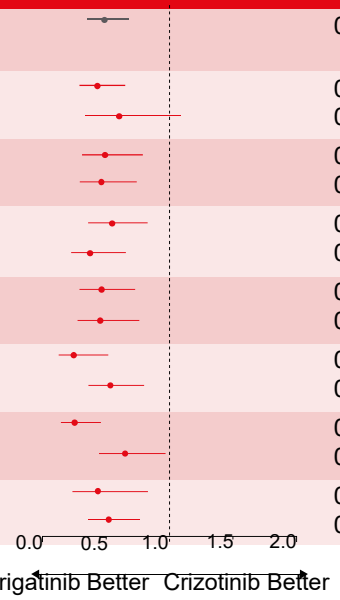


Treatment	No. (%) of Patients With Events	Median PFS (95% CI)	2-Year PFS, % (95% CI)
Brigatinib (n=137)	59 (43)	29.4 mo (21.2–NR)	56 (46–64)
Crizotinib (n=138)	92 (67)	9.2 mo (7.4–12.9)	24 (16–32)

Camidge, R, Annals of Oncology (2019) 30 (suppl_9): ix183-ix202. 10.1093/annonc/mdz446 (ESMO Asia 2019)

Brigatinib had superior overall PFS in patients with baseline brain metastases vs crizotinib across all subgroups (BIRC assessed)

Subgroup		No. of Patients Brigatinib/Crizotinib	Hazard Ratio for Disease Progression or Death (95% CI)
Overall		137/138	0.49 (0.35 to 0.68)
Age:	18 to 64 years	93/95	0.43 (0.29 to 0.65)
	≥65 years	44/43	0.60 (0.33 to 1.09)
Sex:	Female	69/81	0.49 (0.31 to 0.79)
	Male	68/57	0.46 (0.29 to 0.74)
Race:	Non-Asian	78/89	0.54 (0.36 to 0.83)
	Asian	59/49	0.38 (0.22 to 0.65)
Smoking Status:[a]	Never smoker	84/75	0.46 (0.29 to 0.73)
	Former smoker	50/56	0.45 (0.27 to 0.76)
ECOG perfomance status:[b]	0	54/53	0.25 (0.12 to 0.52)
	1	76/78	0.53 (0.36 to 0.80)
Brain metastases at baseline:[c]	Yes	40/41	0.25 (0.14 to 0.46)
	No	97/97	0.65 (0.44 to 0.97)
Prior chemotherapy:[d]	Yes	36/37	0.44 (0.23 to 0.83)
	No	101/101	0.52 (0.35 to 0.77)

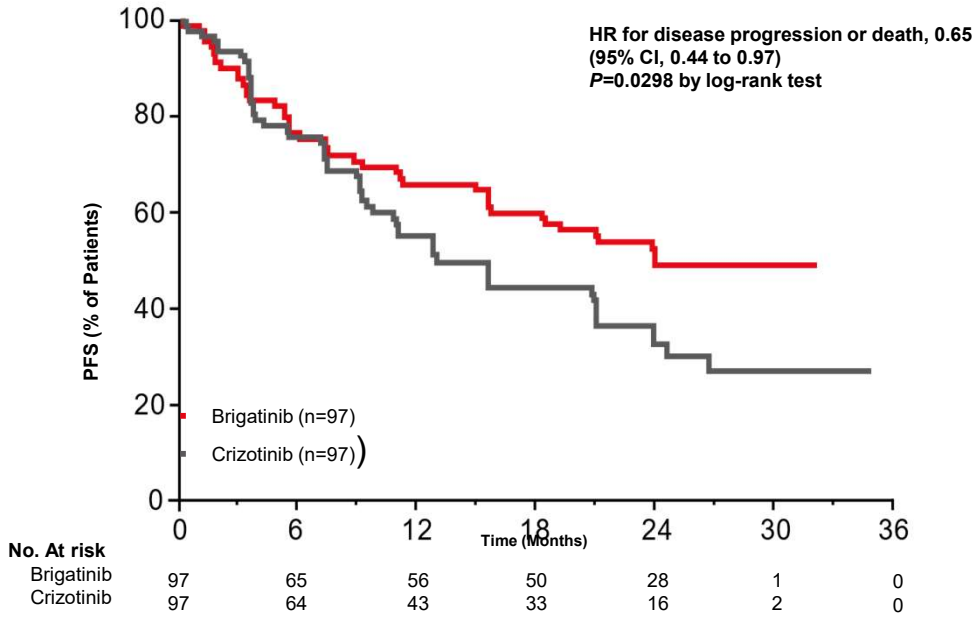


Hazard ratios were not calculated due to insufficient patient numbers, as dictated by the Statistical Analysis Plan, for patients who a) were Current smokers (brigatinib, n=3; crizotinib, n=7) or b) had ECOG performance status of 2 (brigatinib, n=7; crizotinib, n=7). c) Baseline brain metastases as assessed by investigator. d Prior chemotherapy in a locally advanced or metastatic setting

Camidge, R, Annals of Oncology (2019) 30 (suppl_9): ix183-ix202. 10.1093/annonc/mdz446 (ESMO Asia 2019)

Patients without baseline brain metastases benefitted from brigatinib vs crizotinib (BIRC assessed)

Patients Without Brain Metastases at Baseline



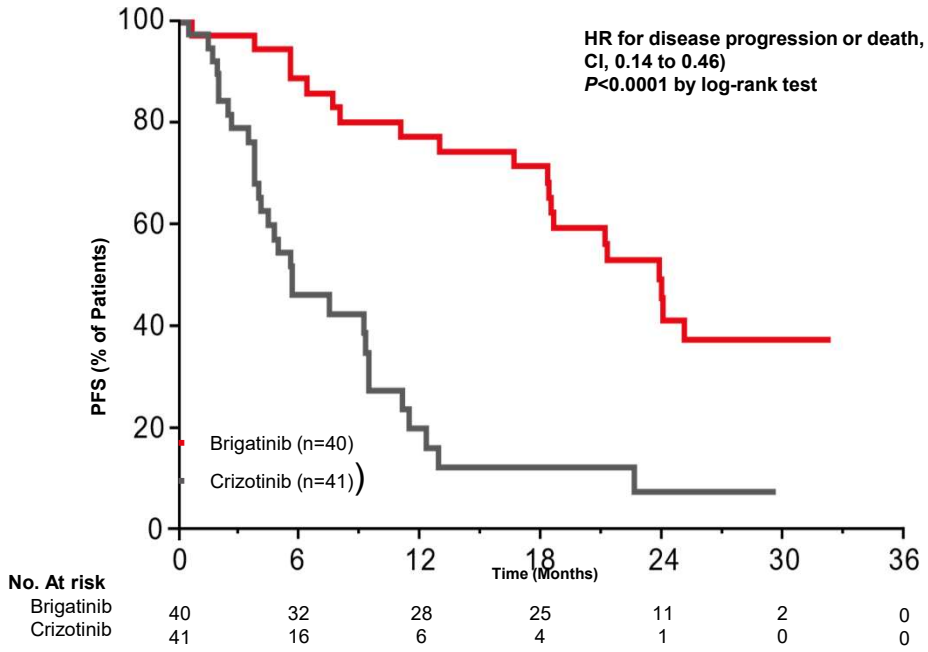
Treatment	No. (%) Patients With Events	Median PFS (95% CI)	2-Year PFS, % (95% CI)
Brigatinib (n=97)[a]	43 (44)	24.0 mo (15.7–NR)	50 (39–61)
Crizotinib (n=97)[a]	57 (59)	13.0 mo (9.5–21.1)	32 (22–43)

[a] *Per investigator assessment*

Camidge, R, Annals of Oncology (2019) 30 (suppl_9): ix183-ix202. 10.1093/annonc/mdz446 (ESMO Asia 2019)

Patients with baseline brain metastases benefitted early from brigatinib and achieved a 75% reduction in the overall risk of progression or death vs crizotinib (BIRC assessed)

Patients With Any Brain Metastases at Baseline



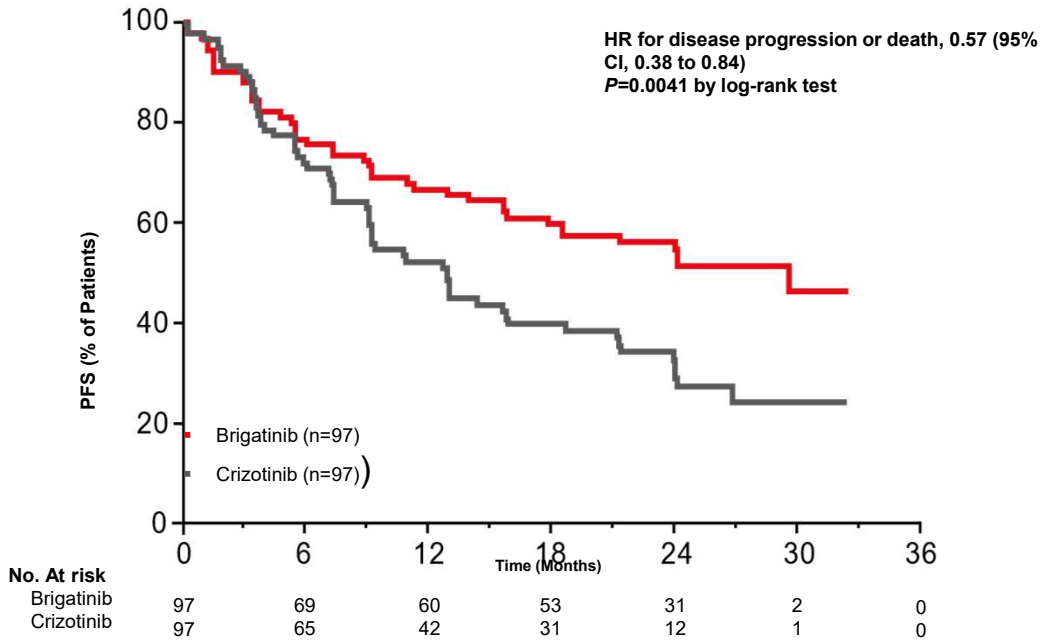
Treatment	No. (%) Patients With Events	Median PFS (95% CI)	2-Year PFS, % (95% CI)
Brigatinib (n=40)[a]	20 (50)	24.0 mo (18.4–NR)	43 (25–59)
Crizotinib (n=41)[a]	30 (73)	5.6 mo (3.8–9.4)	10 (2–25)

[a] *Per investigator assessment*

Camidge, R, Annals of Oncology (2019) 30 (suppl_9): ix183-ix202. 10.1093/annonc/mdz446 (ESMO Asia 2019)

Patients without baseline brain metastases benefitted from brigatinib vs crizotinib (INV assessed)

Patients Without Brain Metastases at Baseline



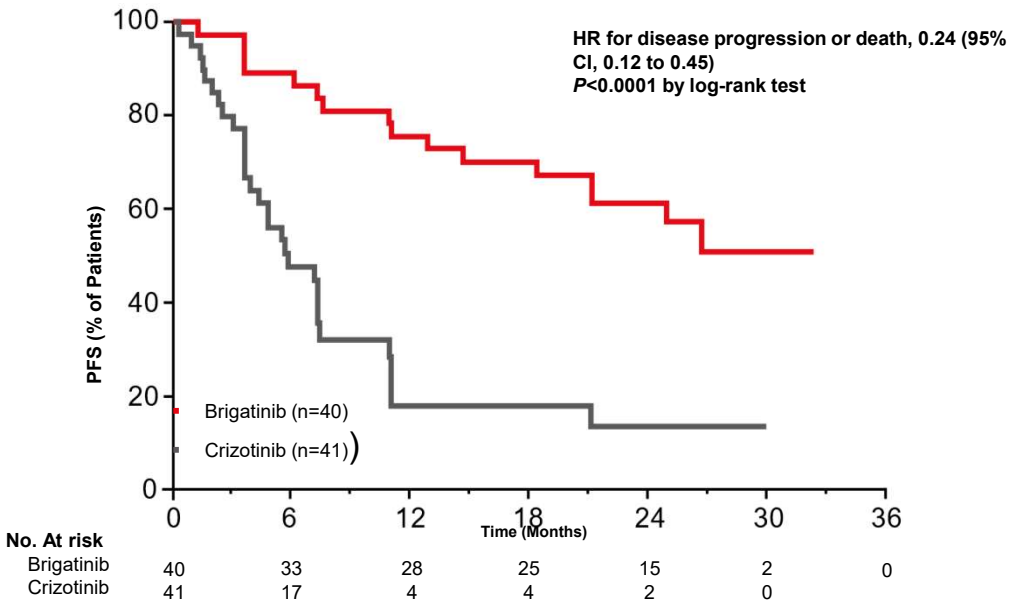
Treatment	No. (%) Patients With Events	Median PFS (95% CI)	2-Year PFS, % (95% CI)
Brigatinib (n=97)[a]	43 (44)	29.4 mo (17.8–NR)	53 (42–63)
Crizotinib (n=97)[a]	62 (64)	12.9 mo (9.2–18.6)	28 (18–38)

[a] *Per investigator assessment*

Camidge, R, Annals of Oncology (2019) 30 (suppl_9): ix183-ix202. 10.1093/annonc/mdz446 (ESMO Asia 2019)

Patients with baseline brain metastases benefitted early from brigatinib and achieved a 76% reduction in the overall risk of progression or death vs crizotinib (INV assessed)

Patients With Any Brain Metastases at Baseline



Treatment	No. (%) Patients With Events	Median PFS (95% CI)	2-Year PFS, % (95% CI)
Brigatinib (n=40)[a]	16 (40)	NR (18.4–NR)	61 (43–75)
Crizotinib (n=41)[a]	30 (73)	5.9 mo (3.7–7.5)	13 (4–28)

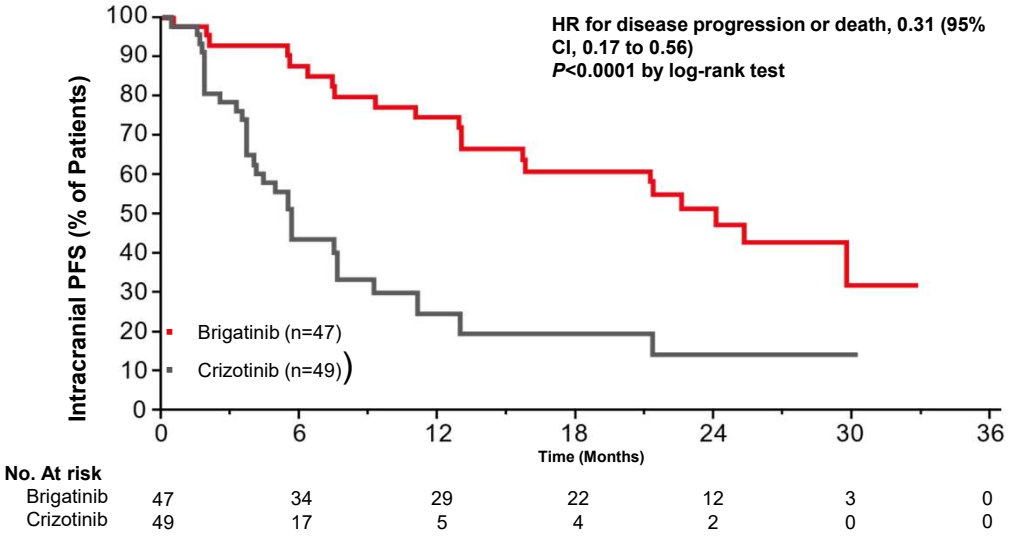
[a] *Per investigator assessment*

Camidge, R, Annals of Oncology (2019) 30 (suppl_9): ix183-ix202. 10.1093/annonc/mdz446 (ESMO Asia 2019)

Intracranial PFS (BIRC) showed a risk reduction of 69% with brigatinib vs crizotinib and confirms the efficacy in overall PFS seen in patients with baseline brain metastases

Only brain lesions were reviewed. Patients are counted as having an event if there was radiological progression, or death, or needed radiotherapy to the brain.

Patients With Any Brain Metastases at Baseline



Treatment	No. (%) Patients With Events		Median Intracranial PFS (95% CI)	2-Year Intracranial PFS, % (95% CI)
	Intracranial progression	Death		
Brigatinib (n=47)	21 (45)[b]	0	24.0 mo (12.9–NR)	48 (30–63)
Crizotinib (n=49)	29 (59)[c]	3 (6)	5.6 mo (3.7–7.5)	15 (5–32)

[a] Intracranial reviewers are independent from systemic reviewers. [b] Includes 1 patient with radiotherapy to the brain. [c] Includes 2 patients with radiotherapy to the brain

Camidge, R, Annals of Oncology (2019) 30 (suppl_9): ix183-ix202. 10.1093/annonc/mdz446 (ESMO Asia 2019)

ORR was high with brigatinib with a long median DoR that was not reached for brigatinib vs 13.8 months for crizotinib

	Brigatinib n=137	Crizotinib n=138	OR[a] (95% CI)
Confirmed ORR, % (95% CI)	74 (66–81)	62 (53–70)	1.73 (1.04–2.88) *P*=0.0342
CR, %	15	9	
PR, %	59	53	
Confirmed and nonconfirmed ORR, % (95% CI)	79 (71–85)	75 (67–82)	1.25 (0.71–2.19) *P*=0.4376
CR, %	20	12	
PR, %	59	62	
Median DoR in confirmed responders, mo (95% CI)	NR (19.4–NR)	13.8 (9.3–20.8)	
24-month probability of maintaining response, % (95% CI)	51 (40–61)	30 (18–42)	

[a] ORs (brigatinib vs crizotinib) and *P* values are from a Cochran-Mantel-Haenszel test stratified by presence of brain metastases at baseline and prior chemotherapy for locally advanced or metastatic disease

[a] ORs (brigatinib vs crizotinib) and P values are from a Cochran-Mantel-Haenszel test stratified by presence of brain metastases at baseline and prior chemotherapy for locally advanced or metastatic disease
Camidge, R, Annals of Oncology (2019) 30 (suppl_9): ix183-ix202. 10.1093/annonc/mdz446 (ESMO Asia 2019)

Intracranial ORR was high in patients with measurable brain metastases with a long median DoR that was not reached for brigatinib vs 9.2 months for crizotinib[a]

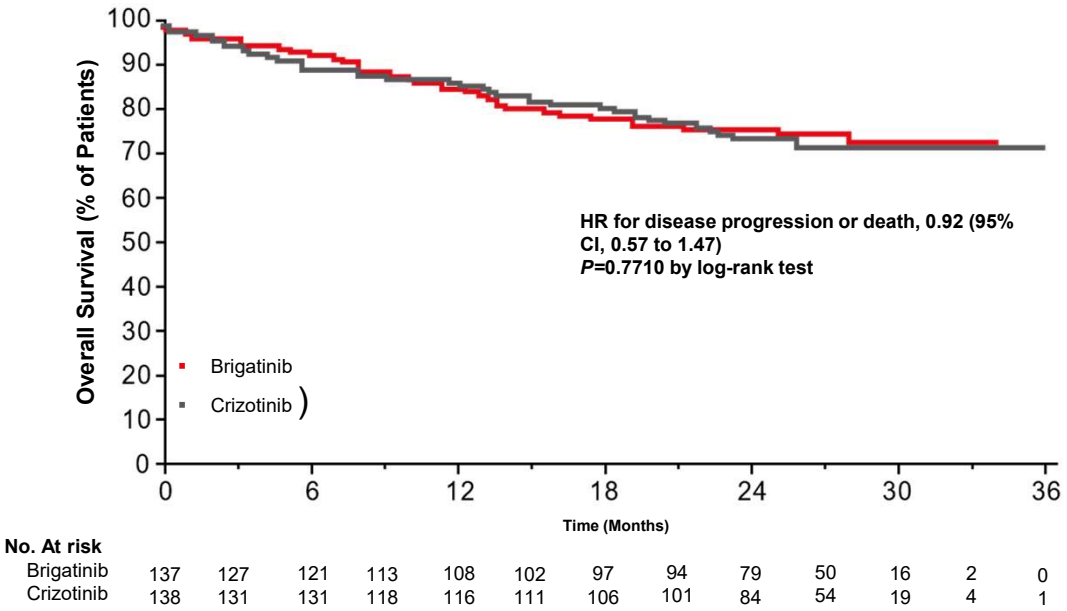
Measurable[b] Brain Metastases at Baseline	Brigatinib n=18	Crizotinib n=23	ORc (95% CI)
Confirmed intracranial ORR, % (95% CI)	78 (52–94)	26 (10–48)	11.67 (2.15–63.27) *P*=0.0014
CR, %	28	0	
PR, %	50	26	
Confirmed and nonconfirmed intracranial ORR, % (95% CI)	78 (52–94)	30 (13–53)	9.22 (1.76–48.43) *P*=0.0036
Median DoR in confirmed responders, mo (95% CI)	NR (5.7–NR)	9.2 (3.9–9.2)	
24-month probability of maintaining response, % (95% CI)	64 (30–85)	(insufficient pts)	
Any Brain Metastases at Baseline	**n=47**	**n=49**	
Confirmed intracranial ORR, % (95% CI)	66 (51–79)	16 (7–30)	11.75 (4.19–32.91) *P*<0.0001
CR, %	45	4	
PR, %	21	12	
Confirmed and nonconfirmed intracranial ORR, % (95% CI)	70 (55–83)	20 (10–34)	11.10 (4.06–30.39) *P*<0.0001
Median DoR in confirmed responders, mo (95% CI)	24.0 (16.9–NR)	9.2 (3.9–NR)	
24-month probability of maintaining response, % (95% CI)	55 (32–73)	(insufficient pts)	

[a] Intracranial reviewers are independent from systemic reviewers. [b] ≥10 mm in diameter. [c] ORs (brigatinib vs crizotinib) and *P* values are from a Cochran-Mantel-Haenszel test stratified by presence of prior chemotherapy for locally advanced or metastatic disease

[a] Intracranial reviewers are independent from systemic reviewers. [b] ≥10 mm in diameter. [c] ORs (brigatinib vs crizotinib) and P values are from a Cochran-Mantel-Haenszel test stratified by presence of prior chemotherapy for locally advanced or metastatic disease

Camidge, R, Annals of Oncology (2019) 30 (suppl_9): ix183-ix202. 10.1093/annonc/mdz446 (ESMO Asia 2019)

OS data was immature, and 44% of patients crossed over to brigatinib



Treatment	Deaths, No. (%) of Patients	2-Year Overall Survival, % (95% CI)
Brigatinib (n=137)	33 (24)	76 (67–82)
Crizotinib (n=138)	37 (27)	74 (65–80)

- 44% of patients in the crizotinib arm crossed over to brigatinib therapy; for these patients
  - Median BIRC-assessed PFS on brigatinib 15.6 mo (95% CI: 9.4–NR) with a median follow-up time of 14.4 mo
  - Confirmed BIRC-assessed ORR: 54.1% (95% CI, 40.8–66.9)

Camidge, R, Annals of Oncology (2019) 30 (suppl_9): ix183-ix202. 10.1093/annonc/mdz446 (ESMO Asia 2019)

Brigatinib was well tolerated, with no new safety findings; dose reductions were predominantly protocol-mandated for asymptomatic laboratory abnormalities (CPK, lipase, amylase, AST)

TEAEs Reported in >20% of All Patients	Brigatinib (n=136), %		Crizotinib (n=137), %	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Diarrhea	52	2	56	3
Increased blood CPK	46	24	17	1
Cough	35	0	20	0
Hypertension	32	12	8	3
Nausea	30	2	58	3
Increased AST	26	4	26	7
Increased lipase	23	14	15	7
Increased ALT	21	4	35	10
Vomiting	21	1	44	2
Dyspnea	21	2	20	4
Fatigue	19	0	23	1
Constipation	18	0	42	0
Pruritus	18	1	5	1
Increased amylase	18	6	9	1
Rash	15	0	3	0
Decreased appetite	9	1	19	3
Dermatitis acneiform	9	0	2	0
Dyspepsia	8	0	16	1
Bradycardia	8	1	15	0
Peripheral edema	7	1	45	1

Camidge, R, Annals of Oncology (2019) 30 (suppl_9): ix183-ix202. 10.1093/annonc/mdz446 (ESMO Asia 2019)

- Dose reduction due to AEs (brigatinib/crizotinib): 38%/25%
  - Brigatinib AEs leading to dose reduction in >1 patient: increased CPK (15%), lipase (7%), amylase (4%), AST (2%), and ALT (1%); hypertension (2%); pneumonitis (1%); pruritic rash (1%)
- Discontinuation due to AEs: 13%/9%

Brigatinib was well tolerated, with no new safety findings; dose reductions were predominantly protocol-mandated for asymptomatic laboratory abnormalities (CPK, lipase, amylase, AST)

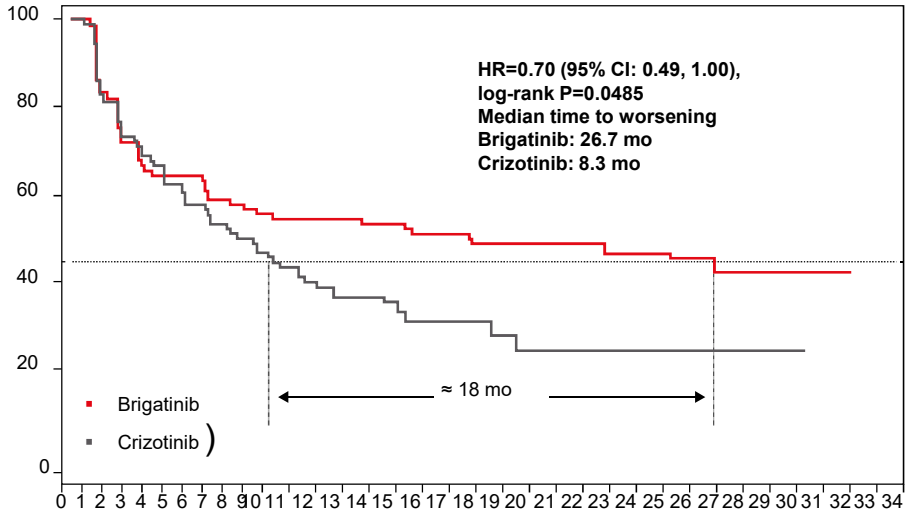
TEAEs That Differed by >5% Points Between Arms	Brigatinib (n=136), %		Crizotinib (n=137), %	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Increased blood cholesterol	7	0	1	0
Epistaxis	7	0	0	0
Upper abdominal pain	6	1	18	1
Hypokalemia	6	0	1	0
Erythematous rash	6	0	1	0
Hypercholesterolemia	6	0	0	0
Pain in extremity	5	0	15	1
Increased blood creatinine	4	0	15	1
Dysgeusia	3	0	14	0
Dysphagia	2	1	9	1
Pleural effusion	2	1	8	2
Decreased neutrophil count	1	0	10	5
Hypocalcemia	1	0	7	0
Taste disorder	1	0	6	0
Photopsia	1	0	20	1
GERD	1	0	11	0
Hypoalbuminemia	1	0	7	1
Hypotension	1	0	7	0
Visual impairment	0	0	17	0
Deep vein thrombosis	0	0	7	0

Camidge, R, Annals of Oncology (2019) 30 (suppl_9): ix183-ix202. 10.1093/annonc/mdz446 (ESMO Asia 2019)

- Interstitial lung disease (ILD)/pneumonitis at any time: brigatinib, 5% (7/136); crizotinib, 2% (3/137)
  - Early-onset ILD/pneumonitis (within 14 days of treatment initiation): brigatinib, 3% (4/136); crizotinib, none reported

Brigatinib delayed time to worsening and prolonged duration of improvement of health-related quality of life

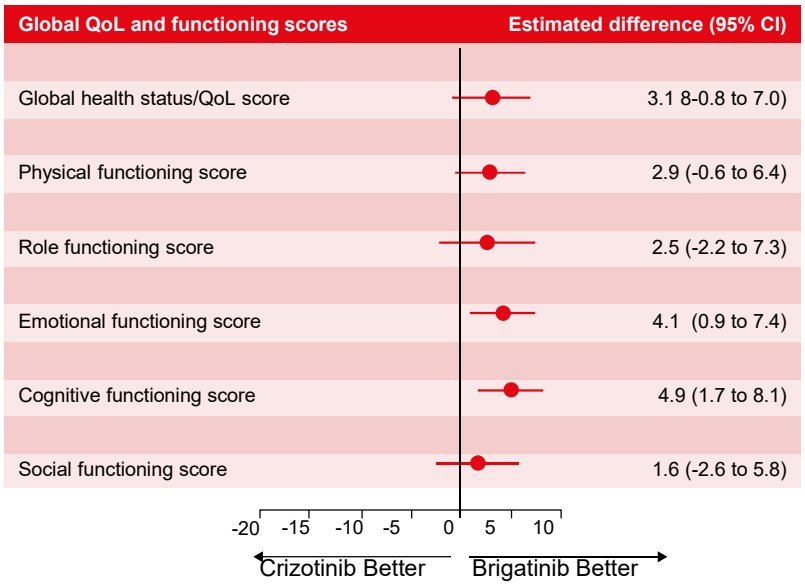
Time to Worsening in GHS/QoL, ITT Population

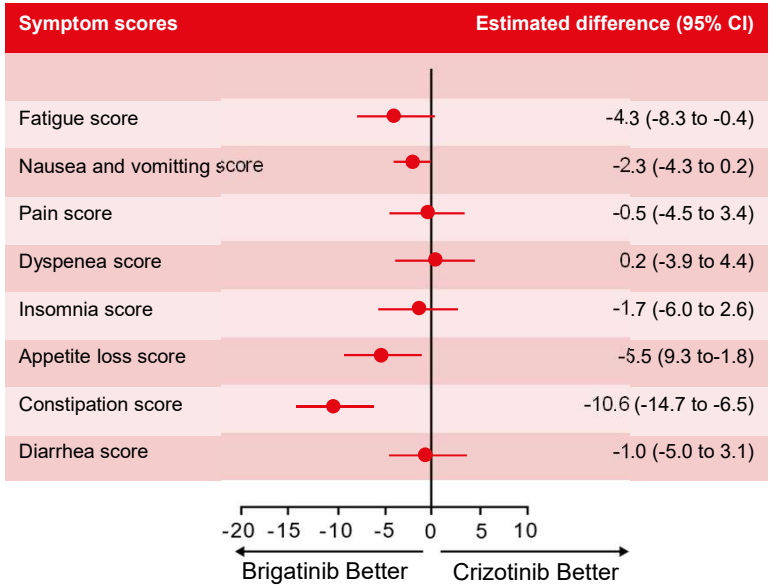


No. At risk

| | | |

Brigatinib achieved significant improvement in health-related quality of life in several function and symptom scores (mean change from baseline)





QoL and functioning improvements from brigatinib vs crizotinib could reflect differences in efficacy (eg, for disease-related symptom improvement) and/or in treatment-related side effects (eg, for gastrointestinal symptoms)

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Alunbrig® 30 mg / Alunbrig® 90 mg / Alunbrig® 180 mg Filmtabletten. Wirkstoff: Brigatinib. **Zusammensetzung:** Jede Filmtablette enthält 30 mg / 90 mg / 180 mg Brigatinib. *Sonstige Bestandteile:* Tablettenkern: Lactose-Monohydrat, mikrokristalline Cellulose, Carboxymethylstärke-Natrium (Typ A), hochdisperses, hydrophobes Siliciumdioxid, Magnesiumstearat. Filmüberzug: Talkum, Macrogol, Poly(vinylalkohol), Titandioxid (E 171). **Anwendungsgebiete:** Alunbrig ist als Monotherapie bei erwachsenen Patienten mit anaplastischer-Lymphomkinase (ALK)-positivem, fortgeschrittenem, nicht- kleinzelligem Lungenkarzinom (NSCLC) angezeigt, die zuvor nicht mit einem ALK-Inhibitor behandelt wurden. Alunbrig ist als Monotherapie bei erwachsenen Patienten mit ALK-positivem, fortgeschrittenem NSCLC angezeigt, die zuvor mit Crizotinib behandelt wurden. **Gegenanzeigen:** Überempfindlichkeit gegen den Wirkstoff oder einen der sonstigen Bestandteile, Stillen. **Nebenwirkungen:** Umgehende Information des Arztes erforderlich bei Auftreten folgender Nebenwirkungen: *Sehr häufig*: Bluthochdruck (Kopfschmerzen, Schwindel, Sehstörungen, Brustschmerzen oder Kurzatmigkeit), Sehstörungen (Blitze sehen, verschwommen sehen oder Schmerzen der Augen durch Licht), erhöhte Kreatinphosphokinase-Werte im Bluttest (unerklärliche Muskelschmerzen, -empfindlichkeit oder -schwäche), erhöhte Amylase- oder Lipasewerte im Bluttest (Schmerzen im Oberbauch, einschließlich Bauchschmerzen, die sich beim Essen verschlimmern und in den Rücken ausstrahlen, sowie Gewichtsverlust oder Übelkeit), erhöhte Leberenzymwerte im Bluttest (Aspartat-Aminotransferase, Alanin-Aminotransferase) (rechtsseitige Bauchschmerzen bzw. eine Gelbfärbung der Haut oder des Augapfels oder dunkler Urin), erhöhter Blutzucker (durstig, häufiger urinieren müssen, sehr hungrig, Übelkeit oder schwach oder müde oder verwirrt). *Häufig:* Lungenentzündung (verschlechternde Lungen- oder Atembeschwerden, einschließlich Brustschmerzen, Husten und Fieber, insbesondere in der 1. Woche der Einnahme von Alunbrig, kann Zeichen für ernsthafte Lungenprobleme sein), niedriger Puls (Schmerzen in der Brust oder Unwohlsein, Veränderungen im Herzschlag, Schwindel, Benommenheit oder Ohnmacht). *Gelegentlich:* Entzündung der Bauchspeicheldrüse, die schwere und anhaltende Magenschmerzen verursachen kann, mit oder ohne Übelkeit und Erbrechen (Pankreatitis). Weitere mögliche Nebenwirkungen: *Sehr häufig*: Pneumonie, Infektion der oberen Atemwege, Anämie, verringerte Anzahl weißer Blutkörperchen, sogenannte Neutrophile und Lymphozyten im Bluttest, verlängerte Blutgerinnungszeit im Test„Aktivierte partielle Thromboplastinzeit“, erhöhte Insulinwerte im Blut, verringerte Phosphorwerte im Blut, verringerte Magnesiumwerte im Blut, erhöhte Kalziumwerte im Blut, verringerte Natriumwerte im Blut, verringerte Kaliumwerte im Blut, verminderter Appetit, Kopfschmerzen, Empfindungsstörungen, wie Taubheit, Kribbeln, Prickeln, Schwäche oder Schmerzen in Händen oder Füßen (periphere Neuropathie), Schwindel, Husten, Kurzatmigkeit, Durchfall, Übelkeit, Erbrechen, Bauchschmerzen, Verstopfung, Stomatitis, erhöhter Wert des Enzyms alkalische Phosphatase im Blut – kann auf Organfunktionsstörungen oder Verletzungen hinweisen, Ausschlag, Juckreiz, Gelenk- oder Muskelschmerzen einschließlich Muskelkrämpfe), erhöhter Kreatininwert im Blut – kann auf eine eingeschränkte Nierenfunktion hindeuten, schwere dauernde Müdigkeit und Erschöpfung, Gewebsschwellung durch eingelagerte Flüssigkeit, Fieber. *Häufig*: Im Bluttest verringerte Anzahl der Blutplättchen (Thrombozyten), was das Risiko von Blutungen und Blutergüssen erhöhen kann. Schlafstörungen (Schlaflosigkeit), Gedächtnisschwäche, Änderung des Geschmackssinns, abnormale elektrische Aktivität des Herzens (verlängertes QT Intervall im EKG), Tachykardie, unregelmäßiger Herzschlag, trockener Mund, Verdauungsstörungen, Blähungen, erhöhte Laktatdehydrogenasewerte im Blut – kann auf einen Gewebeschaden hinweisen, erhöhter Bilirubinspiegel im Blut, trockene Haut, Empfindlichkeit gegenüber Sonnenlicht, Schmerzen der Rippen und Brustmuskulatur, Schmerzen in Armen und Beinen, Muskel- und Gelenksteifigkeit, Brustschmerzen und -beschwerden, Schmerzen, erhöhte Cholesterinwerte im Blut, Gewichtsverlust. **Warnhinweis:** Enthält Lactose. Packungsbeilage beachten. **Wechselwirkungen sowie weitere Hinweise:** siehe Fachinformation. Verschreibungspflichtig. **EU-Zulassungsinhaber:** Takeda Pharma A/S, Taastrup, Dänemark **Kontaktadresse d. Pharm. Unternehmens in Deutschland:** Takeda GmbH, Byk-Gulden-Straße 2, 78467 Konstanz, Tel.: 0800 8253325, medinfo@takeda.de. Stand: 04/2020