Brigatinib vs Crizotinib in Patients With ALK Inhibitor–Naive Advanced ALK+ NSCLC: First Report of a Phase 3 Trial (ALTA-1L)

Guiding 2L treatment in ALK+ patients (sequence of drugs, re-biopsy?)

Crizotinib/Tepotinib in MET exon 14-altered lung cancers

Α. Μπούτης
Ογκολόγος Παθολόγος
Α' Παθολογική Ογκολογική Κλινική
Α.Ν.Θ. «ΘΕΑΓΕΝΕΙΟ»
alboutis@otenet.gr

ΘΕΑΓΕΝΕΙΟ ΑΝΤΙΚΑΡΚΙΝΙΚΟ ΝΟΣΟΚΟΜΕΙΟ ΘΕΣΣΑΛΟΝΙΚΗΣ · 1743 ·

WCLC 2018

IASLC
INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER
IASLC 19th World Conference on Lung Cancer
September 23–26, 2018 Toronto, Canada
WCLC2018.IASLC.ORG
#WCLC2018

Brigatinib vs Crizotinib in Patients With ALK Inhibitor–Naive Advanced ALK+ NSCLC: First Report of a Phase 3 Trial (ALTA-1L)

D Ross Camidge, Hye Ryun Kim, Myung-Ju Ahn, James CH Yang, Ji-Youn Han, Jong-Seok Lee, Maximilian J Hochmair, Jacky Yu-Chung Li, Gee-Chen Chang, Ki Hyeong Lee, Cesare Gridelli, Angelo Delmonte, Maria Rosario Garcia Campelo, Dong-Wan Kim, Alessandra Bearz, Frank Griesinger, Alessandro Morabito, Enriqueta Felip, Raffaele Califano, Sharmistha Ghosh, Alexander Spira, Scott N Gettinger, Marcello Tiseo, Jeff Haney, David Kerstein, Sanjay Popat

D Ross Camidge, University of Colorado Cancer Center, USA

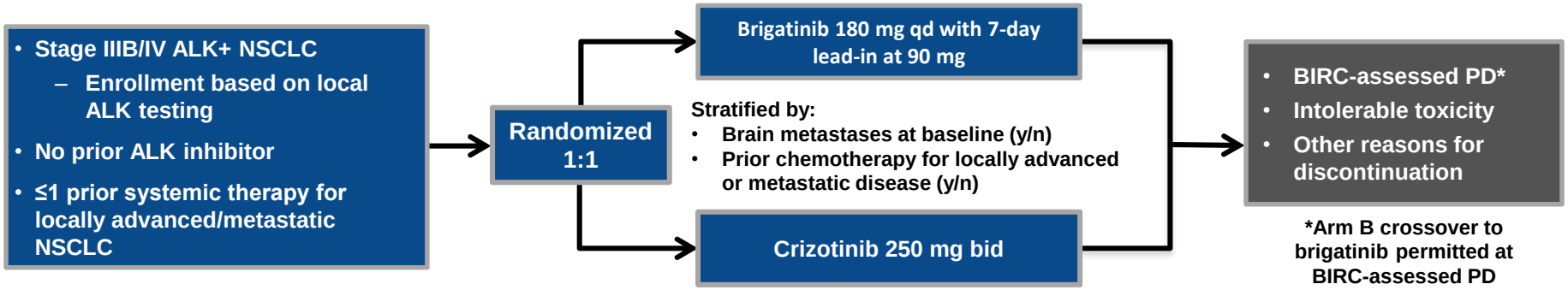
WCLC 2018

Introduction

- **In advanced ALK+ NSCLC, PROFILE 1014 confirmed that crizotinib is superior to platinum-pemetrexed doublet chemotherapy (PFS HR: 0.45; *P*<0.001; median PFS crizotinib: 10.9 months)[1]**
- **Brigatinib is a next-generation ALK/ROS1 inhibitor with broad preclinical activity against ALK resistance mutations and is the only ALK inhibitor to also demonstrate activity against multiple *EGFR*-mutant cell lines[2-5]**
- **Post-crizotinib, brigatinib has demonstrated high systemic and CNS response rates and the longest reported median PFS of any ALK inhibitor in this setting across 2 independent trials (16.3–16.7 months)[6-11]**
- **The ALK in Lung Cancer Trial of brigAtinib in 1st Line (ALTA-1L) trial is a phase 3 study comparing the efficacy and safety of brigatinib versus crizotinib in ALK inhibitor–naive advanced ALK+ NSCLC**

1. Solomon BJ, et al. *N Engl J Med*. 2014;371:2167-77; 2. Katayama R, et al. *Proc Natl Acad Sci U S A*. 2011;108:7535-40; 3. Huang WS, et al. *J Med Chem.* 2016;59:4948-64; 4. Gettinger SN, et al. *Lancet Oncol*. 2016;17:1683-96; 5. Uchibori K, et al. *Nat Commun*. 2017;8:14768; 6. Huber RM, et al. *J Clin Oncol.* 2018;36:9061; 7. Camidge DR, et al. *J Clin Oncol.* 2018:36:2693-701; 8. Bazhenova L, et al. *Ann Oncol.* 2017;28:479-80; 9. Novello S, et al. *Ann Oncol*. 2018;29:1409-1416; 10. Besse B, et al. ASCO. 2018;Poster 9032; 11. Horn L, et al. *Clin Cancer Res*. 2018;24:2771-2779.

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



Disease assessment every 8 weeks, including brain MRI for all patients

- Primary endpoint: 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)

First interim analysis:
- A total of 99 PFS events are included
- According to the prespecified O'Brien-Fleming Lan-DeMets alpha spending function, a 2-sided *P* value of 0.0031 was used to define the threshold for significance

Demographics and Baseline Characteristics		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, Other	55, 43, 1	62, 36, 2	59, 39, 2
ECOG performance status, %	0, 1, 2	42, 53, 4	43, 52, 4	43, 53, 4
Stage of disease at study entry, %	IIIB, IV	6, 94	9, 91	7, 93
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, %		13	14	13
Prior chemotherapy in the locally advanced or metastatic setting,[c] %		26	27	27

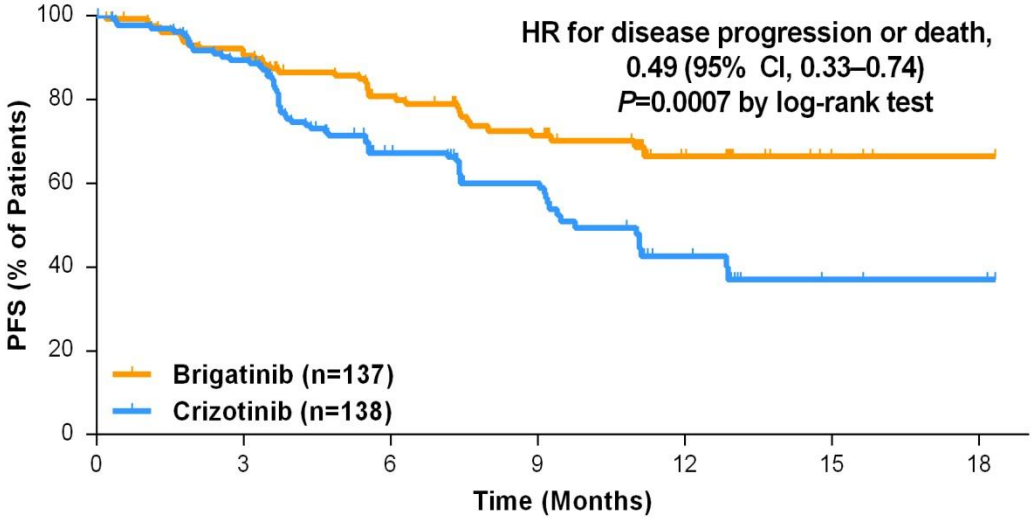
[a]Patients whose ALK+ status was confirmed locally by Vysis FISH or Ventana IHC. [b]As assessed by the investigator. [c]Prior chemotherapy was defined as completion of at least 1 full cycle of chemotherapy in the locally advanced or metastatic setting.

As of the first interim analysis (data cutoff: February 19, 2018):

- **95 patients (69%) in the brigatinib arm and 59 (43%) in the crizotinib arm remained on study treatment**
- **Median (range) follow-up: 11.0 (0–20.0) months and 9.3 (0–20.9) months, respectively**
- **35 patients who discontinued crizotinib due to disease progression crossed over to brigatinib as part of the trial**

Primary Endpoint: BIRC-Assessed PFS

- **Brigatinib met the prespecified threshold for statistical superiority vs crizotinib**

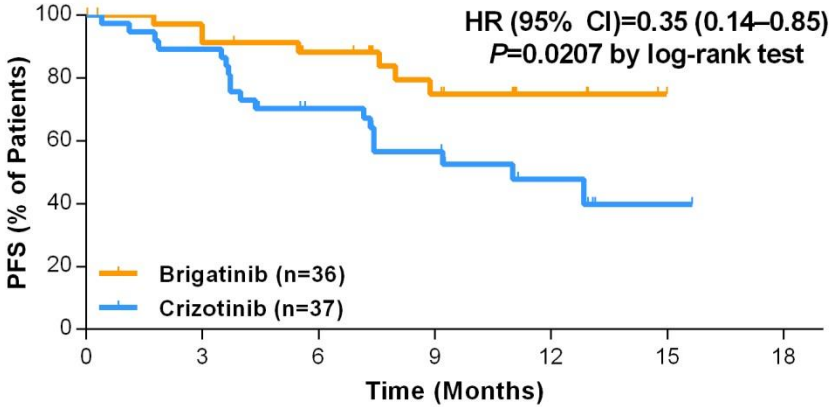


Treatment	No. (%) of Patients With Events	Median PFS (95% CI)	1-Year PFS, % (95% CI)
Brigatinib (n=137)	36 (26)	NR (NR–NR)	67 (56–75)
Crizotinib (n=138)	63 (46)	9.8 months (9.0–12.9)	43 (32–53)

- **Investigator-assessed median PFS was NR (95% CI, NR–NR) in the brigatinib arm and 9.2 months (95% CI, 7.4–12.9 months) in the crizotinib arm (HR, 0.45 [95% CI, 0.30–0.68]; log-rank *P*=0.0001)**
- **1-year OS probability: brigatinib, 85% (95% CI, 76%–91%); crizotinib, 86% (77%–91%)**

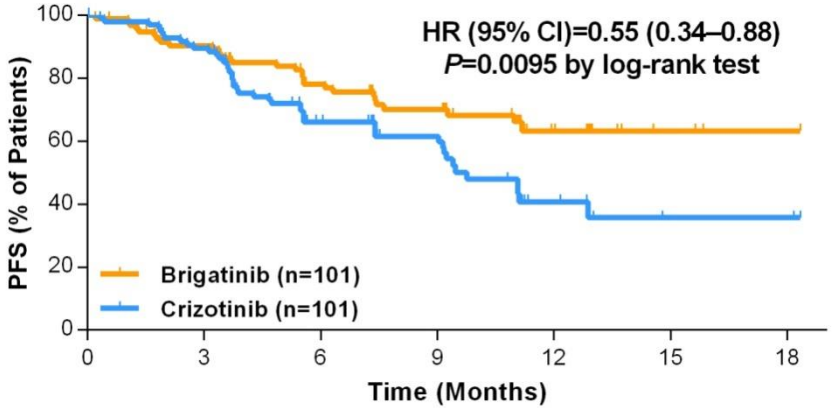
PFS Based on Prior Chemotherapy in the Locally Advanced or Metastatic Setting

Patients With Prior Chemotherapy



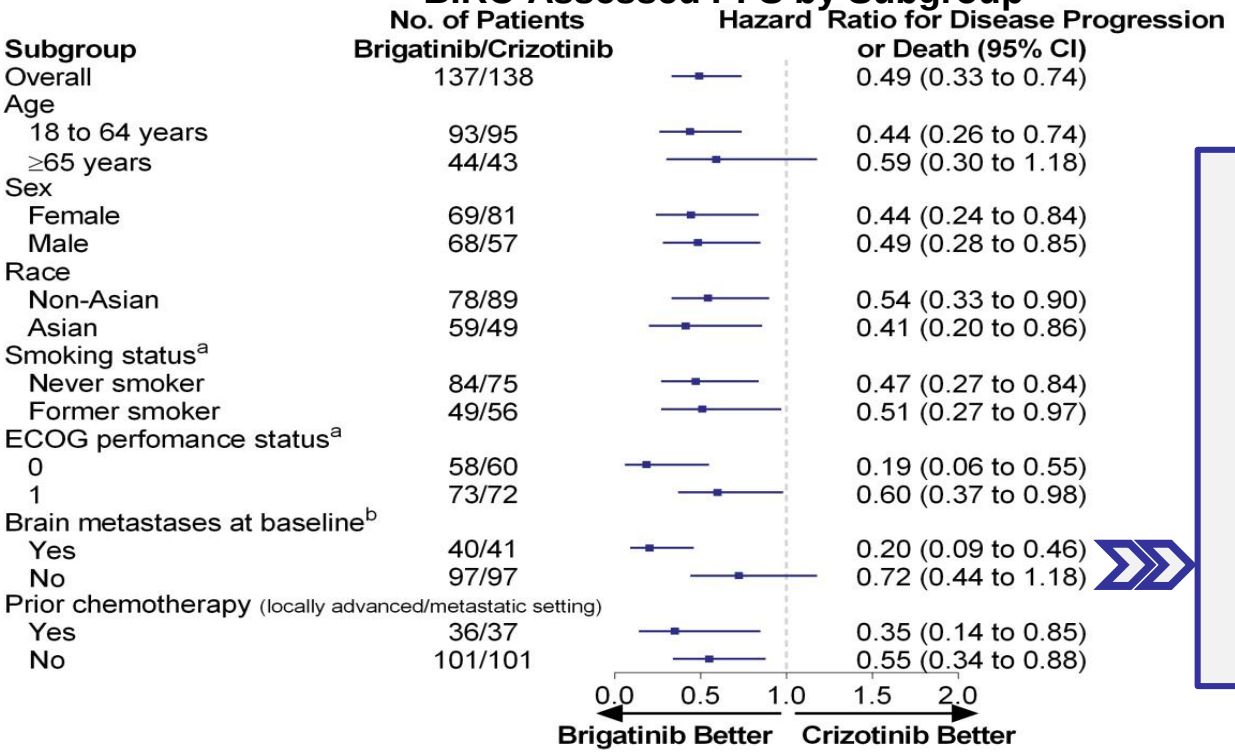
Treatment	Median PFS (95% CI)	1-Year PFS, % (95% CI)
Brigatinib (n=36)	NR (NR–NR)	75 (54–87)
Crizotinib (n=37)	11.0 months (7.2–NR)	48 (29–64)

Patients Without Prior Chemotherapy



Treatment	Median PFS (95% CI)	1-Year PFS, % (95% CI)
Brigatinib (n=101)	NR (NR–NR)	63 (50–74)
Crizotinib (n=101)	9.8 months (9.0–12.9)	41 (28–53)

BIRC-Assessed PFS by Subgroup



At this 1st interim analysis, PFS dataset was more mature in patients with baseline CNS disease, particularly for crizotinib arm, which was driven by CNS events

<u>% with PFS events, Crizotinib vs Brigatinib:</u>

- **Overall: 46% vs 26%**
- Baseline CNS disease: 59% vs 20%[c]
- No Baseline CNS disease: 40% vs 29%[d]

[a]HR not calculated for patients who were current smokers (brigatinib, n=4; crizotinib, n=7) or who had ECOG performance status of 2 (brigatinib, n=6; crizotinib, n=6) due to insufficient patient numbers, as dictated by the Statistical Analysis Plan. [b]Baseline brain metastases as assessed by investigator. [c]Cumulative incidence by competing risk analysis (crizotinib vs brigatinib), 45% vs 26% with CNS progression (without prior systemic progression or death); [d]5% vs 1% with CNS progression (without prior systemic progression or death).

Systemic Objective Response[a] (ITT Population)

	Brigatinib n=137	Crizotinib n=138	OR (95% CI)
Confirmed ORR, % (95% CI)	71 (62–78)	60 (51–68)	1.59 (0.96–2.62) *P*=0.0678
Confirmed CR, %	4	5	
Confirmed PR, %	67	55	
ORR at ≥1 assessment, % (95% CI)	76 (68–83)	73 (65–80)	1.13 (0.66–1.97) *P*=0.6512
CR, %	7	8	
PR, %	69	65	
Median DoR in confirmed responders, mo (95% CI)	NR (NR–NR)	11.1 (9.2–NR)	
12-month probability of maintaining response, % (95% CI)	75 (63–83)	41 (26–54)	

[a]Assessed by the BIRC.

Intracranial Objective Response[a] in Patients with Brain Metastases at Baseline

Measurable[b] Brain Metastases at Baseline	Brigatinib n=18	Crizotinib n=21	OR (95% CI)
Confirmed intracranial ORR, % (95% CI)	78 (52–94)	29 (11–52)	10.42 (1.90–57.05) *P*=0.0028
CR, %	11	0	
PR, %	67	29	
Intracranial ORR at ≥1 assessment, % (95% CI)	83 (59–96)	33 (15–57)	9.29 (1.88–45.85) *P*=0.0023
Any Brain Metastases at Baseline	**n=43**	**n=47**	
Confirmed intracranial ORR, % (95% CI)	67 (51–81)	17 (8–31)	13.00 (4.38–38.61) *P*<0.0001
CR, %	37	4	
PR, %	30	13	
Intracranial ORR at ≥1 assessment, % (95% CI)	79 (64–90)	23 (12–38)	16.30 (5.32–49.92) *P*<0.0001

[a]Assessed by the BIRC.
[b]≥10 mm in diameter.

WCLC 2018

TEAEs Reported in >20% of All Patients or That Differed by >5 Percentage Points Between Arms

	Brigatinib (n=136), %		Crizotinib (n=137), %	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Diarrhea	49	1	55	2
Increased blood CPK	39	16	15	1
Nausea	26	1	56	3
Cough	25	0	16	0
Increased AST	23	1	25	6
Hypertension	23	10	7	3
Increased ALT	19	1	32	9
Increased lipase	19	13	12	5
Vomiting	18	1	39	2
Constipation	15	0	42	1
Increased amylase	14	5	7	1
Pruritus	13	1	4	1
Rash	10	0	2	0
Decreased appetite	7	1	20	3
Dermatitis acneiform	7	0	1	0

	Brigatinib (n=136), %		Crizotinib (n=137), %	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Dyspepsia	6	0	13	0
Epistaxis	6	0	0	0
Bradycardia	5	1	12	0
Peripheral edema	4	1	39	1
Dysgeusia	4	0	19	0
Upper abdominal pain	4	1	13	1
Pain in extremity	4	0	12	1
Increased blood creatinine	2	0	14	1
Neutropenia	1	0	9	4
Pleural effusion	1	1	7	1
Photopsia	1	0	20	1
GERD	1	0	9	0
Hypoalbuminemia	1	0	6	1
Visual impairment	0	0	16	0
Deep vein thrombosis	0	0	6	0

- Interstitial lung disease (ILD)/pneumonitis at any time: brigatinib 4% (5/136); crizotinib 2% (3/137)
  - Early-onset ILD/pneumonitis (within 14 days of treatment initiation): brigatinib, 3% (onset: Days 3–8); crizotinib, none reported
- Dose reduction due to AEs (brigatinib/crizotinib): 29%/21%; discontinuation due to AEs: 12%/9%
  - For brigatinib, reductions due to increased CPK (10.3%), increased lipase (5.1%); increased amylase (2.9%) and increased AST, hypertension, pneumonitis, pruritic rash (1.5% each)
- No clinical cases of pancreatitis in either arm; no difference in incidence of any grade myalgia or musculoskeletal pain between arms (brigatinib/crizotinib: 6%/4% and 4%/6%, respectively); no grade ≥3 myalgia or musculoskeletal pain reported

Summary

- **ALTA-1L was conducted in ALK+ patients defined using multiple ALK diagnostics and allowed for prior chemotherapy exposure**
- **At the first planned interim analysis, brigatinib demonstrated superior PFS versus crizotinib by BIRC (HR, 0.49; *P*=0.0007; 12-month event-free rate: 67%, brigatinib vs 43%, crizotinib)**
- **PFS favored brigatinib across all subgroups, with the short follow-up preferentially emphasizing CNS progression among those with baseline CNS disease as an earlier differentiating event**
- **Brigatinib was well tolerated; dose reductions were predominantly protocol-mandated for asymptomatic laboratory abnormalities (CPK, lipase, amylase, AST)**
- **Early-onset pneumonitis may be unique to brigatinib among ALK TKIs, but is rare (3%) and the event rate appears lower in ALTA-1L than in later line trials[1]**
- **Brigatinib represents a promising new first-line treatment option for ALK+ NSCLC**

1. Kim DW, et al. *J Clin Oncol*. 2017;35:2490-8.

Comparison of Study Designs

	ALTA-1L (brigatinib)	Global ALEX (alectinib)
Number of patients	275	303
ALK testing	Local ALK testing	Central ALK IHC
Prior treatment allowed	1 prior systemic therapy	None
Stratification factors	Brain metastases Prior chemotherapy	Brain metastases ECOG PS Race
Primary endpoint	PFS by BIRC	PFS by investigator
Analysis	First interim (50%) (99 PFS events)	Primary (164 PFS events)
Median follow-up	11.0 mos	18.6 mos

- The ALTA-1L study compared brigatinib to crizotinib in ALK inhibitor-naïve patients with advanced ALK+ NSCLC
- At the first planned interim analysis, brigatinib was superior to crizotinib (HR 0.49, P=0.0007)
- Overall, this interim analysis suggests that brigatinib is highly effective in the first-line setting, and is likely to become another first-line option for ALK+ NSCLC
- However, whether brigatinib has superior efficacy relative to alectinib cannot be determined
- Cross-trial comparisons between ALTA-1L and the global ALEX study are limited:
    - Interim analysis vs primary analysis (50% vs 100% of the required PFS events)
    - Shorter follow-up on ALTA-1L (11 vs 19 mos)
    - Differences in study populations (brain mets, prior chemo)
    - Crizotinib comparator arm performed worse in ALTA-1L than global ALEX
- Safety and tolerability favor alectinib over brigatinib
- For now, the standard of care for first-line treatment of advanced ALK+ NSCLC remains alectinib

Guiding 2L treatment in ALK+ patients (sequence of drugs, re-biopsy?)

Enriqueta Felip
Vall d'Hebron University Hospital, Barcelona, Spain

ALK+, crizotinib as 1L

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

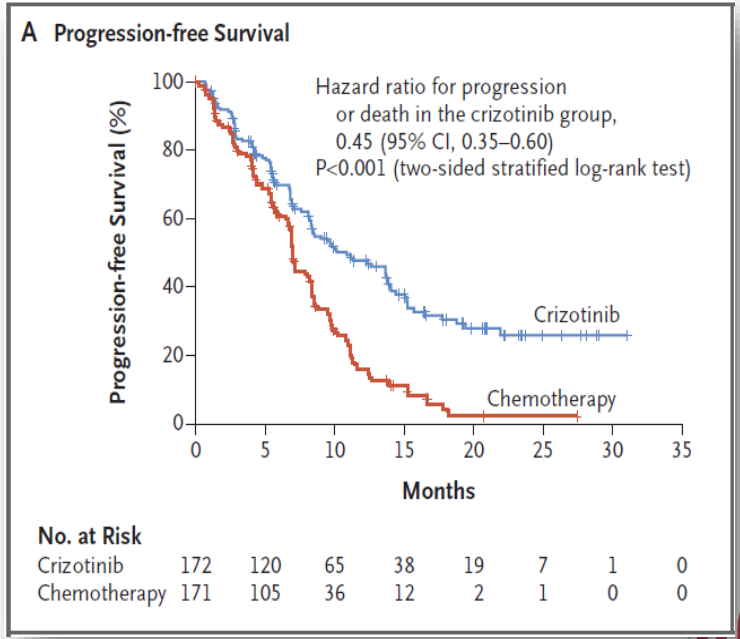
First-Line Crizotinib versus Chemotherapy in *ALK*-Positive Lung Cancer

Benjamin J. Solomon, M.B., B.S., Ph.D., Tony Mok, M.D., Dong-Wan Kim, M.D., Ph.D., Yi-Long Wu, M.D., Kazuhiko Nakagawa, M.D., Ph.D., Tarek Mekhail, M.D., Enriqueta Felip, M.D., Ph.D., Federico Cappuzzo, M.D., Jolanda Paolini, B.Sc., Tiziana Usari, B.Sc., Shrividya Iyer, Ph.D., Arlene Reisman, M.P.H., Keith D. Wilner, Ph.D., Jennifer Tursi, M.Sc., and Fiona Blackhall, M.D., Ph.D., for the PROFILE 1014 Investigators*

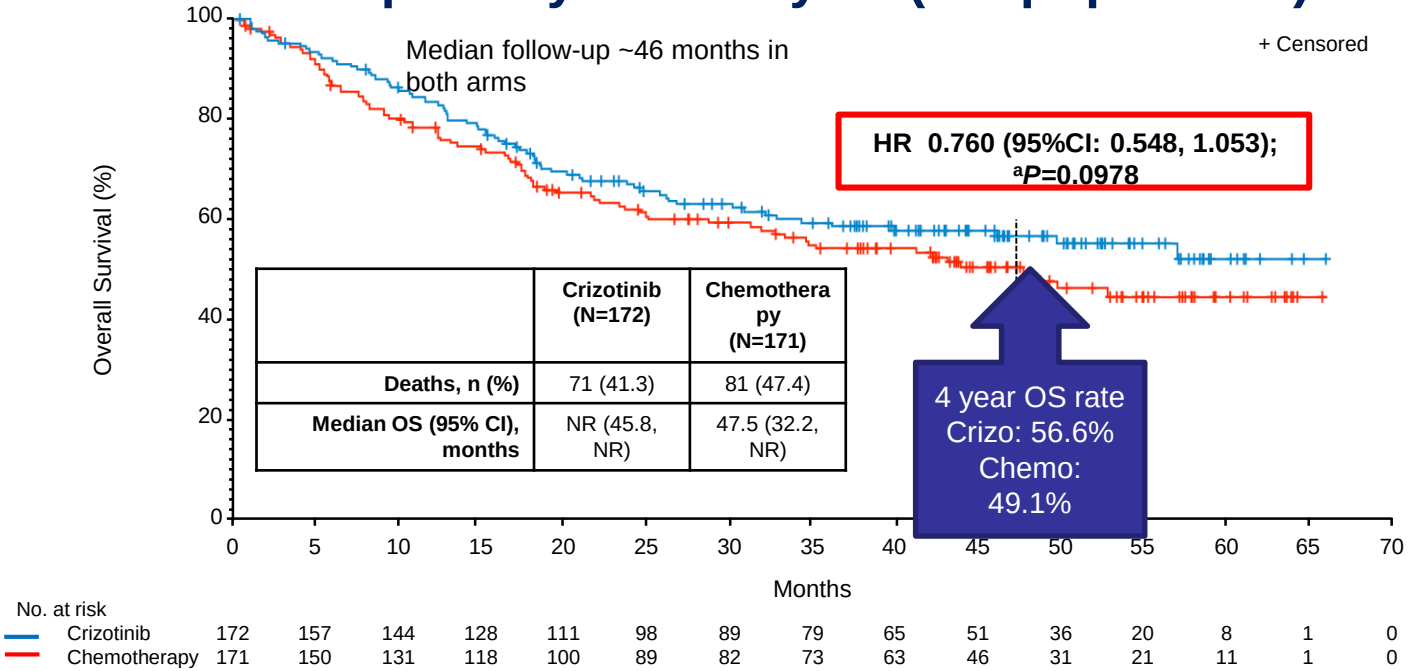
Significantly better efficacy to CT (platin/pem)

mPFS 10.9 *vs* 7.0 mo

(HR=0.45, P<0.0001)



Final primary OS analysis (ITT population)



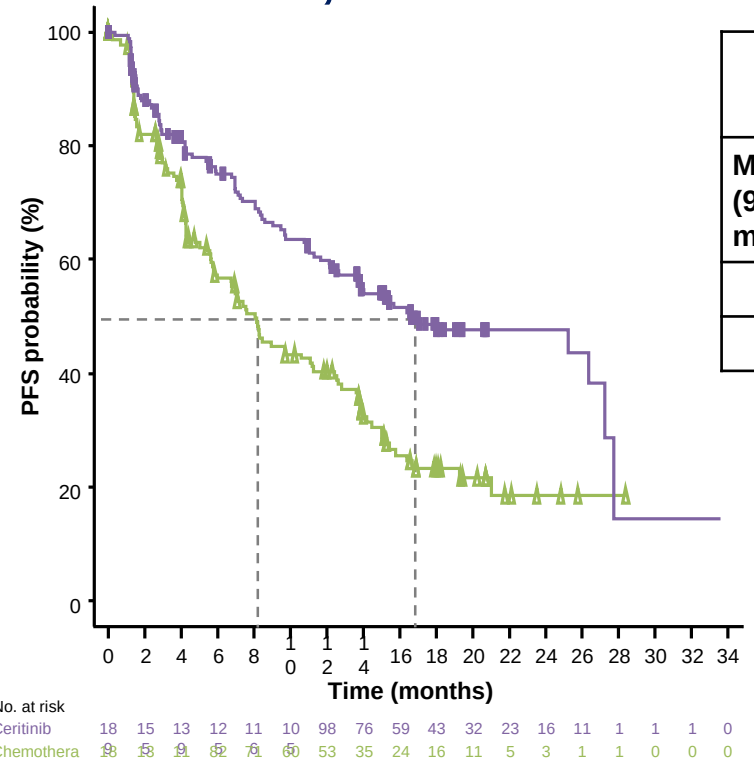
	Crizotinib (N=172)	Chemotherapy (N=171)
Deaths, n (%)	71 (41.3)	81 (47.4)
Median OS (95% CI), months	NR (45.8, NR)	47.5 (32.2, NR)

[a]2-sided p-value from the log-rank test stratified by ECOG PS, race, brain metastases.

Mok JCO 18

ALK+, ceritinib as 1L

Significantly better efficacy to CT (platin/pem, pem maintenance)
mPFS 16.6 *vs* 8.1 mo
(HR=0.45, P<0.0001)



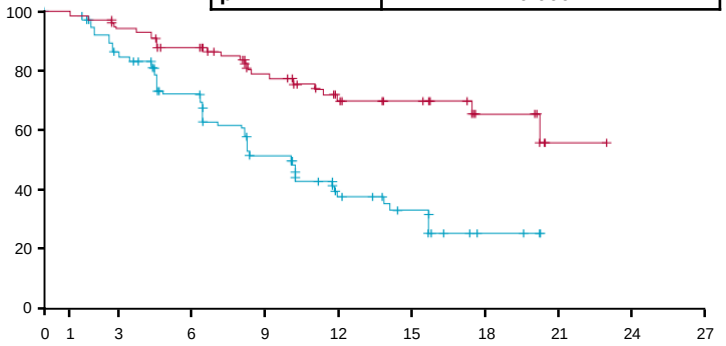
	Ceritinib (N=189)	Chemotherapy (N=187)
Median PFS (95% CI), months	16.6 (12.6, 27.2)	8.1 (5.8, 11.1)
Hazard ratio (95% CI) = 0.55 (0.42, 0.73)		
Stratified log-rank *P* value <0.00001		

Soria Lancet 17

WCLC 2018

ALK+, alectinib as 1L

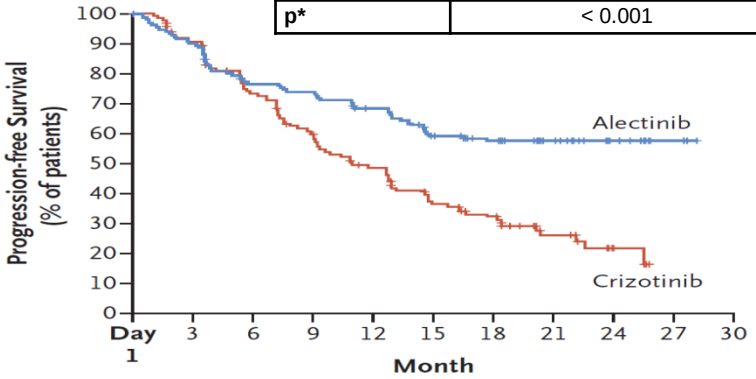
	Alectinib (n = 103)	Crizotinib (n = 104)
Events, n (%)	25 (24.3)	58 (55.8)
Median, mo	25.9	10.2
HR (99.7% CI)	0.38 (0.26–0.55)	
p*	0.0001	



J-ALEX: PFS

Hida Lancet 17 (updated ASCO 17)

	Crizotinib (n = 151)	Alectinib (n = 152)
Events, n (%)	102 (68)	62 (41)
Median, mo	11.1	NR
HR (95% CI)	0.47 (0.34–0.65)	
p*	< 0.001	

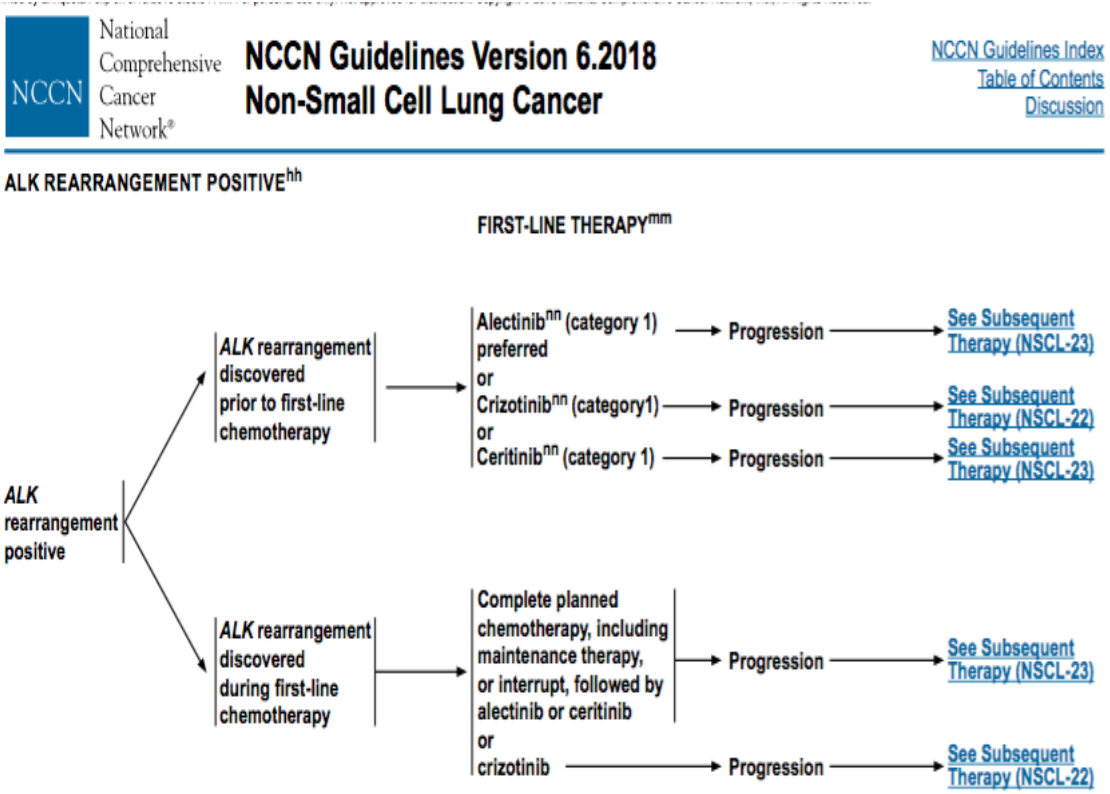


ALEX: PFS

Peters NEJM 2017

1L ALK+ NSCLC

- Good treatment outcomes with sequential crizotinib followed by next-gen ALKi
- Ceritinib longer PFS than platin/pem; toxicity
- Alectinib longer PFS (clinically significant) and higher CNS activity than crizotinib



ALK+ advanced NSCLC: ongoing 1L trials

- Crizotinib *vs* brigatinib
- Crizotinib *vs* lorlatinib
- Crizotinib *vs* ensartinib

ALTA-1L Trial of Brigatinib vs Crizotinib in *ALK*-Positive Advanced NSCLC Meets Primary Endpoint

By The ASCO Post
Posted: 8/1/2018 2:02:26 PM
Last Updated: 8/1/2018 2:02:26 PM
Tweet this page

The global, randomized, phase III ALTA-1L (ALK in Lung Cancer Trial of AP26113 in 1st Line) trial met its primary endpoint at the first prespecified interim analysis, with brigatinib (Alunbrig) demonstrating a statistically significant improvement in progression-free survival (PFS) compared to crizotinib (Xalkori) in adults with anaplastic lymphoma kinase (*ALK*)–positive locally advanced or metastatic non–small cell lung cancer (NSCLC) who had not received a prior ALK inhibitor. The trial was

Presidential Symposium: PL02.03 - Brigatinib vs Crizotinib in Patients With ALK Inhibitor-Naive Advanced ALK+ NSCLC: First Report of a Phase 3 Trial (ALTA-1L); Camidge

Activity of ALKi in crizotinib resistant patients

Drug	Study	RR	mPFS
Ceritinib[1,2,3]	Phase I ASCEND-1 Phase II ASCEND-2 Phase III ASCEND-5	56% 38.6% 39.1%	6.9m 5.7m 5.4m
Alectinib[4--7]	Phase I/II AF-001JP Phase II NP28761 Phase II NP28673 Phase III ALUR	55% 52% 50% 37.5%	NA 8.2m 8.9m 9.6m

1. Kim Lancet Oncol 16; 2. Mok JCO 15 Abstr 8059; 3. Shaw Lancet Oncol 17; 4. Seto Lancet Oncol 13; 5. Shaw Lancet Oncol 16; 6. Ou JCO 16; 7. Novello Ann Oncol 18

ASCEND-5 phase 3 study

Second line ceritinib *vs* CT

Key patient inclusion criteria
- Locally advanced or metastatic ALK+ NSCLC
- Progressive disease
- WHO PS 0–2
- Prior crizotinib (>1 course allowed)
- 1 or 2 prior chemotherapy regimens
- Measurable disease at baseline

(n=231)

R 1:1

Ceritinib 750 mg QD PO (n=115)

Stratification
- WHO PS (0 vs.1–2)
- Brain metastases (yes vs. no)

Chemotherapy Pemetrexed 500 mg/m² (n=40) or docetaxel 75 mg/m² (n=73) q3w

Crossover following BIRC-confirmed PD

Primary endpoint: PFS (BIRC)
Secondary endpoints: OS, PFS (investigator), ORR, DCR, TTR

ALUR phase 3 study

Second line alectinib *vs* CT

KEY ELIGIBILITY
- Advanced or metastatic *ALK+* NSCLC
- One prior line of platinum-based chemotherapy
- Crizotinib failure
- ECOG PS 0–2

R* 2:1

Alectinib 600mg BID

Optional continuation of alectinib if clinical benefit

PD

Pemetrexed 500mg/m² q3w or docetaxel 75mg/m² q3w

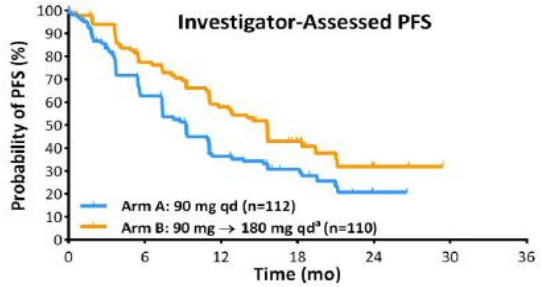
Crossover to alectinib allowed

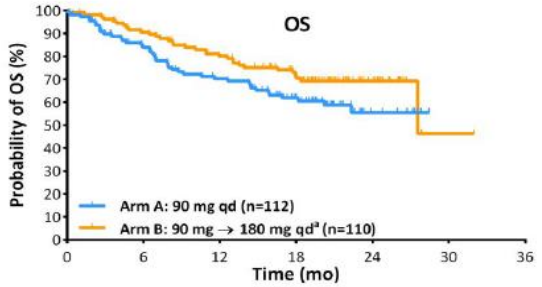
Primary endpoint	PFS Investigator-assessed
Secondary endpoints	CNS ORR by an IRC (key secondary endpoint); IRC-assessed PFS; systemic ORR; DCR and DOR; PFS in patients with CNS metastases at baseline; time to CNS progression by baseline CNS disease status; CNS DCR and CNS DOR in patients with CNS metastases at baseline; OS; safety

Shaw Lancet Oncol 17
Novello Ann Oncol 18

Brigatinib in crizotinib-refractory ALK+ NSCLC: updated efficacy from ALTA

Survival in Crizotinib-Resistant Patients





Treatment	Median PFS (95% CI)	HR (95% CI)
Arm A: 90 mg qd (% events = 65)	9.2 months (7.4–11.1)	0.64 (0.45–0.91)
Arm B: 90 mg → 180 mg qd[a] (% events = 50)	15.6 months (11.1–19.4)	

Treatment	Median OS (95% CI)	HR (95% CI)
Arm A: 90 mg qd (% events = 38)	NR (20.2–NR)	0.67 (0.42–1.06)
Arm B: 90 mg → 180 mg qd[a] (% events = 29)	27.6 months (27.6–NR)	

[a] 180 mg qd with 7-day lead-in at 90 mg. HR, hazard ratio; NR, not reached; qd, once daily

- IRC-assessed median PFS was 9.2 months (95% CI, 7.4–12.8 months) in Arm A and 16.7 months (95% CI, 11.6–NR months) in Arm B

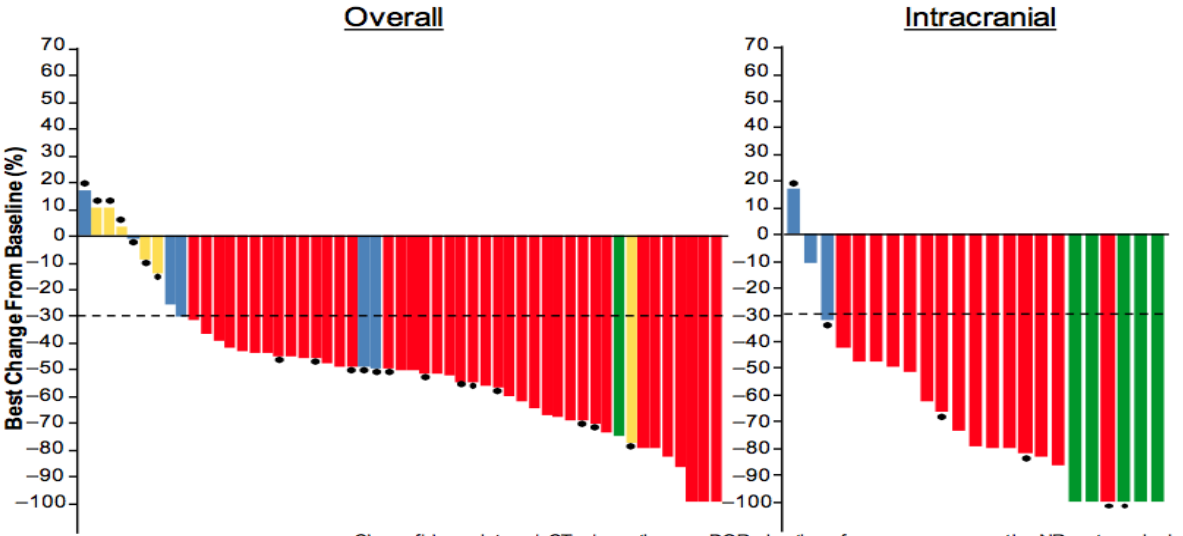
Ahn WCLC 17

Lorlatinib phase I/II study: crizotinib-pretreated patients

Efficacy in EXP2 (ALK+, Crizotinib Only) and EXP3A (ALK+, Crizotinib + CT)

	EXP2+3A (n=59)
ORR, n/N (%) (95% CI)	41/59 (69) (56, 81)
IC ORR, n/N (%) (95% CI)	25/37 (68) (50, 82)
Median DOR, mo (95% CI)	NR (11.1, NR)
DOR ≥6 mo, n°/n (%)	20/41 (49)
Median PFS, mo (95% CI)	NR (12.5, NR)

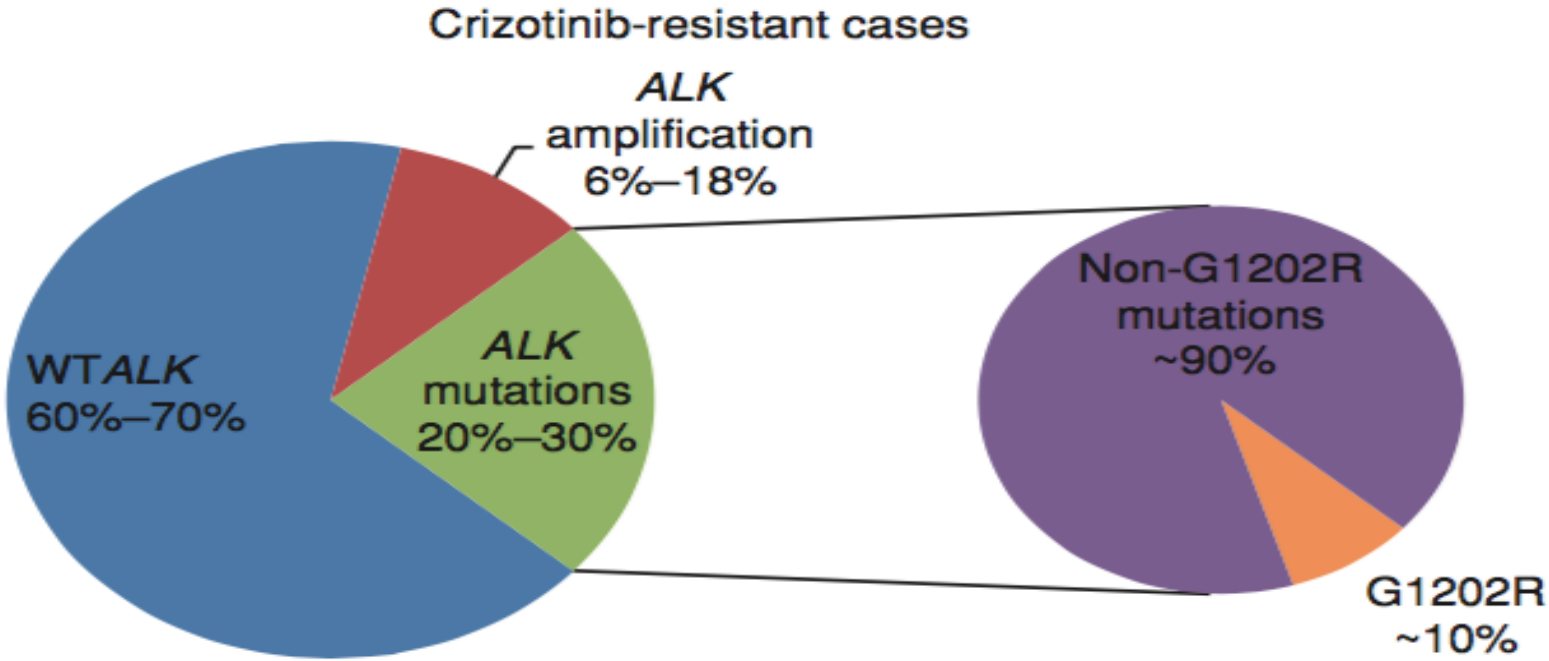
- 37 patients (63%) had brain metastases at baseline.



CI, confidence interval; CT, chemotherapy; DOR, duration of response; mo, months; NR, not reached.

Solomon WCLC 2017

Acquired resistance mechanisms to crizotinib



Lin Cancer Discov 17

Next-gen ALKi show relevant clinical benefit in crizotinib-refractory patients regardless of molecular status

NCCN National Comprehensive Cancer Network®

NCCN Guidelines Version 6.2018
Non-Small Cell Lung Cancer

NCCN Guidelines Index
Table of Contents
Discussion

ALK REARRANGEMENT POSITIVE[hh]

SUBSEQUENT THERAPY[mm,rr]

Progression on crizotinib[uu,vv]

- **Asymptomatic** →
  - Consider local therapy
  - Continue crizotinib or
  - Ceritinib[nn,ww,xx] or alectinib[nn,ww,xx] or brigatinib[nn,xx]
- **Symptomatic**
  - **Brain** →
    - Consider local therapy[yy]
    - Continue crizotinib or
    - Ceritinib[nn,ww,xx] or alectinib[nn,ww,xx] or brigatinib[nn,xx]
    - See NCCN Guidelines for CNS Cancers
  - **Systemic**
    - **Isolated lesion** →
      - Consider local therapy
      - Continue crizotinib
    - **Multiple lesions** →
      - Ceritinib[nn,ww,xx] or alectinib[nn,ww,xx] or brigatinib[nn,xx] or
      - See Initial cytotoxic therapy options[tt] Adenocarcinoma (NSCL-27) or Squamous cell carcinoma (NSCL-28)

→ **Progression** → See Initial cytotoxic therapy options[tt] Adenocarcinoma (NSCL-27) Squamous cell carcinoma (NSCL-28)

J Thorac Oncol. 2018 Jun 20. pii: S1556-0864(18)30714-7. doi: 10.1016/j.jtho.2018.06.005. [Epub ahead of print]

FULL-TEXT ARTICLE

Brigatinib in Patients With Alectinib-Refractory ALK-Positive NSCLC.

Lin JJ[1], Zhu VW[2], Schoenfeld AJ[3], Yeap BY[1], Saxena A[4], Ferris LA[1], Dagogo-Jack I[1], Farago AF[1], Taber A[5],

METHODS: A multicenter, retrospective study was performed at three institutions. Patients were eligible if they had advanced, **alectinib**-refractory ALK-positive NSCLC and were treated with **brigatinib**. Medical records were reviewed to determine clinical outcomes.

RESULTS: Twenty-two patients were eligible for this study. Confirmed objective responses to **brigatinib** were observed in 3 of 18 patients (17%) with measurable disease. Nine patients (50%) had stable disease on **brigatinib**. The median progression-free survival was 4.4 months (95% confidence interval [CI]: 1.8-5.6 months) with a median duration of treatment of 5.7 months

Cancer Sci. 2018 Sep;109(9):2863-2872. doi: 10.1111/cas.13721. Epub 2018

Phase II study of ceritinib in alectinib-pretreated patients with anaplastic lymphoma kinase-rearranged metastatic non-small-cell lung cancer in Japan: ASCEND-9.

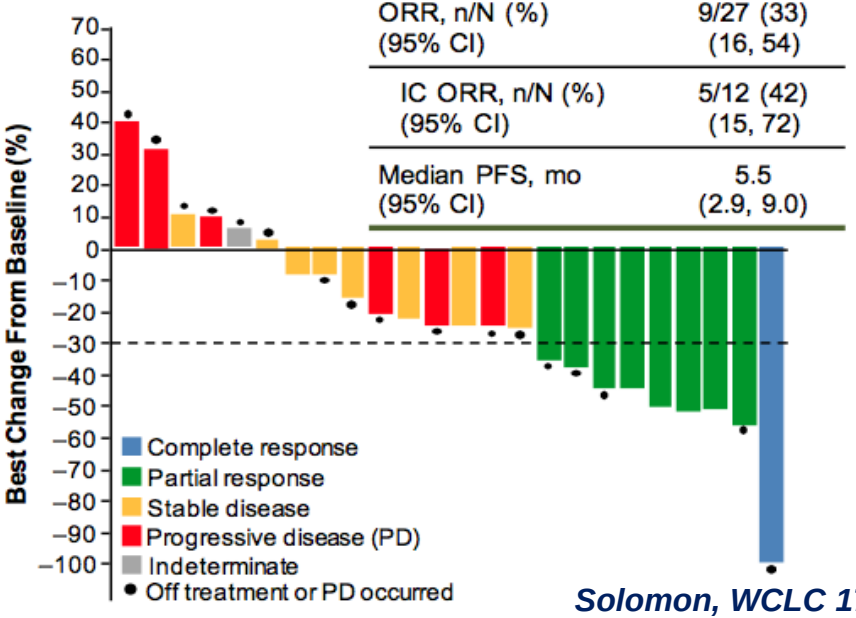
Hida T[1], Seto T[2], Horinouchi H[3], Maemondo M[4], Takeda M[5], Hotta K[6], Hirai F[2], Kim YH[7], Matsumoto S[8], Ito

fasted. A total of 20 patients were enrolled from August 2015 to March 2017. All patients received prior **alectinib** (100%), 13 (65.0%) patients received prior platinum-based chemotherapy, and 4 (20%) patients received prior crizotinib. Median duration of exposure and the follow-up time with **ceritinib** were 3.7 months (range: 0.4-15.1) and 11.6 months (range: 4.8-23.0), respectively. Investigator-assessed ORR was 25% (95% CI: 8.7-49.1). Key secondary endpoints, all investigator assessed, included disease control rate (70.0%; 95% CI: 45.7-88.1), time to response (median, 1.8 months; range: 1.8-2.0), and duration of response (median, 6.3 months; 95% CI: 3.5-9.2). Median progression-free survival was 3.7 months (95% CI: 1.9-5.3).

Lorlatinib phase I/II study: post next-gen ALKi

Overall[a,b]

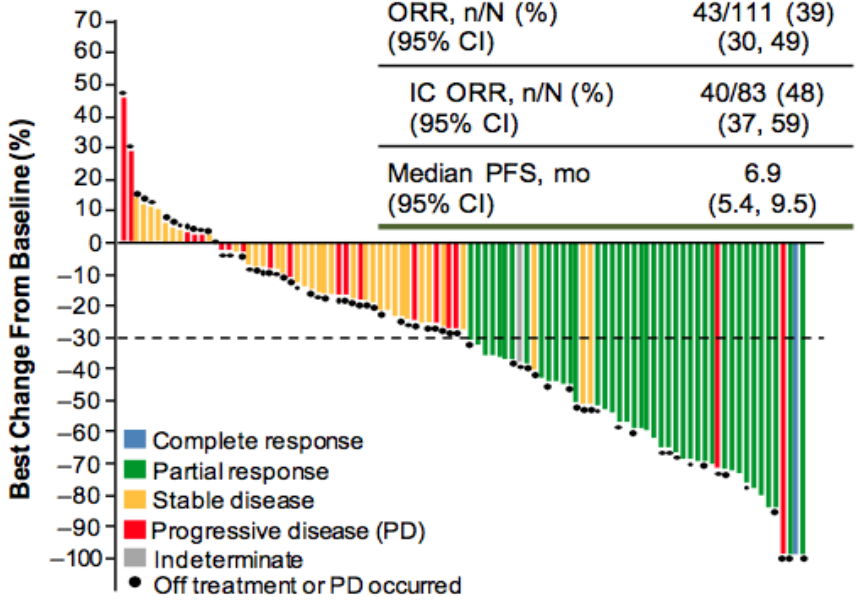
	EXP3B: 1 non-crizotinib TKI ± chemo (n=27)
ORR, n/N (%) (95% CI)	9/27 (33) (16, 54)
IC ORR, n/N (%) (95% CI)	5/12 (42) (15, 72)
Median PFS, mo (95% CI)	5.5 (2.9, 9.0)



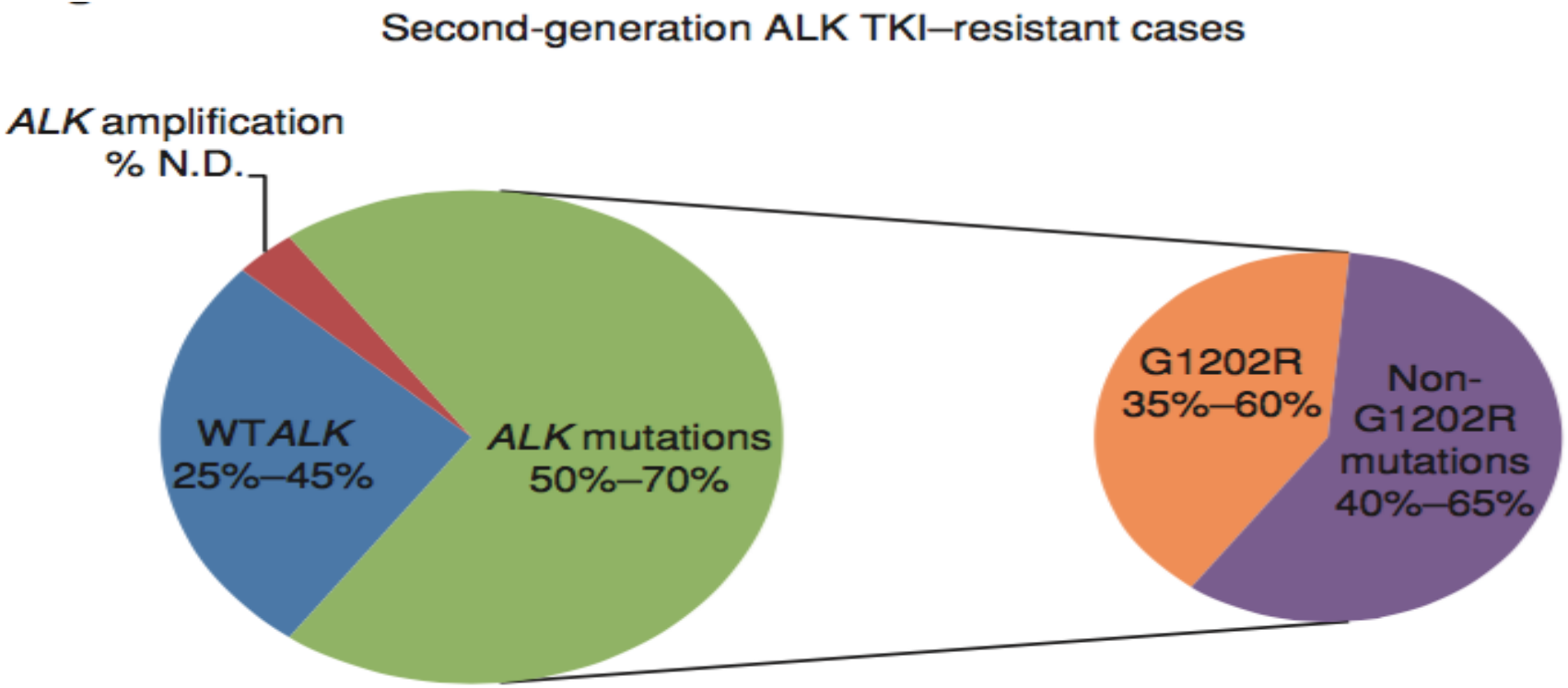
Solomon, WCLC 17

Overall[a,b]

	EXP4–5: ≥2 prior ALK TKIs ± chemo (n=111)
ORR, n/N (%) (95% CI)	43/111 (39) (30, 49)
IC ORR, n/N (%) (95% CI)	40/83 (48) (37, 59)
Median PFS, mo (95% CI)	6.9 (5.4, 9.5)



Acquired resistance mechanisms to next-gen ALKi



Lin Cancer Discov 17

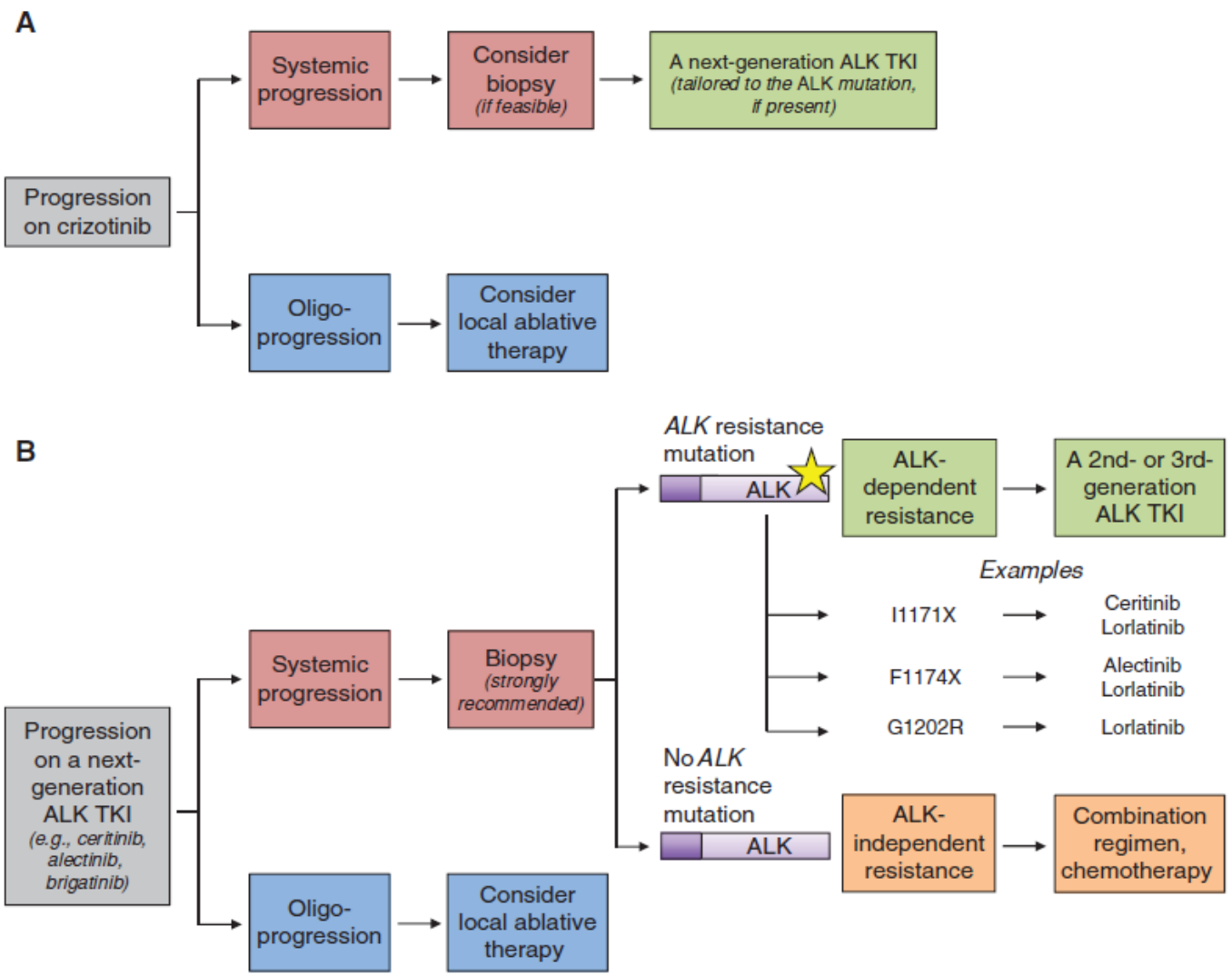
ALK kinase domain mutations – drug efficacy

	Crizotinib	Alectinib	Brigatinib	Ceritinib	Lorlatinib
G1123S	Res	Sens[2]	N/D	Res[2]	N/D
1151Tins	Res	Res[3]	N/D	Res[7]	Sens[9]
L1152P/R	Res	Sens	N/D	Res[7]	Sens[9]
C1156Y/T	Res	Sens	N/D	Res[7]	Sens[9]
I1171T/N	Res	Res[4,5]	N/D	Sens[4,5,7]	N/D
F1174C/L/V	Res	Sens	Sens[6]	Res[7]	Sens[9]
V1180L	Res	Res [4]	N/D	Sens[4]	N/D
L1196M	Res	Sens[3]	Sens[6]	Sens[7]	Sens[9]
L1198F	Sens [1]	Res[1]	Res[1]	Res[1]	Res[1]
G1202R	Res	Res[3]	N/D	Res[7]	Sens[9]
S1206C/Y	Res	Sens[3]	Res[6]	Sens[7]	Sens[9]
F1245C	Res[8]	N/D	N/D	Sens[8]	N/D
G1269A/S	Res	Sens	N/D	Sens[7]	Sens[9]

1.Shaw NEJM 16; 2.Toyokawa JTO 15; 3.Katayama STM 12; 4.Katayama CCR 14; 5.Ou Lung Cancer 15; 6.Ceccon MCR 14; 7.Friboulet Cancer Discov 14; 8.Kodityal Lung Cancer16; 9.Zou Cancer Cell 15; 10.Bayliss Cel Mol Lif Sci 15; 11.Gainor Cancer Discovery 16

IASLC
INTERNATIONAL ASSOCIATION FOR THE STUDY

Potential algorithm

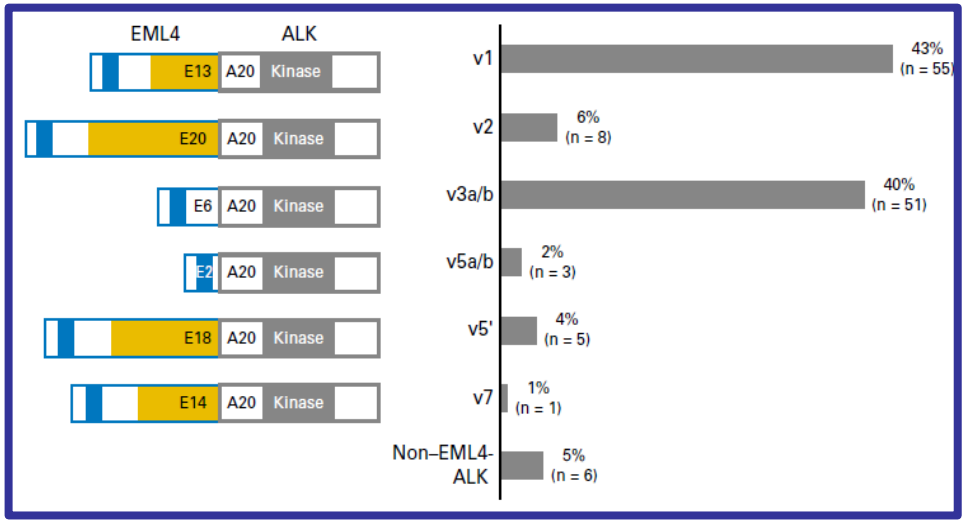


Shaw Cancer Discovery 17

THE TYPE OF FUSION MAY BECOME RELEVANT TO SELECT 1L ALKi

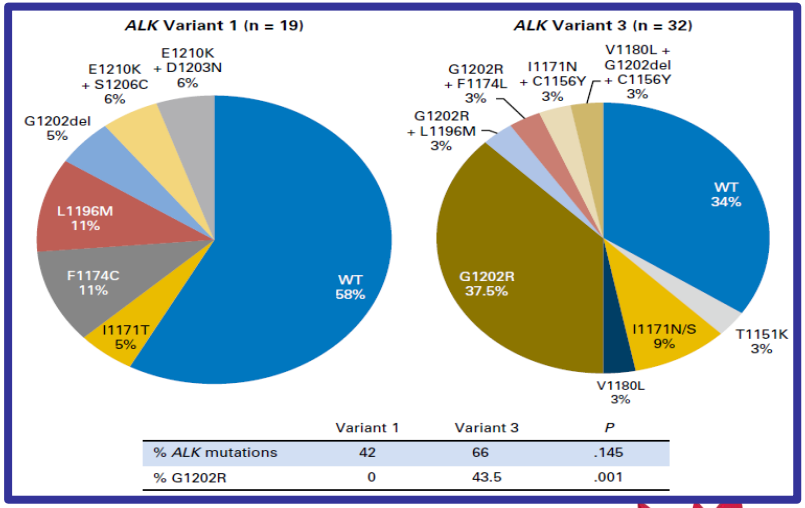
Mechanisms of resistance differ by ALK-fusion variant

Frequency of ALK variants in NSCLC biopsies



Lin JCO 18

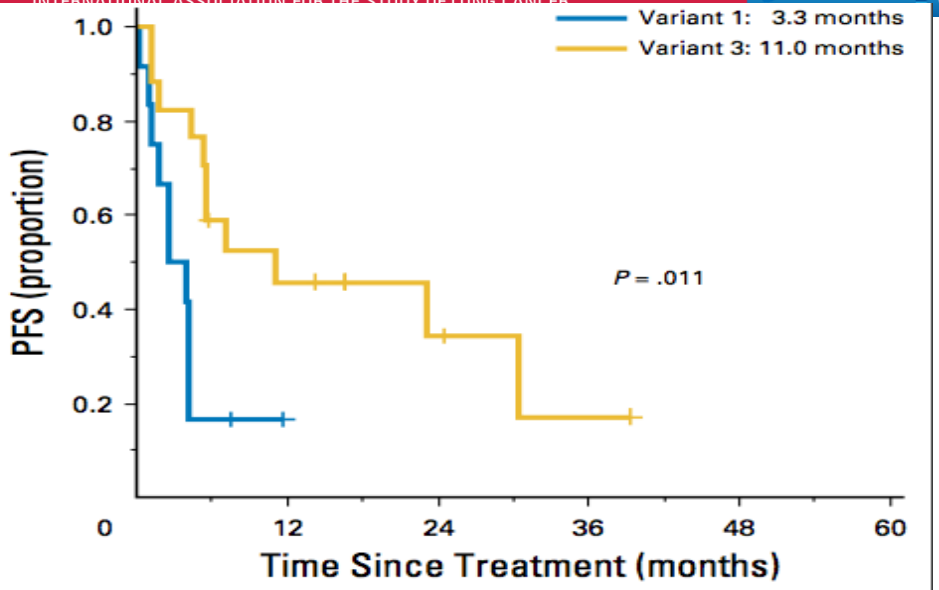
Distribution of ALK resistance mutations in NSCLC biopsies



	Variant 1	Variant 3	*P*
% *ALK* mutations	42	66	.145
% G1202R	0	43.5	.001

Biopsies obtained after disease PD on a next-gen ALKi by EML4-ALK variant

WCLC 2018



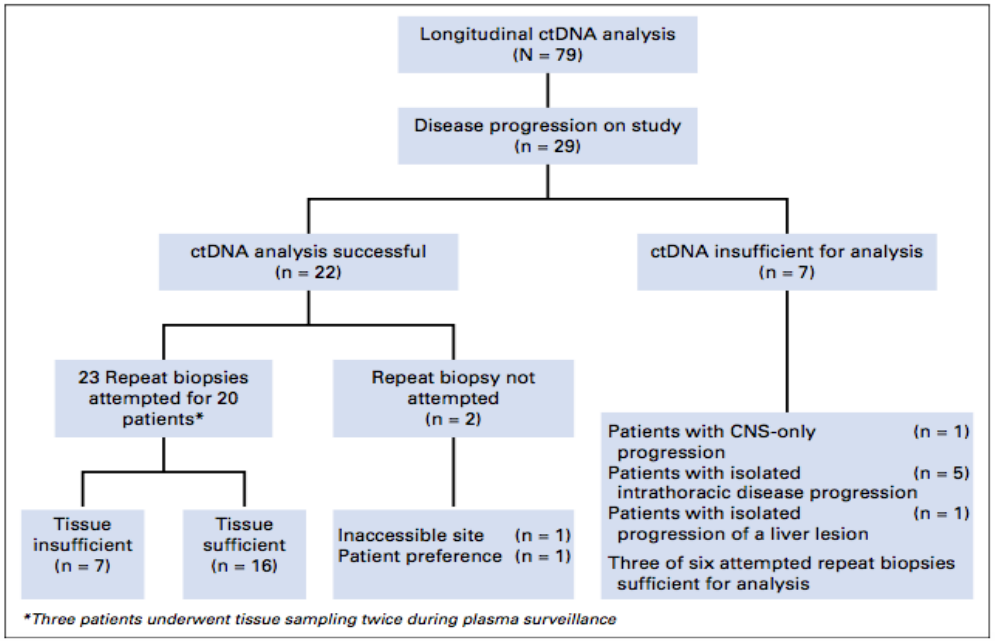
PFS with lorlatinib administered after crizotinib and at least one 2nd-gen ALK TKI in v1 (n = 12) and v3 (n = 17)

Effect of ALK variants on outcomes to ALKi

- EML4-ALK v3 is associated with a significantly higher incidence of ALK resistance mutations, particularly G1202R, and provide a potential molecular link between variant and clinical outcome
- ALK variant status may represent an important emerging factor in guiding the treatment strategy for ALK+ NSCLC

Lin JCO 18

Plasma genotyping by NGS is an effective method for detecting ALK fusions

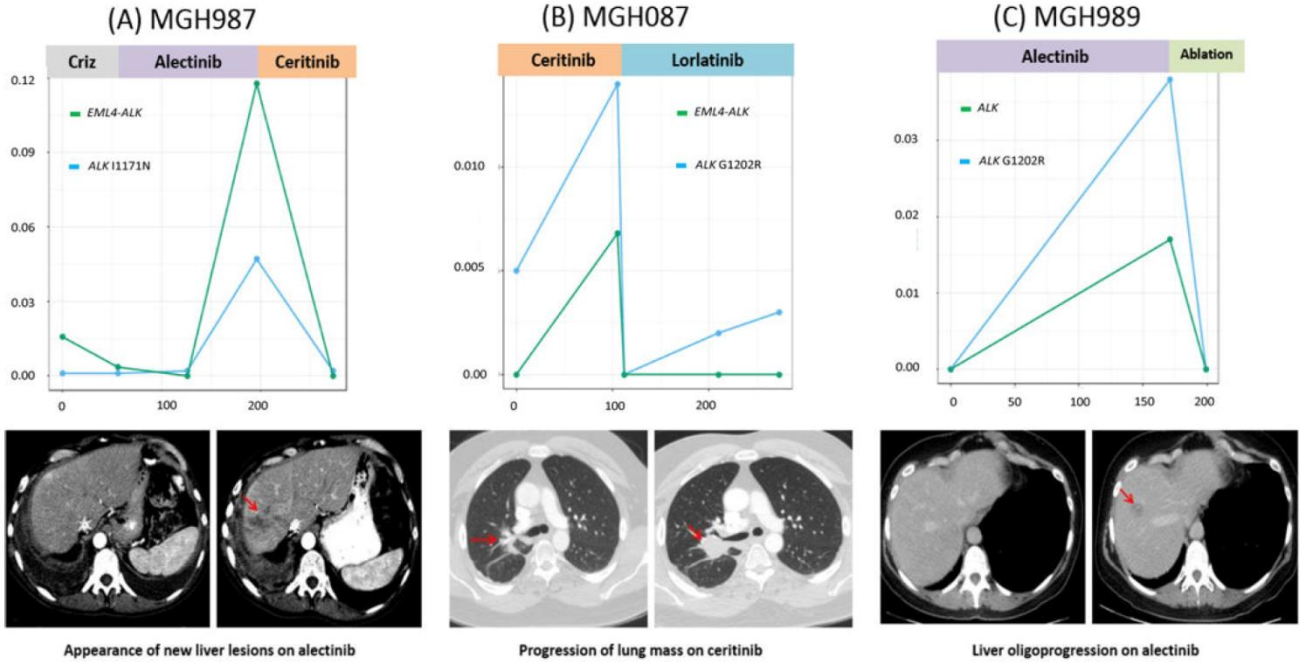


High degree of concordance between plasma and tissue alterations

- At disease PD, ALK fusion was detected in plasma from 19 (86%) of 22 patients
- Among 16 cases where contemporaneous plasma and tissue specimens were available 100% concordance between ALK mutation results observed

Dagogo-Jack JCO Prec Oncol 18

Tracking the evolution of resistance to ALKi



Quantitative assessment of structural variants may be clinically useful and complementary to radiographic assessment in some patients

Dagogo-Jack JCO Prec Oncol 18

CAP/IASLC/AMP Recommendation	ASCO Endorsed Recommendation (with modifications or qualifying statements in ***bold italics***)
No Recommendation: There is currently insufficient evidence to support a recommendation for or against routine testing for *ALK* mutational status for patients with lung adenocarcinoma with sensitizing *ALK* mutations who have progressed after treatment with an ALK-targeted TKI.	There is currently insufficient evidence to support a recommendation for or against routine testing for *ALK* mutational status for patients with lung adenocarcinoma with sensitizing *ALK* mutations who have progressed after treatment with an ALK-targeted TKI.

Kalemkerian JCO 18

REVIEW ARTICLE

IASLC

Liquid Biopsy for Advanced Non-Small Cell Lung Cancer (NSCLC): A Statement Paper from the IASLC

Check for updates

Christian Rolfo, MD, PhD, MBA,[a] Philip C. Mack, PhD,[b] Giorgio V. Scagliotti, MD, PhD,[c] Paul Baas, MD, PhD,[d] Fabrice Barlesi, MD, PhD,[e] Trever G. Bivona, MD, PhD,[f] Roy S. Herbst, MD, PhD,[g] Tony S. Mok, MD,[h] Nir Peled, MD, PhD,[i] Robert Pirker, MD,[j] Luis E. Raez, MD,[k] Martin Reck, MD, PhD,[l] Jonathan W. Riess, MD,[b] Lecia V. Sequist, MD, MPH,[m] Frances A. Shepherd, MD,[n] Lynette M. Sholl, MD,[o] Daniel S. W. Tan, MBBS, PhD,[p] Heather A. Wakelee, MD,[q] Ignacio I. Wistuba, MD,[r] Murry W. Wynes, PhD,[s] David P. Carbone, MD, PhD,[t] Fred R. Hirsch, MD, PhD,[u,*] David R. Gandara, MD[b]

Recommendations

Detection of *ALK* acquired resistance mutations in patients progressing during *ALK* TKIs is not required in clinical practice to switch them to a different *ALK* TKI. However, such information may be valuable in determining the optimum choice of next-generation TKIs, which have differing activity against distinct mutations. When re-biopsy of the progressing site is not feasible, comprehensive testing such as a NGS panel using ctDNA is preferred because this method can provide information not only on *ALK* resistance mutations but also on other molecular mechanisms of resistance for which the patient may receive treatment either through a clinical trial or expanded access.

Guiding second line treatment in ALK+ patients (sequence of drugs, re-biopsy?)
TAKE HOME MESSAGE

- ALKi have favourably transformed the course of disease for ALK+ patients
  - ✓ After crizotinib failure: next-gen ALKi, active
  - ✓ Standard therapy at PD after next-gen ALKi is not well defined: resistance mechanisms may guide treatment after next-gen ALKi
- Plasma genotyping by using NGS technology can reliably detect ALK fusions / ALK resistance mutations
- Specific ALK variants may be associated with the development of resistance mutations to *A*LKi: implementation of NGS for testing
- Re-biopsies / liquid biopsy encouraged in patients with PD to ALKi to better understand resistances mechanisms and develop future therapeutic approaches

Σας ευχαριστώ