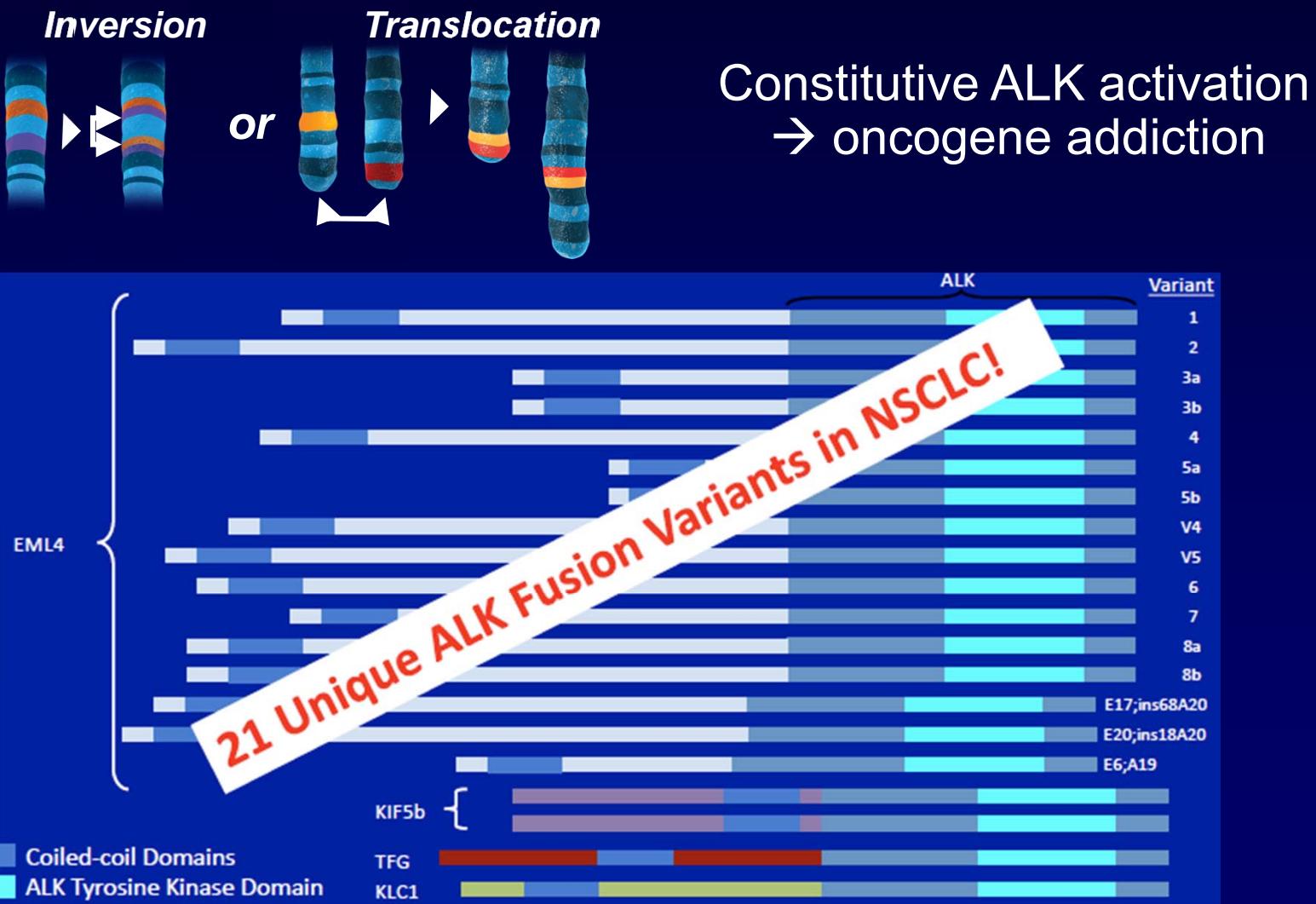


# **Case #3—Adenocarcinoma With *ALK* Rearrangement: Selecting Optimal Approach**

**Natasha Leighl, MD, MMSc, FRCPC**  
OSI Pharmaceuticals Foundation  
Princess Margaret Hospital  
Toronto, Canada

# *EML4–ALK* Fusion Oncogene Key Driver in 2% to 7% NSCLC



ALK, anaplastic lymphoma kinase; EML4, echinoderm microtubule-associated protein like 4

Soda M, et al. *Nature*. 2007;448(7153):561-566. Kwak EL, et al. *N Engl J Med*. 2010;363(18):1693-1703.

# ALK-Positive NSCLC: Clinical Characteristics

- Higher prevalence of *EML4-ALK* fusion in patients with:
  - Adenocarcinoma histology
  - Never/light smoking history
  - Younger
- Incidence similar: Europe (3.7%), US (8% ADC), Asia (5.8% ADC)

Example: Lung Cancer Mutation Consortium Analysis of Adenocarcinomas

N = 643	ALK-positive	ALK-negative	P
Mean age	52.3 years	59.9 years	<.0001
Smoking history			
Current	3%	8%	.0001
Former	33%	61%	
Never	64%	31%	

Rodig SJ, et al. *Clin Cancer Res.* 2009;15(16):5216-5223. Shaw AT, et al. *J Clin Oncol.* 2009;27(26):4247-4253. Varella Garcia M, et al. *J Thorac Oncol.* 2011;6(Suppl 2): Abstract O05.01. Barlesi F, et al. *J Clin Oncol.* 2013;31(Suppl): Abstract 8000. Kris MG, et al. *JAMA.* 2014;311(19):1998-2006. Sun Y, et al. *J Clin Oncol.* 2010;28(30):4616-4620.

# Which Is Best First-Line? Crizotinib vs Chemotherapy

## PROFILE 1014

### Key entry criteria

- ALK-positive by central FISH testing<sup>a</sup>
- Locally advanced, recurrent, or metastatic non-squamous NSCLC
- No prior systemic treatment for advanced disease
- ECOG PS 0-2
- Measurable disease
- Stable treated brain metastases allowed

R  
A  
N  
D  
O  
M  
I  
Z  
E<sup>b</sup>  
N = 343

Crizotinib  
250 mg BID PO,  
continuous dosing  
(n = 172)

Pemetrexed  
500 mg/m<sup>2</sup>  
+  
cisplatin 75 mg/m<sup>2</sup> or  
carboplatin AUC 5-6  
q3w for ≤6 cycles  
(n = 171)

CROSSOVER TO CRIZOTINIB  
PERMITTED AFTER PROGRESSION<sup>c</sup>

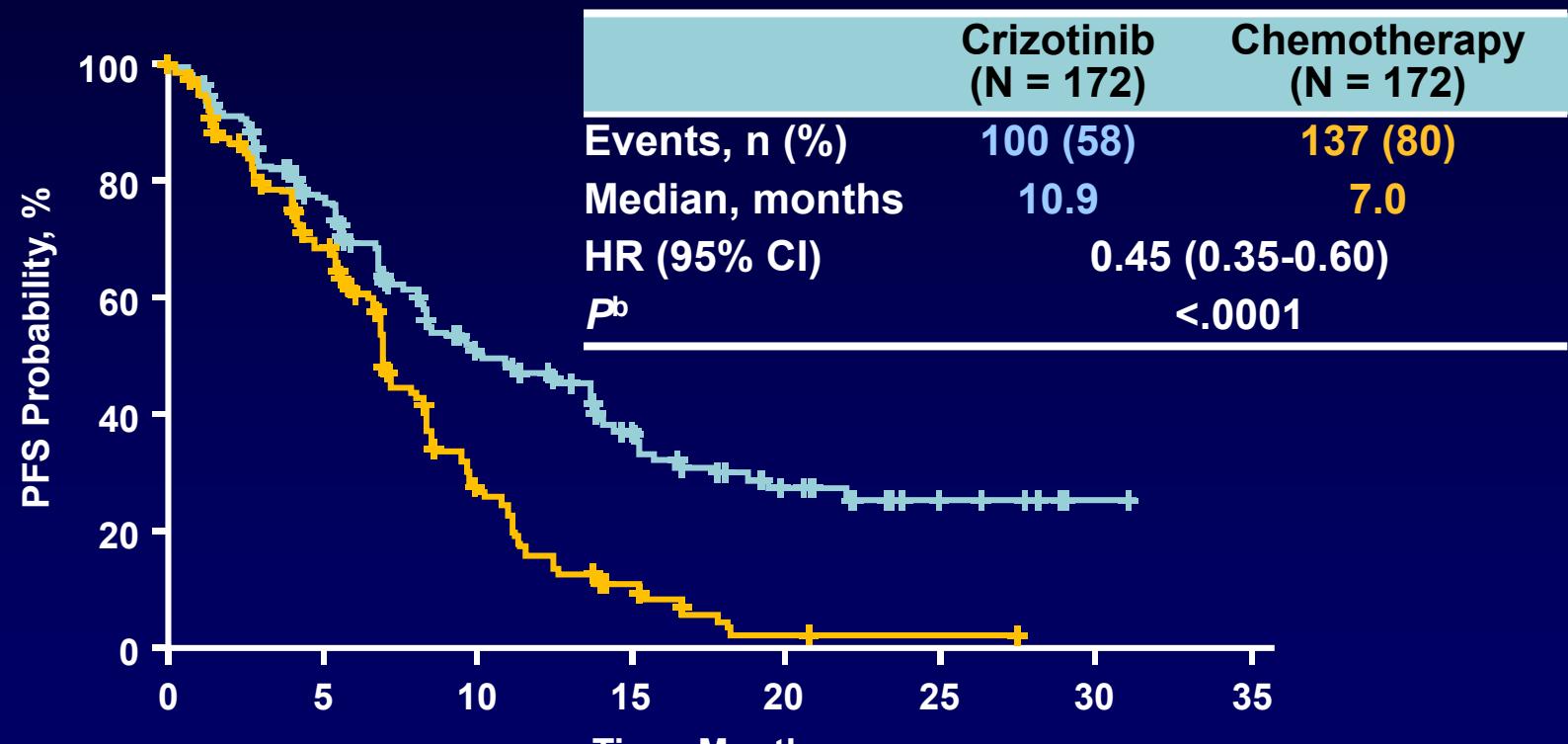
### Endpoints

- Primary
  - PFS (RECIST 1.1, independent radiologic review [IRR])
- Secondary
  - ORR
  - OS
  - Safety
  - Patient-reported outcomes (EORTC QLQ-C30, LC13)

<sup>a</sup>ALK status determined using standard ALK break-apart FISH assay <sup>b</sup>Stratification factors: ECOG PS (0/1 vs. 2), Asian vs non-Asian race, and brain metastases (present vs absent) <sup>c</sup>Assessed by IRR

# PROFILE 1014

## Primary Endpoint Met: Crizotinib Superior to 1L Pemetrexed-Based Chemotherapy in Prolonging PFS<sup>a</sup>



No. at risk								
Crizotinib	172	120	65	38	19	7	1	0
Chemotherapy	171	105	36	12	2	1	0	0

Data cutoff: November 30, 2013

<sup>a</sup>Assessed by IRR <sup>b</sup>1-sided stratified log-rank test

Mok T, et al. *J Clin Oncol*. 2014;32(5s): Abstract 8002.

# PROFILE 1014

## Secondary Endpoints: ORR<sup>a</sup> and OS

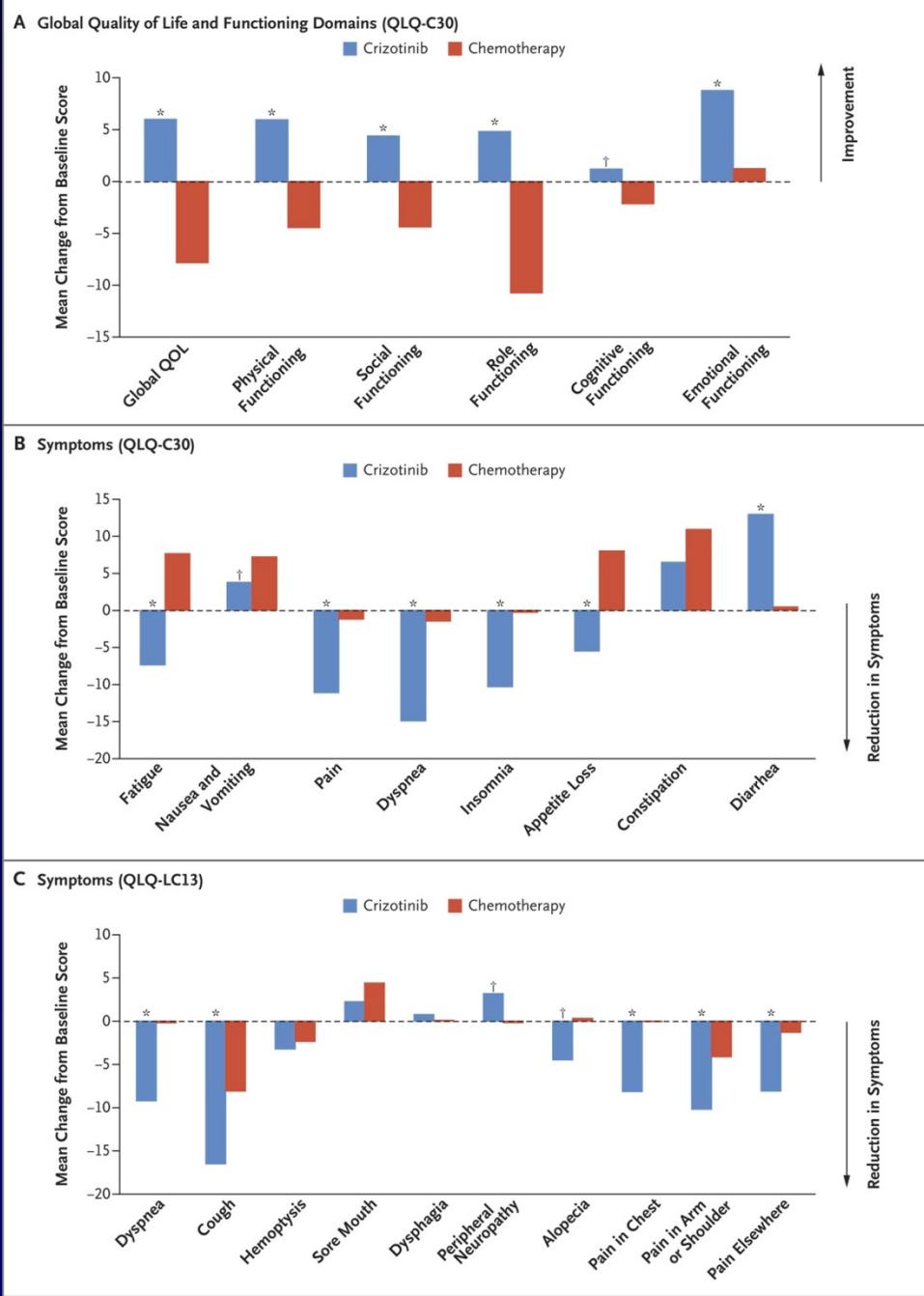
	Crizotinib (N = 172)	Chemotherapy <sup>b</sup> (N = 171)
<b>ORR, % (n)</b>	<b>74 (128)</b>	<b>45 (77)</b>
95% exact CI of ORR	67-81	37-53
<b>Treatment difference, % (95% CI<sup>c</sup>)</b>		<b>29 (20-39)</b>
<i>P</i> <sup>c</sup>		<.0001
<b>Median time to response,<sup>d</sup> weeks</b>	<b>6.1</b>	<b>12.1</b>
Range	2.7-41.4	5.1-36.7
<b>Median duration of response,<sup>d,e</sup> weeks</b>	<b>49.0</b>	<b>22.9</b>
<b>95% CI<sup>f</sup></b>	<b>35.1-60.0</b>	<b>18.0-25.1</b>

- Objective responses with crizotinib were rapid and durable
- With 68% of patients still in follow-up, median OS was not reached in either arm
  - A significant difference was not demonstrated (HR: 0.82; 95% CI: 0.54-1.26; *P* = .180)
  - Analysis was not adjusted for the potentially confounding effects of crossover
  - 120/171 chemotherapy patients (70%) received crizotinib after progression

<sup>a</sup>By IRR; <sup>b</sup>before crossover to crizotinib; <sup>c</sup>Pearson  $\chi^2$  test; <sup>d</sup>in patients with an objective response <sup>e</sup>Kaplan-Meier method;

<sup>f</sup>Brookmeyer-Crowley method

Mok T, et al. *J Clin Oncol.* 2014;32(5s): Abstract 8002.



**Crizotinib  
improves quality of  
life and cancer-  
related symptoms  
over first-line  
chemotherapy**

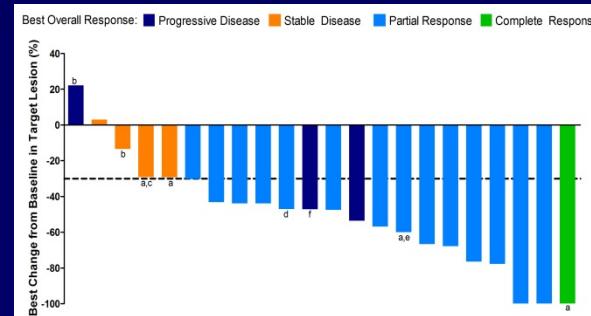
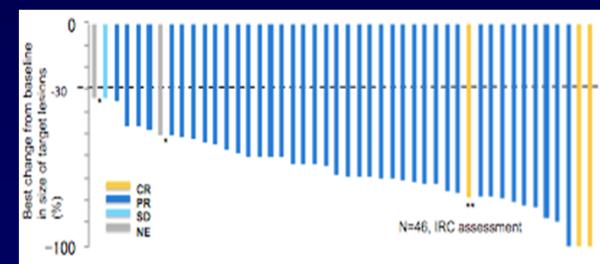
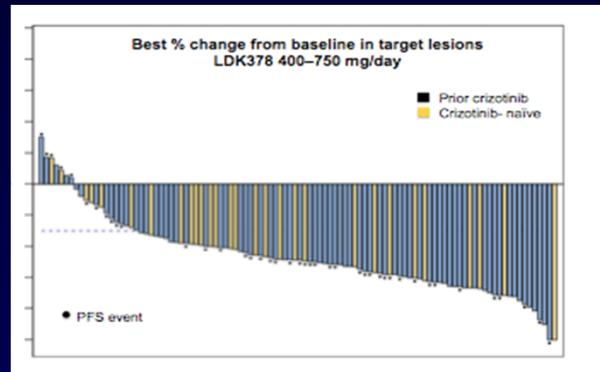
# Chemotherapy in ALK-Positive NSCLC

	Line	N	ORR	PFS
Platinum/pemetrexed <sup>1</sup> ≤6 cycles	1st	171	45%	7.0 months
Crizotinib <sup>1</sup>	1st	172	74%	10.9 months
Pemetrexed <sup>2</sup>	2nd	99	29%	4.2 months
Docetaxel <sup>2</sup>	2nd	72	7%	2.6 months
Crizotinib <sup>2</sup>	2nd	172	65%	7.7 months

1. Mok T, et al. *J Clin Oncol.* 2014;32(5s): Abstract 8002. 2. Shaw AT, et al. *N Engl J Med.* 2013;368(25):2385-2394.

# Activity of Other ALK TKIs

ALK TKI	RR, % (n) Crizotinib Naïve	RR, % (n) Crizotinib Resistant	mPFS, m
Ceritinib			
LDK378 (Novartis)	72% (83)	56% (163)	9.0 (6.9-18.4)
Alectinib CH5425802 (Roche)	93.5% (46)	60% (47)	>14
AP26113 (Araid)	100% (7)	69% (45/65)	13



Felipe E, et al. *Ann Oncol.* 2014; Abstract 4380. Shaw AT, et al. *N Engl J Med.* 2014;370(26):2537-2539. Gadgeel SM, et al. *Lancet Oncol.* 2014;15(10):1119-1128. Nakagawa K, et al. *J Clin Oncol.* 2013;31(Suppl): Abstract 8033; Gettinger, S, et al. ESMO 2014: Abstract 5146

# Alectinib and Ceritinib: First-Line Phase III Studies

## Alectinib<sup>1</sup> (ALEX Trial)

**Eligibility criteria:**

- ALK-positive locally advanced/metastatic NSCLC
- No prior treatment for advanced disease

R  
A  
N  
D  
O  
M  
I  
Z  
E

Alectinib 600 mg BID  
(n = 143)

Crizotinib 250 mg BID  
(n = 143)

**Primary endpoint = PFS\***

\*Determined by investigators, based on RECIST v1.1

## Ceritinib<sup>2</sup>

**Eligibility criteria:**

- ALK-positive locally advanced/metastatic nonsquamous NSCLC
- No prior treatment for advanced disease

R  
A  
N  
D  
O  
M  
I  
Z  
E

Ceritinib 750 mg  
(n = 174)

Pemetrexed/cisplatin  
OR  
pemetrexed/carboplatin q3w  
(n = 174)

Pemetrexed  
q3w

**Primary endpoint: PFS**

1. National Institutes of Health. Available at: <http://clinicaltrials.gov/ct2/show/NCT02075840>. Accessed 12 December 2014. 2. National Institutes of Health. Available at: <http://clinicaltrials.gov/ct2/show/NCT01828099>. Accessed 12 December 2014

# Common Crizotinib Toxicities (PROFILE 1014)

	Crizotinib (n = 171), n (%)	
	Any Grade	Grade 3/4
Vision disorder <sup>c</sup>	122 (71)	1 (1)
Diarrhea	105 (61)	4 (2)
Edema <sup>c</sup>	83 (49)	1 (1)
Vomiting	78 (46)	3 (2)
Constipation	74 (43)	3 (2)
Elevated transaminases <sup>c</sup>	61 (36)	24 (14)
Abdominal pain <sup>c</sup>	45 (26)	0
Dysgeusia	45 (26)	0
Headache	37 (22)	2 (1)

- Permanent treatment discontinuations due to treatment-related AEs: 5% and 8%, respectively<sup>b</sup>
- No grade 5 AEs were reported to be related to treatment; 1 patient in the chemotherapy arm had grade 5 pneumonitis after crossover to crizotinib, considered to be treatment-related

<sup>a</sup>Not adjusted for differential treatment duration; <sup>b</sup>Before crossover to crizotinib; <sup>c</sup>clustered term

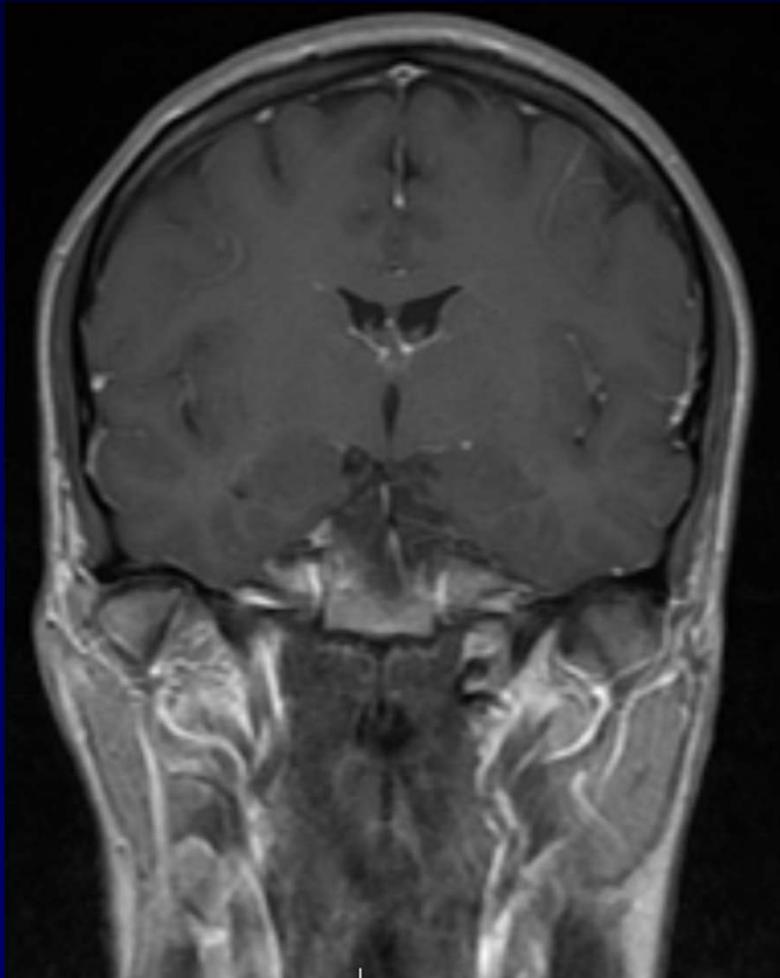
Solomon BJ, et al. *N Engl J Med.* 2014;371(23):2167-2177.

# Dose Modification Scheme

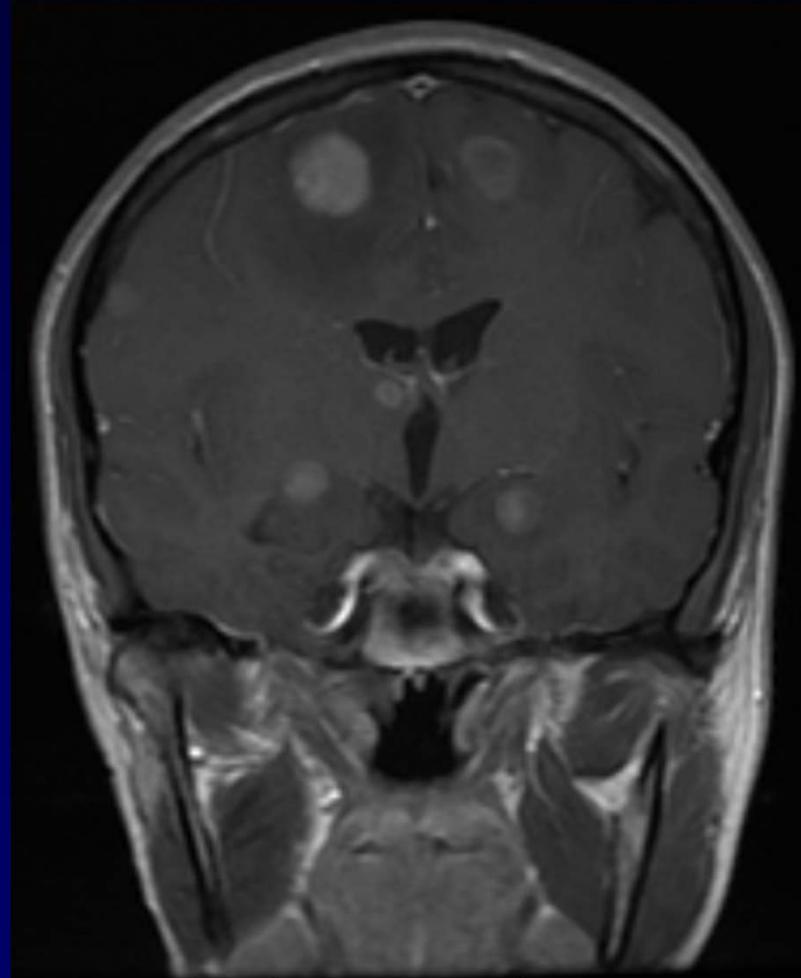
CTCAE <sup>b</sup> Grade	Crizotinib Dosing
<b>Hematologic Toxicities<sup>a</sup></b>	
Grade 3	Withhold until recovery to grade ≤2, then resume at the same dose schedule
Grade 4	Withhold until recovery to grade ≤2, then resume at 200 mg twice daily <sup>c</sup>
<b>Nonhematologic Toxicities</b>	
Grade 3 or 4 ALT or AST elevation with grade ≤1 total bilirubin	Withhold until recovery to grade ≤1 or baseline, then resume at 200 mg twice daily <sup>d</sup>
Grade 2, 3 or 4 ALT or AST elevation with grade 2, 3 or 4 total bilirubin elevation	Permanently discontinue
Any Grade pneumonitis <sup>e</sup>	Permanently discontinue
Grade 3 QTc prolongation	Withhold until recovery to grade ≤1, then resume at 200 mg twice daily <sup>d</sup>
Grade 4 QTc prolongation	Permanently discontinue

<sup>a</sup> Except lymphopenia (unless associated with clinical events, eg, opportunistic infections); <sup>b</sup> NCI Common Terminology Criteria for Adverse Events; <sup>c</sup> In case of recurrence, withhold until recovery to grade ≤2, then resume at 250 mg once daily. Permanently discontinue in case of grade 4 recurrence; <sup>d</sup> In case of recurrence, withhold until recovery to grade ≤1, then resume at 250 mg once daily. Permanently; discontinue in case of further grade 3 or 4 recurrence; <sup>e</sup> Not attributable to NSCLC progression, other pulmonary disease, infection, or radiation effect.

# A Common Scenario

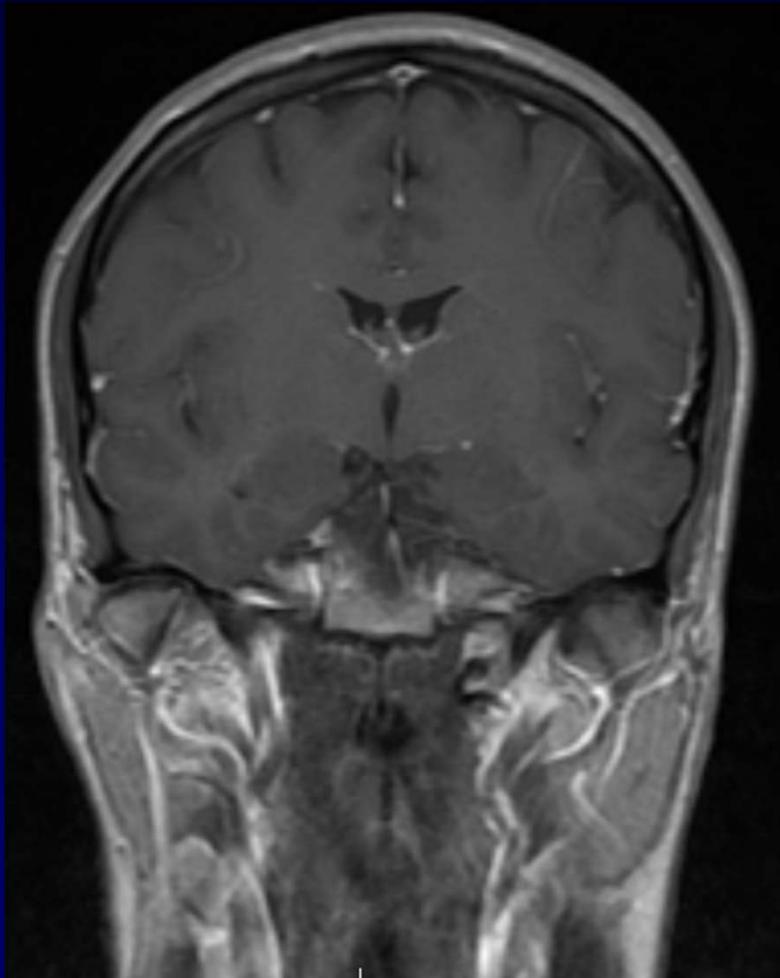


Baseline

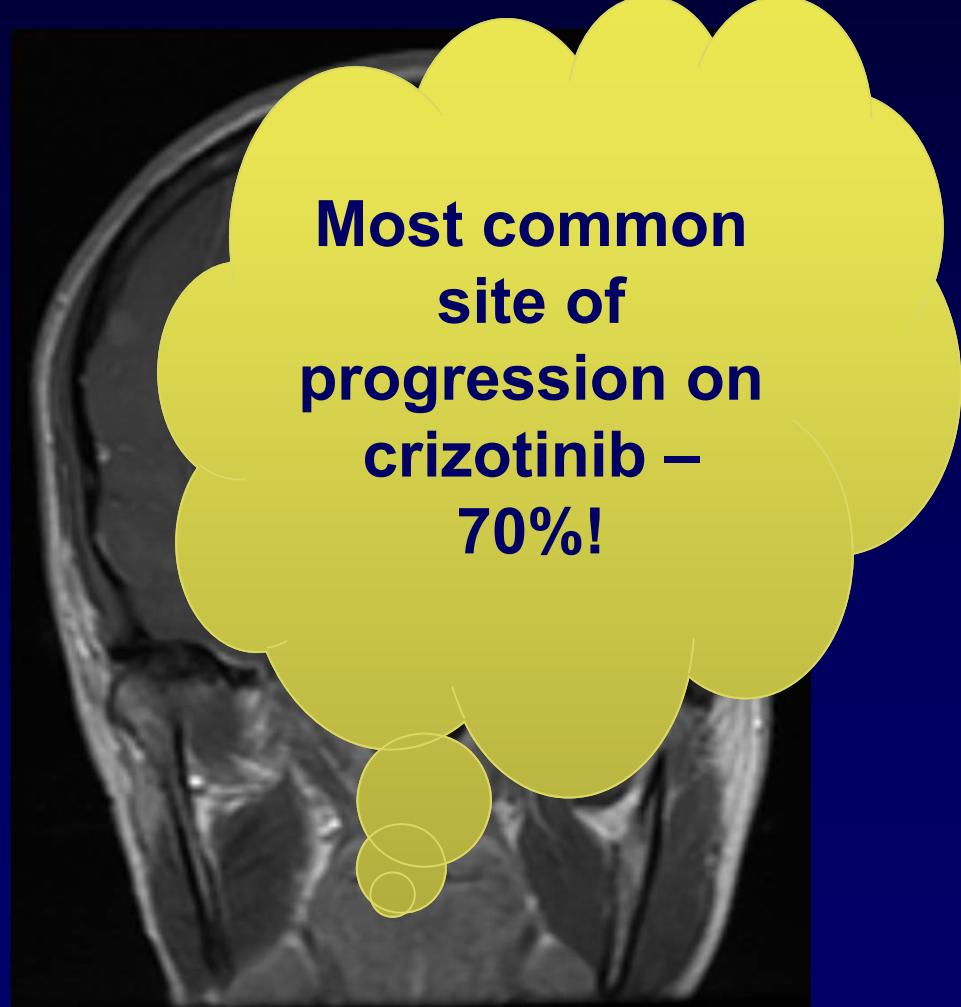


After 9 months of crizotinib

# A Common Scenario



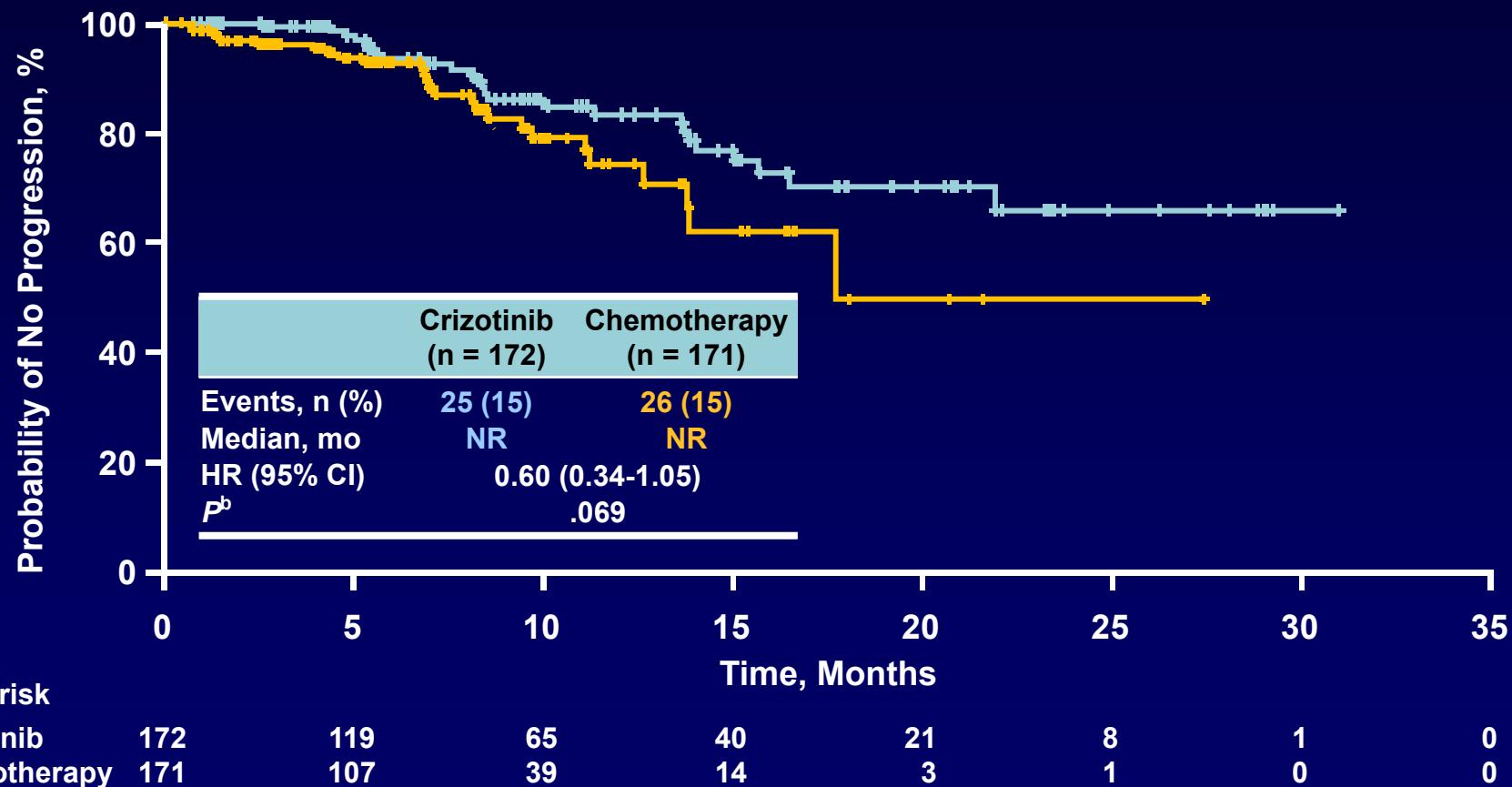
Baseline



After 9 months of crizotinib

**Most common  
site of  
progression on  
crizotinib –  
70%!**

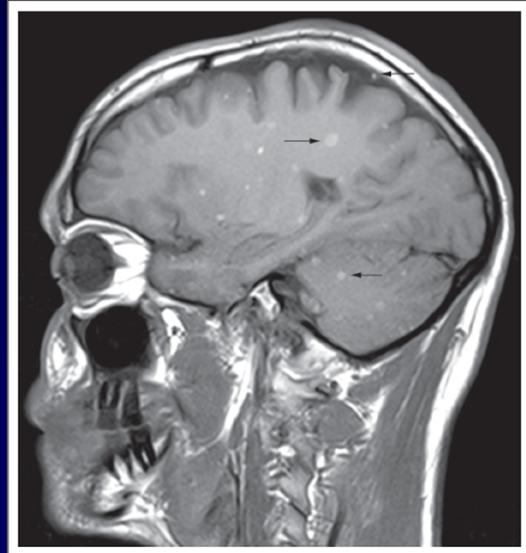
# Intracranial TTP<sup>a</sup> by IRR in ITT Population



NR, not yet reached; <sup>a</sup>Time from randomization to first documentation of intracranial tumor progression; <sup>b</sup>2-sided log-rank test

Solomon BJ, et al. Ann Oncol. 2014;25(Suppl 4):iv426-iv470

# CNS Relapses Represent Pharmacokinetic Failure Rather Than Biologic Resistance

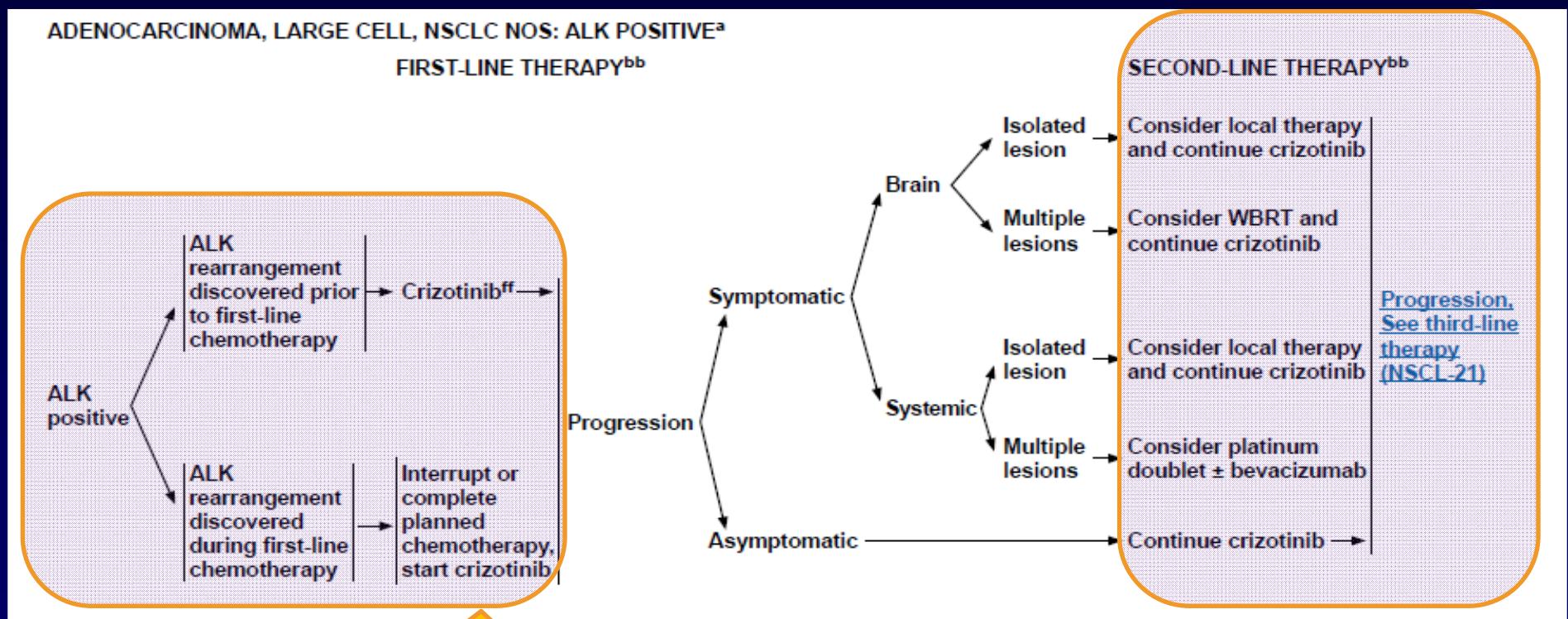


	Crizotinib	PF-06463922
<b>ALK WT NIH3T3 IC<sub>50</sub> (nM)</b>	<b>80</b>	<b>1.5</b>
<b>ALK L1196M NIH3T3 IC<sub>50</sub> (nM)</b>	<b>843</b>	<b>21</b>
<b>ROS1-CD74 IC<sub>50</sub> (nM)</b>	<b>11</b>	<b>0.24</b>
MDR BA/AB	<b>45</b>	<b>1.5</b>
CSF or free brain:free plasma (rodent)	--	0.23-0.33
Log D	2.0	2.3

CSF: Plasma ratio 0.0026

Costa DB, et al. *J Clin Oncol*. 2011;29(15):e443-445. Smeal. Presented at: 14th Annual Targeted Therapies of the Treatment of Lung Cancer Meeting, February 19-22, 2014; Santa Monica, California.

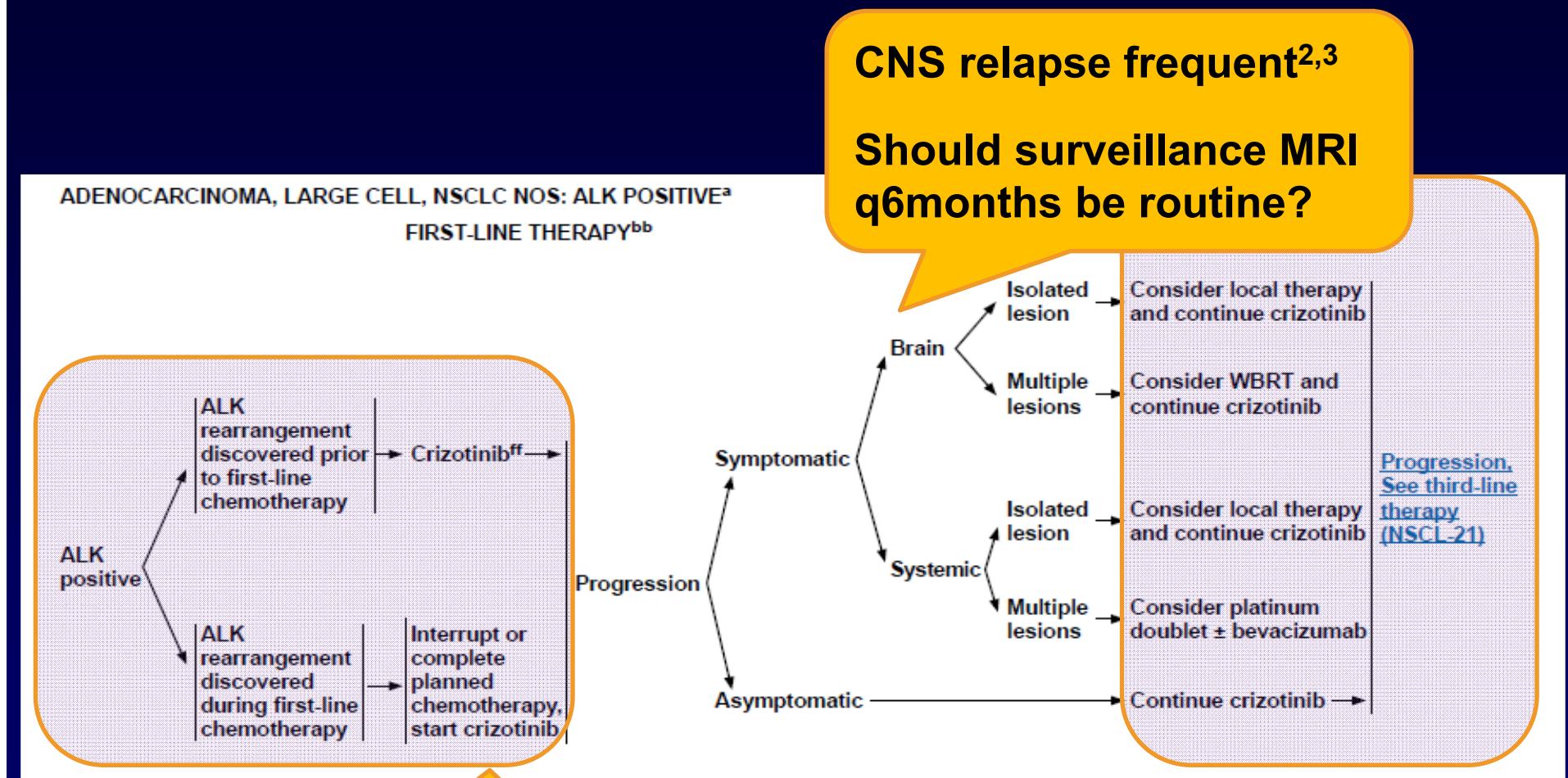
# Current Recommendations and Guidelines



<sup>ff</sup>Consider ROS1 testing; if positive, may treat with crizotinib (Bergethon K, et al. *J Clin Oncol.* 2012;30(8):863-870.); \*All recommendations are category 2A unless otherwise indicated

1. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines<sup>®</sup>) – Non-Small Cell Lung Cancer. Version 3.2014. 2. Otterson GA, et al. *J Clin Oncol.* 2012;30(Suppl): Abstract 7600. 3. Weickhardt AJ, et al. *J Clin Oncol.* 2012;30(Suppl): Abstract 7526.

# Current Recommendations and Guidelines



Crizotinib is the only approved ALK inhibitor in the 1L setting

<sup>ff</sup>Consider ROS1 testing; if positive, may treat with crizotinib (Bergethon K, et al. *J Clin Oncol.* 2012;30(8):863-870.); \*All recommendations are category 2A unless otherwise indicated

1. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines<sup>®</sup>) – Non-Small Cell Lung Cancer. Version 3.2014. 2. Otterson GA, et al. *J Clin Oncol.* 2012;30(Suppl): Abstract 7600. 3. Weickhardt AJ, et al. *J Clin Oncol.* 2012;30(Suppl): Abstract 7526.

# Surveillance Brain MRI?

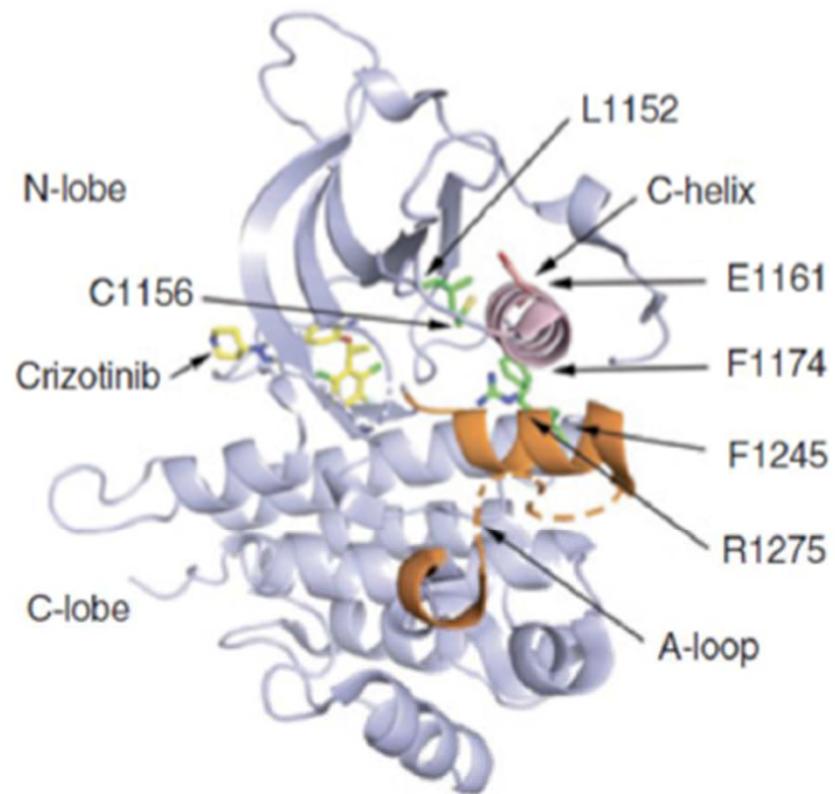
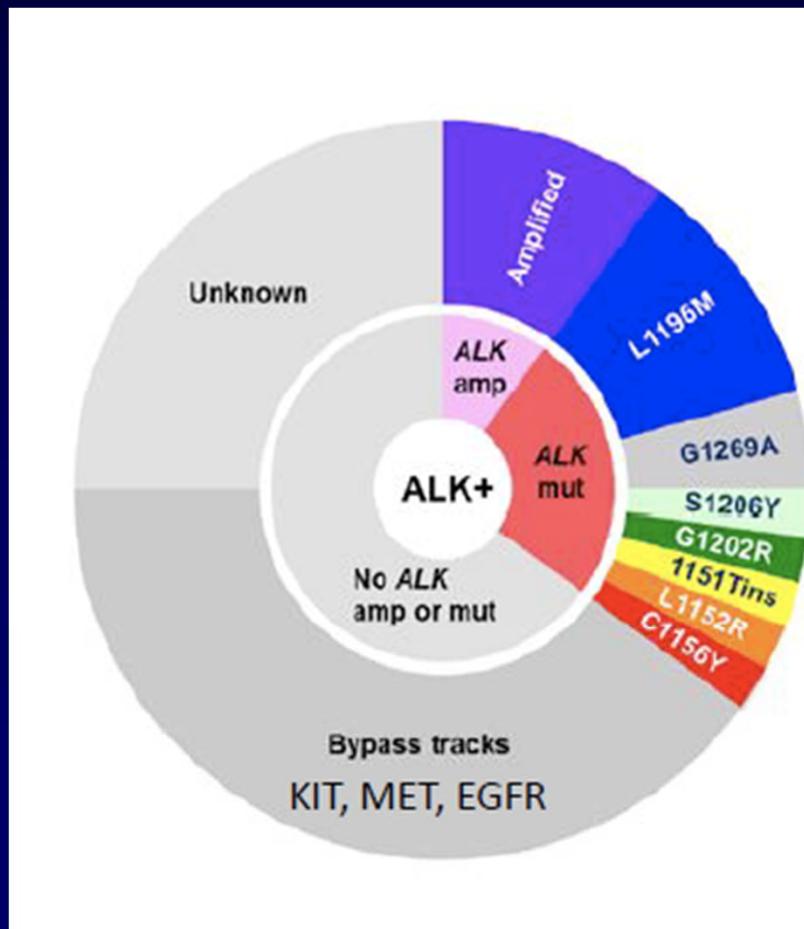
1. No, only if symptoms
2. Yes, brain MRI as often as systemic imaging
3. Yes, brain MRI every 6 months - 9 months

No clear evidence to support

Most experts choose #3 or #1

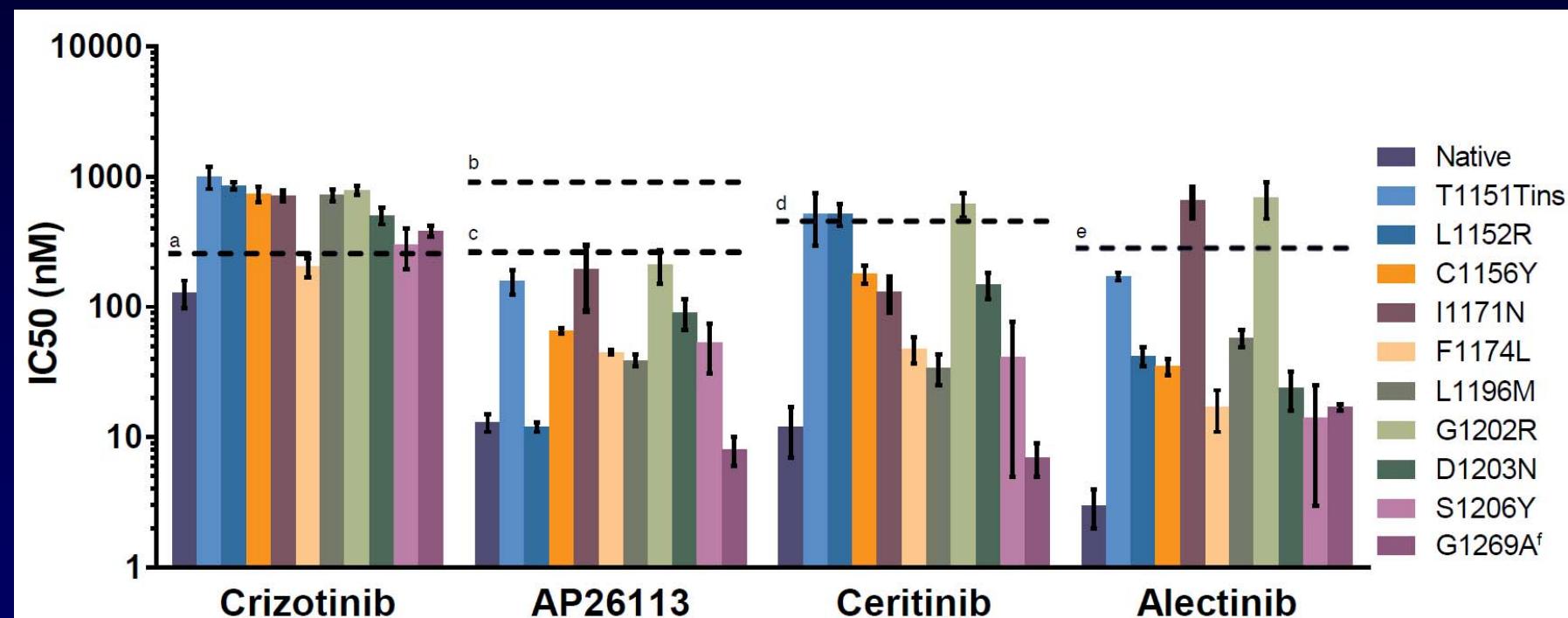
# What About Resistance?

Crizotinib RR 65% to 75%; Median PFS 8-11 Months



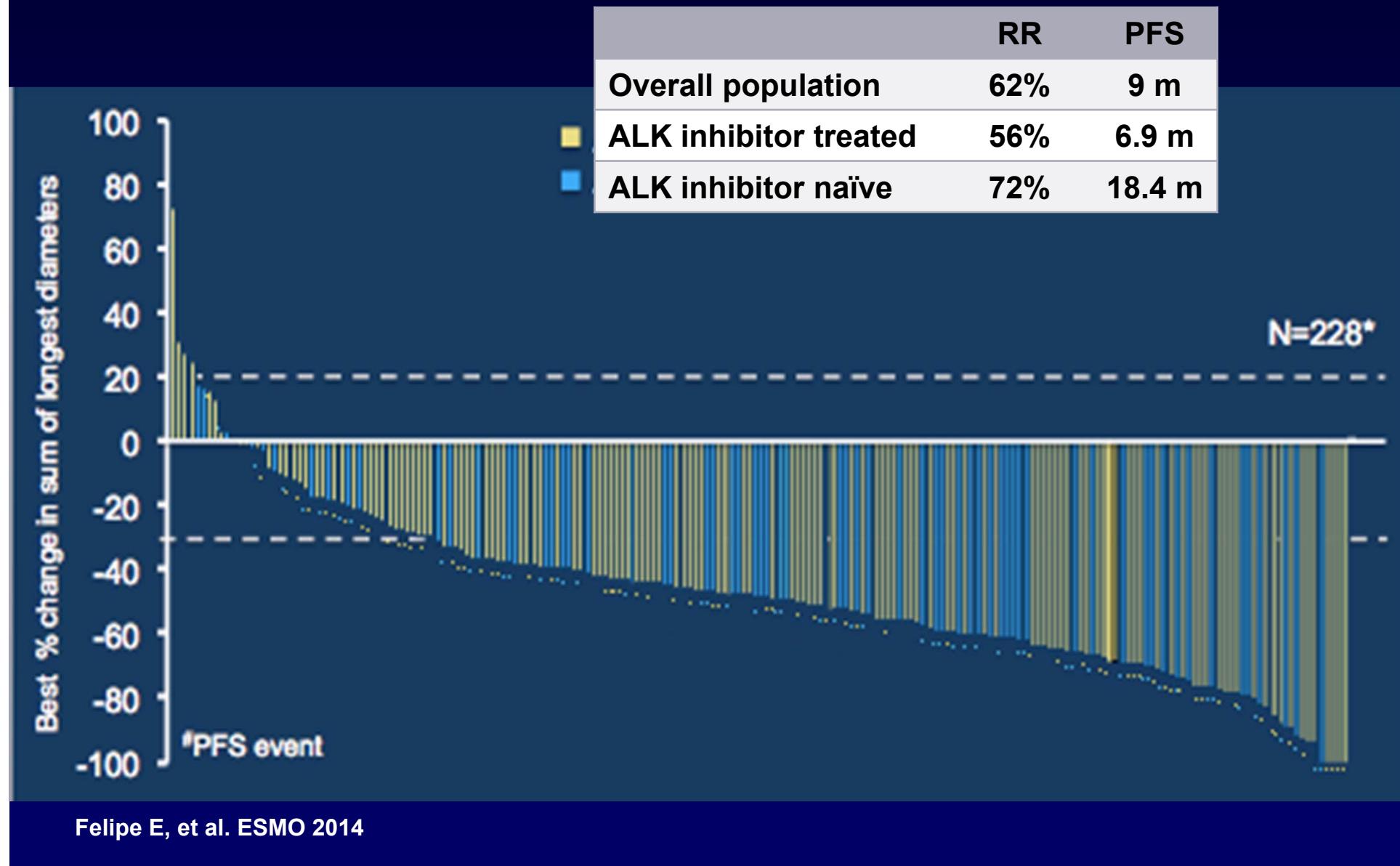
Courtesy A. Shaw.

# Next Generation ALK TKIs



50% maximal inhibitory concentration (IC50) values of Ba/F3 cells dependent on expression of EML4-ALK (native) or kinase domain mutated EML4-ALK variants (n = 10). Data for each cell line are derived from at least 4 independent experiments (error bars = standard deviation). Dashed horizontal lines indicate the mean steady-state exposure concentrations of each drug corrected for the functional effects of protein binding at the recommended phase 2 doses: <sup>a</sup>Crizotinib: 250 mg BID, 259 nM<sup>9</sup>; AP26113: <sup>b</sup>180 mg QD, 899 nM and <sup>c</sup>90 mg QD, 264 nM<sup>10</sup>; <sup>d</sup>Ceritinib: 750 mg QD, 456 nM<sup>11</sup>; <sup>e</sup>Alectinib: 600 mg BID, 277 nM<sup>12</sup>; <sup>f</sup>n = 2

# Ceritinib Activity in ALK+ NSCLC



# Side Effects of Ceritinib

Preferred Term, n (%)	Ceritinib Dose, mg/day						All Patients (N = 130)
	50-300 (n = 10)	400 (n = 14)	500 (n = 10)	600 (n = 10)	700 (n = 5)	750 (n = 81)	
<b>Nausea</b>	5 (50)	10 (71)	9 (90)	10 (100)	5 (100)	67 (83)	<b>106 (82)</b>
<b>Diarrhea</b>	3 (30)	9 (64)	7 (70)	8 (80)	4 (80)	67 (83)	<b>98 (75)</b>
<b>Vomiting</b>	5 (50)	8 (57)	6 (60)	8 (80)	4 (80)	53 (65)	<b>84 (65)</b>
<b>Fatigue</b>	3 (30)	5 (36)	4 (40)	8 (80)	0	41 (51)	<b>61 (47)</b>
<b>ALT increased</b>	1 (10)	2 (14)	3 (30)	2 (20)	4 (80)	33 (41)	<b>45 (35)</b>
<b>Constipation</b>	1 (10)	3 (21)	3 (30)	4 (40)	2 (40)	29 (36)	<b>42 (32)</b>
<b>Abdominal pain</b>	2 (20)	1 (7)	2 (20)	2 (20)	1 (20)	31 (28)	<b>39 (30)</b>
<b>↓Appetite</b>	2 (20)	0	3 (30)	4 (40)	3 (60)	26 (32)	<b>38 (29)</b>
<b>AST increased</b>	1 (10)	3 (21)	2 (20)	2 (20)	3 (60)	22 (27)	<b>33 (25)</b>

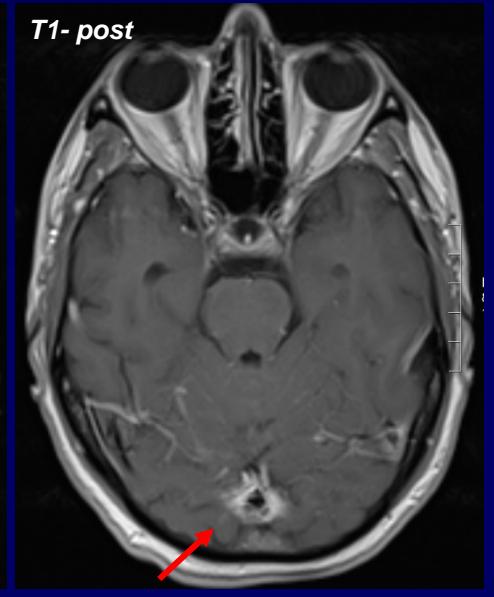
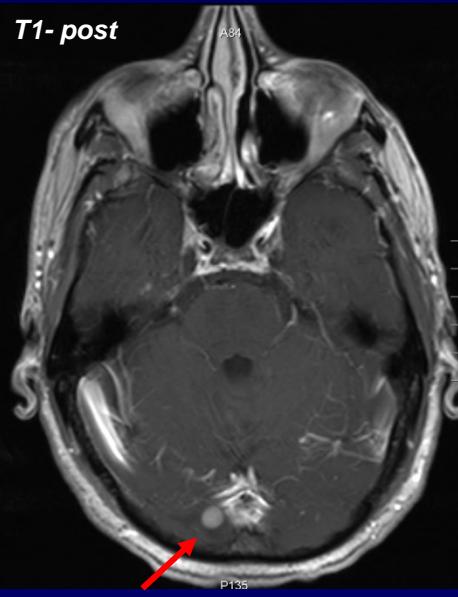
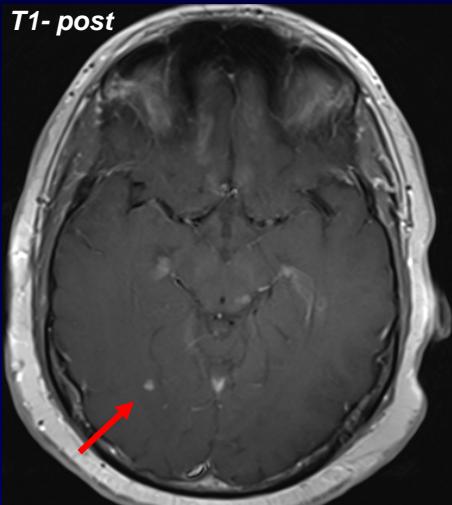
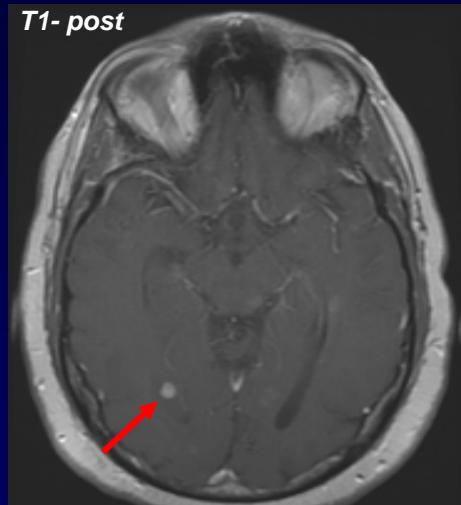
Shaw AT, et al. *N Engl J Med.* 2014;370:1189-1197.

# Side Effects of Ceritinib

Preferred Term, n (%)	Ceritinib Dose, mg/day					% Interruption (% Reduction)	% Discontinuation
	50-300 (n = 10)	400 (n = 14)	500 (n = 14)	600 (n = 14)	700 (n = 14)		
<b>Nausea</b>	5 (50)	10 (71)	9 (64)	10 (71)	10 (71)	<b>75% at least 1 interruption</b>	<b>62% discontinuations</b>
<b>Diarrhea</b>	3 (30)	9 (64)	7 (50)	8 (57)	8 (57)		
<b>Vomiting</b>	5 (50)	8 (57)	6 (43)	7 (50)	7 (50)		
<b>Fatigue</b>	3 (30)	5 (36)	4 (40)	8 (80)	0	41 (51)	<b>61 (47)</b>
<b>ALT increased</b>	1 (10)	2 (14)	3 (30)	2 (20)	4 (80)	33 (41)	<b>45 (35)</b>
<b>Constipation</b>	1 (10)	3 (21)	3 (30)	4 (40)	2 (40)	29 (36)	<b>42 (32)</b>
<b>Abdominal pain</b>	2 (20)	1 (7)	2 (20)	2 (20)	1 (20)	31 (28)	<b>39 (30)</b>
<b>↓Appetite</b>	2 (20)	0	3 (30)	4 (40)	3 (60)	26 (32)	<b>38 (29)</b>
<b>AST increased</b>	1 (10)	3 (21)	2 (20)	2 (20)	3 (60)	22 (27)	<b>33 (25)</b>

Shaw AT, et al. *N Engl J Med.* 2014;370:1189-1197.

# CNS Responses to Ceritinib



# CNS Responses With ALK TKIs

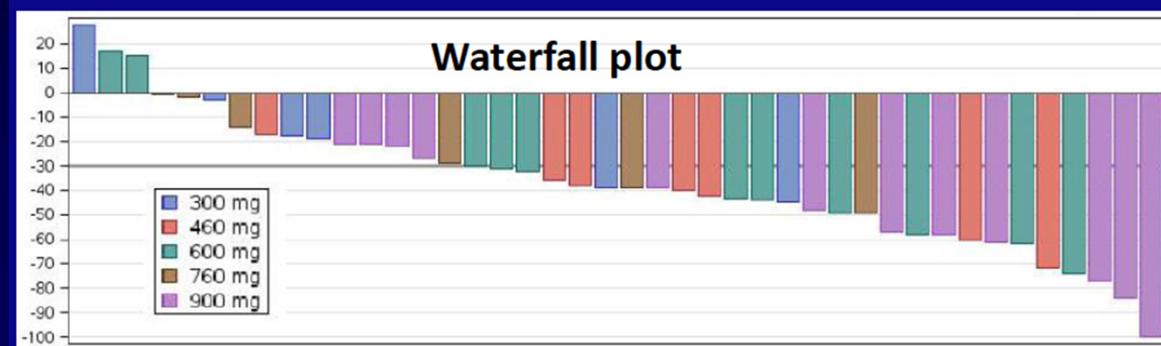
Agent	Intracranial RR (n)	Median duration of response
Crizotinib	25% (10/40)	≥ 6.5 months
Ceritinib	36% (10/28) pretreated 63% (5/8) crizotinib naive	≥ 7 months
Alectinib	52% (11/21) pretreated	Not reported
AP26113	43% (6/14)	Not reported

Costa D, et al. WCLC. 2014; Abstract 2932; Shaw AT, et al. ESMO. 2014; Gadgeel SM, et al. *Lancet Oncol.* 2014;15(10):1119-1128; Gettinger S, et al. ESMO. 2014; Abstract 5146

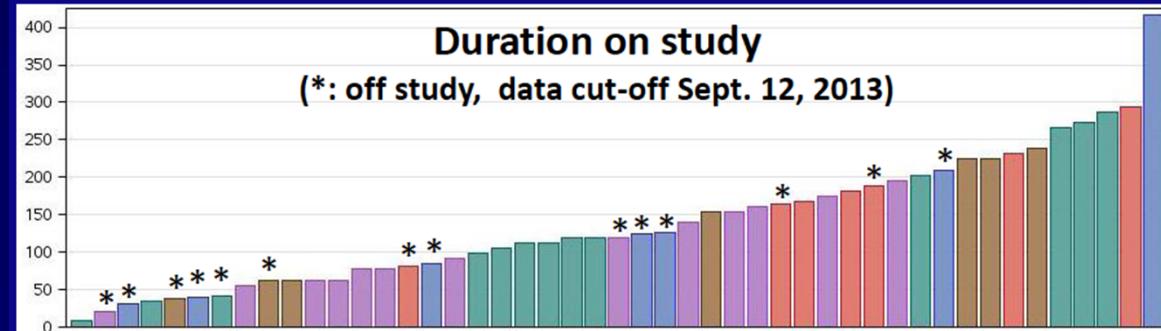
# Clinical Activity of Alectinib in Crizotinib-Resistant ALK-Positive NSCLC

ORR 54.5% across all cohorts for all patients

% tumor shrinkage



Days on study



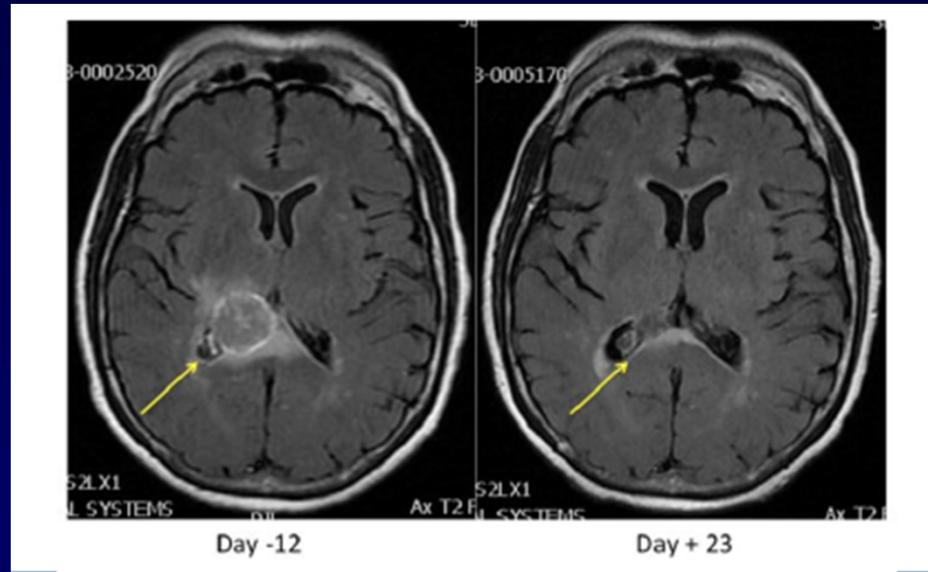
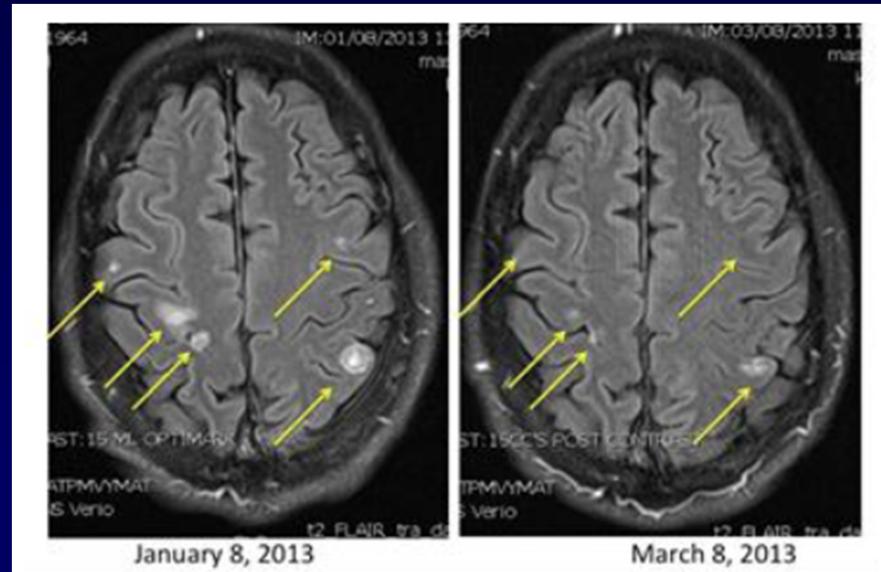
ORR 54.5%  
all cohorts

Dose (mg BID)	300	460	600	760	900
RR %	2/7 29%	5/7 71%	7/10 (70%) 3 unconfirmed	2/7 29%	8/13 (62%), 1 CR 4 unconfirmed

# **Side Effects of Alectinib**

<b>Side Effect</b>	<b>N = 47 (%)</b>
<b>Fatigue</b>	<b>14 (30)</b>
<b>Myalgia</b>	<b>8 (17)</b>
<b>Peripheral edema</b>	<b>8 (17)</b>
<b>Increased blood CPK</b>	<b>7 (15)</b>
<b>Nausea</b>	<b>7 (15)</b>
<b>ALT increased</b>	<b>6 (13)</b>
<b>Photosensitivity</b>	<b>6 (13)</b>
<b>Constipation</b>	<b>5 (11)</b>
<b>Rash</b>	<b>5 (11)</b>

# CNS Responses to Alectinib



Ou S-H, et al. *Eur J Cancer*. 2013;49(Suppl 3): Abstract 44.

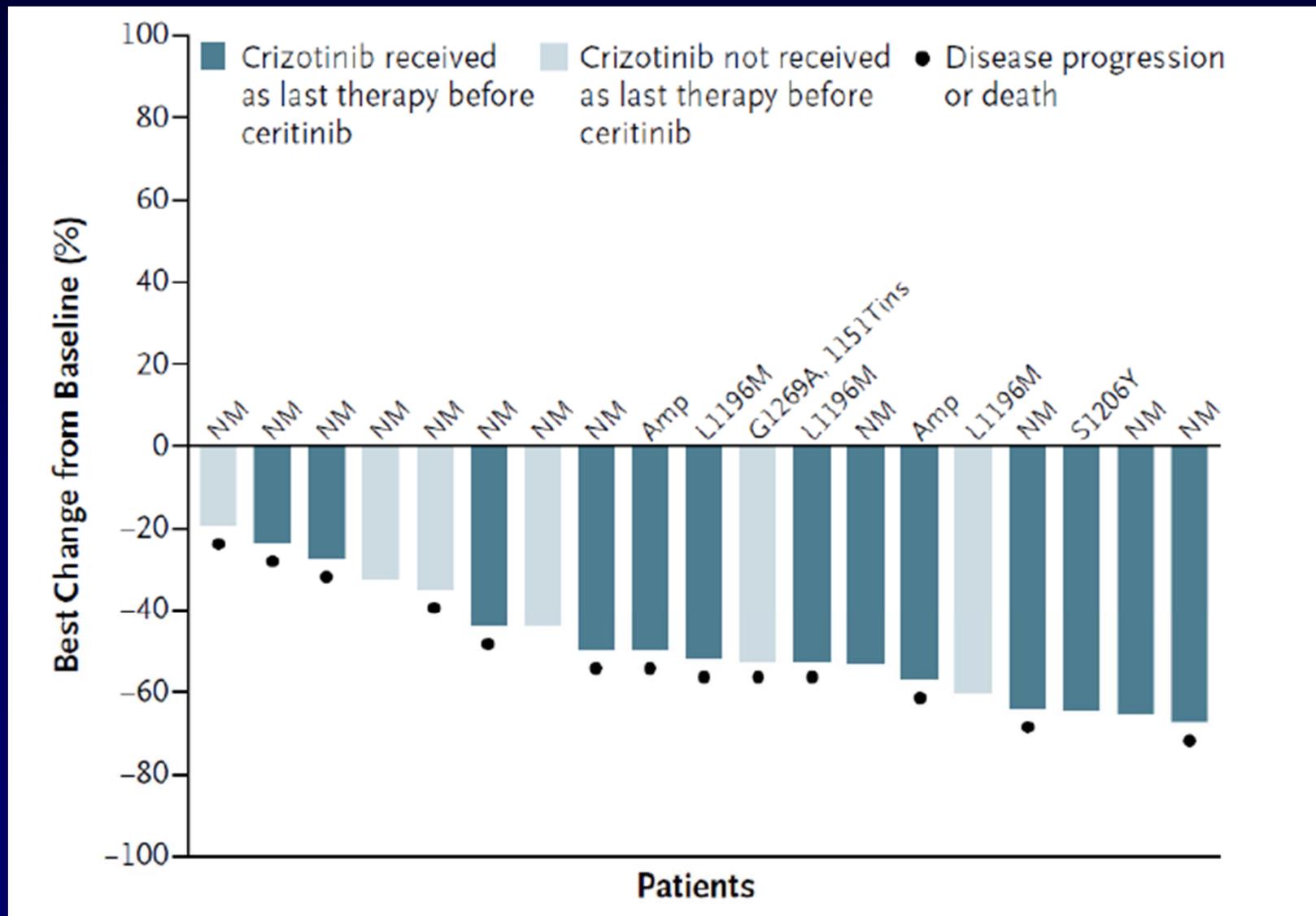
# My Opinion: CNS Only Relapse

1. **Surgical resection of the brain metastases (S) or stereotactic radiosurgery (SRS) + continuation of crizotinib** **REASONABLE**
  2. **S or SRS →WBRT →continue crizotinib**
  3. **WBRT →continue crizotinib**
  4. **S or SRS →discontinue crizotinib and start chemotherapy** **NO**
  5. **S or SRS →discontinue crizotinib and start ceritinib** **NO**
  6. **No local therapy for brain mets at this time; discontinue crizotinib and consider clinical trial with alectinib** **REASONABLE**
- [ AVOID WBRT  
IF POSSIBLE ]

# What About Extracranial Progression?

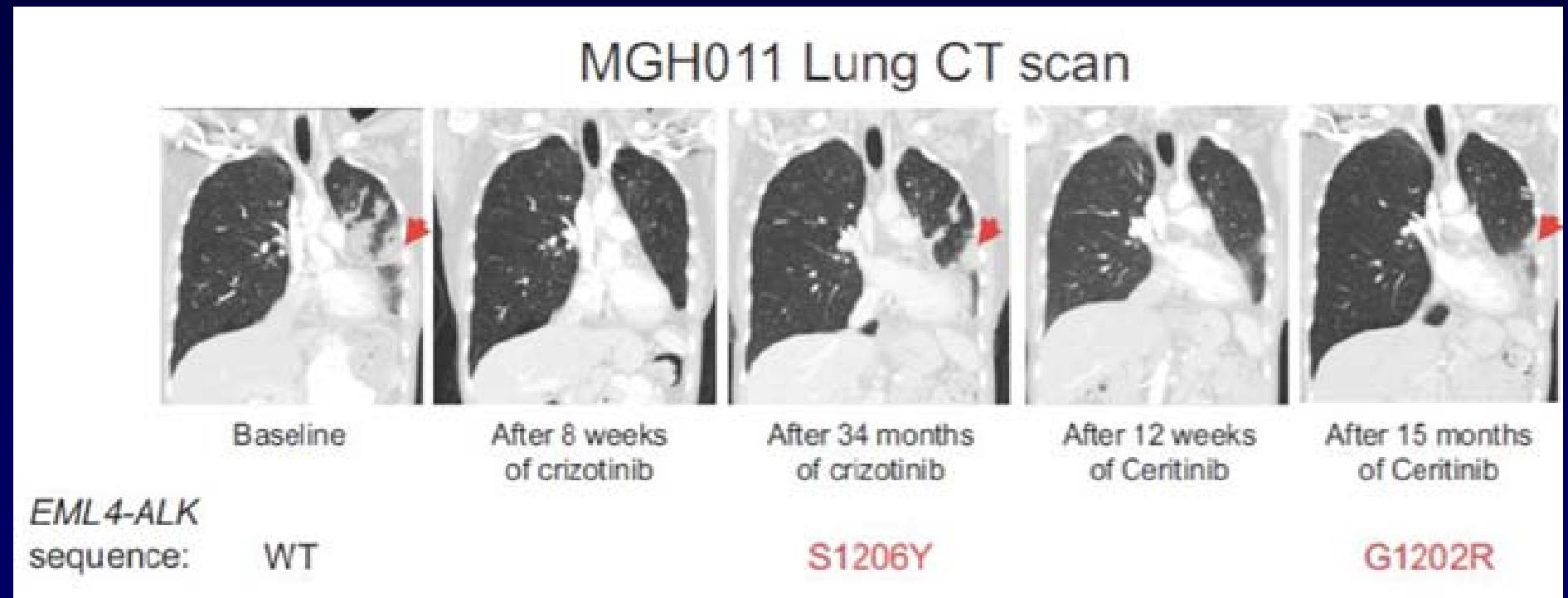
1. Continue crizotinib and add chemotherapy NO
2. Stop crizotinib and start cisplatin/pemetrexed **REASONABLE**
3. Clinical trial of second generation ALK inhibitor if available
4. Rebiopsy for additional mutation testing and clinical trial of targeted therapy
5. Ceritinib, if available (eg, compassionate access)

# Ceritinib Activity by ALK Gene Alteration



Shaw AT, et al. *N Engl J Med.* 2014;370(26):2537-2539.

# Ceritinib Resistance Is Associated With ALK G1202R



# Next Generation ALK Inhibitors

Inhibitor	Targets	Development stage	Recent reports
Ceritinib	ALK/ROS	FDA approved	Shaw, <i>NEJM</i> 2014
		Phase III/CUP	Kim, <i>ASCO</i> 2014
Alectinib	ALK	Approved in Japan	Seto, <i>Lancet Oncol</i> 2014
		FDA fast-track	Gadgeel, <i>Lancet Oncol</i> 2014
		Phase III/CUP	Nakagawa, <i>ASCO</i> 2014
AP26113	ALK/EGFR/ROS	Phase I/II	Gettinger, <i>ASCO</i> 2104
TSR-011	ALK/TRK	Phase I/II	Weiss, <i>ASCO</i> 2014
X-396	ALK/ROS	Phase I/II	Horn, <i>ASCO</i> 2014
RXDX-101	ALK/ROS/TRK	Phase I/II	De Braud, <i>ASCO</i> 2014
PF-06463922	ALK/ROS/TRK	Phase I/II	Johnson, <i>J Med Chem</i> 2014
CEP-37440	ALK/FAK	Phase I/II	-

Adapted from Award MM, Shaw A. *Clin Adv Hematol Oncol.* 2014;12(7):429-439

# Conclusion

- All patients with advanced nonsquamous NSCLC should be assessed for *ALK* rearrangement**
- Patients with advanced *ALK+* NSCLC should receive crizotinib first-line**
- Continuation of TKI beyond progression can often be done, sometimes with the use of local therapy**
- Patients who develop resistance to crizotinib can be treated with a second-generation *ALK* inhibitor (eg, ceritinib) or on clinical trial (alectinib, ceritinib, etc)**
- Chemotherapy is always an option**