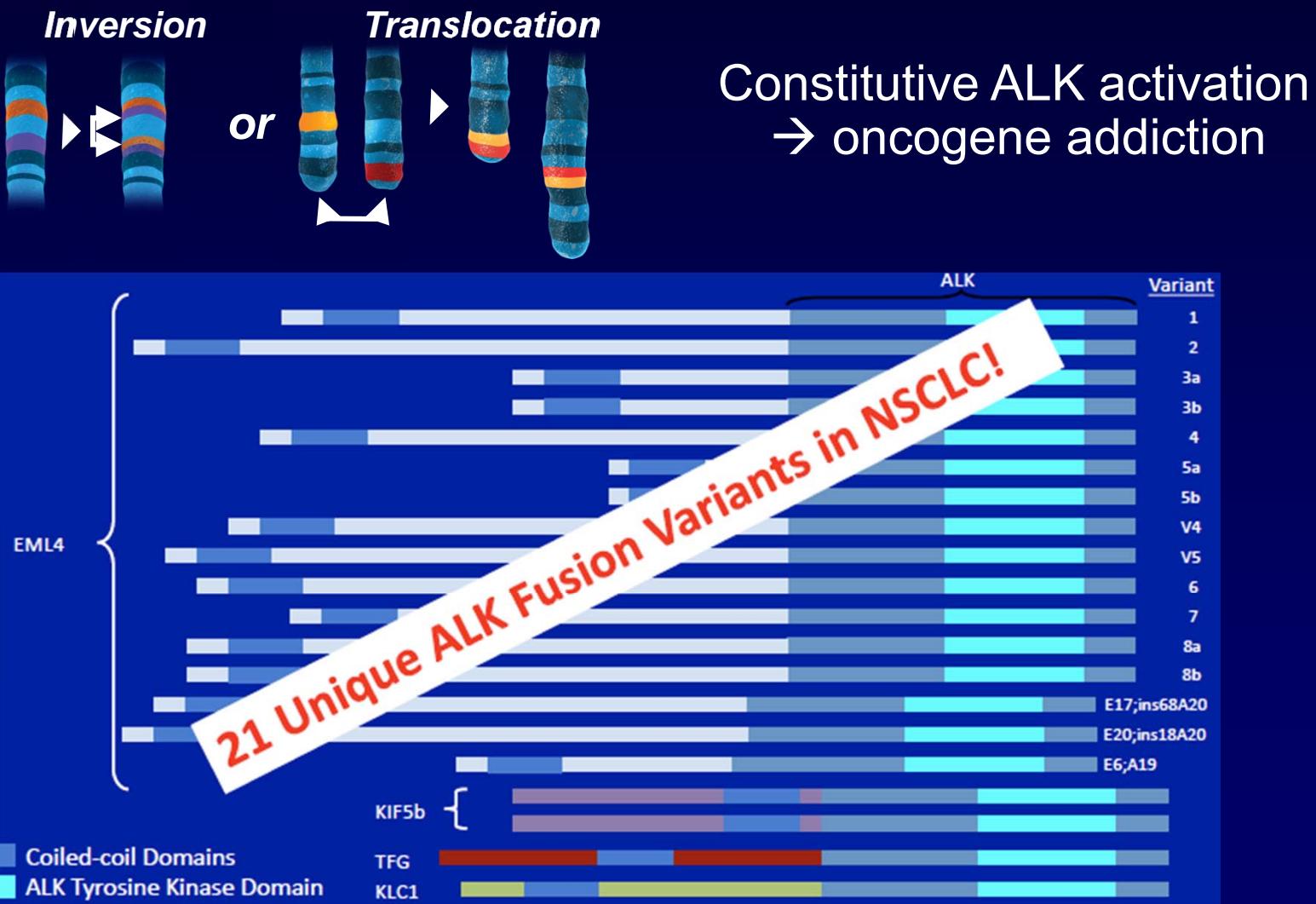


Case #3—Adenocarcinoma With *ALK* Rearrangement: Selecting Optimal Approach

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^a
- 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

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N = 343

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

Pemetrexed
500 mg/m²
+
cisplatin 75 mg/m² or
carboplatin AUC 5-6
q3w for ≤6 cycles
(n = 171)

CROSSOVER TO CRIZOTINIB
PERMITTED AFTER PROGRESSION^c

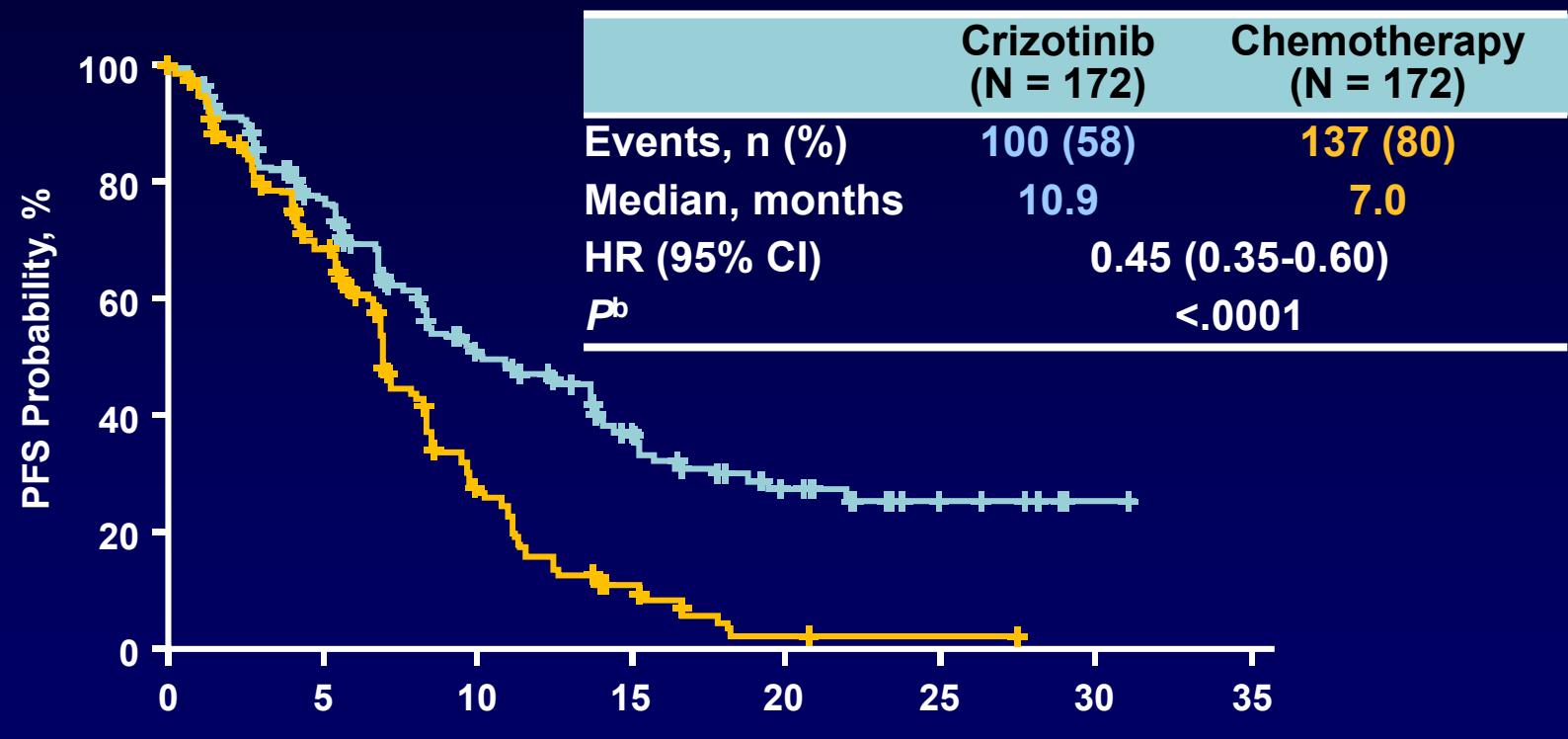
Endpoints

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

^aALK status determined using standard ALK break-apart FISH assay ^bStratification factors: ECOG PS (0/1 vs. 2), Asian vs non-Asian race, and brain metastases (present vs absent) ^cAssessed by IRR

PROFILE 1014

Primary Endpoint Met: Crizotinib Superior to 1L Pemetrexed-Based Chemotherapy in Prolonging PFS^a



Data cutoff: November 30, 2013

^aAssessed by IRR ^b1-sided stratified log-rank test

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

PROFILE 1014

Secondary Endpoints: ORR^a and OS

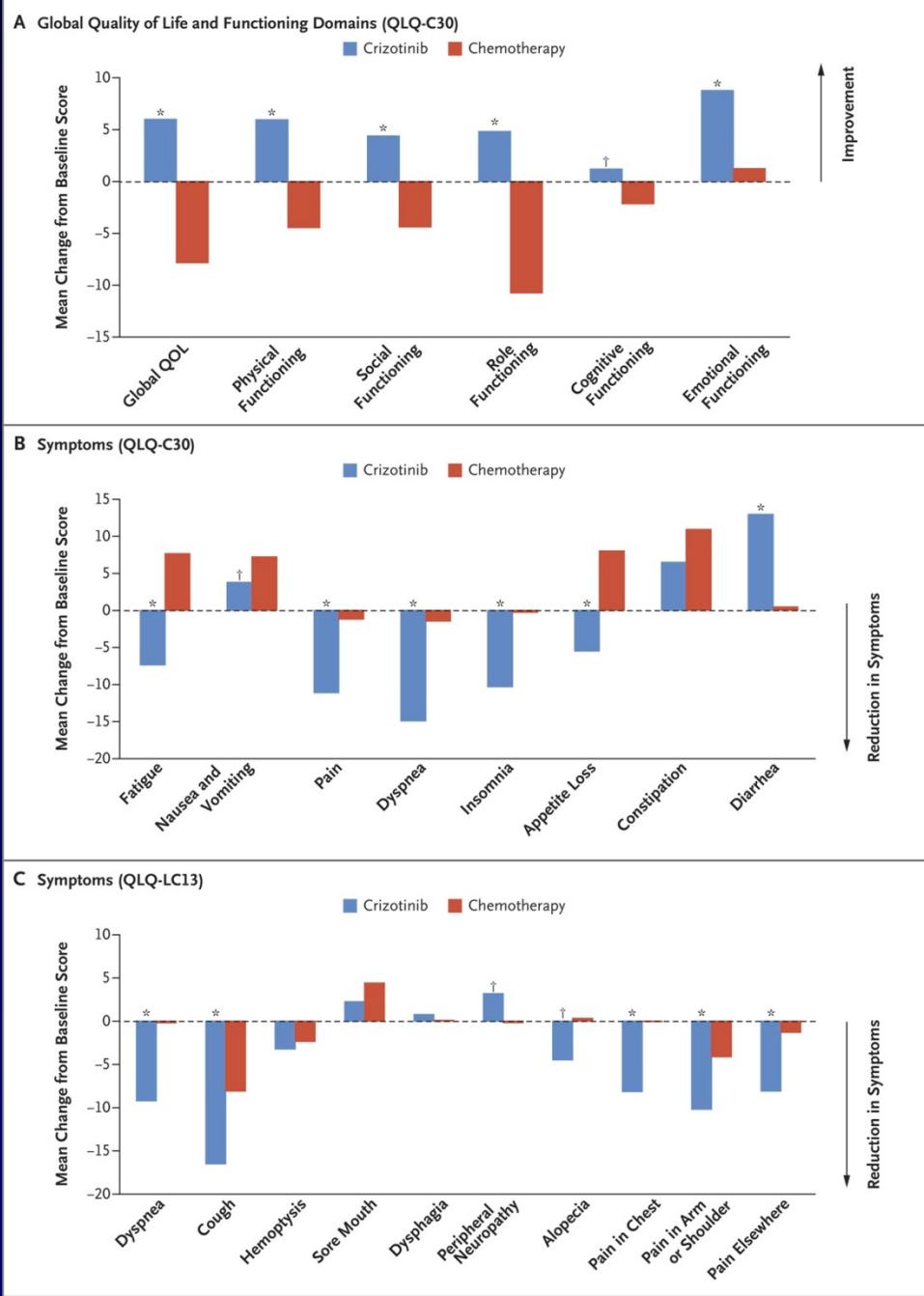
	Crizotinib (N = 172)	Chemotherapy ^b (N = 171)
ORR, % (n)	74 (128)	45 (77)
95% exact CI of ORR	67-81	37-53
Treatment difference, % (95% CI^c)		29 (20-39)
<i>P</i> ^c		<.0001
Median time to response,^d weeks	6.1	12.1
Range	2.7-41.4	5.1-36.7
Median duration of response,^{d,e} weeks	49.0	22.9
95% CI^f	35.1-60.0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

- 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

^aBy IRR; ^bbefore crossover to crizotinib; ^cPearson χ^2 test; ^din patients with an objective response ^eKaplan-Meier method;

^fBrookmeyer-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

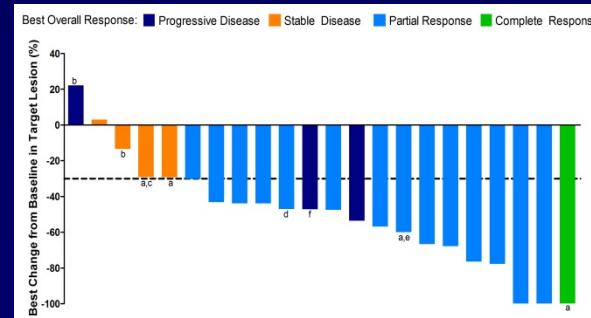
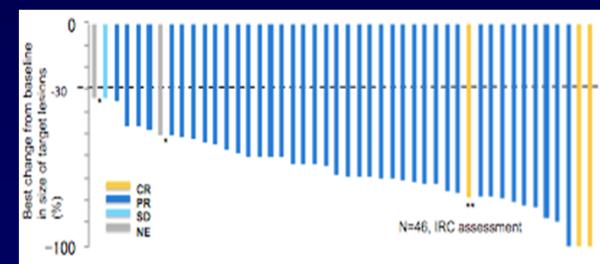
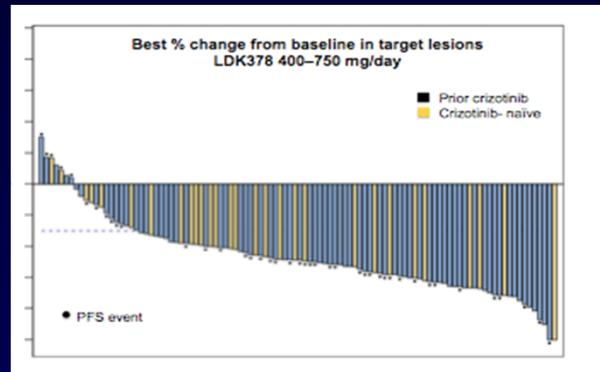
Chemotherapy in ALK-Positive NSCLC

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

Alectinib¹ (ALEX Trial)

Eligibility criteria:

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

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Alectinib 600 mg BID
(n = 143)

Crizotinib 250 mg BID
(n = 143)

Primary endpoint = PFS*

*Determined by investigators, based on RECIST v1.1

Ceritinib²

Eligibility criteria:

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

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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 ^c	122 (71)	1 (1)
Diarrhea	105 (61)	4 (2)
Edema ^c	83 (49)	1 (1)
Vomiting	78 (46)	3 (2)
Constipation	74 (43)	3 (2)
Elevated transaminases ^c	61 (36)	24 (14)
Abdominal pain ^c	45 (26)	0
Dysgeusia	45 (26)	0
Headache	37 (22)	2 (1)

- Permanent treatment discontinuations due to treatment-related AEs: 5% and 8%, respectively^b
- 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

^aNot adjusted for differential treatment duration; ^bBefore crossover to crizotinib; ^cclustered term

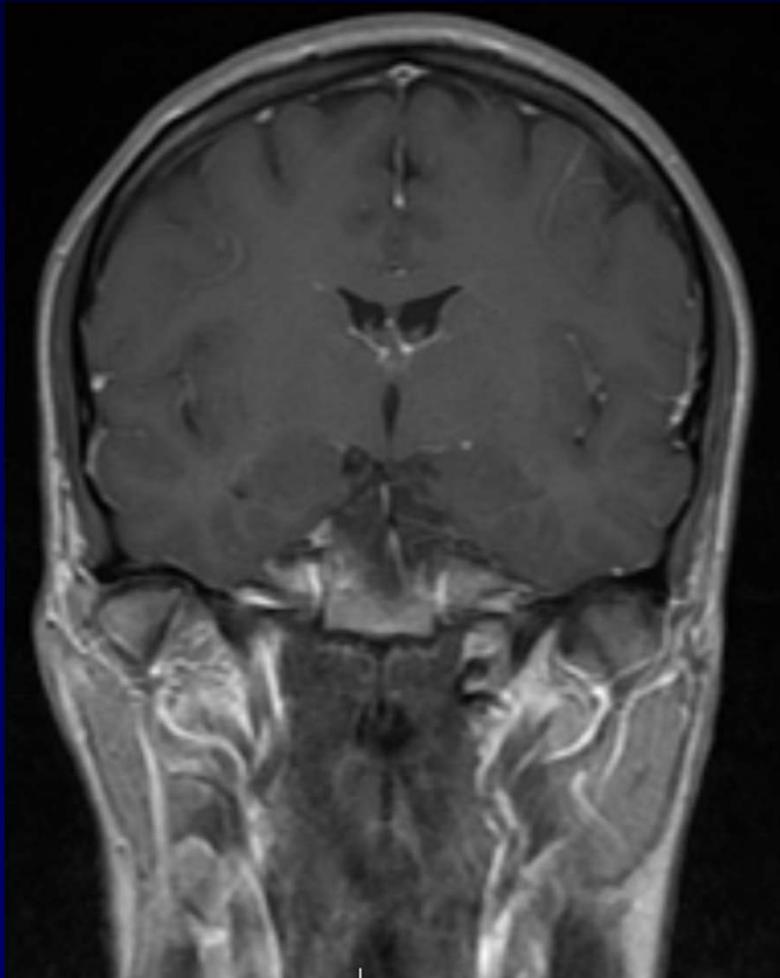
Solomon BJ, et al. *N Engl J Med.* 2014;371(23):2167-2177.

Dose Modification Scheme

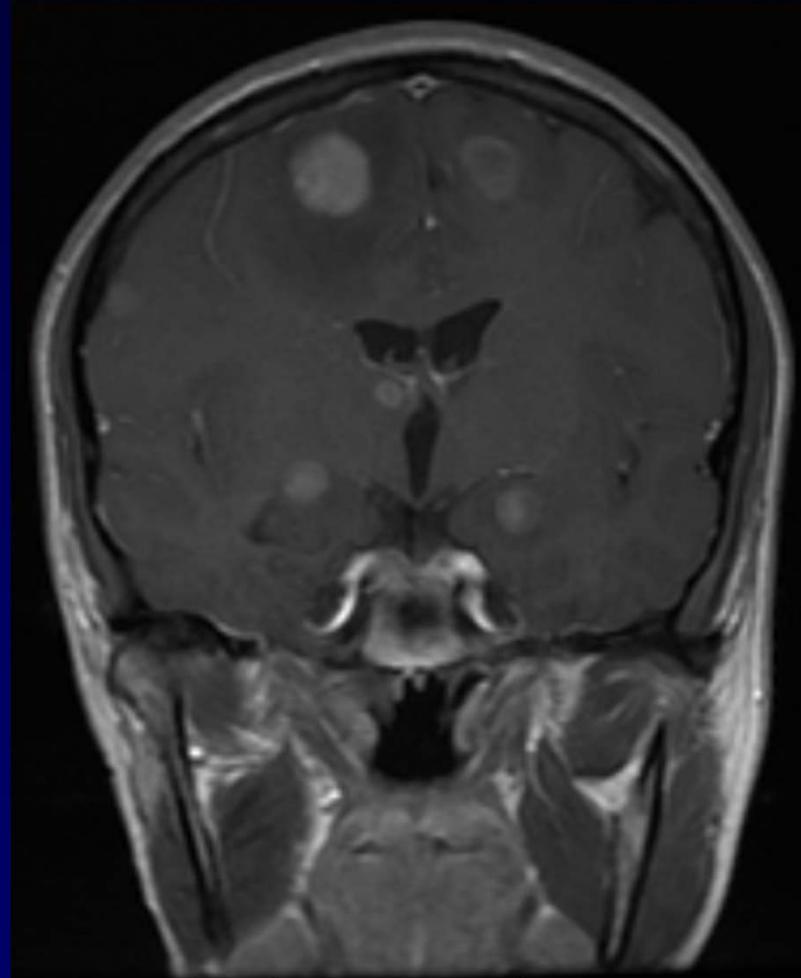
CTCAE ^b Grade	Crizotinib Dosing
Hematologic Toxicities^a	
Grade 3	Withhold until recovery to grade ≤2, then resume at the same dose schedule
Grade 4	Withhold until recovery to grade ≤2, then resume at 200 mg twice daily ^c
Nonhematologic Toxicities	
Grade 3 or 4 ALT or AST elevation with grade ≤1 total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

^a Except lymphopenia (unless associated with clinical events, eg, opportunistic infections); ^b NCI Common Terminology Criteria for Adverse Events; ^c 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; ^d 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; ^e Not attributable to NSCLC progression, other pulmonary disease, infection, or radiation effect.

A Common Scenario

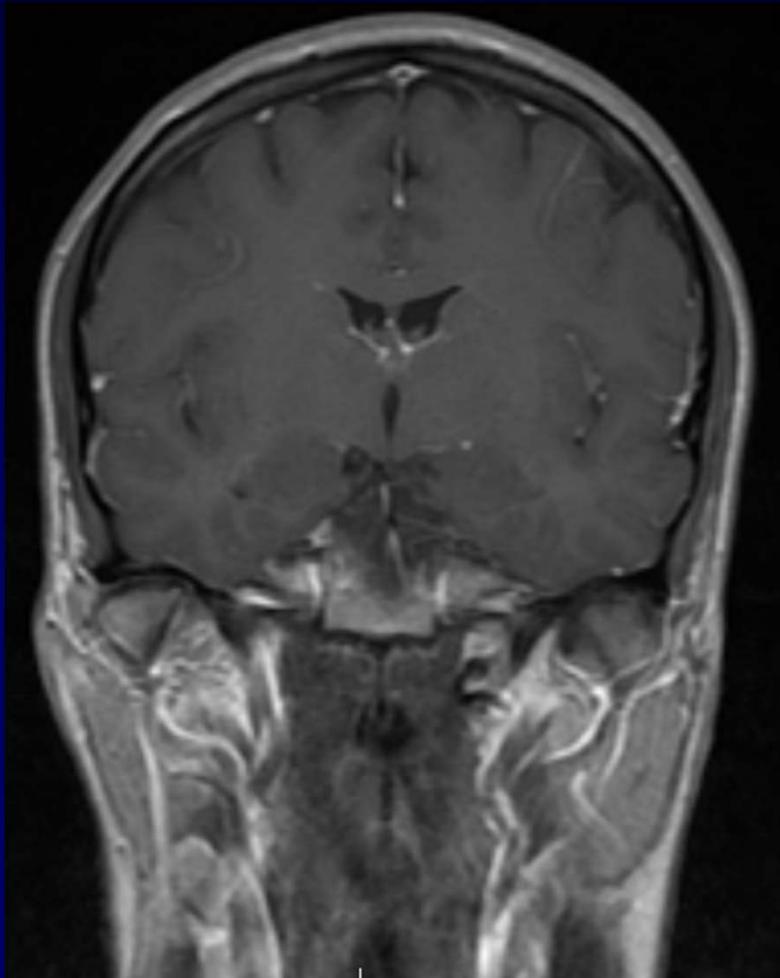


Baseline

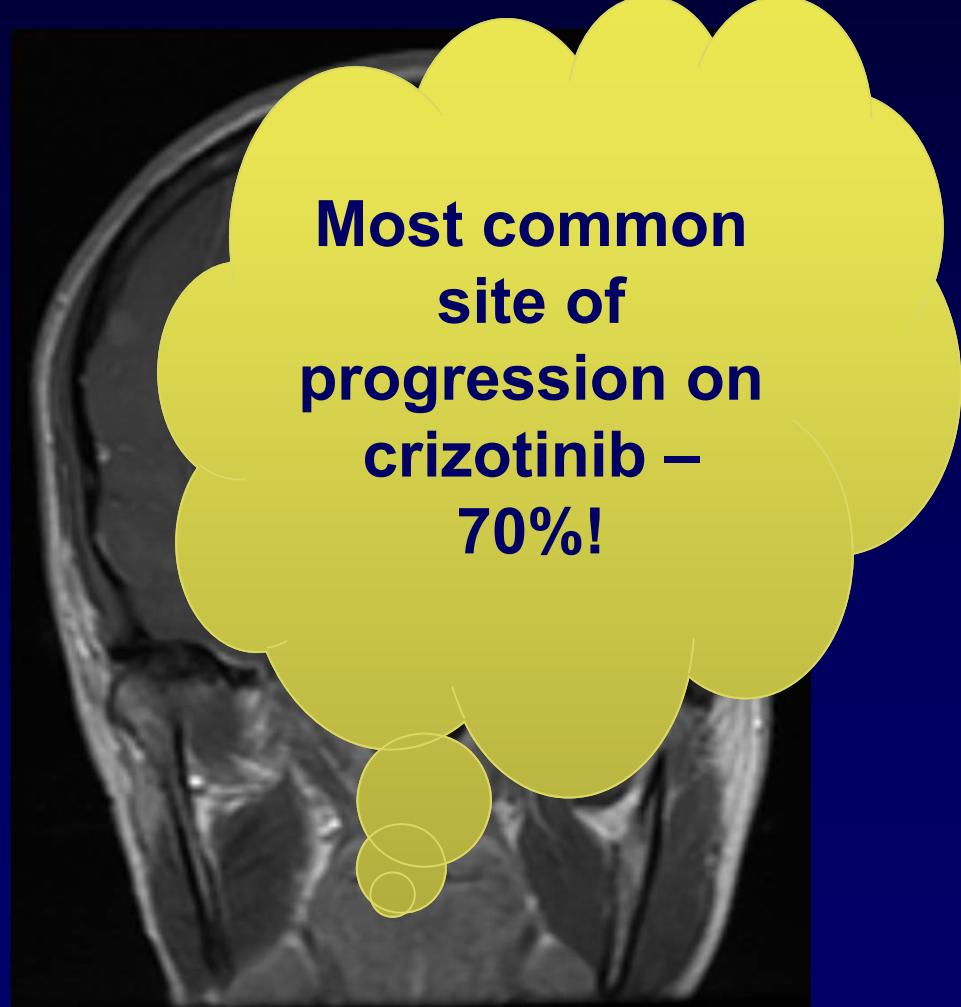


After 9 months of crizotinib

A Common Scenario



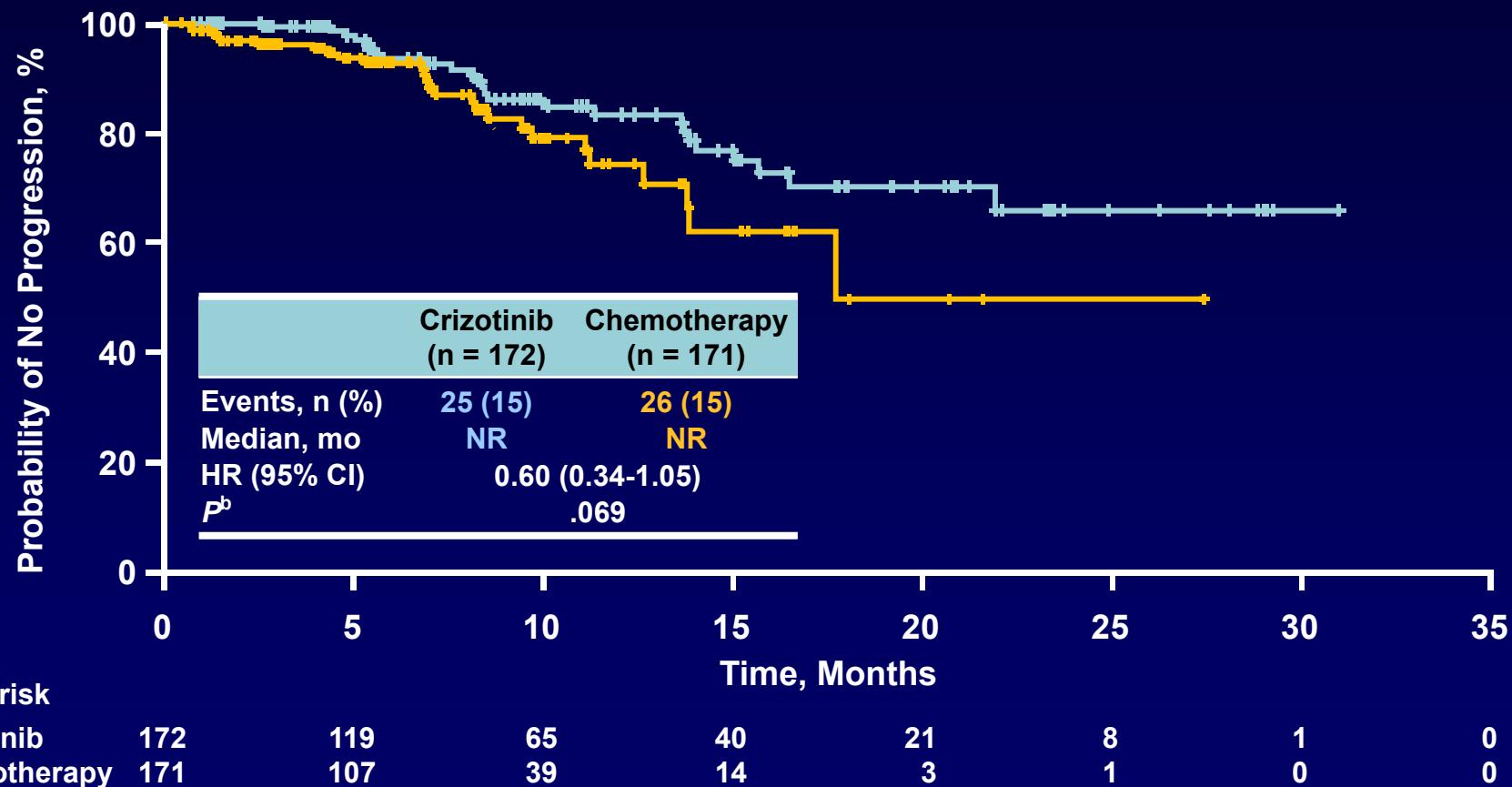
Baseline



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

After 9 months of crizotinib

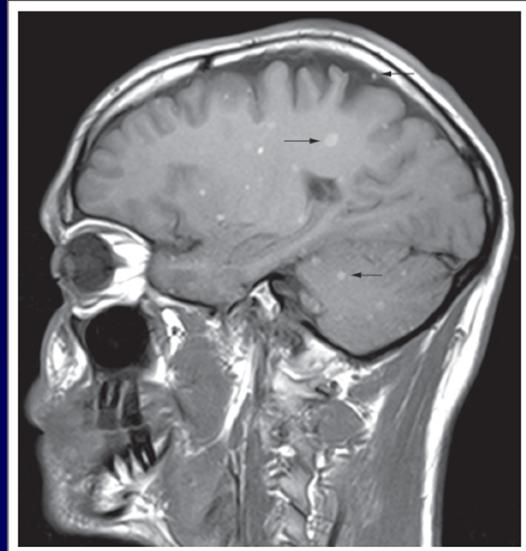
Intracranial TTP^a by IRR in ITT Population



NR, not yet reached; ^aTime from randomization to first documentation of intracranial tumor progression; ^b2-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

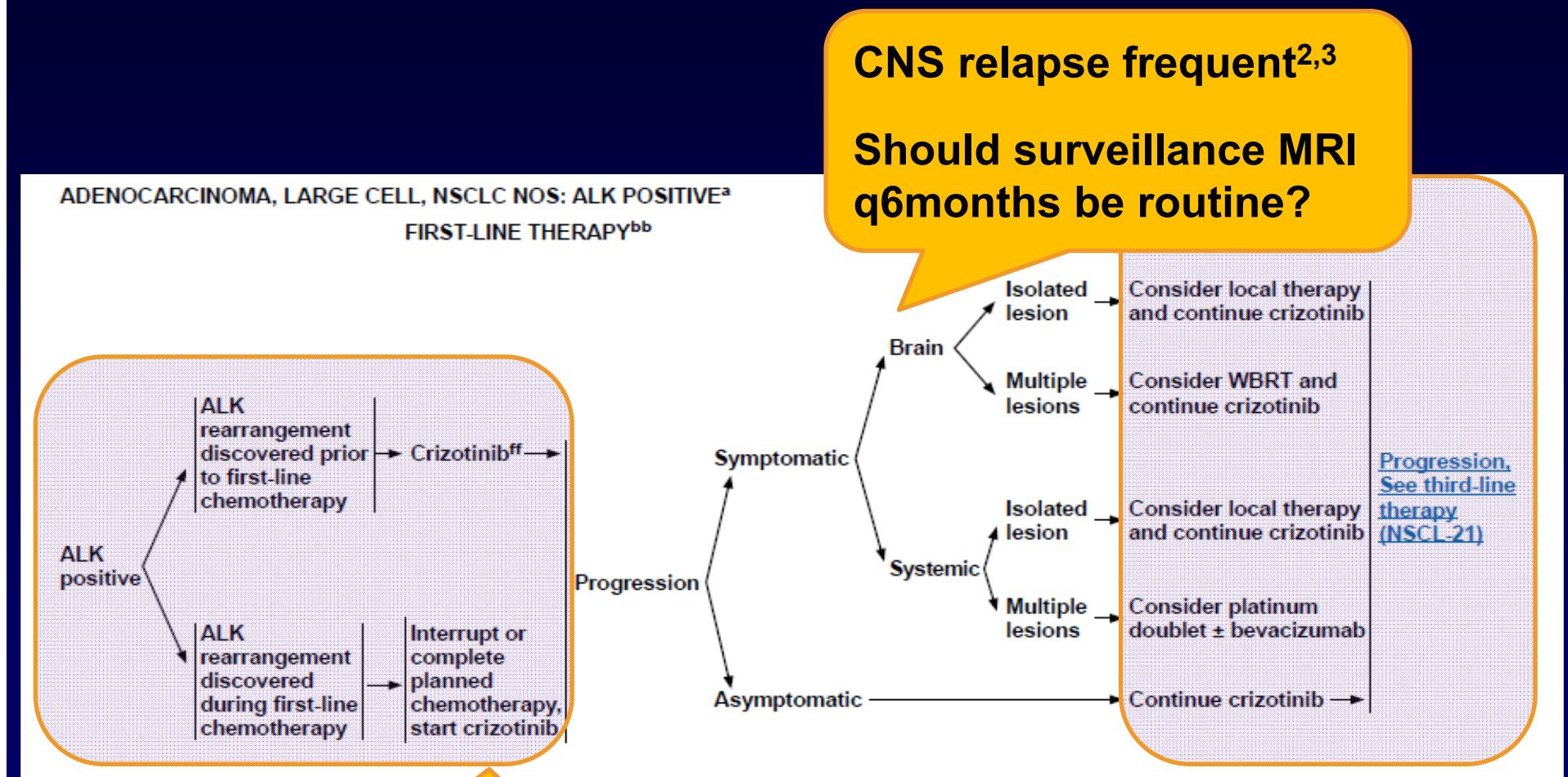


	Crizotinib	PF-06463922
ALK WT NIH3T3 IC₅₀ (nM)	80	1.5
ALK L1196M NIH3T3 IC₅₀ (nM)	843	21
ROS1-CD74 IC₅₀ (nM)	11	0.24
MDR BA/AB	45	1.5
CSF or free brain:free plasma (rodent)	--	0.23-0.33
Log D	2.0	2.3

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



^{ff}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[®]) – 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?

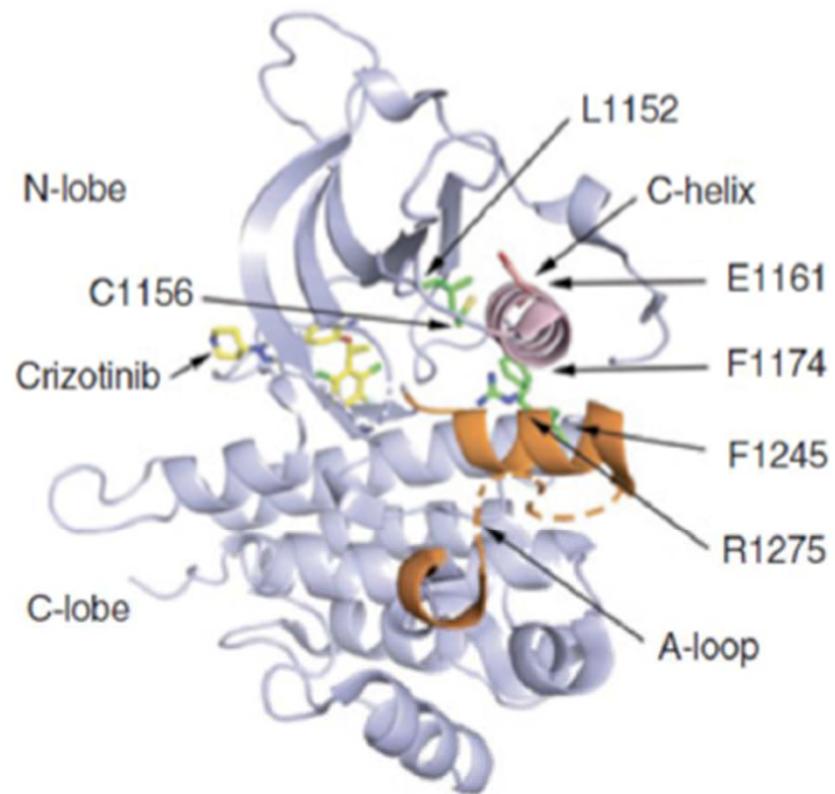
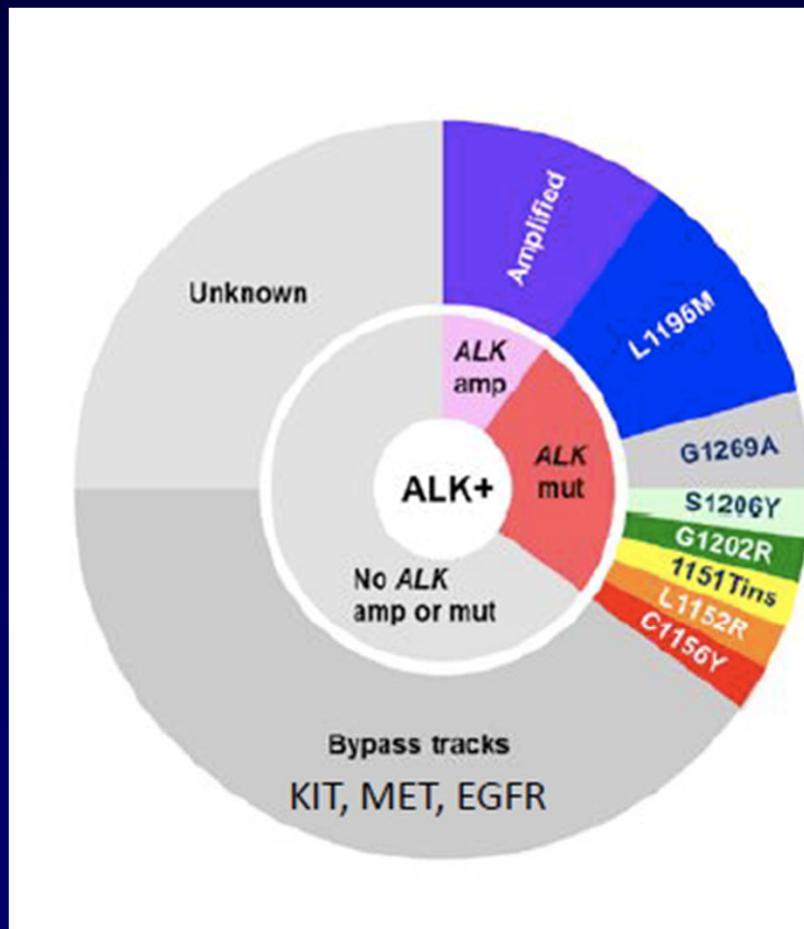
1. No, only if symptoms
2. Yes, brain MRI as often as systemic imaging
3. Yes, brain MRI every 6 months - 9 months

No clear evidence to support

Most experts choose #3 or #1

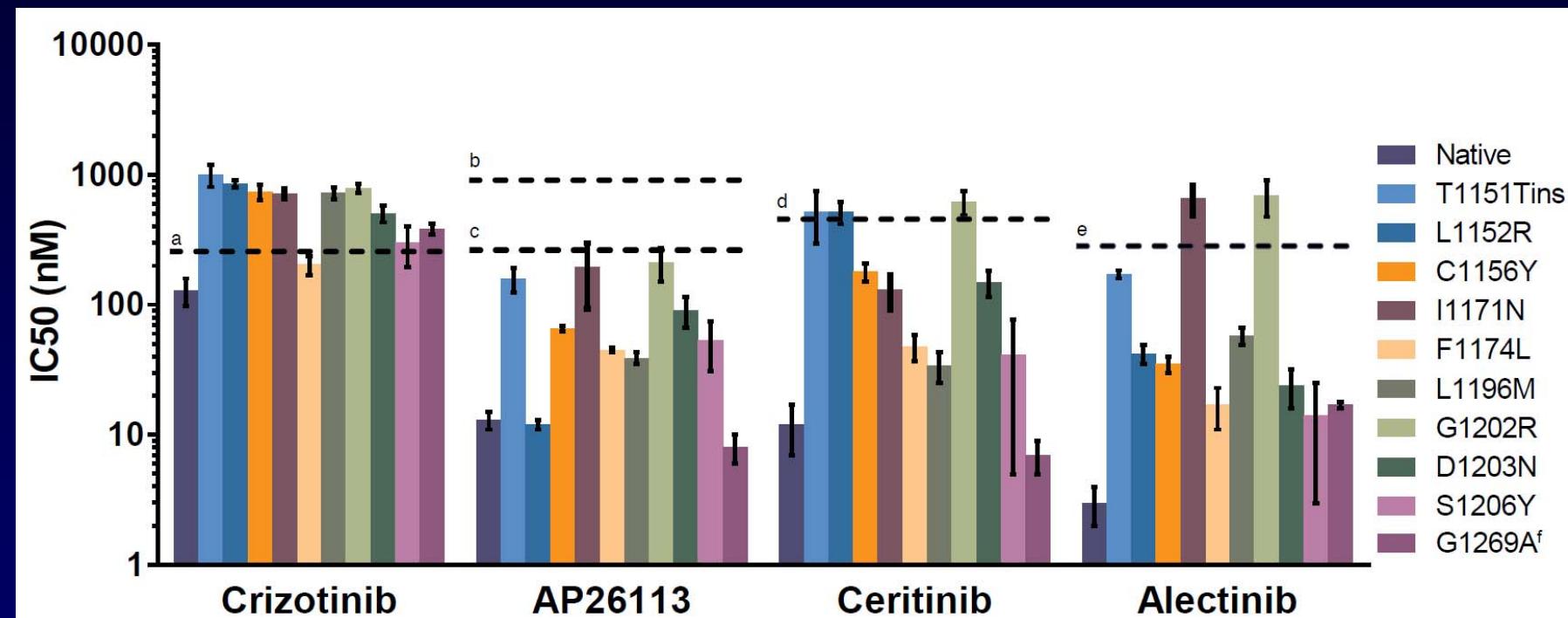
What About Resistance?

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



Courtesy A. Shaw.

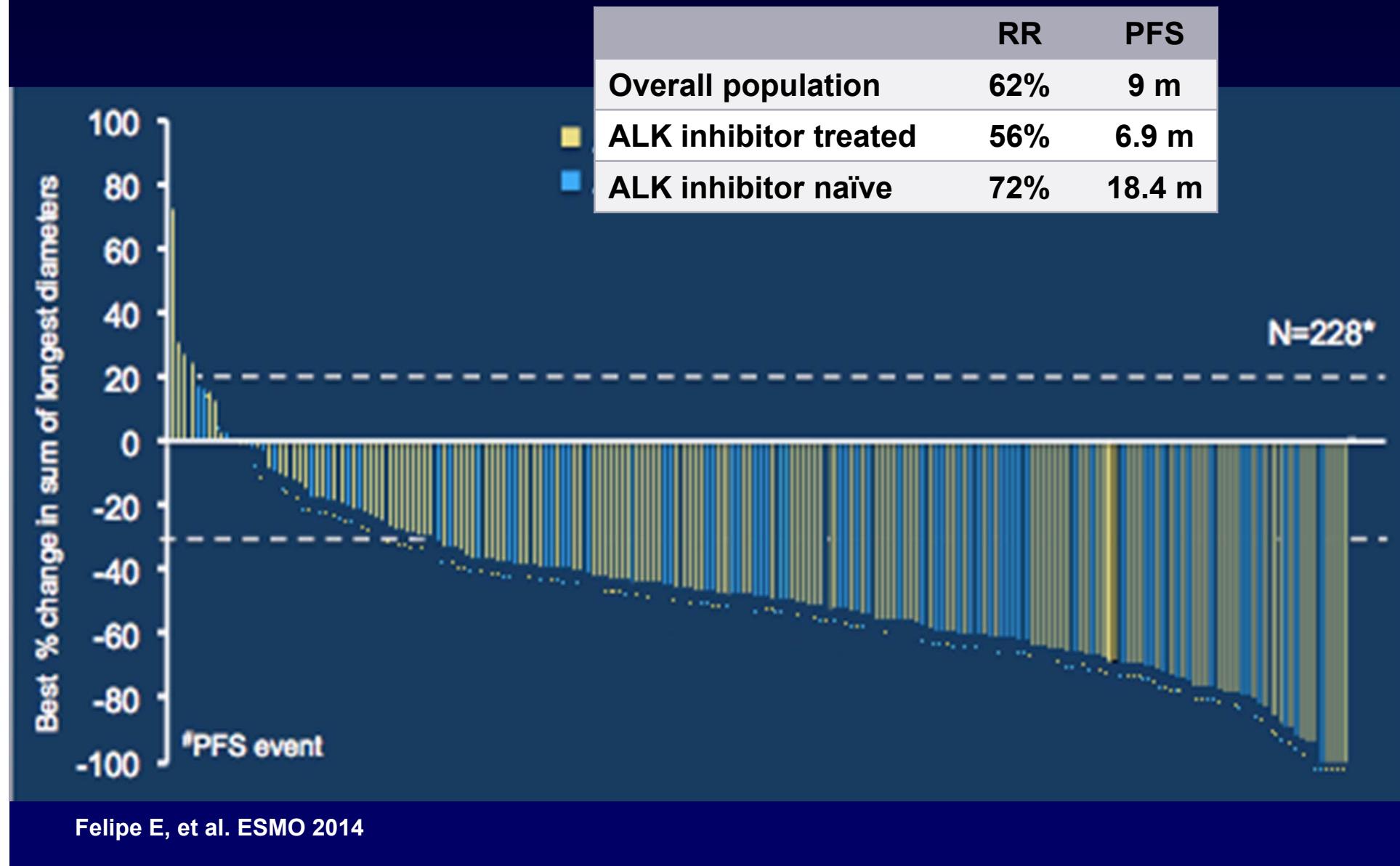
Next Generation ALK TKIs



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: ^aCrizotinib: 250 mg BID, 259 nM⁹; AP26113: ^b180 mg QD, 899 nM and ^c90 mg QD, 264 nM¹⁰; ^dCeritinib: 750 mg QD, 456 nM¹¹; ^eAlectinib: 600 mg BID, 277 nM¹²; ^fn = 2

Ou SH. *Drug Des Devel Ther*. 2011;5:471-485. Shaw AT, et al. *N Engl J Med*. 2014;370(13):1189-1197. Ou S, et al. *Eur J Cancer*. 2013;49(Suppl 2): Abstract 44.

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)	
Nausea	5 (50)	10 (71)	9 (90)	10 (100)	5 (100)	67 (83)	106 (82)
Diarrhea	3 (30)	9 (64)	7 (70)	8 (80)	4 (80)	67 (83)	98 (75)
Vomiting	5 (50)	8 (57)	6 (60)	8 (80)	4 (80)	53 (65)	84 (65)
Fatigue	3 (30)	5 (36)	4 (40)	8 (80)	0	41 (51)	61 (47)
ALT increased	1 (10)	2 (14)	3 (30)	2 (20)	4 (80)	33 (41)	45 (35)
Constipation	1 (10)	3 (21)	3 (30)	4 (40)	2 (40)	29 (36)	42 (32)
Abdominal pain	2 (20)	1 (7)	2 (20)	2 (20)	1 (20)	31 (28)	39 (30)
↓Appetite	2 (20)	0	3 (30)	4 (40)	3 (60)	26 (32)	38 (29)
AST increased	1 (10)	3 (21)	2 (20)	2 (20)	3 (60)	22 (27)	33 (25)

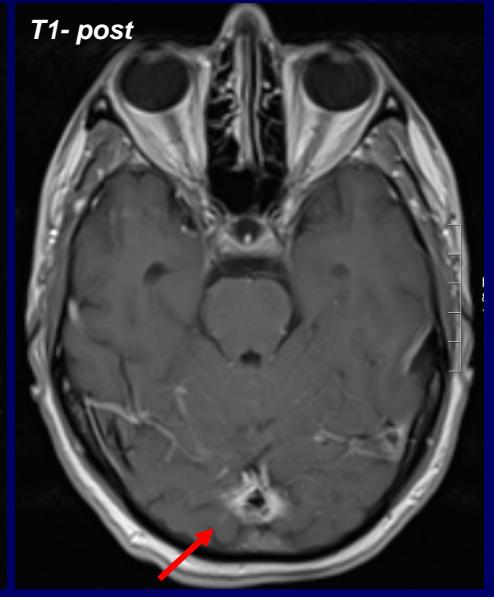
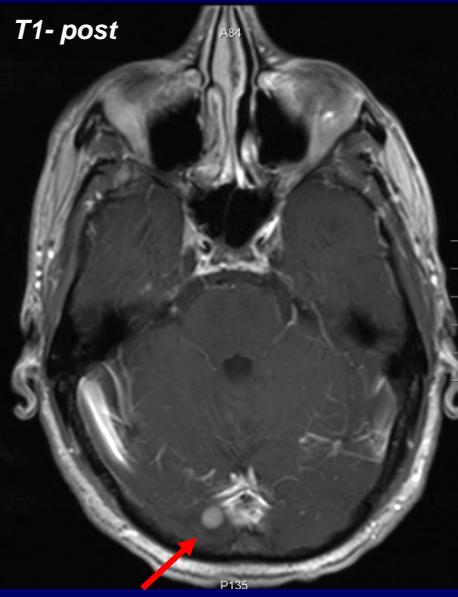
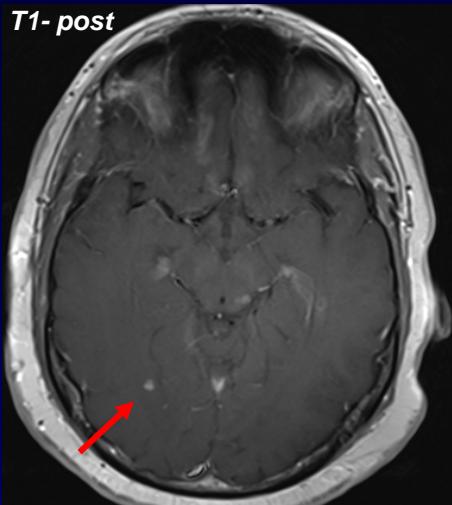
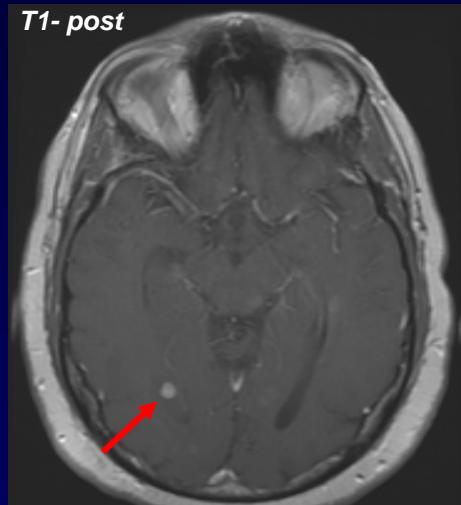
Shaw AT, et al. *N Engl J Med.* 2014;370:1189-1197.

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)		
Nausea	5 (50)	10 (71)	9 (64)	10 (71)	10 (71)	75% at least 1 interruption	62% discontinuations
Diarrhea	3 (30)	9 (64)	7 (50)	8 (57)	8 (57)		
Vomiting	5 (50)	8 (57)	6 (43)	7 (50)	7 (50)		
Fatigue	3 (30)	5 (36)	4 (40)	8 (80)	0	41 (51)	61 (47)
ALT increased	1 (10)	2 (14)	3 (30)	2 (20)	4 (80)	33 (41)	45 (35)
Constipation	1 (10)	3 (21)	3 (30)	4 (40)	2 (40)	29 (36)	42 (32)
Abdominal pain	2 (20)	1 (7)	2 (20)	2 (20)	1 (20)	31 (28)	39 (30)
↓Appetite	2 (20)	0	3 (30)	4 (40)	3 (60)	26 (32)	38 (29)
AST increased	1 (10)	3 (21)	2 (20)	2 (20)	3 (60)	22 (27)	33 (25)

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

CNS Responses to Ceritinib



CNS Responses With ALK TKIs

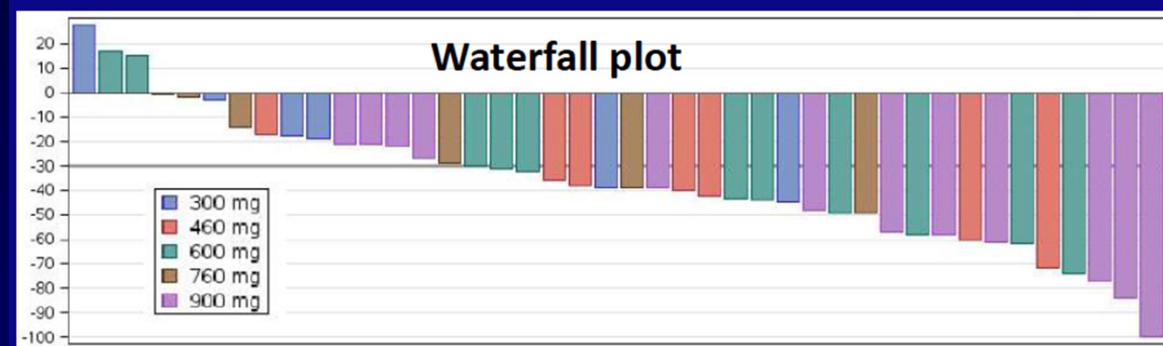
Agent	Intracranial RR (n)	Median duration of response
Crizotinib	25% (10/40)	≥ 6.5 months
Ceritinib	36% (10/28) pretreated 63% (5/8) crizotinib naive	≥ 7 months
Alectinib	52% (11/21) pretreated	Not reported
AP26113	43% (6/14)	Not reported

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

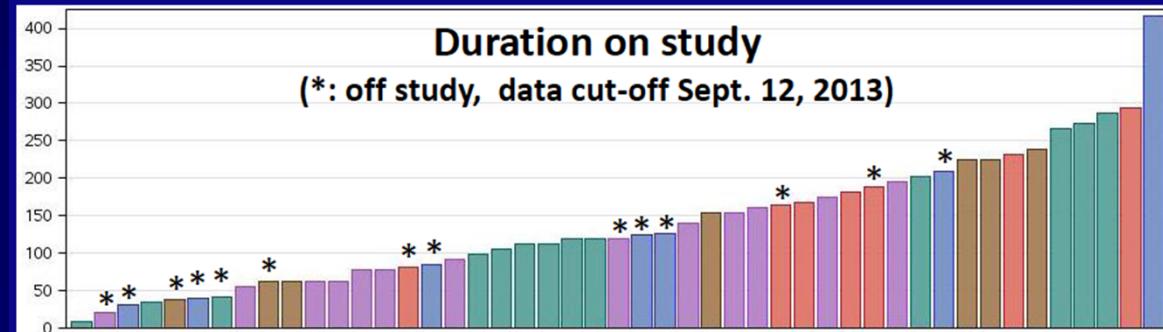
Clinical Activity of Alectinib in Crizotinib-Resistant ALK-Positive NSCLC

ORR 54.5% across all cohorts for all patients

% tumor shrinkage



Days on study



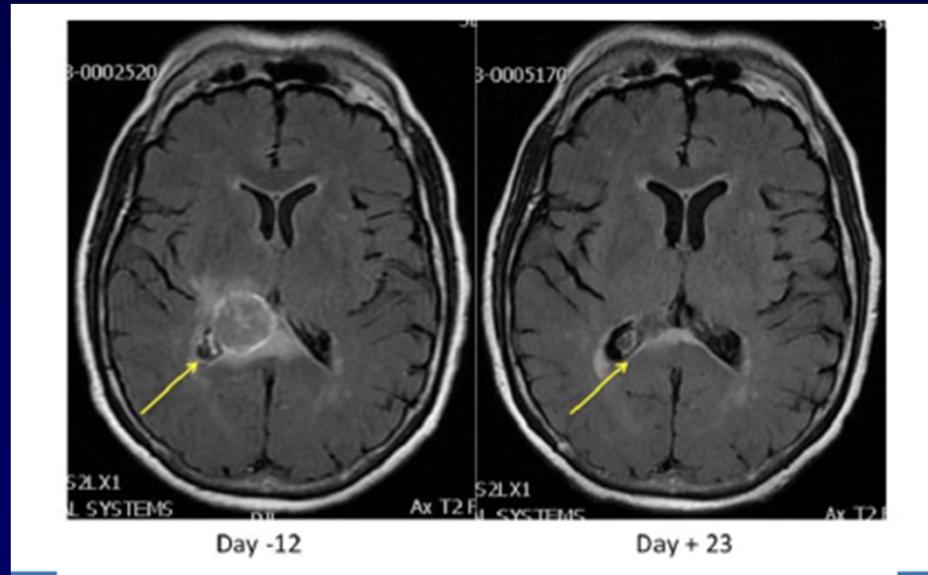
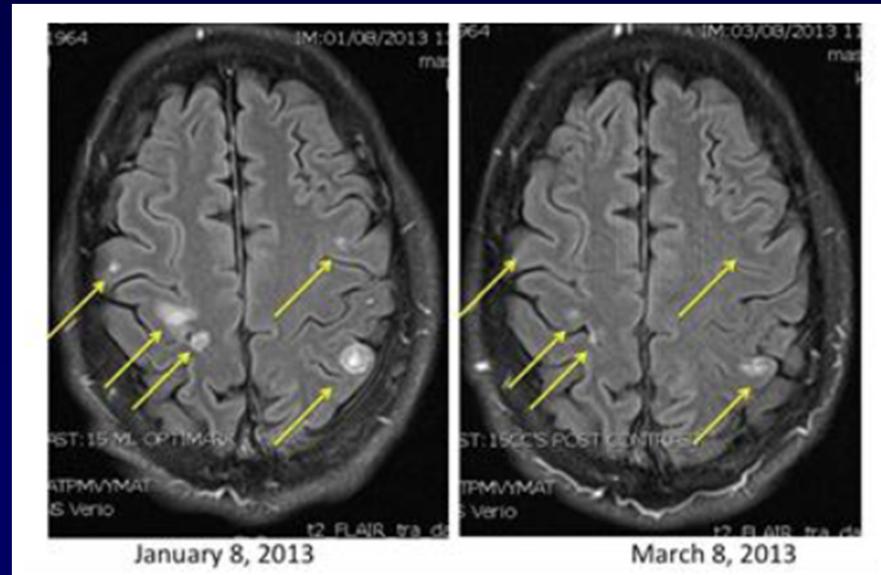
ORR 54.5%
all cohorts

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

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

CNS Responses to Alectinib



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

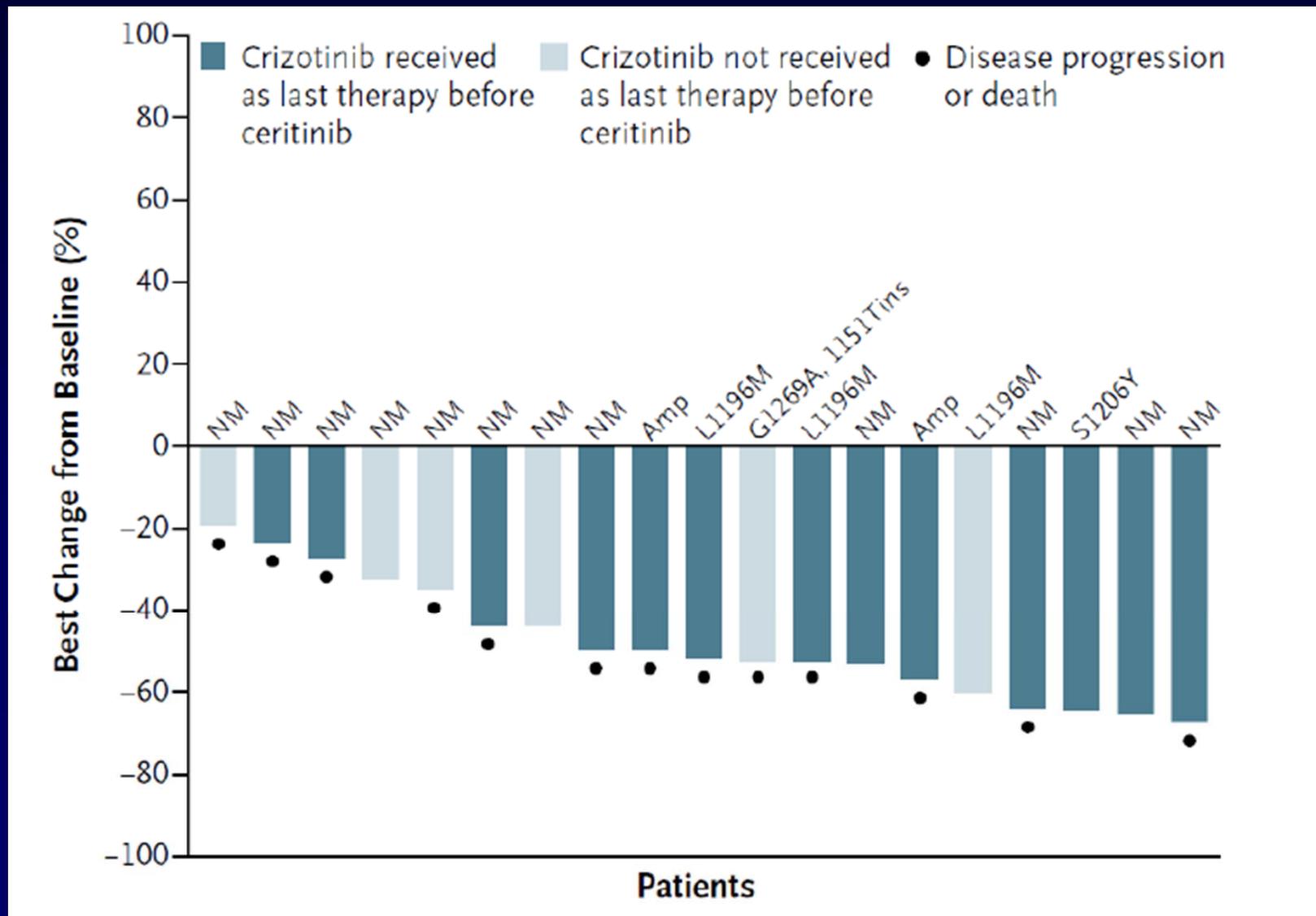
My Opinion: CNS Only Relapse

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?

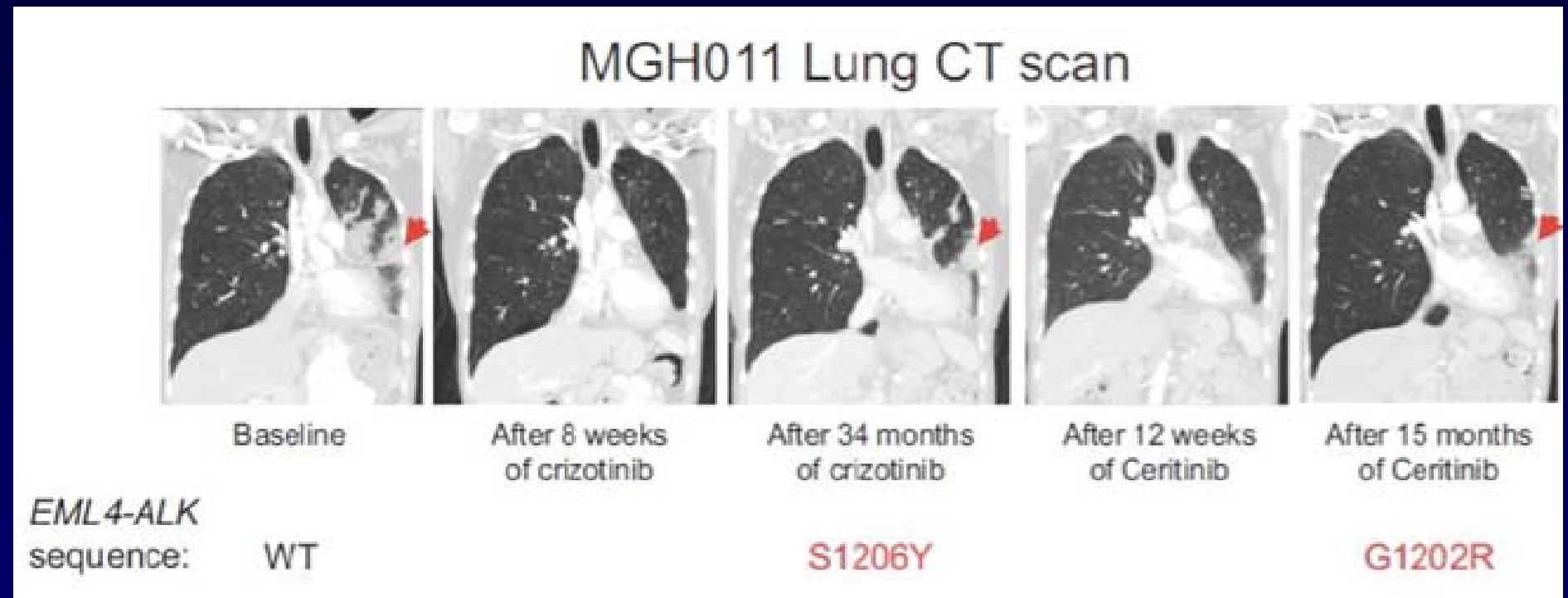
1. Continue crizotinib and add chemotherapy NO
2. Stop crizotinib and start cisplatin/pemetrexed **REASONABLE**
3. Clinical trial of second generation ALK inhibitor if available
4. Rebiopsy for additional mutation testing and clinical trial of targeted therapy
5. Ceritinib, if available (eg, compassionate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

prIME POINTS™

- 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**