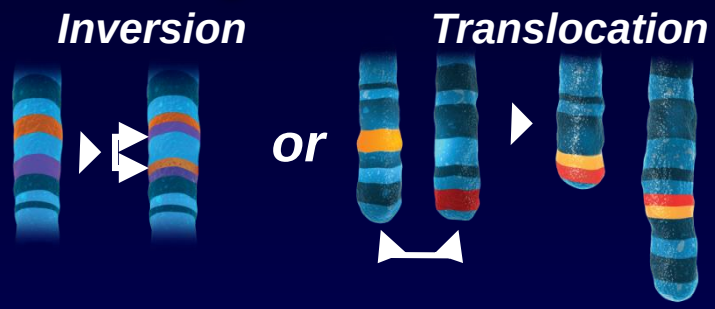
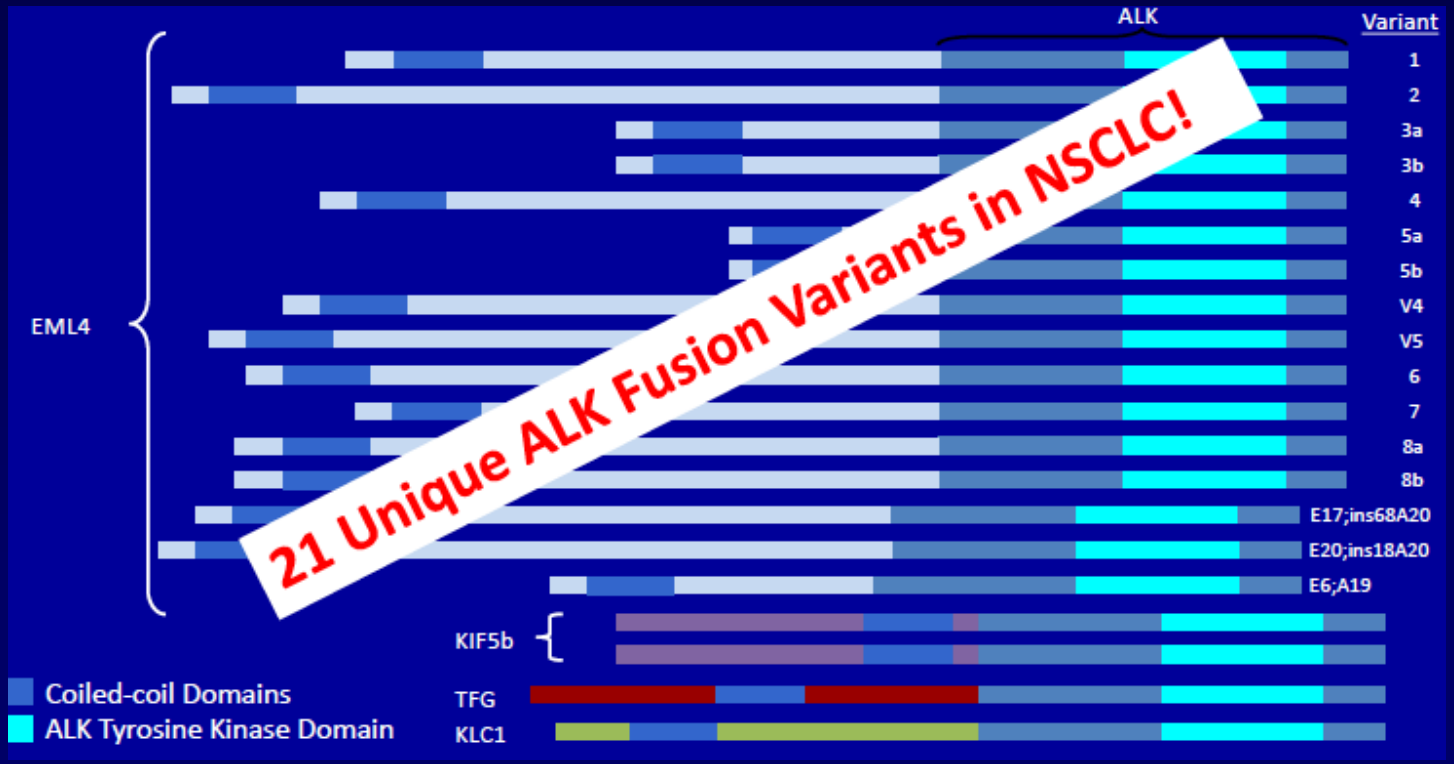
Case #3—Adenocarcinoma With *ALK* Rearrangement: Selecting Optimal Approach

Natasha Leighl, MD, MMSc, FRCPC
Princess Margaret Hospital
Toronto, Canada

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



Constitutive ALK activation
→ oncogene addiction



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

RANDOMIZE[b]

N = 343

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

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

CROSSOVER TO CRIZOTINIB PERMITTED AFTER PROGRESSION[c]

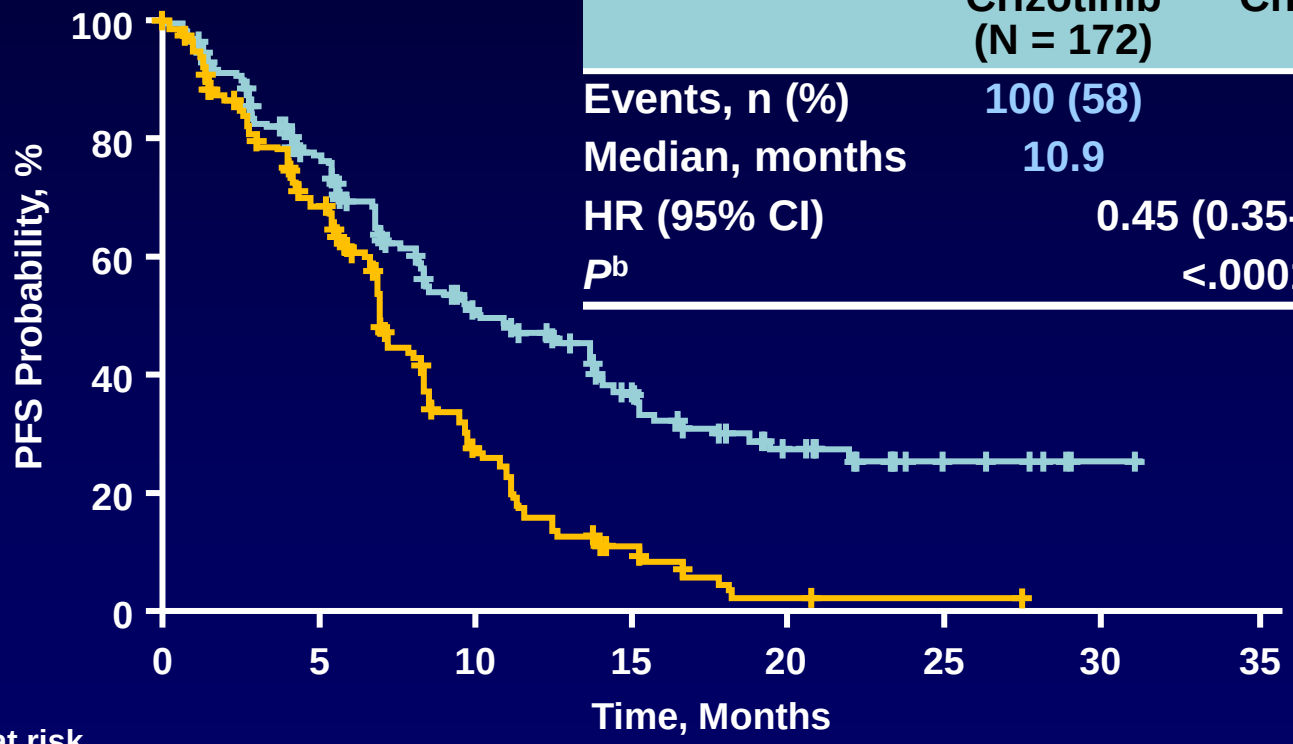
Endpoints

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

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

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

PROFILE 1014
Primary Endpoint Met: Crizotinib Superior to 1L Pemetrexed-Based Chemotherapy in Prolonging PFS[a]



	Crizotinib (N = 172)	Chemotherapy (N = 172)
Events, n (%)	100 (58)	137 (80)
Median, months	10.9	7.0
HR (95% CI)	0.45 (0.35-0.60)	
P[b]	<.0001	

Data cutoff: November 30, 2013
[a]Assessed by IRR [b]1-sided stratified log-rank test

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

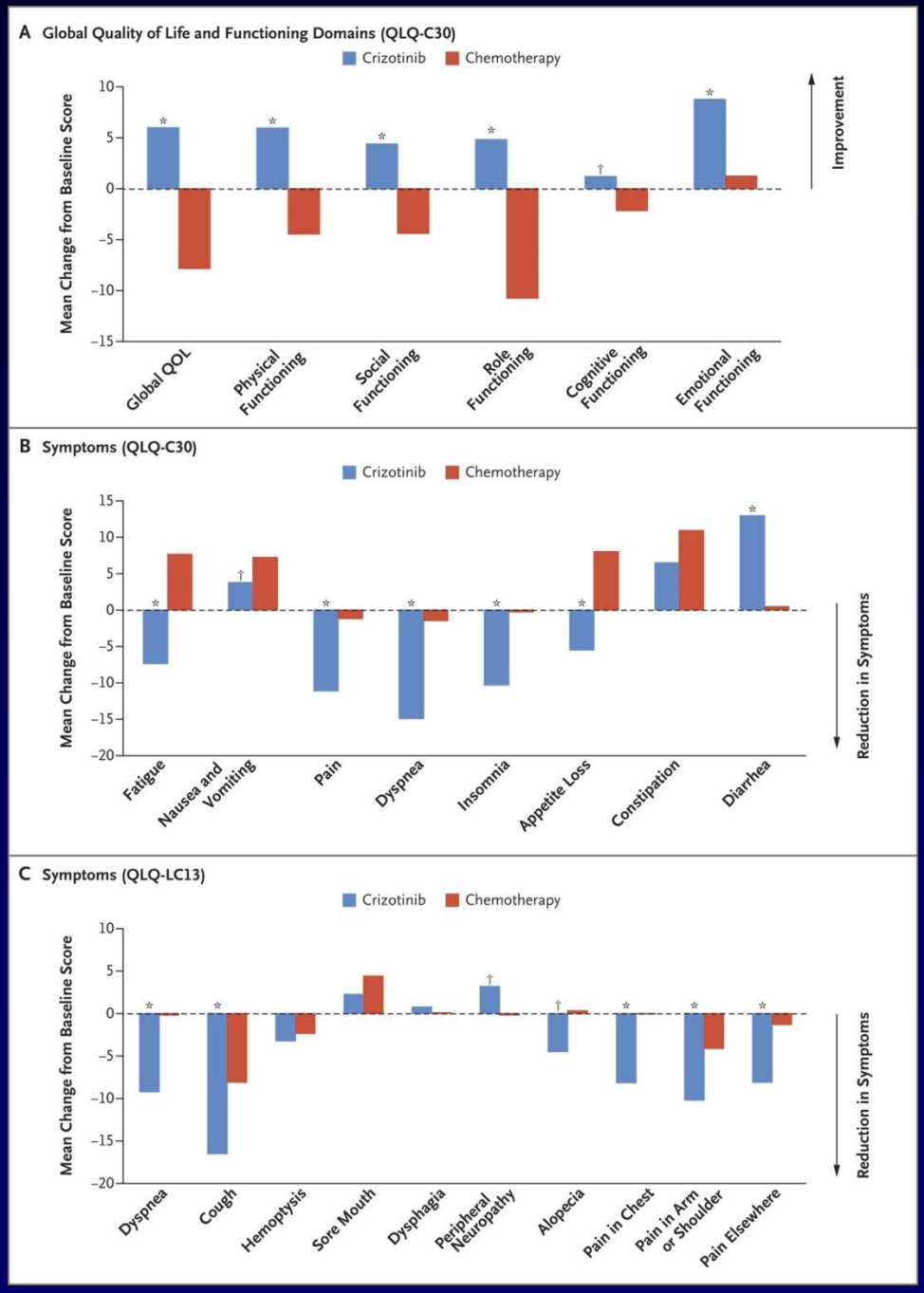
PROFILE 1014
Secondary Endpoints: ORR[a] and OS

	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)	
P[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

[a]By IRR; [b]before crossover to crizotinib; [c]Pearson χ^2 test; [d]in patients with an objective response [e]Kaplan–Meier method; [f]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

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

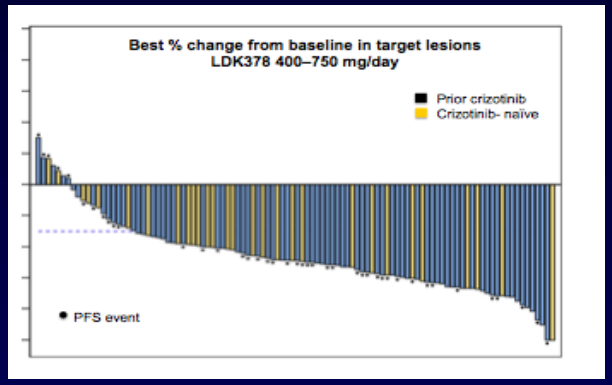
Chemotherapy in *ALK*-Positive NSCLC

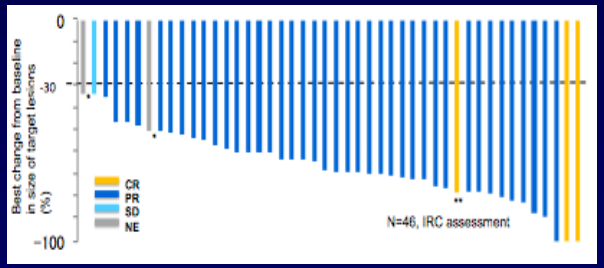
	Line	N	ORR	PFS
Platinum/pemetrexed[1] ≤6 cycles	1st	171	45%	7.0 months
Crizotinib[1]	1st	172	74%	10.9 months
Pemetrexed[2]	2nd	99	29%	4.2 months
Docetaxel[2]	2nd	72	7%	2.6 months
Crizotinib[2]	2nd	172	65%	7.7 months

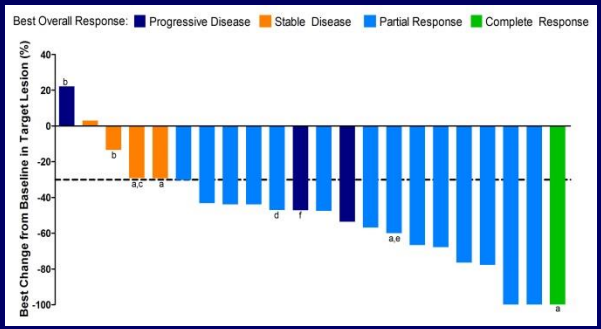
1. Mok T, et al. *J Clin Oncol.* 2014;32(5s): Abstract 8002. 2. Shaw AT, et al. *N Engl J Med*. 2013;368(25):2385-2394.

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

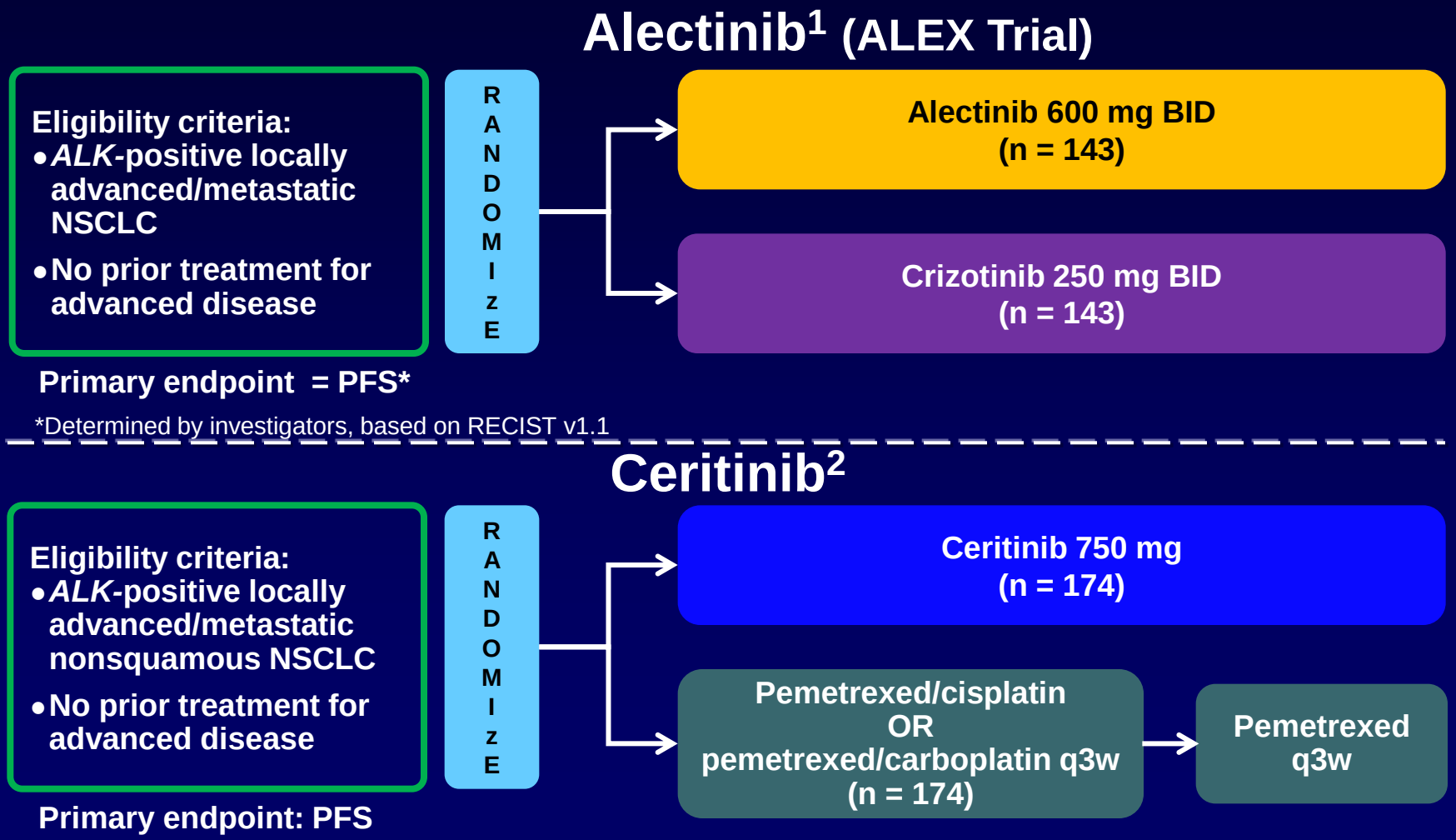






Felipe E, et al. *Ann Oncol.* 2014; Abstract 4380. Shaw AT, et al. *N Engl J Med.* 2014;370(26):2537-2539. Gadgeel SM, et al. *Lancet Oncol.* 2014;15(10):1119-1128. Nakagawa K, et al. *J Clin Oncol.* 2013;31(Suppl): Abstract 8033; Gettinger, S, et al. ESMO 2014: Abstract 5146

Alectinib and Ceritinib: First-Line Phase III Studies



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

Case 3—Optimal First-Line

1. Cisplatin + Pemetrexed 
2. Crizotinib 
3. Clinical trial: Ceritinib vs chemotherapy 
4. Clinical trial: Alectinib vs crizotinib 

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

[a]Not adjusted for differential treatment duration; [b]Before crossover to crizotinib; [c]clustered term

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

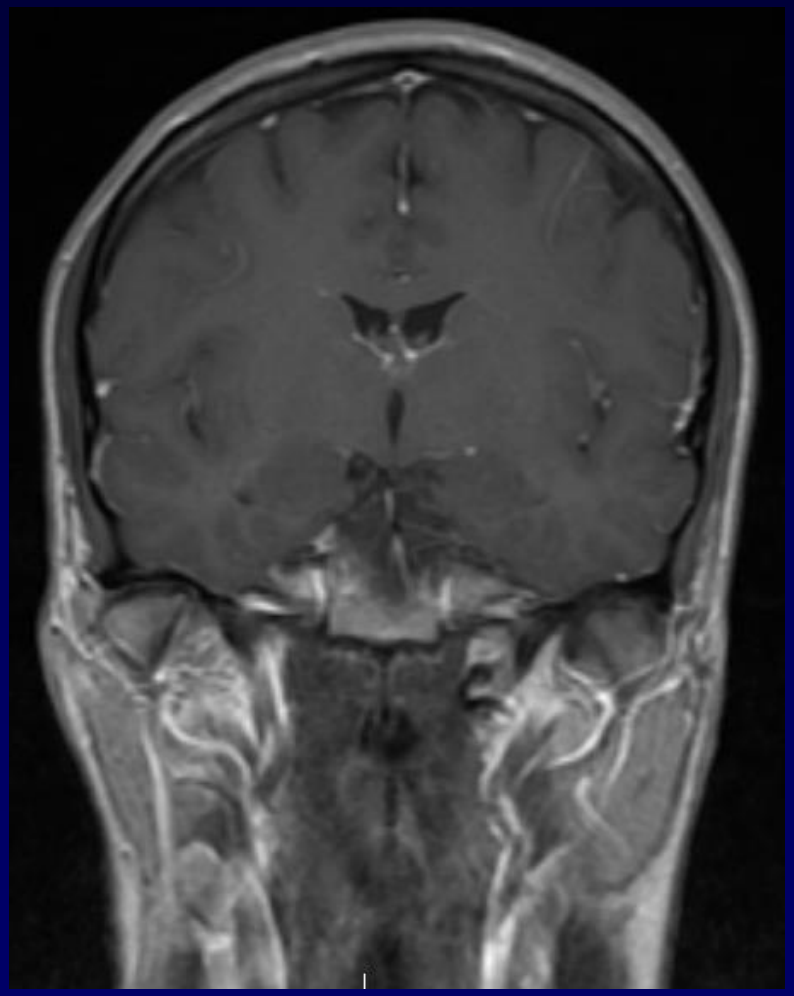
Dose Modification Scheme

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.

Crizotinib [prescribing information]. New York, New York: Pfizer, Inc; 2013.

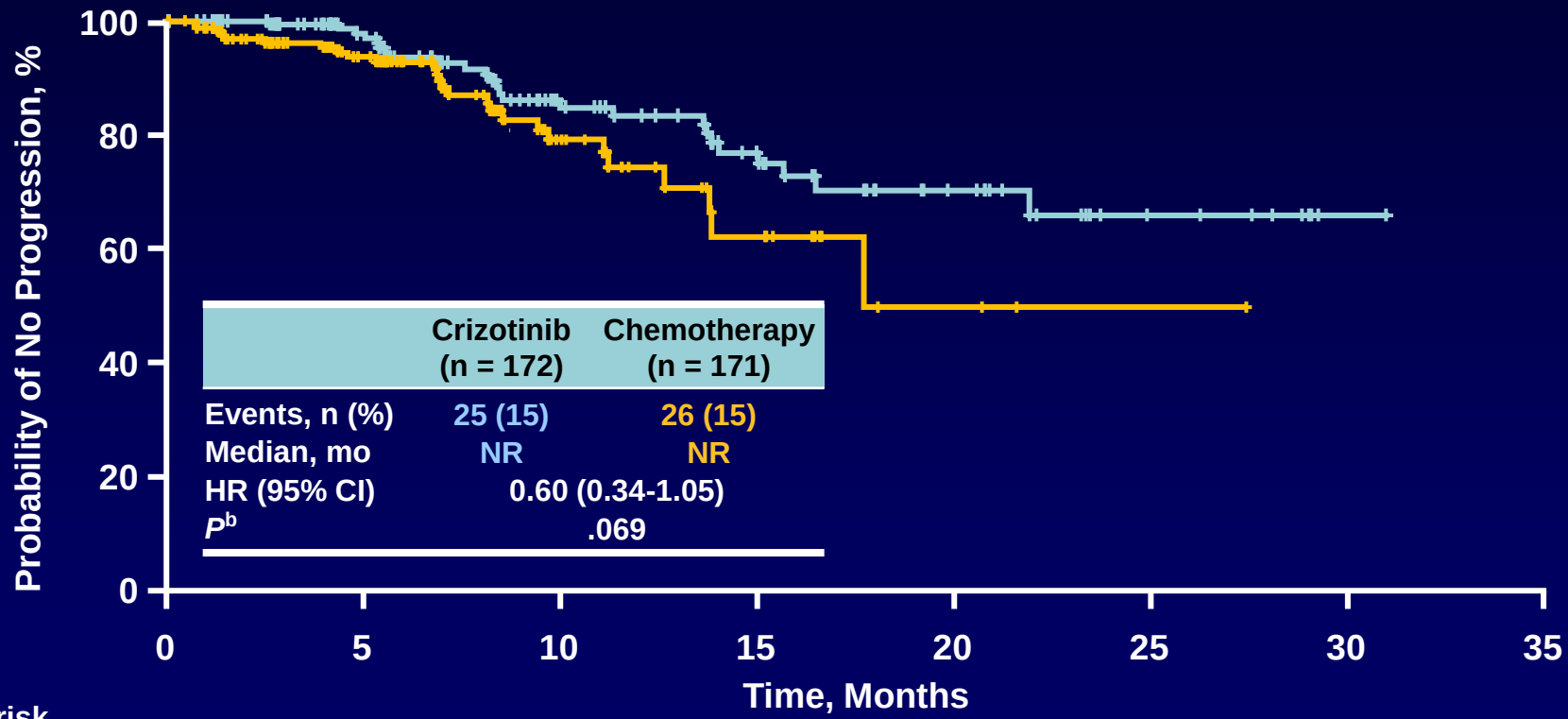
A Common Scenario



Baseline

After 9 months of crizotinib

Intracranial TTP[a] by IRR in ITT Population

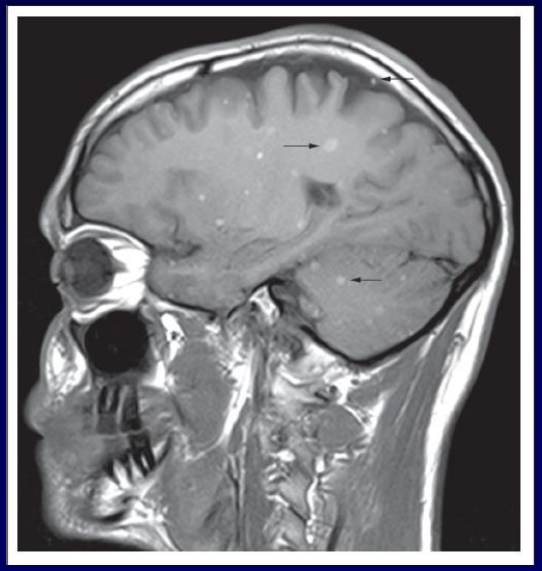


No. at risk								
Crizotinib	172	119	65	40	21	8	1	0
Chemotherapy	171	107	39	14	3	1	0	0

NR, not yet reached; [a]Time from randomization to first documentation of intracranial tumor progression; [b]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
ALK WT NIH3T3 IC_{50} (nM)	**80**	**1.5**
ALK L1196M NIH3T3 IC_{50} (nM)	**843**	**21**
ROS1-CD74 IC_{50} (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

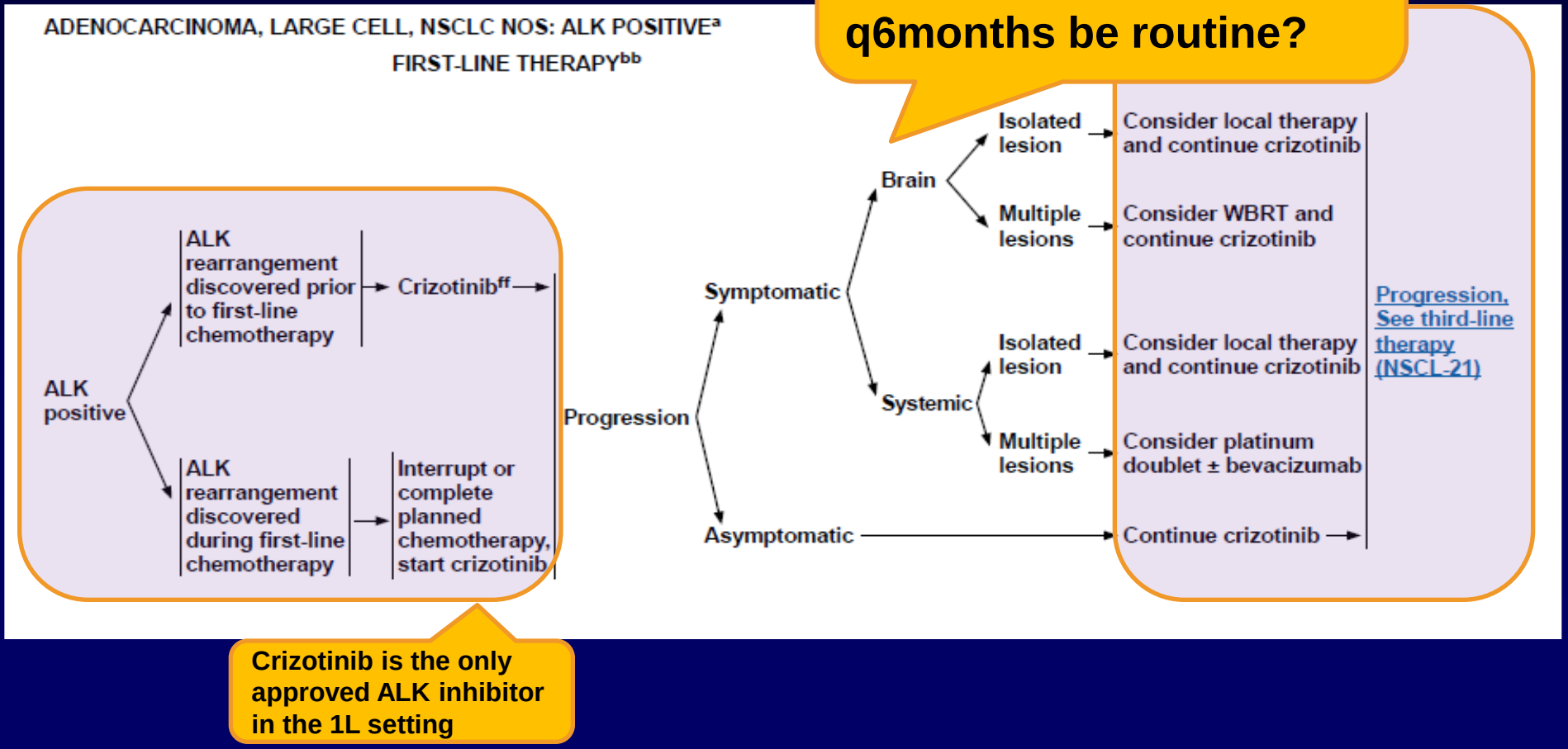
CSF: Plasma ratio 0.0026

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

CNS relapse frequent[2,3]

Should surveillance MRI q6months be routine?



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

[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.

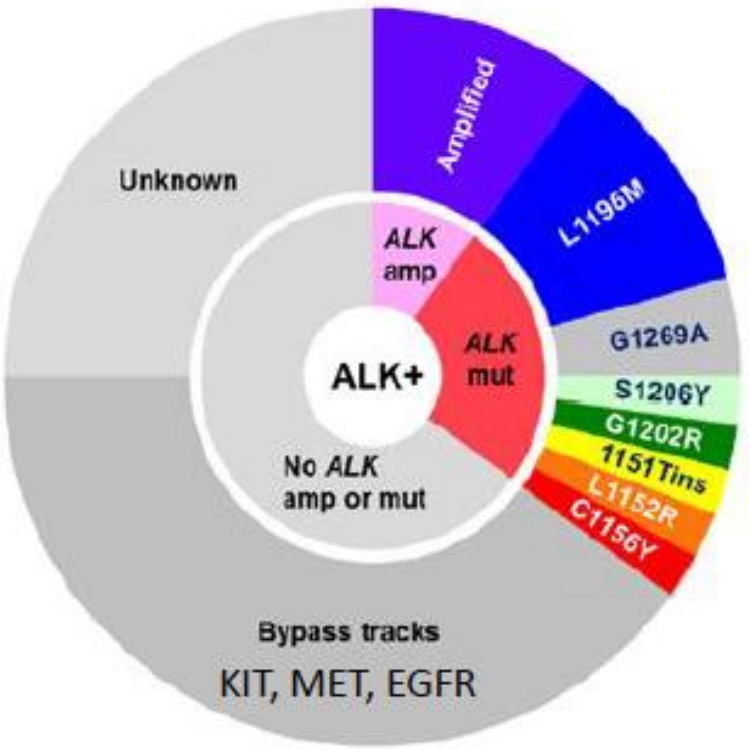
Surveillance Brain MRI?

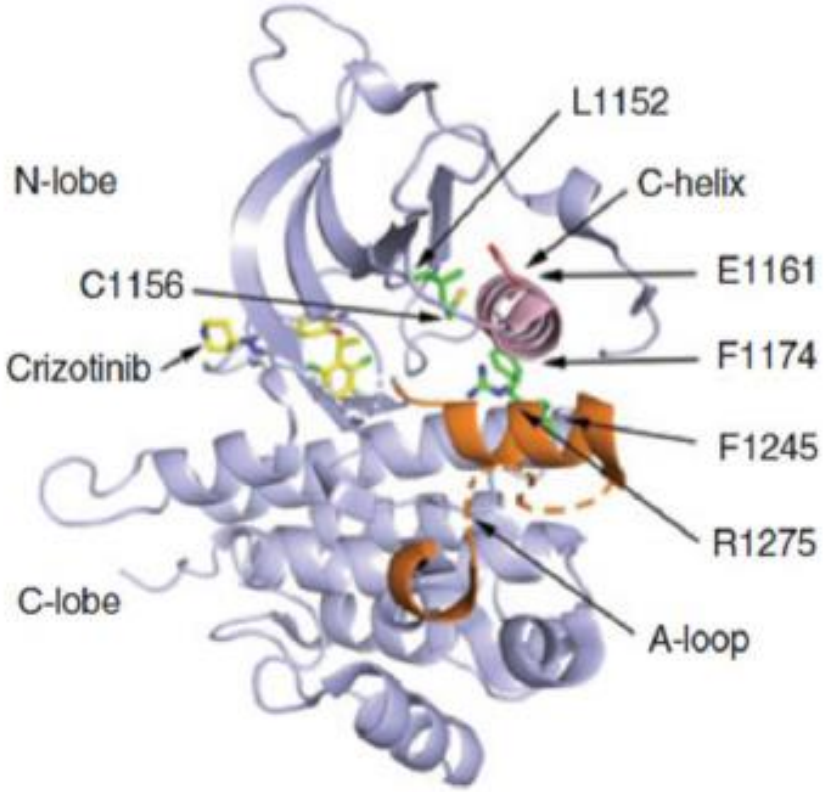
1. No, only if symptoms
2. Yes, brain MRI as often as systemic imaging
3. Yes, brain MRI every 6 months - 9 months

No clear evidence to support

Most experts choose #3 or #1

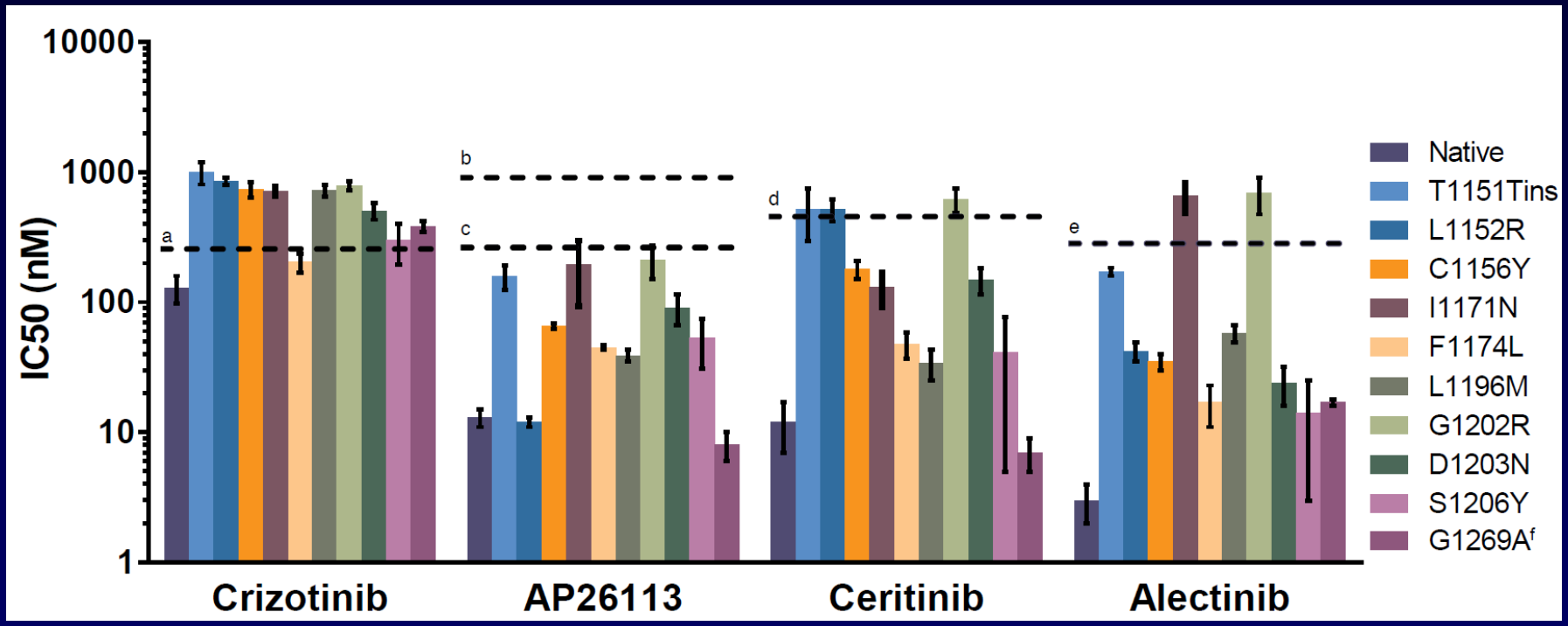
What About Resistance?
Crizotinib RR 65% to 75%; Median PFS 8-11 Months





Courtesy A. Shaw.

Next Generation ALK TKIs

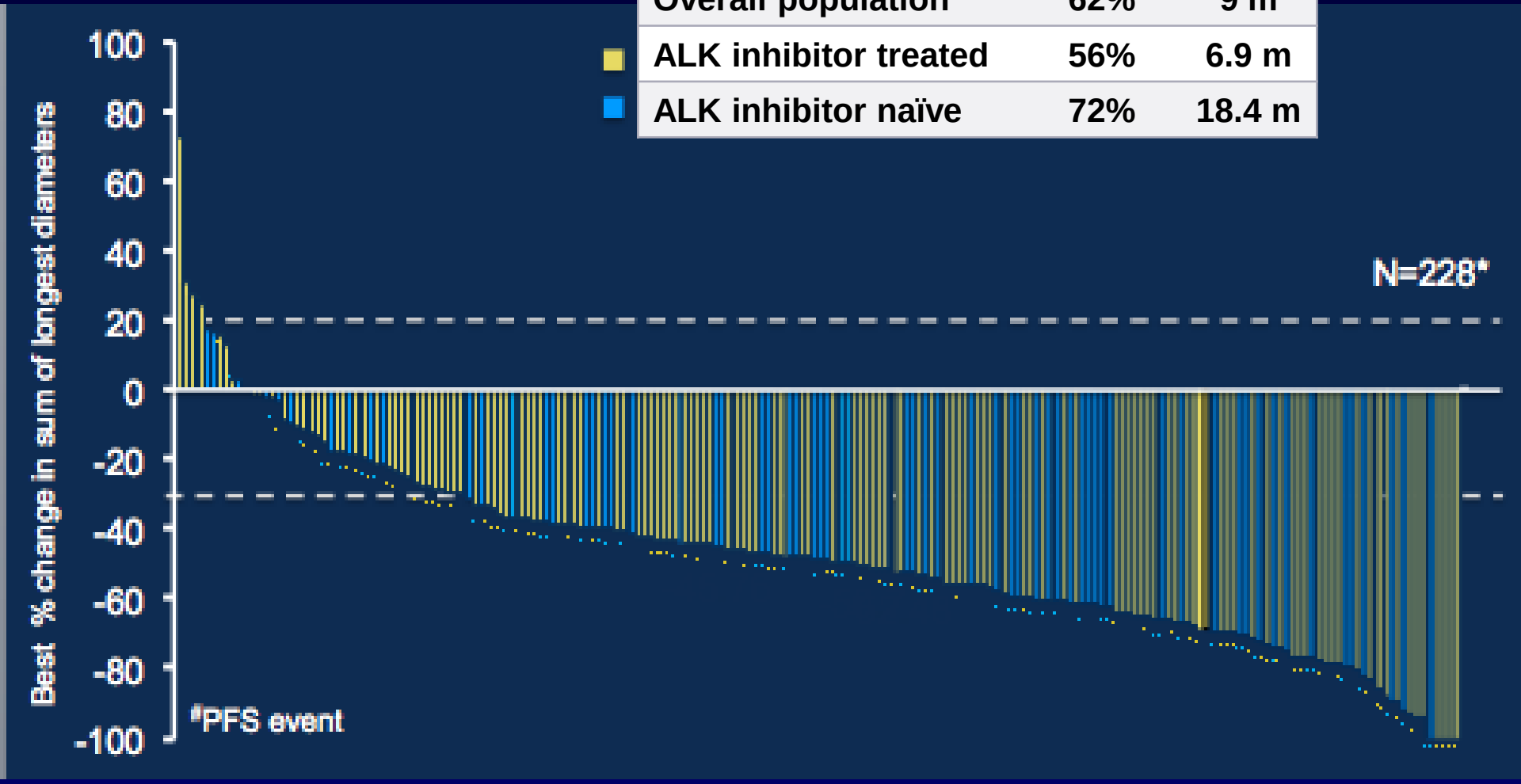


50% maximal inhibitory concentration (IC50) values of Ba/F3 cells dependent on expression of EML4-ALK (native) or kinase domain mutated *EML4-ALK* variants (n = 10). Data for each cell line are derived from at least 4 independent experiments (error bars = standard deviation). Dashed horizontal lines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

	RR	PFS
Overall population	62%	9 m
ALK inhibitor treated	56%	6.9 m
ALK inhibitor naïve	72%	18.4 m



Felip E, et al. *Ann Oncol.* 2014;25(Suppl 4): Abstract 1295P

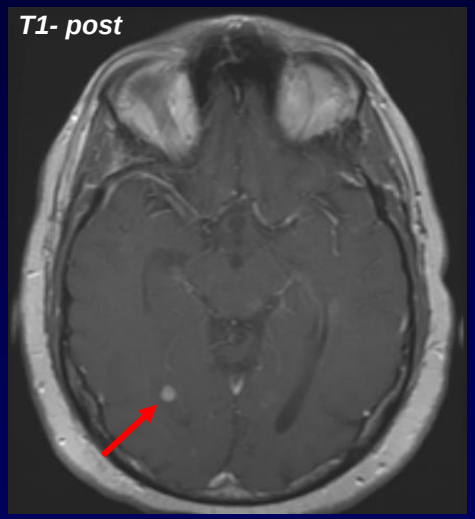
Side Effects of Ceritinib

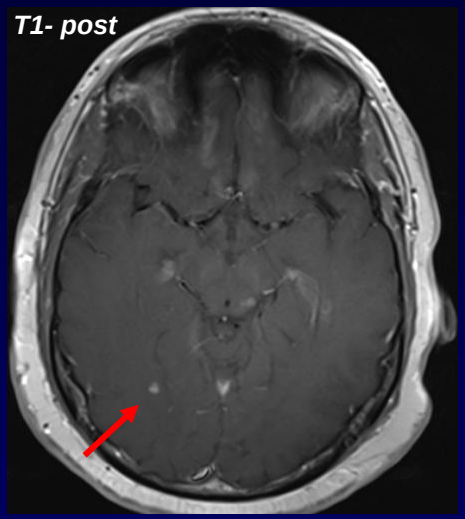
Preferred Term, n (%)	Ceritinib Dose, mg/day						
	50-300 (n = 10)	400 (n = 14)	5((n =				
Nausea	5 (50)	10 (71)	9 (				
Diarrhea	3 (30)	9 (64)	7 (				
Vomiting	5 (50)	8 (57)	6 (				
Fatigue	3 (30)	5 (36)	4 (40)	8 (80)	0	41 (51)	**61 (47)**
ALT increased	1 (10)	2 (14)	3 (30)	2 (20)	4 (80)	33 (41)	**45 (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)**

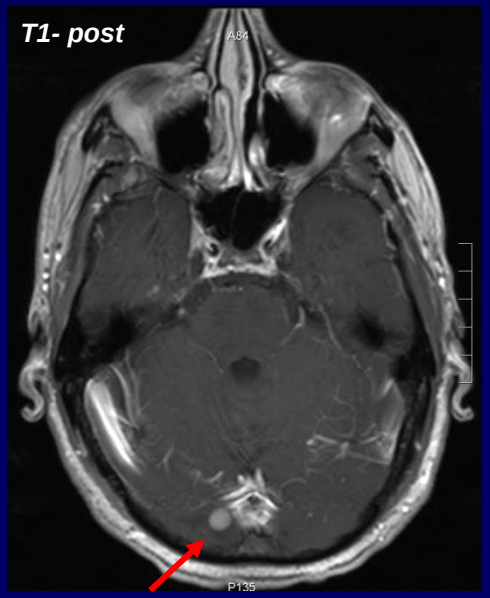
75% at least 1 interruption
62% reductions

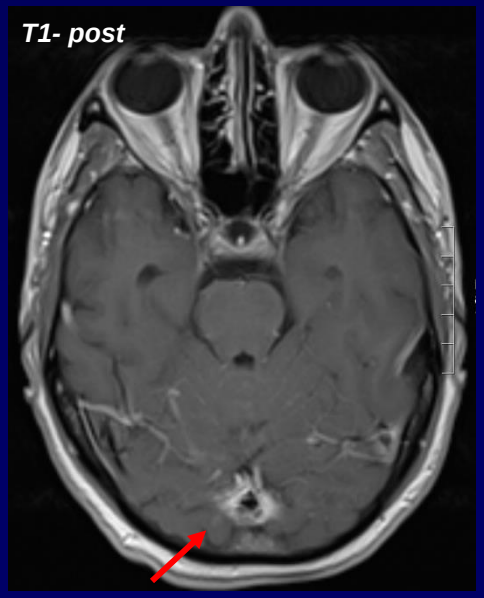
Shaw AT, et al. *N Engl J Med*. 2014(13);370:1189-1197.

CNS Responses to Ceritinib









CNS Responses With ALK TKIs

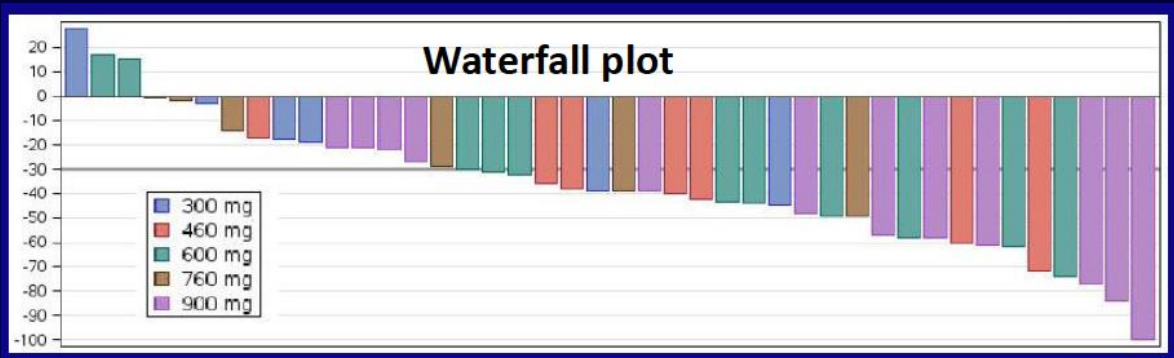
Agent	Intracranial RR (n)	Median duration of response
Crizotinib[1]	25% (10/40)	≥ 6.5 months
Ceritinib[2]	36% (10/28) pretreated 63% (5/8) crizotinib naive	≥ 7 months
Alectinib[3]	52% (11/21) pretreated	Not reported
AP26113[4]	43% (6/14)	Not reported

1. Costa D, et al. J Thorac Oncol. 2014; Abstract 2932; 2. Shaw AT, et al. *Ann Oncol.* 2014;25(Suppl 4): Abstract ; 1293P 3. Gadgeel SM, et al. *Lancet Oncol.* 2014;15(10):1119-1128; 4. Gettinger S, et al. *Ann Oncol.* 2014;25(Suppl 4): Abstract 5146

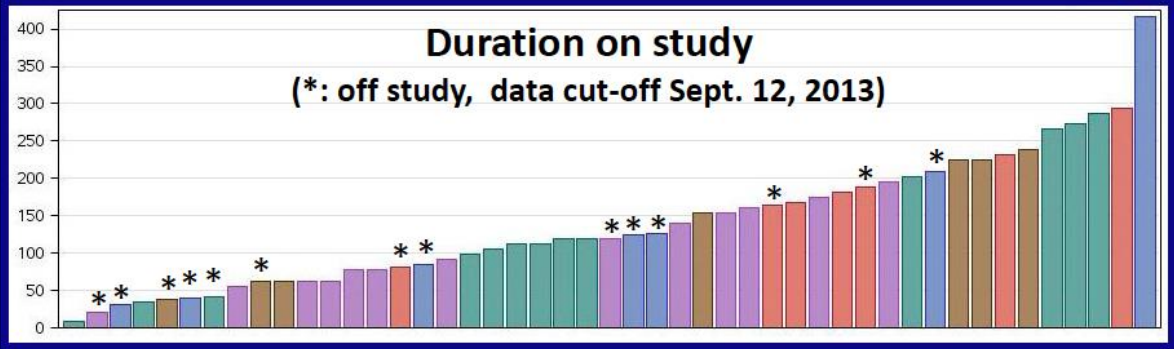
Clinical Activity of Alectinib in Crizotinib-Resistant *ALK*-Positive NSCLC

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

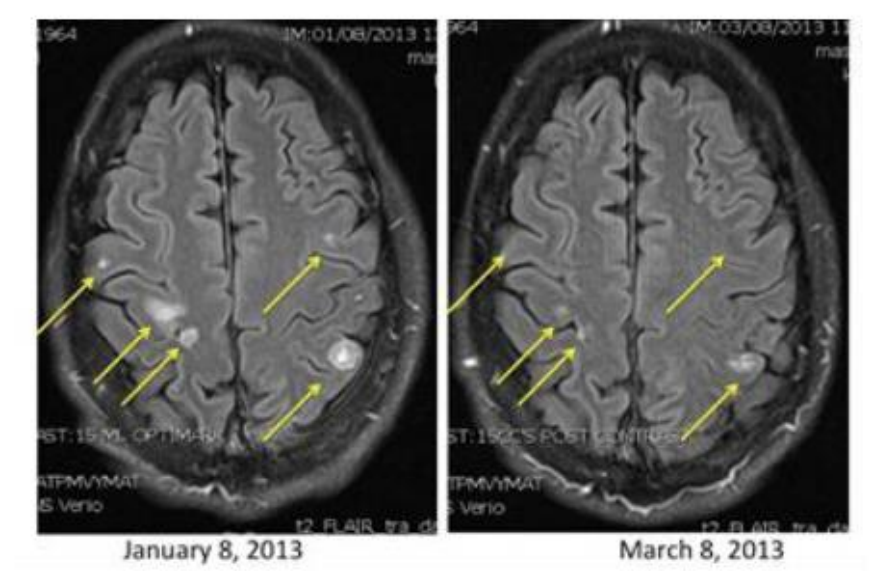
Ou S-H, et al. *Eur J Cancer.* 2013;49(Suppl 3): Abstract 44.

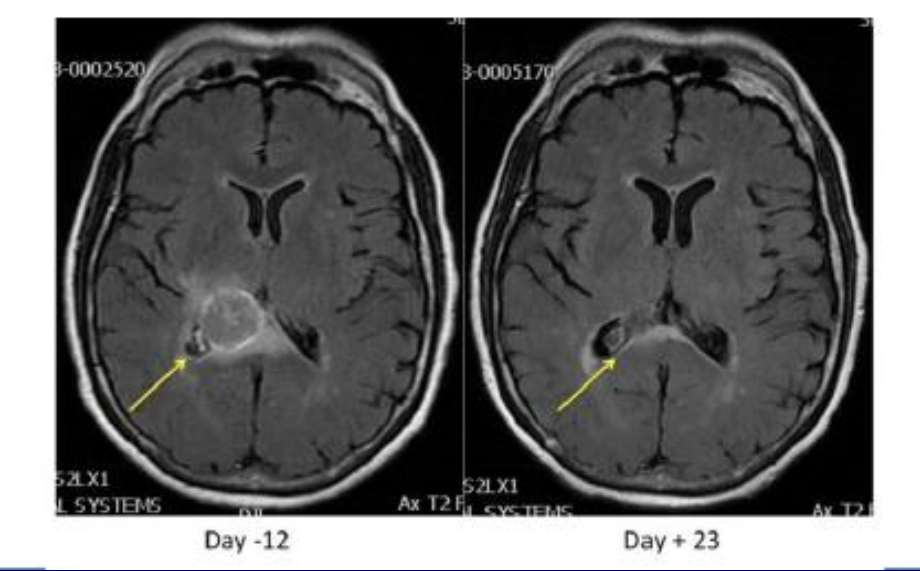
Side Effects of Alectinib

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)

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

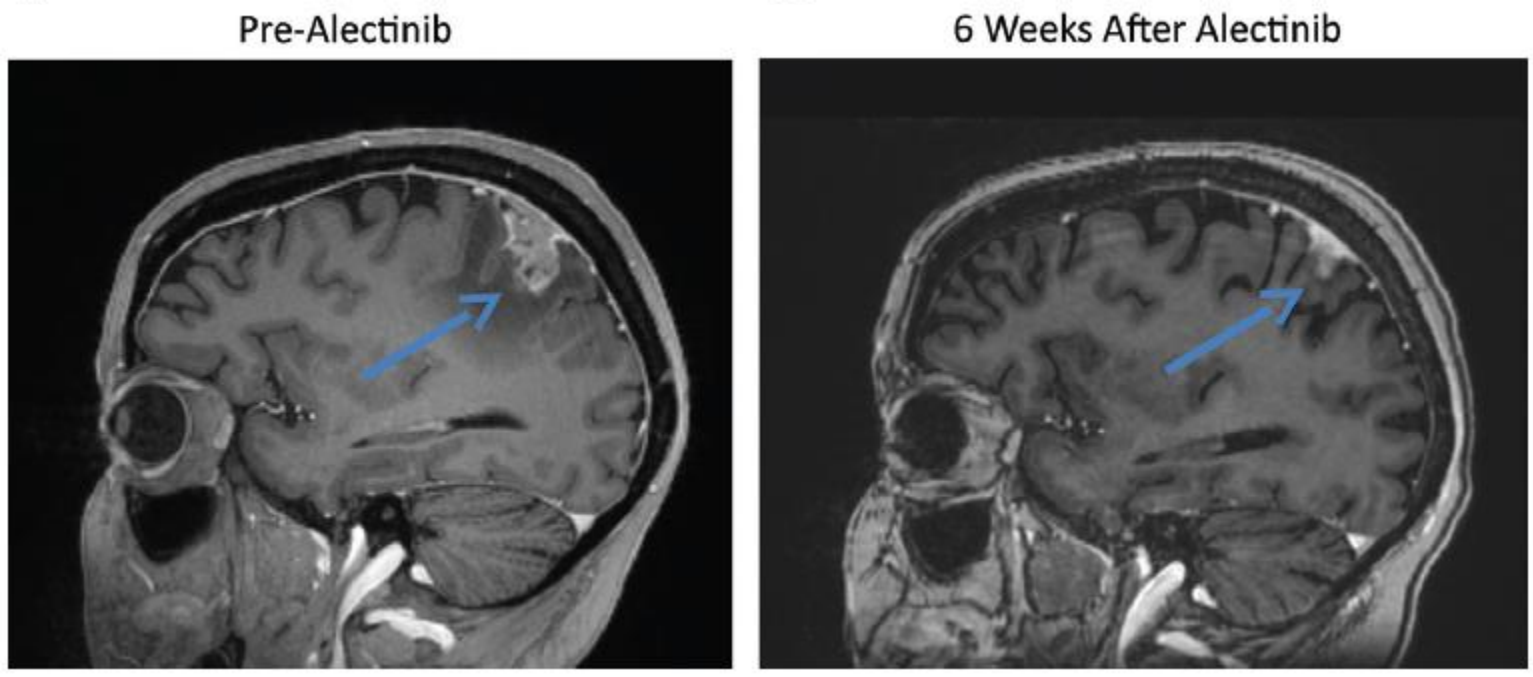
CNS Responses to Alectinib





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

CNS Responses to Alectinib
Leptomeningeal Metastasis



Gainor JF, et al. *J Thorac.* 2015;10(2):232-236

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

AVOID WBRT IF POSSIBLE

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**

What About Extracranial Progression?

1. Continue crizotinib and add chemotherapy NO

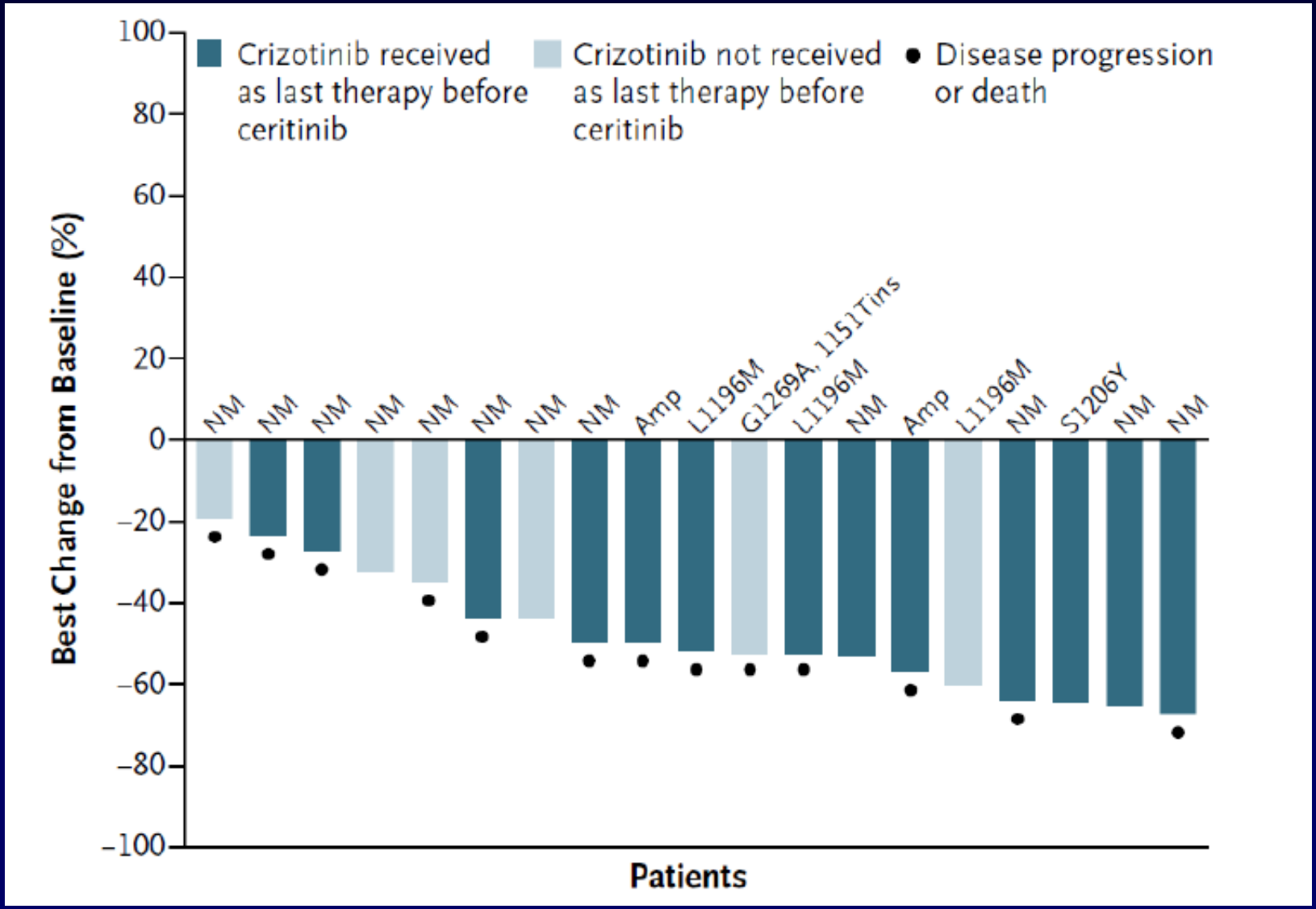
2. Stop crizotinib and start cisplatin/pemetrexed
   REASONABLE

3. Clinical trial of second generation ALK inhibitor if available +

4. Rebiopsy for additional mutation testing and clinical trial of targeted therapy +

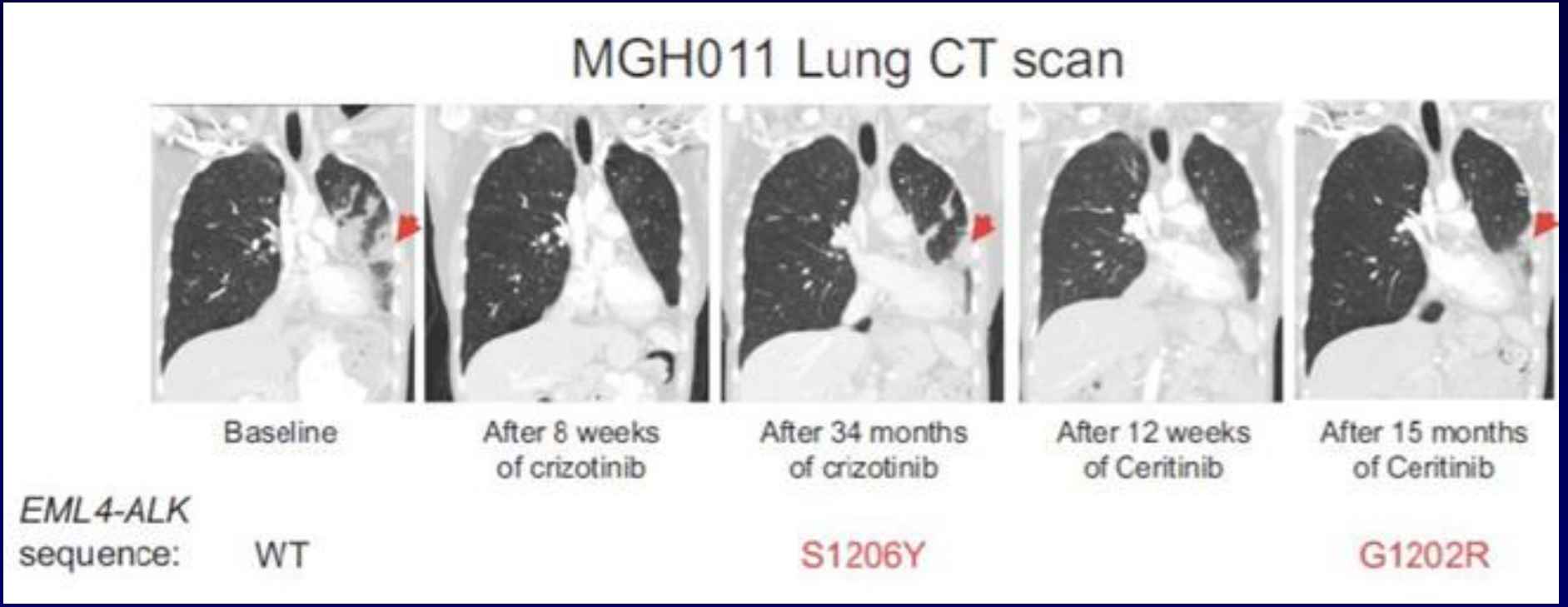
5. Ceritinib, if available (eg, compassionate access) +

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



Friboulet L, et al. *Cancer Discov.* 2014;4(6):662-673.

Next Generation ALK Inhibitors

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