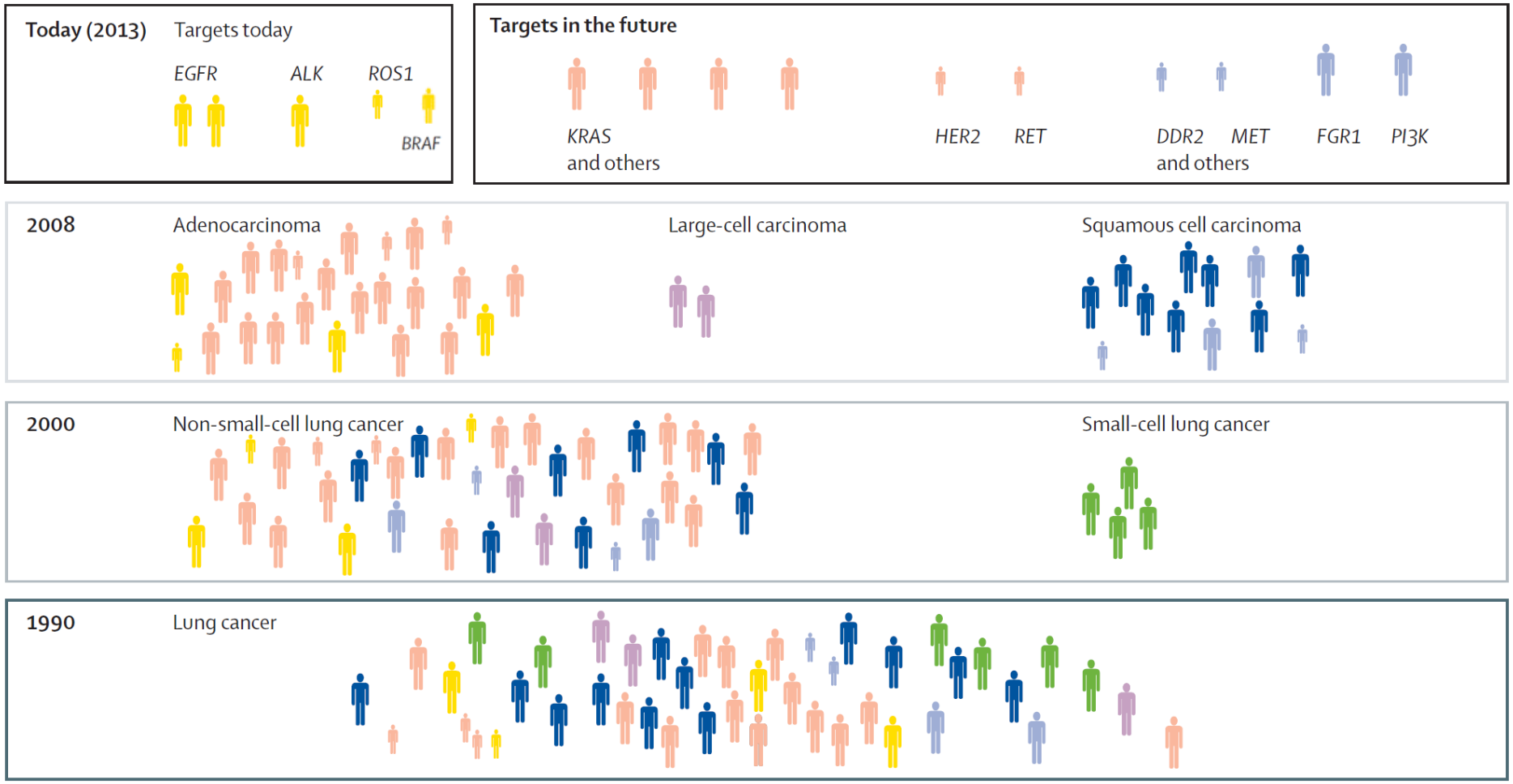
Lung cancer patient "segments" have evolved over time



Martin Reck et al, *Lancet*. 2013

NIH NATIONAL CANCER INSTITUTE

Drugs Approved for Non-Small Cell Lung Cancer

Afatinib Dimaleate

Alectinib

Atezolizumab

Bevacizumab

Brigatinib

Carboplatin

Ceritinib

Crizotinib

Dabrafenib

Docetaxel

Erlotinib Hydrochloride

Everolimus

Gefitinib

Gemcitabine Hydrochloride

Mechlorethamine Hydrochloride

Methotrexate

Necitumumab

Nivolumab

Osimertinib

Paclitaxel

Paclitaxel Albumin-stabilized Nanoparticle Formulation

Pembrolizumab

Pemetrexed Disodium

Ramucirumab

Trametinib

Vinorelbine Tartrate

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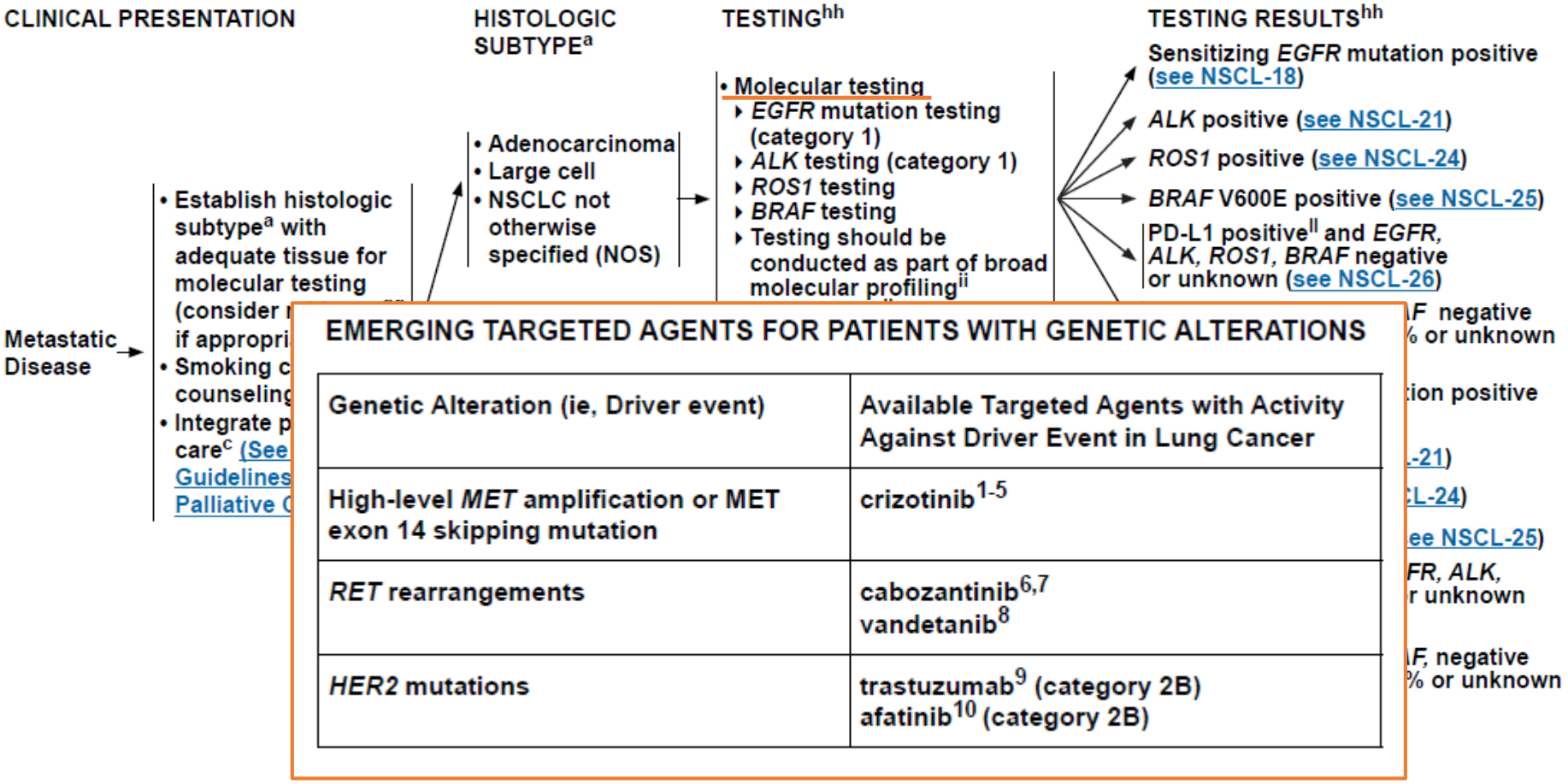


EMERGING TARGETED AGENTS FOR PATIENTS WITH GENETIC ALTERATIONS

Genetic Alteration (ie, Driver event)	Available Targeted Agents with Activity Against Driver Event in Lung Cancer
High-level *MET* amplification or MET exon 14 skipping mutation	crizotinib[1-5]
RET rearrangements	cabozantinib[6,7] vandetanib[8]
HER2 mutations	trastuzumab[9] (category 2B) afatinib[10] (category 2B)

Updated Molecular Testing Guideline for the Selection of Lung Cancer Patients for Treatment With Targeted Tyrosine Kinase Inhibitors

Guideline From the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology

Strength of Recommendations[a]

Designation	Recommendation	Rationale
Strong recommendation	Recommend for or against a particular molecular testing practice in lung cancer (can include must or should)	Supported by convincing (high) or adequate (intermediate) quality of evidence and clear benefit that outweighs any harms.
Recommendation	Recommend for or against a particular molecular testing practice in lung cancer (can include should or may)	Some limitations in quality of evidence (adequate [intermediate] or inadequate [low]), balance of benefits and harms, values, or costs, but panel concludes that there is sufficient evidence to inform a recommendation.
Expert consensus opinion	Recommend for or against a particular molecular testing practice in lung cancer (can include should or may)	Serious limitations in quality of evidence (inadequate [low, very low] or insufficient), balance of benefits and harms, values, or costs, but panel consensus is that a statement is necessary.
No recommendation	No recommendation for or against a particular molecular testing practice in lung cancer	Insufficient evidence, confidence, or agreement to provide a recommendation.

[a]Data derived from Andrews et al.

Lindeman NI, et al. *J Thorac Oncol* 2018;13(3):323-358

Summary of 2018 Guideline Statements

Guideline Statements	Strength of Recommendation
Which new genes should be tested for lung cancer patients?	
1. *ROS1* testing must be performed on all lung adenocarcinoma patients, irrespective of clinical characteristics.	(Strong recommendation)
2. *BRAF, RET, HER2, KRAS, MET* molecular testings are currently not indicated as a routine stand-alone assay outside the context of a clinical trial. It is appropriate to include these testings as part of larger testing panels performed either initially or when routine *EGFR, ALK,* and *ROS1* testing are negative.	(Expert consensus opinion)
What methods should be used to perform molecular testing?	
1. IHC is an equivalent alternative to FISH for *ALK* testing.	(Recommendation)
What testing is indicated for patients with targetable mutations who have relapsed on targeted therapy?	
1. In lung adenocarcinoma patients who harbor sensitizing *EGFR* mutations and have progressed after treatment with an *EGFR*-tyrosine kinase inhibitor, physicians must use *EGFR* T790M mutational testing when selecting patients for third-generation *EGFR*-targeted therapy	(Strong recommendation)
2. There is currently insufficient evidence to support a recommendation for or against routine testing for *ALK* mutational status for lung adenocarcinoma patients with sensitizing *ALK* mutations who have progressed after treatment with an *ALK*-tyrosine kinase inhibitor	(No recommendation)
What is the role of testing for circulating cell-free DNA for lung cancer patients?	
1. In some clinical settings in which tissue is limited and/or insufficient for molecular testing, physicians may use a cell-free plasma DNA assay to identify *EGFR* mutations.	(Recommendation)
2. There is currently insufficient evidence to support the use of circulating tumor cell molecular analysis for the diagnosis of primary lung adenocarcinoma, the identification of *EGFR* or other mutations, or the identification of *EGFR* T790M mutations at the time of *EGFR* TKI resistance.	(No recommendation)

Abbreviations: FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; TKI, tyrosine kinase inhibitor.

Molecular Testing Guideline for the Selection of Patients With Lung Cancer for Treatment With Targeted Tyrosine Kinase Inhibitors: American Society of Clinical Oncology Endorsement of the College of American Pathologists/ International Association for the Study of Lung Cancer/ Association for Molecular Pathology Clinical Practice Guideline Update

Purpose

In response to advances in the field, the College of American Pathologists (CAP), the International Association for the Study of Lung Cancer (IASLC), and the Association for Molecular Pathology (AMP) recently updated their recommendations for molecular testing for the selection of patients with lung cancer for treatment with targeted tyrosine kinase inhibitors. ASCO has a policy and set of procedures for endorsing clinical practice guidelines that have been developed by other professional organizations.

Methods

The molecular testing guideline was reviewed for developmental rigor by methodologists. Then an ASCO Expert Panel reviewed the content and the recommendations.

Results

The ASCO Expert Panel determined that the recommendations from the CAP/IASLC/AMP molecular testing guideline are clear, thorough, and based upon the most relevant scientific evidence. ASCO endorsed the guideline with minor modifications.

Kalemkerian GP, et al. *J Clin Oncol* 2018; 36:911-919

Comparison of CAP/IASLC/AMP Recommendations and ASCO Endorsed Recommendations

CAP/IASLC/AMP Recommendation	ASCO Endorsed Recommendation
Key Question 1: Which genes should be tested for patients with lung cancer?	
Expert Consensus Opinion: *BRAF* molecular testing is currently not indicated as a routine stand-alone assay outside the context of a clinical trial. It is appropriate to include *BRAF* as part of larger testing panels performed either initially or when routine *EGFR, ALK, and ROS1* testing is negative.	*BRAF* testing should be performed on all patients with advanced lung adenocarcinoma, irrespective of clinical characteristics.
Key Question 2: What methods should be used to perform molecular testing?	
Expert Consensus Opinion: Physicians may use molecular biomarker testing in tumors with histologies other than adenocarcinoma when clinical features indicate a higher probability of an oncogenic driver.	Physicians may use molecular biomarker testing in tumors with: a. an adenocarcinoma component; b. nonsquamous non–small-cell histology; c. any non–small-cell histology when clinical features indicate a higher probability of an oncogenic driver (eg, young age [< 50 years]; light or absent tobacco exposure).

Kalemkerian GP, et al. *J Clin Oncol* 2018; 36:911-919

Actionable Target

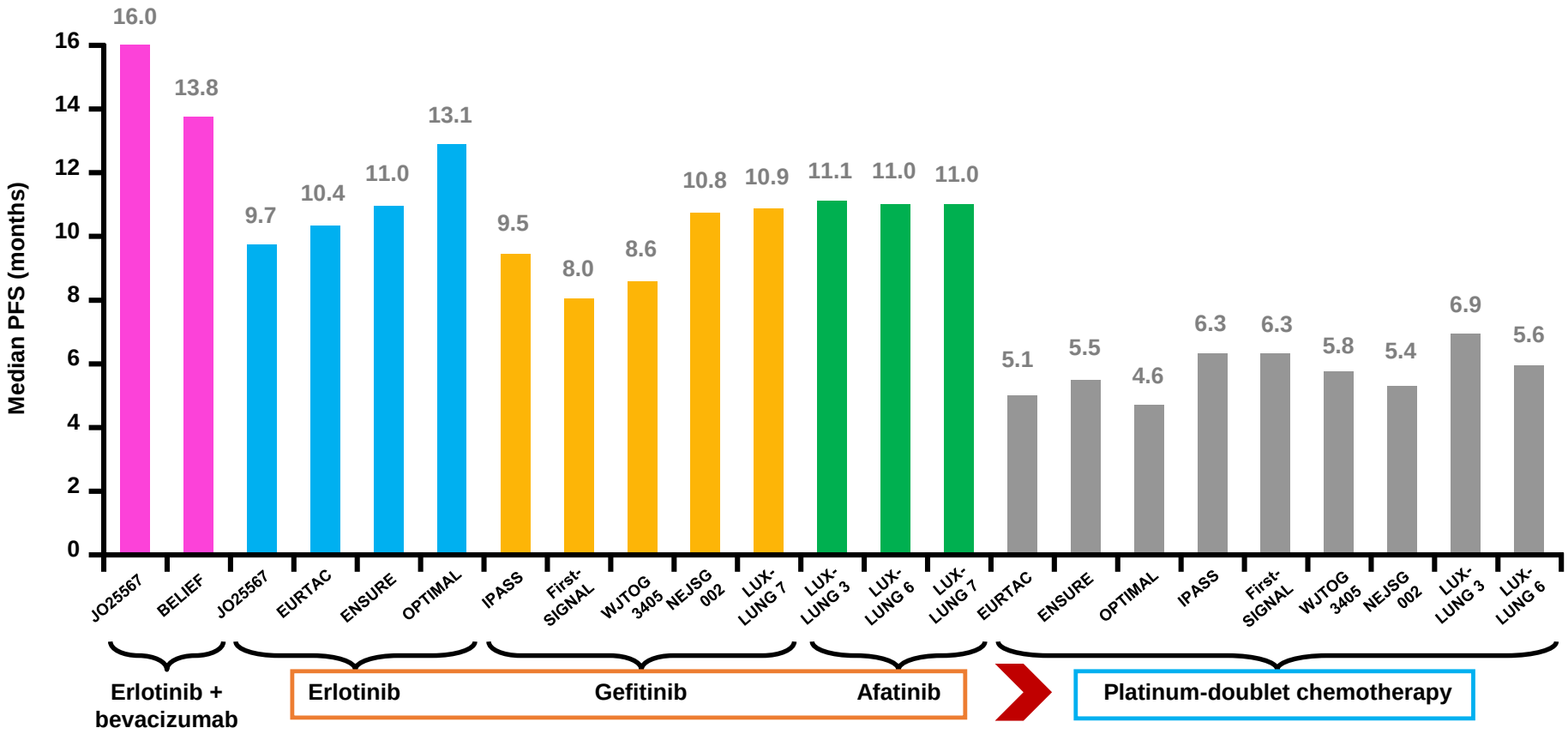
- ***EGFR*** gene mutation
- ***ALK*** rearrangement
- ***ROS1*** rearrangement
- ***BRAF*** gene mutation (V600E)

Epidermal Growth Factor Receptor

Currently available EGFR TKIs

	1st generation (Reversible)	2nd generation (irreversible/pan-HER)	3rd generation (EGFR mutation selective)
Drugs	**Gefitinib** **Erlotinib** Icotinib	**Afatinib** Dacomitinib	Rociletinib **Osimertinib** **Olmutinib** Nazartinib
WT EGFR : skin toxicity	++	+++	+-
Activating mutation	+++	+++(++++?)	+++(++++?)
Resistance mutation : T790M	-	+	+++

Median PFS in first-line *EGFR* Mutant NSCLC



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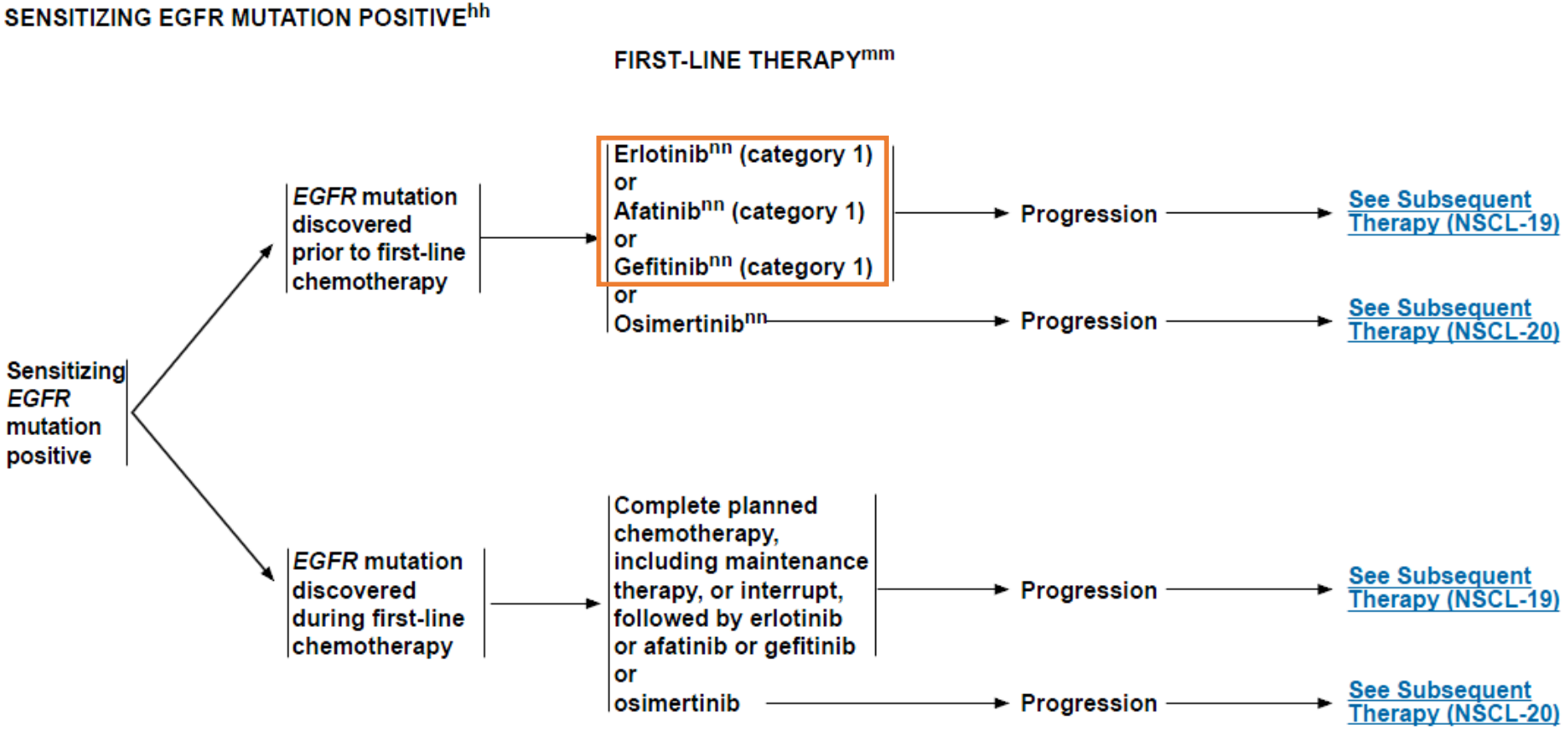
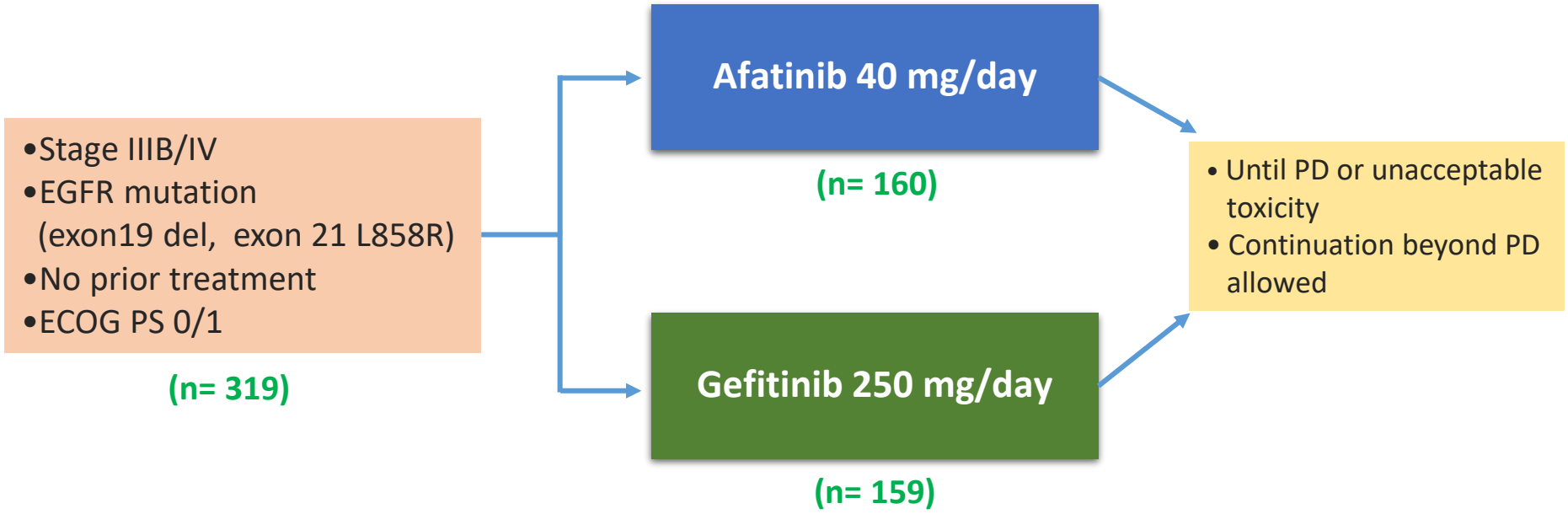


LUX-Lung 7: Afatinib *vs* Gefitinib (Phase IIb)

First head-to-head study of EGFR-TKIs in 1st line Tx of *EGFR* (+) NSCLC

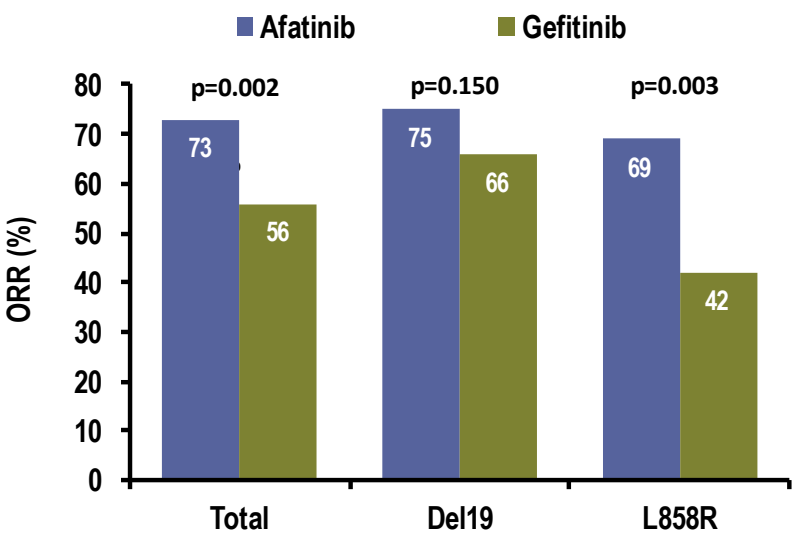


- Co-primary end points: progression free survival (PFS), time to treatment failure (TTF), overall response rate (ORR)

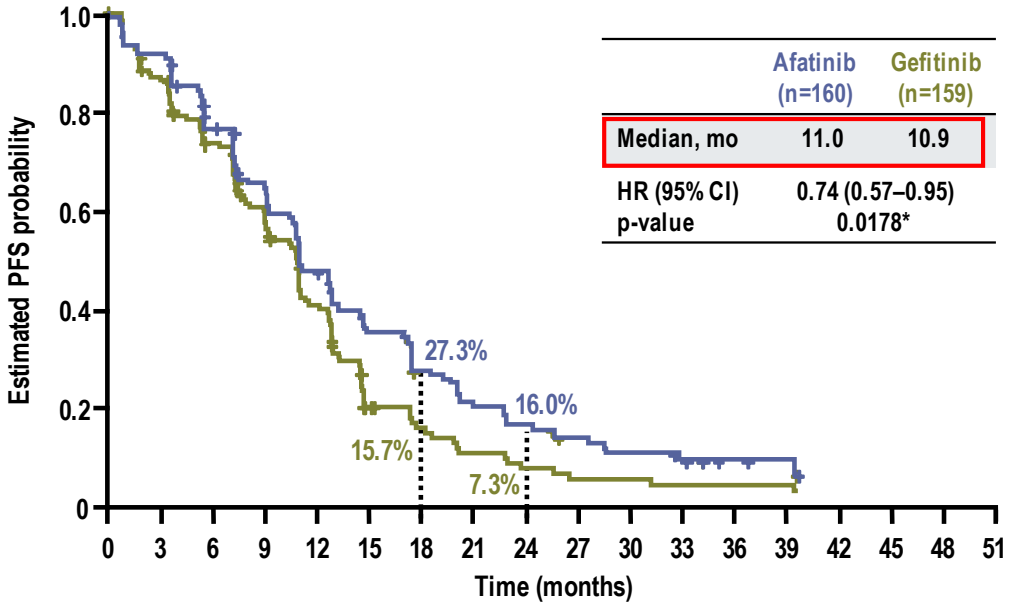
Park K, et al. *Lancet Oncol* 2016;17:577-89

LUX-Lung 7: PFS/ORR

ORR



PFS



Park K, et al. *Lancet Oncol* 2016;17:577-89

Not all epidermal growth factor receptor mutations in lung cancer are created equal: Perspectives for individualized treatment strategy

G719X (3.1%)	
G719A	27
G719A+S768I/L861Q/L861R	11
G719S	25
G719S+S768I/L861Q/E709A	13
G719C	12
G719C+S768I/E709K/E709H	9
others	3

E709X (0.3%)	
E709K+G719S/G719C/L858R	44
E709A+G719S/G719E	33
others	22

Del 18 (0.3%)	
delE709_T710insD	100

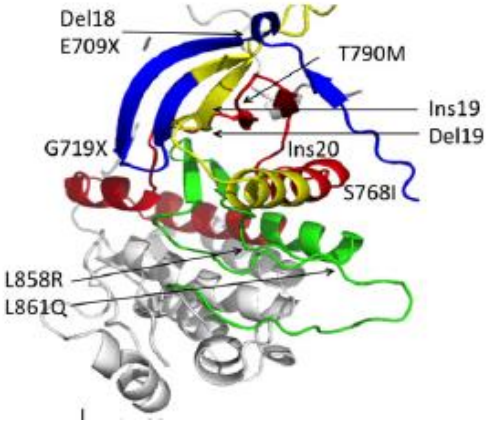
Del 19 (44.8%)	
delE746_A750	67
delL747_P753insS	8
delL747_T751	5
delL747_A750insP	3
delL747_S752	3
delE746_S752insV	2
delE746_P753insVS	1
delL747_T751insP	1
delE746_T751insA	1
delL747_P753	1
delS752_I759	1
others	8

Ins 19 (0.6%)	
I744_K745insKIPVAI	58
K745_E746insIPVAIK	26
K745_E746insVPVAIK	11
K745_E746insTPVAIK	5

Ins 20 (5.8%)	
V769_D770insASV	20
D770_N771insSVD	19
H773_V774insH	8
A763_Y764insFQEA	7
H773_v774insPH	5
H773_V774insNPH	4
N771_P772insN	3
H773_V774insAH	3
D770delinsGY	2
V774_C775insHV	2
others	25

S768I (1.1%)

L858R (39.8%)
L861Q (0.9%)



Cancer Sci 2016;107:1179–1186

<In vitro sensitivities of Ba/F3 cells expressing each EGFR mutation to varioius TKI>

Exon	Category	Mutations	First generation		Second generation			Third generation	
			Gefitinib	Erlotinib	Afatinib	Dacomitinib	Neratinib	Osimertinib	Rociletinib
18	Del 18	delE709_T710insD	882	884	1.7	29	27	93	999
	E709X	E709K	187	215	0.7	16	6	62	706
	G719X	G719A	213	167	0.9	6	1.1	53	214
19	Del19	delE746_A750	4.8	4.9	0.9	<1	60	1.1	19
	Del19	delE746_S752insV	306	14	0.2	1.4	86		
	Del19	delE747_A750insP	7.4	13	1	1.6	30		
	Del19	delL747_P753ins	4.1	5.4	2	1.9	38		
	Del19	delS752_I759	35	7.9	0.2	2	6.7		
	Ins19	I744_K745insKIPVAI	400		7				
	Ins19	K745_E746insTPVAIK	100		0.9				
20	Ins20	A763_Y764insFQEA	174	48	3.7			44	673
	Ins20	Y764_V765insHH	>1000	3845	79			237	1730
	Ins20	M766_A767insAI		34.3	79				
	Ins20	V769_D770insASV	3100	4400	72	230	48	333	5290
	Ins20	D770_N771insNPG	3356	3700	72		230	42	262
	Ins20	D770_N771insSVD		3187	86				
	Ins20	H773_V774insH		>10000	268		550		
	S768I	S768I	315	250	0.7			49	
	T790M	T790M+delE746_A750	8300	>10000	64	140		3	28
	T790M	T790M+L858R	>10000	>10000	119	300		21	13
21	L858R	L858R	26	16	4	2.6	1.4	9	140
	L861Q	L861Q	170	103	0.5		3.3	9	
EGFR wild type with interleukin-3			9350	>10000	>100	>1000	>1000	3078	1549
Plasma drug concentration			(448-2717)	(2717-4040)	(69-130)	(166-238)	(N/A-132)	(400-600)	N/A-N/A

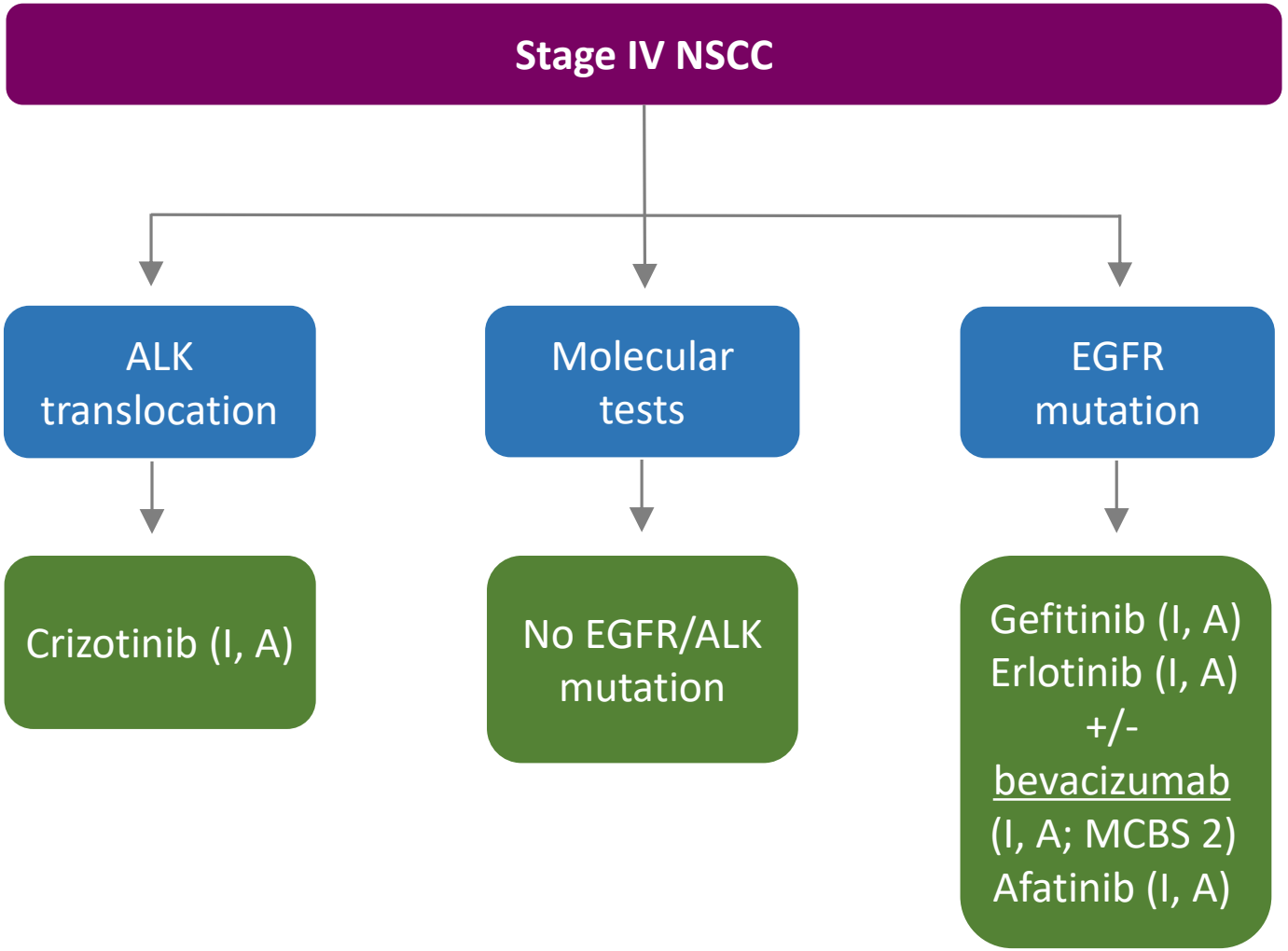
IC50 values (nM) of <10, 10–99, 100–999 and ≥1000 are shown in **blue, green, yellow and red,** respectively. EGFR, epidermal growth factor receptor; N/A, not availabe TKI, tyrosine kinase inhibitors

Cancer Sci 2016;107:1179–1186

Our current view on treatment strategy for patients with lung cancer harboring each EGFR mutation

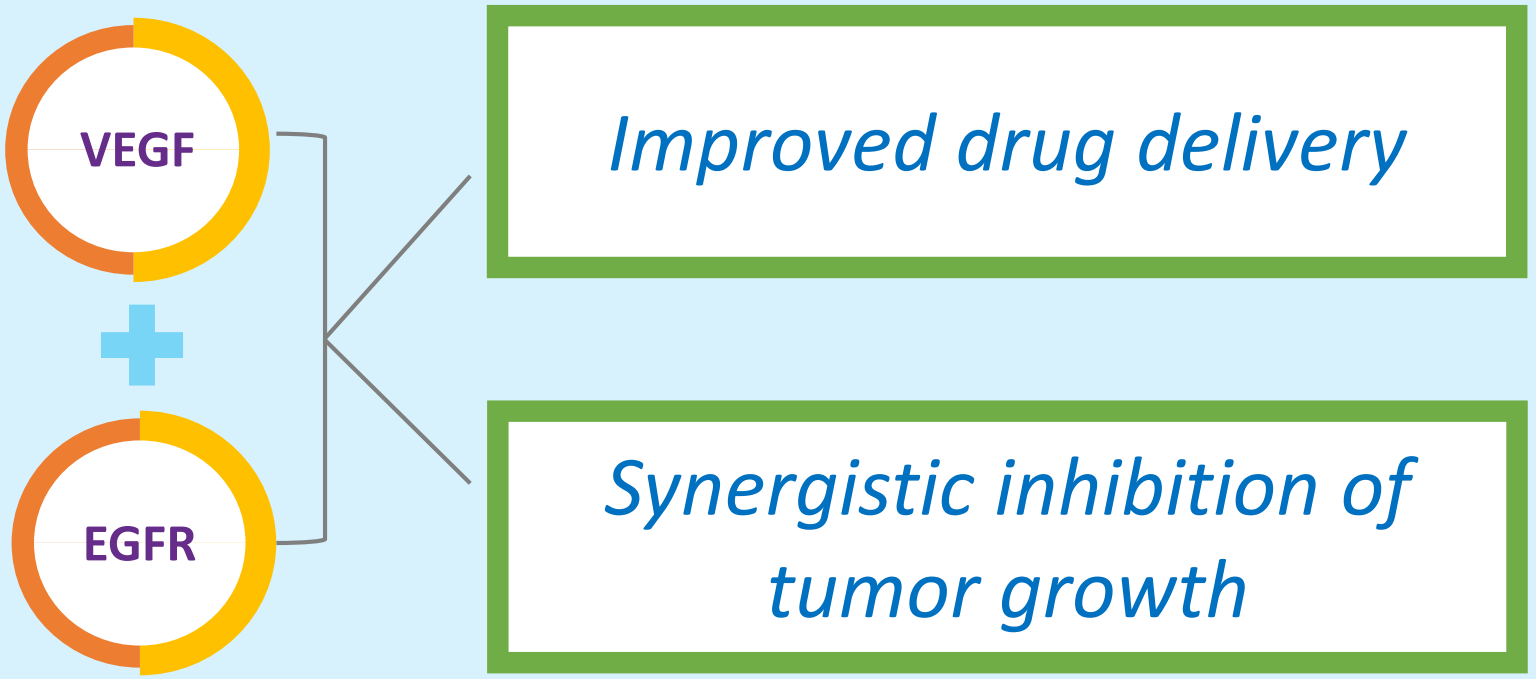
	First generation		Second generation			Third generation			
	Gefitinib	Erlotinib	Afatinib	Dacomitinib	Neratinib	Osimertinib	Rociletinib	Olmutinib	Nazartinib
Del 18	—	±	+	±?	±?	±?	±?	?	?
E709X	±	±	++	+?	+?	±?	±?	?	?
G719X	±	±	++	+?	++	+?	+?	?	?
Del19	++	++	+++	++	—	++	±?	+?	+?
Ins19	+	+	++	?	?	?	?	?	?
Ins20 (insFQEA)	+	+	+?	?	?	+?	±?	?	?
Ins20 (others)	—	—	—	—	—	±?	—	?	+?
S768I	±	±	+	?	?	±?	?	?	?
T790M+Del19/L858R	—	—	—	—	—	++	+	++	+?
L858R	++	++	+	++	—	++	±?	+?	+?
L861Q	±	±	+	?	±?	±?	?	?	?

Cancer Sci 2016;107:1179–1186

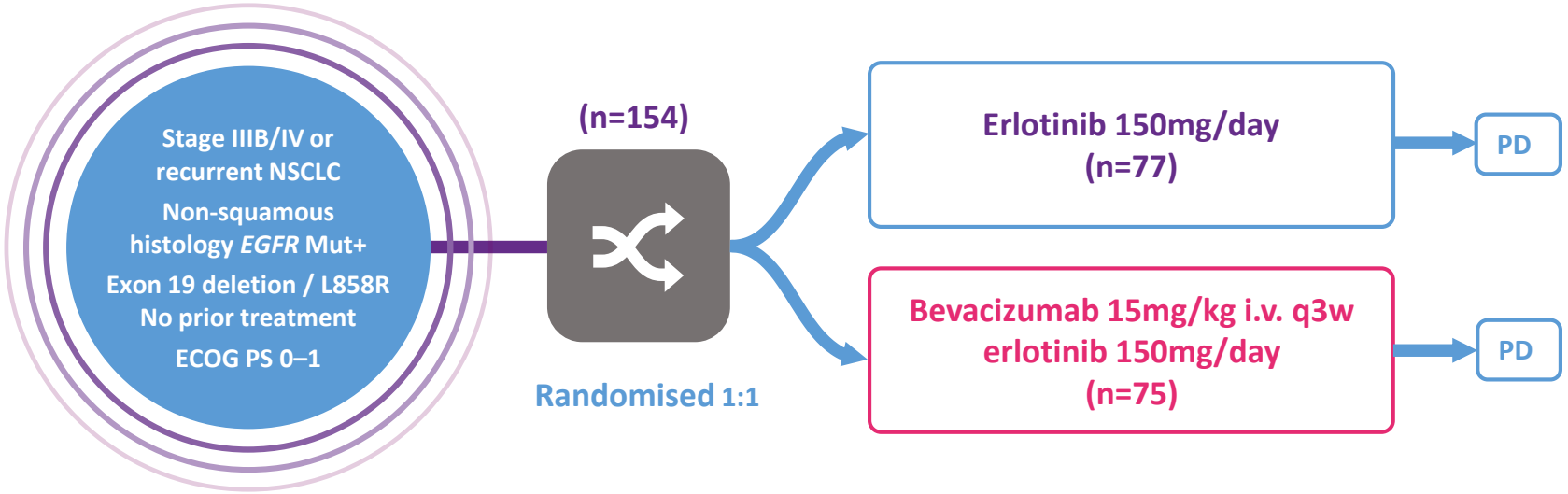


Annals of Oncology 2016;27(5): 1–27

Mode of Action (*erlotinib + bevacizumab*)



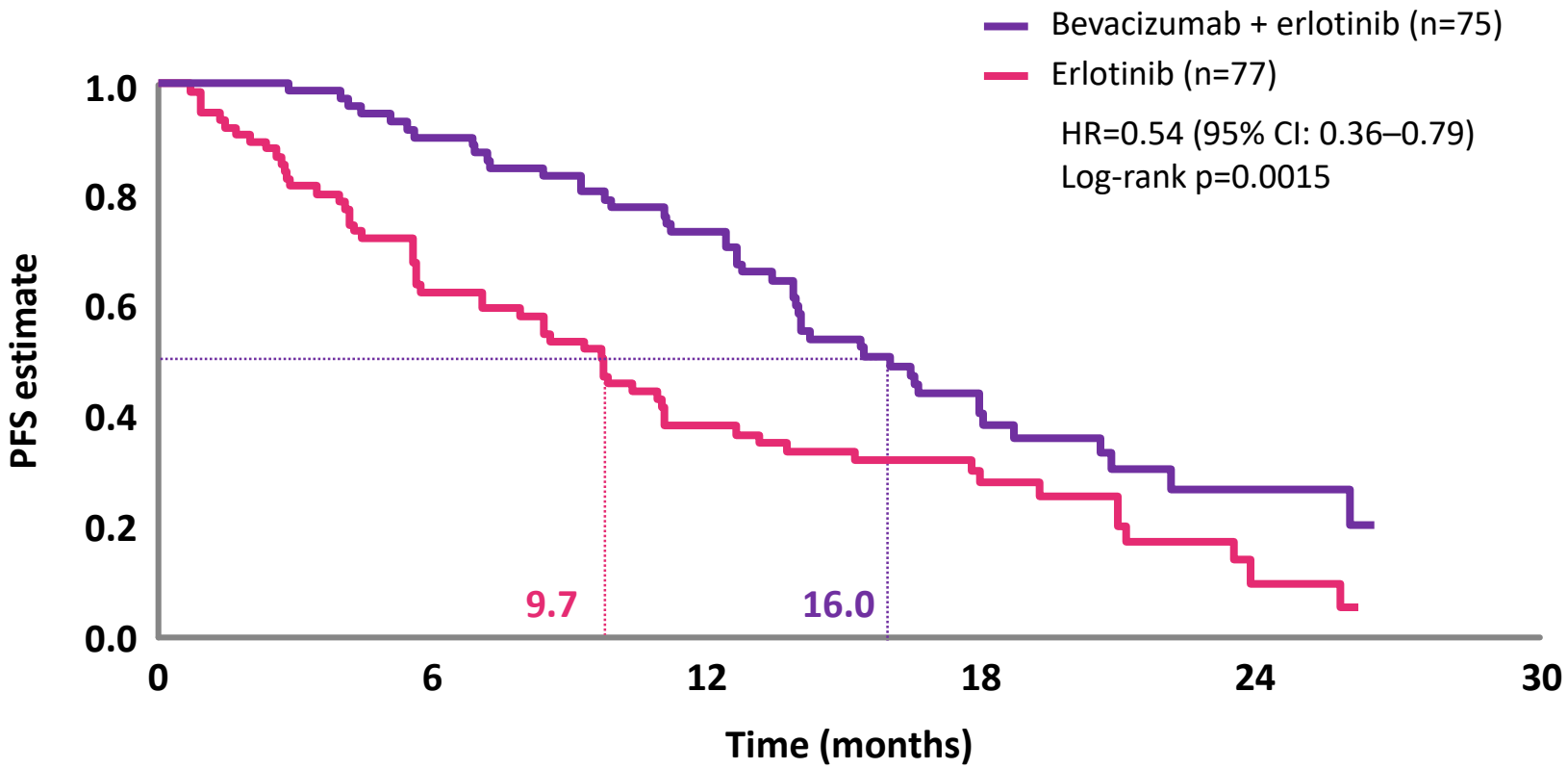
Erlotinib alone or with bevacizumab as first-line therapy in patients with advanced non-squamous non-small-cell lung cancer harbouring *EGFR* mutations (JO25567): an open-label, randomised, multicentre, phase 2 study



Primary end point: progression-free survival (independent review committee)
Secondary end points: overall survival, tumor response, quality of life, symptom improvement, safety profile
Key exclusion criteria : brain metastasis, presence of T790M mutation, history of hemoptysis or bloody sputum, presence of coagulation disorder, history of interstitial Lung disease, tumor invading major blood vessels, history of administration of EGFR inhibitors or VEGF receptor inhibitors

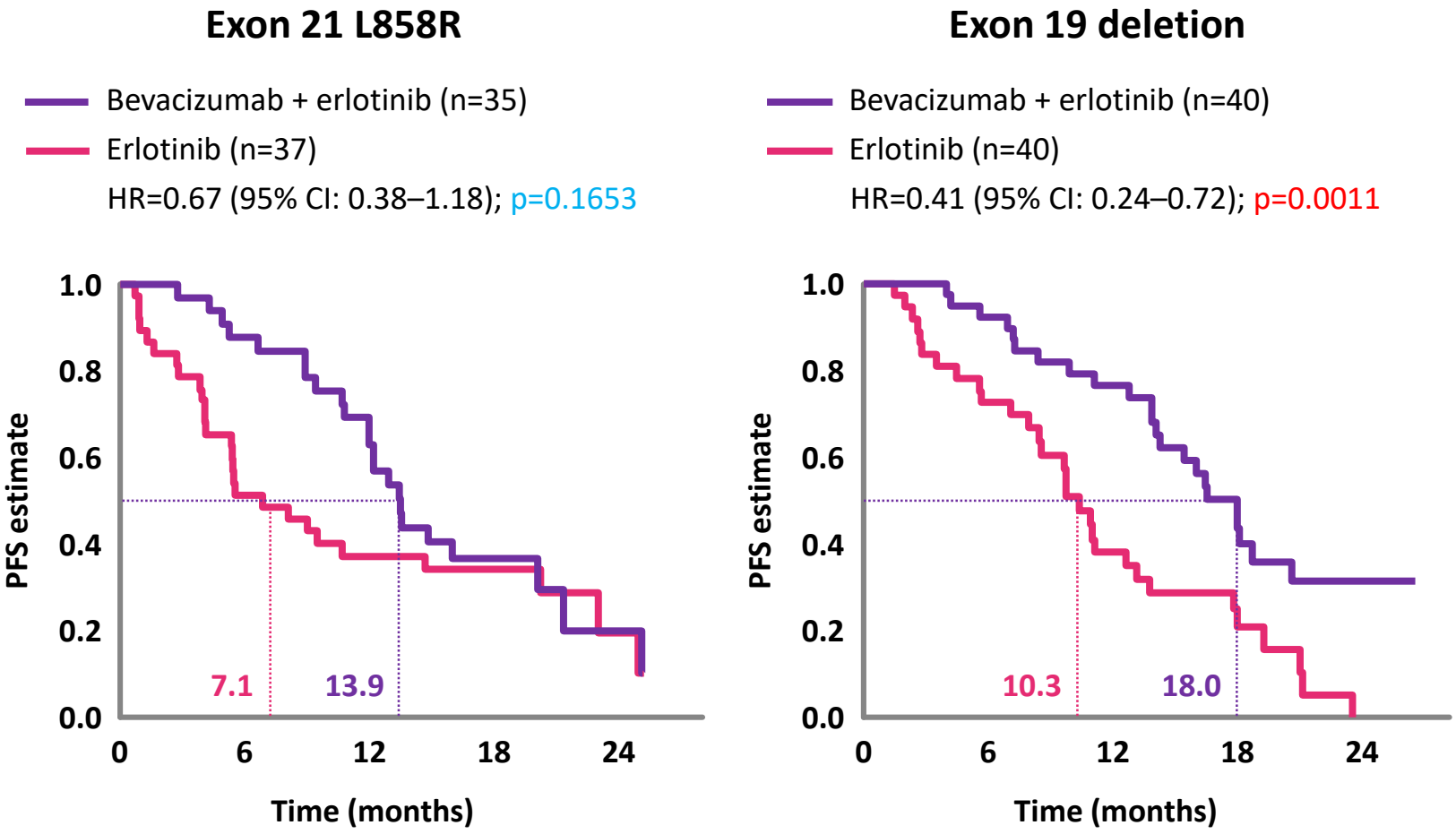
Lancet Oncol 2014; 15: 1236–44

JO25567: PFS in ITT



Lancet Oncol 2014; 15: 1236–44

JO25567: PFS by *EGFR* mutation type



Lancet Oncol 2014; 15: 1236–44

JO25567: AEs

AE, %	All grades		Grade ≥3	
	Bevacizumab/erlotinib (n=75)	Erlotinib (n=77)	Bevacizumab/erlotinib (n=75)	Erlotinib (n=77)
Rash	99	99	25	19
Diarrhoea	81	78	1	1
Paronychia	76	65	3	4
Dry skin	75	58	3	0
Stomatitis	63	60	1	3
Haemorrhagic event	72	29	3	0
Hepatic dysfunction	44	51	8	18
Hypertension	76	13	60	10
Pruritus	45	42	1	0
Decreased weight	44	25	0	0
Decreased appetite	35	34	1	1
Proteinuria	52	4	8	0
Dysgeusia	27	22	0	0
Nasopharyngitis	27	19	0	0
Constipation	23	19	0	1

Lancet Oncol 2014; 15: 1236–44

Overview: ongoing studies of bevacizumab + erlotinib

	ACCRU RC1126 (ML28158) *USA*	BEVERLY (ML29757) *Italy*	NEJ026 (UMIN000017069) *Japan*	ARTEMIS (ML29943) China
Trial				
Trial design	Randomised, phase II trial of 1L bev + erl vs erl in *EGFR* Mut+ patients	Randomised, phase III trial of 1L bev + erl vs erl in *EGFR* Mut+ patients	Randomised, phase III trial of 1L bev + erl vs erl in *EGFR* Mut+ patients	Randomised, phase IV trial of 1L bev + erl vs erl in *EGFR* Mut+ patients
Status	Ongoing	Ongoing	Ongoing	Ongoing
1 Primary endpoint	PFS	PFS	PFS	PFS
2 Secondary endpoints	OS, response rate, PFS by mutation status, safety	OS, QoL, ORR, safety	OS, response rate, DCR, DoR, safety, QoL	OS, ORR, DCR, safety, QoL
Study period	2012–2017	2016–2018	2015–2018	2016–2019

IST = investigator-suggested trial

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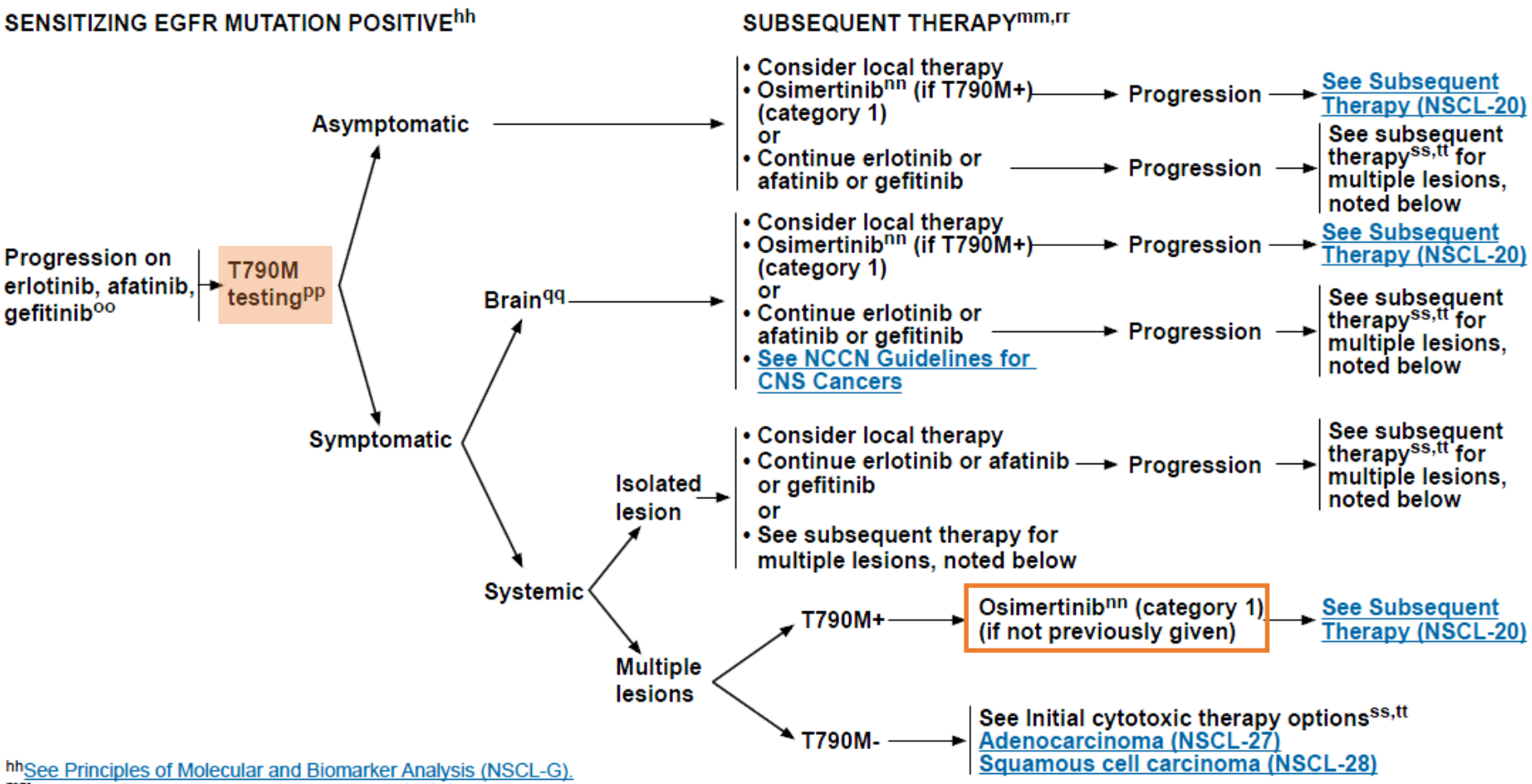
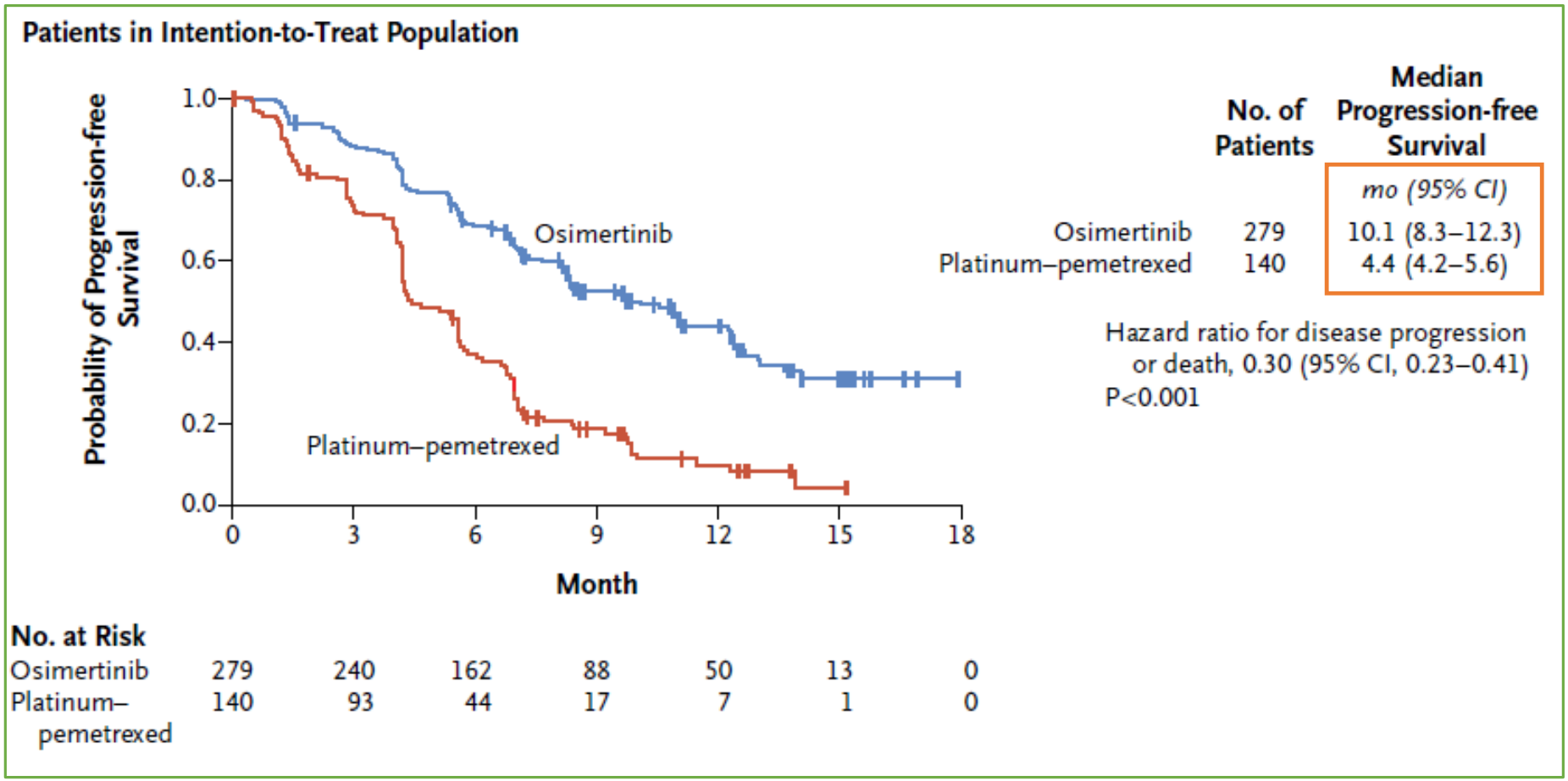


[hh] See Principles of Molecular and Biomarker Analysis (NSCL-G).
[mm] See Targeted Therapy for Advanced or Metastatic Disease (NSCL-I).
[nn] For performance status 0-4.
[oo] Beware of flare phenomenon in a subset of patients who discontinue EGFR TKI. If disease flare occurs, restart EGFR TKI.
[pp] If tissue biopsy is not feasible, plasma biopsy should be considered. Consider reflex to tissue-based testing, if plasma test is negative for the T790M mutation.
[qq] Consider osimertinib (regardless of T790M status) or pulse erlotinib for progressive leptomeningeal disease.
[rr] For rapid radiologic progression or threatened organ function, alternate therapy should be instituted.
[ss] Afatinib + cetuximab may be considered in patients with disease progression on EGFR TKI therapy.
[tt] The data in the second-line setting suggest that immunotherapy is less effective, irrespective of PD-L1 expression, in tumors with an actionable mutation.

Osimertinib or Platinum–Pemetrexed in *EGFR* T790M–Positive Lung Cancer

AURA3



N Engl J Med December 6, 2016

SINGAPORE 2017 ESMO ASIA

A GLOBAL PROSPECTIVE PHASE II STUDY OF OLMUTINIB(HM61713) IN PATIENTS WITH T790M-POSITIVE NSCLC AFTER FAILURE OF FIRST-LINE EGFR-TKI

The First Results of Olmutinib Global Phase II study

Keunchil Park[1], Pasi A. Jänne[2], Chong-Jen Yu[3], Lyudmila Bazhenova[4], Luis Paz-Ares[5], Eunhye Baek[6], OakPil Han[6], Ka Young Hong[6], Hyeyoung Kwon[6], Yohan Kim[6], Suk Ran Kim[6]

[1]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea, [2]Dana-Farber Cancer Institute, Boston, MA, USA, [3]National Taiwan University College of Medicine and National Taiwan University Hospital, Taipei, Taiwan, [4]University of California San Diego Moores Cancer Center, La Jolla, CA, USA, [5]University Hospital 12 De Octubre, Madrid, Spain, [6]Hanmi Pharmaceutical Co., Ltd., Seoul, South Korea

EMSI-202: Phase II Trial of olmutinib for the treatment of ≥2nd Line T790M Mutation Positive Adenocarcinoma of the Lung [NCT02485652]

Study Design

Eligibility

- Advanced or metastatic NSCLC
- Harboured both activating EGFR & T790M mutation
- Prior EGFR TKI with or without additional lines of chemotherapy
- ECOG 0-1

(N= 162, from 68 sites in 10 countries)

Olmutinib
800mg QD, continuous daily dosing in 21-day cycles

Efficacy endpoints

- Primary: ORR (indep. assessment)
- Secondary: DCR, DoR, PFS, OS, TTP, Tumor shrinkage

- **Cut-off Date: 2017.07.05**
- **Median Study duration: 12.8 month** (0.0, 21.7)

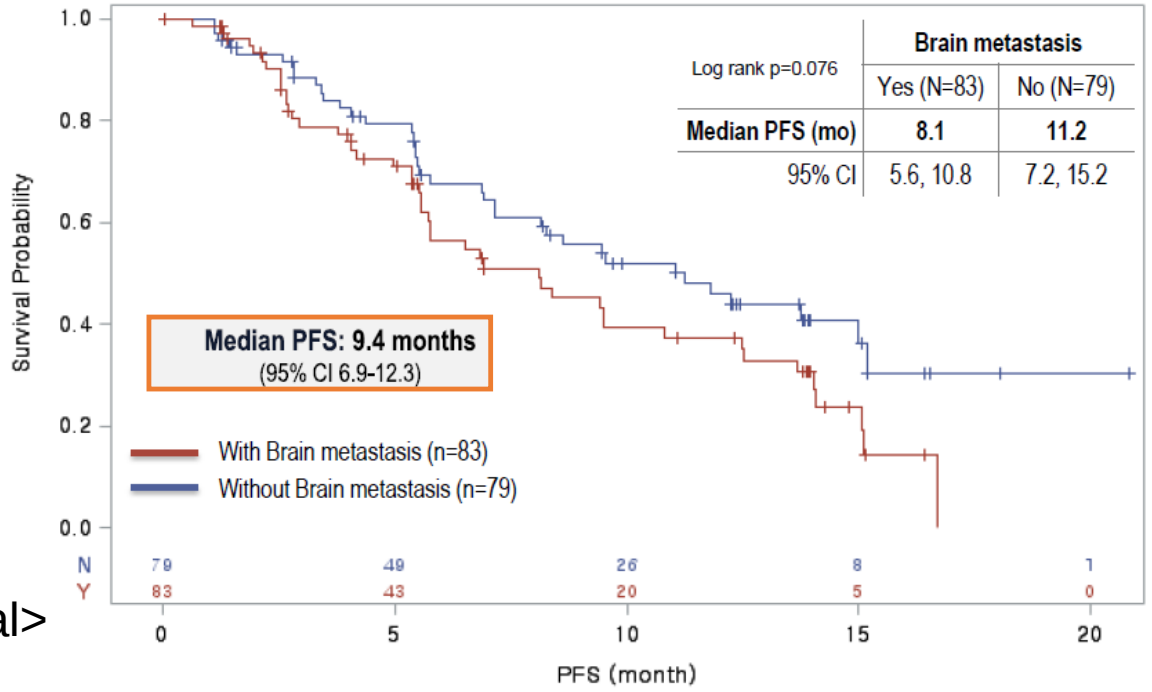
SINGAPORE 2017 ESMO ASIA

* Study duration (month) = (End of Study or cut-off date whichever occurred first – first IP date +1) / (365.25/12)

Cut-off Date: 2017.07.05

<Overall Response>

Overall Response	Independent review (N=162)
Overall Response Rate , n (%)	84 (51.9)
95% CI	(43.9, 59.8)
Overall Response Rate (confirmed), n (%)	75 (46.3)
95% CI	(38.4, 54.3)
Disease Control Rate (confirmed), n (%)	140 (86.4)
95% CI	(80.2, 91.3)
Best Overall Response (confirmed), n (%)	
PR	75 (46.3)
SD	65 (40.1)
PD	8 (4.9)
Non-CR/Non-PD	2 (1.2)
Not Evaluable	12 (7.4)



<Progression free survival>

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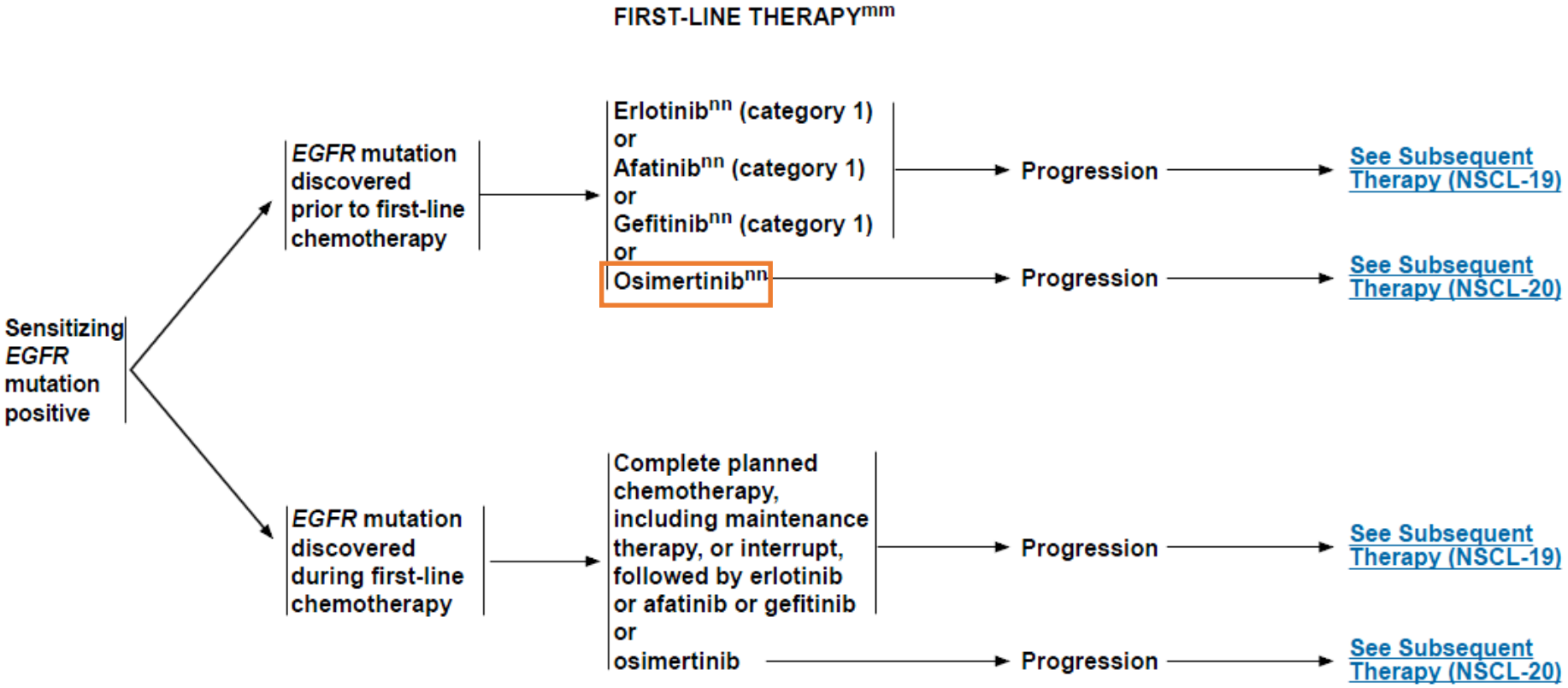
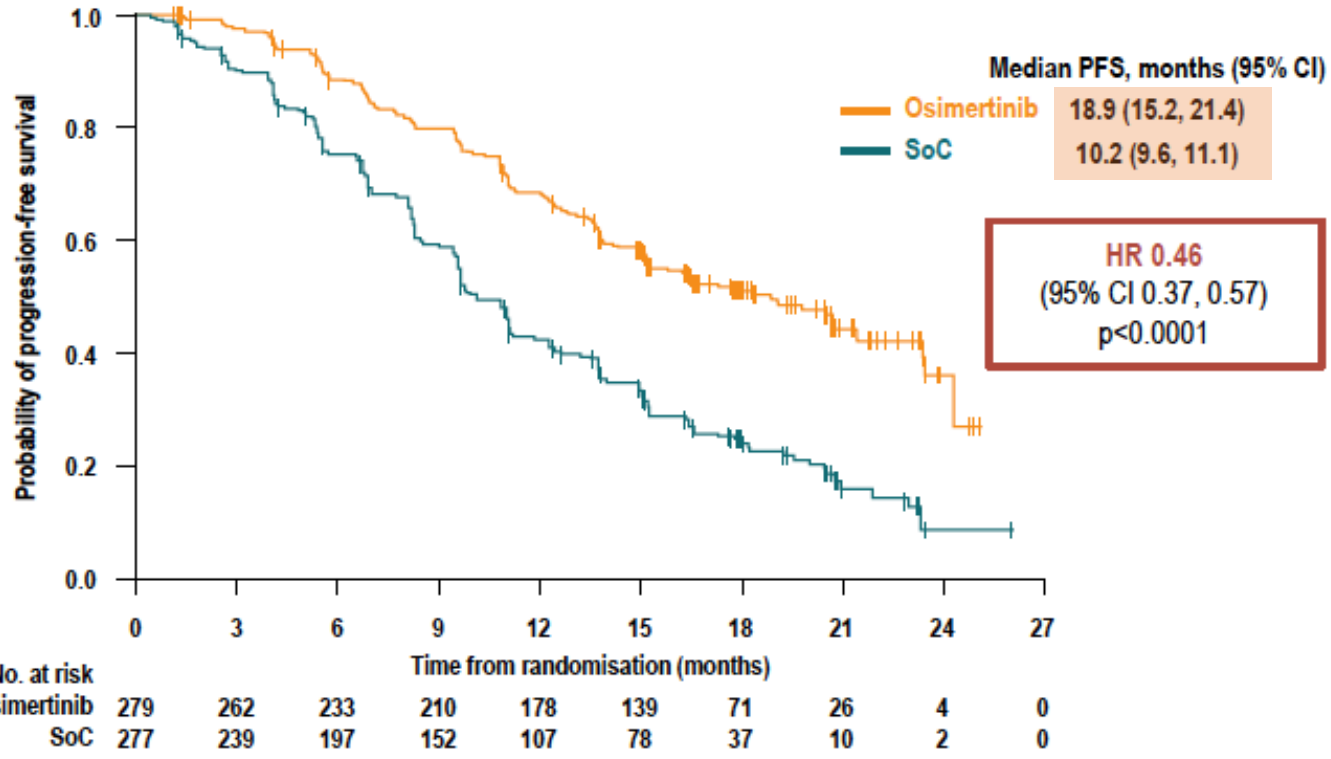
SENSITIZING EGFR MUTATION POSITIVE[hh]



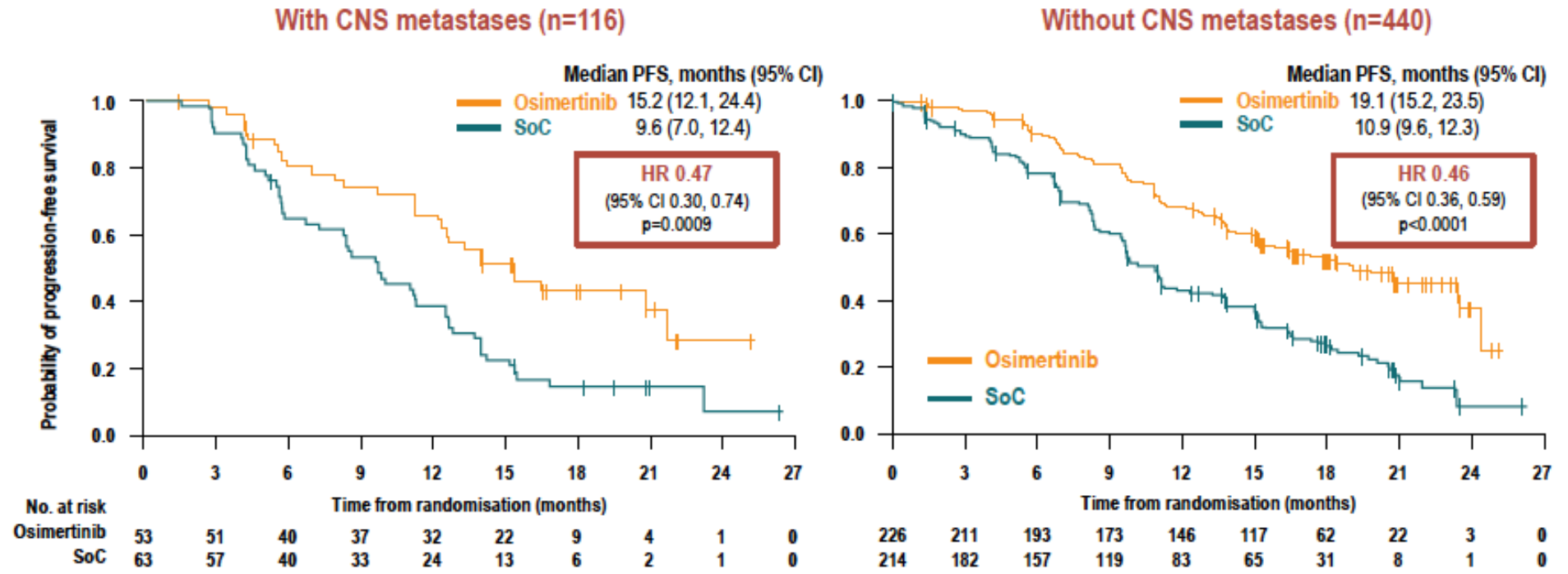
OSIMERTINIB VS STANDARD-OF-CARE EGFR-TKI AS FIRST-LINE TREATMENT IN PATIENTS WITH E GFRm ADVANCED NSCLC: FLAURA

- 342 events in 556 patients at DCO: 62% maturity; osimertinib: 136 events (49%), SoC: 206 events (74%)



Presented by SS Ramalingam at the European Society of Medical Oncology Congress 2017

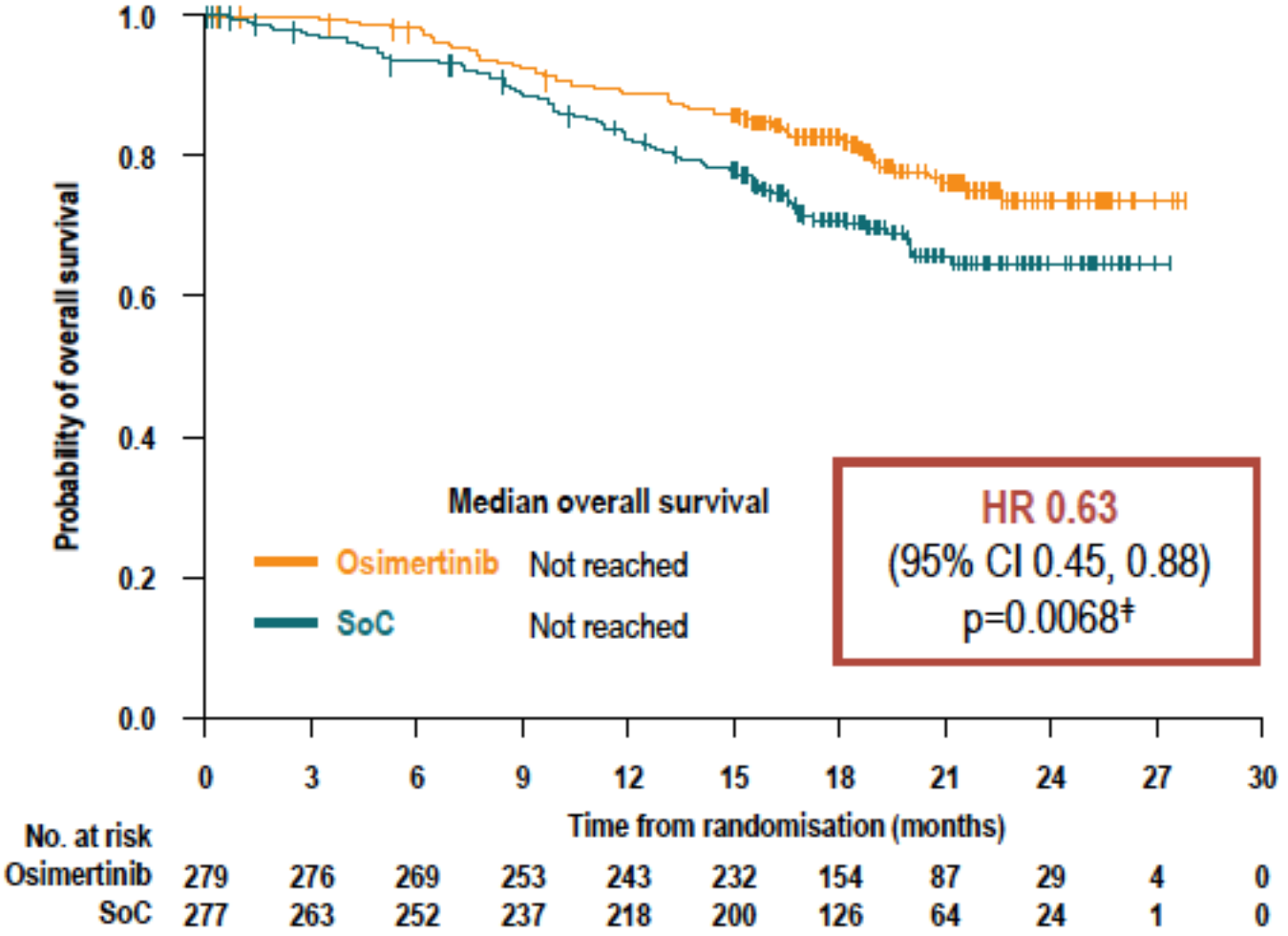
FLAURA: PFS according to CNS metastasis



CNS progression events occurred in 17 (6%) vs 42 (15%) patients receiving osimertinib vs SoC (all patients)

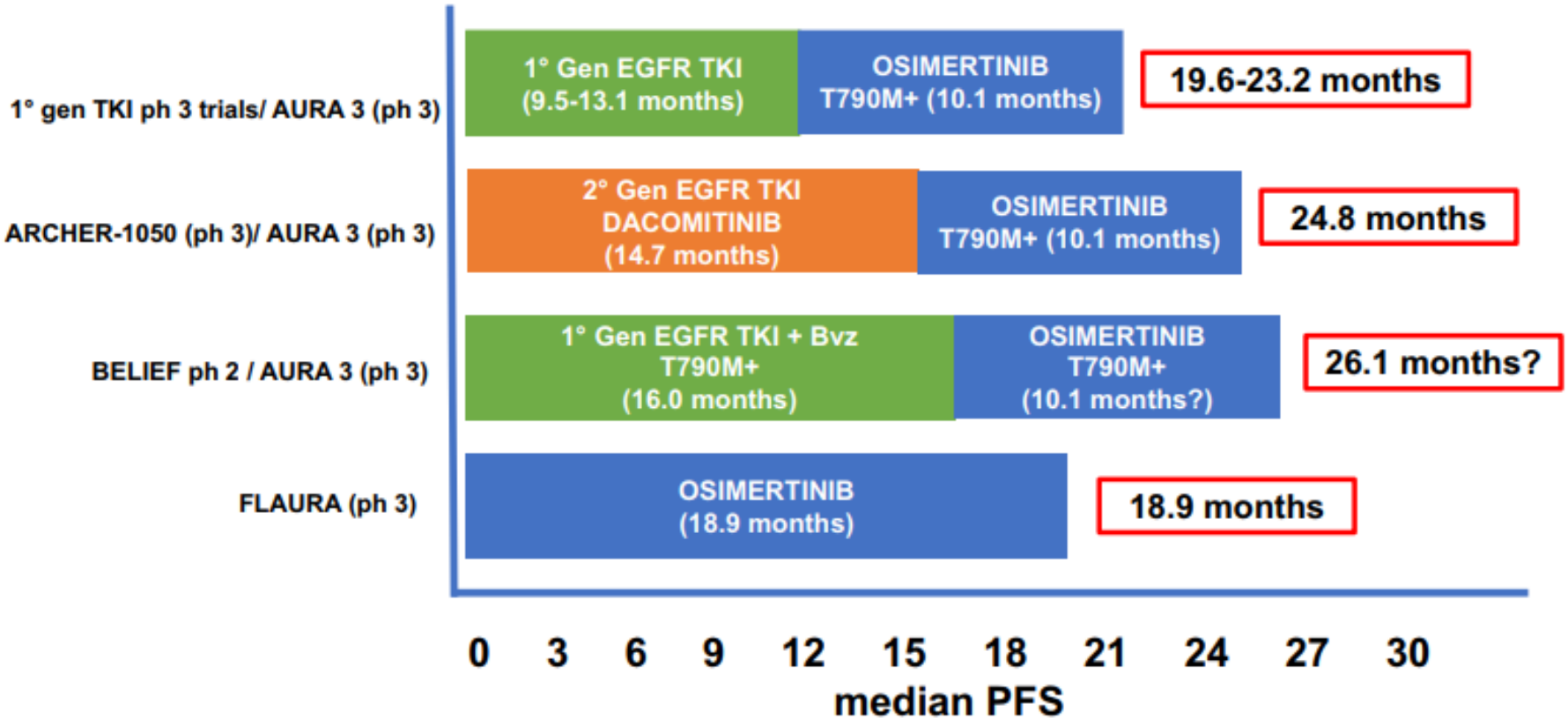
Ramalingam S, et al. *N Engl J Med* 2018;378:113-25

FLAURA: OS - not reached



Ramalingam S, et al. *N Engl J Med* 2018;378:113-25

Optimal sequence for *EGFR* mutant NSCLC



J Thorac Oncol 2018;13(3):301-322

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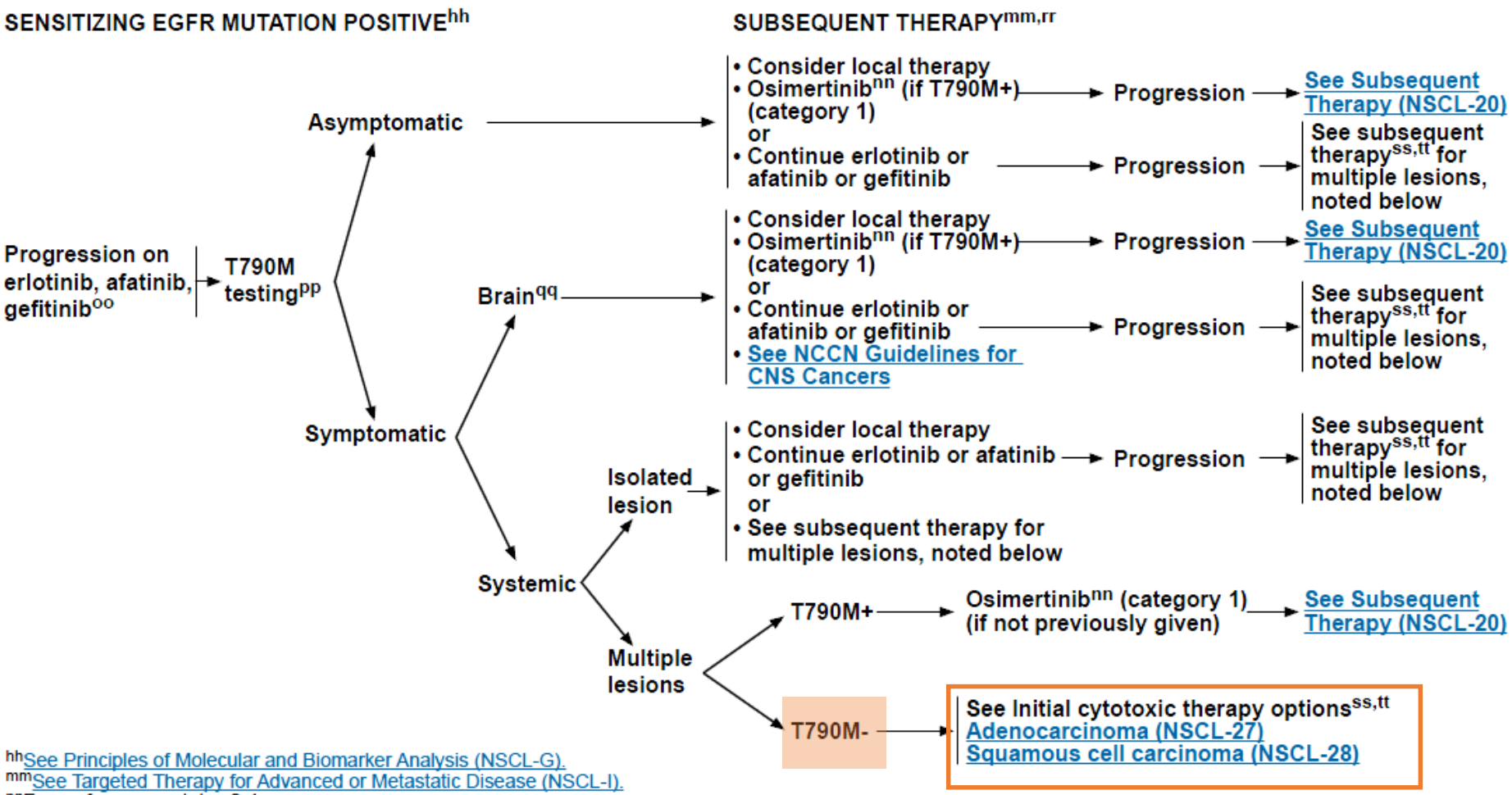


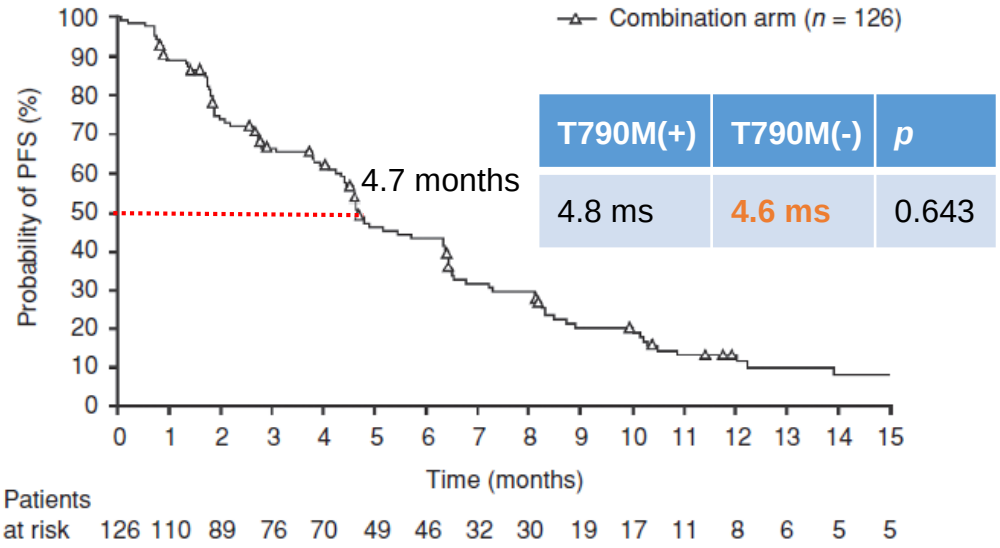
[hh] See Principles of Molecular and Biomarker Analysis (NSCL-G).
[mm] See Targeted Therapy for Advanced or Metastatic Disease (NSCL-I).
[nn] For performance status 0-4.
[oo] Beware of flare phenomenon in a subset of patients who discontinue EGFR TKI. If disease flare occurs, restart EGFR TKI.
[pp] If tissue biopsy is not feasible, plasma biopsy should be considered. Consider reflex to tissue-based testing, if plasma test is negative for the T790M mutation.
[qq] Consider osimertinib (regardless of T790M status) or pulse erlotinib for progressive leptomeningeal disease.
[rr] For rapid radiologic progression or threatened organ function, alternate therapy should be instituted.
[ss] Afatinib + cetuximab may be considered in patients with disease progression on EGFR TKI therapy.
[tt] The data in the second-line setting suggest that immunotherapy is less effective, irrespective of PD-L1 expression, in tumors with an actionable mutation.

Dual Inhibition of EGFR with Afatinib and Cetuximab in Kinase Inhibitor–Resistant *EGFR*-Mutant Lung Cancer with and without T790M Mutations

* Preclinical data: Afatinib/cetuximab overcomes T790M-mediated resistance

	All (N=126)	T790M (+) (n=71)	T790M (-) (n=53)	P value
ORR,%	29	32	25	0.341

ORR, objective response rate



T790M(+)	T790M(-)	*p*
4.8 ms	4.6 ms	0.643

Janjigian YY, et al. Cancer Discov; 2014;4(9); 1036–45

Retreatment of EGFR-TKIs

ORR	median PFS	Predictor
20%	2-8ms	Time interval

ORIGINAL

Effect of
advanced
EGFR-TKI

Guo-Hao Xia, Yu
Feng Feng

Department of Me

ABSTRACT

KEYWORDS

Retreatment of g
previously contr

In-Jae Oh[a,b], Hee-Jun

[a] Lung and Esophageal Cancer Clinic
[b] Department of Internal Medicine,

A B S T R A C T

Most patients with nor
receptor tyrosine kina
previous trials which
that the reintroduction
This was a single-arm,
metastatic NSCLC. Eligi
with, initial gefitinib tr
be observed, with at lea
were recruited and defi
(86.9%), never-smoker
partial response (PR) i
observed in 21.7% (5 pa
had either exon 19 dele
gene. Re-initiation of E
patients who previous

ORIGINAL

Predicti
Retreatı
Non-Sm

Byoung Soo K
Joon Seon So
and Jae Cheo
Departments of [1]
[5]Department of C

Background: T
proved efficacio
T790M mutatio
retreatment witl
positive respons
failure.
Methods: This
cancers had pro
generation EGFI
retreatment, we
following retreat
Results: Overall
treatment. Follo
and 64.3%, respe
free survival (PF
progression was
interval was <90
Conclusion: In
salvage therapy

Keywords: Ca
Retreatment; Pre

Predictive factors for *EGFR*-tyrosine kinase inhibitor retreatment in patients with *EGFR*-mutated non-small-cell lung cancer – A multicenter retrospective SEQUENCE study

Lung Cancer 104 (2017) 58–64

A B S T R A C T

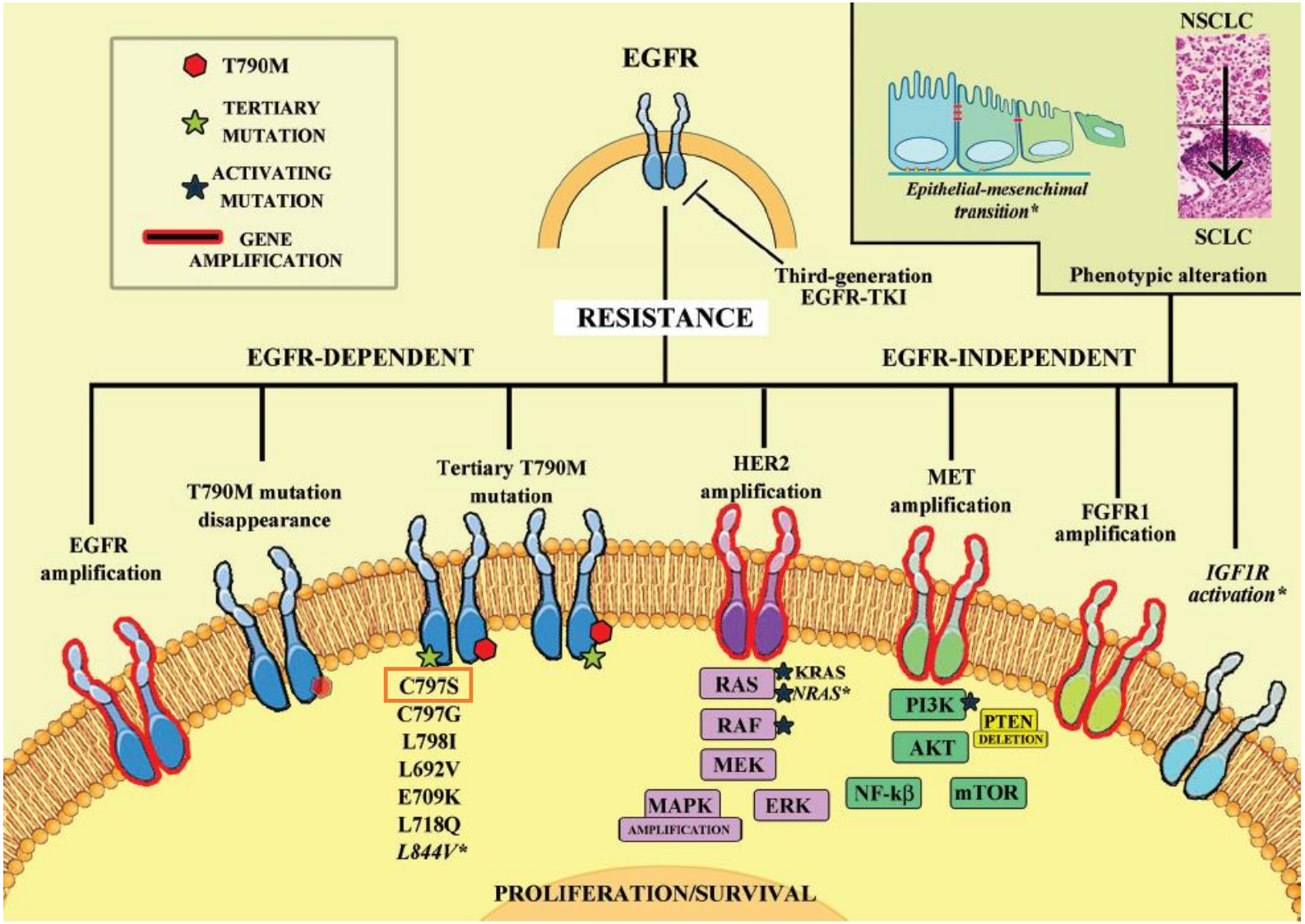
Background: Acquired resistance occurs in most non-small cell lung cancer (NSCLC) patients with epidermal growth factor receptor (*EGFR*) mutations experiencing a response to *EGFR*-tyrosine kinase inhibitor (TKI) initially. We investigated *EGFR*-TKI retreatment in patients who had previously received *EGFR*-TKI followed by chemotherapy.

Materials and methods: This was a retrospective multicenter study. Patients with locally advanced or metastatic adenocarcinoma or TTF-1 (+) NSCLC, positive *EGFR* sensitive mutation, and *EGFR*-TKI reuse after initial EGFR-TKI followed by chemotherapy were enrolled. The objectives were to assess the objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), and overall survival (OS) of *EGFR* TKI switched retreatment.

Results: In total, 205 patients were enrolled, with a median age of 61.8 years (range 31.4–92.9). There was a larger proportion of females (62.9%) than males, and more never-smokers (73.2%) than ever-smokers. In the initial *EGFR*-TKI administration, 57.6% of patients showed a complete response (CR) or partial response (PR), and 34.6% had stable disease (SD); in the second-line chemotherapy, 13.7% had PR, and 58.0% had SD; in the *EGFR*-TKI retreatment, 7.3% had PR, and 37.1% had SD.

The median PFS of first-line *EGFR*-TKI was 8.0 months (95% CI 7.3–8.2), and retreatment *EGFR*-TKI was 4.1 months (95% CI 2.7–4.6). The median OS since the start of the first-line *EGFR*-TKI therapy was 35.9 months (95% CI 28.8–50.9), and since the start of *EGFR*-TKI retreatment was 12.6 months (95% CI 10.4–20.9).

Mechanisms of resistance to third-generation EGFR TKIs



Minari R, et al. *Transl Lung Cancer Res* 2016;5(6):695-708

REVIEW

EGFR C797S mu to third-genera positive non-sm

Shuhang Wang[1], Stella T. Tsui[2], Chr

Abstract

T790M mutation is the most comm inhibitors (TKI) for epidermal growt being explored to conquer this res metastatic *EGFR* T790M mutation-p C797S mutation was reported to b review summarizes the latest deve inhibitor overcoming the C797S m

LETTI

Overcom resistance

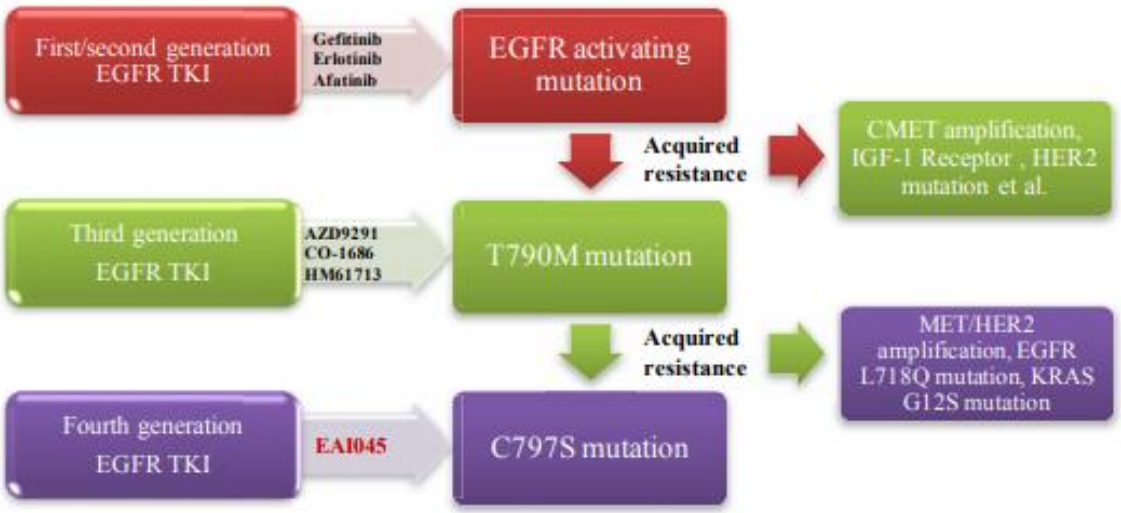
The epidermal g kinase inhibito approved treatm activating muta rapidly, most fre within the ATP s selective irrevers mutant[5,6], but t mutation of C7 key covalent bo of the kinase, hi alternative mec discovery of EA drug-resistant E The crystal struc site created by t inactive conform T790M-mutant l assays. Howeve EGFR-driven pr on the two subu asymmetric man of EAI045 with EGFR dimerizati to the allosteric effective in mou T790M) and by resistant to all cu findings illustrat to obtain mutant

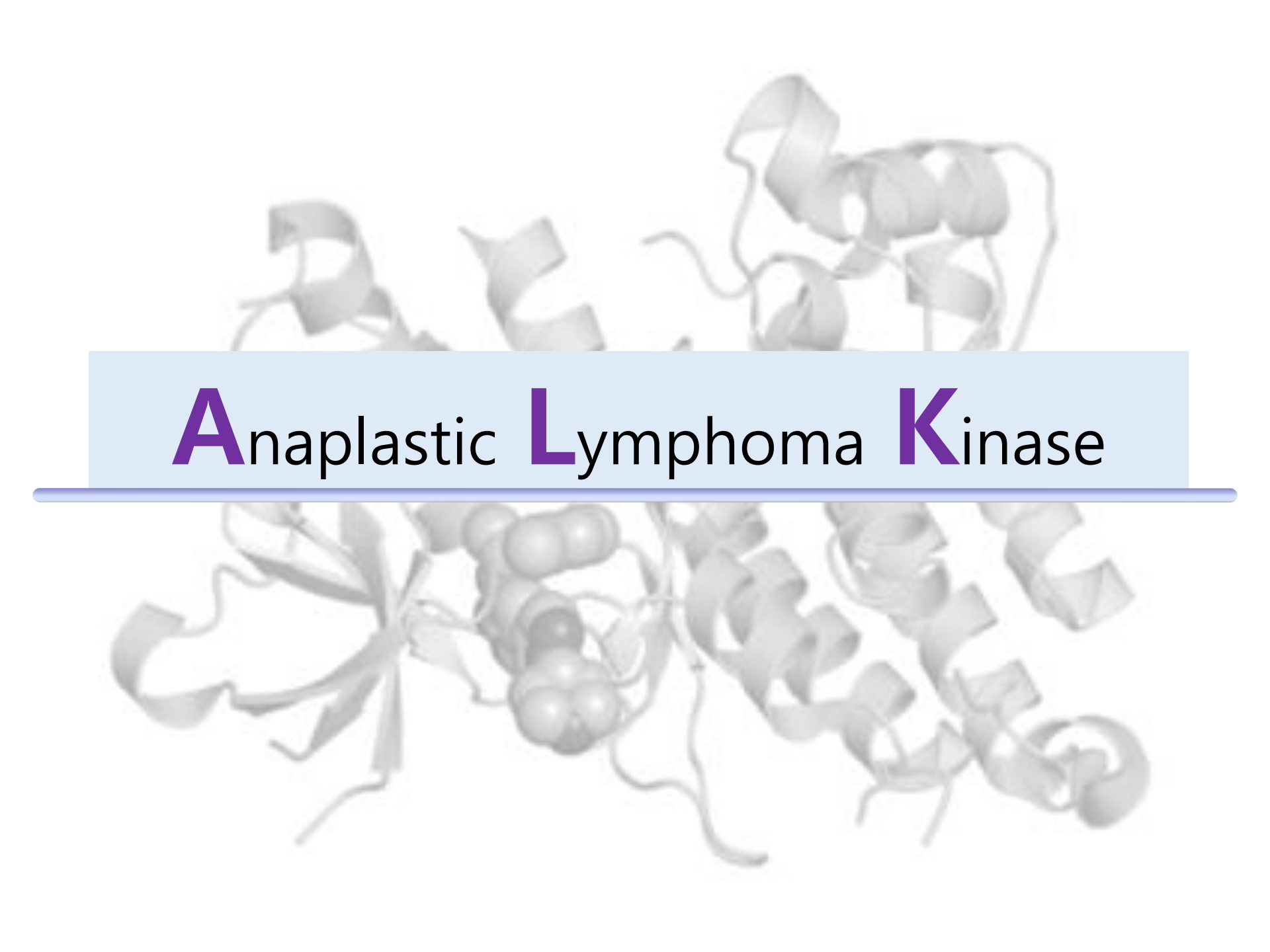
EAI045: The fourth-generation EGFR inhibitor overcoming T790M and C797S resistance

A B S T R A C T

Cancer Letters 385 (2017) 51–54

The third-generation tyrosine kinase inhibitors (TKI), AZD9291 (osimertinib) and CO-1686 (rociletinib) of epidermal growth factor receptor (EGFR) are highly active against T790M positive non-small cell lung cancer (NSCLC). However, resistance develops rapidly. EGFR *C797S* mutation was reported to be a leading mechanism of resistance to the third-generation inhibitors. The *C797S* mutation appears to be an ideal target for overcoming the acquired resistance to the third-generation inhibitors. This review summarizes the latest development on the discovery of a fourth-generation EGFR TKI, EAI045.3.

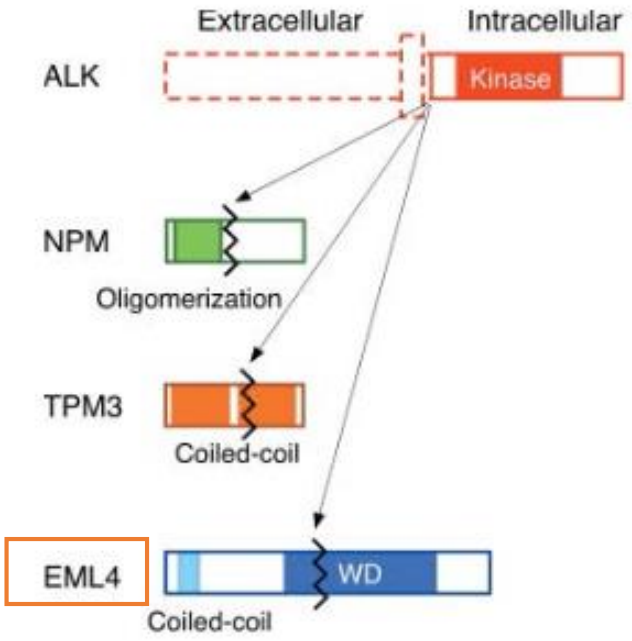


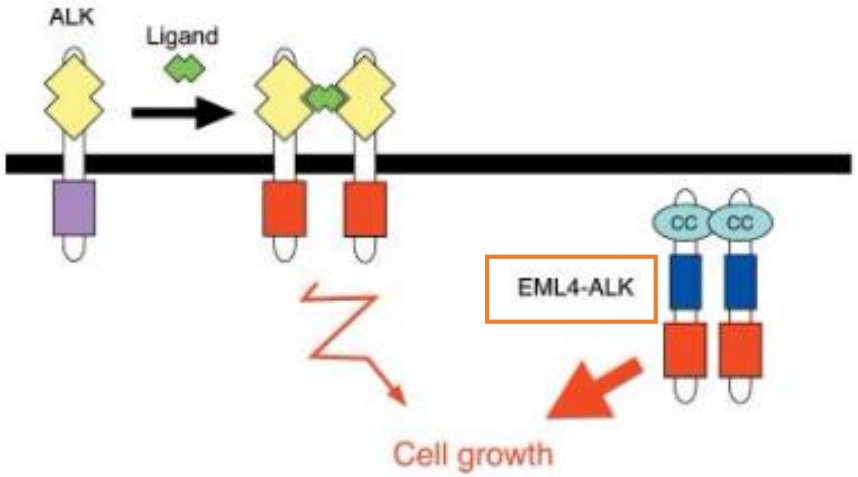


Anaplastic Lymphoma Kinase

Discovery of the ***EML4-ALK*** **fusion** in NSCLC

Initially reported in 2007 as a result of an inversion in chromosome 2p, which results in the fusion of the echinoderm microtubule-associated protein-like 4 (***EML4***) with the kinase domain of ***ALK*** (prevalence: 2-7%)





Hiroyuki M. *Cancer Sci* 2008; 99: 2349–2355

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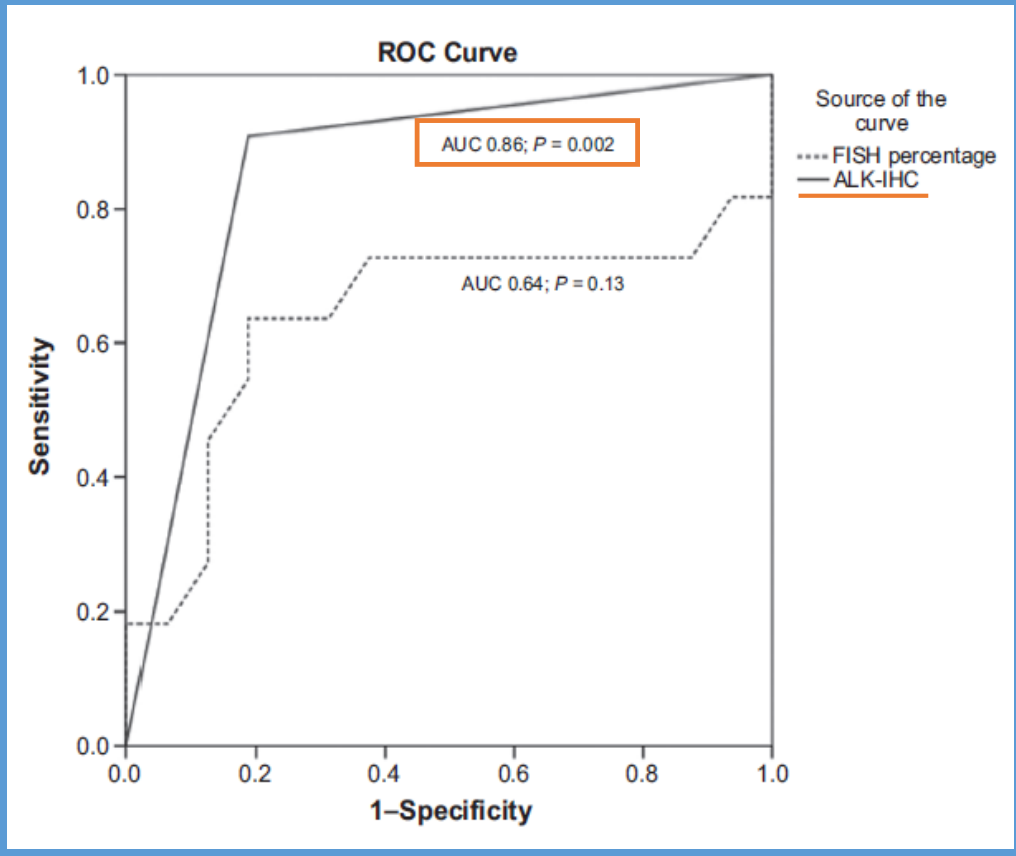
PRINCIPLES OF MOLECULAR AND BIOMARKER ANALYSIS

- Molecular Targets for Analysis
  - In general, the mutations/alterations described below are seen in a non-overlapping fashion, although between 1%–3% of NSCLC may harbor concurrent alterations.
  - *EGFR* (Epidermal Growth Factor Receptor) Gene Mutations: EG
    cells and is often overexpressed in a variety of human malignar
    - ◊ The most commonly described mutations in *EGFR* (exon 19
      responsiveness to EGFR tyrosine kinase inhibitor (TKI) thera
      EGFR mutation should not be treated with EGFR TKI in any li
    - ◊ Many of the less commonly observed alterations in EGFR, wi
      insertions, p.L861Q, p.G719X, p.S768I) are also associated w
      patients is lower.
    - ◊ Some mutations in *EGFR* are associated with lack of respons
      p.T790M.
      - – Most *EGFR* exon 20 insertion mutations predict resistance
      - – The exception is a rare *EGFR* exon 20 insertion variant, p.A
        therapy. Therefore, knowledge of an *EGFR* exon 20 insertio
      - – The finding of p.T790M is most commonly associated with
        mechanism of resistance. If identified prior to TKI exposure
        associated with familial lung cancer predisposition and ad
    - ◊ As use of NGS testing increases, additional *EGFR* variants ar
      alterations are unlikely to be well established.
    - ◊ Some clinicopathologic features—such as smoking status, e
      mutation; however, these features should not be utilized in s
    - ◊ Testing Methodologies: Real-time PCR, Sanger sequencing (i
      deployed methodologies for examining *EGFR* mutation statu

Testing Methodologies: **FISH break-apart pr**
deployed widely. **IHC** can be deployed as an
(ALK[D5F3] CDx assay) can be utilized as a
FISH, although confirmation is encouraged.
fusions, and **targeted real-time PCR assays**
unlikely to detect fusions with novel partners

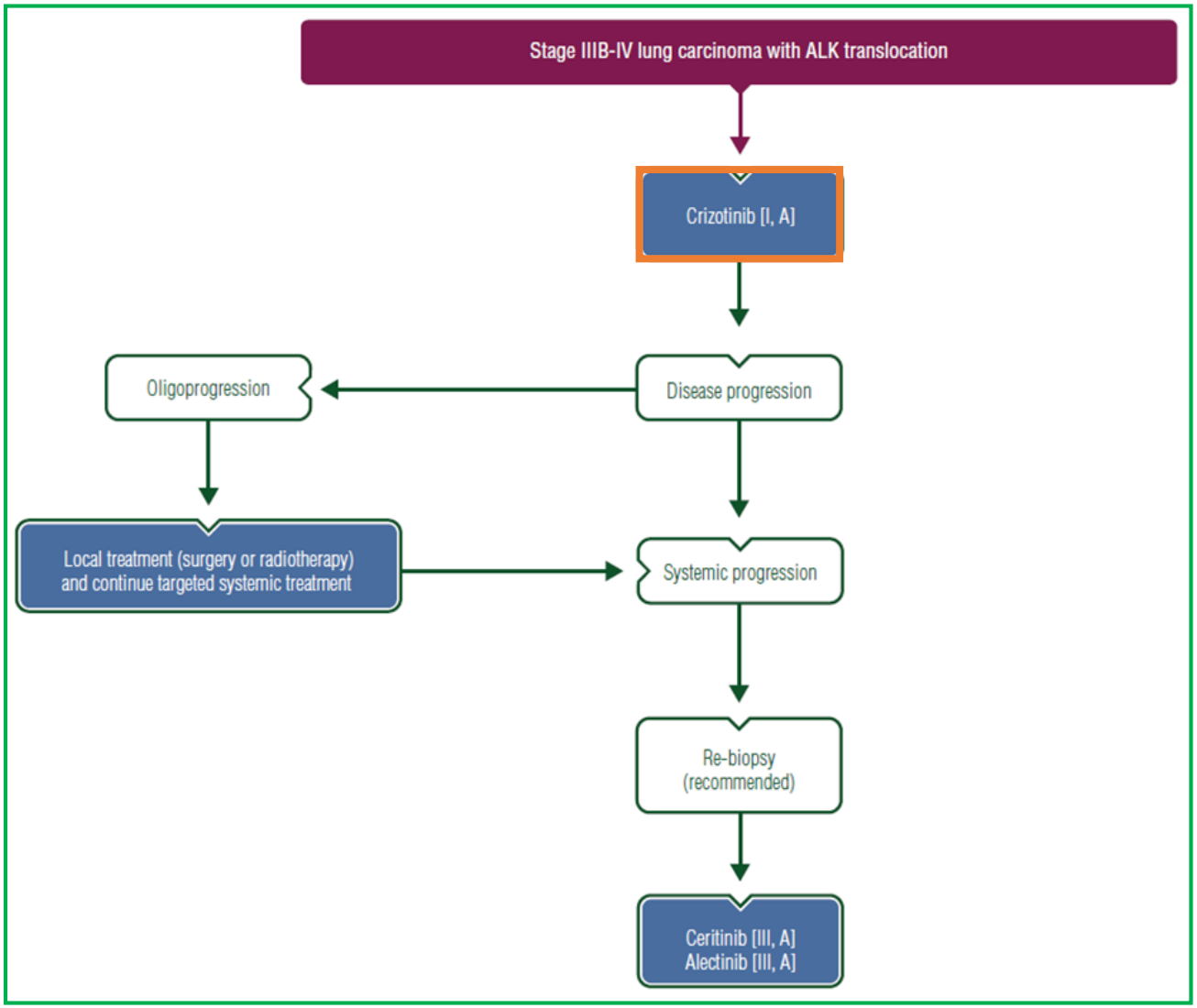
ROC plot of IHC and FISH to predict tumor response to crizotinib



Clin Cancer Res 2017; 23(15); 4251–8

Currently available ALK inhibitors

1st generation	2nd generation	3rd generation
• **Crizotinib**	• **Alectinib** • **Brigatinib** • **Ceritinib**	• **Lorlatinib** • **Ensartinib** • **Entrectinib**



Novello et al. *Ann Oncol* 2016;27(Suppl. 5):v1

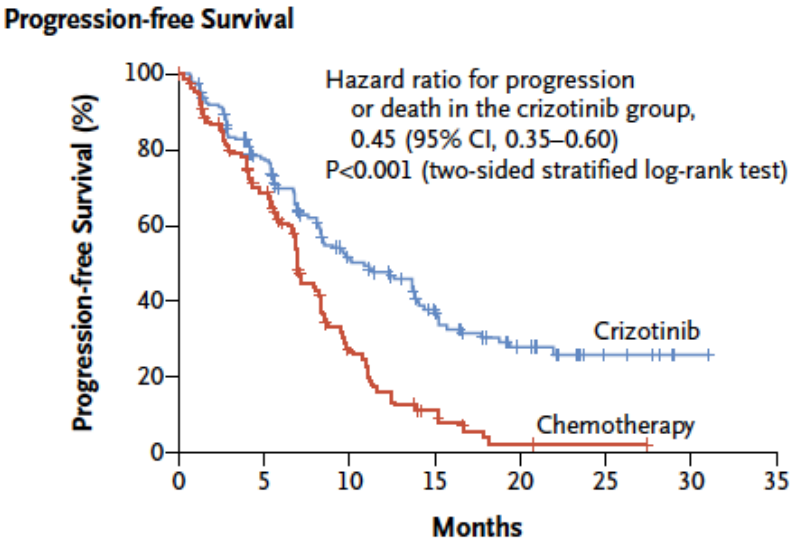
PROFILE 1014

first-line crizotinib vs. chemotherapy

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.,



	All patients		Asian patients	
	Crizotinib (N=172)	Chemo. (N=171)	Crizotinib (n=77)	Chemo. (n=80)
Events, n (%)	100 (58)	137 (80)	46 (60)	73 (91)
Median, mo	10.9	7.0	**13.6**	7.0
HR (95% CI)	0.45 (0.35−0.60)		0.44 (0.30−0.65)	
P	<0.0001		<0.0001	

PFS: 10.9 vs. 7.0 months

Solomon BJ, et al. *N Engl J Med* 2014;371:2167–77

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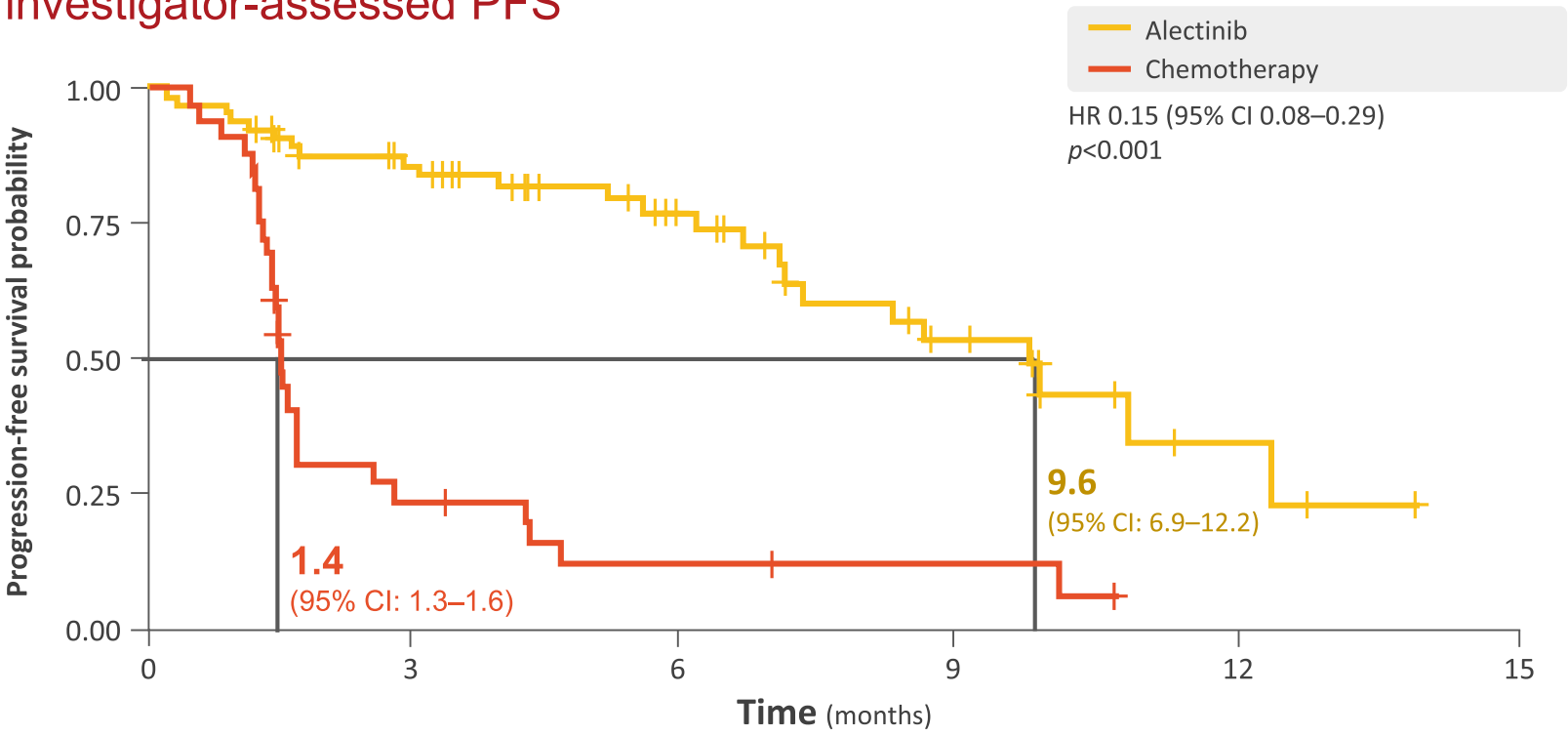
ALK REARRANG

ASCEND 5
(Ceritinib)

ALUR
(Alectinib)

hhSee Principles of
mmSee Targeted Th
nnFor performance

ALUR primary endpoint:
investigator-assessed PFS

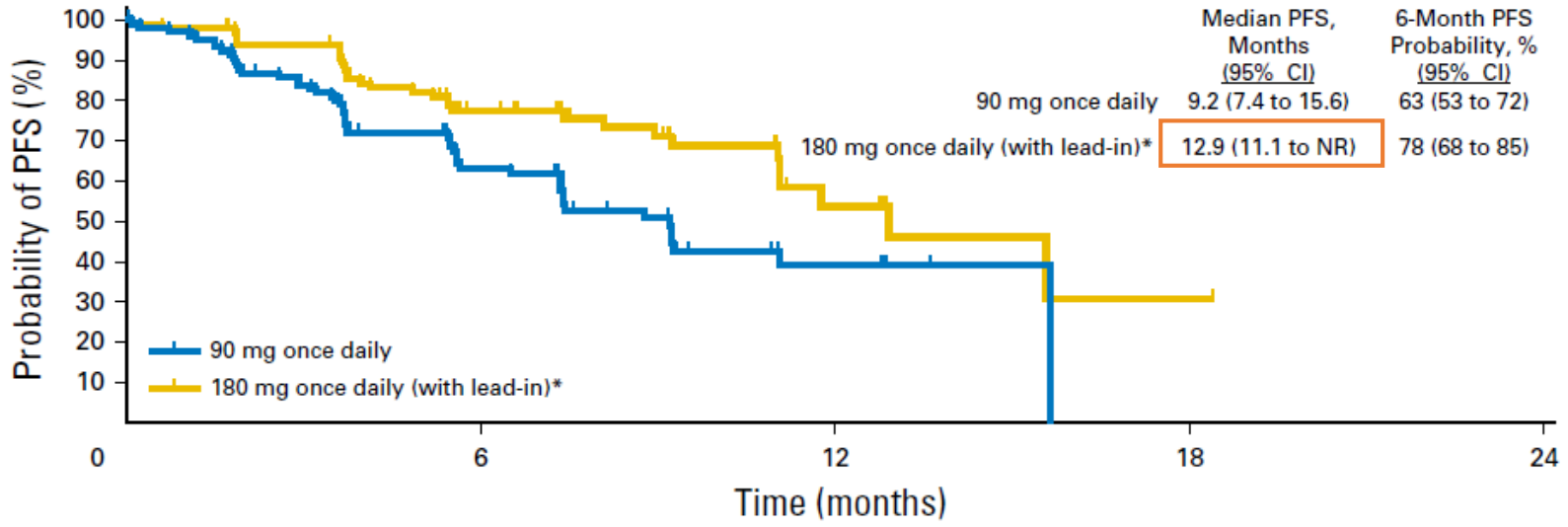


Novello, *et al.* ESMO 2017 (updated data from congress presentation)

Brigatinib in Patients With Crizotinib-Refractory Anaplastic Lymphoma Kinase–Positive Non–Small-Cell Lung Cancer: A Randomized, Multicenter Phase II Trial (ALTA study)

Patients and Methods

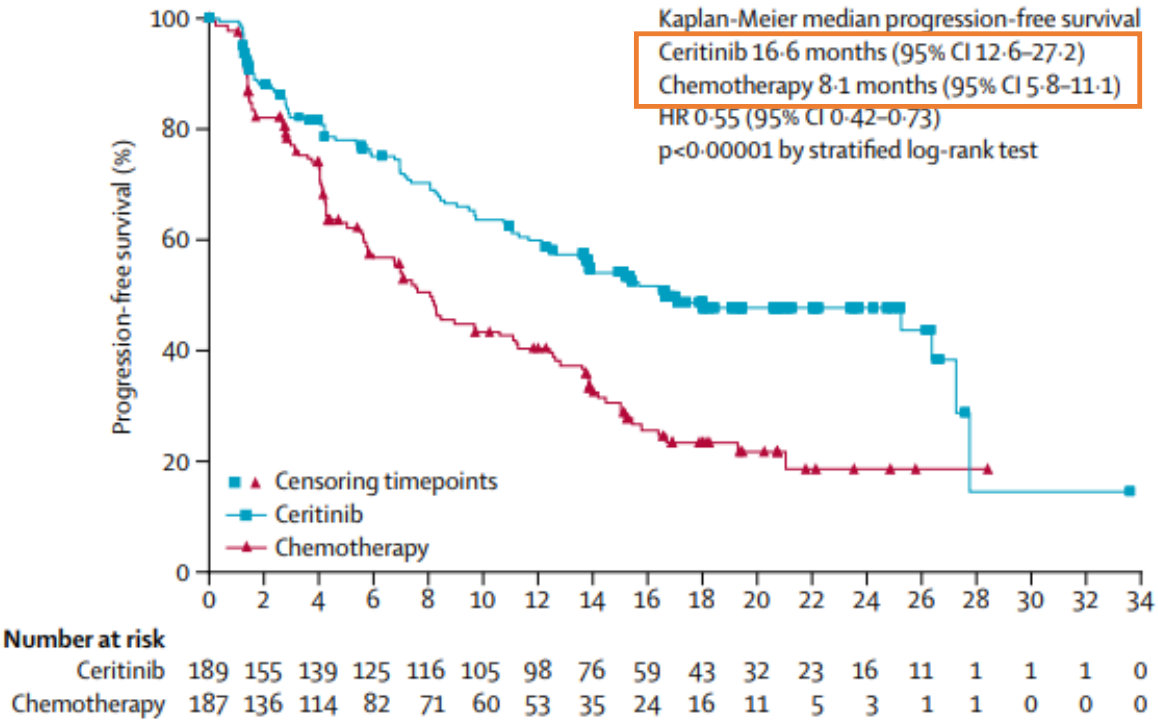
Patients were stratified by brain metastases and best response to crizotinib. They were randomly assigned (1:1) to oral brigatinib 90 mg once daily (arm A) or 180 mg once daily with a 7-day lead-in at 90 mg (180 mg once daily [with lead-in]; arm B). Investigator-assessed confirmed objective response rate (ORR) was the primary end point.



No. at risk					
90 mg once daily	112	46	11	0	0
180 mg once daily (with lead-in)*	110	53	11	1	0

Kim DW, et al. J Clin Oncol 2017;35(22):2490-2498

First-line ceritinib versus platinum-based chemotherapy in advanced *ALK*-rearranged non-small-cell lung cancer (ASCEND-4): a randomised, open-label, phase 3 study

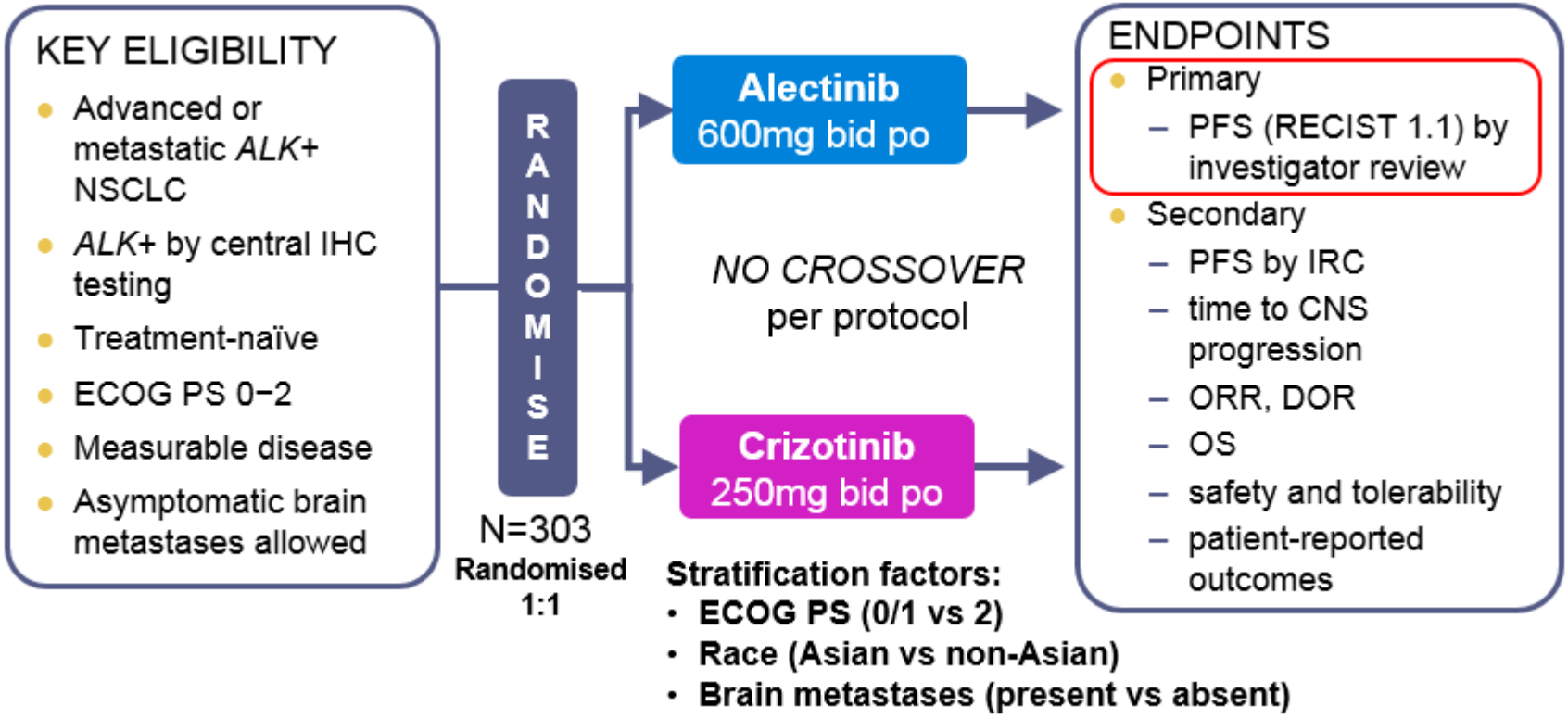


<Adverse events>

	All grades	Grade 3/4
Diarrhea	85%	5%
Nausea	69%	3%
Vomiting	66%	5%
ALT increased	60%	31%
AST increased	53%	17%
Fatigue	29%	4%

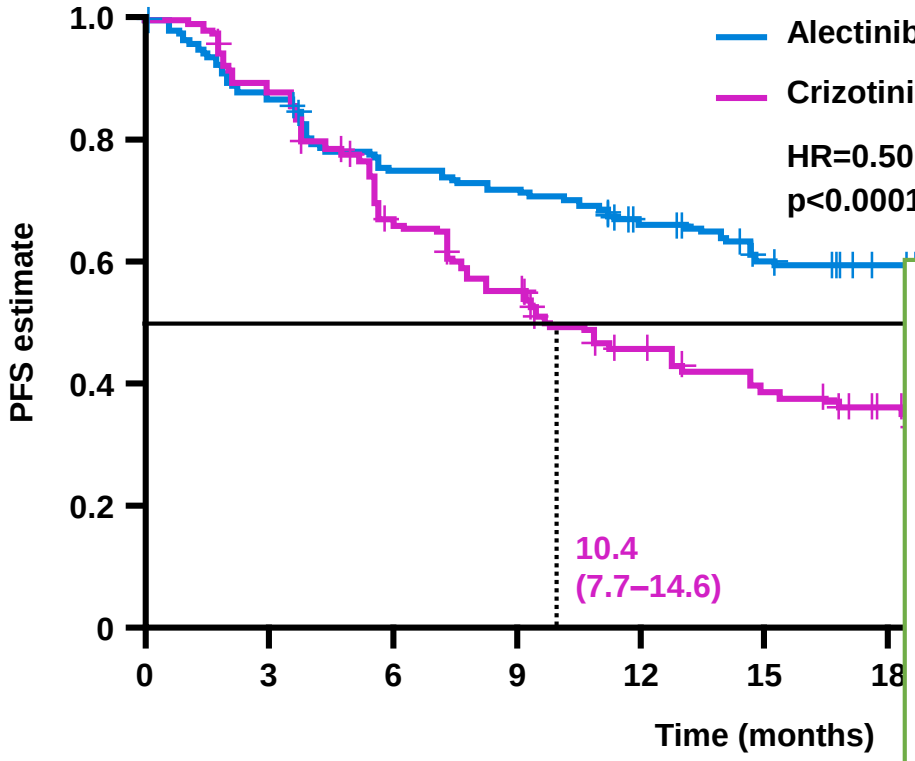
Soria JC, et al. *Lancet* 2017;389:917-929

Alectinib versus crizotinib in treatment-naïve advanced ALK-positive non-small cell lung cancer (NSCLC): primary results of the global phase III ALEX study



Shaw, et al. ASCO 2017 (Abstract LBA9008)

ALEX: Progression Free Survival (IRC assessed)

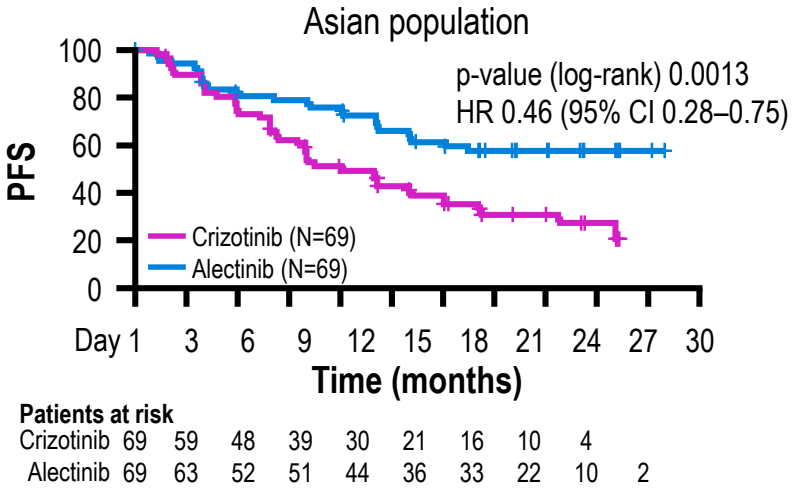


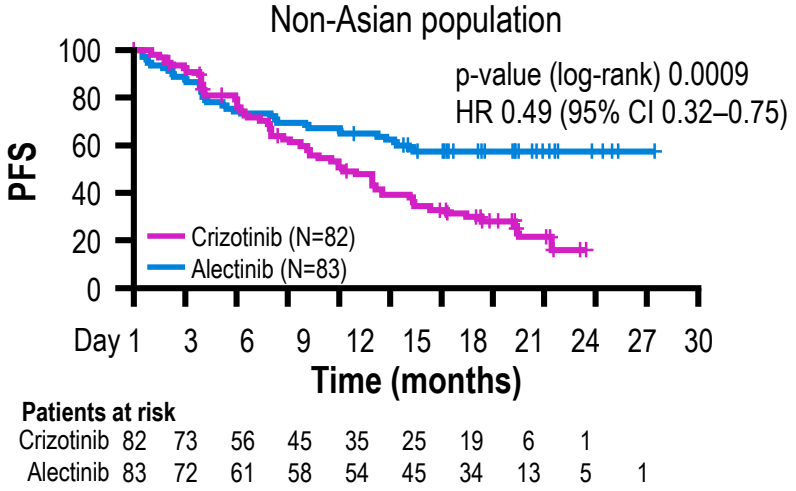
<Adverse events>

	All grades	Grade 3/4
Diarrhea	12%	0%
Nausea	14%	1%
Vomiting	7%	0%
ALT increased	15%	5%
AST increased	14%	5%
Anemia	20%	5%

Peters S, et al. *N Engl J Med* 2017;377:829-838

Alectinib (ALC) vs crizotinib (CRZ) in treatment-naïve *ALK*+ non-small-cell lung cancer (NSCLC): Asian vs non-Asian subgroup analysis of the ALEX study

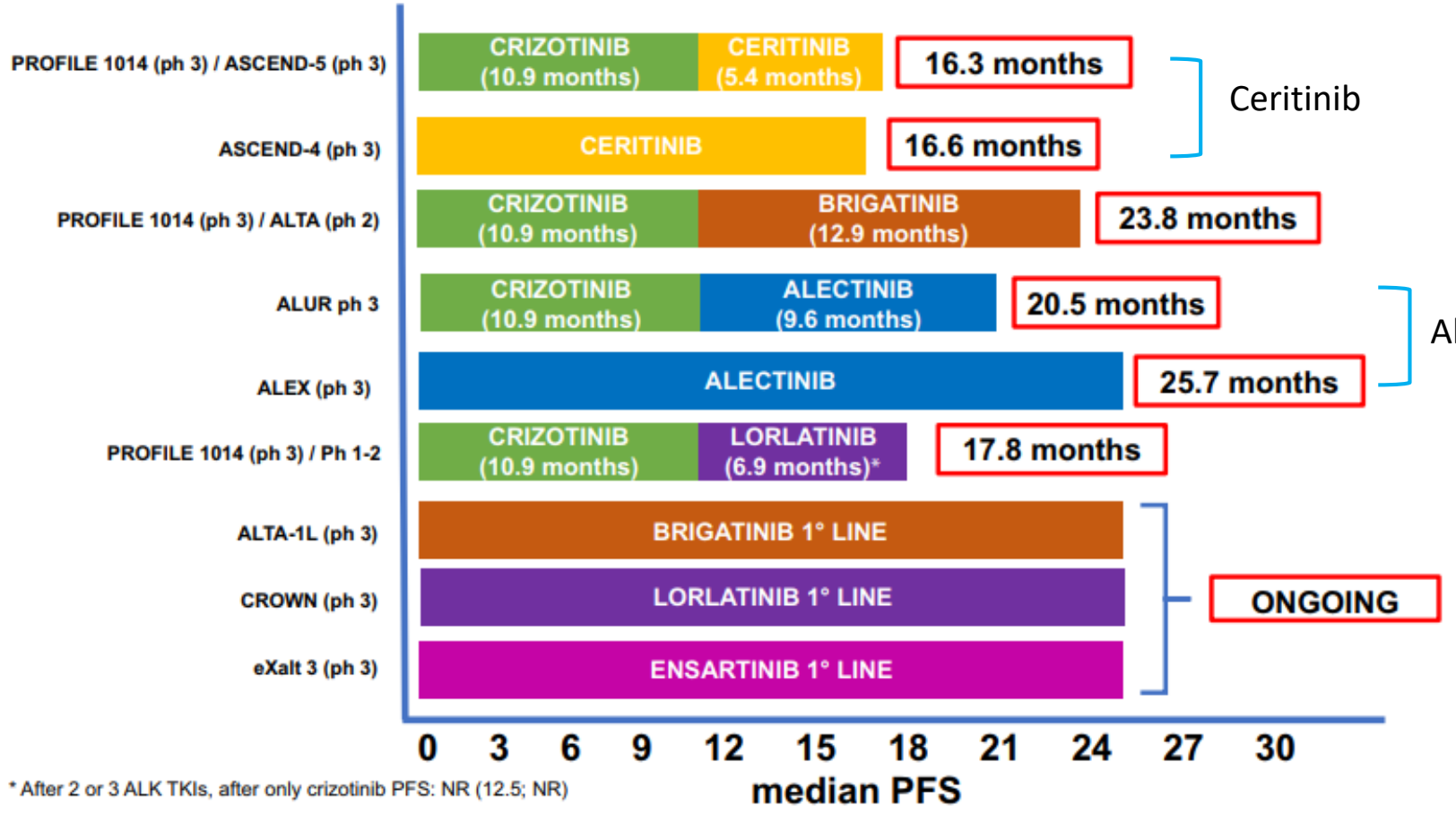




	Alectinib (n=69)	Crizotinib (n=69)
Median PFS (95% CI), INV	NE (14.7–NE)	10.9 (8.6–16.4)
HR (95% CI)	**0.46** (0.28–0.75)	
p-value	0.0013	
Median PFS (95% CI), IRC	25.7 (14.7–NE)	10.8 (7.5–16.4)
HR (95% CI)	0.49 (0.30–0.79)	
p-value	0.0026	

	Alectinib (n=83)	Crizotinib (n=82)
Median PFS (95% CI), INV	NE (14.0–NE)	11.1 (8.8–14.6)
HR (95% CI)	**0.49** (0.32–0.75)	
p-value	0.0009	
Median PFS (95% CI), IRC	NE (14.6–NE)	9.8 (7.3–16.7)
HR (95% CI)	0.56 (0.36–0.87)	
p-value	0.0091	

Optimal sequence for ALK (+) NSCLC



J Thorac Oncol 2018;13(3):301-322

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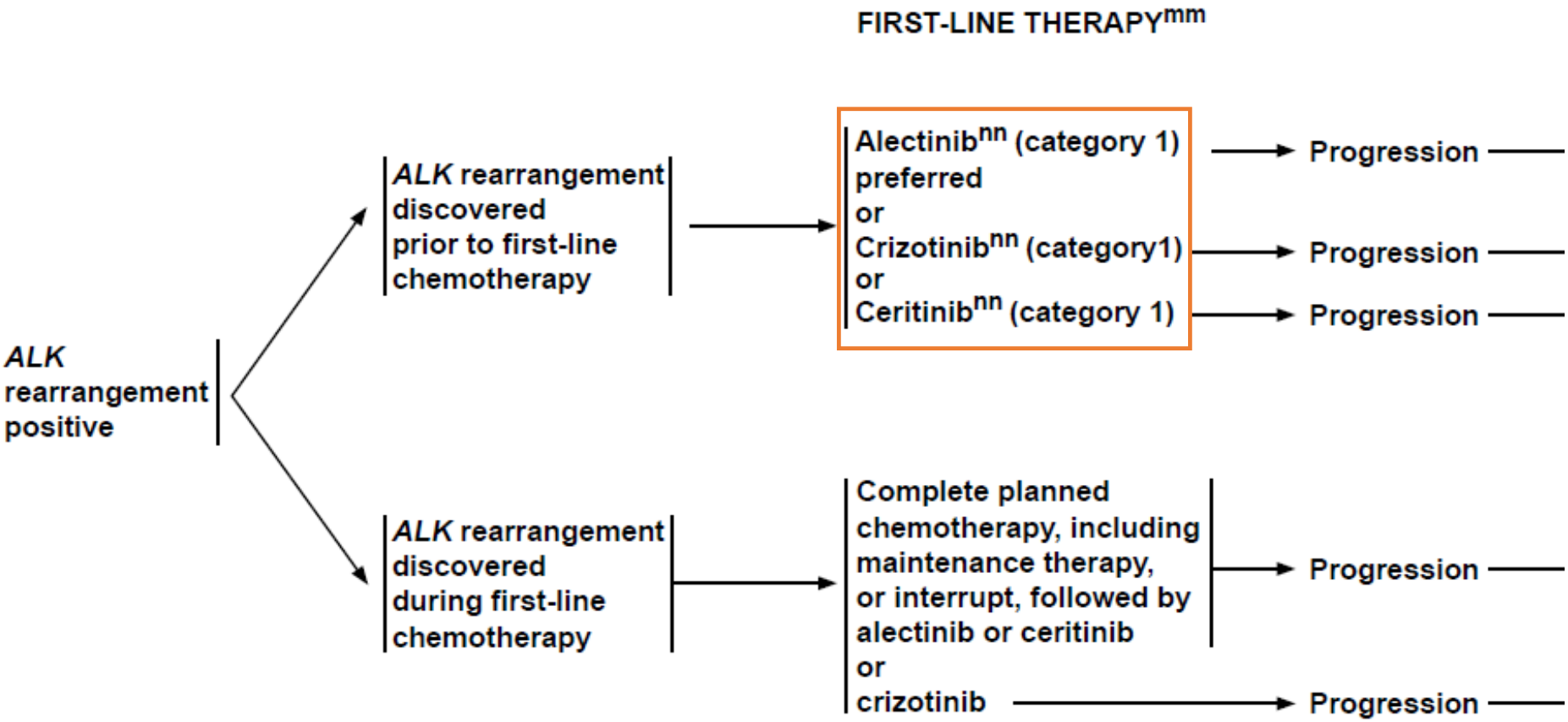
ALK REARRANGEMENT POSITIVE[hh]



IASLC
INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER
IASLC 18TH WORLD CONFERENCE ON LUNG CANCER
October 15–18, 2017 | Yokohama, Japan
WWW.IASLC.ORG

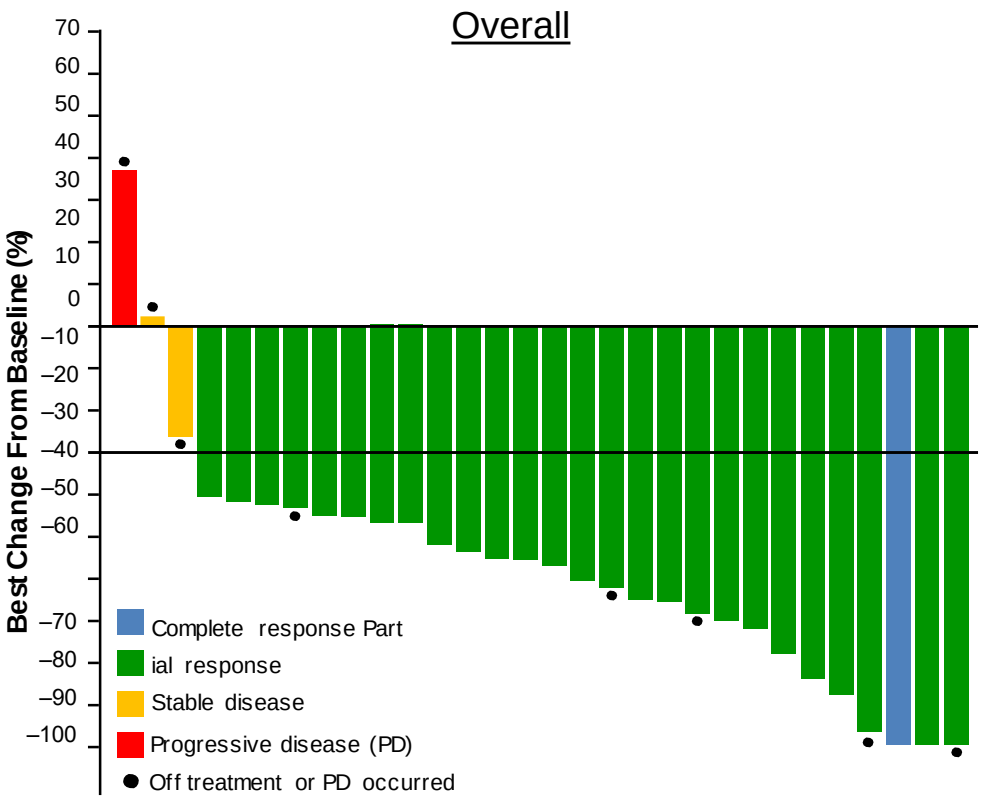
Phase 2 Study of Lorlatinib in Patients With Advanced ALK+/ROS1+ Non-Small Cell Lung Cancer

Benjamin J. Solomon,[1] Alice T. Shaw,[2] Sai-Hong I. Ou,[3] Benjamin Besse,[4] Enriqueta Felip,[5] Todd M. Bauer,[6] Ross A. Soo,[7] Alessandra Bearz,[8] Chia-Chi Lin,[9] Jill S. Clancy,[10] Antonello Abbattista,[11] Holger Thurm,[12] Gerson Peltz,[13] Elizabeth T. Masters,[14] Jean-François Martini,[12] Leonard P. James,[14] Takashi Seto[15]

[1]Peter MacCallum Cancer Centre, Melbourne, Australia; [2]Massachusetts General Hospital, Boston, MA, USA; [3]University of California Irvine, Irvine, CA, USA; [4]Gustave Roussy Cancer Campus, Villejuif, France, and Paris-Sud University, Orsay, France; [5]Vall d'Hebron Institute of Oncology, Barcelona, Spain; [6]Sarah Cannon Cancer Research Institute/Tennessee Oncology, PLLC, Nashville, TN, USA; [7]National University Hospital Singapore, Singapore; [8]National Cancer Institute, Aviano, Italy; [9]Taipei Medical University, Taipei, Taiwan; [10]Inventiv Clinical, Princeton, NJ, USA; [11]Pfizer Oncology, Milan, Italy; [12]Pfizer Oncology, La Jolla, CA, USA; [13]Pfizer Oncology, Groton, CT, USA; [14]Pfizer Oncology, New York, NY, USA; [15]National Kyushu Cancer Center, Fukuoka, Japan

IASLC 2017

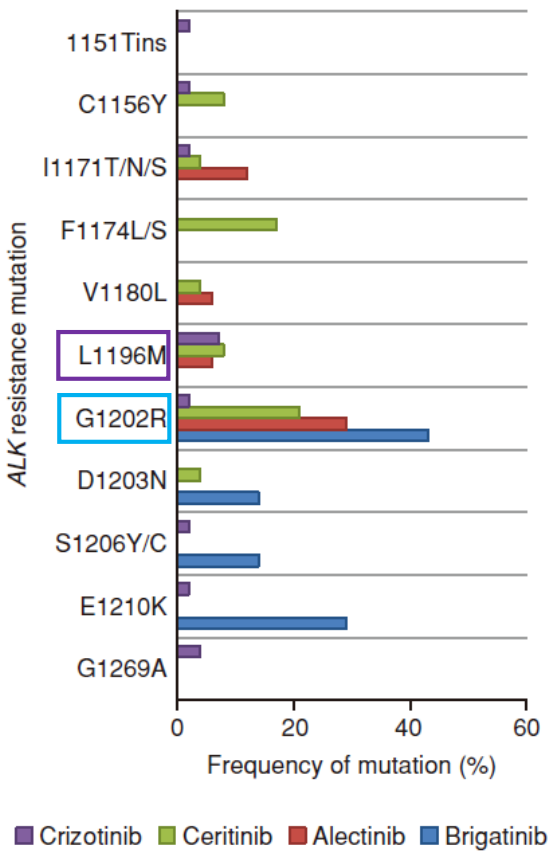
Efficacy in EXP1 (ALK+ Treatment-Naïve Patients)

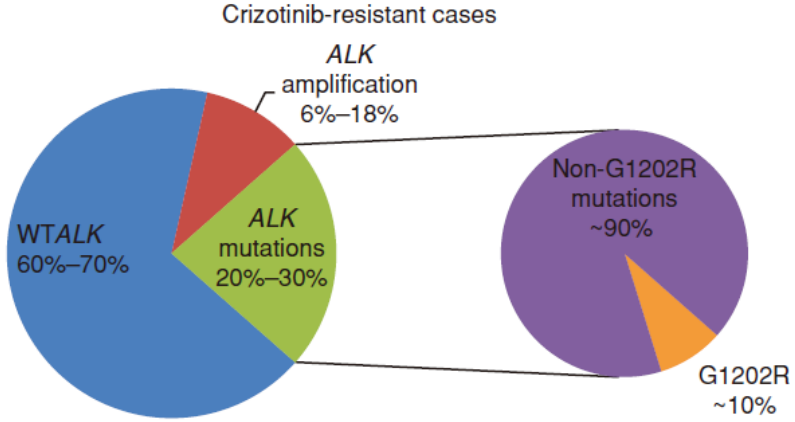


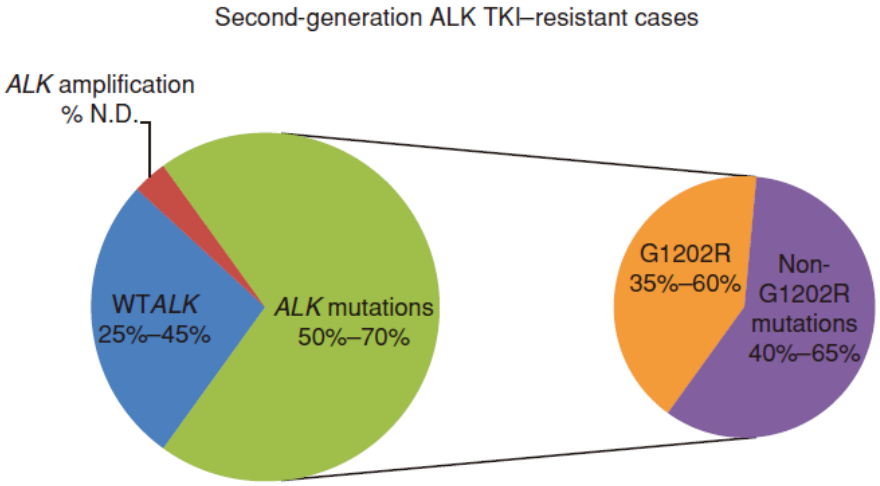
	EXP1 (n=30)
ORR, n/N (%) (95% CI)	27/30 (90) (74,98)
Median DOR, mo (95% CI)	NR (10.2, NR)
DOR ≥ 6 mo, n°/n (%)	16/27 (59)
Median PFS, mo (95% CI)	NR (11.4, NR)

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

Mechanisms of acquired resistance to ALK inhibitors







Lin JJ, et al. *Cancer Discov* 2017;7(2):137-155

Acquired resistant mutations to ALK inhibitors

Cellular ALK Phosphorylation Mean IC50 (nM)					
Mutation status	**Crizotinib**	**Ceritinib**	**Alectinib**	**Brigatinib**	**Lorlatinib**
Parental Ba/F3	763.9	885.7	890.1	2774.0	11293.8
EML4-ALK V1	38.6	4.9	11.4	10.7	2.3
EML4-ALK C1156Y	61.9	5.3	11.6	4.5	4.6
EML4-ALK I1171N	130.1	8.2	397.7	26.1	49.0
EML4-ALK I1171S	94.1	3.8	177.0	17.8	30.4
EML4-ALK I1171T	51.4	1.7	33.6[a]	6.1	11.5
EML4-ALK F1174C	115.0	38.0[a]	27.0	18.0	8.0
EML4-ALK L1196M	339.0	9.3	117.6	26.5	34.0
EML4-ALK L1198F	0.4	196.2	42.3	13.9	14.8
EML4-ALK G1202R	381.6	124.4	706.6	129.5	49.9
EML4-ALK G1202del	58.4	50.1	58.8	95.8	5.2
EML4-ALK D1203N	116.3	35.3	27.9	34.6	11.1
EML4-ALK E1210K	42.8	5.8	31.6	24.0	1.7
EML4-ALK G1269A	117.0	0.4	25.0	ND	10.0
EML4-ALK D1203N+F1174C	338.8	237.8	75.1	123.4	69.8
EML4-ALK D1203N+E1210K	153.0	97.8	82.8	136.0	26.6

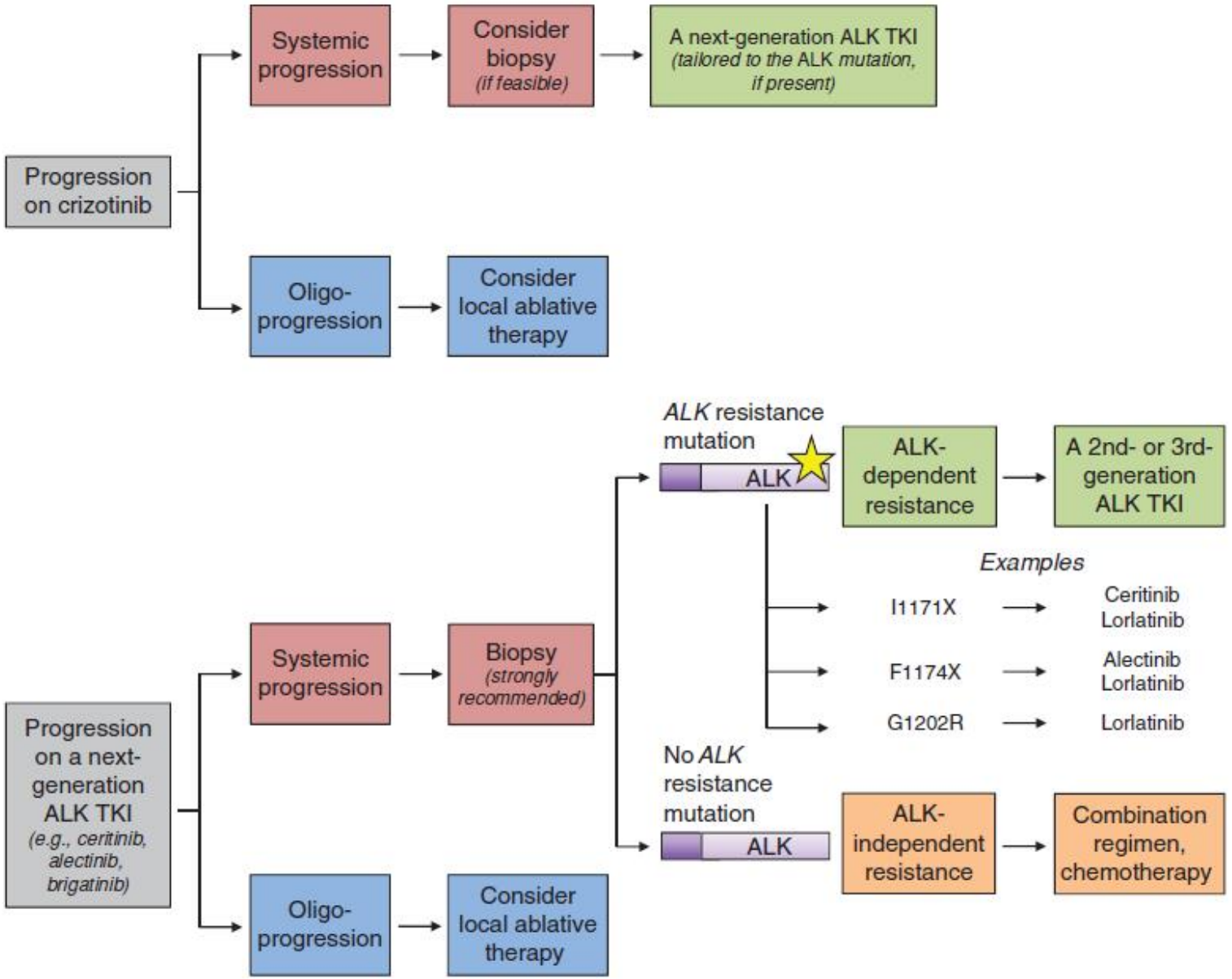
IC50 ≤ 50 nM

IC50 > 50 <200 nM

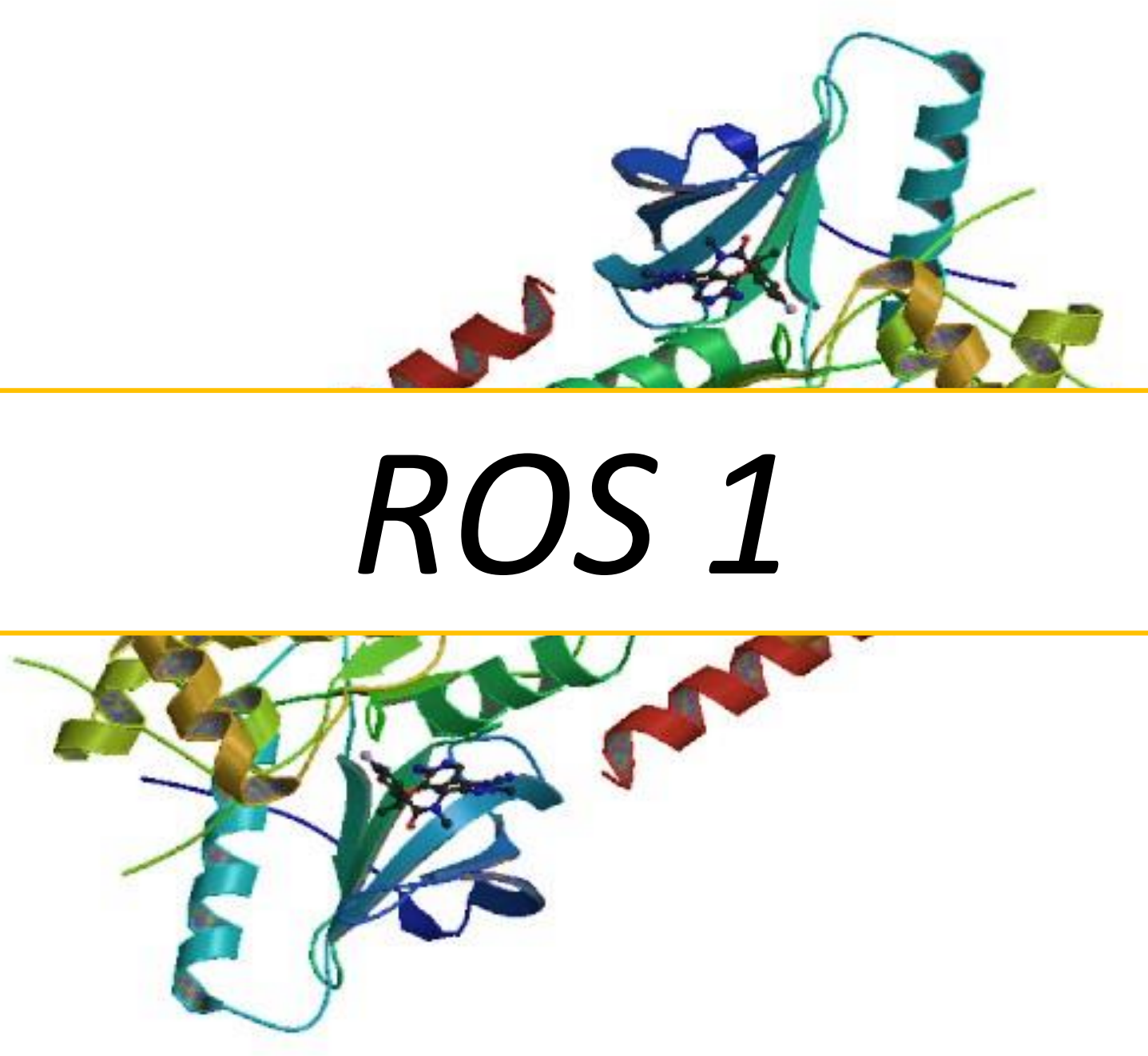
IC50 ≥ 200 nM

Gainor JF et al., *Cacner Discov* 2016;6:1118-33

Guidelines for selecting treatment after progression on an ALK TKIs

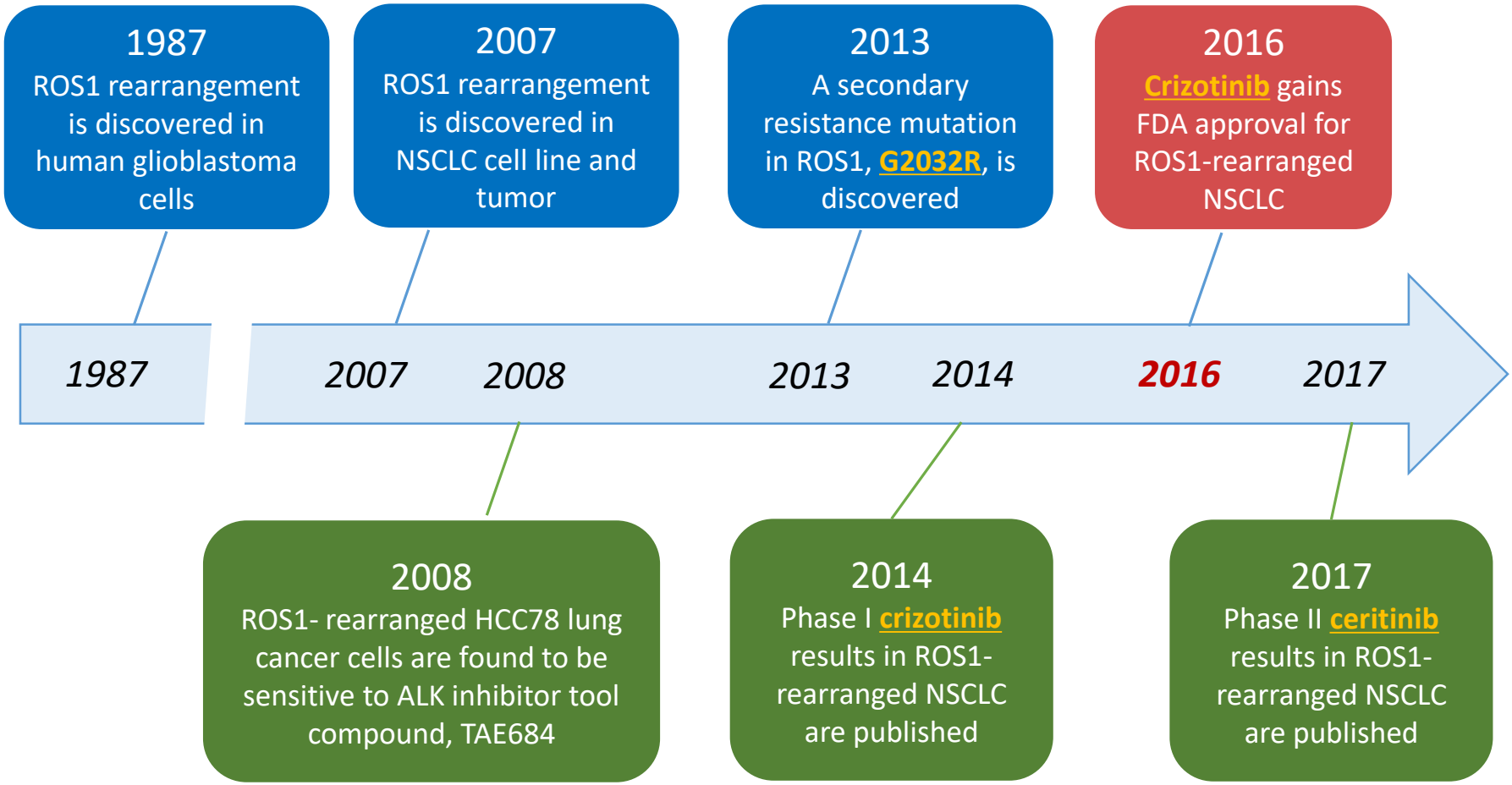


Lin JJ, et al. *Cancer Discov* 2017;7(2):137-155



ROS 1

Timeline

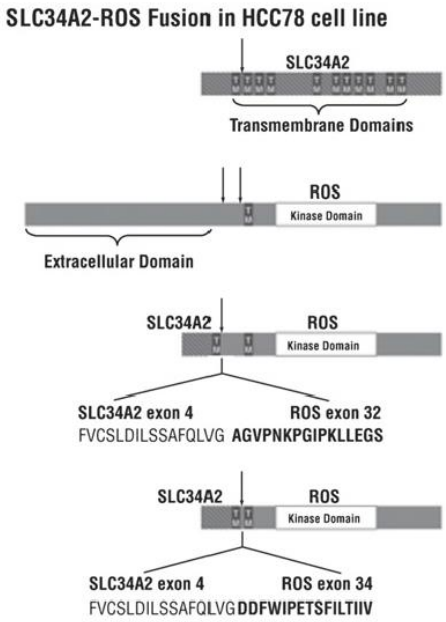


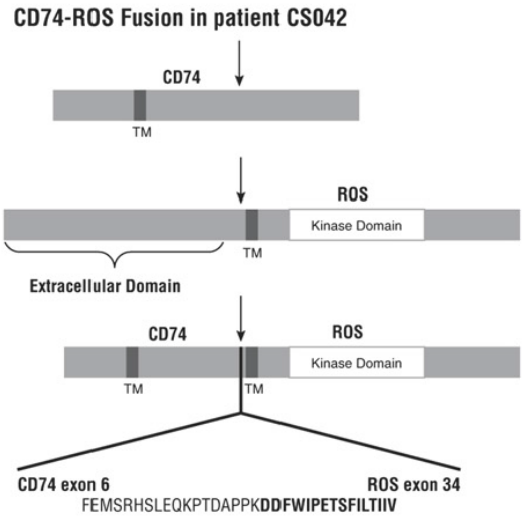
Lin JJ, et al. *J Thorac Oncol* 2017

Cell

Cell *131*, 1190–1203, December 14, 2007

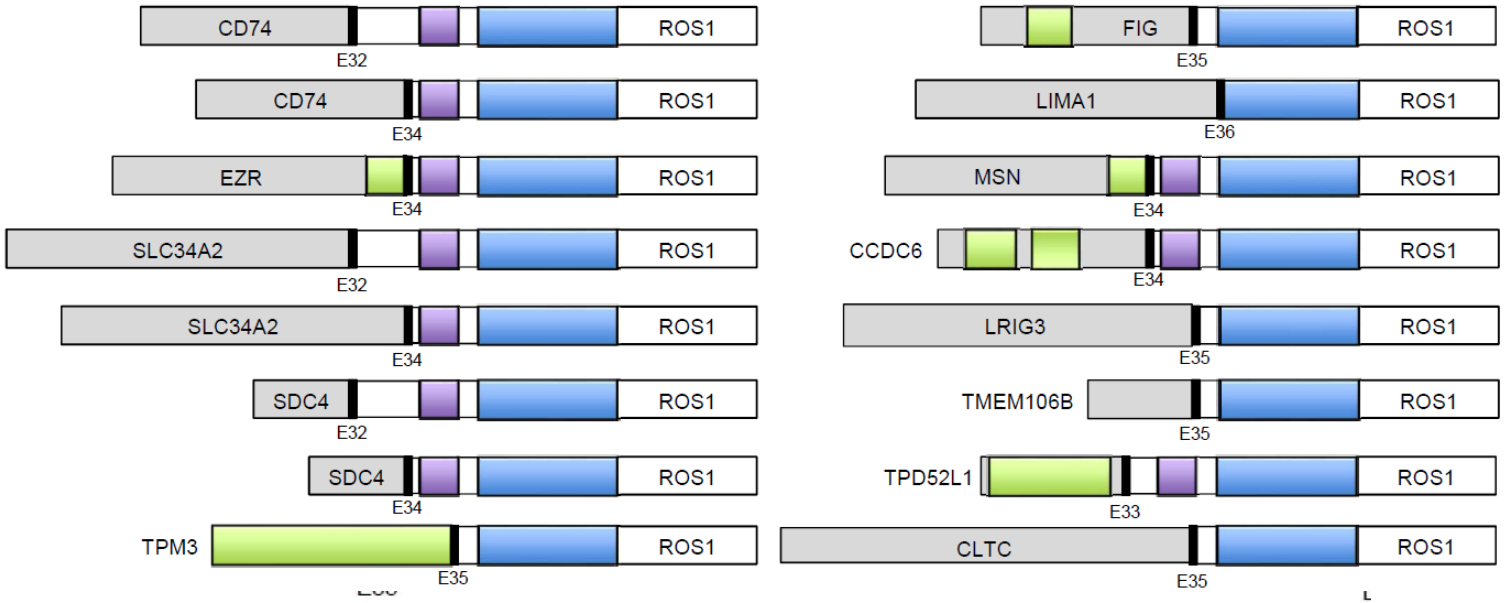
Global Survey of Phosphotyrosine Signaling Identifies Oncogenic Kinases in Lung Cancer

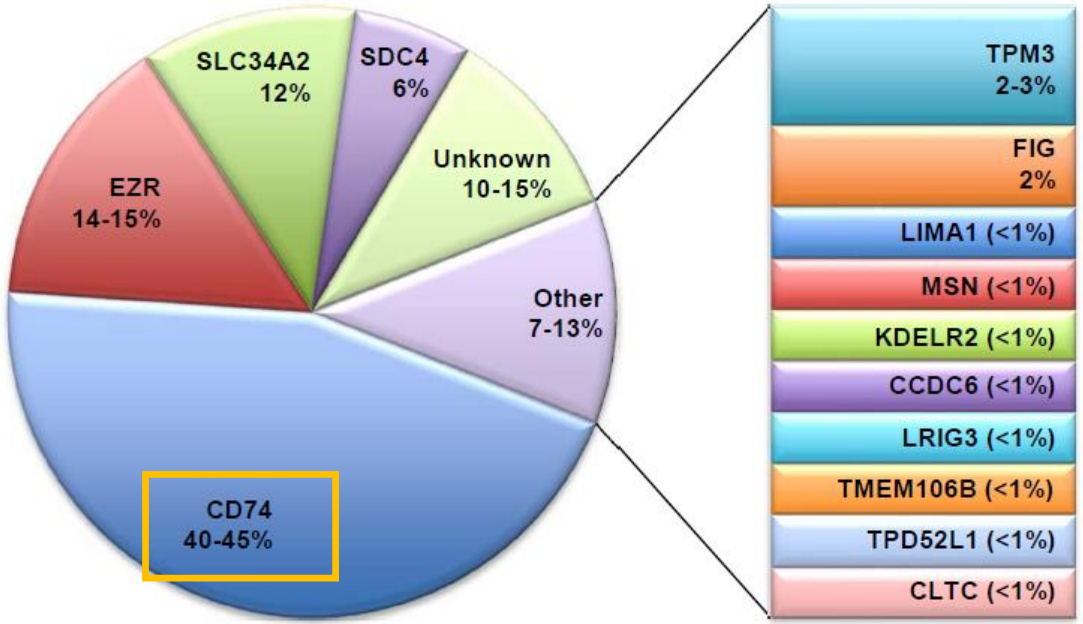




Despite the success of tyrosine kinase-based cancer therapeutics, for most solid tumors the tyrosine kinases that drive disease remain unknown, limiting our ability to identify drug targets and predict response. Here we present the first large-scale survey of tyrosine kinase activity in lung cancer. Using a phosphoproteomic approach, we characterize tyrosine kinase signaling across 41 non-small cell lung cancer (NSCLC) cell lines and over 150 NSCLC tumors. Profiles of phosphotyrosine signaling are generated and analyzed to identify known oncogenic kinases such as EGFR and c-Met as well as novel ALK and ROS fusion proteins. Other activated tyrosine kinases such as PDGFRα and DDR1 not previously implicated in the genesis of NSCLC are also identified. By focusing on activated cell circuitry, the approach outlined here provides insight into cancer biology not available at the chromosomal and transcriptional levels and can be applied broadly across all human cancers.

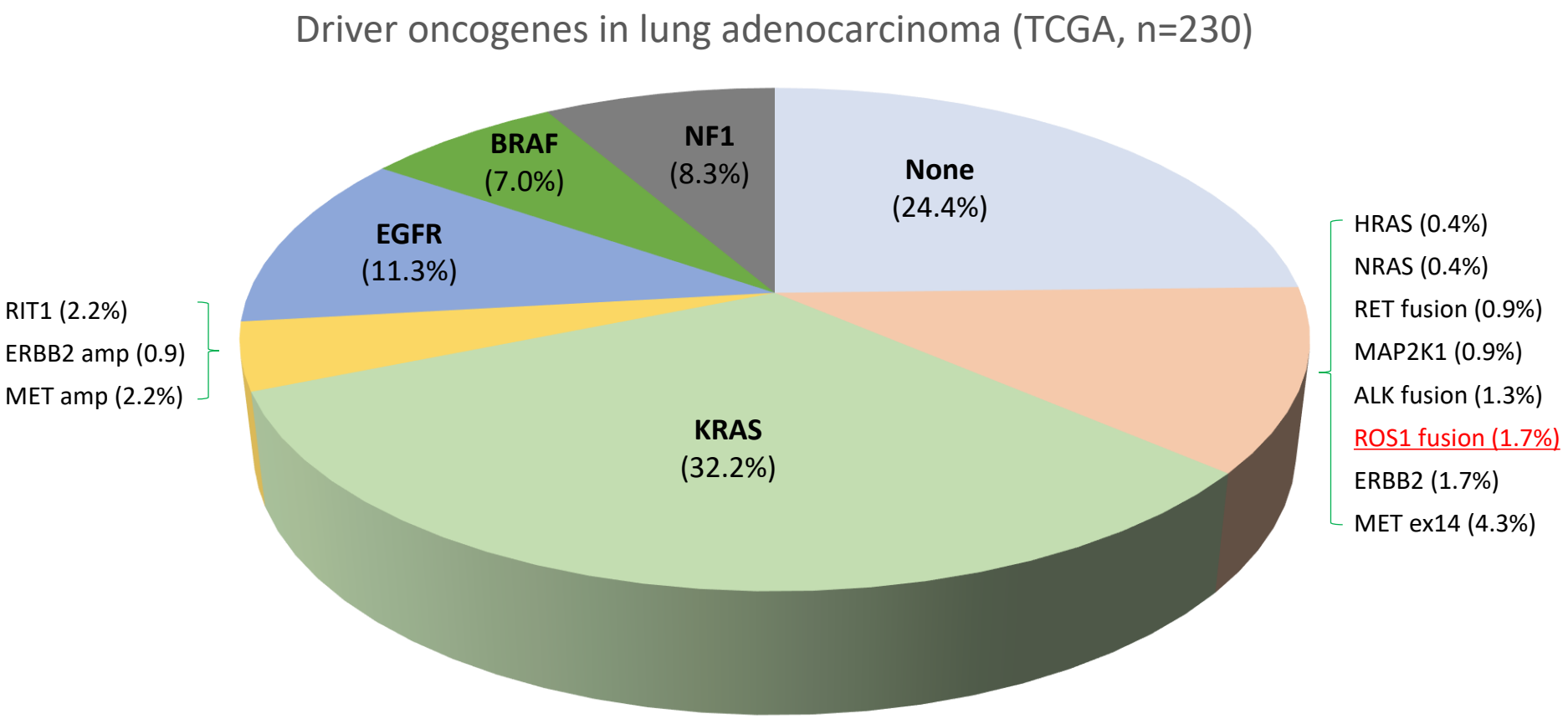
ROS1 rearrangements in NSCLC





Lin JJ, et al. *J Thorac Oncol* 2017

Prevalence (1-2%)



Nature 2014;511:543–550

Clinical characteristics

Demographic or Clinical Characteristic	All Patients (n = 1,073) No.	%	ROS1 positive (n=18) No.	%	ROS1 negative (n=1,055) No.	%	P (ROS1 positive vs ROS1 negative)
Age, years							
Median	62						< 0.001
Range	32-87						
Sex							
Male	523	49					0.480
Female	550	51					
Smoking history							
Never-smoker	239	22					< 0.001
Light-smoker	62	6					
Smoker	695	65					
Ethnicity							
Asian	45	4	5	28	40	4	<0.001
Non-Asian	942	88	13	72	929	88	
NA	86	8	0	0	86	8	
Pathology							
Adenocarcinoma	694	65	18	100	676	64	0.019
Squamous	200	19	0	0	200	19	
NSCLC, NOS	59	5	0	0	59	6	
Adenosquamous	10	1	0	0	10	1	
Other	38	4	0	0	38	4	
NA	72	7	0	0	72	7	

ROS1 positive patients

1. Younger
2. Never-smoker
3. Asian
4. Adenocarcinoma

J Clin Oncol 2012;30:863-870

Molecular testing for ROS1 rearrangement

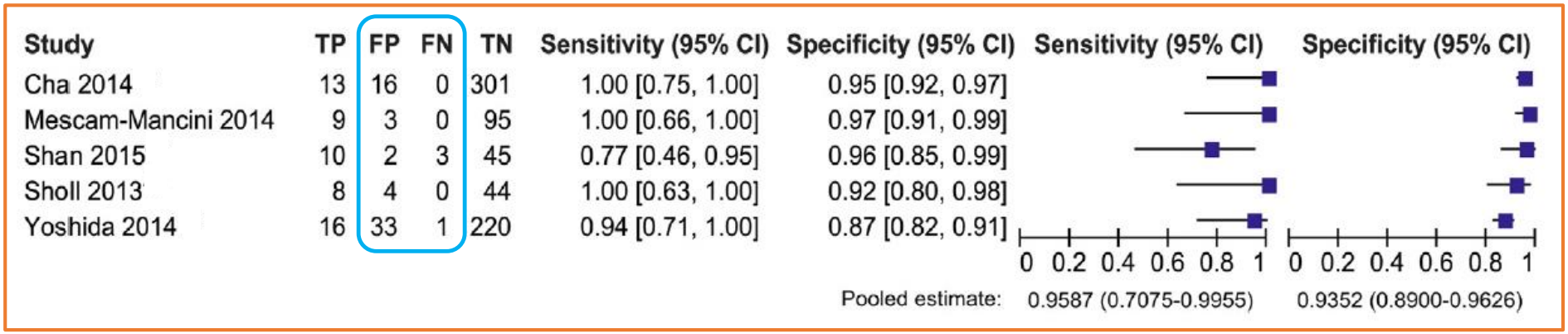
Immunohistochemical stain
D4D6 antibody
staining intensity of at least 2+

Screening assay

Cytogenetic method (FISH)
or
Molecular method (RT-PCR/NGS)

Confirmation assay

<Forest plot of sensitivity and specificity for immunohistochemistry (IHC) for ROS1 rearrangement>



FN, false-negative; FP, false-positive; TN, true-negative; TP, true-positive

Lindeman NI, et al. *J Mol Diagn* 2018, 20: 129-159

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 20, 2014 VOL. 371 NO. 21

Crizotinib in *ROS1*-Rearranged Non–Small-Cell Lung Cancer

<Study design : PROFILE 1001>

Eligible criteria

- ROS1 rearrangement (FISH)
- advanced NSCLC
- ECOG 0-2
- Age of at least 18 years

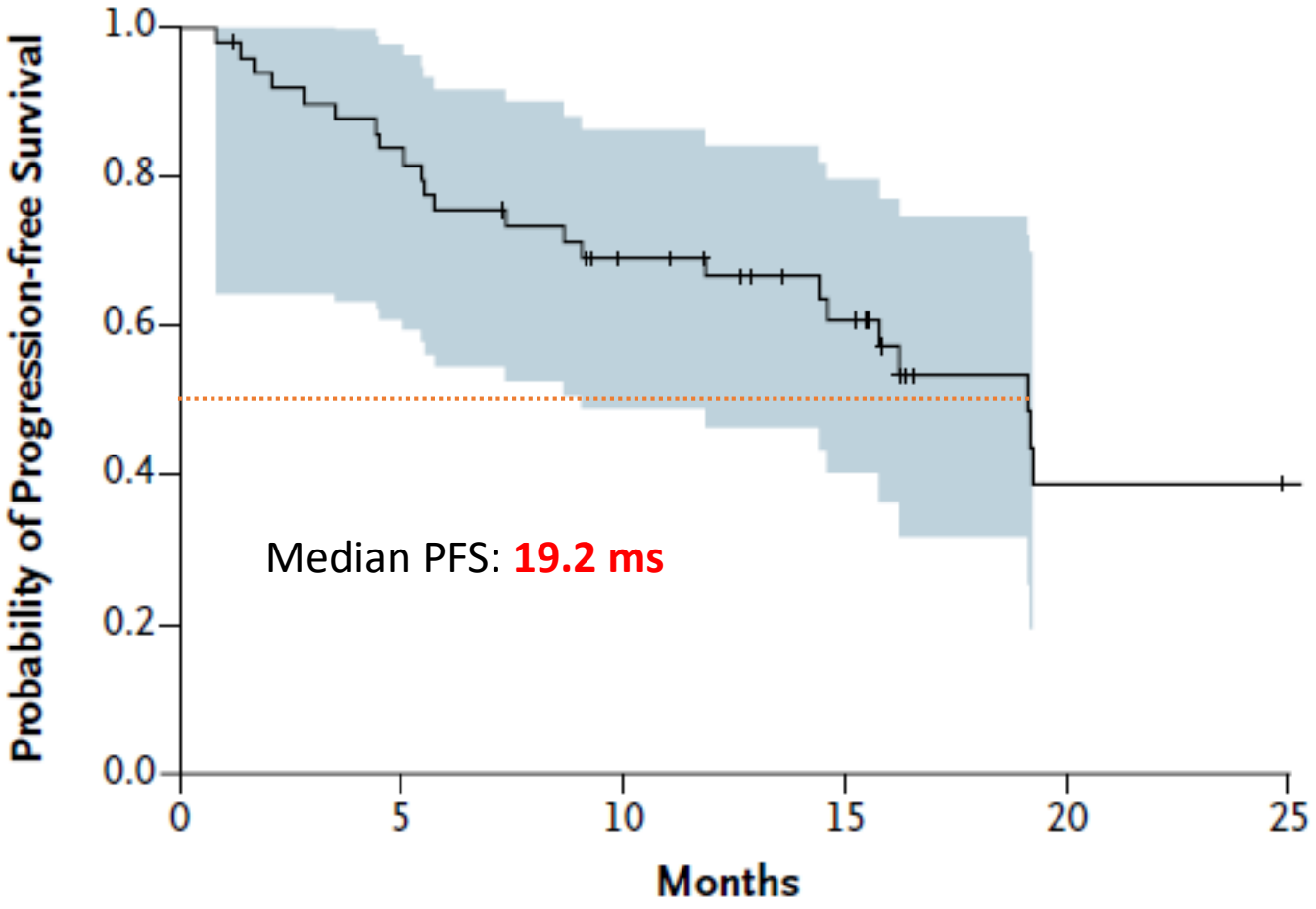
(n= 50)

→ **Crizotinib 250mg bid** → PD†

* **Primary end point** : overall response rate
*** Secondary end point** : progression free survival, duration of response, adverse events
† According to the Response Evaluation Criteria in Solid tumors (RECIST), version 1.0

N Engl J Med 2014;371:1963-71

Progression-free Survival

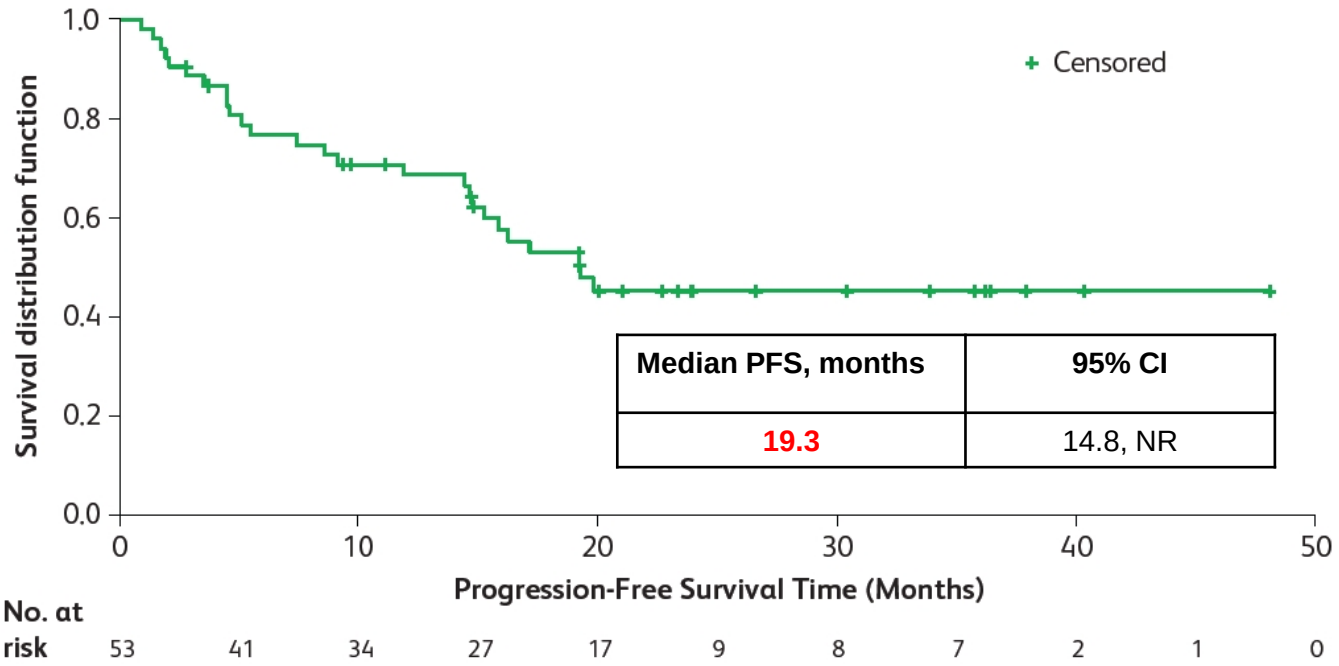


No. at Risk						
Crizotinib	50	41	30	21	8	7

N Engl J Med 2014;371:1963-71

Crizotinib in Advanced ROS1-Rearranged Non-Small Cell Lung Cancer (NSCLC): Updated Results From PROFILE 1001

Progression-Free Survival[a]



Median PFS, months	95% CI
19.3	14.8, NR

NR, not reached

[a]Data as of cutoff date of 30 November 2014.

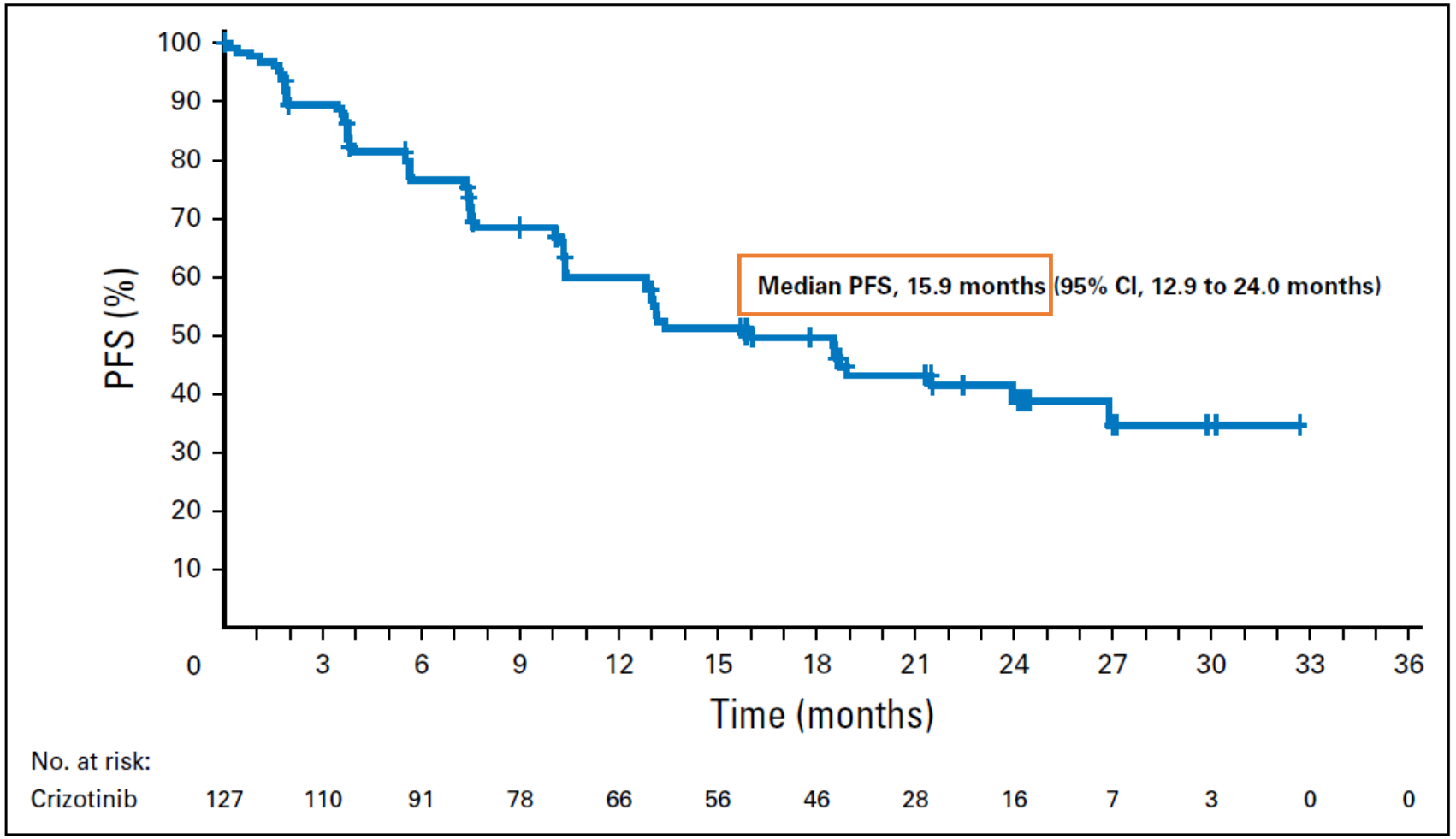
Phase II Study of Crizotinib in East Asian Patients With ROS1-Positive Advanced Non–Small-Cell Lung Cancer

This phase II, open-label, single-arm trial enrolled East Asian patients with ROS1-positive (assessed through validated AmoyDx assay [Amoy Diagnostics, Xiamen, China] at three regional laboratories) advanced NSCLC who had received three or fewer lines of prior systemic therapies. Patients were to receive oral crizotinib at a starting dose of 250 mg twice daily and continued treatment until Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1–defined progression (by independent radiology review [IRR]), unacceptable toxicity, or withdrawal of consent. The primary end point was objective response rate (ORR) by IRR.

End Point	Total, No. (%)
No. of patients	127
Best overall response	
Complete response	17 (13.4)
Partial response	74 (58.3)
Stable disease	21 (16.5)
Progressive disease	9 (7.1)
Early death	2 (1.6)
Indeterminate	4 (3.1)
ORR	91 (71.7)
95% CI	63.0 to 79.3

Wu YL, et al. *J Clin Oncol* 2018

Progression-free survival (PFS) as assessed by independent radiology review



Wu YL, et al. *J Clin Oncol* 2018

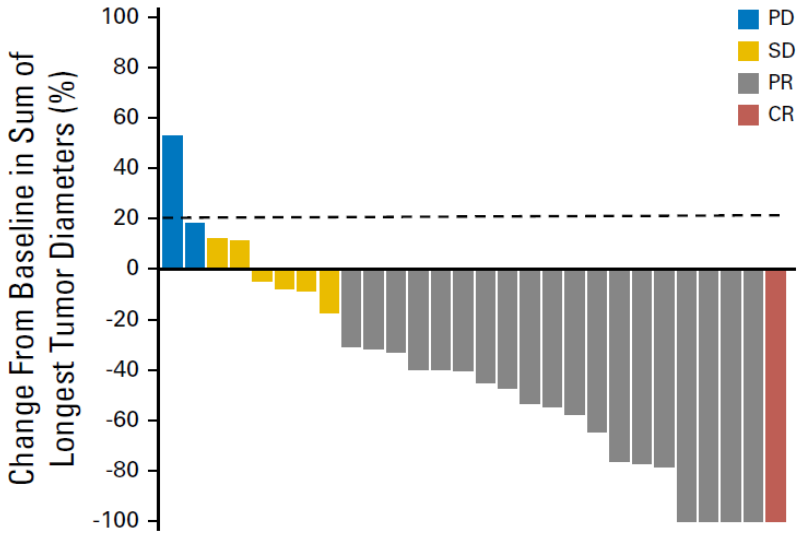
Open-Label, Multicenter, Phase II Study of Ceritinib in Patients With Non–Small-Cell Lung Cancer Harboring *ROS1* Rearrangement

We enrolled 32 patients with advanced NSCLC who tested positive for *ROS1* rearrangement by fluorescent in situ hybridization. Ceritinib 750 mg was administered once daily. The primary end point was objective response rate. The secondary end points were disease control rate; duration of response; progression-free survival; overall survival; toxicity; and concordance among fluorescent in situ hybridization, immunohistochemistry, and next-generation sequencing.

<Independent Review Committee-Assessed Activity>

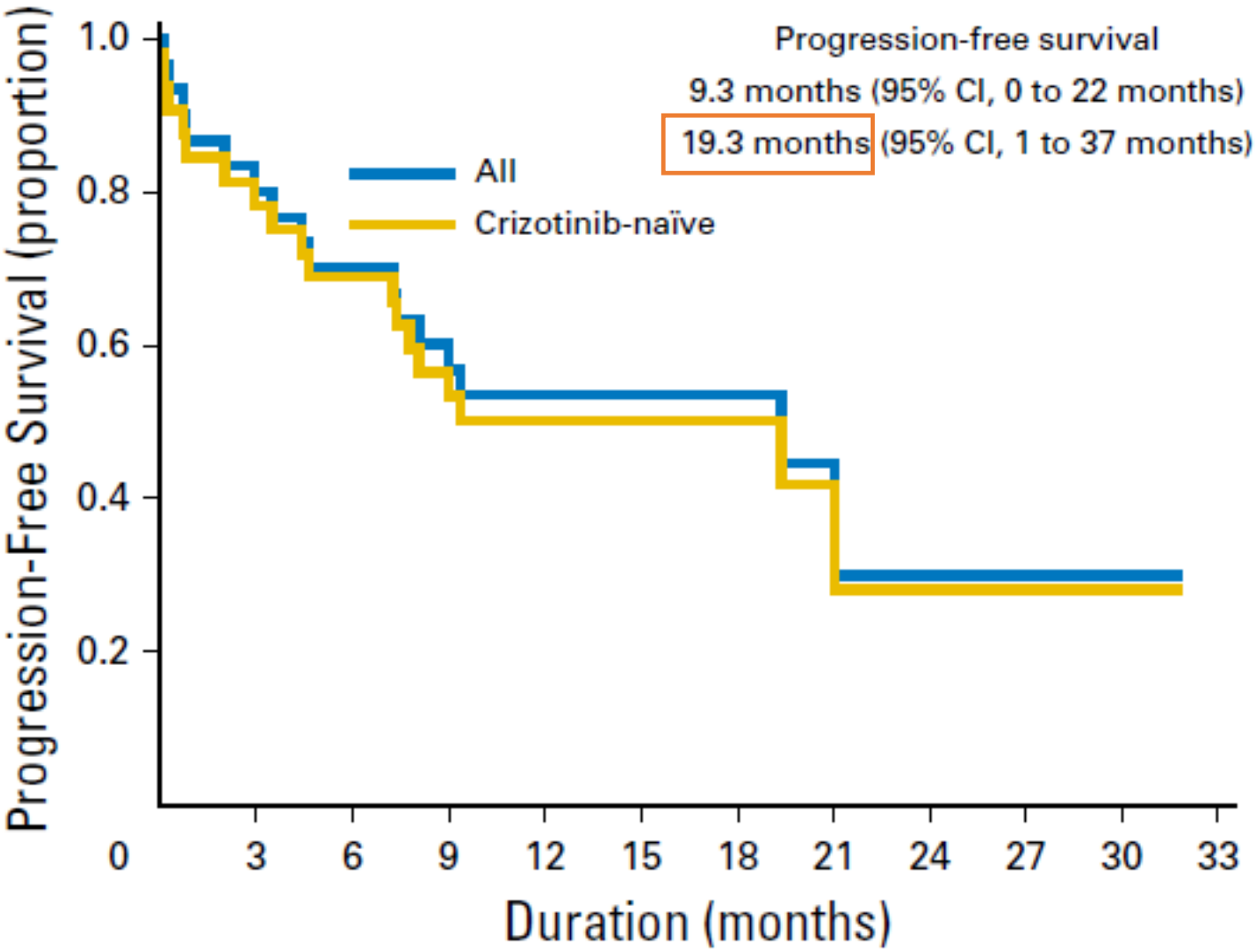
Best Response	All Patients, No. (%)	Crizotinib-Naïve Patients, No. (%)
No. of patients	32	30
CR	1 (3)	1 (3)
PR	19 (59)	19 (63)
SD	6 (19)	6 (20)
PD	2 (6)	2 (7)
Not evaluable*	4 (12)	2 (7)
ORR, % (95% CI)	62 (45 to 77)	67 (48 to 81)
DCR (CR + PR + SD), % (95% CI)	81 (65 to 91)	87 (70 to 95)

* Intracranial ORR: 25%/Intracranial disease control: 63%



Lim SM, et al. *J clin Oncol* 2017;35:2613-2618

Progression-free survival



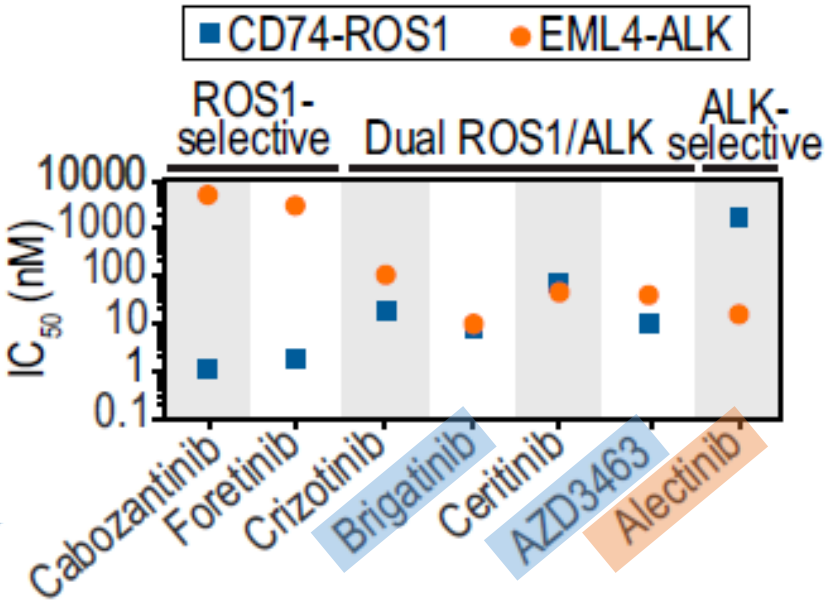
Lim SM, et al. *J clin Oncol* 2017;35:2613-2618

National Comprehensive Cancer Network®

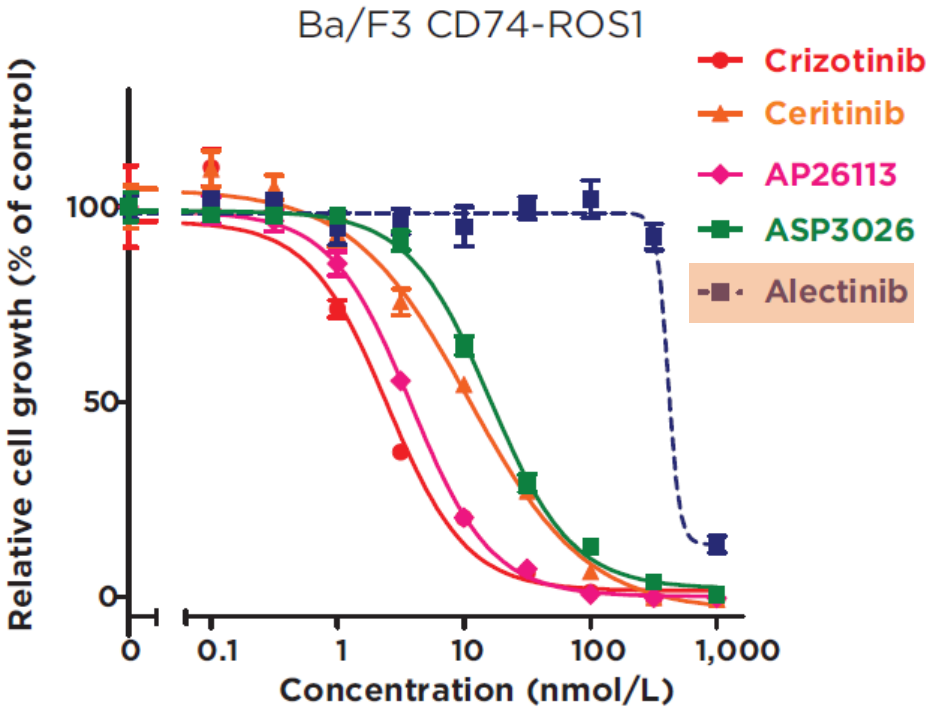
NCCN Guidelines Version 3.2018
Non-Small Cell Lung Cancer

ROS1 REARRANGEMENT POSITIVE[hh]

Other ALK inhibitors



Davare MA, et al.*PNAS* 2015



Clin Cancer Res 2015;21(1):166-174

IASLC
INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER
IASLC 18TH WORLD CONFERENCE ON LUNG CANCER
October 15–18, 2017 | Yokohama, Japan
WWW.IASLC.ORG

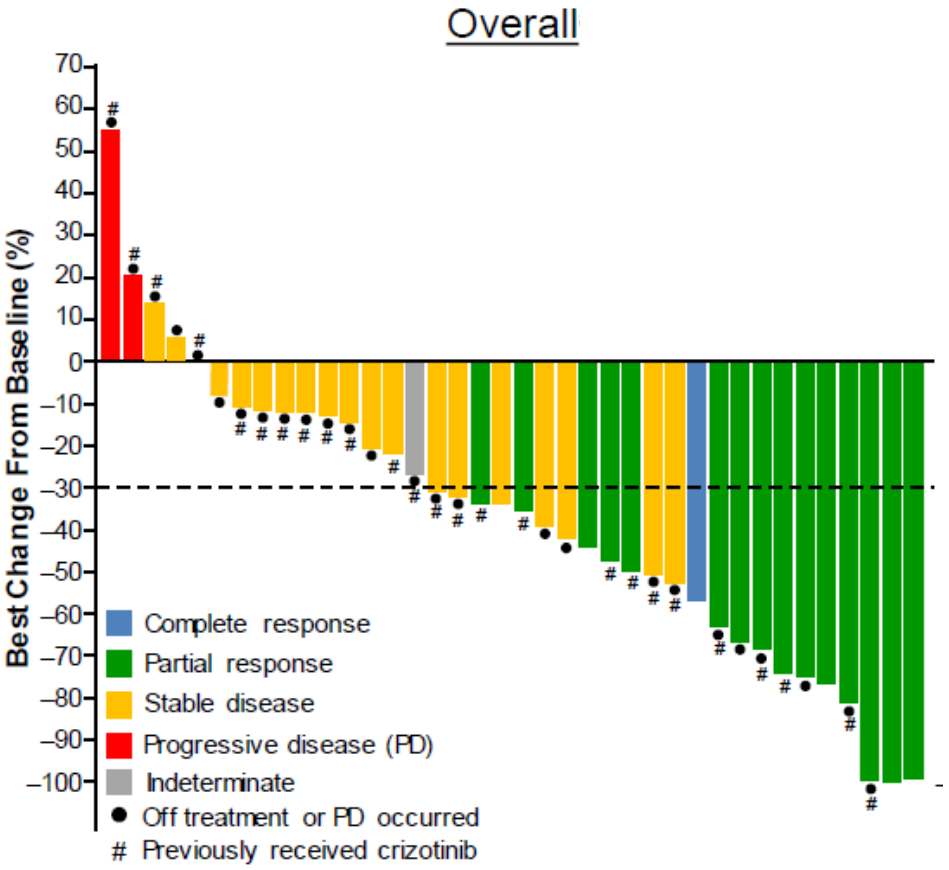
Phase 2 Study of Lorlatinib in Patients With Advanced ALK+/ROS1+ Non-Small Cell Lung Cancer

Benjamin J. Solomon,[1] Alice T. Shaw,[2] Sai-Hong I. Ou,[3] Benjamin Besse,[4] Enriqueta Felip,[5] Todd M. Bauer,[6] Ross A. Soo,[7] Alessandra Bearz,[8] Chia-Chi Lin,[9] Jill S. Clancy,[10] Antonello Abbattista,[11] Holger Thurm,[12] Gerson Peltz,[13] Elizabeth T. Masters,[14] Jean-François Martini,[12] Leonard P. James,[14] Takashi Seto[15]

[1]Peter MacCallum Cancer Centre, Melbourne, Australia; [2]Massachusetts General Hospital, Boston, MA, USA; [3]University of California Irvine, Irvine, CA, USA; [4]Gustave Roussy Cancer Campus, Villejuif, France, and Paris-Sud University, Orsay, France; [5]Vall d'Hebron Institute of Oncology, Barcelona, Spain; [6]Sarah Cannon Cancer Research Institute/Tennessee Oncology, PLLC, Nashville, TN, USA; [7]National University Hospital Singapore, Singapore; [8]National Cancer Institute, Aviano, Italy; [9]Taipei Medical University, Taipei, Taiwan; [10]Inventiv Clinical, Princeton, NJ, USA; [11]Pfizer Oncology, Milan, Italy; [12]Pfizer Oncology, La Jolla, CA, USA; [13]Pfizer Oncology, Groton, CT, USA; [14]Pfizer Oncology, New York, NY, USA; [15]National Kyushu Cancer Center, Fukuoka, Japan

IASLC 2017

Efficacy in EXP6 (ROS1+ with prior treatment)



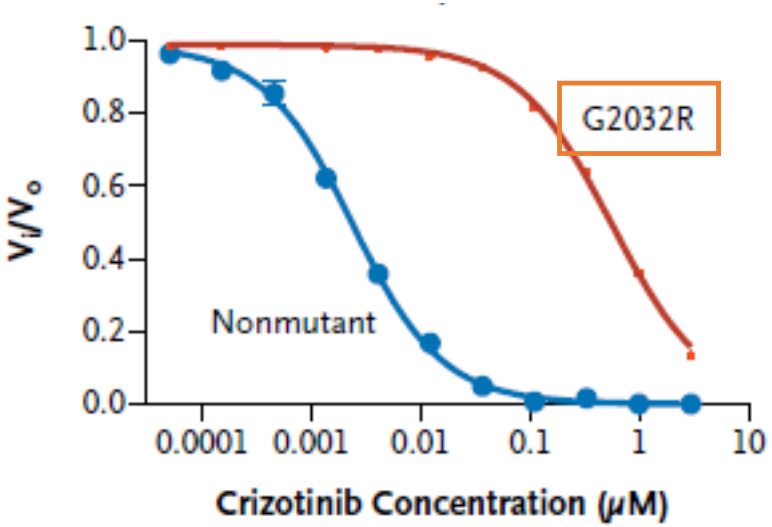
	EXP6 (n=47)
ORR, n/N (%) (95% CI)	17/47 (**36%**) (23,52)
Median DOR, mo (95% CI)	13.8 (11.1, NR)
DOR ≥ 6 mo, n^{o}/n (%)	12/17 (71)
Median PFS, mo (95% CI)	**9.6** (4.7, NR)

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

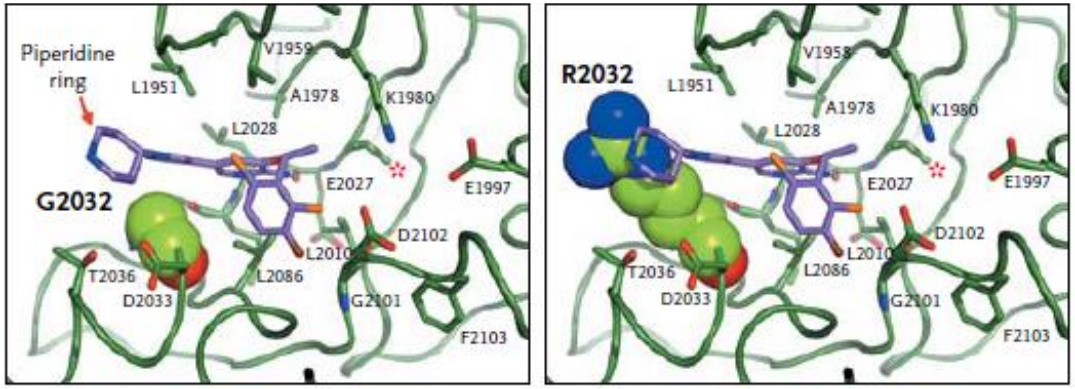
BRIEF REPORT

Acquired Resistance to Crizotinib from a Mutation in *CD74–ROS1*

ROS1 In Vitro Kinase Assay



Proposed Structural Basis for G2032R-Mediated Resistance to Crizotinib



Awad MM, et al. *N Engl J Med* 2013;368:2395-401

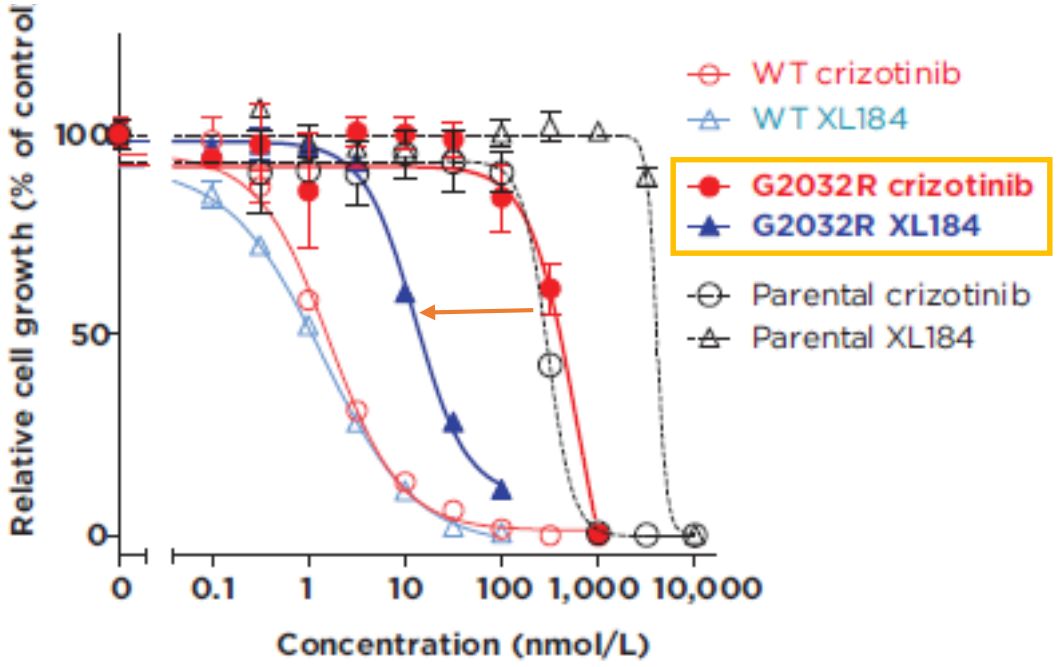
Cancer Therapy: Preclinical

Clinical Cancer Research

Cabozantinib Overcomes Crizotinib Resistance in ROS1 Fusion–Positive Cancer

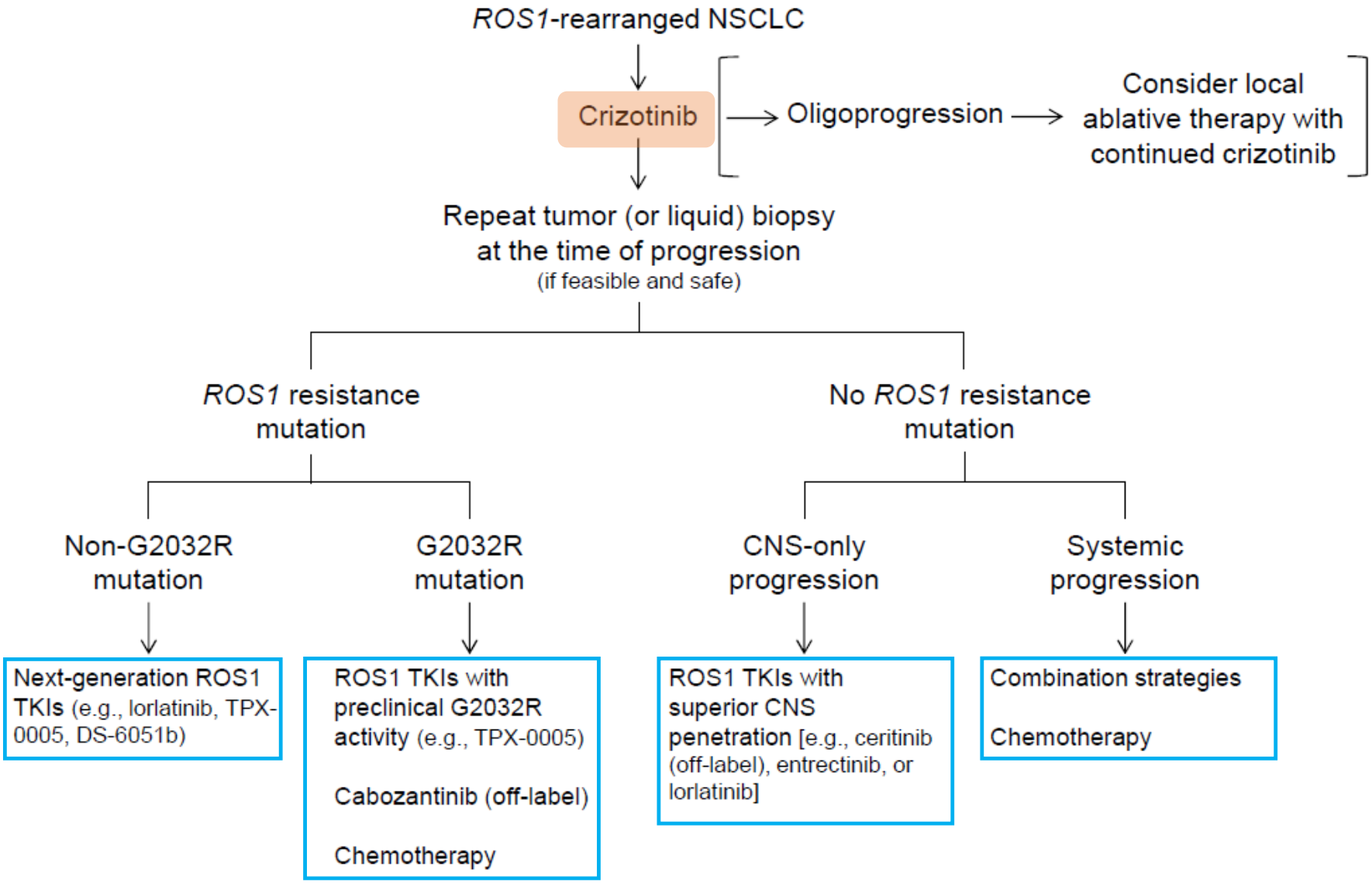
Results: We identified multiple novel crizotinib-resistance mutations in the ROS1 kinase domain, including the G2032R mutation. As the result of high-throughput drug screening, we found that the cMET/RET/VEGFR inhibitor cabozantinib (XL184) effectively inhibited the survival of CD74–ROS1 wild-type (WT) and resistant mutants harboring Ba/F3 and MGH047 cells. Furthermore, cabozantinib could overcome all the resistance by all newly identified secondary mutations.

Clin Cancer Res 2015;21(1):166-174

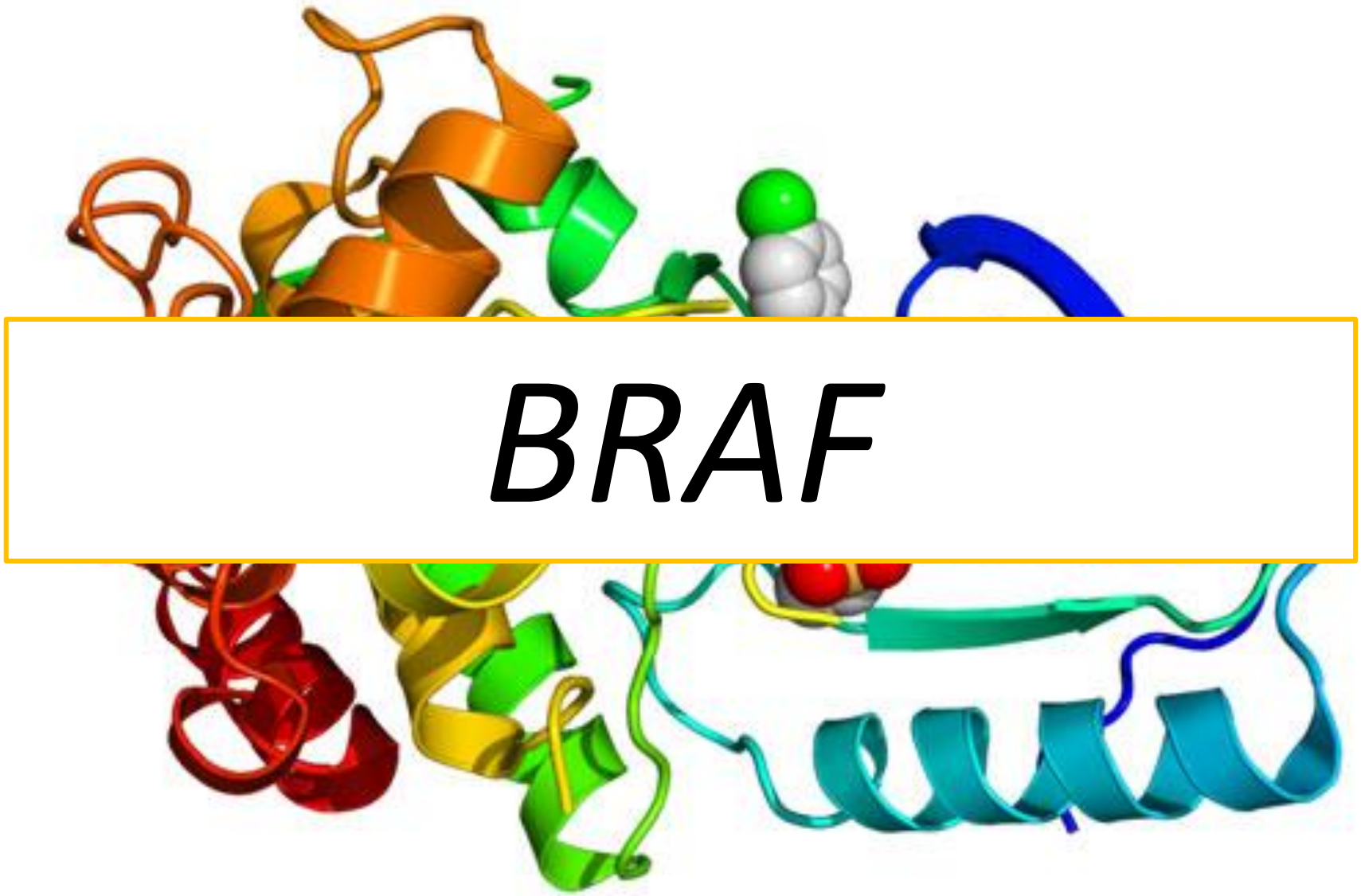


	Parental Ba/F3 (+IL3)				CD74-ROS1 WT				CD74-ROS1 (G2032R)			
	3 μmol/L	1 μmol/L	100 nmol/L	10 nmol/L	3 μmol/L	1 μmol/L	100 nmol/L	10 nmol/L	3 μmol/L	1 μmol/L	100 nmol/L	10 nmol/L
AP26113	**2.4**	**16.6**	101.6	104.7	**0.2**	**0.5**	**1.5**	**30.0**	**0.4**	**1.2**	76.5	114.8
Crizotinib	**2.5**	**5.2**	102.7	106.0	**1.4**	**1.9**	**4.4**	42.0	**2.7**	**2.3**	109.8	120.2
Ceritinib	**1.3**	74.8	104.6	103.0	**0.6**	**0.8**	**5.2**	62.1	**1.1**	**9.7**	102.2	109.3
ASP3026	69.4	96.3	110.7	100.9	**0.3**	**0.8**	**8.5**	74.9	**6.0**	58.8	101.0	110.0
SB218078	**4.1**	**5.9**	41.8	104.7	**1.3**	**1.9**	**1.9**	40.0	**2.2**	**3.1**	**28.9**	96.4
CEP701	**1.6**	**2.5**	47.3	96.6	**1.5**	**1.2**	**1.4**	**32.5**	**1.4**	**1.6**	**12.9**	97.0
TAE684	**1.6**	**8.9**	99.4	102.6	**0.3**	**0.5**	**0.9**	**10.7**	**0.5**	**0.5**	**10.1**	110.2
XL184	77.1	105.7	111.2	101.1	**0.3**	**1.0**	**1.1**	**21.2**	**0.5**	**0.6**	5.6	90.4
Foretinib	**3.3**	**2.8**	94.0	108.5	**0.5**	**0.7**	**1.7**	**32.3**	**0.7**	**0.7**	14.9	110.9

Clin Cancer Res 2015;21(1):166-174

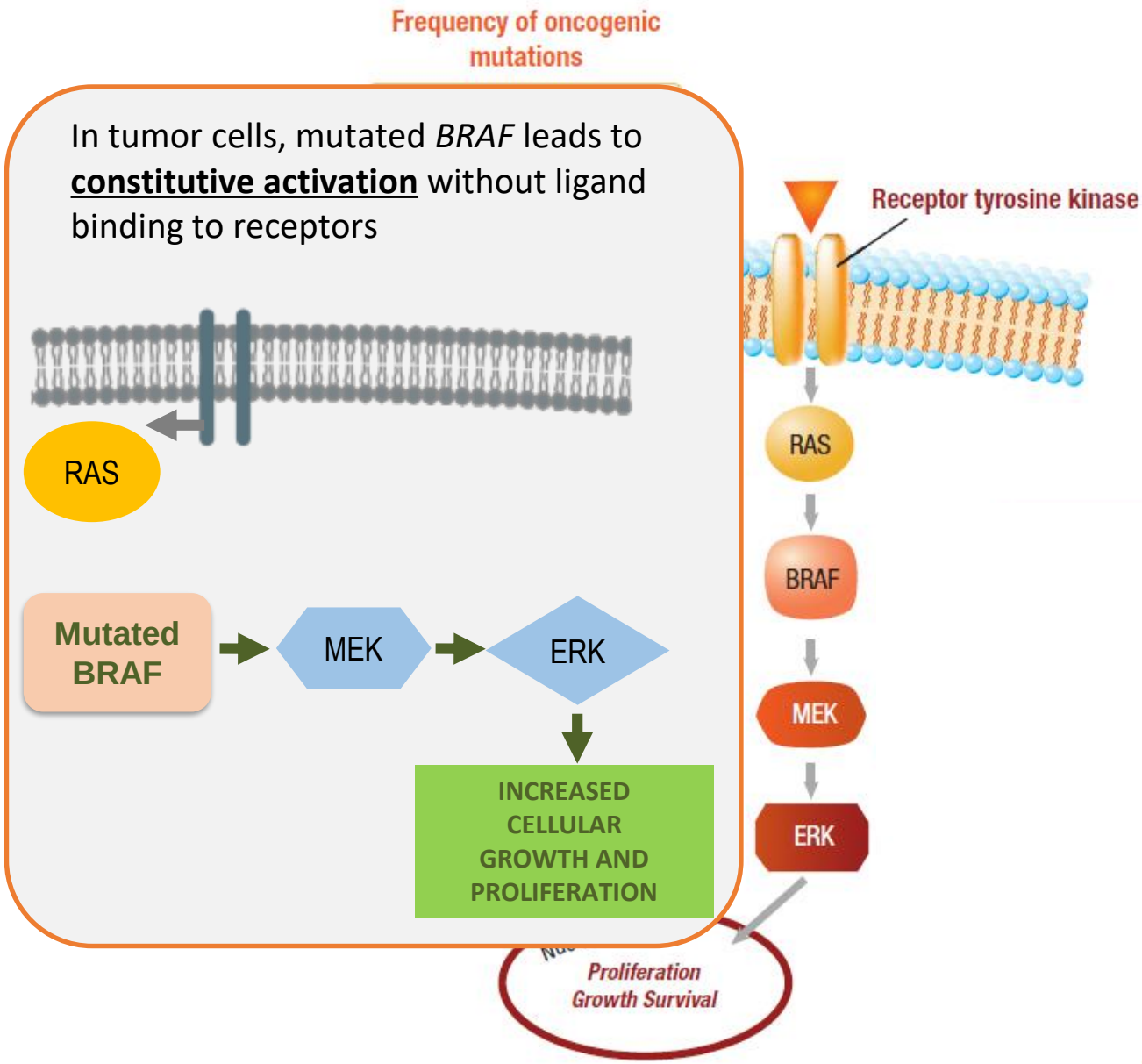


Lin JJ, et al. *J Thorac Oncol* 2017



BRAF

BRAF mutations in the context of mitogen-activated protein kinase (MAPK)

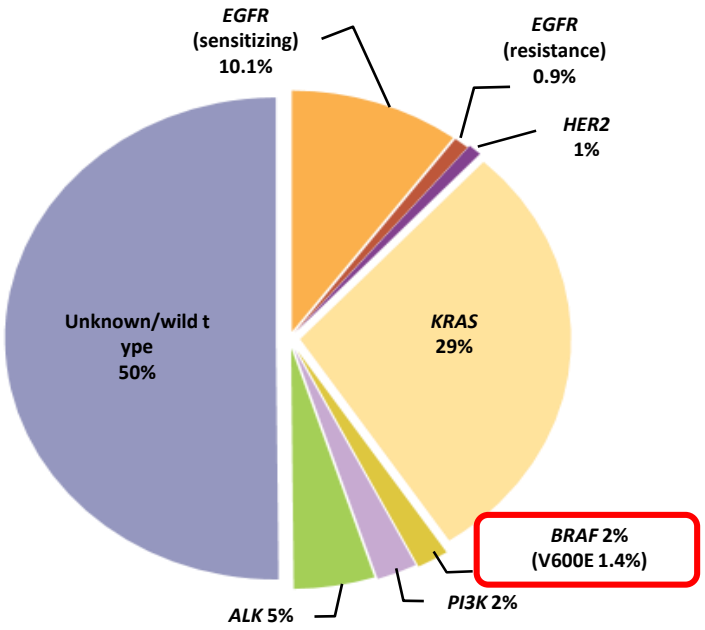


The Oncologist 2017;22:786–796

BRAF mutations in NSCLC

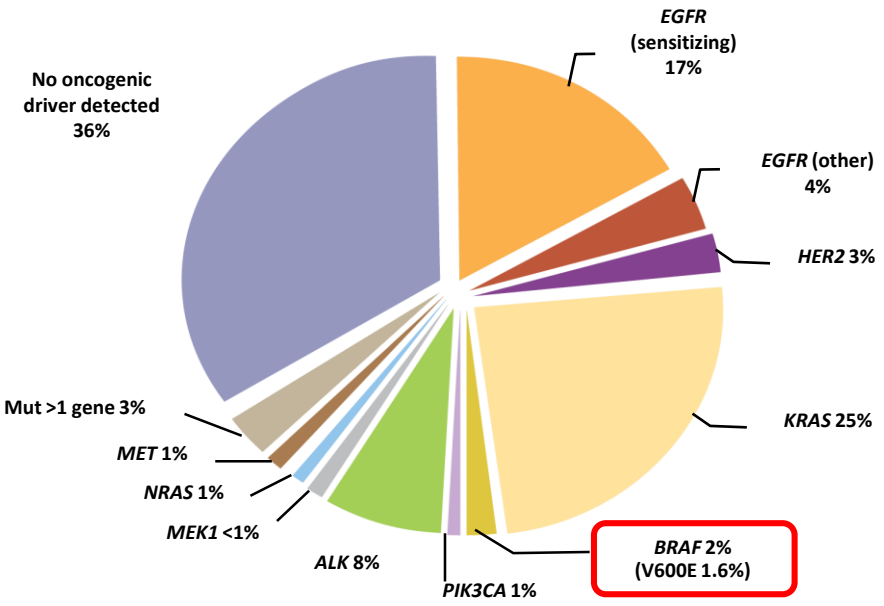
France[1]

NSCLC
(Biomarkers France [IFCT])
(N = 17,664)



US[2]

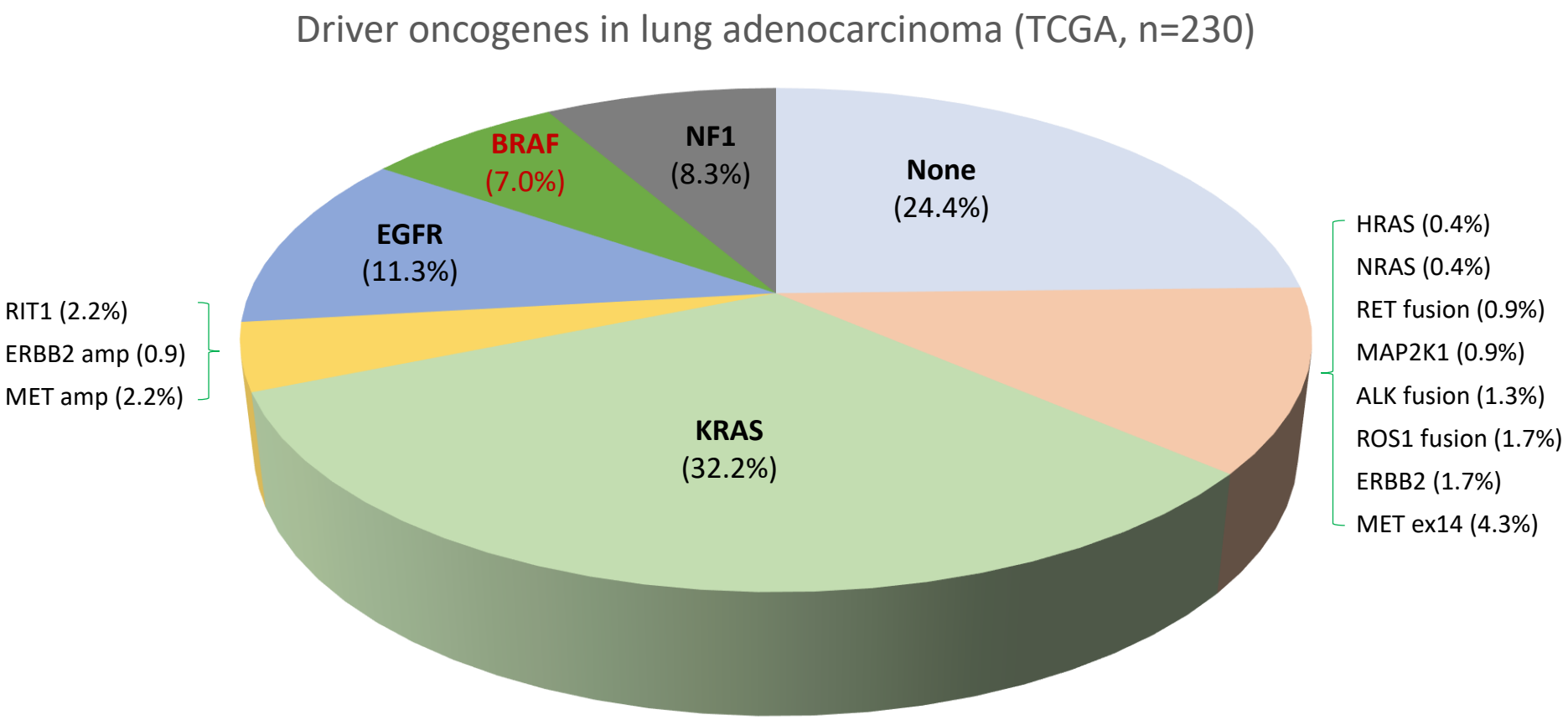
Adenocarcinoma
(Lung Cancer Mutation Consortium)
(N = 733)



- NSCLC with *BRAF* V600E mutations has histological features suggestive of an aggressive tumor
- Patients with *BRAF* V600E–mutant NSCLC demonstrated less-favorable outcomes with platinum-based chemotherapy

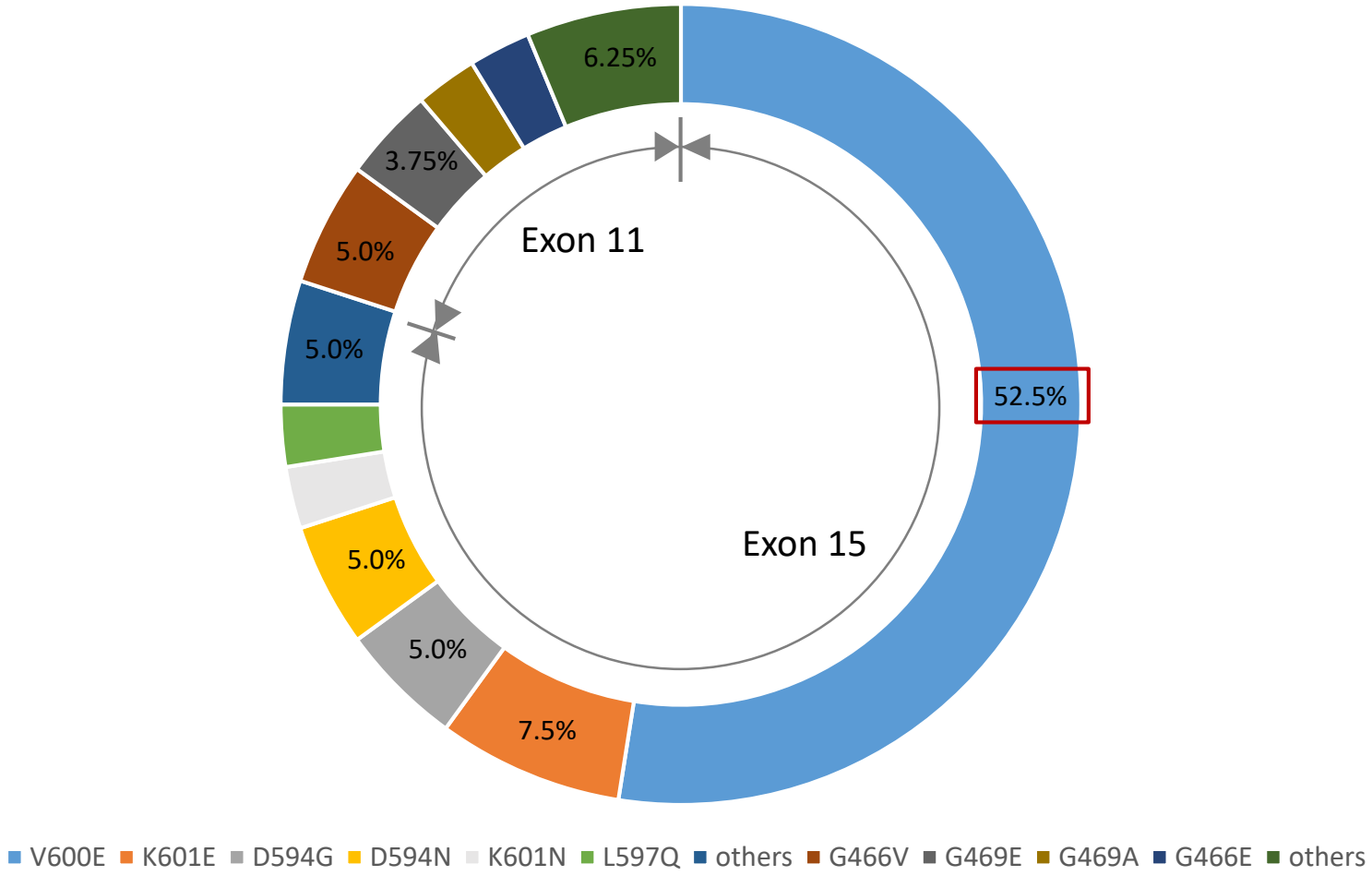
1. Barlesi F, et al. *Lancet.* 2016;387:1415-1426; 2. Kris MG, Johnson BE, et al. *JAMA*. 2014;311(19):1998-2006

Prevalence (2-4%)



Nature 2014;511:543–550

Frequency of V600E (1-2%)



Lung Cancer 2016;91:23-28

Comparison of available tests for BRAF mutations

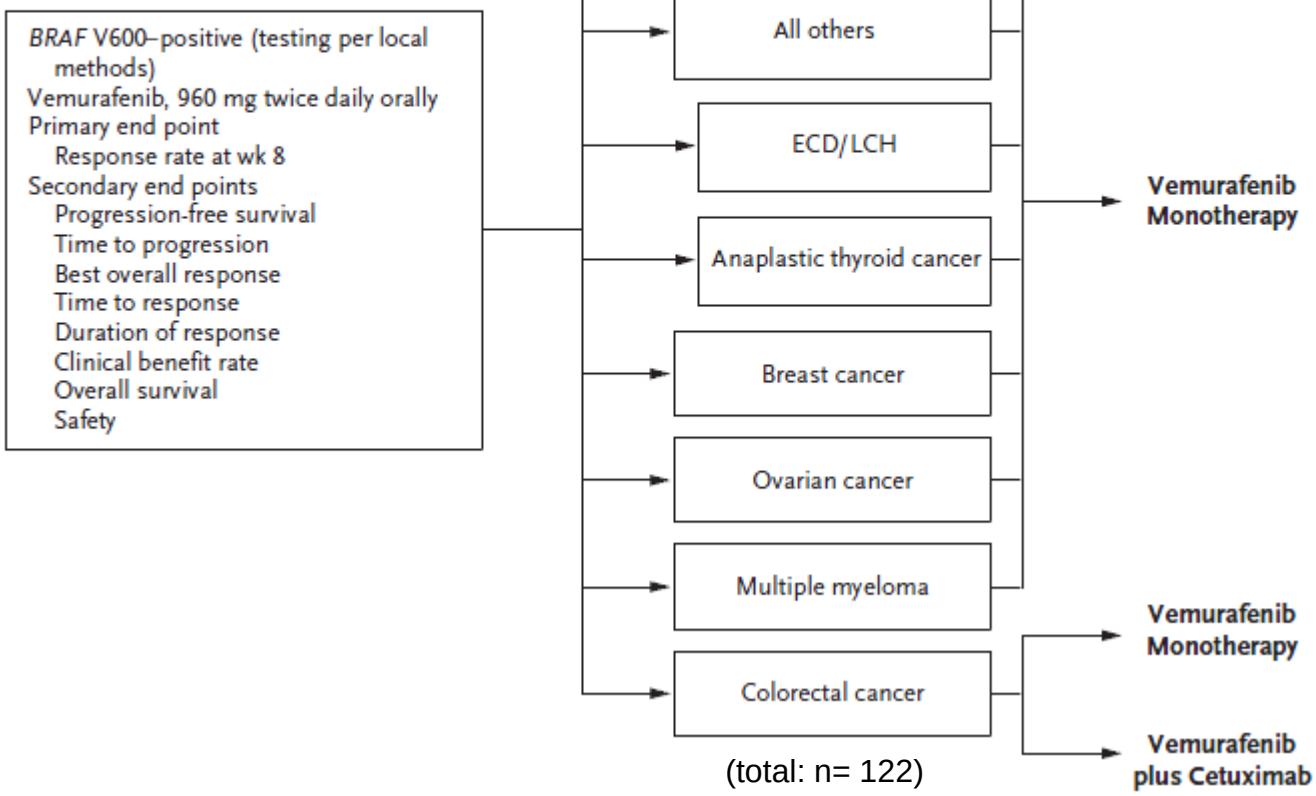
	THxID™-BRAF Kit[1,2]	cobas® 4800 BRAF V600 Mutation Test[3-5]	Sanger sequencing[3]	HRM Analysis[3]	Pyro-sequencing[3]	NGS[3]	IHC[3]
Sensitivity	96.3% for V600E and 92.2% for V600K	97.3% for V600E and 62.9% for V600K	98%	98%	> 98%	98.6%	97%-100%
Specificity	100%	98.3%	100%	100%	90%	100%	98%
Limit of detection	5% for V600E and V600K	5%-7% for V600E; 35% for V600K	6.6%	6.6%	5%	2%	5%
Mutations detected	Approved for V600E and V600K	Approved for V600E only	99% of all mutations detectable	99% of all mutations detectable	Optimized for V600E	Multiplex detection of mutations	Antibody specific for V600E
Costs[a]	Medium	Medium	Medium	Low	High	Very high	Low

1. Marchant J, et al. *BMC Cancer.* 2014;14(519):1-9; 2. THxID™-BRAF [package insert]. Marcy-l'Etoile, France: bioMérieux; 2013; 3. Ihle MA, et al. *BMC Cancer.* 2014;14(13):1-13; 4. cobas® 4800 BRAF V600 Mutation Test [package insert]. Branchburg, NJ: Roche Molecular Systems; 2011; 5. Qu K, et al. *J Mol Diag.* 2013;15(6):790-795.

Vemurafenib in Multiple Nonmelanoma Cancers with *BRAF* V600 Mutations

Study Design and Cohorts

- Phase 2 “basket trial”
- Primary end point: response rate



Hyman DM, et al. *N Engl J Med* 2015;373:726-36

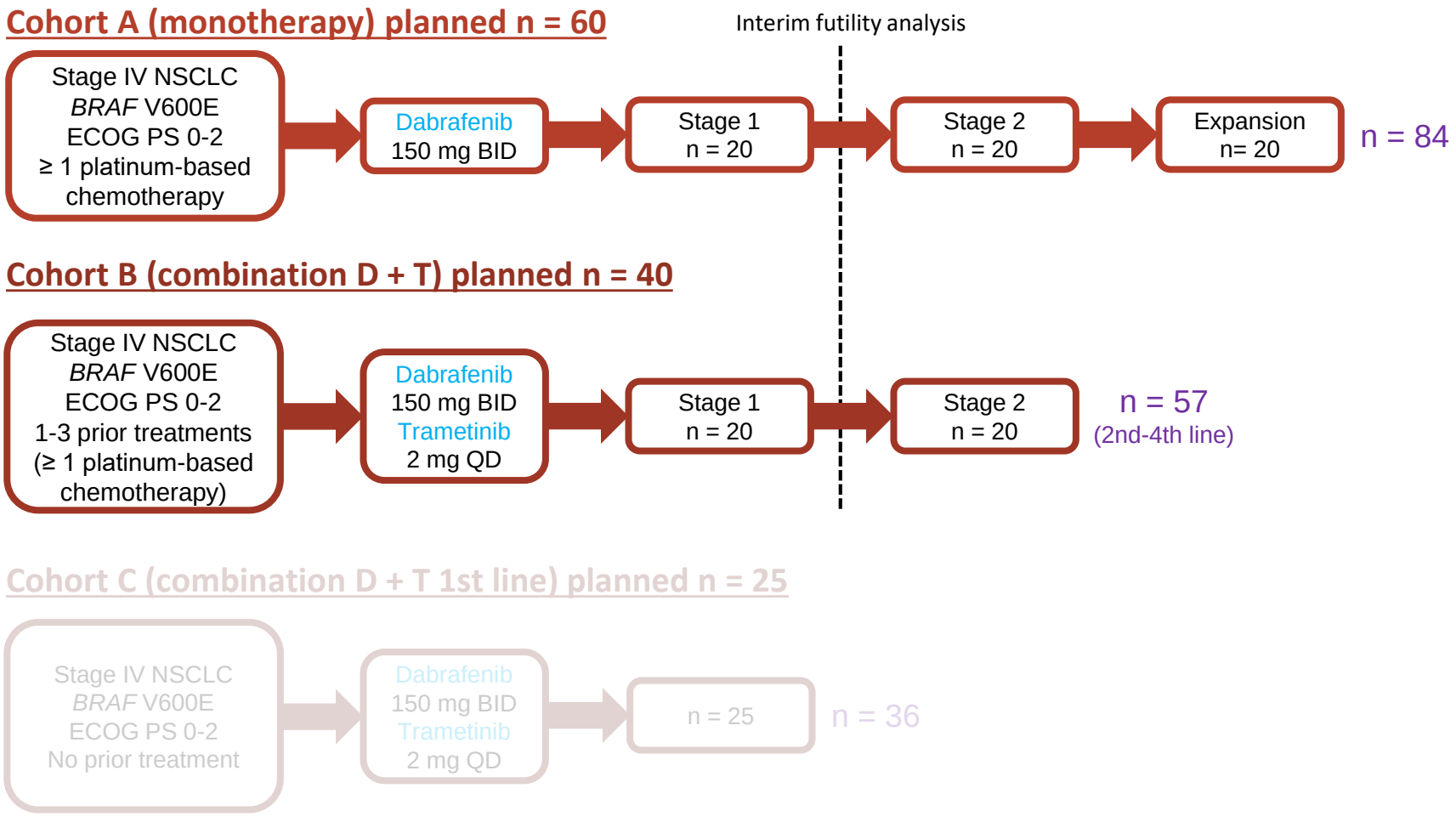
Preliminary Best Response According to Cohort

Variable	NSCLC (n=20)
Patients with ≥ 1 postbaseline assessment - no.	19
Complete response - no. (%)	0
Partial response - no. (%)	8 (42)
Stable disease - no. (%)	8 (42)
Progressive disease - no. (%)	2 (11)
Missing data - no. (%)	1 (5)
Overall response - no. (%) [95% CI]	8 (42) [20-67]

<mPFS = 7.3 months>

Hyman DM, et al. *N Engl J Med* 2015;373:726-36

BRF113928 (NCT01336634): study design

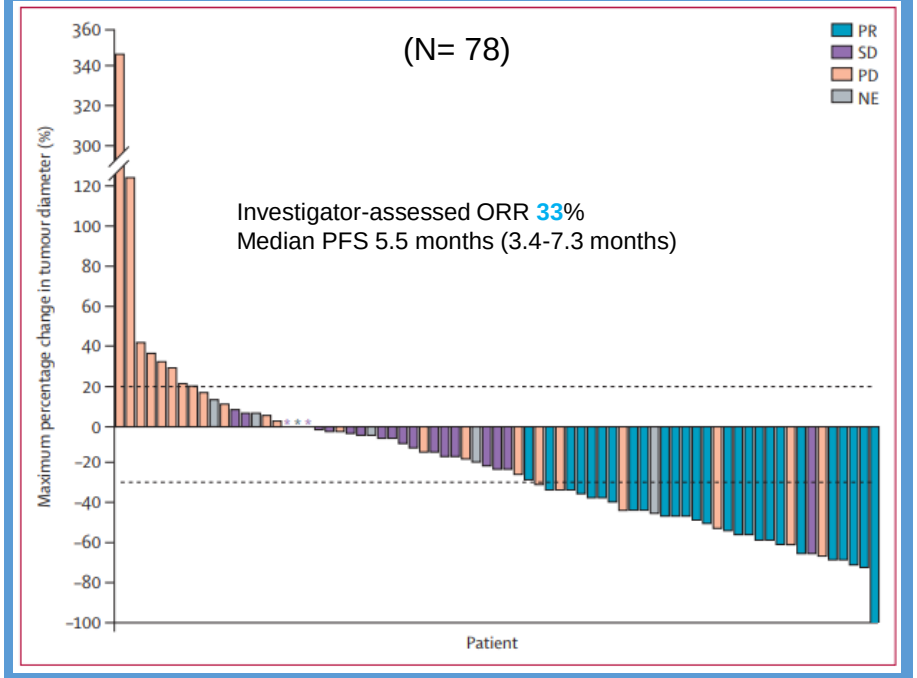


- Primary endpoint for each cohort: **investigator-assessed overall response rate**
- Secondary endpoints: duration of response, progression free survival, overall survival, and safety

Planchard et al. ASCO 2017

THE LANCET Oncology

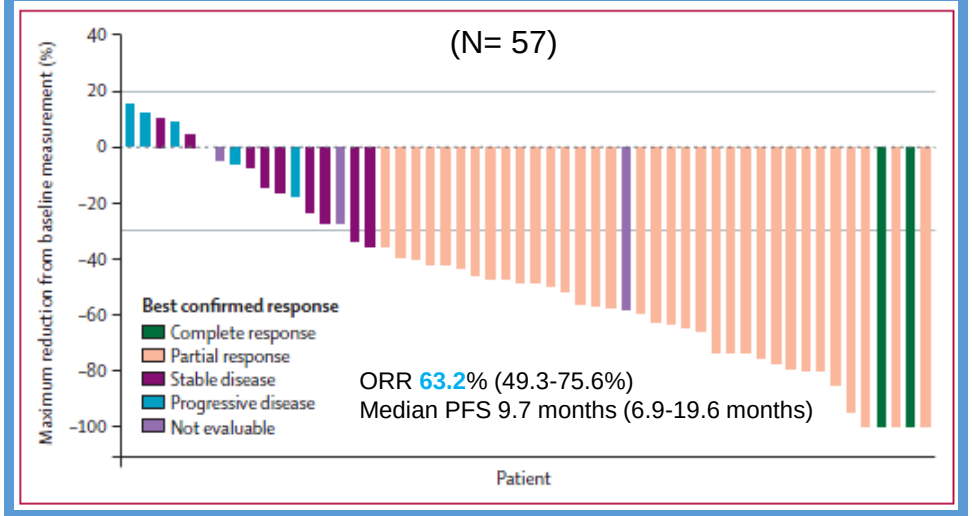
Dabrafenib in patients with *BRAF*^{V600E}-positive advanced non-small-cell lung cancer: a single-arm, multicentre, open-label, phase 2 trial



Planchard D, et al. *Lancet Oncol* 2016;17:642-50

Dabrafenib plus trametinib in patients with previously treated *BRAF*^{V600E}-mutant metastatic non-small cell lung cancer: an open-label, multicentre phase 2 trial

1st - 3rd line failure, *BRAF*600E-mutant NSCLC



Planchard D, et al. *Lancet Oncol* 2016;17:948-93

Clinical activity of targeted therapy in BRAF-mutant metastatic non-small cell lung cancer

Clinical activity	Vemurafenib	Dabrafenib	Dabrafenib + trametinib
Overall response rate, %	42	33	63
Median PFS, months	7.3	5.5	9.7

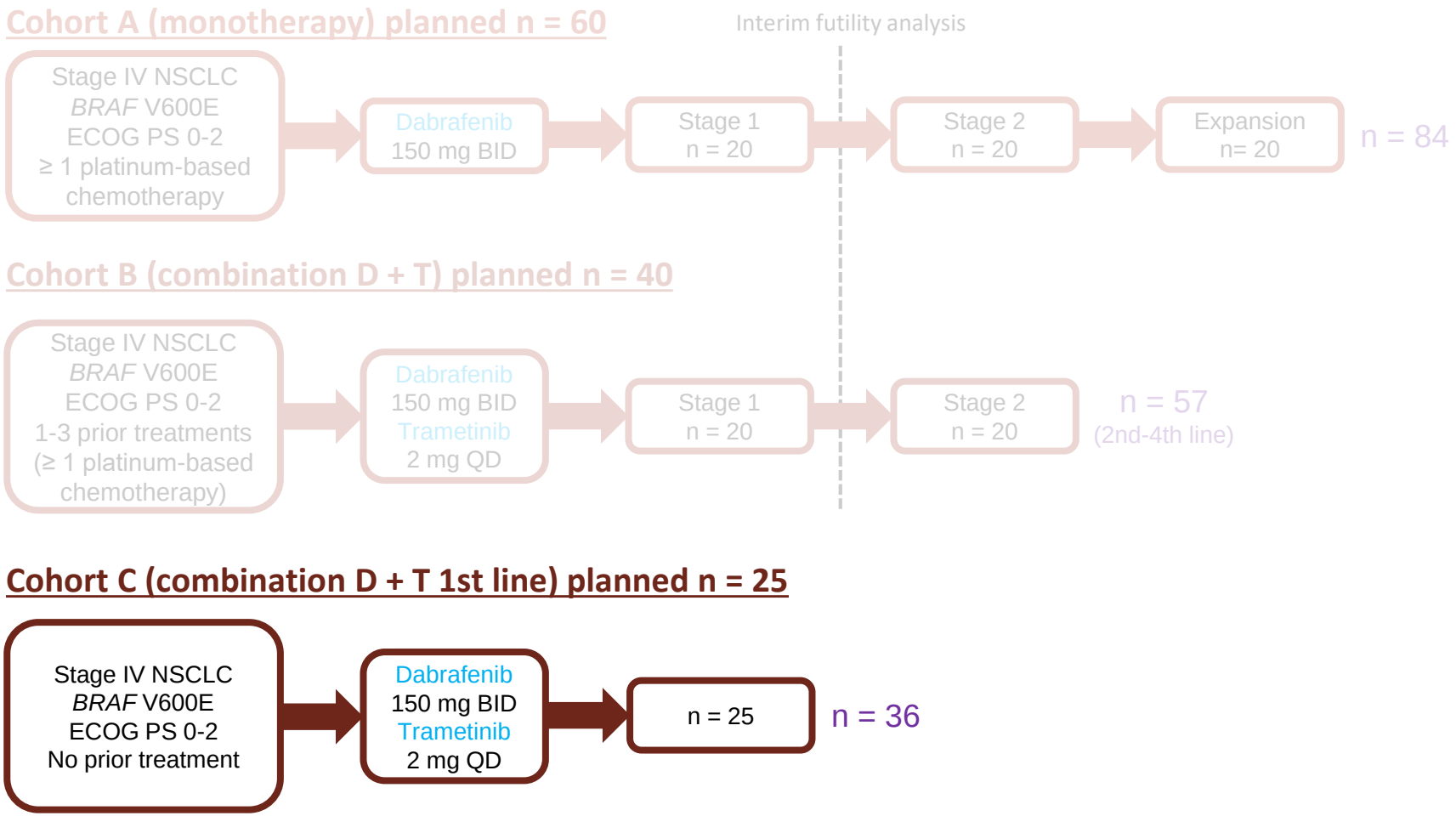
Common grade 3/4 adverse events with vemurafenib, dabrafenib, and dabrafenib plus trametinib

Adverse events, *n* (%)	Vemurafenib (*n* = 20)	Dabrafenib (*n* = 84)	Dabrafenib + trametinib (*n* = 57)
Neutropenia	—	—	5 (9)
Hyponatremia	—	2 (2)	4 (7)
Anemia	—	2 (2)	3 (5)
Asthenia	—	4 (5)	2 (4)
Dyspnea	3 (15)	2 (2)	2 (4)
Hypertension	3 (15)	1 (1)	2 (4)
Squamous cell carcinoma	7 (35)	10 (12)	2 (4)
Basal-cell carcinoma	—	4 (5)	1 (2)
Fatigue	4 (20)[a]	1 (1)	1 (2)
Hypophosphatemia	—	3 (4)	1 (2)
Pyrexia	0	2 (2)	1 (2)
Anxiety	—	2 (2)	—
Decreased appetite	2 (10)	1 (1)	0
Headache	—	2 (2)	0
Palmar-plantar erythrodysesthesia syndrome	—	2 (2)	—
White blood cell count increased	—	2 (2)	—

[a]Includes fatigue, asthenia, and cachexia.
Abbreviation: —, not reported.

The Oncologist 2017;22:786–796

BRF113928 (NCT01336634): study design

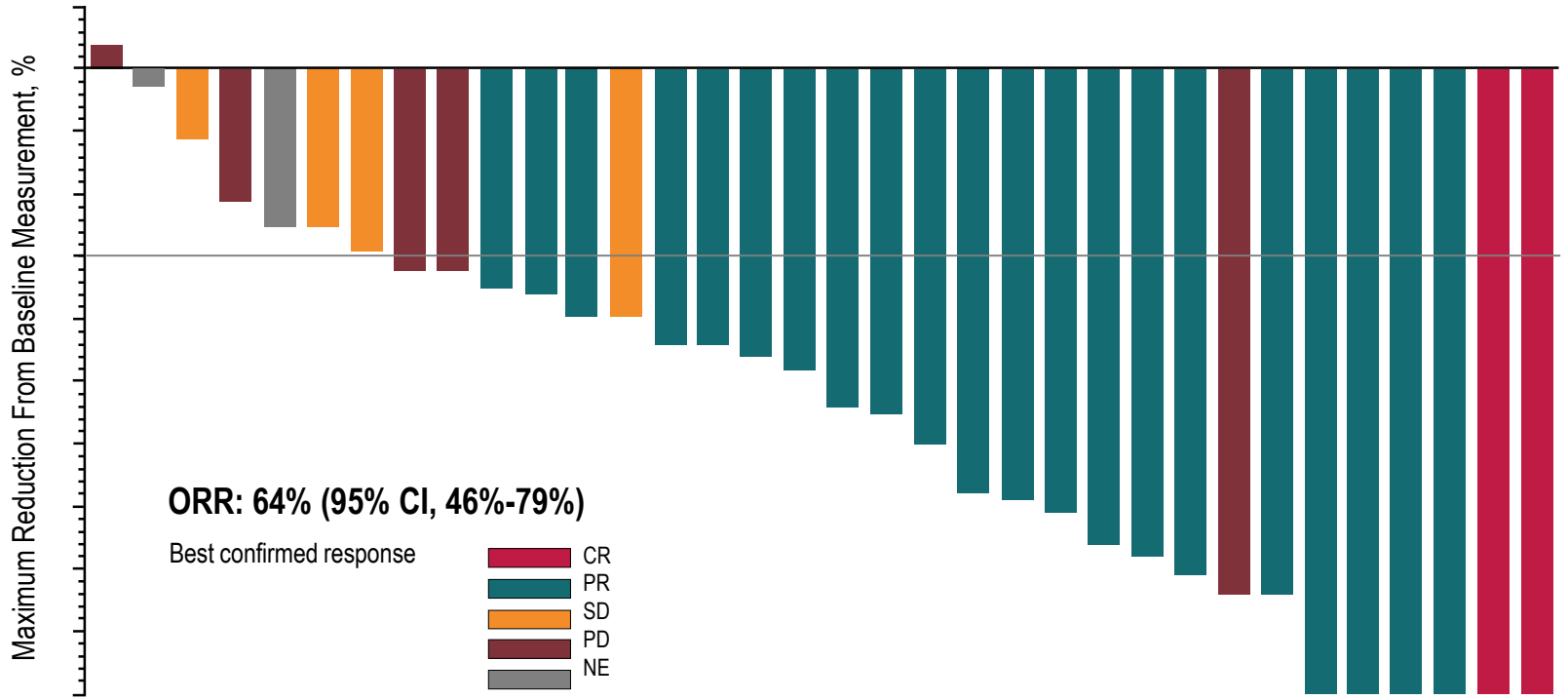


- Primary endpoint for each cohort: **investigator-assessed overall response rate**
- Secondary endpoints: duration of response, progression free survival, overall survival, and safety

Planchard et al. ASCO 2017

Dabrafenib plus trametinib in patients with previously untreated *BRAF*^{V600E}-mutant metastatic non-small-cell lung cancer: an open-label, phase 2 trial

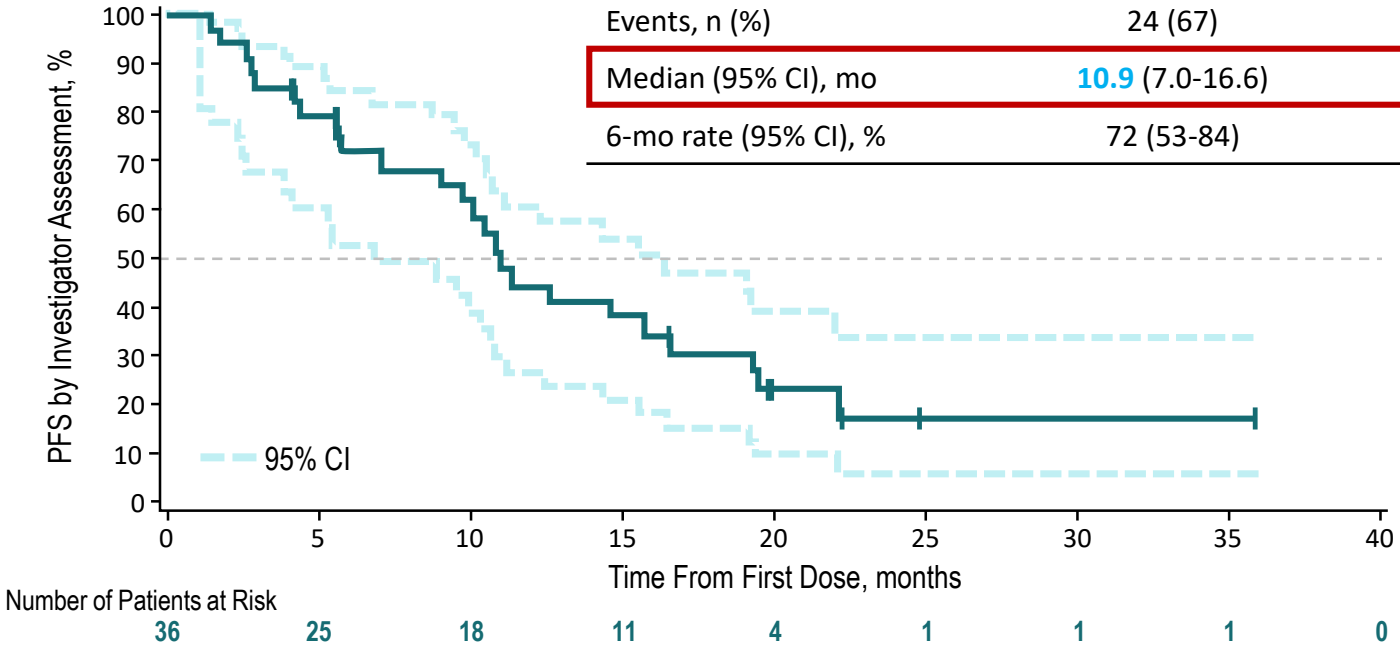
Investigator-assessed maximum change in target lesion by best response



Planchard D, et al. *Lancet Oncol* 2017;18:1307-16

BRF113928 cohort C: Progression-free survival

	Investigator Assessed (n = 36)	IRC Assessed (n = 36)
Events, n (%)	24 (67)	22 (61)
Median (95% CI), mo	**10.9** (7.0-16.6)	14.6 (7.0-22.1)
6-mo rate (95% CI), %	72 (53-84)	69 (51-82)



Planchard D, et al. *Lancet Oncol* 2017;18:1307-16

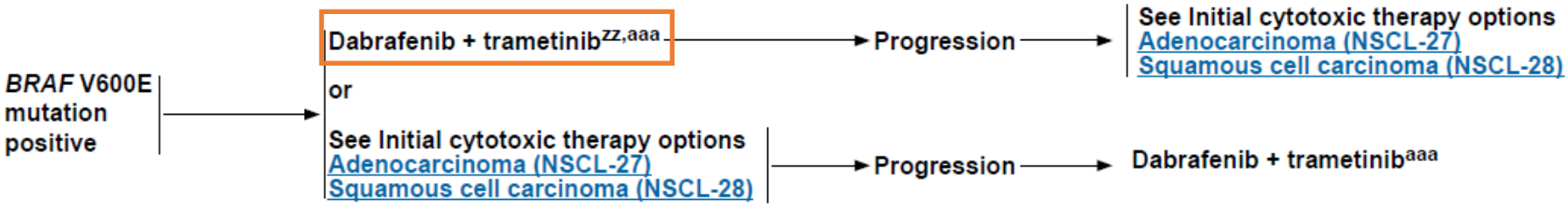
New Treatments Available in United States for BRAF-Mutated NSCLC

On 22 June 2017, the United States Food and Drug Administration (FDA) granted approval to the combination of the BRAF and MEK inhibitors dabrafenib and trametinib (Tafinlar® and Mekinist®, Novartis) for patients with metastatic non-small cell lung cancer (NSCLC) harboring *BRAF V6000E* mutation detected by an FDA approved test.

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2018
Non-Small Cell Lung Cancer

BRAF V600E MUTATION POSITIVE[hh]



Trials evaluating targeted therapies in BRAF-mutant NSCLC

Agent(s)	Mechanism of action	Development phase	Sponsor	ClinicalTrials.gov identifier
Dabrafenib + trametinib	BRAF + MEK inhibitor	Phase II	Novartis	NCT01336634
Vemurafenib	BRAF inhibitor	Phase II	Genentech	NCT01524978
Selumetinib	MEK inhibitor	Phase II	National Cancer Institute	NCT01306045
Binimetinib	MEK inhibitor	Phase II	Novartis	NCT02276027
PLX8394	BRAF inhibitor (paradox breaker)	Phase I/II	Plexxikon	NCT02428712
RXDX-105	BRAF, RET, CSF-1 inhibitor	Phase I/Ib	Ignyta	NCT01877811
LXH254 + LTT462	Pan-RAF inhibitor + ERK inhibitor	Phase Ib	Novartis	NCT02974725
AUY922	Heat shock protein 90 inhibitor	Phase II	National Taiwan University Hospital	NCT01922583
Regorafenib	Multikinase inhibitor	Phase II	Sarah Cannon Research Institute Development Innovations, LLC	NCT02795156

Abbreviations: *BRAF*, B-Raf proto-oncogene, serine/threonine kinase; CSF-1, colony stimulating factor 1; ERK, extracellular signal-regulated kinase; MEK, mitogen-activated protein kinase kinase.

The Oncologist 2017;22:786–796

`라핀나 매큐셀`, BRAF표적 폐암치료제로 국내 승인

치료 전력이 없는 변이 양성 전이성 비소세포폐암 환자에서 반응률 64%

2018-03-14 16:42

한국노바티스는 자사의 흑색종 치료제 `라핀나(성분명: 다브라페닙메실산염)`와 `매큐셀(성분명: 트라메티닙디메틸설폭시드)`을 병용한 치료제 `라핀나 매큐셀`이 지난 12일 BRAF V600E 유전자 변이 양성 전이성 비소세포폐암치료제로서 식품의약품안전처의 승인을 획득했다.

라핀나 매큐셀 병용요법은 BRAF V600E변이가 확인된 수술이 불가능하거나 전이성인 흑색종 환자의 치료제로 지난해 12월11일 국내에 출시된 바 있으나, 이번 승인으로 BRAF V600E 변이 양성 전이성 비소세포폐암 환자 치료에도 사용이 가능하게 됐다.

BRAF변이는 전 세계 비소세포폐암 환자들 중 약 1~3%에서 발견되는데, 공격적이고 환자의 예후를 악화시킬 수 있기 때문에 신속한 치료가 중요한 것으로 알려져 있다.

라핀나 매큐셀 병용요법의 적응증 확대 승인은 BRAF V600E 변이 양성 비소세포폐암 환자를 대상으로 한 글로벌2상 임상에 기반해 이뤄졌다. 연구에 참여한 환자는 3개의 환자군(Cohort)으로 분류됐으며 라핀나 단독요법 치료군(Cohort A)과 라핀나 매큐셀 병용요법 군으로 구분됐다.

Summary

- Next-generation tyrosine kinase inhibitors (TKIs) have shown increased response rates and progression-free survival compared with first-generation TKIs in *EGFR*-mutated and *ALK*-rearranged NSCLC.

- However, because of the lack of overall survival data, definitive conclusions concerning the best treatment sequence can not yet be drawn in especially *EGFR*-mutated NSCLC.

- Emerging oncogenes such as rearranged *ROS1* and mutant *BRAF* (V600E) have joined the list of targetable drivers.

- Optimal therapeutic combinations to overcome the resistance and treatment sequence represent the toughest upcoming challenges in the domain of targeted therapy.

Thank you for your attention!!