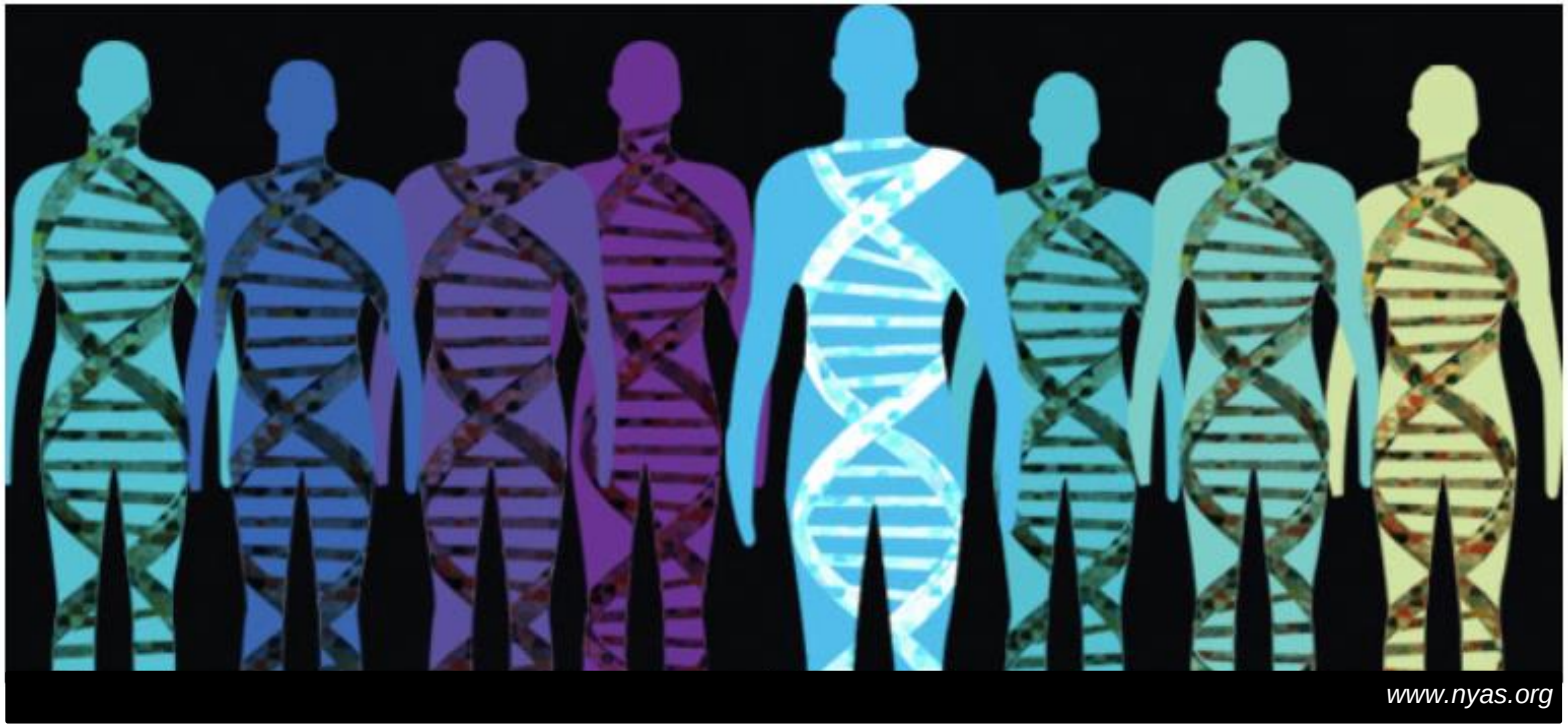
Advances in Targeted Therapies for Lung Cancer



Alice T. Shaw, MD PhD

March 11, 2016

Overview

- Introduction to Lung Cancer
- First Generation Targeted Therapies
- Second Generation Targeted Therapies
- Evolution of Resistance
- Summary and Future Directions

Overview

- **Introduction to Lung Cancer**
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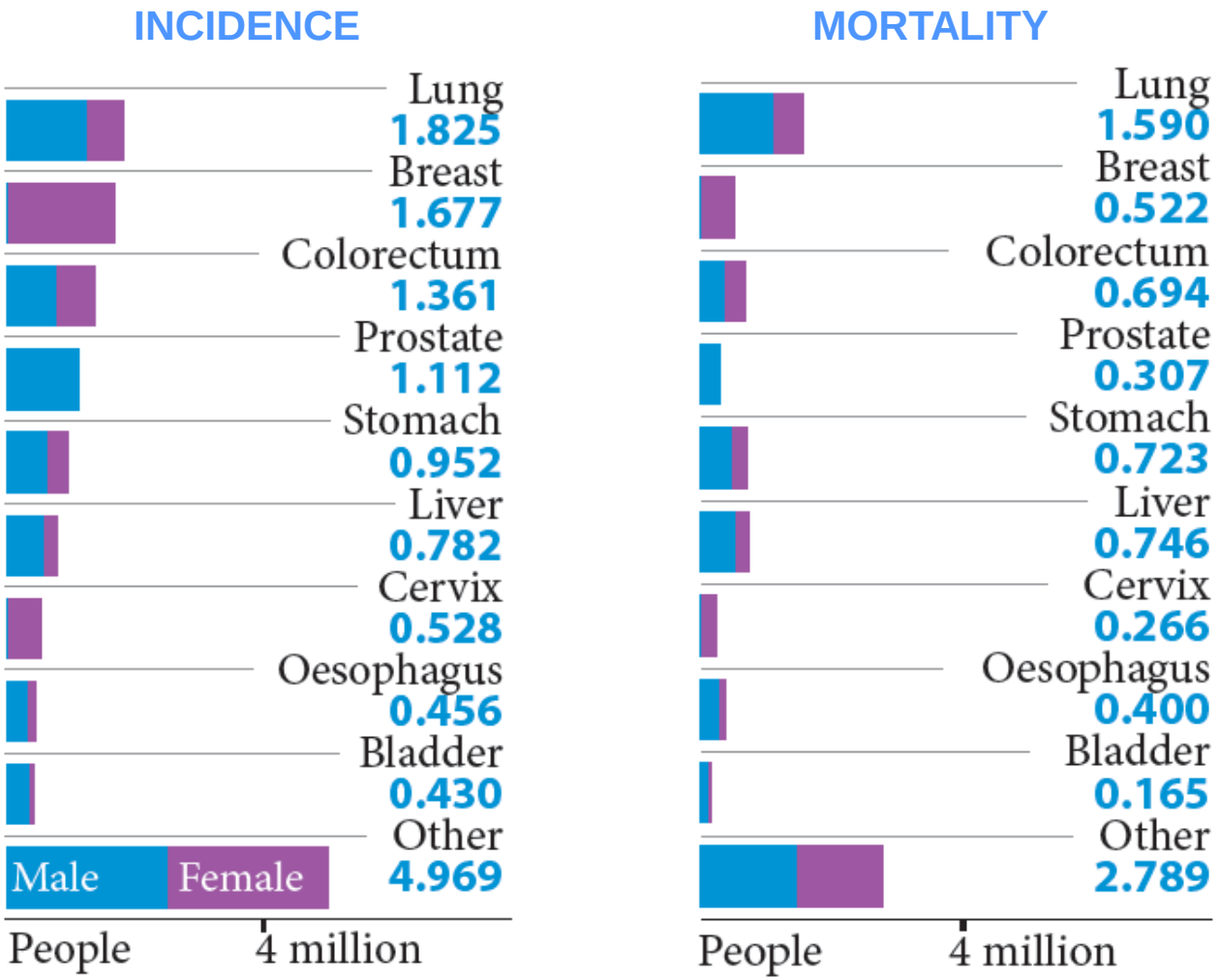
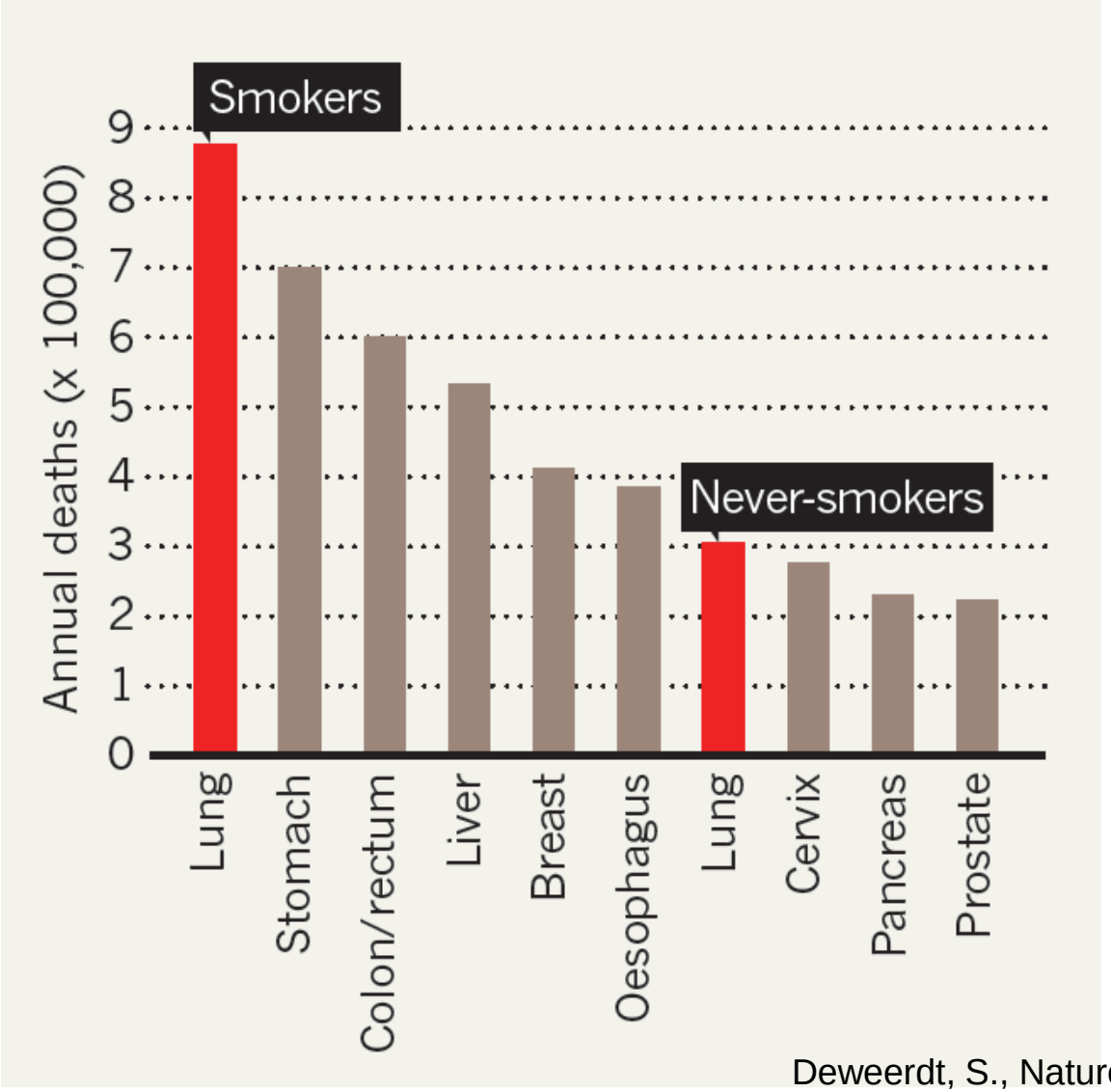
Lung Cancer is the Leading Cause of Cancer Deaths Worldwide



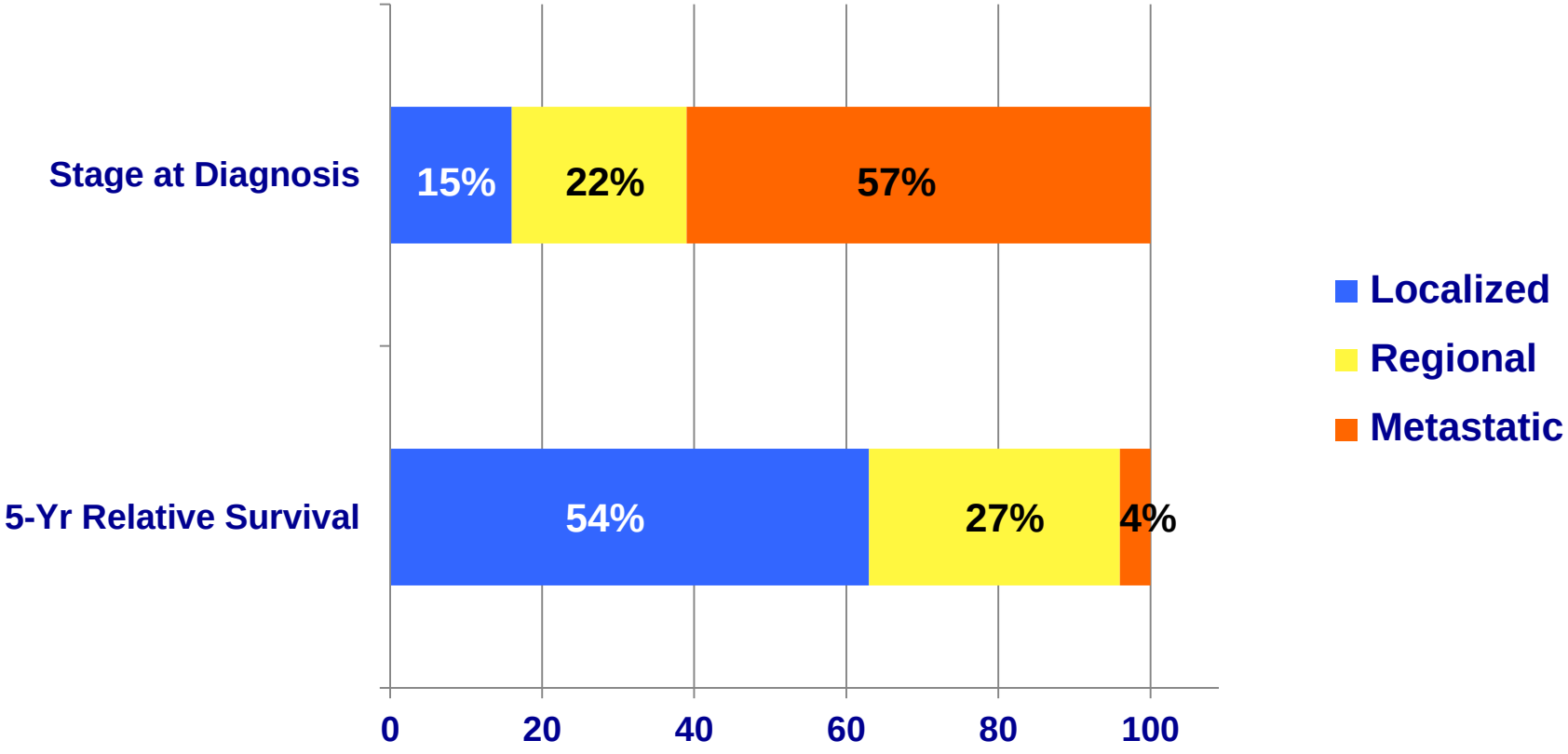
WHO IARC, January 2014

Lung Cancer Occurs in Never Smokers



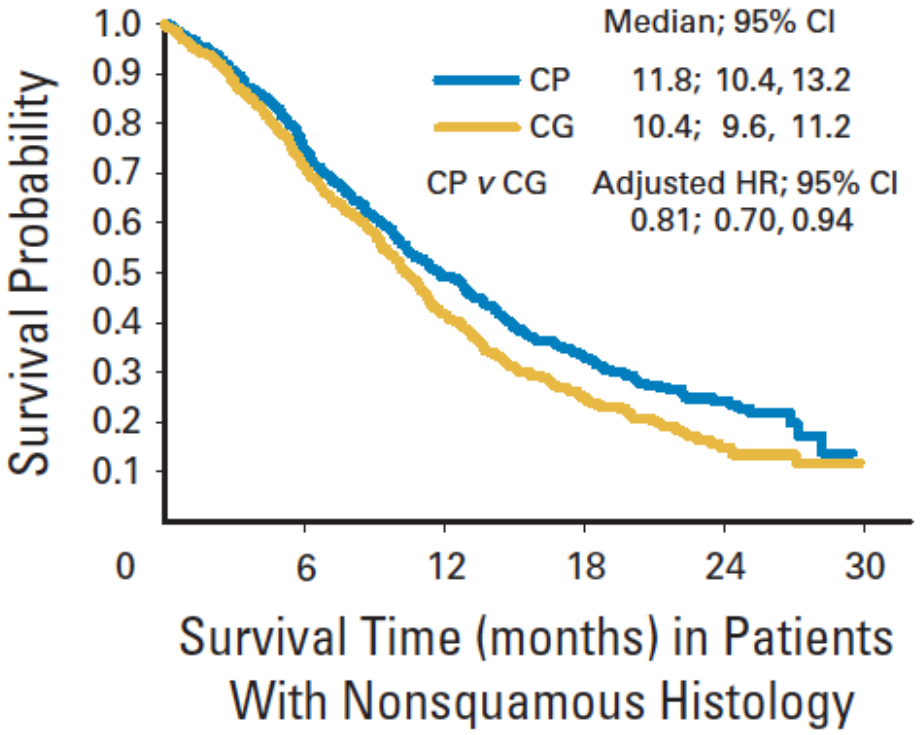
Deweerdt, S., Nature 513: S12-3, 2014

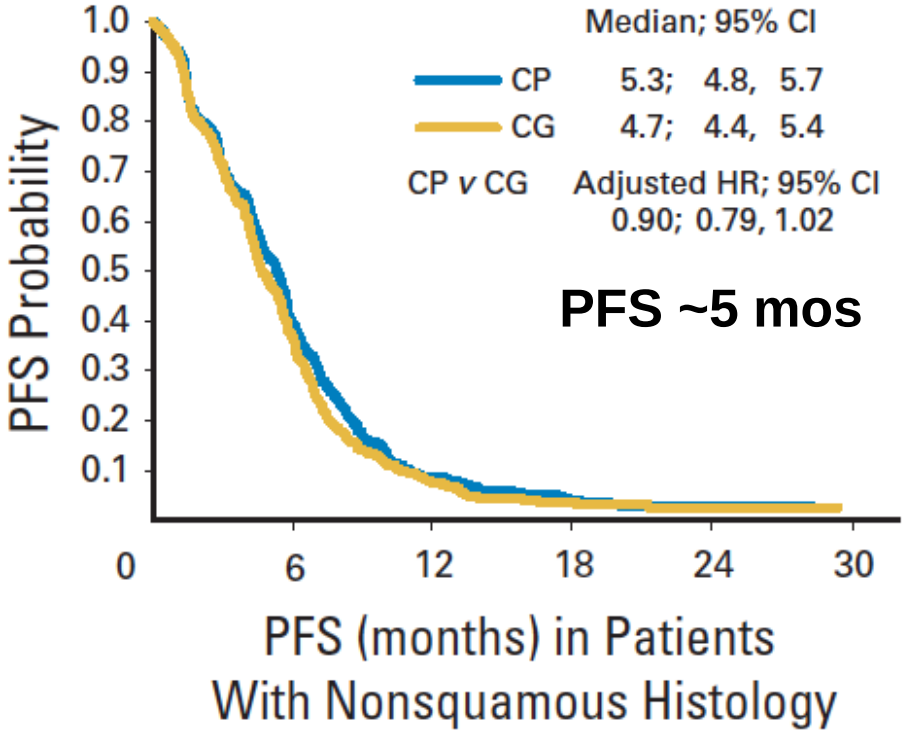
Lung Cancer Is Often Diagnosed at an Advanced Incurable Stage



2004-2010, SEER Cancer Statistics Review

Standard Chemotherapy Provides Modest Benefit in Lung Cancer

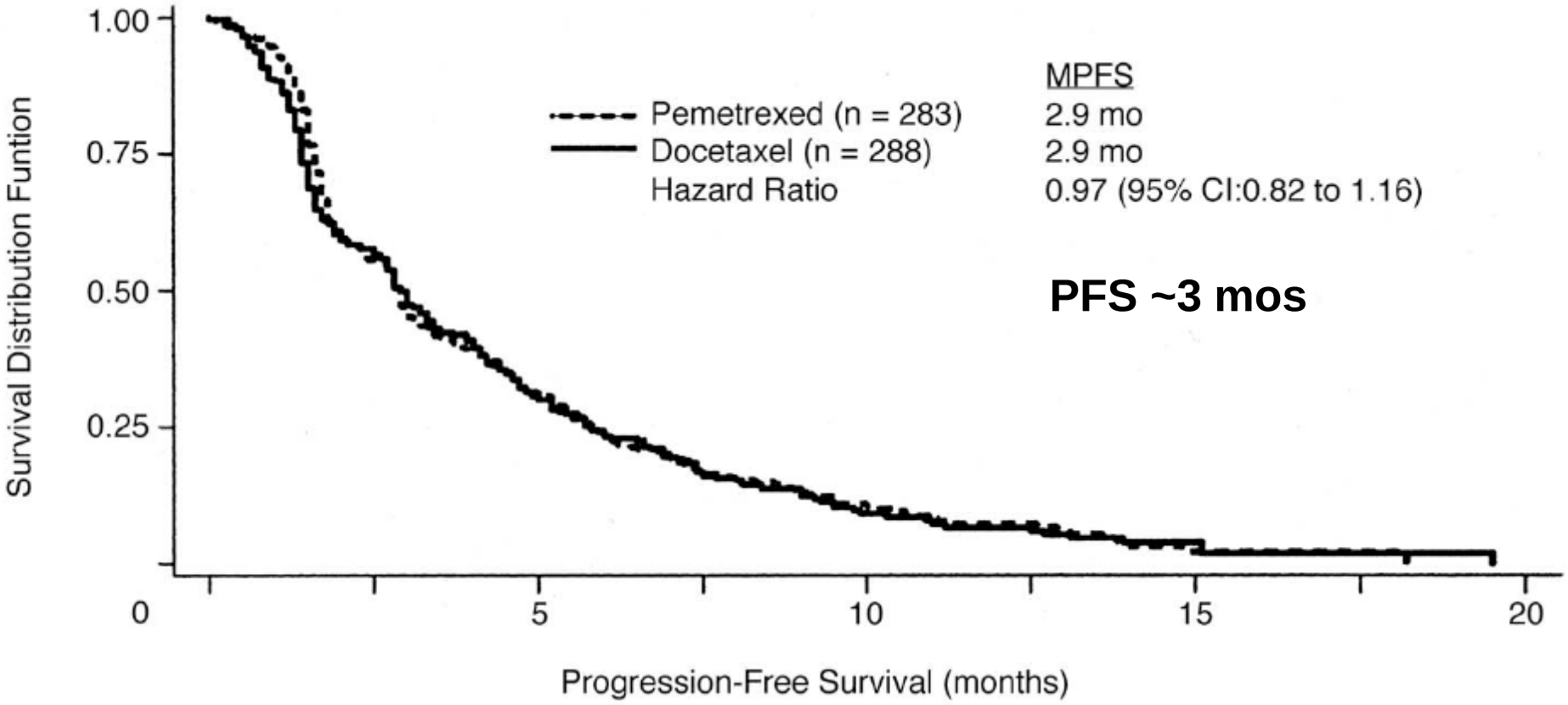




Overall survival ~12 mos

Scagliotti et al., JCO 26(21): 3543-3551, 2008

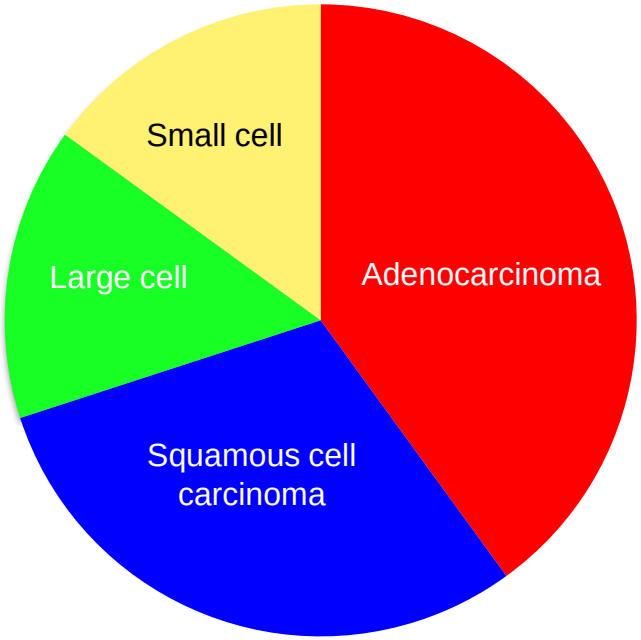
Limited Benefit of Second-Line Chemotherapy



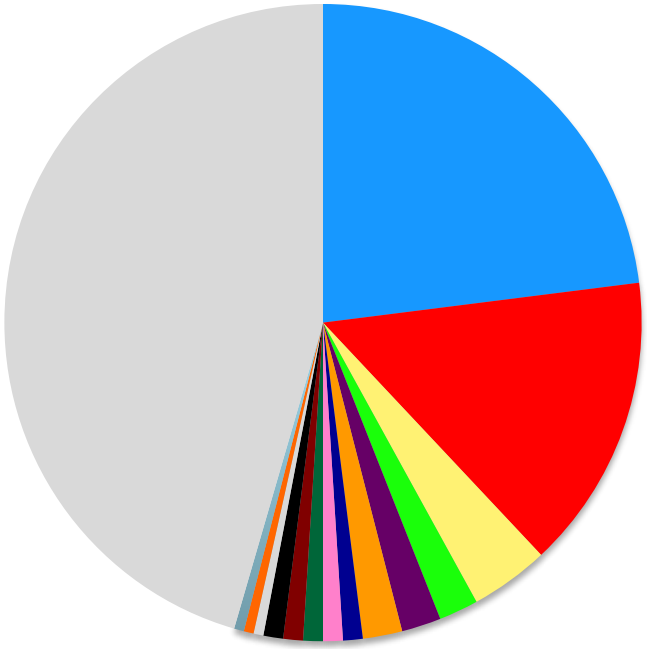
Overall survival ~8 mos

Hanna et al., JCO 22(9): 1589-1597, 2004

A New View of Lung Cancer



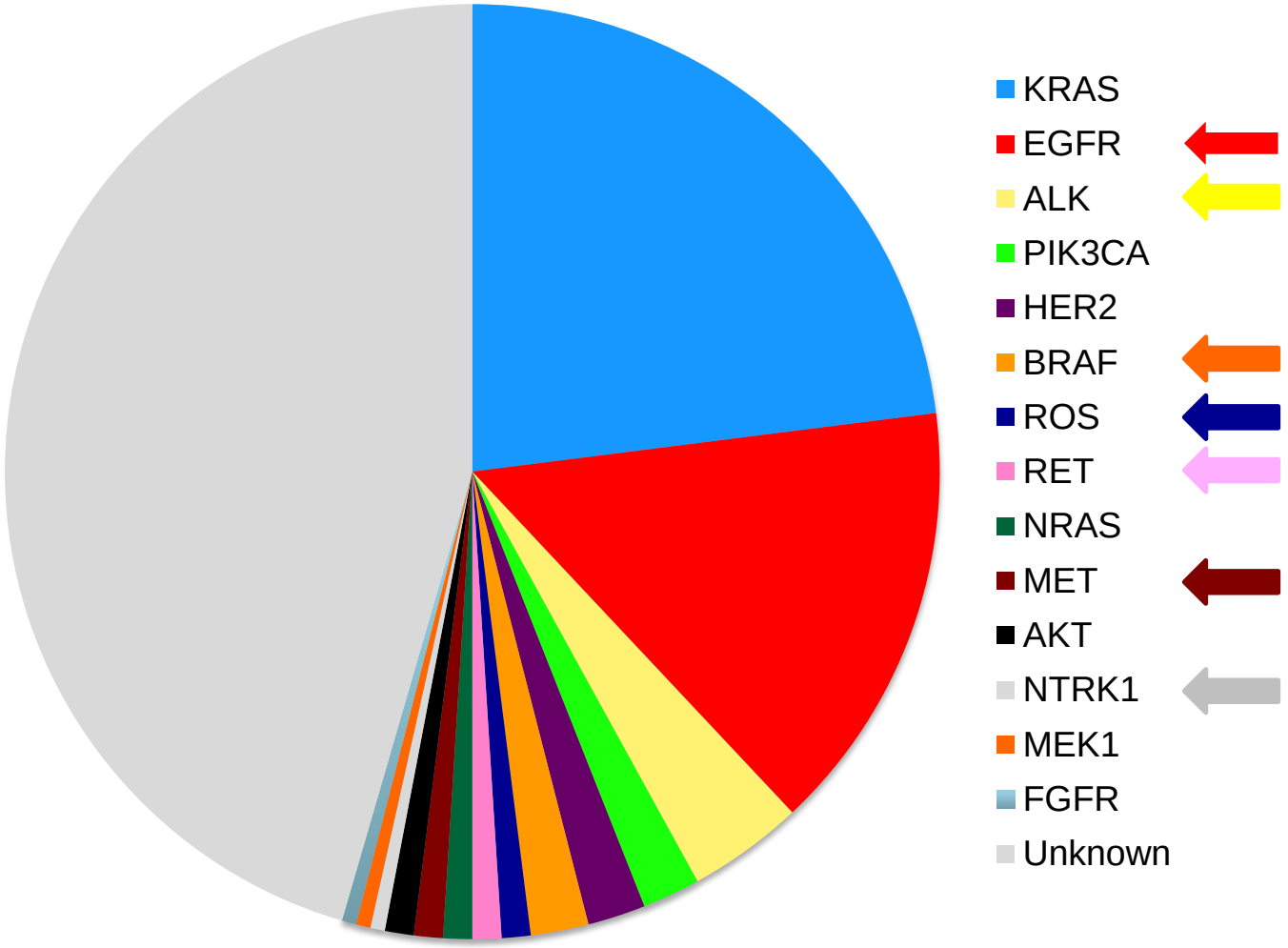
HISTOLOGIC SUBTYPES



MOLECULAR SUBTYPES

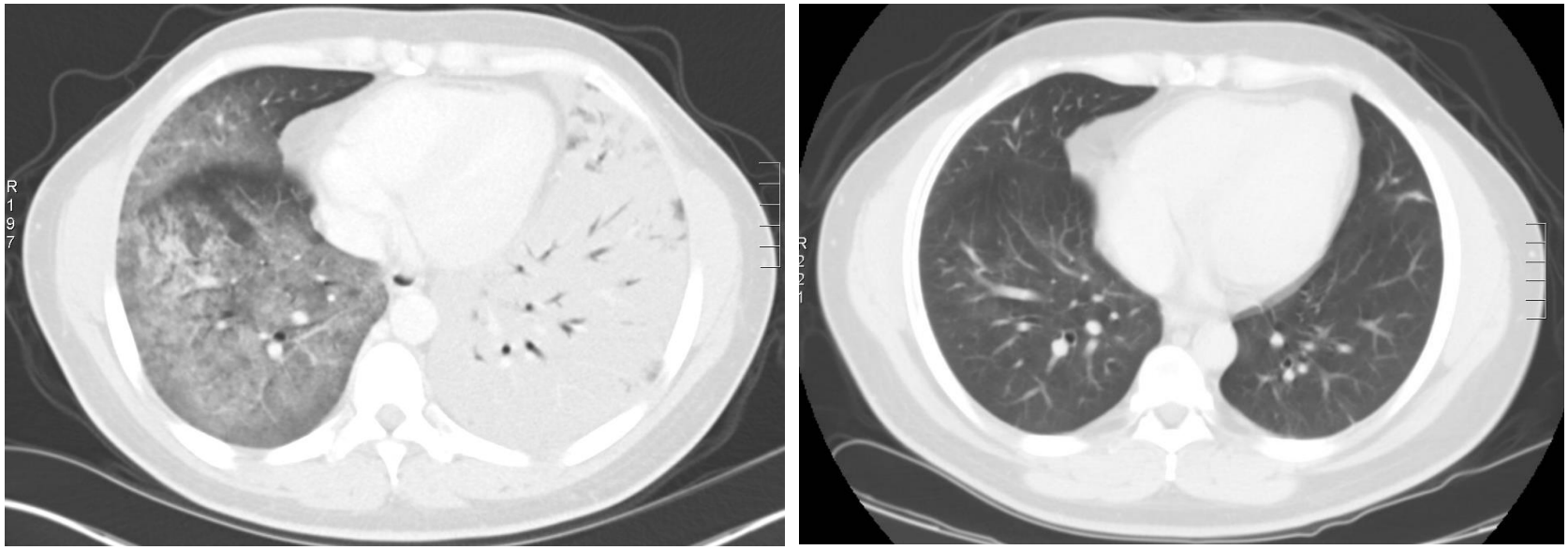
Molecular Classification of Lung Cancer

Oncogenic Drivers



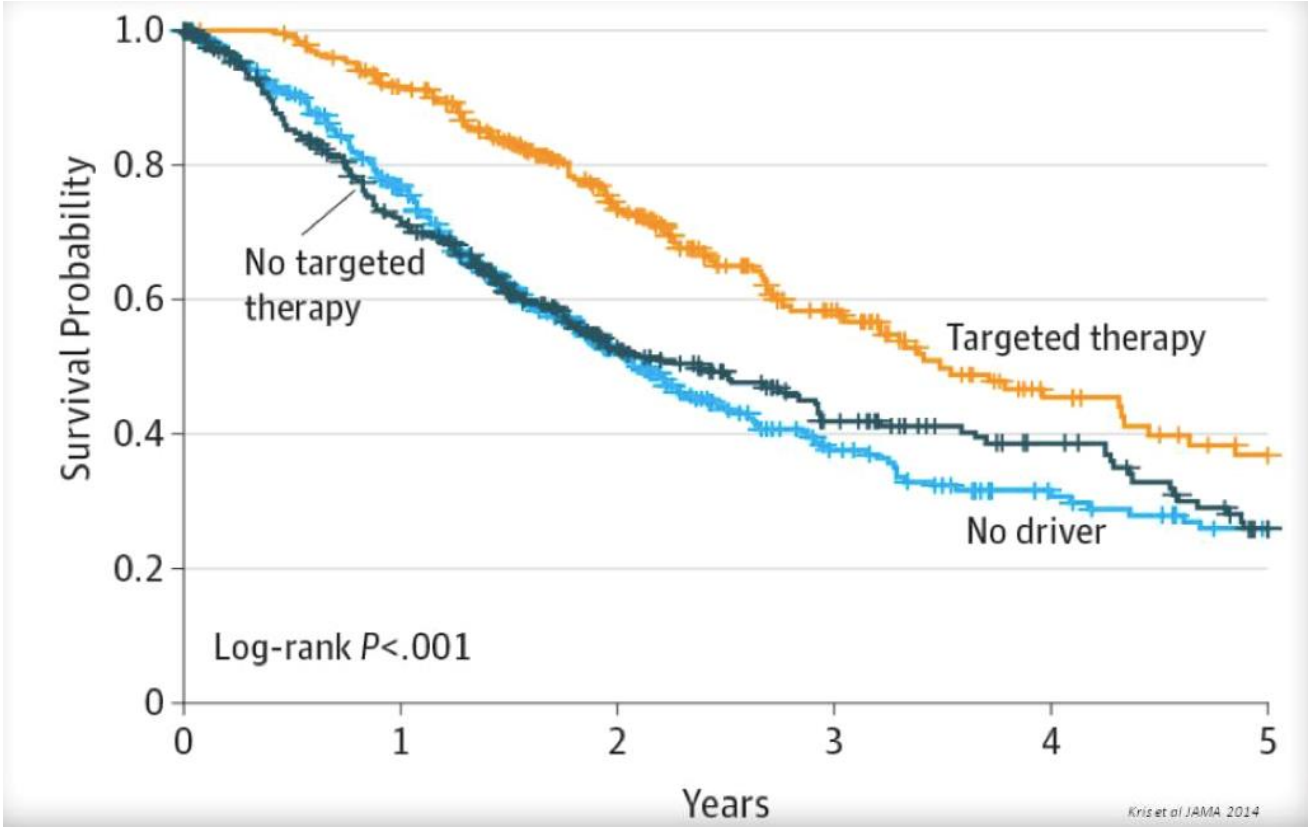
Oncogenic Drivers Confer Sensitivity to Targeted Therapies: Oncogene Addiction

ROS1+ NSCLC



Pre-Treatment **Crizotinib x 8 weeks**

Impact of Matching Targets and Targeted Therapies: Improved Survival



Overview

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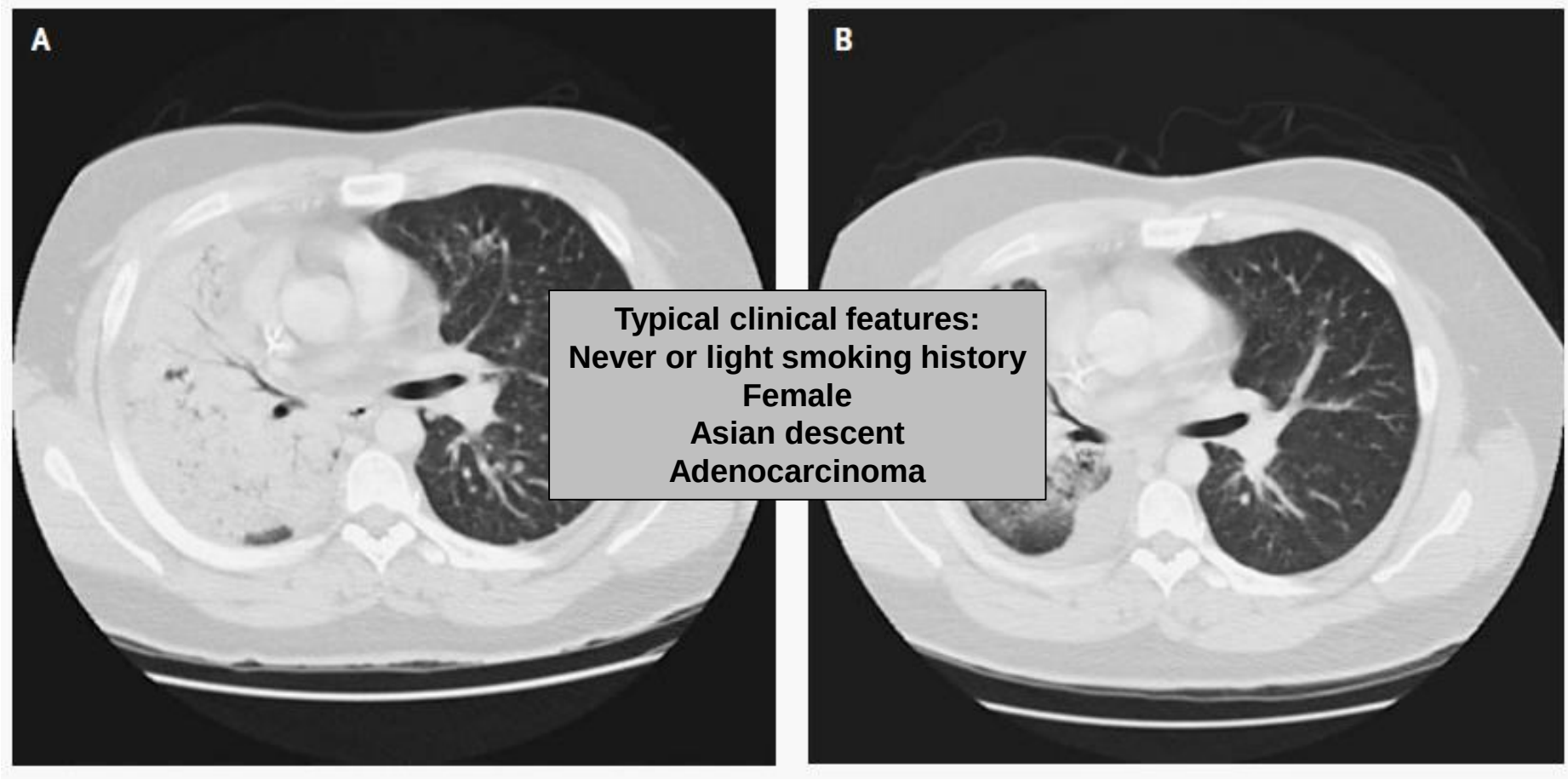
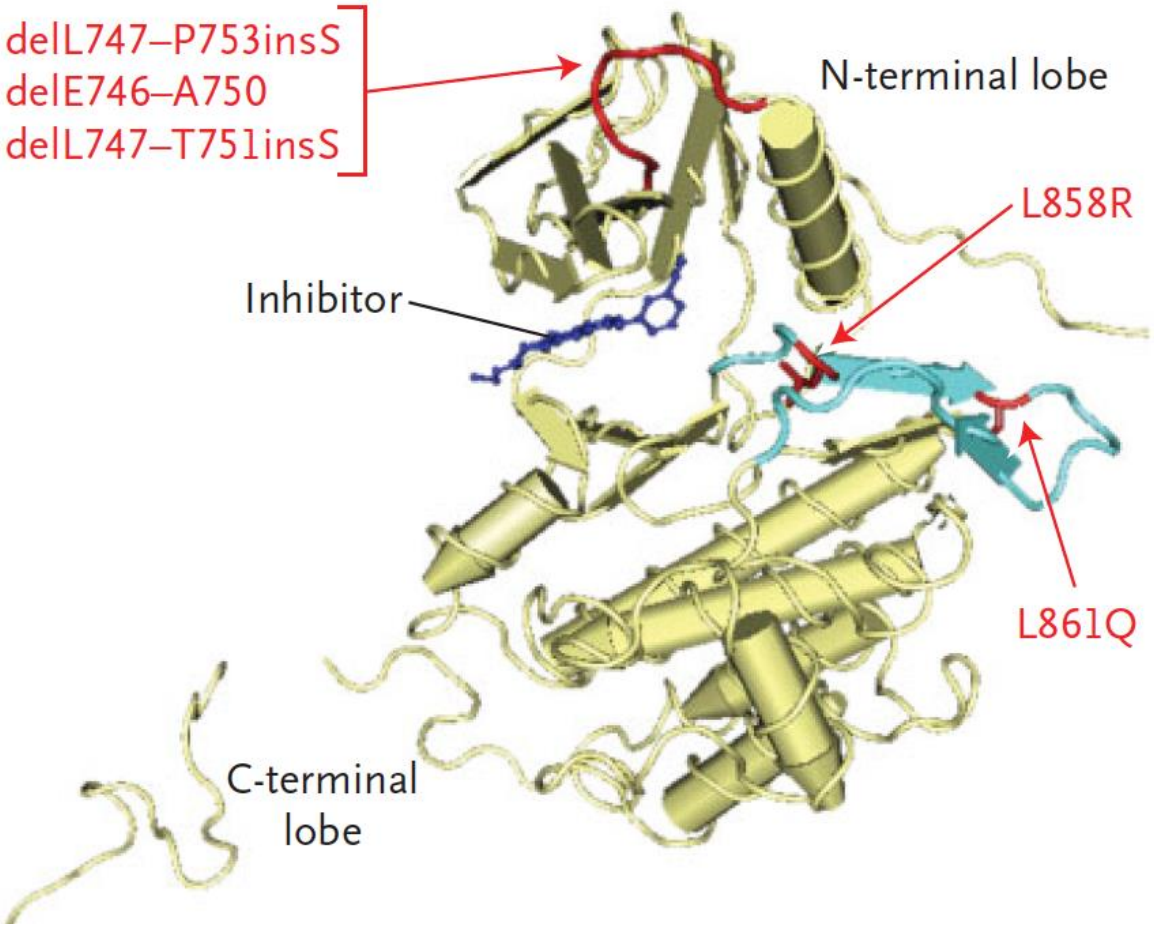
Clinical Activity of an EGFR Inhibitor Leads to Discovery of Oncogenic EGFR Mutations



Baseline **After 6 weeks of gefitinib**

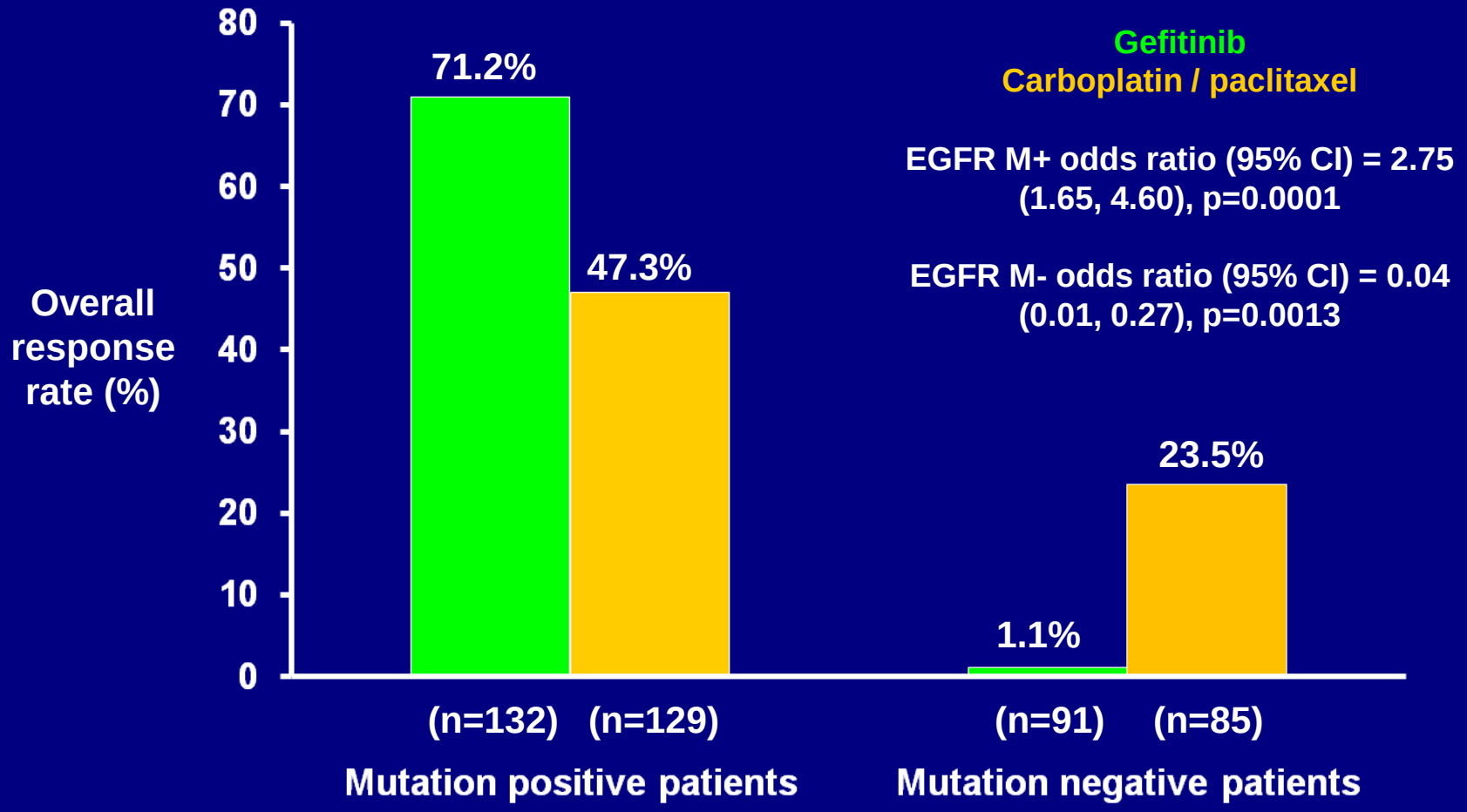
Lynch et al., NEJM 350: 2129-39, 2004

Mutant EGFR is Effectively Inhibited by Gefitinib and Other EGFR Inhibitors



Lynch et al., NEJM 350: 2129-39, 2004

EGFR Inhibitors are Effective in Patients Harboring Mutant EGFR But Not Wildtype EGFR



Odds ratio >1 implies greater chance of response on gefitinib

Mok et al., NEJM 361:947-57, 2009

EGFR Inhibitors are Standard First-Line Therapies for Patients with Sensitizing EGFR Mutations

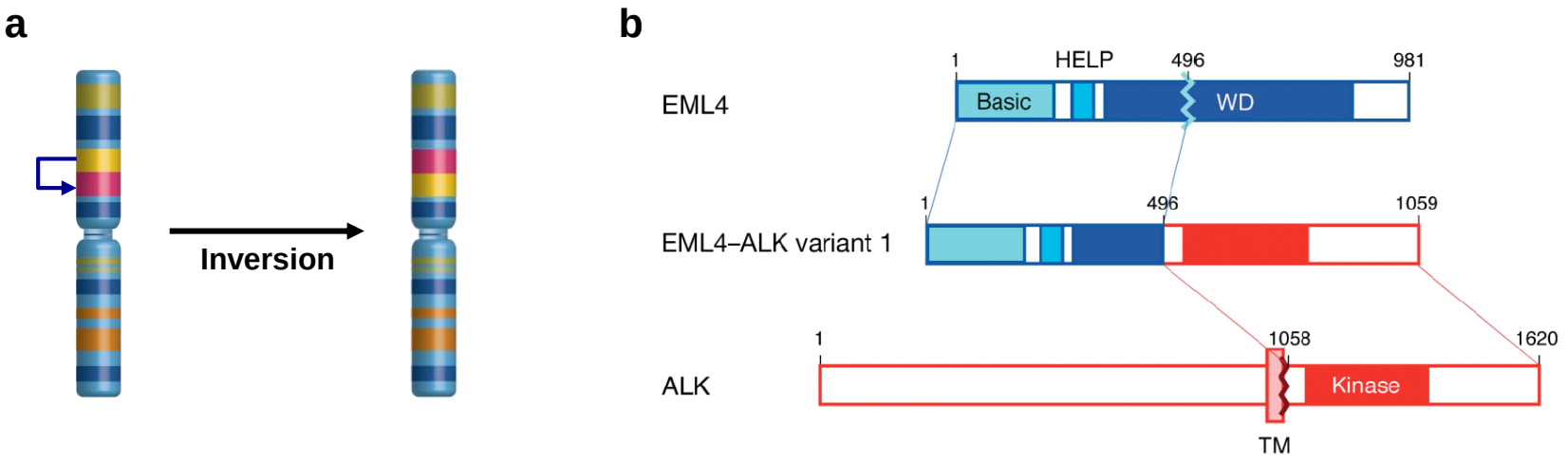
			RR	(%)	Median PFS (mo)		Median OS (mo)	
Country	Trial	Agent	TKI	Chemo	TKI	Chemo	TKI	Chemo
	IPASS Mut +	gefitinib	71.2	47.3	9.5	6.3	21.6	21.9
	First-SIGNAL Mut +	gefitinib	84.6	37.5	8.4	6.7	30.6	26.5
	WJTOG	gefitinib	62.1	32.2	9.2	6.3	30.9	NR
	NEJ002	gefitinb	73.7	30.7	10.8	5.4	27.7	26.6
	OPTIMAL	erlotinib	83	36	13.7	4.6	22.6	28.8
	EURTAC	erlotinib	58	15	9.7	5.2	19.3	19.5
	LUX-Lung 3	afatinib	56.1	22.6	11.1	6.9	NR	NR
	LUX-Lung 6	afatinib	66.9	23.0	11.0	5.6	NR	NR

Vol 448|2 August 2007|doi:10.1038/nature05945

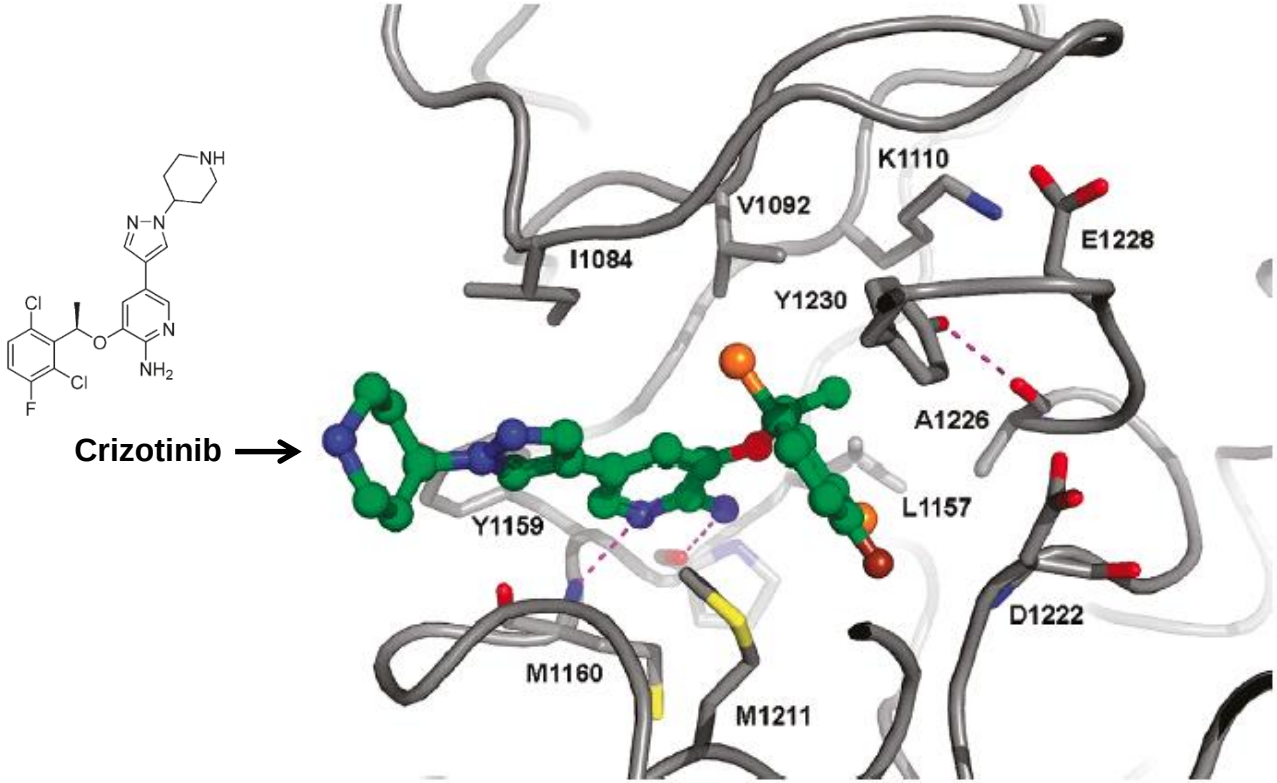
ARTICLES

Identification of the transforming *EML4–ALK* fusion gene in non-small-cell lung cancer

Manabu Soda[1,2], Young Lim Choi[1], Munehiro Enomoto[1,2], Shuji Takada[1], Yoshihiro Yamashita[1], Shunpei Ishikawa[5], Shin-ichiro Fujiwara[1], Hideki Watanabe[1], Kentaro Kurashina[1], Hisashi Hatanaka[1], Masashi Bando[2], Shoji Ohno[2], Yuichi Ishikawa[6], Hiroyuki Aburatani[5,7], Toshiro Niki[3], Yasunori Sohara[4], Yukihiko Sugiyama[2] & Hiroyuki Mano[1,7]



Crizotinib Was Initially Developed to Target a Different Kinase CMET



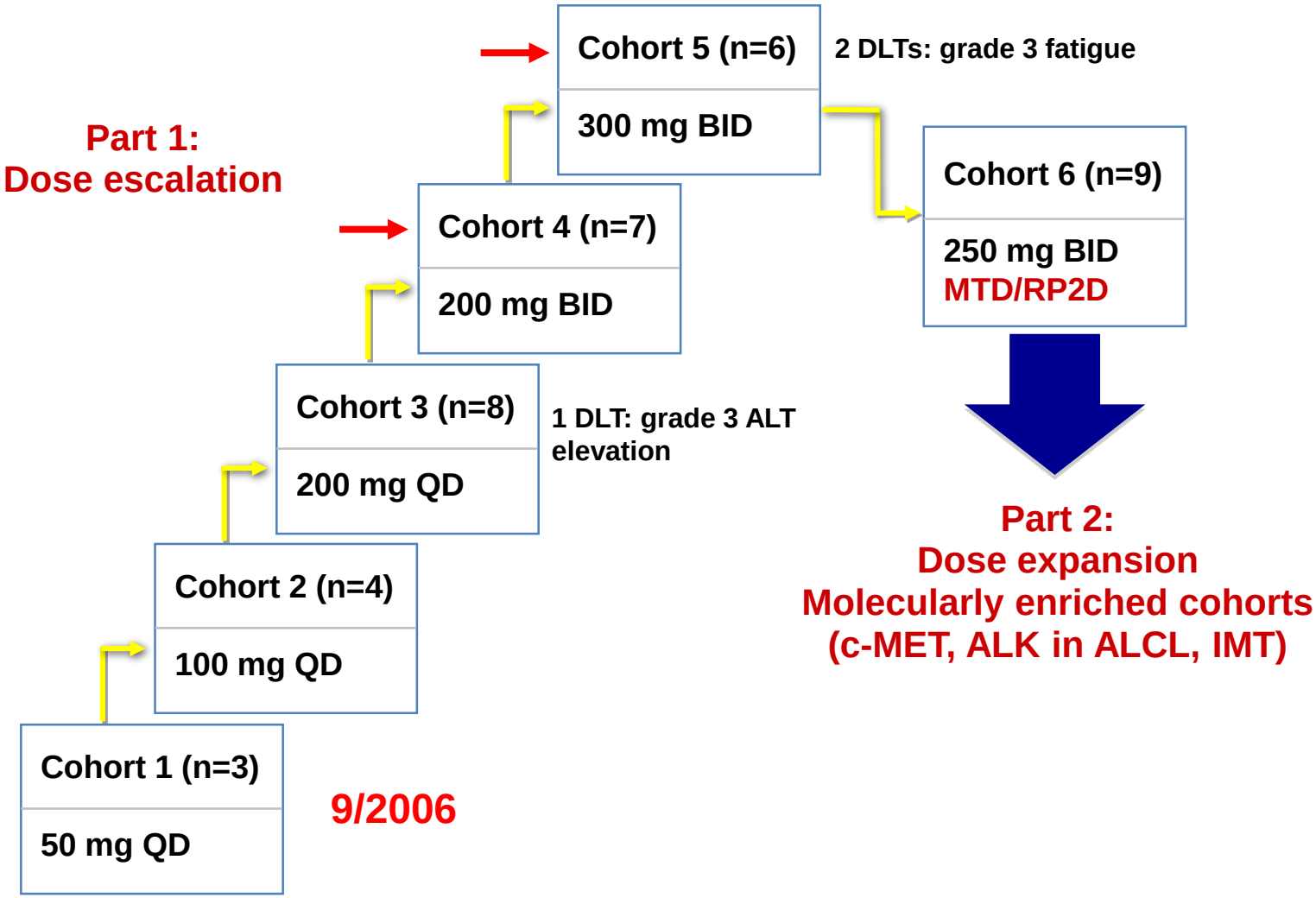
Co-crystal structure of crizotinib (PF-02341066) bound to c-MET

Crizotinib Inhibits Multiple Kinase Targets Including ALK

Kinase	IC_{50} (nM) mean*	Selectivity ratio
c-MET	8	–
ALK	40-60	5-8X
ROS	60	7X
RON	80	10X
Axl	294	34X
	322	37X
Tie-2	448	52X
Trk A	580	67X
Trk B	399	46X
Abl	1,159	166X
IRK	2,887	334X
Lck	2,741	283X
Sky	>10,000	>1,000X
VEGFR2	>10,000	>1,000X
PDGFRβ	>10,000	>1,000X

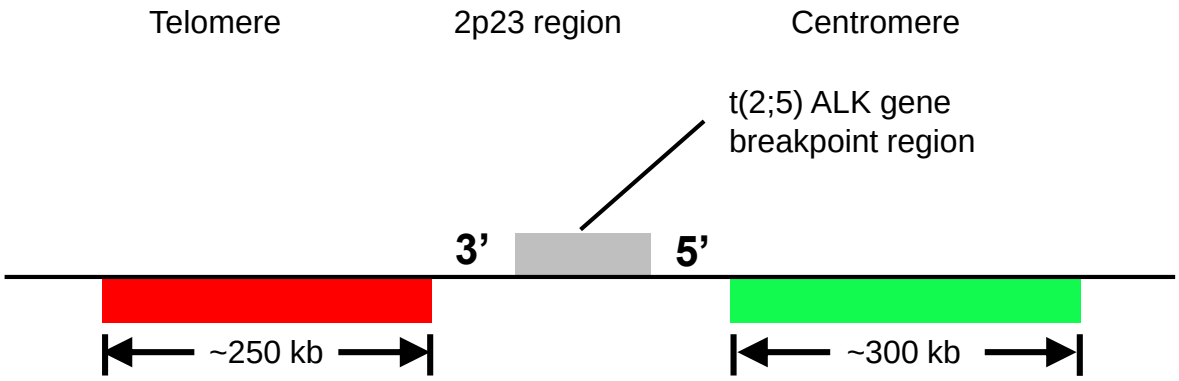
Cui et al. J. Med. Chem. 54:6342-63, 2011 and Pfizer data on file

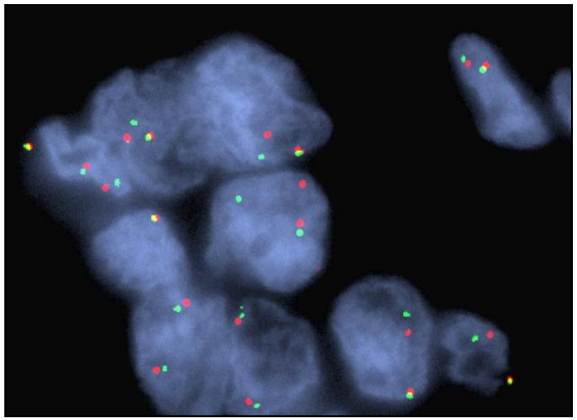
Study Design of Phase 1 Trial of Crizotinib



Kwak et al. NEJM 363:1693-1703, 2010

The Key: Finding the Right Patient



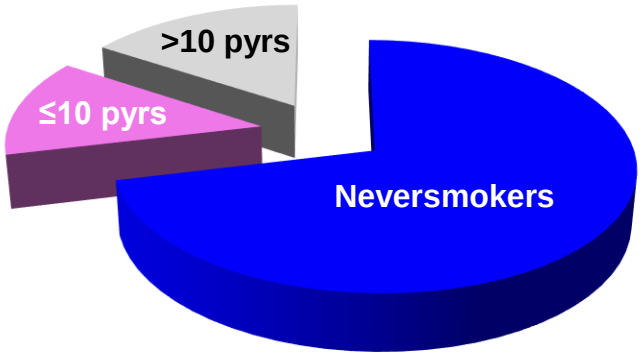


ALK break-apart FISH assay
[Courtesy John Iafrate, Massachusetts General Hospital]

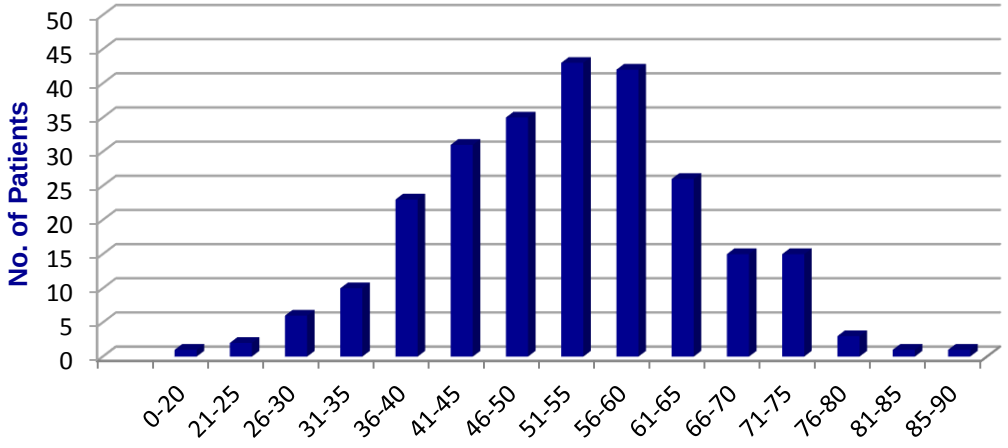
Patients screened: 1500
ALK-positive patients: 82

Kwak et al. NEJM 363:1693-1703, 2010

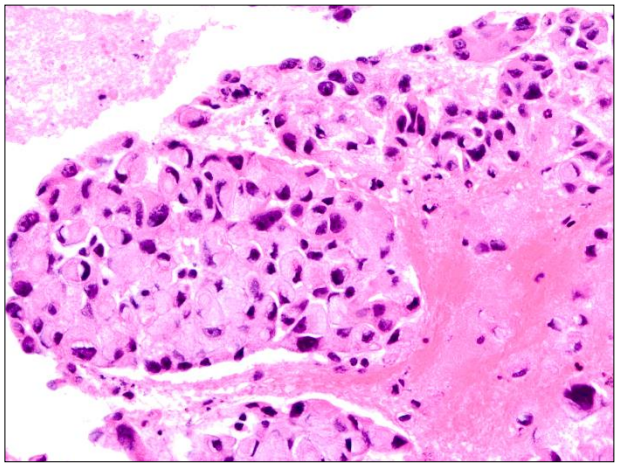
Clinical and Diagnostic Features of ALK-Rearranged Lung Cancer



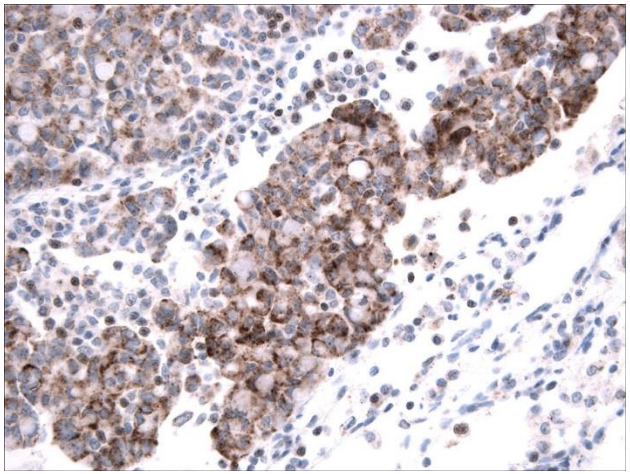
Smoking history



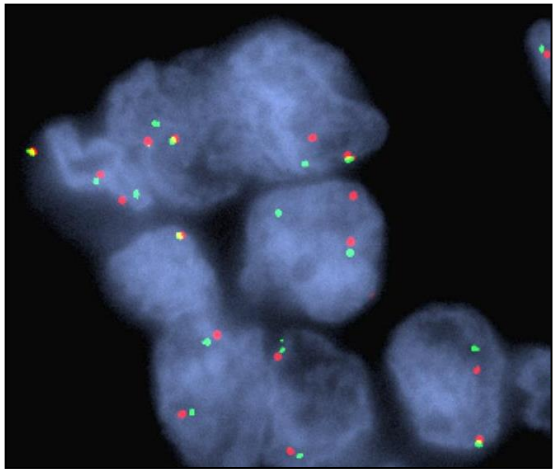
Age



Adenocarcinoma

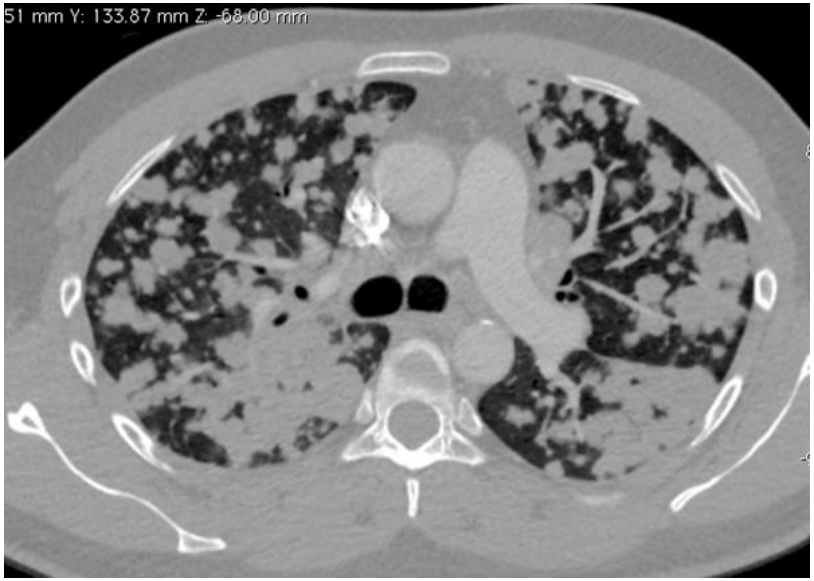


ALK IHC (FDA approved)

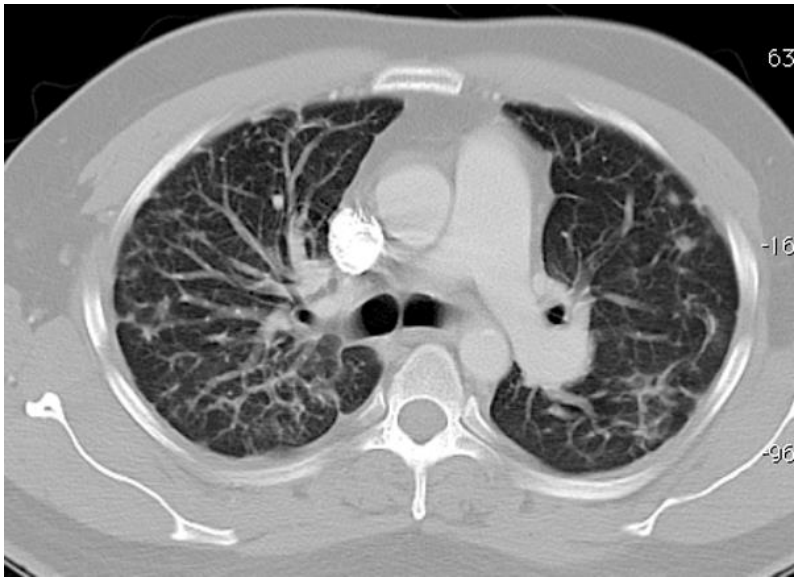


ALK FISH (FDA approved)

ALK Rearrangement Confers Marked Sensitivity to Crizotinib

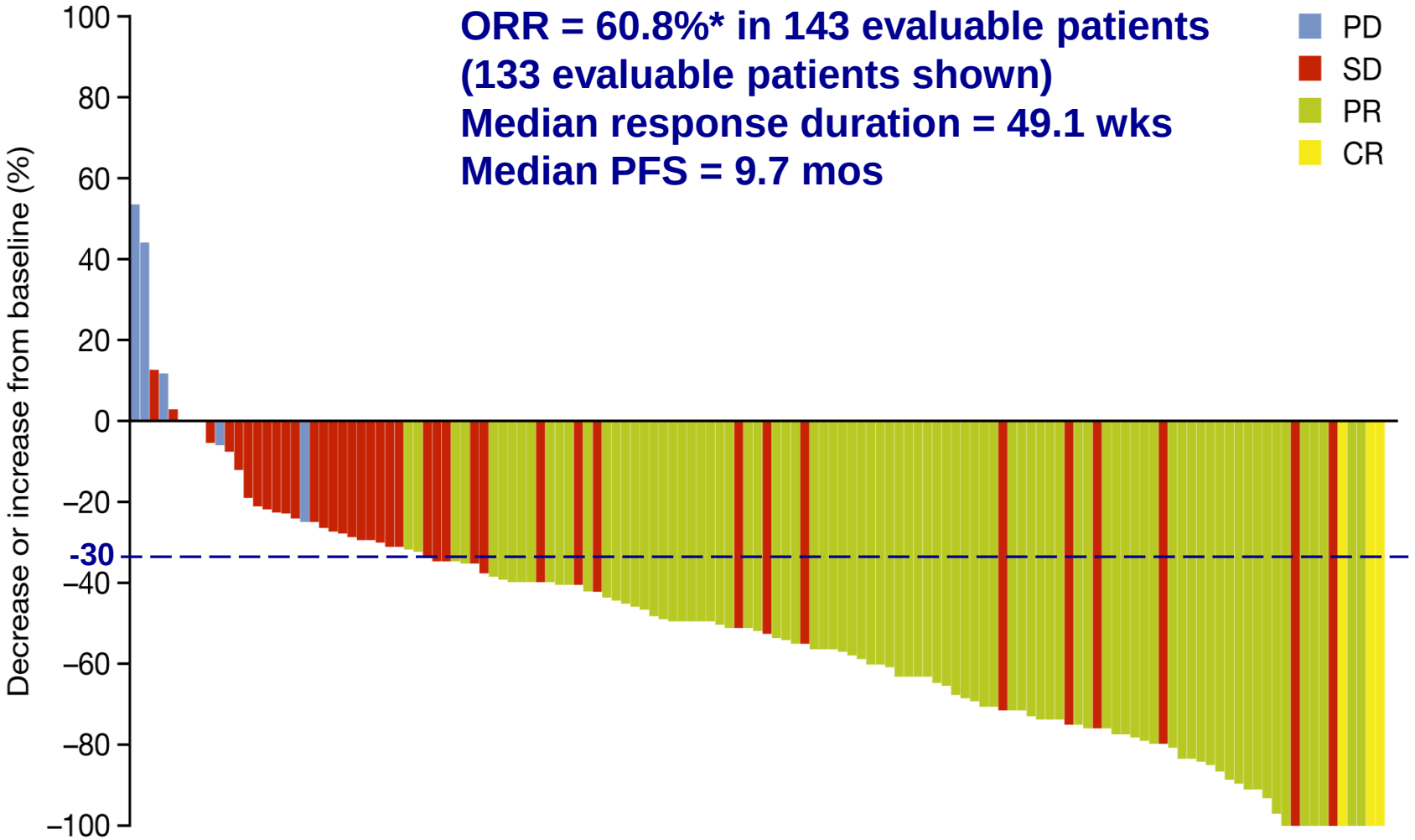


Pre-Treatment



Crizotinib x 12 weeks

Activity of Crizotinib Established in a Molecularly Defined Subset of NSCLC



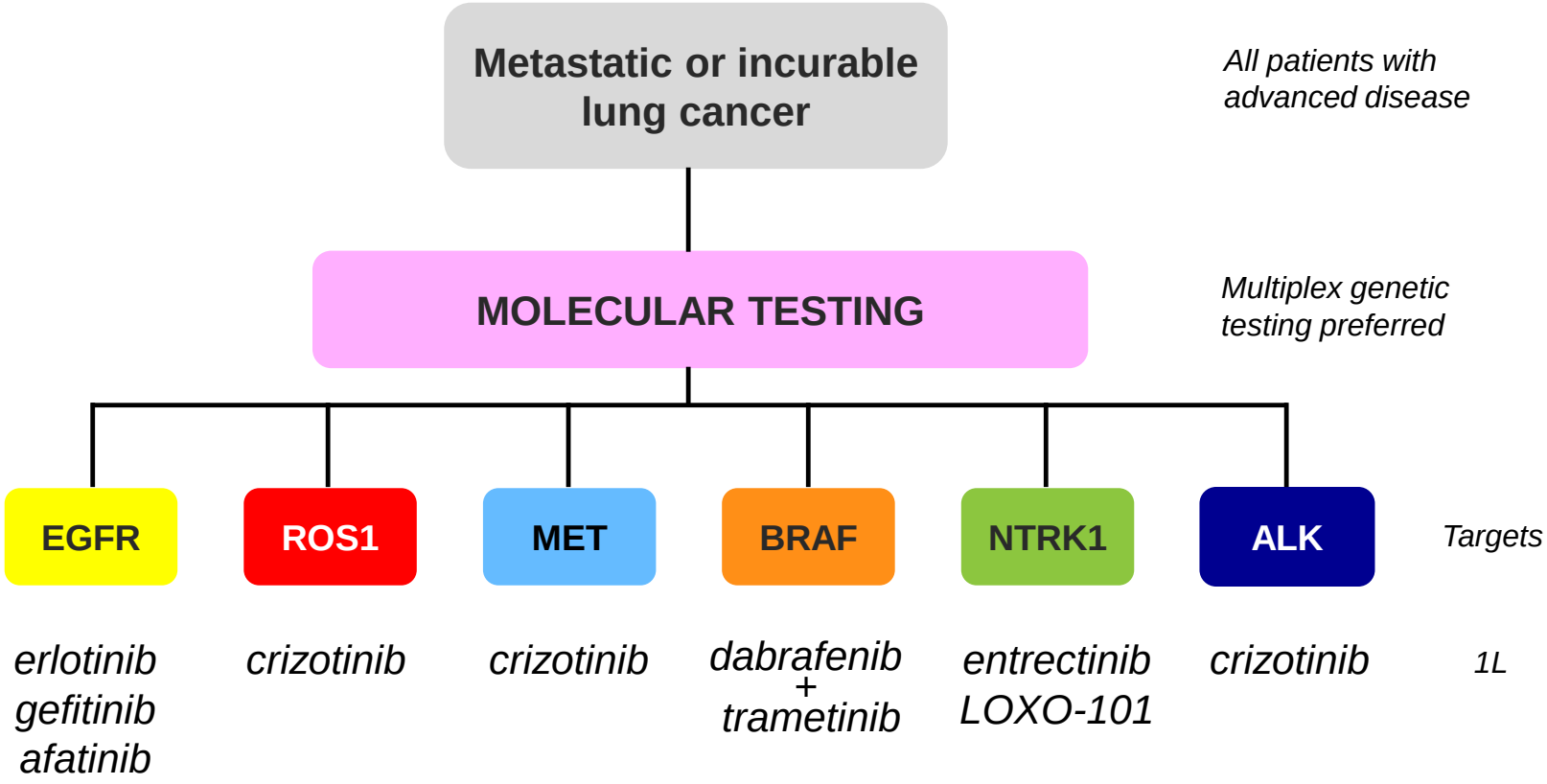
Camidge et al., Lancet Onc 13(10): 1011-9, 2012

Crizotinib is a Standard Therapy for Patients with Metastatic ALK+ NSCLC

	PROFILE 1001[1] (N=143)	PROFILE 1005[2] (N=259)	PROFILE 1007[3] (N=172)	PROFILE 1014[4] (N=172)
Phase	1	2	3	3
Line of therapy	Any line	2nd line and beyond	2nd line	1st line
Response rate	61%	60%	65%	74%
PFS, median (mos)	9.7	8.1	7.7	10.9
Survival probability at 12 mos	75%	NA	70%	84%

[1]Camidge et al., Lancet Onc 13(10): 1011-9, 2012
[2]Kim et al., ASCO 2012
[3]Shaw et al., NEJM 368(25): 2385-94 , 2013
[4]Solomon et al., NEJM 371(23): 2167-77, 2014

Matching Targets with Targeted Therapies in Advanced Lung Cancer



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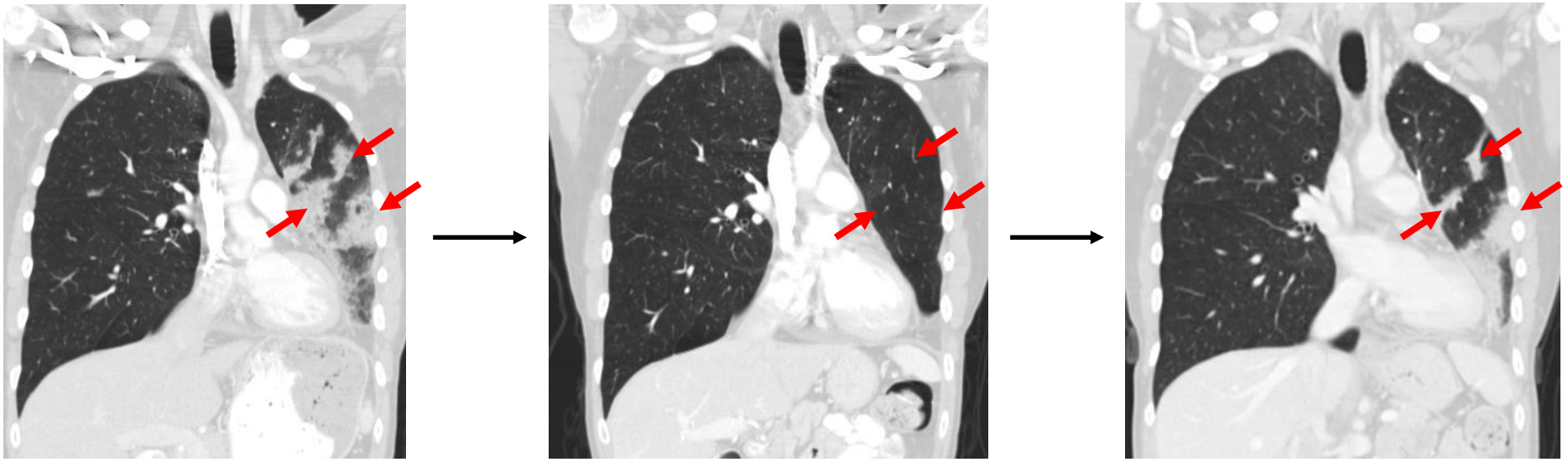
Almost All Patients Develop Resistance to Targeted Therapies Over Time

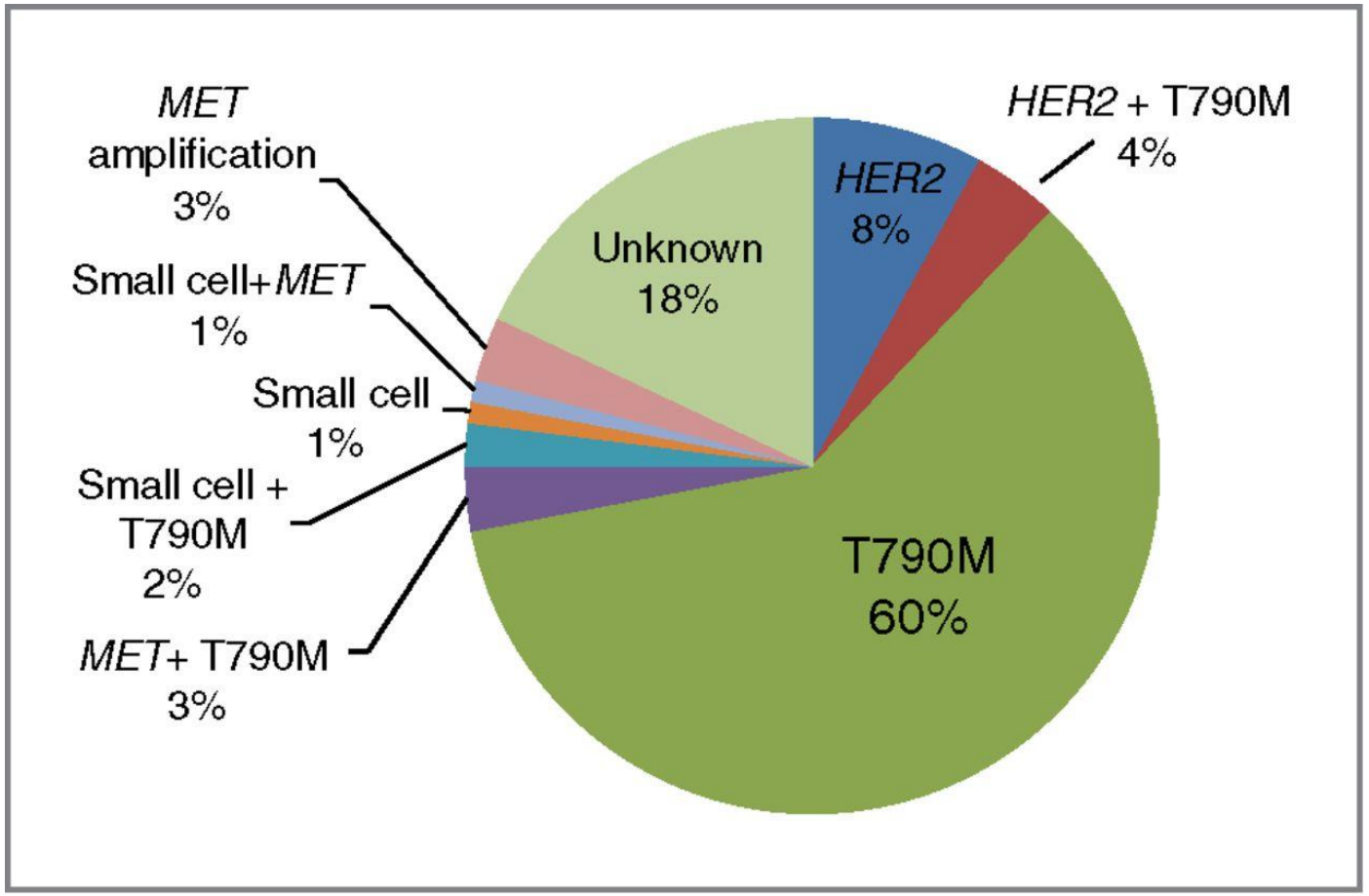


Baseline

After 8 weeks of crizotinib

After 34 months of crizotinib

Mechanisms of Resistance to 1st Generation EGFR Inhibitors



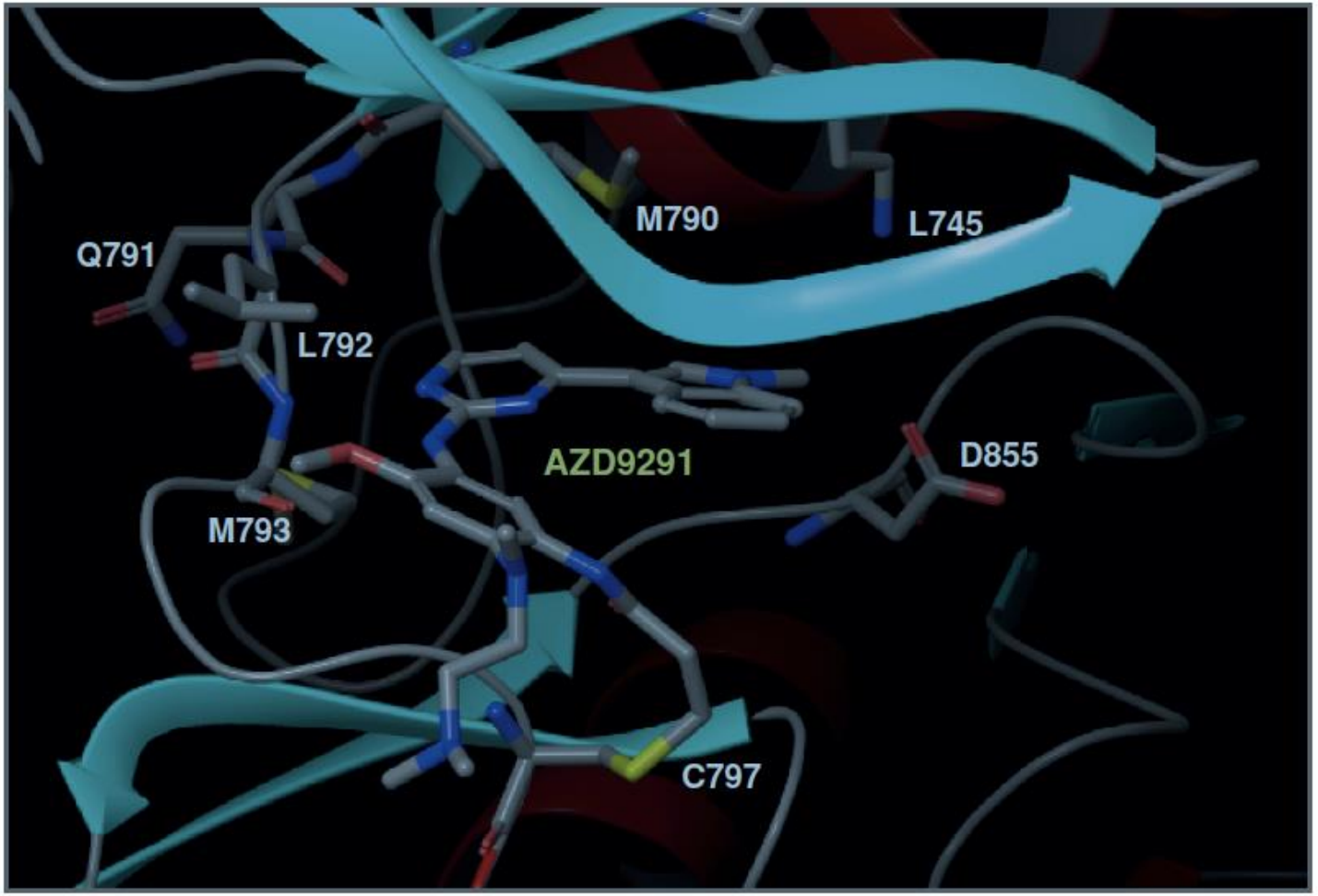
Yu H A et al. Clin Cancer Res 19:2240-2247, 2013

The 3rd Generation Inhibitor AZD9291 (Osimertinib) Is A T790M Mutant-Selective EGFR Inhibitor

		H1975 (T790M/L858R)	PC-9 VanR (ex19del/T790M)	PC-9 (ex19del)	Calu 3 (WT)	NCI-H2073 (WT)
3rd	AZD9291	11 (6, 19)	40 (30, 54)	8 (7, 9)	650 (457, 924)	461 (230, 924)
2nd	Dacomitinib	335 (265, 424)	531 (465, 607)	0.4 (0.3, 1)	65 (37, 116)	54 (ND)
2nd	Afatinib	483 (403, 579)	679 (532, 868)	0.8 (0.7, 0.9)	71 (35, 144)	30 (9, 99)
1st	Gefitinib	6962 (6304, 7688)	4232 (1998, 8965)	23 (20, 25)	1933 (1299, 2876)	200 (41, 974)
1st	Erlotinib	6165 (5392, 7050)	5778 (4766, 7029)	28 (22, 36)	4101 (2732, 6156)	692 (193, 2478)

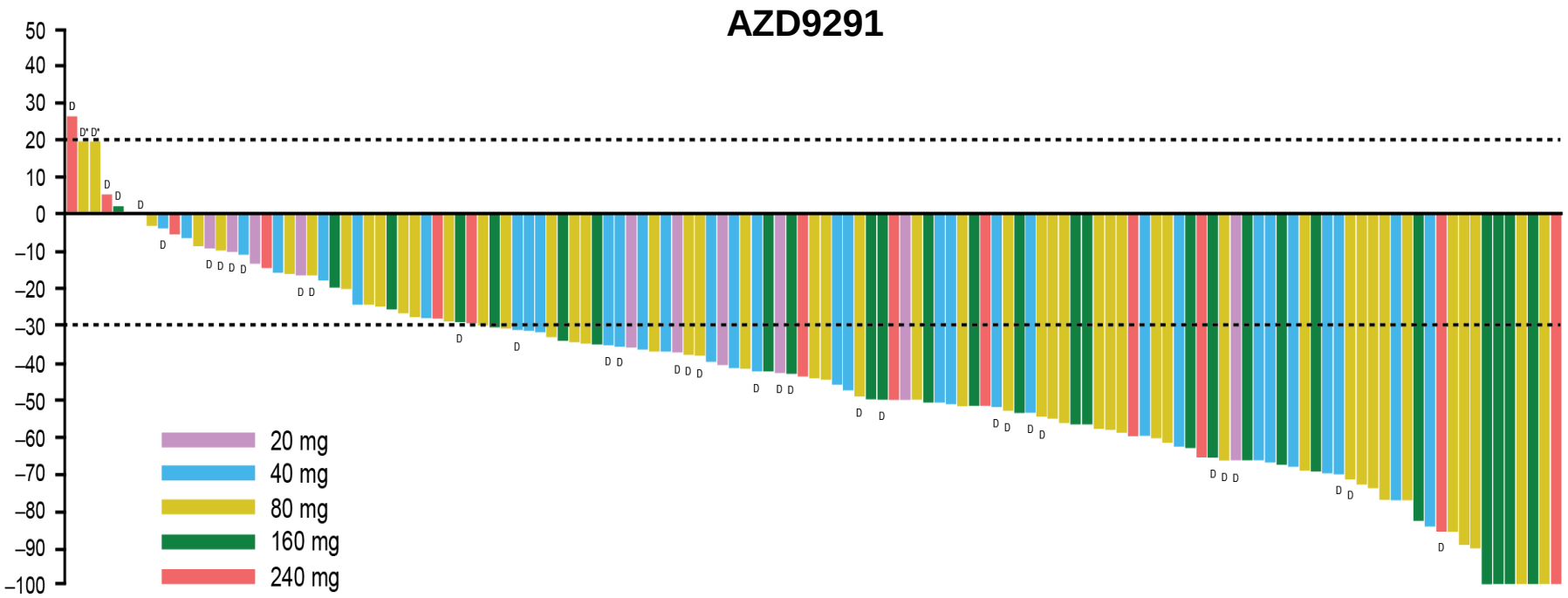
Cross et al., Canc Discovery 4: 1046-61, 2014

Osimertinib Binds to EGFR T790M Via Cys797



Cross et al., Canc Discovery 4: 1046-61, 2014

Third Generation EGFR T790M Inhibitors Can Overcome T790M-Mediated Resistance

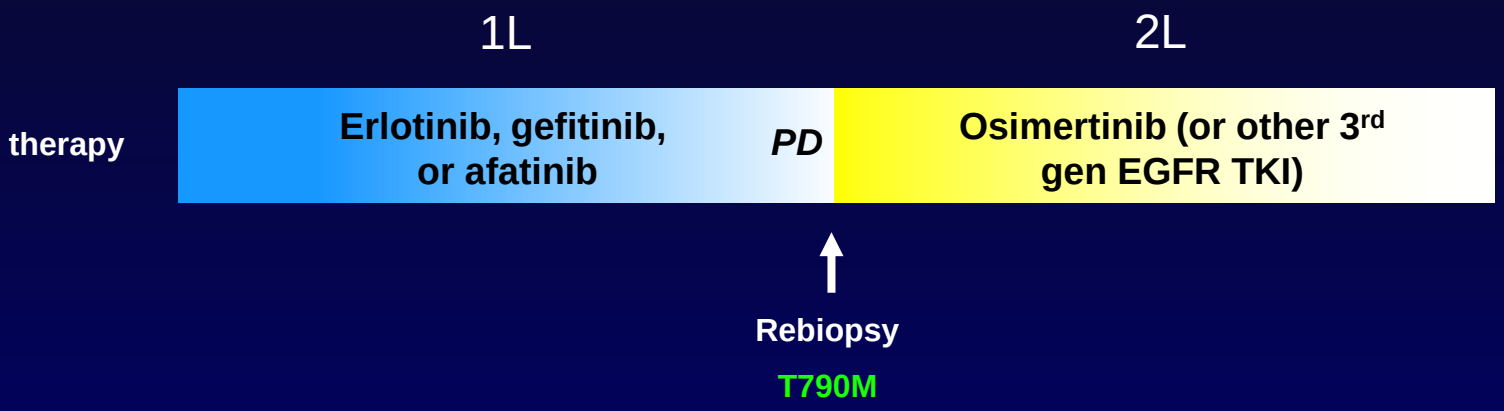


- Confirmed ORR in patients with centrally tested T790M+ tumours was **61%** (78/127; 95% CI 52%, 70%)
- Disease control rate (CR+PR+SD) was 95% (121/127; 95% CI 90%, 98%)

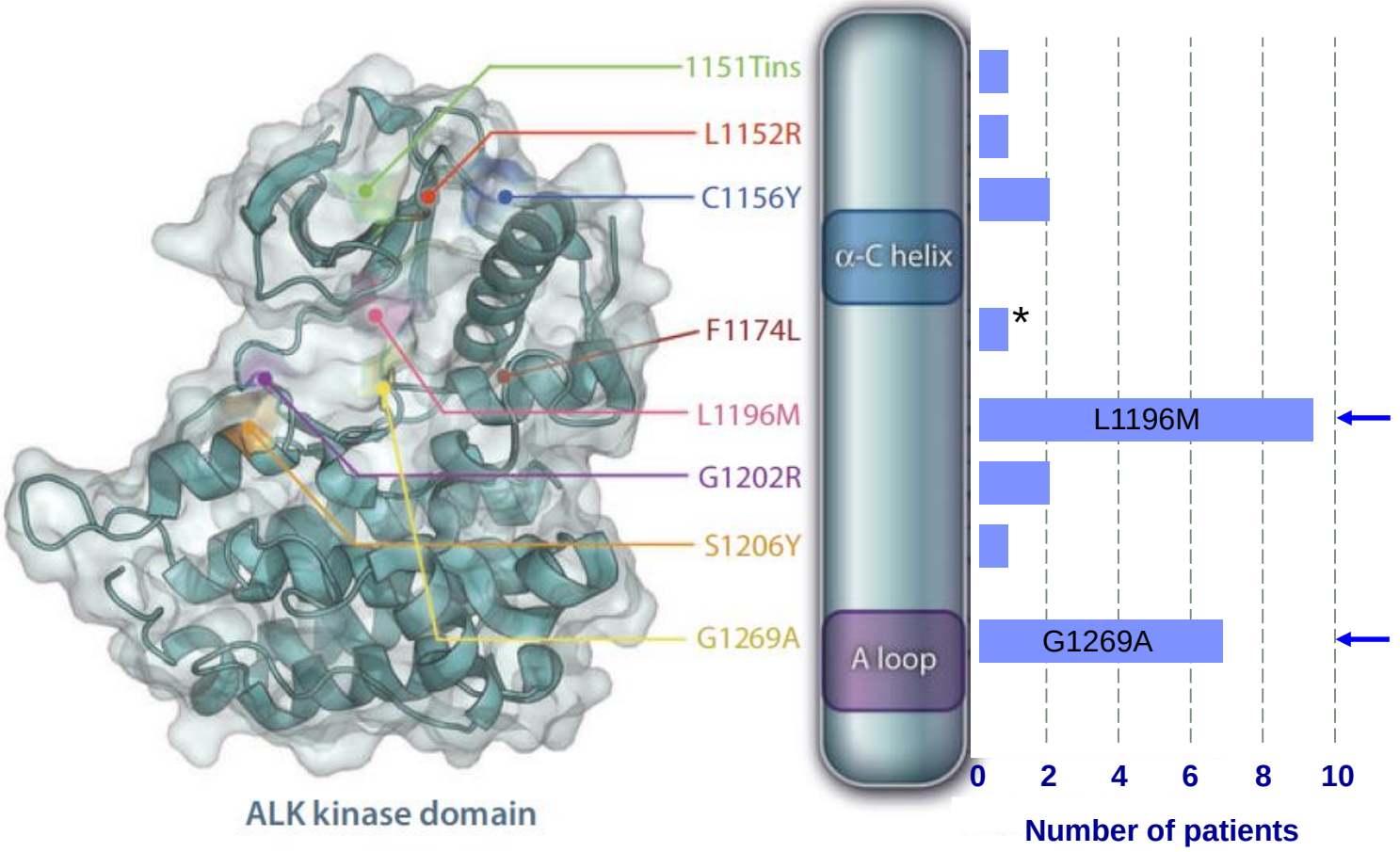
- Median PFS **9.6 mos** (95% CI 8.3 – NR)

Yang et al., ESMO 2014
Janne et al., NEJM 2015

Sequential EGFR Inhibitor Therapy in Patients Who Relapse due to T790M



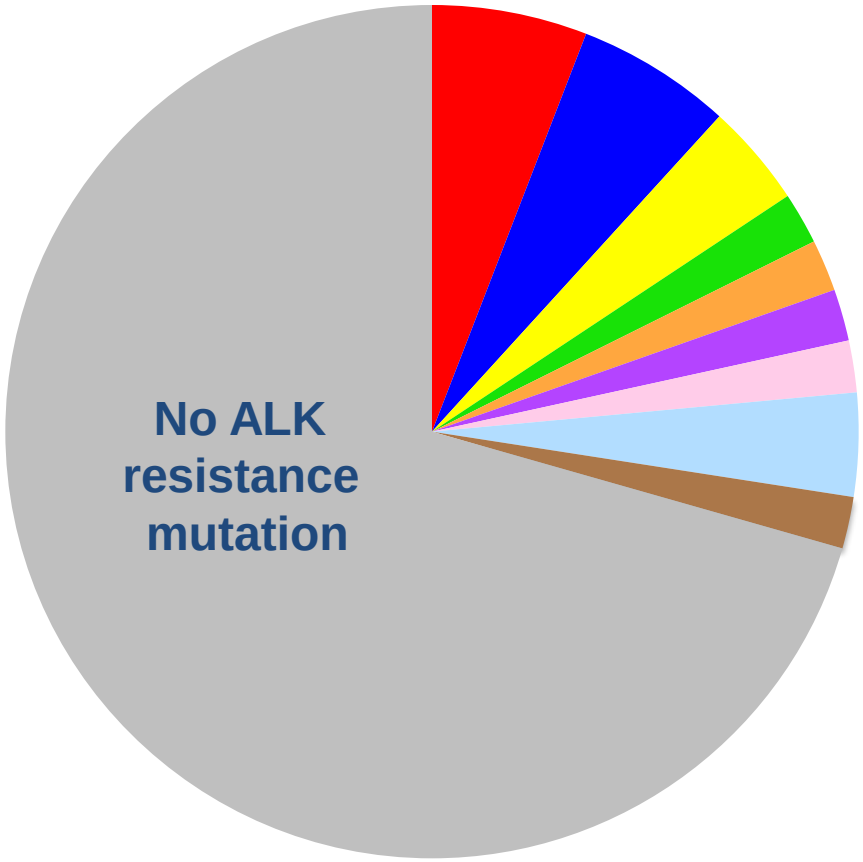
Multiple Secondary ALK Mutations Can Mediate Resistance to Crizotinib



- F1174C/V

Modified from Lovly and Pao, Sci Transl Med 4(120): 120ps2, 2012

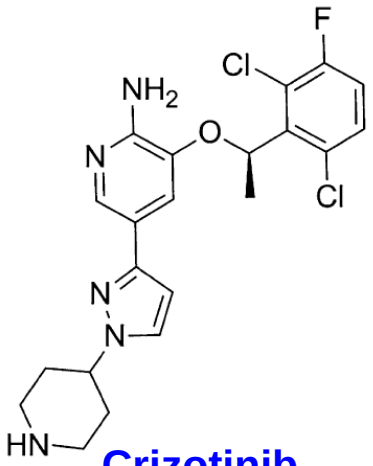
Less Than 30% of Crizotinib-Resistant Tumors Harbor Secondary ALK Resistance Mutations



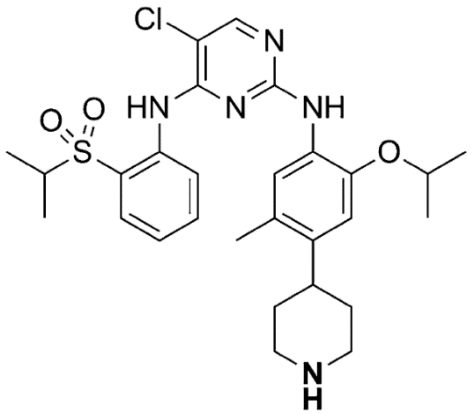
Next Generation ALK Inhibitors

ALK TKI	ROS1 activity	Status	Ongoing Studies
Ceritinib	Yes	FDA Approved (4-29-2014)	Phase 3 (vs chemo)
Alectinib	No	Approved in Japan (7-4-2014) FDA Approved (12-11-15)	Phase 3 (vs crizotinib)
Brigatinib	Yes	Investigational FDA Breakthrough Therapy	Phase 2 (90 vs 180 mg)
X-396	Yes	Investigational	Phase 1/2
Entrectinib	Yes	Investigational	Phase 2
CEP-37440	Unk	Investigational	Phase 1
Lorlatinib	Yes	Investigational	Phase 2

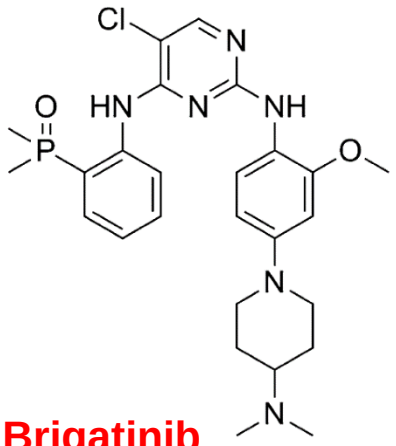
First and Next Generation ALK Inhibitors



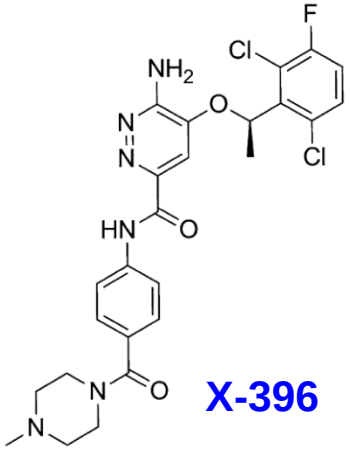
Crizotinib



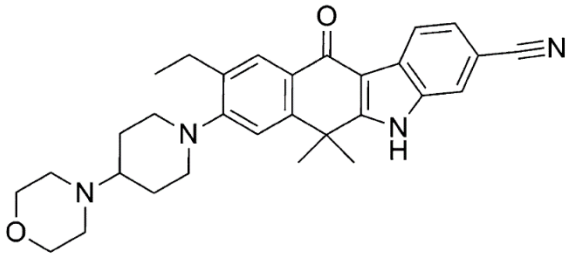
Ceritinib



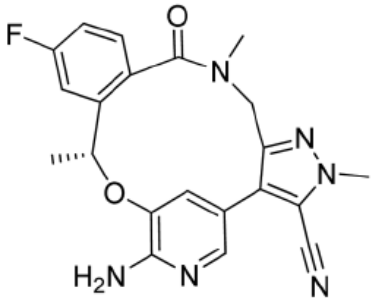
Brigatinib



X-396



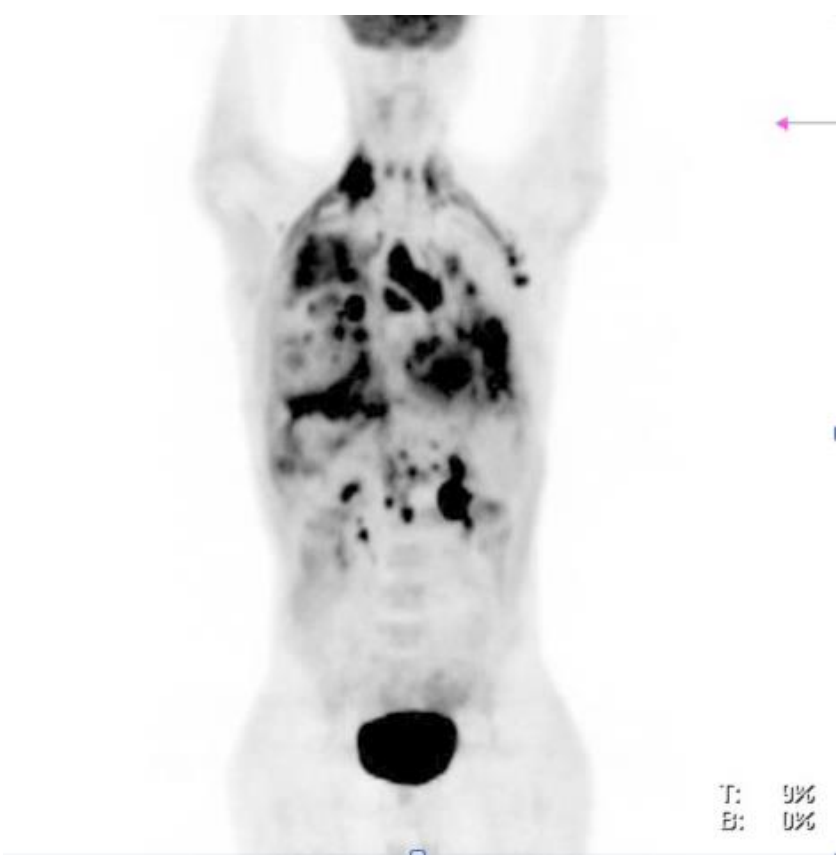
Alectinib



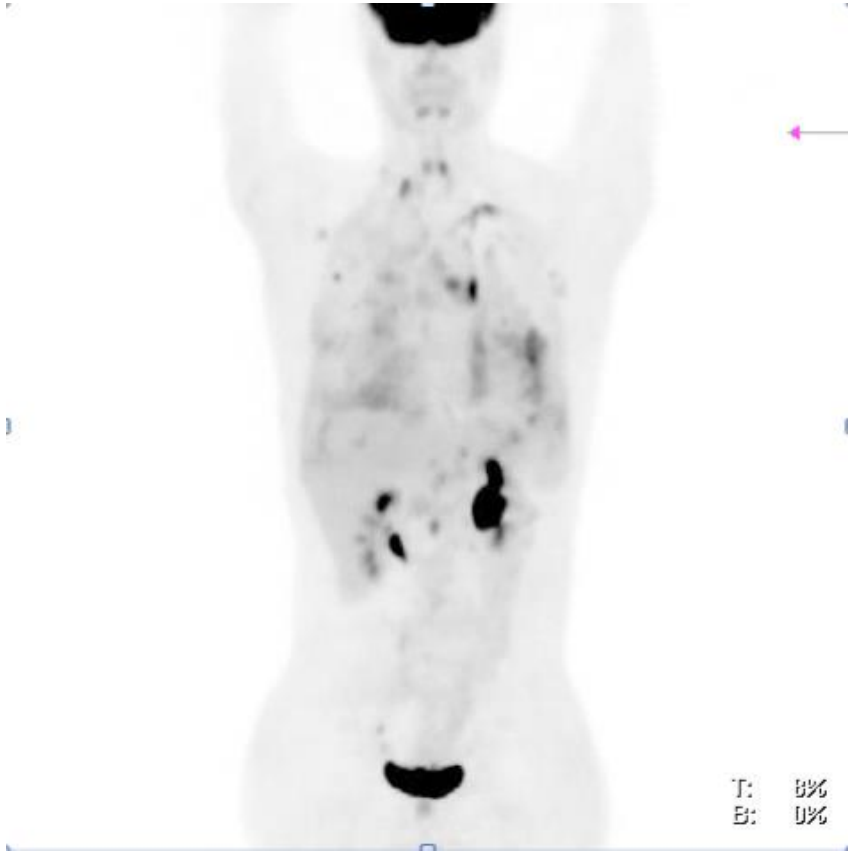
Lorlatinib

Marsilje et al., J Med Chem 56:5675-90, 2013; Johnson et al., J Med Chem 57:4720-44, 201

Next Generation ALK Inhibitors Can Induce Rapid Responses in Crizotinib-Resistant Patients



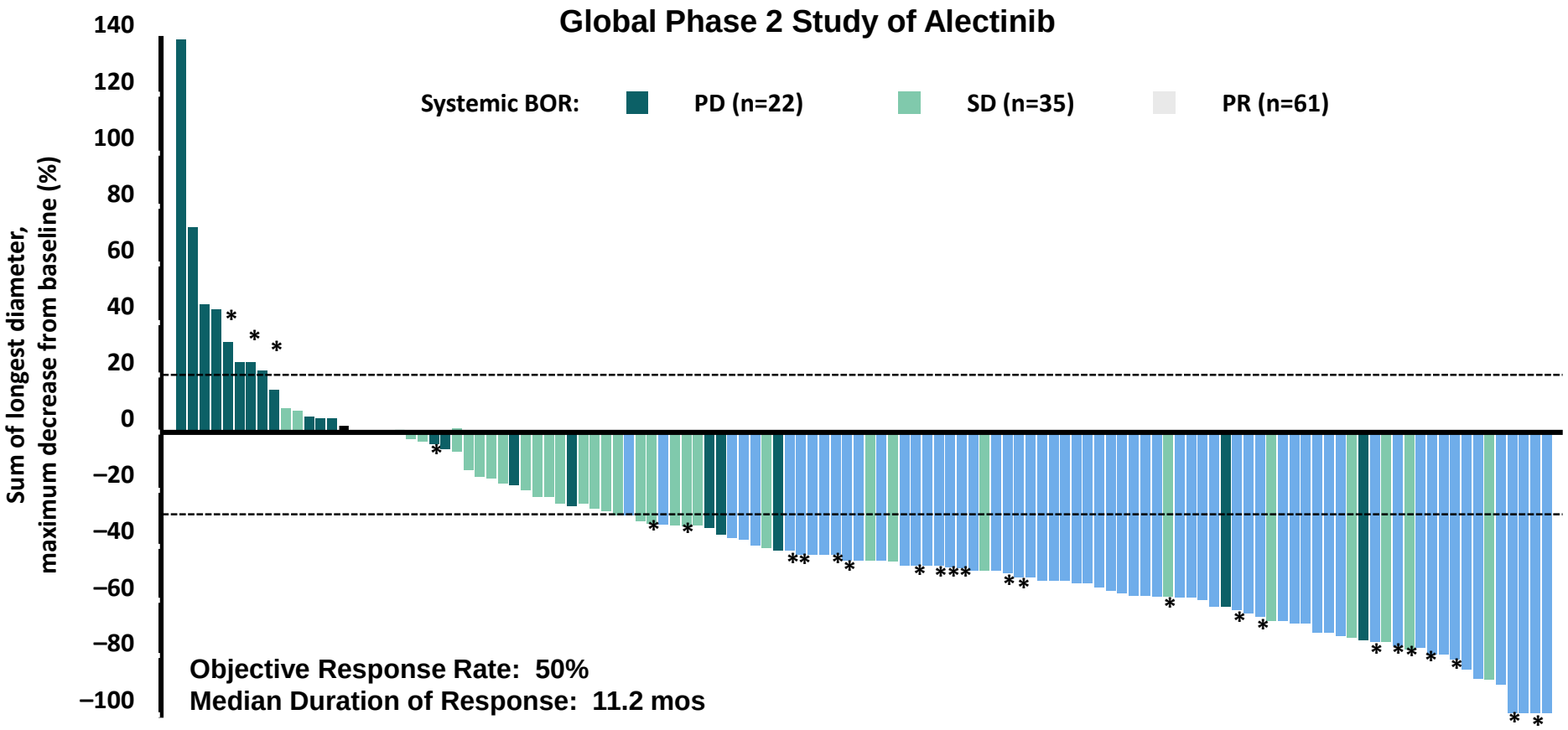
Baseline



After 3.5 weeks
of ceritinib

Shaw et al., NEJM 370(13): 1189-97, 2014

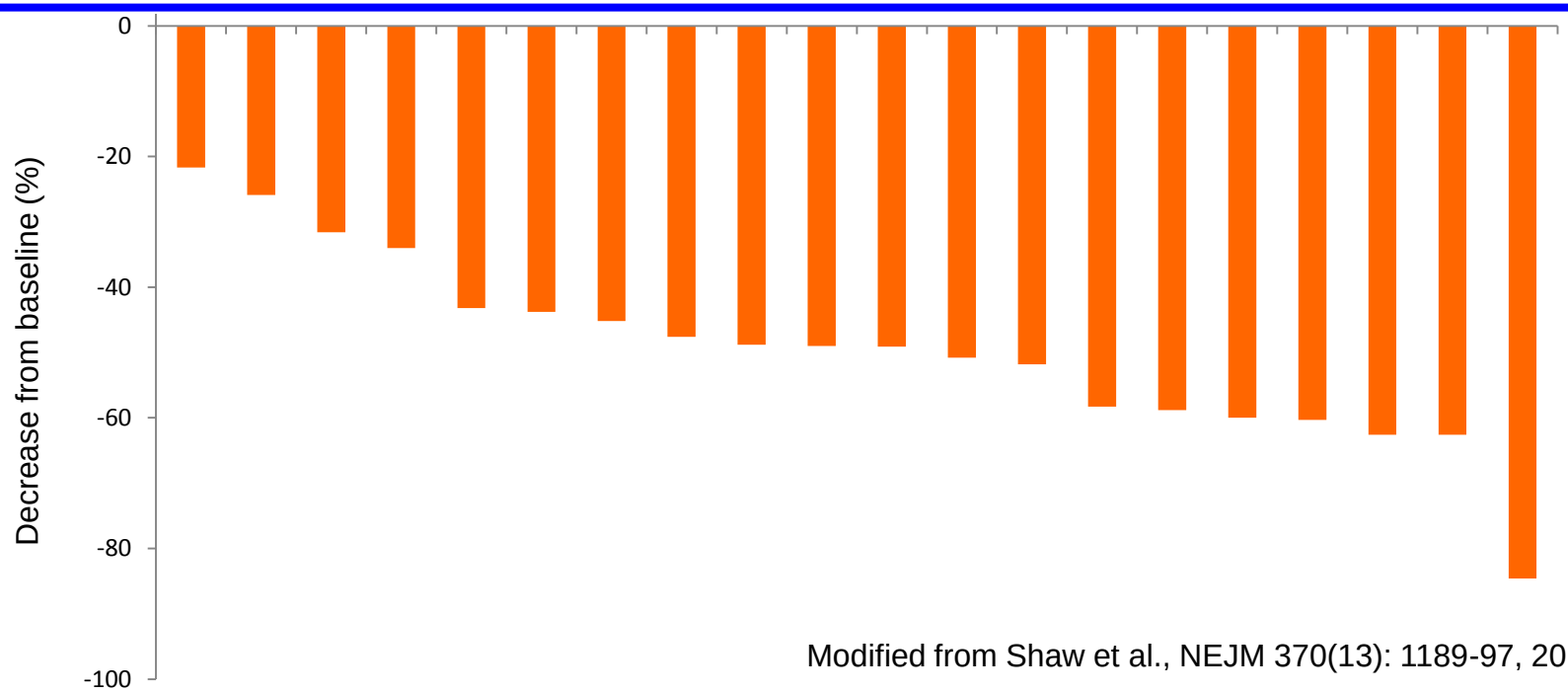
Next Generation ALK Inhibitors Induce Durable Responses in Most Crizotinib-Resistant, ALK+ NSCLC Patients



Ou et al., ASCO 2015

Next Generation Inhibitors are Active Against Tumors Without ALK Resistance Mutations

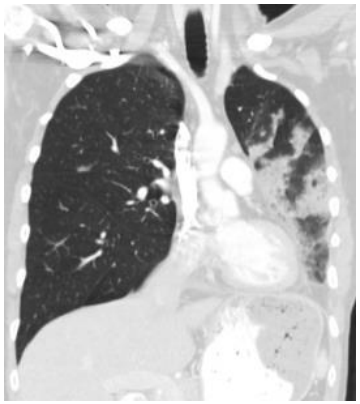
Best % response	22	26	32	34	43	44	45	48	49	49	49	51	52	58	59	60	60	63	63	85
PFS on LDK378 (wks)	19	71	12	8	36	49	18	29	30	41	31	23	12	18	71	77	21	42	61	39
ALK FISH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALK amplification	-	-	-	-	-	-	-	-	-	+	-	-	-	+	-	-	-	-	-	-
ALK mutation	-	-	-	-	-	-	+	-	-	-	+	+	+	-	+	-	-	-	+	-



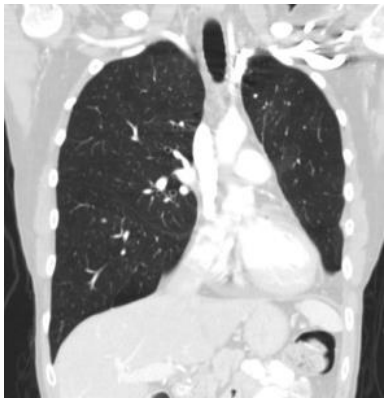
Modified from Shaw et al., NEJM 370(13): 1189-97, 2014

Current Treatment Strategy for Metastatic ALK+ NSCLC

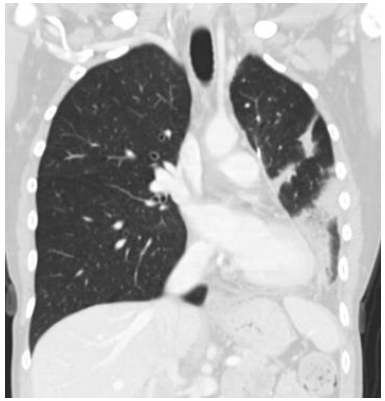
Acquired Resistance to Next Generation ALK Inhibitors



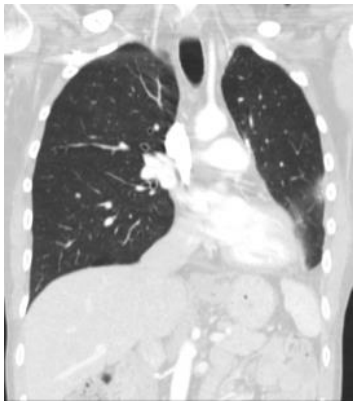
Baseline



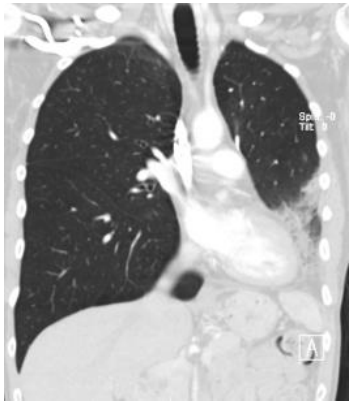
After 8 weeks of crizotinib



After 34 months of crizotinib



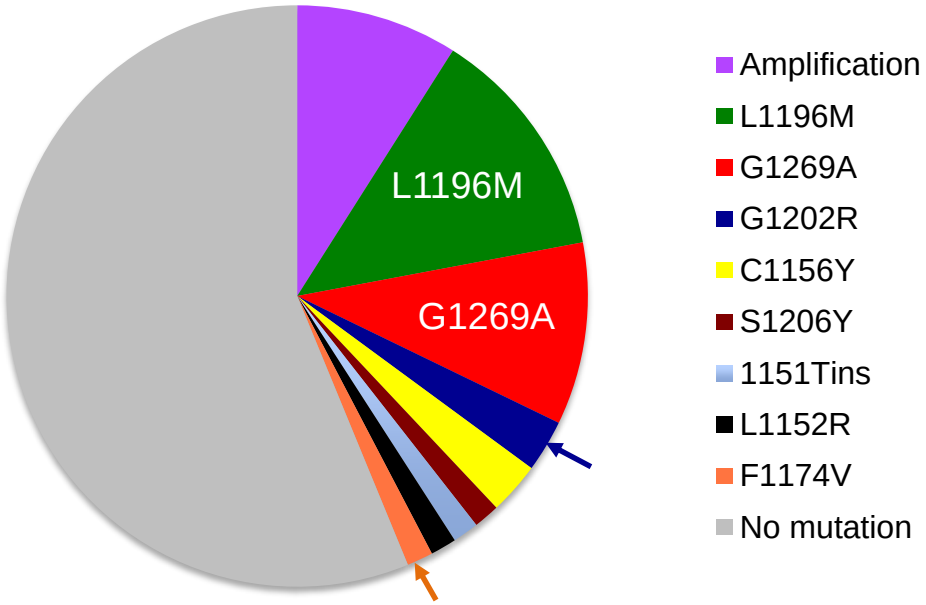
After 12 weeks of ceritinib



After 15 months of ceritinib

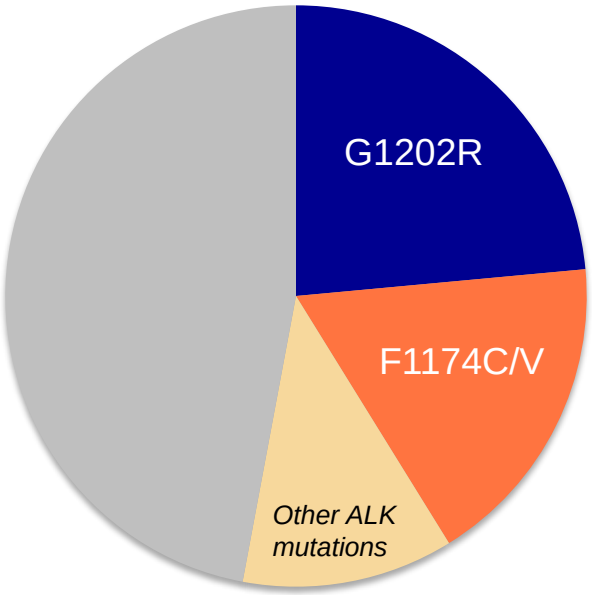
Friboulet et al., Cancer Discov 4(6): 662-73, 2014

Shifting Profile of ALK Resistance Mutations Depending on the ALK Inhibitor



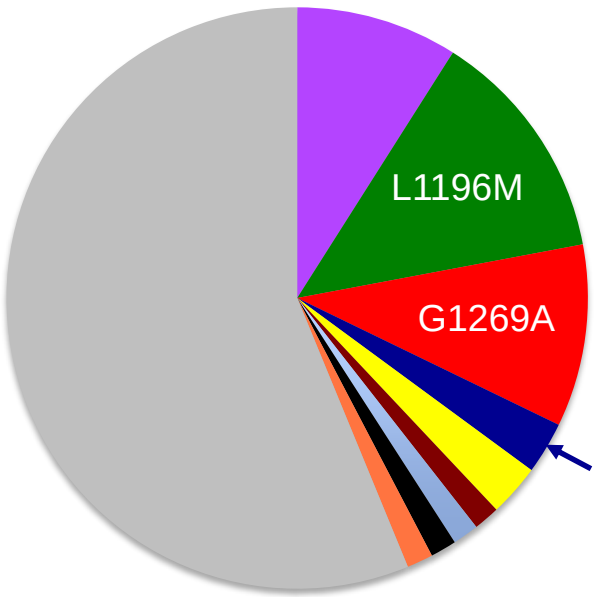
Post-crizotinib

- Amplification
- L1196M
- G1269A
- G1202R
- C1156Y
- S1206Y
- 1151Tins
- L1152R
- F1174V
- No mutation



Post-ceritinib

Shifting Profile of ALK Resistance Mutations Depending on the ALK Inhibitor



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- Amplification
- L1196M
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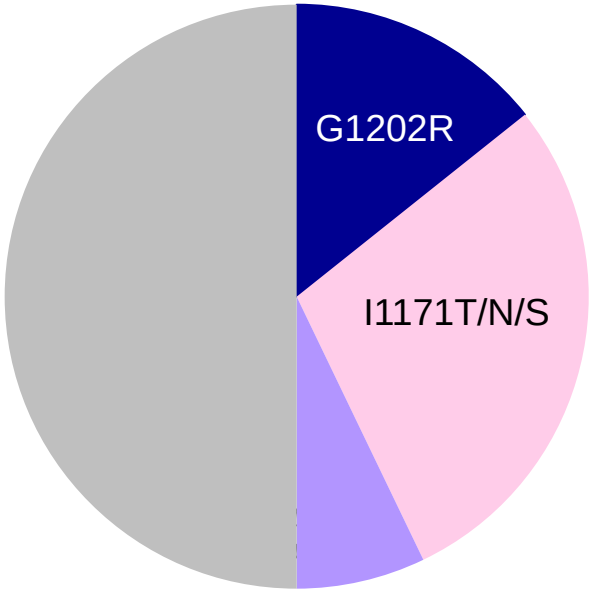
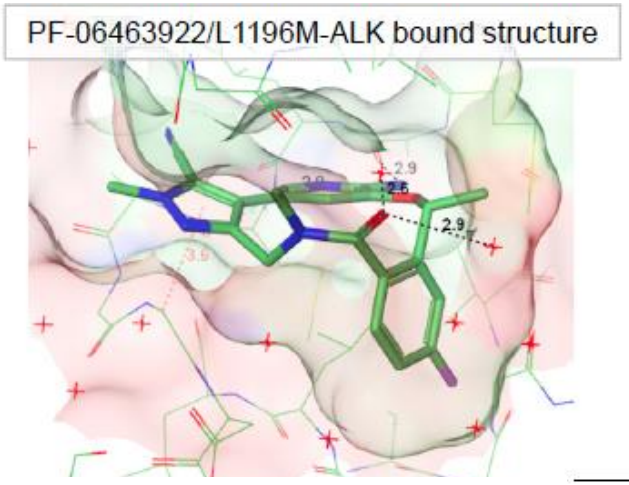
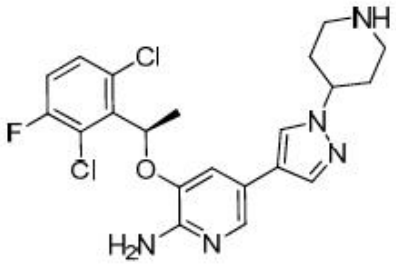
- L1152R
- F1174V
- No mutation

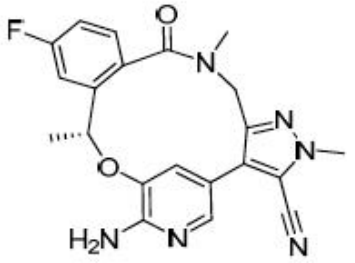


Post-alectinib

Lorlatinib is a Highly Potent, CNS Penetrant ALK/ROS1 TKI



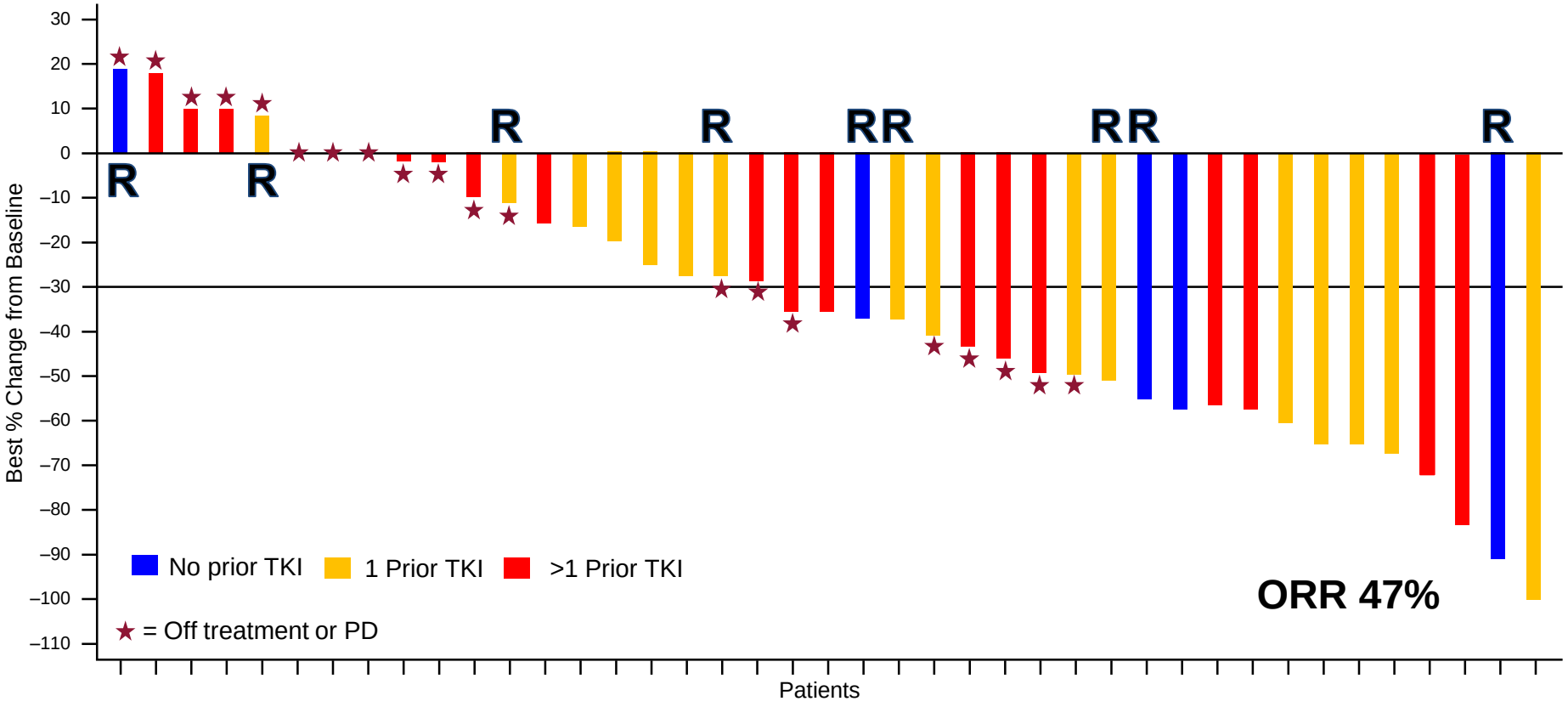




	crizotinib	PF-06463922
ALK WT NIH3T3 IC50 (nM)	80	1.3
ALK L1196M NIH3T3 IC50 (nM)	843	21
ALK G1202R NIH3T3 IC50 (nM)	**1148**	**77**
ROS1-CD74 IC50 (nM)	11	0.24
MDR BA/AB	45	1.5

Johnson et al., J Med Chem 57: 4720-4, 2014

Clinical Activity of Lorlatinib in ALK- and ROS1-Rearranged NSCLC

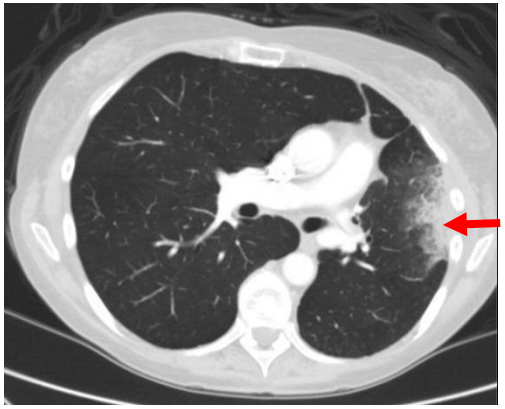


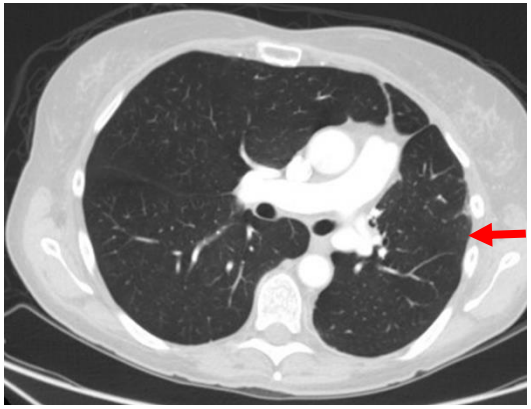
PD occurred in 14 patients: new lesions (n=8), non-target lesions (n=2), both new and non-target lesions (n=4).

PD=progressive disease; R=ROS1+; ROS1=c-ros oncogene 1; TKI=tyrosine kinase inhibitor

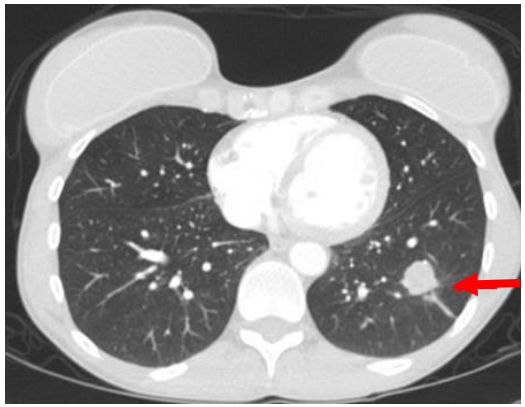
Bauer et al., WCLC 2015

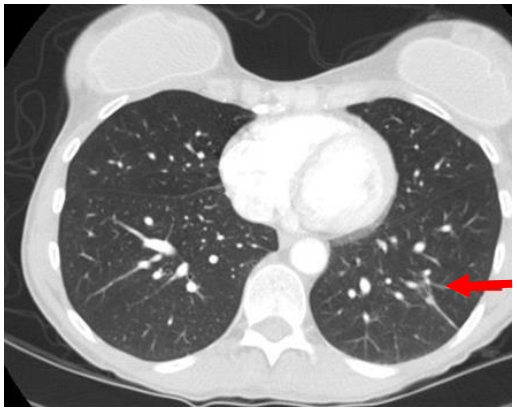
Lorlatinib Can Overcome the ALK G1202R Resistance Mutation





Patient 1: ALK+ NSCLC
Previously treated with crizotinib and ceritinib
Local molecular testing after ceritinib with ALK G1202R
Started lorlatinib at 75 mg QD
Dose reduced to 50 mg QD
Ongoing at >12 months

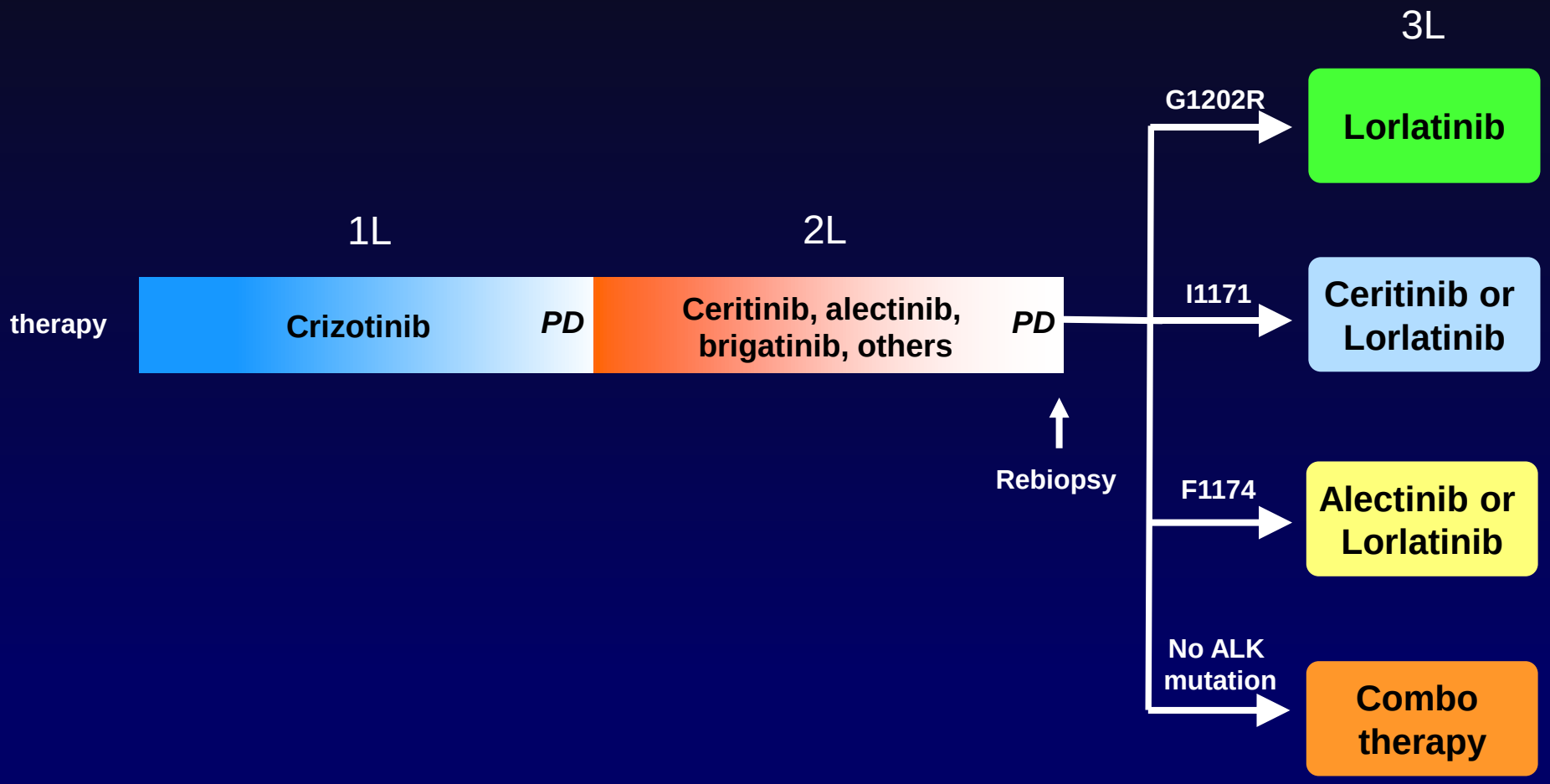




Patient 2: ALK+ NSCLC
Previously treated with crizotinib and brigatinib
Local molecular testing after brigatinib with ALK G1202R
Started lorlatinib at 200 mg QD
Dose reduced to 100 mg QD
Ongoing at >8 months

Shaw et al., ASCO 2015

Current Treatment Strategy for Metastatic ALK+ NSCLC

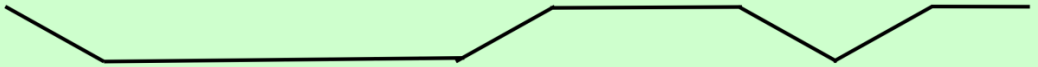


Overview

- Introduction to Lung Cancer
- First Generation Targeted Therapies
- Second Generation Targeted Therapies
- **Evolution of Resistance**
- Summary and Future Directions

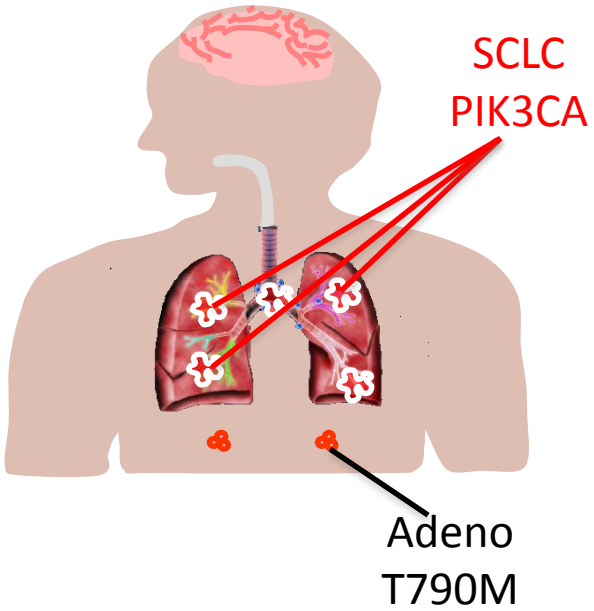
Serial Biopsies Reveal Dynamic Populations of Different Tumor Clones

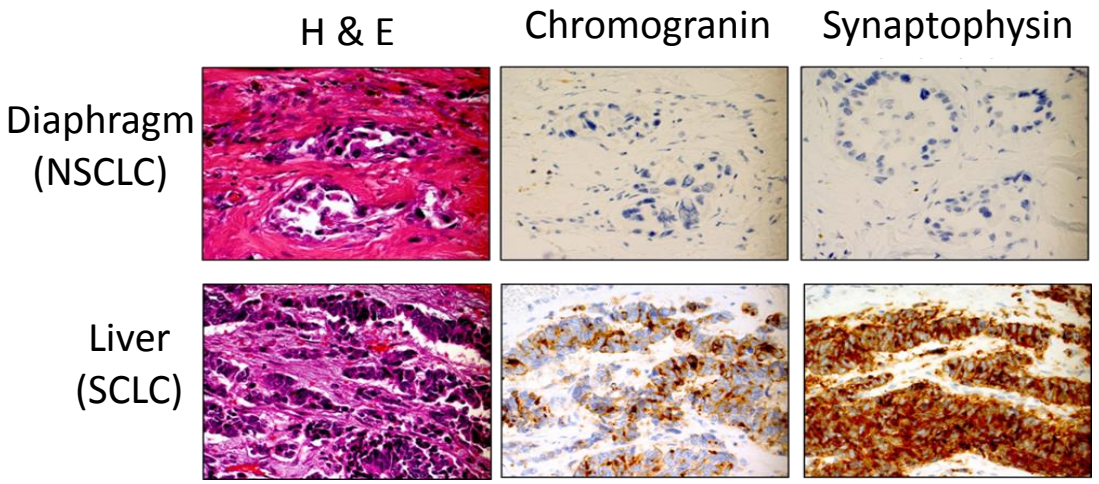
Histology	Adeno	Adeno	Adeno
Genotype	L858R TP53	L858R TP53 T790M	L858R TP53
EGFR TKI status	Sensitive	Resistant	Sensitive
Tumor Burden			
Treatment	Chemo / Erlotinib	Chemo	Chemo / Erlotinib*
Timeline	2007 – 2008	2009	2010

Histology	Adeno	SCLC	Adeno	SCLC
Genotype	L858R	L858R PIK3CA	L858R	L858R PIK3CA
EGFR TKI status	Sensitive	Resistant	Sensitive	Resistant
Tumor Burden				
Treatment	Erlotinib	C+RT	Erlotinib	C+ RT
Timeline	2008 – 2009		2010	

Sequist et al, Sci Transl Med 2011

Heterogeneity of Resistance Mechanisms Discovered at Autopsy

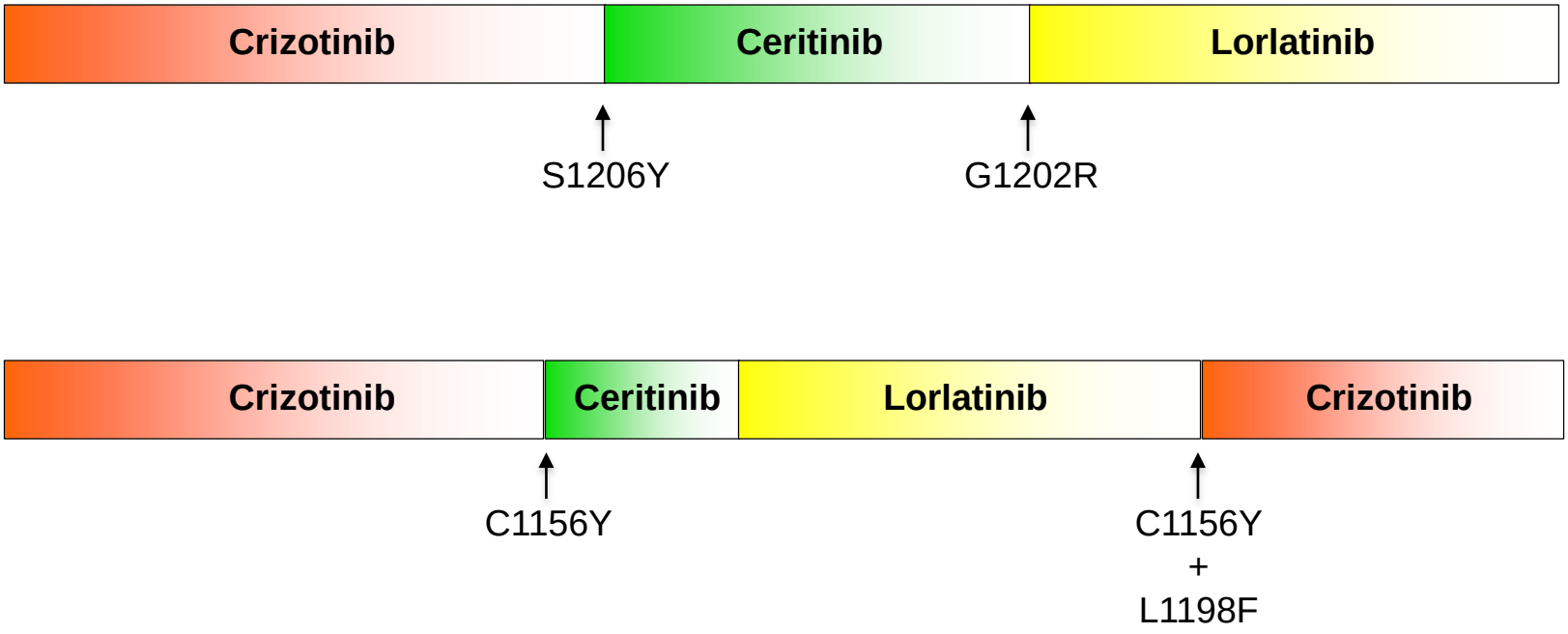




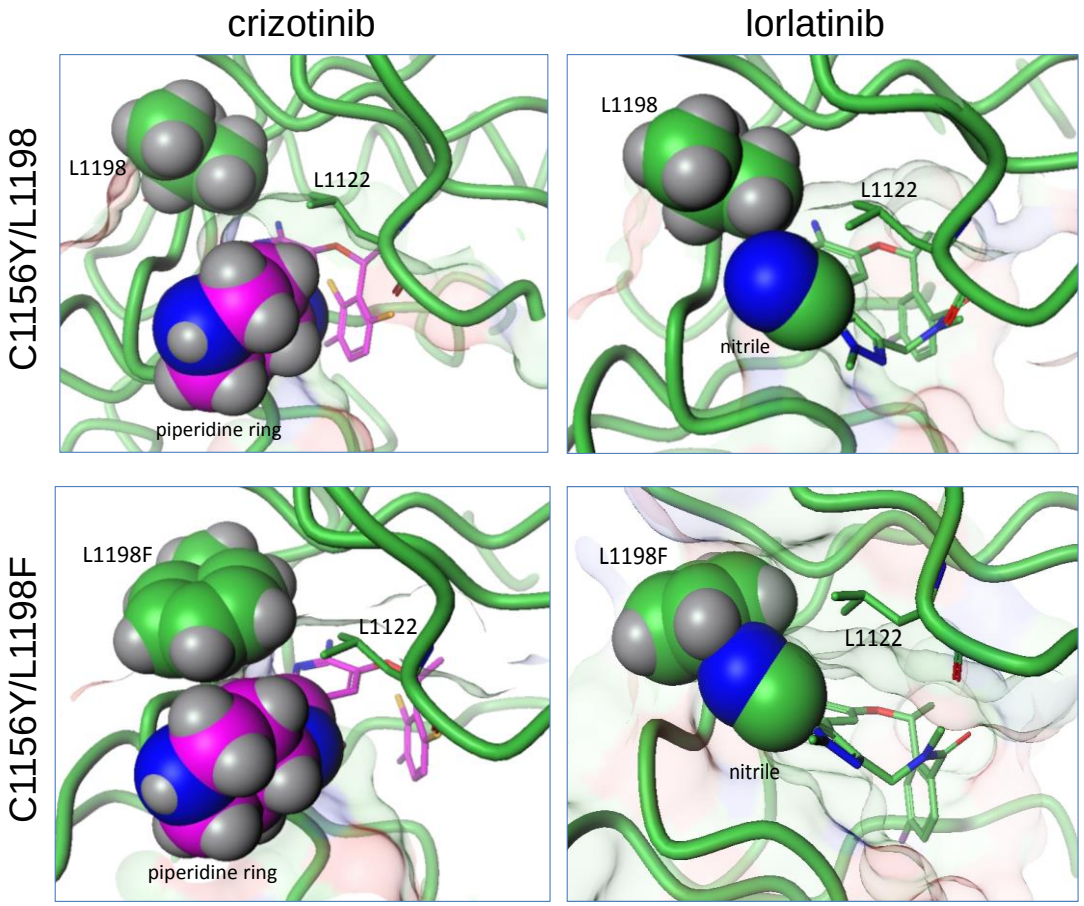
Sample	Normal Liver	Diaphragm Tumor	Lung Tumor	Liver Tumor
Histological Features	Normal Tissue	Adenocarcinoma	SCLC	SCLC
Number of Reads	179,298,190	350,864,233	388,189,232	318,482,313
Average Coverage	146	287	319	253
Primary *EGFR* Mutation	WT	L858R	L858R	L858R
Secondary *EGFR* Mutation	WT	T790M	WT	WT
PIK3CA Status	WT	WT	E545K	E545K
TP53 Status	WT	WT/Δ154-163	-/Δ154-163	-/Δ154-163
RB1 status	WT	WT	-/-	-/-

Niederst et al., Nat Commun 6: 6377, 2015

Longitudinal Evolution of Resistance in ALK+ NSCLC

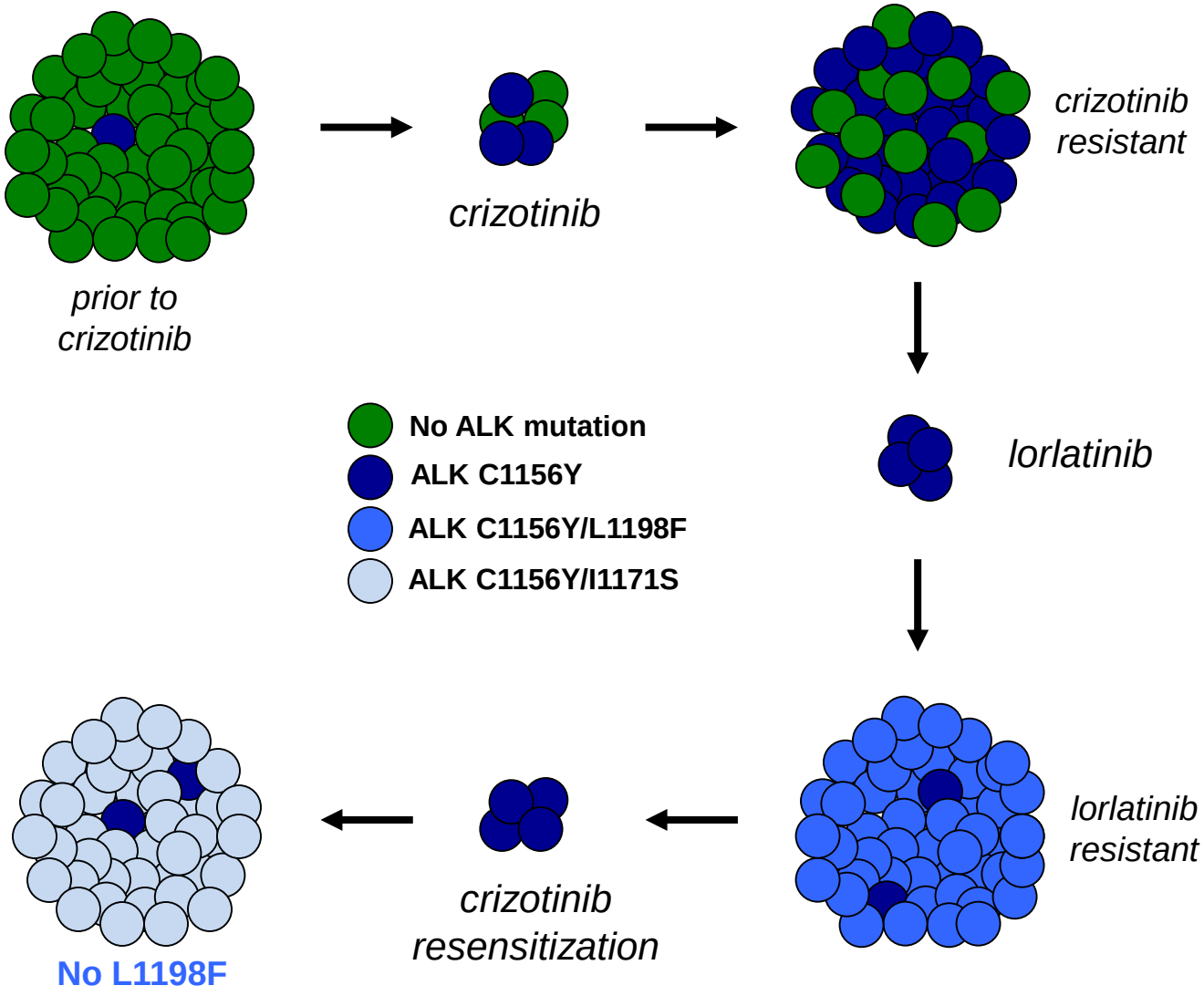


Structural Basis for ALK L1198F-Mediated Resistance to Lorlatinib and Sensitivity to Crizotinib



Shaw et al., NEJM 2015 Dec 23

The Selective Pressure of Each ALK Inhibitor Shapes the Longitudinal Evolution of Resistance



Summary

- All patients with newly diagnosed metastatic lung cancer should undergo multiplex molecular testing
- For patients with oncogene-addicted lung cancers, targeted therapies have transformed the natural history of disease
- Essentially all patients will develop resistance to targeted therapies over time
- There are new and emerging treatment strategies for patients who relapse on targeted therapies; these will be most effective when tailored based on the underlying resistance mechanism

Adapted from Nature 513: S8-9, 2014

Future Directions

- Liquid biopsies (ie blood-based assays of circulating tumor DNA) to allow noninvasive, dynamic monitoring of response and resistance in real time
- Combinations of ALK inhibitors and other targeted agents to overcome resistance due to off-target mechanisms
- Upfront drug combinations, possibly in an intercalated manner, to prevent the emergence of resistant clones
- Multimodality treatment regimens involving targeted therapies, local therapies like radiation, and even immune or vaccine-based strategies

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National Foundation for Cancer Research
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MGH Pathology
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