

Molecular Alterations in Non-Small Cell Lung Cancer

Andrew T. Turk, MD
att2101@columbia.edu

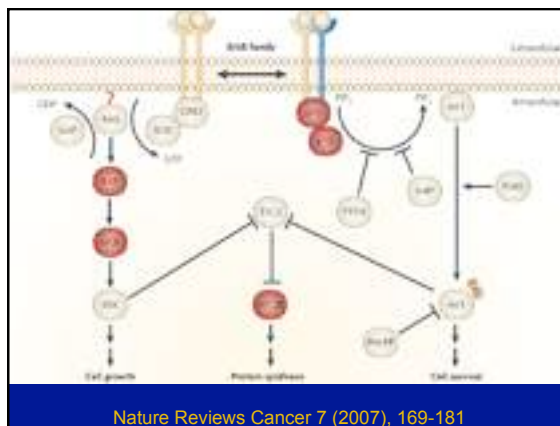
- I. *EGFR* Mutations
 - 1. Demographics & Pathophysiology
 - 2. Tyrosine Kinase Inhibitors
- II. *ErbB2* & *KRAS* Mutations
- III. *ALK* Rearrangements
 - 1. Soda *et al.* 2007
 - 2. Kwak *et al.* 2010
 - 3. Case 1
- IV. Clinical Practice Guideline: Lindeman *et al.* 2013
- V. Case 2: *EGFR* T790M
 - 1. Test Methodology
 - 2. Kobayashi *et al.* 2005
 - 3. Gazdar *et al.* 2014
- VI. Case 3: Multiple Tumors
 - 1. Girard *et al.* 2009
- VII. *ROS1* Rearrangements: Bergethon *et al.* 2012
- VIII. *BRAF* Mutations: Cardarella *et al.* 2013

(as of 6/10/14)
<http://www.cancer.gov/cancertopics/druginfo/lungcancer#dal1>

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Epidermal growth factor receptor mutations in lung cancer
Sreenivath V. Sharma*, Dipankar W. Bell*, Jeffrey Settleman* and Daniel A. Haber
Nature Reviews Cancer 7 (2007), 169-181

Epidermal Growth Factor Receptor Mutations in Non-Small-Cell Lung Cancer: Implications for Treatment and Tumor Biology
Fati A. Mino, Jeffrey A. Engelman, and Bruce E. Johnson
J Clin Oncol 23:3227-3234



EGFR Mutations (et cetera): Janne et al.

Family of closely related receptors
 ErbB1: EGFR
 ErbB2: HER-2/*neu*
 ErbB3: HER-3
 ErbB4: HER-4

EGFR Mutations (et cetera): Lindeman et al.

Table 4. EGFR Mutation Prevalence in EGFRwt Lung Adenocarcinoma Patient Populations

Study	EGFR Mutation Prevalence, %	EGFR Mutation Positive	EGFR Mutation Negative	n (%)
Wang et al ¹²	20	111	469	580 (100)
Wang et al ¹³	20	92	370	462 (100)
Wang et al ¹⁴	27	92	247	339 (100)
Wang et al ¹⁵	38	114	186	300 (100)

EGFR Mutations (et cetera): Lindeman et al.

Table 5. Clinicopathologic Characteristics of Patients in EGFR Mutation Status in Tissues Containing Primary Tumor

	EGFR Mutation Prevalence, %	EGFR Mutation Positive	EGFR Mutation Negative	n (%)
Age at diagnosis, yr				
<60	38	270	313	583 (100)
≥60	38	431	709	1140 (100)
Sex				
Male	38	1077	171	1248 (100)
Female	38	359	501	860 (100)
Smoking				
Never	38	361	599	960 (100)
Ever	38	369	717	1086 (100)
History of smoking, pack-years				
<10	37	150	310	460 (100)
11-20	38	9	31	40 (100)
≥21	37	8	27	35 (100)
Unknown	38	10	88	98 (100)
Pathology				
Adenocarcinoma	38	1076	144	1220 (100)
Squamous	38	9	136	145 (100)
Adenocarcinoma/squamous	38	9	3	12 (100)
Squamous/adeno	38	1	14	15 (100)
Unclassified	38	0	3	3 (100)
Unknown	37	87	307	394 (100)
Metastatic to primary	38	37	111	148 (100)
Stage, TNM				
Stage I	38	29	33	62 (100)
Stage II	38	29	31	60 (100)
Stage III	38	107	114	221 (100)

EGFR Mutations (et cetera): Lindeman et al.

Table 6. Clinicopathologic Characteristics in Patients in EGFR Mutation Status in Tissues Containing Primary Tumor

	EGFR Mutation Prevalence, %	EGFR Mutation Positive	EGFR Mutation Negative	n (%)
Sex				
Female	38	339	521	860 (100)
Male	38	347	710	1057 (100)
Smoking				
Never	38	349	611	960 (100)
Ever	38	349	611	960 (100)
History of smoking, pack-years				
<10	38	146	314	460 (100)
11-20	38	9	31	40 (100)
≥21	38	8	27	35 (100)
Unknown	38	9	88	97 (100)
Adenocarcinoma	38	1076	144	1220 (100)
Squamous	38	9	136	145 (100)
Adenocarcinoma/squamous	38	9	3	12 (100)
Squamous/adeno	38	1	14	15 (100)
Unclassified	38	0	3	3 (100)
Unknown	38	87	307	394 (100)

EGFR Mutations (et cetera): Janne et al.

Three types of mutations
 Missense mutations: exons 18, 20, and 21
 Deletions: exon 19
 Insertions: exon 20

Most common
 E746_A750 exon 19 deletion
 L858R

EGFR Mutations (et cetera): Lindeman et al.

Table 11. EGFR mutations according to prevalence (at least 1% of all EGFR mutations)

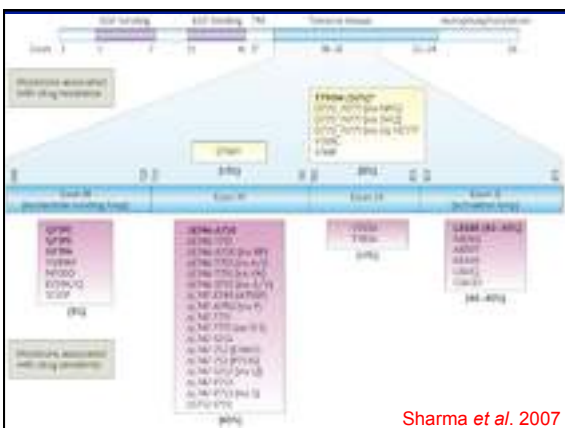
EGFR exon	EGFR codon	Mutation	Prevalence	Approximate % of all EGFR mutations
18	E746	E746V	1.0%	7%
		E746L	0.7%	
		E746A	0.7%	
		E746G	0.7%	
		E746S	0.7%	
		E746D	0.7%	
		E746K	0.7%	
19	E746	E746V	1.0%	1%
		E746L	0.7%	
		E746A	0.7%	
20	E858	E858R	1.0%	50%
		E858K	0.7%	
		E858Q	0.7%	
		E858L	0.7%	
21	E911	E911V	1.0%	1%
		E911L	0.7%	
		E911A	0.7%	
		E911G	0.7%	
21	E911	E911V	1.0%	5%
		E911L	0.7%	
		E911A	0.7%	
21	E911	E911V	1.0%	1%
		E911L	0.7%	

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Tyrosine Kinase Inhibitors: Lindeman *et al.*

Outcome	Mean ± SD		Percentage		n (N)
	<i>EGFR</i> Mutation Positive	<i>EGFR</i> Mutation Negative	<i>EGFR</i> Mutation Positive	<i>EGFR</i> Mutation Negative	
Response rate, % ^a			50	11	51 (364)
Disease control rate, % ^b			50	42	26 (204)
Time to progression (progression-free survival), mo ^c	11.0 ± 7.86	3.4 ± 2.59			27 (244)
Median survival time, mo ^d	11.1 ± 18.1	2.1 ± 1.4			27 (249)

Outcomes in patients treated with tyrosine kinase inhibitors



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EGFR Mutations (et cetera): Janne *et al.*

Family of closely related receptors
 ErbB1: *EGFR*
 ErbB2: *HER-2/neu*
 ErbB3: *HER-3*
 ErbB4: *HER-4*

ErbB2 mutations
 10% of unselected lung adenocarcinomas

Exon 20 insertions
 (analogous to exon 20 insertions found in *EGFR*)

KRAS Mutations: Janne *et al.*

~30% of lung adenocarcinomas

KRAS and *EGFR* mutations are mutually exclusive in lung adenocarcinomas

Most closely associated with a history of smoking
 Almost never found in tumors from lifelong nonsmokers

More common in women

Activating missense mutations affecting G12, G13

[KRAS Mutations: Janne et al.](#)

Associated with **shorter survival** in early-stage and locally advanced NSCLC

Found more frequently in patients who develop **disease progression** with TKI therapy

Associated with **worse outcome** when patients are treated with chemotherapy in combination with erlotinib

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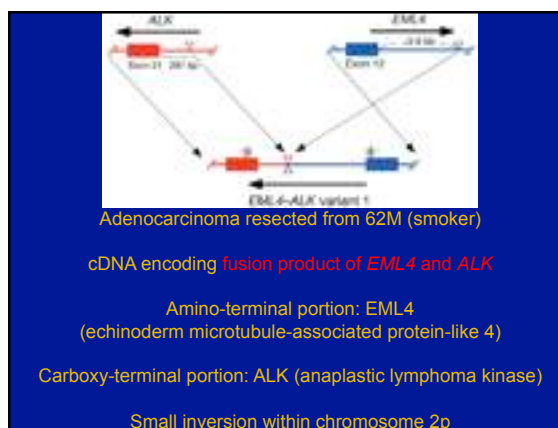
VIII. [BRAF Mutations](#): Cardarella et al. 2013

[ALK rearrangements: Soda et al.](#)

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

Yoshinori Soda¹, Young Lim Choi², Mutsaers Emmert³, Hiroaki Takada⁴, Yoshitaka Terauchi⁵, Hiroshi Nakamura⁶, Shin-ichiro Eguchi⁷, Masahito Watanabe⁸, Kazuo Kurashina⁹, Hiroyuki Mizuno¹⁰, Masashi Nishio¹¹, Shoji Ohno¹², Naoki Ishikawa¹³, Hiroaki Kohno¹⁴, Toshiro Mori¹⁵, Kazuo Sekine¹⁶, Yukihiko Suganuma¹⁷ & Shojiro Minami¹⁸

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



[ALK rearrangements: Kwak et al.](#)

Anaplastic Lymphoma Kinase Inhibition in Non-Small-Cell Lung Cancer

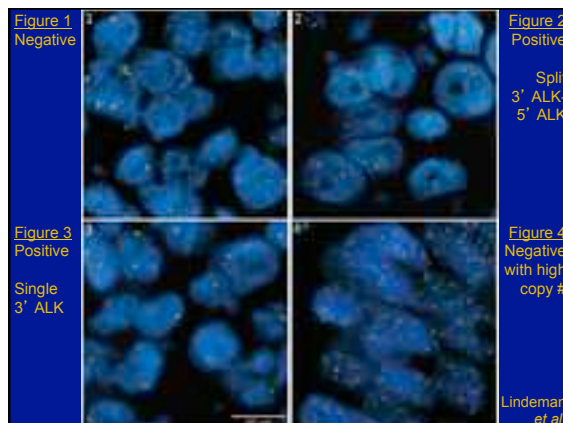
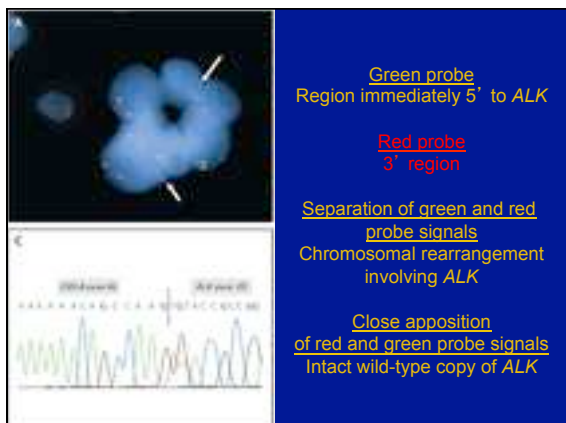
Yuanxin Li, Raek M.D., Ph.D., Yangjun Song, M.D., Ph.D., D. Ryan Compton, M.D., Ph.D., Paul T. Shou, M.D., Ph.D., Benjamin Solomon, M.B., B.S., Ph.D., Robert G. Maki, M.D., Ph.D., Yi-Hong Li, M.D., Ph.D., David J. Brantner, M.D., Theodor A. Jänne, M.D., Ph.D., Robert E. Johnson, M.D., Ph.D., Masahito Watanabe, Ph.D., Hiroaki Kohno, M.D., Thomas J. Lynch, M.D., Victor Falck, M.D., Harwan Zaidi, M.S., Jeffrey A. Engelman, M.D., Ph.D., Louis R. Sordani, M.D., M.F.H., Weiwei Tay, Ph.D., Junya Gotoh, M.D., Ph.D., Myr Mon Rosales, M.D., Cong E. Wu, Ph.D., S. Martin Shreeve, M.D., Ph.D., Matt J. Kazan, M.D., Jeffrey Settleman, Ph.D., James L. Christman, Ph.D., David R. Hildreth, M.D., Ph.D., Keith Wilson, Ph.D., Niall Talbot, M.D., Ph.D., Geoffrey I. Shapiro, M.D., Ph.D., Jeffrey W. Clark, M.D., and R. James Gray, M.D., Ph.D.

N Engl J Med 2010;363:1693-703

[ALK rearrangements: Kwak et al.](#)

Screened tumor samples from “approximately 1500” patients with advanced NSCLC from August 2008 through February 2010

Identified **82 patients** with advanced ALK-positive disease



ALK rearrangements / EML4-ALK fusion gene

Soda et al.
5 of 75 (7%) NSCLC patients

Kwak et al.
82 of 1500 (5%) NSCLC patients

Other references
Prevalence is about 2% to 7% of all NSCLCs in the United States

Other fusion partners
(e.g. *KIF5B* and *TGF*) have also been reported

ALK Rearrangements: Lindeman et al.

Table 1. Clinicopathologic Characteristics in Relation to ALK Rearrangement Status

	ALK Rearrangement Positive, %	ALK Rearrangement Positive	ALK Rearrangement Negative	n (%)
Age (years)		41	210	1123 (12.5)
Sex		74	331	1135 (12.6)
Male	61	22	278	460 (5.0)
Female	13	52	73	175 (1.9)
Smoking		33	161	102 (1.1)
Never	78	20	102	167 (1.8)
Former	22	80	90	145 (1.6)
Current	0	18	69	105 (1.2)
Unknown	0	12	174	186 (2.1)
Stage		47	218	1214 (13.5)
Adenocarcinoma	67	23	102	127 (1.4)
Adenocarcinoma	17	71	74	156 (1.7)
Unknown	16	60	67	123 (1.4)
NSCLC	16	60	101	167 (1.8)

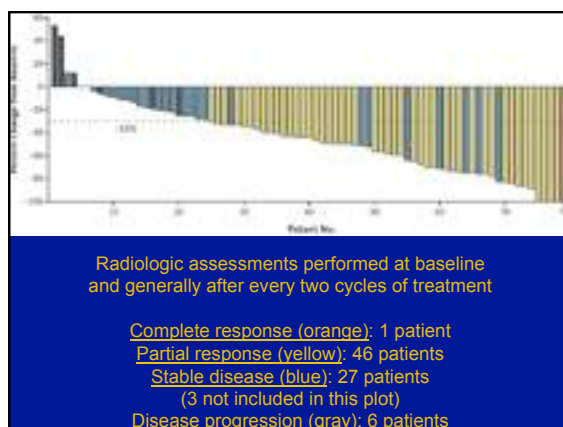
Patients with ALK rearrangements tend to:
be younger than those without the rearrangements;
have little or no exposure to tobacco;
have adenocarcinomas

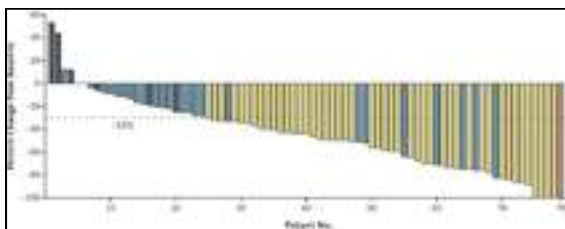
Kwak et al.: ALK inhibitor

Early phase clinical trial of **crizotinib** (PF-02341066)

Cohort with FISH-positive results for ALK rearrangement received 250 mg twice daily in 28-day cycles

Therapy continued as long as patients did not have progressive disease or intolerable side effects

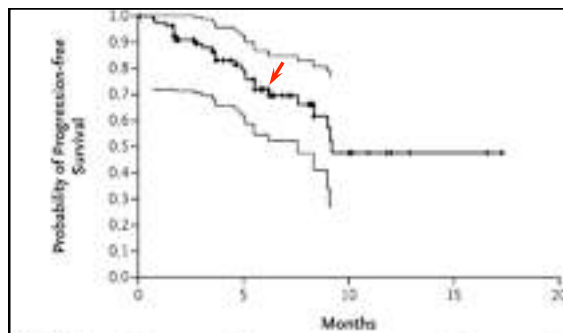




Overall response rate: **57%** (47/82)
 (confirmed partial and complete responses)

Rate of stable disease: **33%** (27/82)
 (stable disease plus unconfirmed partial response)

Response rate with second-line chemotherapy:
 Approximately **10%**



Estimated 6-month probability of progression-free survival: **72%**
 (95% Hall-Wellner confidence limits)

6-month PFS with second-line multiagent chemotherapy: **27.2%**

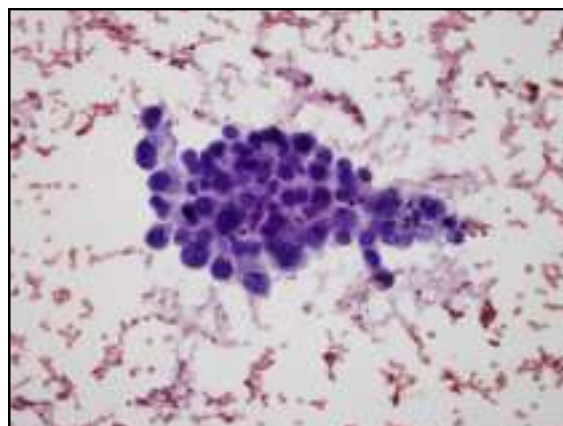
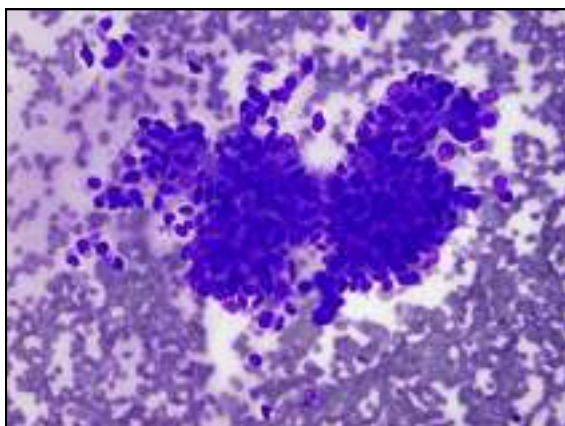
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Case 1

49M, 20 pack-year smoking history
 (quit 12/31/1992)

Chest CT angiography 12/23/13
 LUL spiculated opacity (14 mm)

FNA 1/8/14
 Adenocarcinoma, consistent with origin from lung



I. When should molecular testing for NSCLC be performed?

1. Which patients should be tested for EGFR mutations and ALK rearrangements?
2. When should a patient specimen be tested for EGFR mutations or ALK rearrangements?
3. How rapidly should test results be available?

II. How should EGFR testing be performed?

4. How should specimens be processed for EGFR mutation testing?
5. What are the specimen requirements for EGFR testing?
6. How should EGFR testing be performed?
7. What is the role of KRAS analysis in selecting patients for targeted therapy with EGFR TKIs?
8. What additional testing considerations are important in the setting of secondary or acquired EGFR TKI resistance?

III. How should ALK testing be performed?

9. What methods should be used for ALK testing?

IV. Should other genes be routinely tested in lung adenocarcinoma?

10. Are other molecular markers suitable for testing in lung cancer?

V. How should molecular testing of lung adenocarcinoma be implemented and operationalized?

11. Must all adenocarcinomas be tested for both EGFR and ALK?
12. How should EGFR and ALK results be reported?
13. How should EGFR and ALK testing be validated?
14. How should quality assurance be maintained?

Clinical Practice Guideline: Lindeman et al.

Question 1. When should EGFR testing be performed for NSCLC patients with ALK rearrangements?

1.1a Recommendation: EGFR mutation testing should be used to select patients for EGFR-targeted therapy, and patients with lung adenocarcinoma should not be included from testing on the basis of their histomorphology.

1.1b Recommendation: ALK molecular testing should be used to select patients for ALK tyrosine kinase inhibitors with lung adenocarcinoma. ALK testing should not be included from testing on the basis of clinical histomorphology.

1.2 Recommendation: In the setting of lung adenocarcinoma specimens, EGFR and ALK testing is recommended for patients with adenocarcinoma histology, regardless of histologic grade or the presence of squamous components. EGFR and ALK testing is not recommended for lung adenocarcinoma that lack an adenocarcinoma component, such as pure squamous cell carcinoma, and mixed cell carcinoma, including any adenocarcinoma component, including an adenocarcinoma component, except for specimens collected for EGFR and ALK testing that are generated to verify ongoing surveillance and not for testing for clinical response (eg, drug-agnostic trial or smoking history) that are used to inform a patient's clinical response.

1.3 Recommendation: In specimens with adenocarcinoma histology, genetic testing of specimens from non-purely adenocarcinoma specimens is not recommended.

1.4 Recommendation: For patients with multiple adenocarcinoma specimens using adenocarcinoma-rich tissue for the initial diagnosis, testing of multiple adenocarcinoma-rich tissue for EGFR testing is not recommended.

Clinical Practice Guideline: Lindeman et al.

Table 7. Major Studies Specifically Reporting EGFR Mutation Analysis in Surgically Resected Squamous Cell Carcinomas as Compared to Adenocarcinomas

Author, y	Proportion of Major Type of Study Population	EGFR Mutation in Resected Adenocarcinoma, No. (%)	EGFR Mutation in Resected Squamous Cell Carcinoma, No. (%)
Chen et al. ¹⁷ (2009)	Retrospective	100/131 (76%)	0/100 (0%)
Ng et al. ¹⁸ (2009)	Retrospective	13/141 (9%)	0/141 (0%)
Lee et al. ¹⁹ (2009)	Prospective	13/141 (9%)	0/141 (0%)
Lee et al. ²⁰ (2010)	Retrospective	13/141 (9%)	0/141 (0%)
Lee et al. ²¹ (2010)	Retrospective	13/141 (9%)	0/141 (0%)
Lee et al. ²² (2010)	Retrospective	13/141 (9%)	0/141 (0%)
Lee et al. ²³ (2010)	Retrospective	13/141 (9%)	0/141 (0%)
Lee et al. ²⁴ (2010)	Retrospective	13/141 (9%)	0/141 (0%)
Lee et al. ²⁵ (2010)	Retrospective	13/141 (9%)	0/141 (0%)

Table 8. Studies Specifically Reporting Outcomes of ALK Rearrangement Studies in Squamous Cell Carcinomas

Author, y	n	ALK Rearrangement Positive, %
Chen et al. ¹⁷ (2009)	100	0
Chen et al. ¹⁸ (2009)	141	0
Lee et al. ¹⁹ (2009)	141	0
Lee et al. ²⁰ (2010)	141	0

Clinical Practice Guideline: Lindeman et al.

Question 2. What is the role of KRAS analysis in selecting patients for targeted therapy with EGFR TKIs?

2.1 Recommendation: KRAS mutation testing should be performed in the setting of diagnosis for patients presenting with adenocarcinoma histology, regardless of histologic grade or the presence of squamous components. KRAS testing is not recommended for lung adenocarcinoma that lack an adenocarcinoma component, such as pure squamous cell carcinoma, and mixed cell carcinoma, including any adenocarcinoma component, except for specimens collected for EGFR testing that are generated to verify ongoing surveillance and not for testing for clinical response (eg, drug-agnostic trial or smoking history) that are used to inform a patient's clinical response.

2.2 Recommendation: In specimens with adenocarcinoma histology, genetic testing of specimens from non-purely adenocarcinoma specimens is not recommended.

2.3 Recommendation: For patients with multiple adenocarcinoma specimens using adenocarcinoma-rich tissue for the initial diagnosis, testing of multiple adenocarcinoma-rich tissue for KRAS testing is not recommended.

Clinical Practice Guideline: Lindeman et al.

Question 3. What is the role of ALK testing in selecting patients for targeted therapy with EGFR TKIs?

3.1 Recommendation: ALK testing should be performed in the setting of diagnosis for patients presenting with adenocarcinoma histology, regardless of histologic grade or the presence of squamous components. ALK testing is not recommended for lung adenocarcinoma that lack an adenocarcinoma component, such as pure squamous cell carcinoma, and mixed cell carcinoma, including any adenocarcinoma component, except for specimens collected for ALK testing that are generated to verify ongoing surveillance and not for testing for clinical response (eg, drug-agnostic trial or smoking history) that are used to inform a patient's clinical response.

3.2 Recommendation: In specimens with adenocarcinoma histology, genetic testing of specimens from non-purely adenocarcinoma specimens is not recommended.

3.3 Recommendation: For patients with multiple adenocarcinoma specimens using adenocarcinoma-rich tissue for the initial diagnosis, testing of multiple adenocarcinoma-rich tissue for ALK testing is not recommended.

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Case 2

52M, never-smoker
Intermittent cough beginning February 2012
Worsened in May 2012

CT chest 6/8/12

RLL mass, very suspicious for neoplasm

Bronchoscopy 6/13/12

Invasive adenocarcinoma

EGFR analysis

Exon 19 analysis positive for 9 base-pair deletion
Exon 20 analysis negative

PET 6/18/12

RLL opacity (7.4 x 3.8 cm)

Bilateral lung nodules "too numerous to count" highly suspicious

Focus in T8 (SUV = 3.1, 8 mm) consistent with metastatic disease

Highly suspicious for metastatic disease
involving right femoral head, right acetabulum, right iliac crest,
Most notable at T9 vertebral body (SUV = 4.2, 7 mm)

MR thoracic spine 6/20/12

Focus in T9 consistent with metastasis
Signal change in T8 also suspicious for metastasis

MR pelvis 6/20/12

Multiple osseous lesions concerning for metastatic disease

Case 2

2 cycles of systemic chemotherapy
(pemetrexed, cisplatin, bevacizumab)

Erlotinib daily beginning 8/13/12

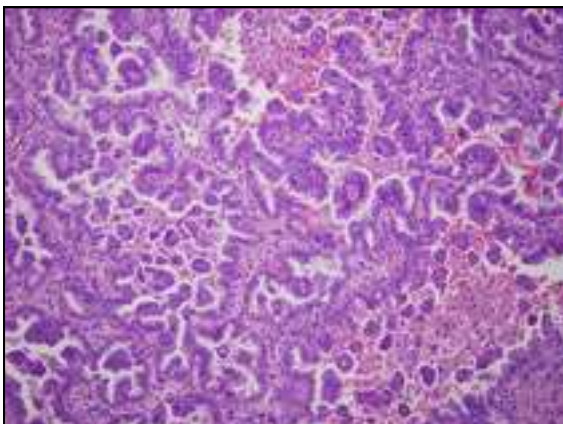
Surveillance chest CT: "excellent tumor response"

CT chest 5/30/13

Minimal increase in irregular nodular RLL densities
Stable sclerotic lesions in spine

RLL wedge resection 7/3/13

Adenocarcinoma



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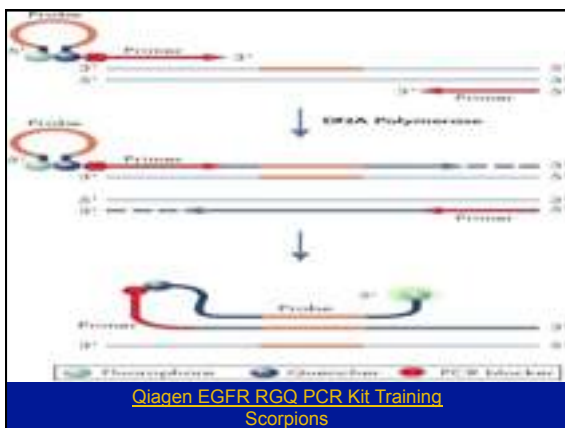
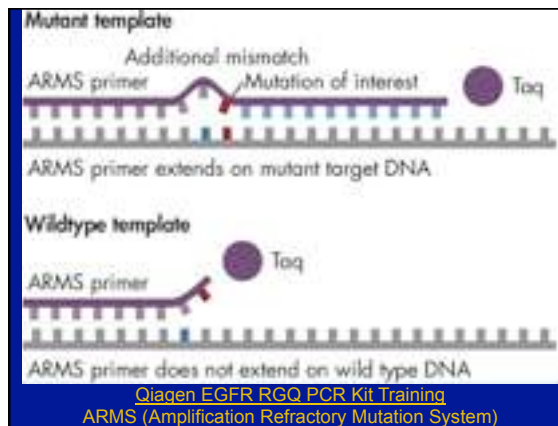
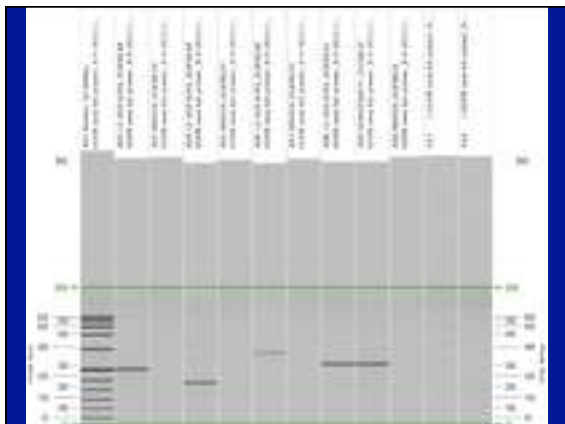
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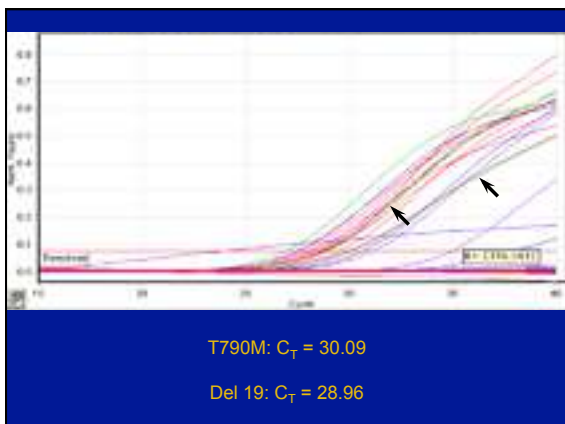


EGFR Mutation Status using EGFR RQq PCR Kit

Run Name: EGFR_KRAS RQq 2013-07-25 (1)ms
Date: 7/22/13
Time: 12:14:41

Rotor Layout:

	Controls			Sample number								
	PC	NTC		1	2	3	4	5	6	7	8	9
Ctrl	1	2	3	4	5	6	7	8	9	10	11	12
T790M	3	11	19	27	35	43	51	59	67	75	83	91
Deletions	3	11	19	27	35	43	51	59	67	75	83	91
L858R	4	12	20	28	36	44	52	60	68	76	84	92
L841Q	3	10	18	26	34	42	50	58	66	74	82	90
G719X	4	12	20	28	36	44	52	60	68	76	84	92
S768I	7	15	23	31	39	47	55	63	71	79	87	95
Ins	5	13	21	29	37	45	53	61	69	77	85	93



Case 2

CTRL | 184-7532
VALID

Rotor Position	Assay	Internal Ctl	Mutation Status
17	Ctrl	-	VALID
18	T790M	PASS	POSITIVE
19	Deletions	PASS	POSITIVE
20	L858R	PASS	NOT DETECTED
21	L861Q	PASS	NOT DETECTED
22	G719X	PASS	NOT DETECTED
23	S768I	PASS	NOT DETECTED
24	Insertions	PASS	NOT DETECTED

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- VIII. *BRAF* Mutations: Cardarella *et al.* 2013

Case 2: Kobayashi *et al.*

EGFR Mutation and Resistance of Non-Small-Cell Lung Cancer to Gefitinib

Sutomo Kobayashi, M.D., Ph.D., Tsun-J. Baggon, Ph.D., Tajhal Deyaram, B.A.,
 Paul A. Jänne, M.D., Ph.D., Oliver Kocher, M.D., Ph.D.,
 Matthew Meyerson, M.D., Ph.D., Bruce E. Johnson, M.D.,
 Michael J. Eck, M.D., Ph.D., Daniel G. Tenen, M.D., and Balazs Halmos, M.D.

N Engl J Med 2005;352:786-92

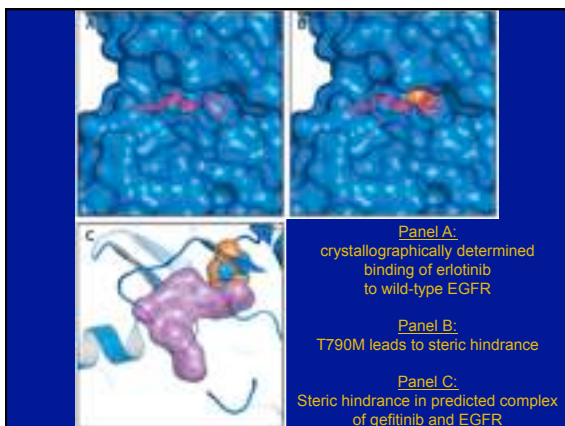
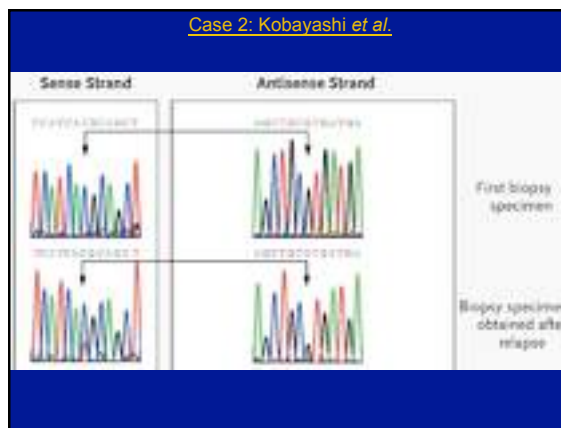
71M, former smoker

May 2001
Advanced, moderately differentiated adenocarcinoma

August 2002
Started gefitinib monotherapy
...

24 months of complete remission
...

Symptoms worsened
CT showed progressive abnormalities consistent with relapse

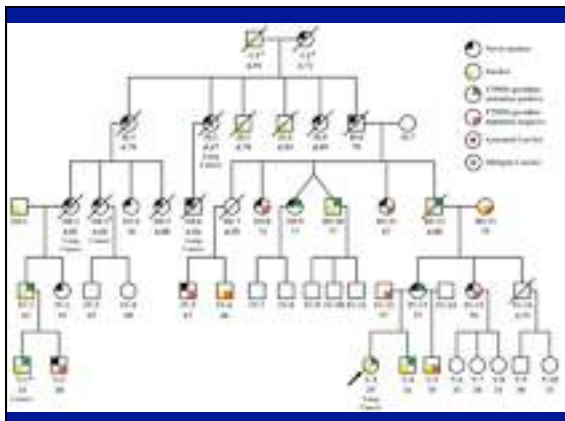


Hereditary Lung Cancer Syndrome Targets Never Smokers with Germline *EGFR* Gene T790M Mutations

M.D. Gao, M.D., Ph.D. Jinda Robinson, M.D., Dwight Christ, M.D., Chao-Feng Peng, William B. Barlow, M.D.,
 Anshu Soti, M.D.,† Shashini Sivarama, M.D.,† Lora Hunsberger, M.D.,† Hong Guo, Ph.D.,††
 Rong Chen, M.D.,†† and Joon H. Schiller, M.D.,†

Germline T790M mutations result in a unique hereditary lung cancer syndrome with a preliminary estimate of 31% risk for lung cancer in never smoker carriers

J Clin Oncol. 2014;9: 456-463



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VIII. *BRAF* Mutations: Cardarella *et al.* 2013

Case 3

68F

30 pack-year smoking history

CT chest 5/10/13

Multiple nodules throughout lungs

FNA 6/21/13

A (RUL posterior): Adenocarcinoma c/w origin from lung

B (RUL apex): Adenocarcinoma c/w origin from lung

VATS 7/1/13

RUL (lobectomy)

Adenocarcinoma, acinar predominant, x4

B3 ("most superior"): 1.5 x 1.2 x 0.7 cm (?FNA: B)

B5 ("inferior to" B3): 0.9 x 0.9 x 0.6 cm

B9 ("posterosuperior"): 1.8 x 1.7 x 0.9 cm (?FNA: A)

B13: 0.6 x 0.4 x 0.4 cm

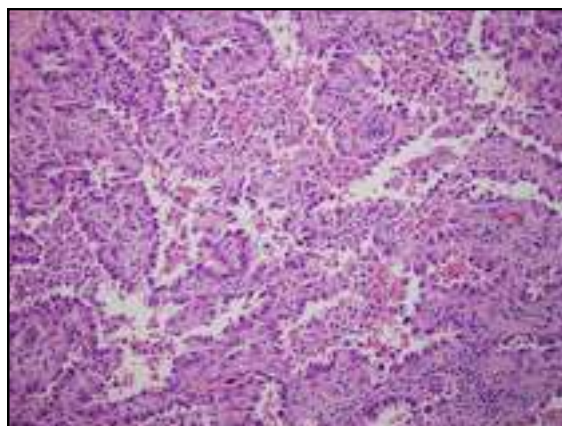
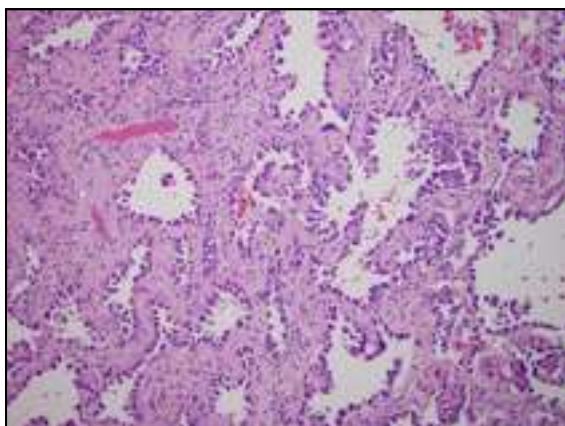
Lymph nodes

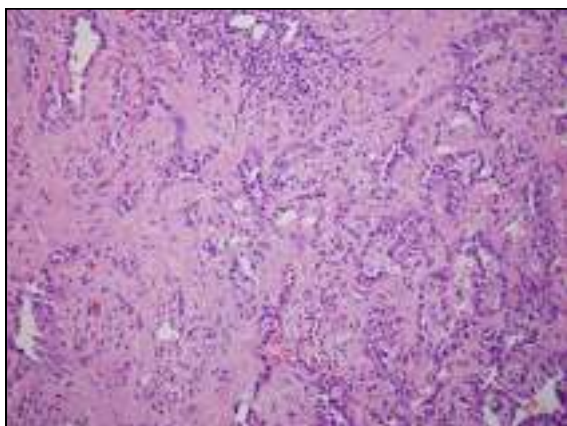
R4: 0/"multiple"

Level 7: 0/2

R10: 0/2

R12-14: 0/"multiple"





Project Update (1)

1) Primary tumor status for subjects in cancer genome study: analysis of mutational activation of loss-of-function oncogenes that are mutated by multiple cancer types.

2) The incidence of driver mutations

3) Candidate genes

4) Targeted sequencing of 100 cancer genomes, including 100 normal genomes, was completed by May 2012. Genomes were sequenced using Illumina HiSeq 2500. The genomes were then analyzed for mutations using the Illumina pipeline. The results of the analysis are available in the public domain.

5) The results of the analysis are available in the public domain.

6) The results of the analysis are available in the public domain.

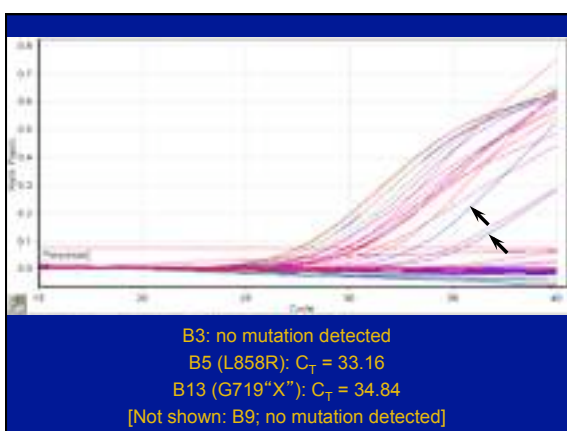
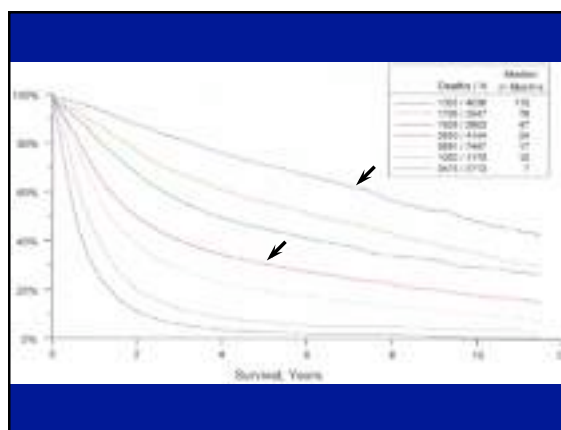
7) The results of the analysis are available in the public domain.

8) The results of the analysis are available in the public domain.

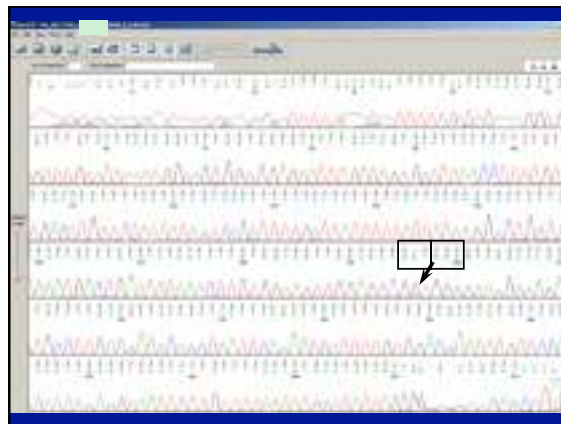
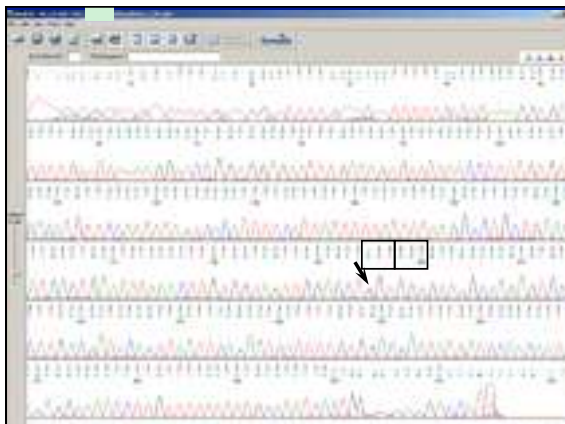
9) The results of the analysis are available in the public domain.

10) The results of the analysis are available in the public domain.

Sample	Genome	Genome	Genome
Sample 1	Genome 1	Genome 2	Genome 3
Sample 2	Genome 4	Genome 5	Genome 6
Sample 3	Genome 7	Genome 8	Genome 9
Sample 4	Genome 10	Genome 11	Genome 12
Sample 5	Genome 13	Genome 14	Genome 15
Sample 6	Genome 16	Genome 17	Genome 18
Sample 7	Genome 19	Genome 20	Genome 21
Sample 8	Genome 22	Genome 23	Genome 24
Sample 9	Genome 25	Genome 26	Genome 27
Sample 10	Genome 28	Genome 29	Genome 30
Sample 11	Genome 31	Genome 32	Genome 33
Sample 12	Genome 34	Genome 35	Genome 36
Sample 13	Genome 37	Genome 38	Genome 39
Sample 14	Genome 40	Genome 41	Genome 42
Sample 15	Genome 43	Genome 44	Genome 45
Sample 16	Genome 46	Genome 47	Genome 48
Sample 17	Genome 49	Genome 50	Genome 51
Sample 18	Genome 52	Genome 53	Genome 54
Sample 19	Genome 55	Genome 56	Genome 57
Sample 20	Genome 58	Genome 59	Genome 60
Sample 21	Genome 61	Genome 62	Genome 63
Sample 22	Genome 64	Genome 65	Genome 66
Sample 23	Genome 67	Genome 68	Genome 69
Sample 24	Genome 70	Genome 71	Genome 72
Sample 25	Genome 73	Genome 74	Genome 75
Sample 26	Genome 76	Genome 77	Genome 78
Sample 27	Genome 79	Genome 80	Genome 81
Sample 28	Genome 82	Genome 83	Genome 84
Sample 29	Genome 85	Genome 86	Genome 87
Sample 30	Genome 88	Genome 89	Genome 90
Sample 31	Genome 91	Genome 92	Genome 93
Sample 32	Genome 94	Genome 95	Genome 96
Sample 33	Genome 97	Genome 98	Genome 99
Sample 34	Genome 100	Genome 101	Genome 102
Sample 35	Genome 103	Genome 104	Genome 105
Sample 36	Genome 106	Genome 107	Genome 108
Sample 37	Genome 109	Genome 110	Genome 111
Sample 38	Genome 112	Genome 113	Genome 114
Sample 39	Genome 115	Genome 116	Genome 117
Sample 40	Genome 118	Genome 119	Genome 120
Sample 41	Genome 121	Genome 122	Genome 123
Sample 42	Genome 124	Genome 125	Genome 126
Sample 43	Genome 127	Genome 128	Genome 129
Sample 44	Genome 130	Genome 131	Genome 132
Sample 45	Genome 133	Genome 134	Genome 135
Sample 46	Genome 136	Genome 137	Genome 138
Sample 47	Genome 139	Genome 140	Genome 141
Sample 48	Genome 142	Genome 143	Genome 144
Sample 49	Genome 145	Genome 146	Genome 147
Sample 50	Genome 148	Genome 149	Genome 150



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Sample 15	Genome 43	Genome 44	Genome 45
Sample 16	Genome 46	Genome 47	Genome 48
Sample 17	Genome 49	Genome 50	Genome 51
Sample 18	Genome 52	Genome 53	Genome 54
Sample 19	Genome 55	Genome 56	Genome 57
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Sample 21	Genome 61	Genome 62	Genome 63
Sample 22	Genome 64	Genome 65	Genome 66
Sample 23	Genome 67	Genome 68	Genome 69
Sample 24	Genome 70	Genome 71	Genome 72
Sample 25	Genome 73	Genome 74	Genome 75
Sample 26	Genome 76	Genome 77	Genome 78
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Sample 29	Genome 85	Genome 86	Genome 87
Sample 30	Genome 88	Genome 89	Genome 90
Sample 31	Genome 91	Genome 92	Genome 93
Sample 32	Genome 94	Genome 95	Genome 96
Sample 33	Genome 97	Genome 98	Genome 99
Sample 34	Genome 100	Genome 101	Genome 102
Sample 35	Genome 103	Genome 104	Genome 105
Sample 36	Genome 106	Genome 107	Genome 108
Sample 37	Genome 109	Genome 110	Genome 111
Sample 38	Genome 112	Genome 113	Genome 114
Sample 39	Genome 115	Genome 116	Genome 117
Sample 40	Genome 118	Genome 119	Genome 120
Sample 41	Genome 121	Genome 122	Genome 123
Sample 42	Genome 124	Genome 125	Genome 126
Sample 43	Genome 127	Genome 128	Genome 129
Sample 44	Genome 130	Genome 131	Genome 132
Sample 45	Genome 133	Genome 134	Genome 135
Sample 46	Genome 136	Genome 137	Genome 138
Sample 47	Genome 139	Genome 140	Genome 141
Sample 48	Genome 142	Genome 143	Genome 144
Sample 49	Genome 145	Genome 146	Genome 147
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1. Girard *et al.* 2009

VII. *ROS1* Rearrangements: Bergethon *et al.* 2012

VIII. *BRAF* Mutations: Cardarella *et al.* 2013

Case 3: Girard *et al.*

Comprehensive Histologic Assessment Helps to Differentiate Multiple Lung Primary Nonsmall Cell Carcinomas From Metastases

Nicolas Girard, MD,* Charuhar Deshpande, MD, PhD,† Christopher Lau, PhD,‡
David Finley, MD,§ Valerie Rusch, MD,§ William Pan, MD, PhD,¶,¶¶
and William D. Travis, MD†

(*Am J Surg Pathol* 2009;33:1752–1764)

All consecutive patients:

- (1) Who received multiple operations for NSCLC from 1999-2007
- (2) For whom specimens from at least 2 tumors were frozen

42 NSCLCs from 20 patients

32 tumors: adenocarcinoma
8 tumors: squamous cell carcinoma
2 tumors: large-cell neuroendocrine carcinoma

6 patients with synchronous tumors
14 patients with metachronous tumors

18 patients with 2 tumors
2 patients with 3 tumors
(24 tumor pair comparisons)

Case 3: Girard *et al.*

Perform comparisons using three methods

- [A] Martini and Melamed criteria (1975)
- [B] Comprehensive histologic assessment
- [C] "Molecular consensus"

Multiple primary tumors versus metastases

Different: multiple primaries
Similar: metastases

Which method(s) facilitate(s) distinction between patients with shorter time to progression versus longer time to progression?

Case 3: Girard et al.

Perform comparisons using three methods
 [A] Martini and Melamed criteria (1975)
 [B] Comprehensive histologic assessment
 [C] "Molecular consensus"

Multiple primary tumors versus metastases
 Different: multiple primaries
 Similar: metastases

Which method(s) facilitate(s) distinction between patients with shorter time to progression (**metastases**) versus longer time to progression (**multiple primaries**)?

Case 3: Girard et al.

Different (multiple primaries): 21 cases
 Similar (metastases): 3 cases

Comprehensive Histologic Assessment
 Different: 16 cases
 Similar: 8 cases

Molecular consensus

First based on genomic profiling / array-CGH data (18 pairs)

Alternatively based on mutational analysis (4 equivocal pairs)

Mass spectrometry-based genotyping (Sequenom):
 EGFR, KRAS, HRAS, NRAS, BRAF, PIK3CA, AKT1, ERBB2, MEK1

Dideoxynucleotide-based sequencing:
 EGFR exon 19
 TP53 (all exons)

Molecular consensus
 Different (multiple primaries): 14 cases
 Similar (metastases): 8 cases
 Unavailable for 2 comparisons
 Contradicted Martini-Melamed in 7 cases
 Contradicted comprehensive histologic assessment in 2 cases

Case 3: Girard et al.

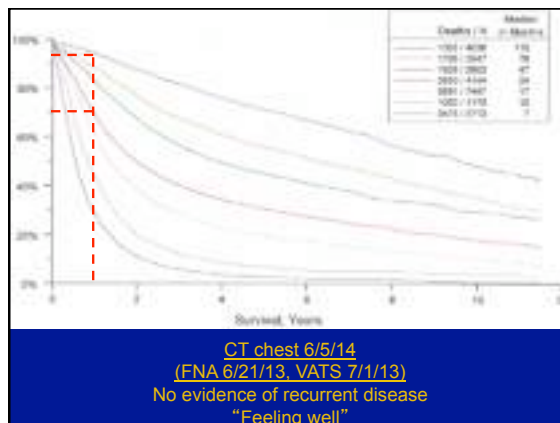
Time to progression
 Molecular consensus and comprehensive histologic assessment facilitate distinction between patients with shorter time to progression (**metastases**) versus longer time to progression (**multiple primaries**)

Conclusions

Molecular consensus and comprehensive histologic assessment
consistent in 20/22 pairs (91%)

Molecular consensus and comprehensive histologic assessment
facilitate distinction between patients with
 shorter time to progression (**metastases**)
 versus longer time to progression (**multiple primaries**)

Cases 5 and 19: clinical outcome more consistent with histologic
 rather than molecular interpretation



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ROS1 Rearrangements: Bergethon *et al.*

***ROS1* Rearrangements Define a Unique Molecular Class of Lung Cancers**

Grigori Bergethon, Alex T. Alex, An Hong Nguyen, Ho-Spyoung Kim, Christine M. Lovly, Martin T. Jänne, Peter F. Hainke, Christina Hoek-Yang, Adriana Giacinto, Hong Fang, Eugene J. Mark, Julia M. Butler, Haqeen Ghossein, Keith C. Wilson, Eunice L. Kwak, Jeffrey W. Clark, David P. Carbone, Douglas S. Johnson, Amy E. Hughes, Mary Ellen Kiesler, William Fan, and A. John Iafrate

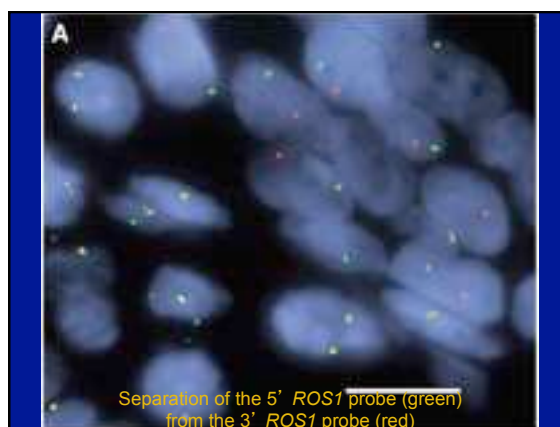
J Clin Oncol 30:863-870

ROS1 Rearrangements: Bergethon *et al.*

1073 patients with NSCLC seen at four centers

18 *ROS1* FISH-positive NSCLCs (1.7%)

Mutually exclusive from *ALK* rearrangement



ROS1 Rearrangements: Bergthson et al.

ROS1-positive patients tend to be **younger never-smokers** with a histologic diagnosis of **adenocarcinoma**

There is an over-representation of **Asians** and patients presenting with **stage IV** disease

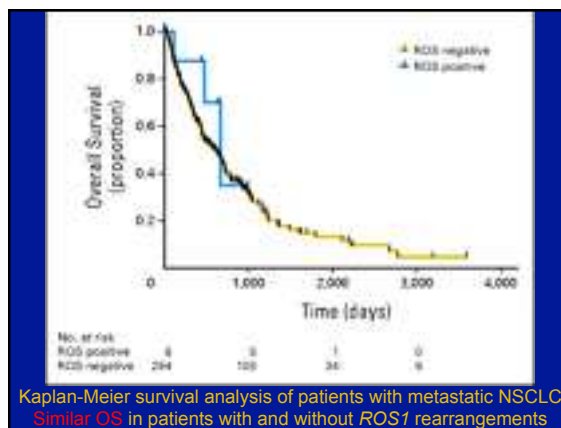
Characteristic	All Patients (n = 1,078)	ROS1-positive (n = 100)	ROS1-negative (n = 978)	P-value
Age (years)	62.2	60.1	62.3	<.001
Sex				
Male	561	57	504	.99
Female	517	43	474	
Smoking Status				<.001
Never smoker	412	48	364	
Light smoker	40	1	39	
Heavy	566	51	515	
Unknown	60	0	60	
All	1,078	100	978	
Stage				<.001
I	10	0	10	
II	100	10	90	
III	100	10	90	
IV	868	80	788	
All	1,078	100	978	
Pathologic Complete Response	100	100	0	100%
Yes	100	100	0	
No	978	0	978	
All	1,078	100	978	
Age				
< 40	212	11	201	.001
40-49	112	11	101	
50-59	212	11	201	
60-69	212	11	201	
≥ 70	742	56	686	
All	1,078	100	978	

ROS1 Rearrangements: Bergthson et al.

C

RT-PCR and sequencing to identify the translocation partner

- 5 specimens: CD74
- 1 specimen: SLC34A2
- 8 specimens: no partner identified
- 4 specimens: insufficient tissue

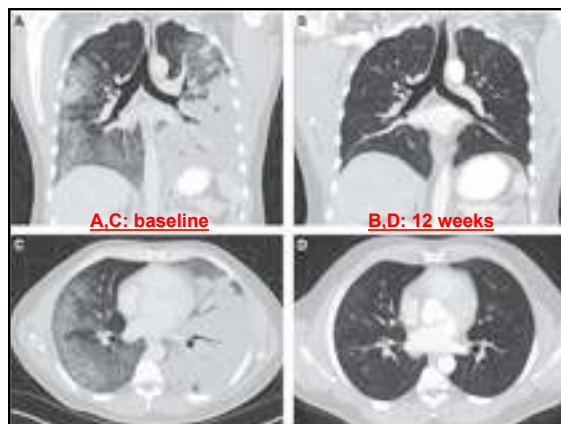


ROS1 Rearrangements: Bergthson et al.

Enrolled one ROS1-positive patient with advanced NSCLC into an expansion cohort of the early phase study of crizotinib

31M never-smoker

Restaging scans at 8 weeks: **near complete resolution**
Confirmed at 12 weeks



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BRAF Mutations: Cardarella *et al.*

Clinical, Pathologic, and Biologic Features Associated with *BRAF* Mutations in Non-Small Cell Lung Cancer

Giuseppe Cardarella^{1,2,3}, Alvaro Ojeda¹, Marco Sordani^{1,2}, Moha Razaee¹, Jerome Eber^{1,2}, Christian Lohse¹, Simon Y. Yoon^{1,2}, Lynette M. Sholl^{1,2}, Bruce E. Johnson^{1,2,3}, and Peter A. Jänne^{1,2,3}

Clin Cancer Res; 19(16) August 15, 2013

883 patients with NSCLC
(Lowie Center for Thoracic Oncology, Dana-Farber Cancer Inst.)
between 7/1/09 and 7/16/12

Analyzed for somatic alteration of *BRAF*, *KRAS*, *EGFR*, and *ALK*

BRAF mutations: 36 / 883 (4%)
V600E: 18
Non-V600E: 18

Activating *EGFR* mutations: 157
KRAS mutations: 267
ALK rearrangements: 41

"Wild-type": 257

Characteristics	Mutation Status			
	All pt - 883 N (%)	V600E pt - 18 N (%)	Non-V600E pt - 18 N (%)	Wild-type ^a pt - 257 N (%)
Median age, y	62	64	61	62
Female	21 (24)	2 (11)	2 (11)	28 (11)
Male	17 (20)	16 (89)	16 (89)	149 (58)
Race	19 (23)	10 (56)	9 (50)	124 (48)
White, non-Hispanic	14 (17)	10 (56)	10 (56)	171 (66)
Asian	2 (3)	0 (0)	0 (0)	11 (4)
Black	1 (2)	1 (6)	1 (6)	16 (6)
White, Hispanic	2 (3)	0 (0)	0 (0)	1 (0)
Unknown	1 (2)	0 (0)	0 (0)	1 (0)
Smoking history ^b				
Never smoker	1 (2)	0 (0)	0 (0)	16 (6)
< 10 pack-years	1 (2)	1 (6)	1 (6)	24 (9)
> 10 pack-years	21 (26)	17 (94)	17 (94)	117 (45)
Staging				
Adenocarcinoma	14 (17)	17 (94)	17 (94)	122 (47)
Adenosquamous	0 (0)	0 (0)	0 (0)	1 (0)
Squamous	0 (0)	0 (0)	0 (0)	0 (0)
LLNCC ^c	0 (0)	0 (0)	0 (0)	0 (0)
NSCLC, NOS ^d	1 (2)	1 (6)	1 (6)	1 (0)
Stage ^e				
I	4 (5)	0 (0)	0 (0)	14 (5)
II	1 (2)	1 (6)	1 (6)	17 (7)
III	19 (23)	17 (94)	17 (94)	149 (58)
IV	22 (27)	10 (56)	10 (56)	149 (58)

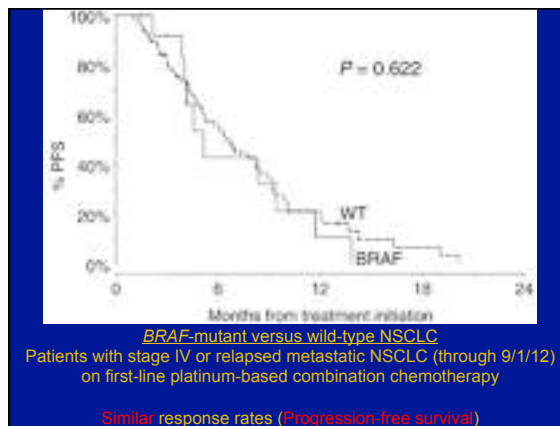
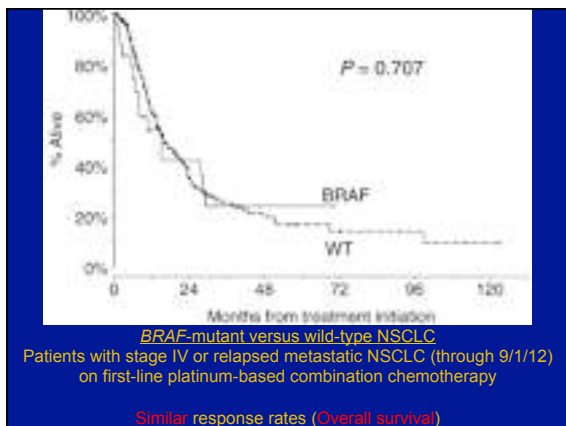
No distinguishing clinical features between *BRAF*-mutant and wild-type patients

Characteristics	Mutation Status			
	All pt - 883 N (%)	V600E pt - 18 N (%)	Non-V600E pt - 18 N (%)	Wild-type ^a pt - 257 N (%)
Median age, y	62	64	61	62
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White, Hispanic	2 (3)	0 (0)	0 (0)	1 (0)
Unknown	1 (2)	0 (0)	0 (0)	1 (0)
Smoking history ^b				
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Adenosquamous	0 (0)	0 (0)	0 (0)	1 (0)
Squamous	0 (0)	0 (0)	0 (0)	0 (0)
LLNCC ^c	0 (0)	0 (0)	0 (0)	0 (0)
NSCLC, NOS ^d	1 (2)	1 (6)	1 (6)	1 (0)
Stage ^e				
I	4 (5)	0 (0)	0 (0)	14 (5)
II	1 (2)	1 (6)	1 (6)	17 (7)
III	19 (23)	17 (94)	17 (94)	149 (58)
IV	22 (27)	10 (56)	10 (56)	149 (58)

Hammerman *et al.* 2012
BRAF mutations in ~4% of squamous cell lung carcinomas

Exon	Nucleotide change	Amino acid change	Frequency, N
II	1301G>A	G484E ^f	1
	1301G>T	G484V ^f	1
	1360G>A	G456R ^f	1
	1360G>T	G456V ^f	4
	1400G>C	G469A	2
	1405_1427delGGA	G489del	1
III	1400G>T	G456V ^f	1
	1782G>A	D594V	1
	1781A>G	D594G	2
	1801A>G	R601E	1
	1794_1796dupTAC	T598_V600insT	1
	1798_1801delTGA	V600_K601delinsE	1
1797T>A	V600E ^g	18	
1798G>T	V600L	1	

Abbreviations: del, deletion; dup, duplication; ins, insertion.
^fOne patient had both *BRAF* G484E and *KRAS* G12A.
^gOne patient had both *BRAF* G456V and *KRAS* G13C.
^hOne patient had both *BRAF* G456V and *KRAS* G13C.
ⁱOne patient had both *BRAF* V600E and *PIK3CA* E545K.



Conclusions

EGFR Mutations

FDA-approved targeted therapy: erlotinib, gefitinib, afatinib
 Most associated with **TKI sensitivity** (e.g. L858R)
 T790M associated with **TKI resistance**

ALK Rearrangements

FDA-approved targeted therapy: crizotinib, ceritinib

Conclusions

KRAS Mutations

KRAS and **EGFR** mutations are mutually exclusive
 Associated with **shorter survival**

ROS1 Rearrangements

Similar OS in patients with and without **ROS1** rearrangements

BRAF Mutations

Similar OS, PFS on platinum-based chemotherapy

	<u>Female</u>	<u>Never-Smoker</u>	<u>Asian Heritage</u>	<u>Younger</u>
<u>EGFR</u>	X	X	X	
<u>ALK</u>		X		X
<u>KRAS</u>	X	Smokers		
<u>ROS1</u>		X	X	X
<u>BRAF</u>				

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