Molecular Alterations in Non-Small Cell Lung Cancer

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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
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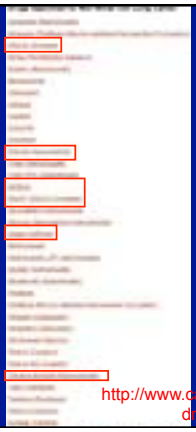

(as of 6/10/14)
http://www.cancer.gov/cancertopics/druginfo/lungcancer#dal1

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Epidermal growth factor receptor mutations in lung cancer

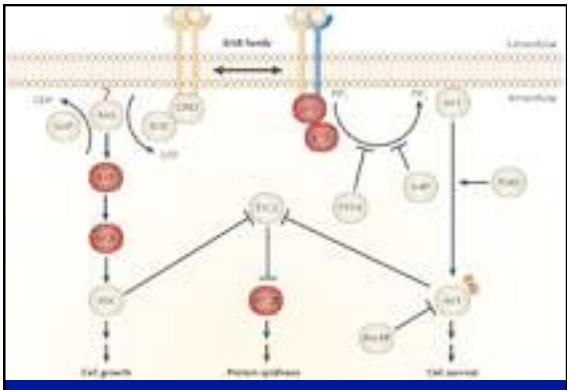
Sreenath V. Sharma*, Daphne W. Bell*†, Jeffrey Settleman* and Daniel A. Haber

Nature Reviews Cancer 7 (2007), 169-181

Epidermal Growth Factor Receptor Mutations in Non–Small-Cell Lung Cancer: Implications for Treatment and Tumor Biology

Paul A. Jänne, Jeffrey A. Engelman, and Bruce E. Johnson

J Clin Oncol 23:3227-3234



Nature Reviews Cancer 7 (2007), 169-181

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.*

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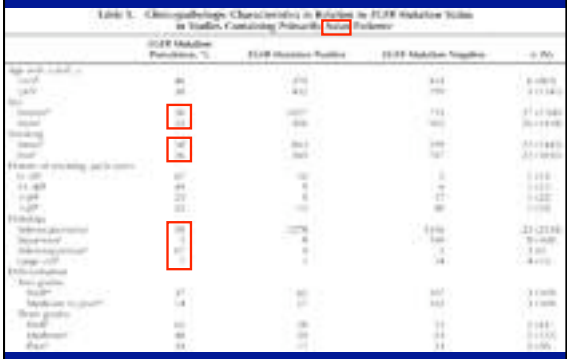

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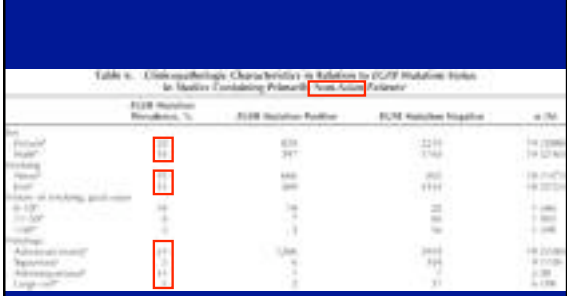
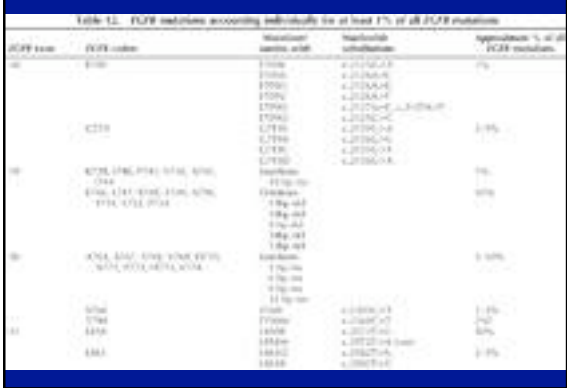


EGFR Mutations (et cetera): Janne *et al.*

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.*



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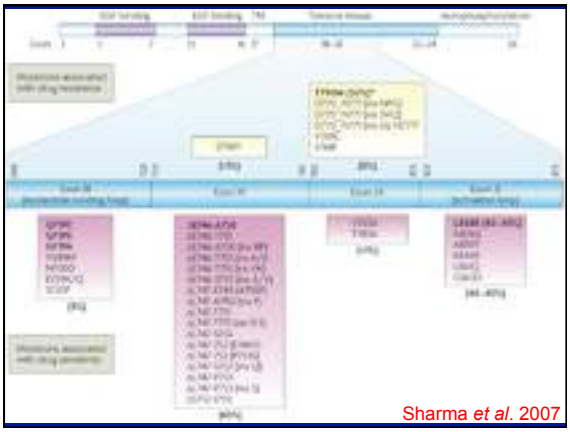
Tyrosine Kinase Inhibitors: Lindeman *et al*.

Outcome	Mean ± SD		Percentage		
	EGFR Mutation Positive	*EGFR* Mutation Negative	*EGFR* Mutation Positive	*EGFR* Mutation Negative	n (%)
Response rate, %			60	11	51 (36.4)
Disease control rate, %			86	42	28 (20.0)
Time to progression/ progression-free survival, mo	12.0 ± 7.86	3.4 ± 2.59			27 (23.1)
Median survival time, mo	21.3 ± 18.4	12.1 ± 13.9			27 (24.8)

Outcomes in patients treated with tyrosine kinase inhibitors



Sharma *et al*. 2007

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Family of closely related receptors
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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

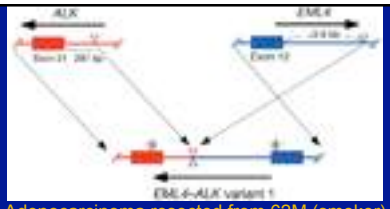
Associated with worse outcome when patients are treated with chemotherapy in combination with erlotinib

ALK rearrangements: Soda *et al.*

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

Mineha Soda[1], Young Lim Choi[1], Mutsuko Enomoto[1], Shuji Takada[2], Yoshihiro Yamashita[3], Shunpei Ishikawa[3], Shin-ichiro Fujiwara[3], Hideki Watanabe[3], Kentaro Kurashina[3], Hitoshi Hanaoka[3], Masashi Basaki[3], Shuji Ohno[3], Yuichi Ishikawa[4], Hiroyuki Kikuchi[4], Yoshino Niki[1], Yasunori Sohara[5], Yukihiko Sugiyama[5] & Hiroyuki Mano[1]

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



Adenocarcinoma resected from 62M (smoker)

cDNA encoding fusion product of *EML4* and *ALK*

Amino-terminal portion: EML4
(echinoderm microtubule-associated protein-like 4)

Carboxy-terminal portion: ALK (anaplastic lymphoma kinase)

Small inversion within chromosome 2p

ALK rearrangements: Kwak *et al.*

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

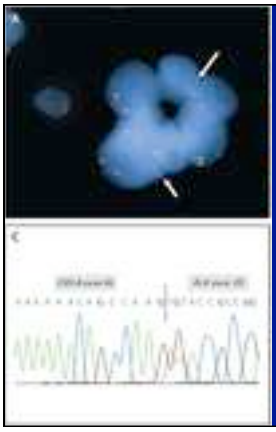
Eunice L. Kwak, M.D., Ph.D., Yung-Jue Bang, M.D., Ph.D., D. Ross Camidge, M.D., Ph.D., Alice T. Shaw, M.D., Ph.D., Benjamin Solomon, M.B., B.S., Ph.D., Robert G. Maki, M.D., Ph.D., Sai-Hong I. Ou, M.D., Ph.D., Bruce J. Dezube, M.D., Pasi A. Jänne, M.D., Ph.D., Dennie B. Costa, M.D., Ph.D., Mariella Varella-Garcia, Ph.D., Won-Hee Kim, M.D., Thomas J. Lynch, M.D., Patrick Fidias, M.D., Hironori Stubbs, M.S., Jeffrey A. Engelman, M.D., Ph.D., Lecia V. Sequist, M.D., M.P.H., Wei-Wei Tan, Ph.D., Lynette Gandhi, M.D., Ph.H., Mari Mino-Kenudson, M.D., Greg J. Wei, Ph.D., S. Martin Shreeve, M.D., Ph.D., Mark J. Ratain, M.D., Jeffrey Settleman, Ph.D., James G. Christensen, Ph.D., Daniel A. Haber, M.D., Ph.D., Keith Wilner, Ph.D., Raul Salgia, M.D., Ph.D., Geoffrey I. Shapiro, M.D., Ph.D., Jeffrey W. Clark, M.D., and A. John Iafrate, 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



Green probe
Region immediately 5′ to *ALK*

Red probe
3′ region

Separation of green and red probe signals
Chromosomal rearrangement involving *ALK*

Close apposition of red and green probe signals
Intact wild-type copy of *ALK*

Figure 1
Negative

Figure 2
Positive

Split 3′ ALK-5′ ALK

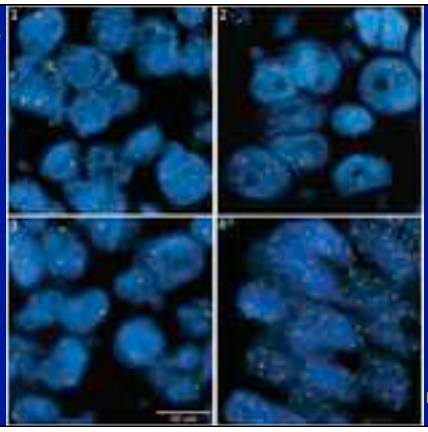


Figure 3
Positive

Single 3′ ALK

Figure 4
Negative with high copy #

Lindeman *et al.*

ALK rearrangements / *EML4-ALK* fusion gene

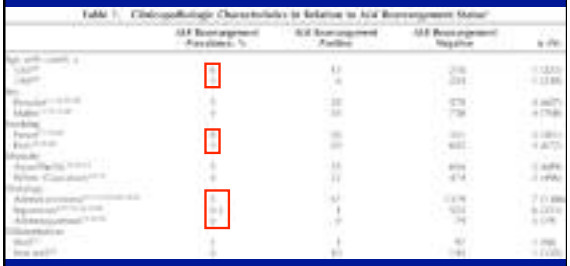
Soda *et al.*
5 of 75 (7%) NSCLC patients

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.*



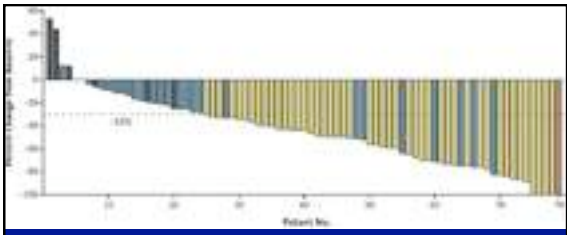
Patients with *ALK* rearrangements tend to:
be younger than those without the rearrangements;
have little or no exposure to tobacco;
have adenocarcinomas

Kwak *et al.*: ALK inhibitor

Early phase clinical trial of crizotinib (PF-02341066)

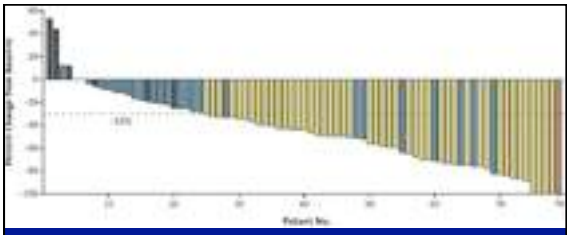
Cohort with FISH-positive results for *ALK* rearrangement received 250 mg twice daily in 28-day cycles

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



Radiologic assessments performed at baseline and generally after every two cycles of treatment

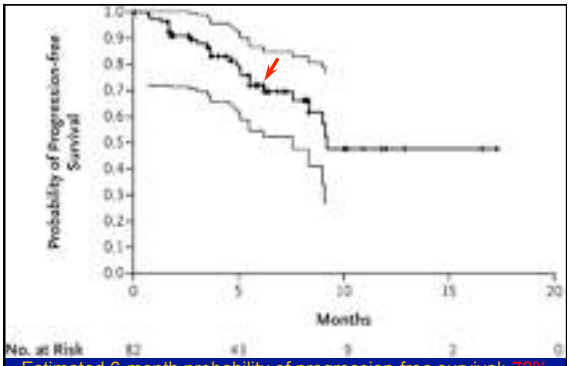
Complete response (orange): 1 patient
Partial response (yellow): 46 patients
Stable disease (blue): 27 patients
(3 not included in this plot)
Disease progression (gray): 6 patients



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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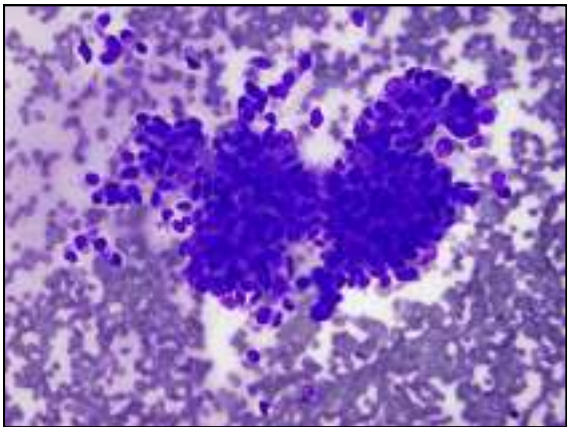
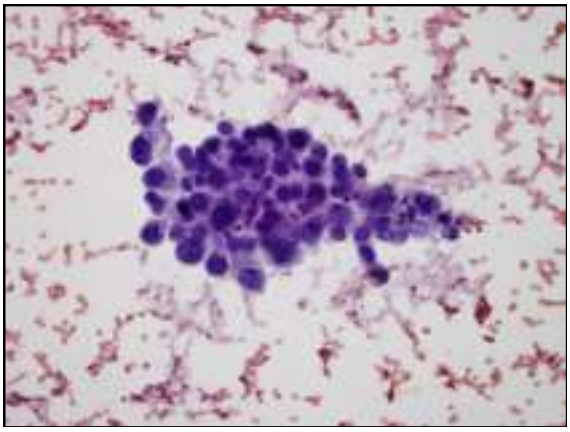
Case 1

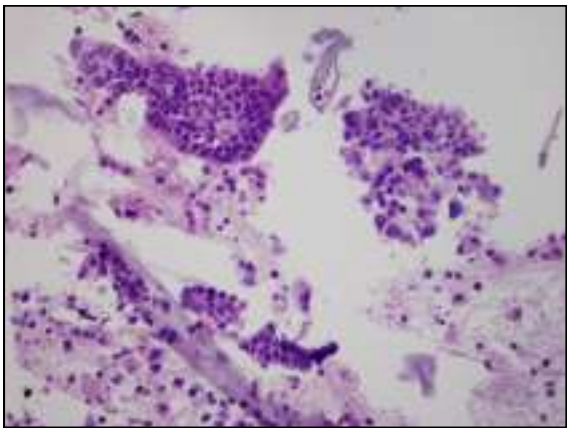
49M, 20 pack-year smoking history
(quit 12/31/1992)

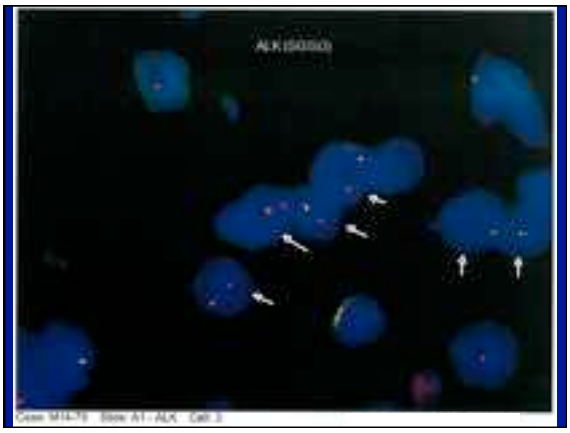
Chest CT angiography 12/23/13
LUL spiculated opacity (14 mm)

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









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Clinical Practice Guideline: Lindeman *et al*.

Molecular Testing Guideline for Selection of Lung Cancer Patients for EGFR and ALK Tyrosine Kinase Inhibitors

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

Arch Pathol Lab Med. 2013;137:828–860

Clinical Practice Guideline: Lindeman *et al*.

Review of published data

Evidence-based recommendations
for the molecular testing of lung cancers

5 principal questions
14 corollary questions

Clinical Practice Guideline: Lindeman *et al*.

Review of published data

Evidence-based recommendations
for the molecular testing of lung cancers

5 principal questions
14 corollary questions

Recommendations regarding context in which *EGFR*, *ALK*, other testing should be performed

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?*

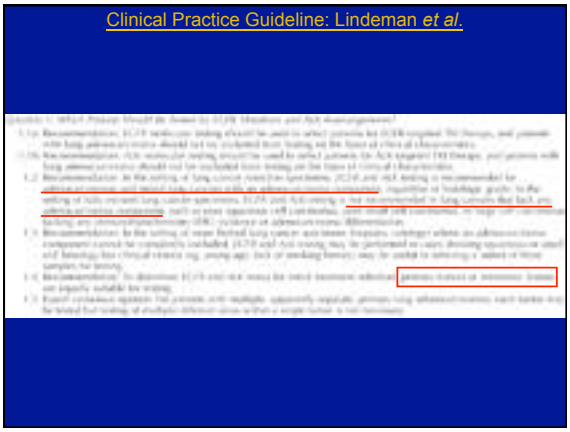
IV. Should other genes be routinely tested in lung adenocarcinoma?

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

V. How should molecular testing of lung adenocarcinomas 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.*



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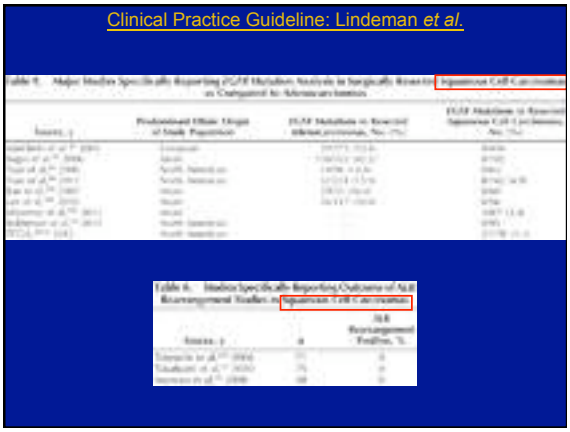

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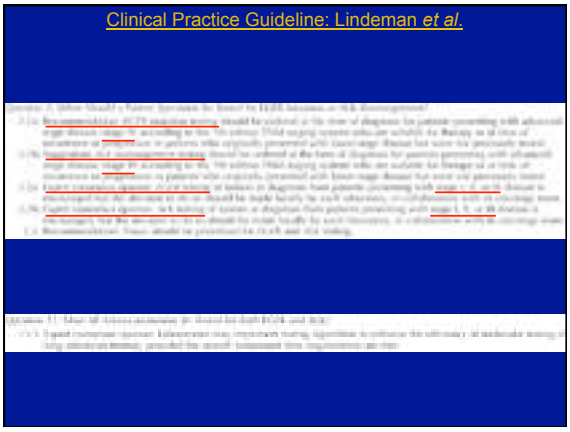

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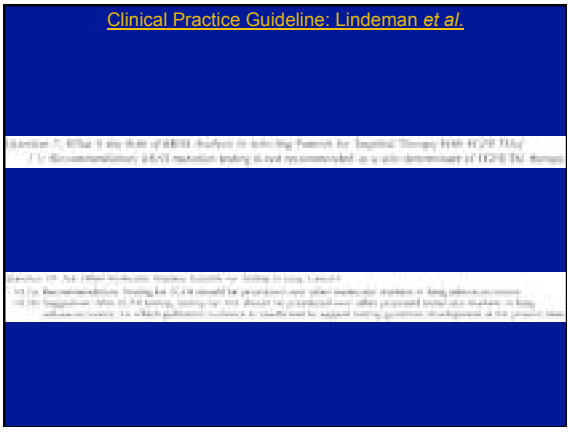

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Case 2

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

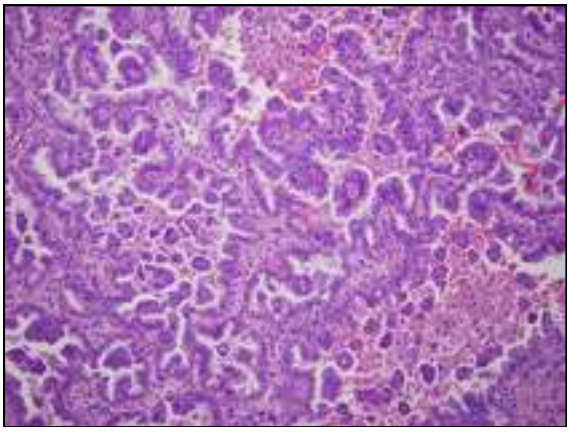
2 cycles of systemic chemotherapy
(pemetrexed, cisplatin, bevacizumab)

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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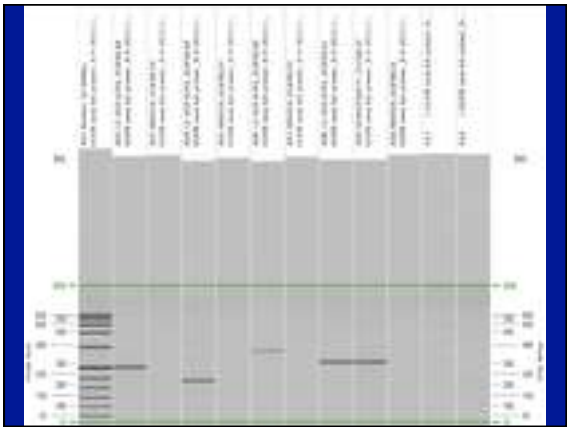
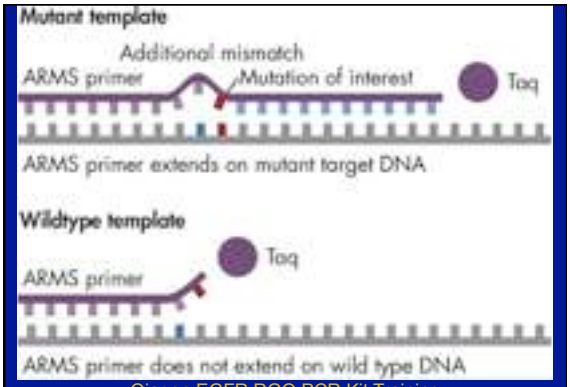
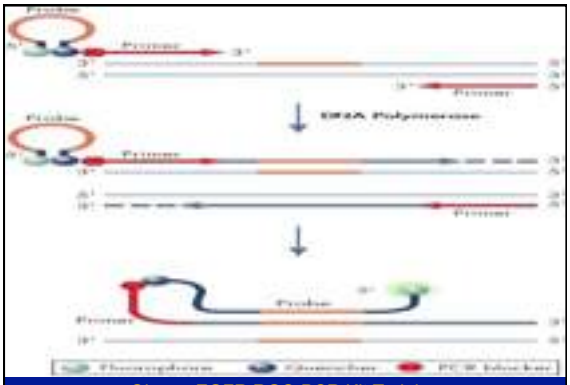
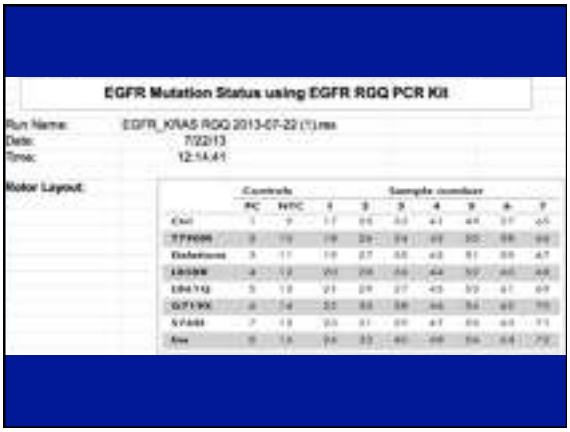


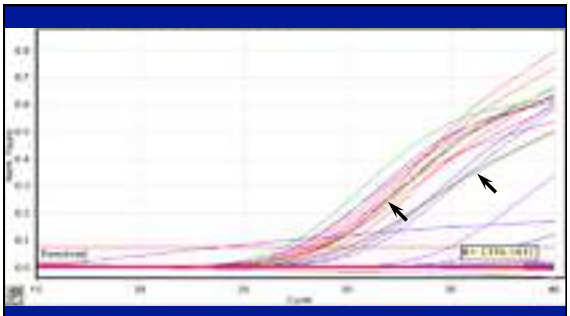


Qiagen EGFR RGQ PCR Kit Training
ARMS (Amplification Refractory Mutation System)



Qiagen EGFR RGQ PCR Kit Training
Scorpions





T790M: C_T = 30.09

Del 19: C_T = 28.96

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

Sutoshu Kobayashi, M.D., Ph.D., Titus J. Boggon, Ph.D., Tariq Dayaram, B.A., Pasi 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 Balázs Halmos, M.D.

N Engl J Med 2005;352:786-92

71M, former smoker

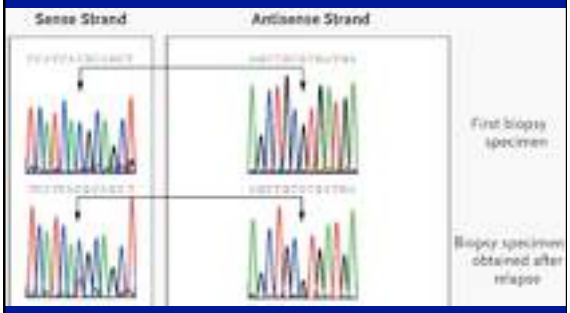
May 2001
Advanced, moderately differentiated adenocarcinoma

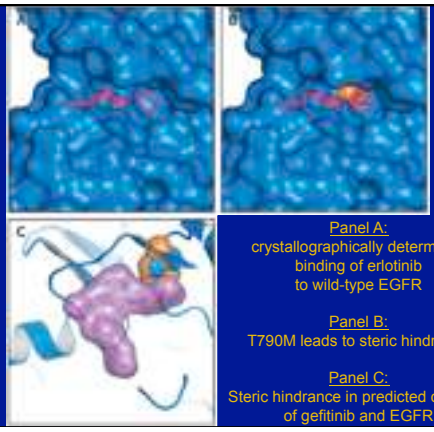
August 2002
Started gefitinib monotherapy
…

24 months of complete remission
…

Symptoms worsened
CT showed progressive abnormalities consistent with relapse

Case 2: Kobayashi *et al.*





Panel A:
crystallographically determined binding of erlotinib to wild-type EGFR

Panel B:
T790M leads to steric hindrance

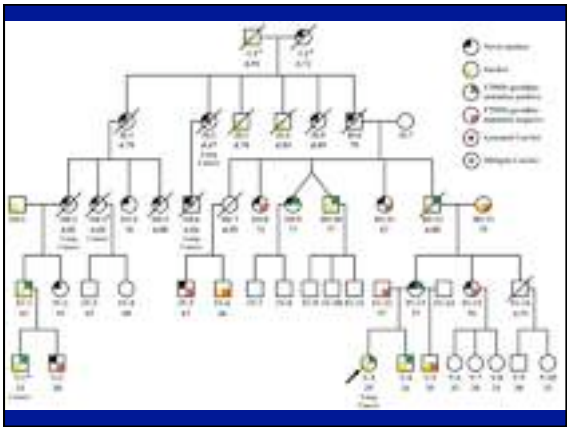
Panel C:
Steric hindrance in predicted complex of gefitinib and EGFR

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

Jill Gazdar, MD,** Linda Robinson, NP,† Dwight Oliver, MD,† Chao Xing, PhD,‡ William D. Travis, MD,§ Annicke Soh, MD,† Shunichi Toyooka, MD,¶ Lori Ramirez, MD,† Jung Kir Pass,** Kenji Kamiyama, MD,†† and Ann M. Gilliland, MD,††

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 Thorac Oncol. 2014;9:456–463



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Case 3

68F
30 pack-year smoking history

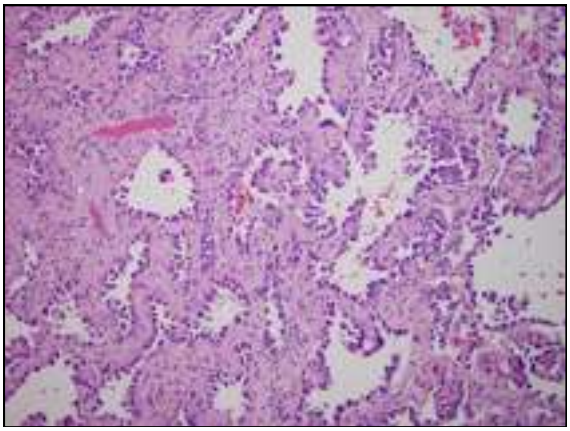
CT chest 5/10/13
Multiple nodules throughout lungs

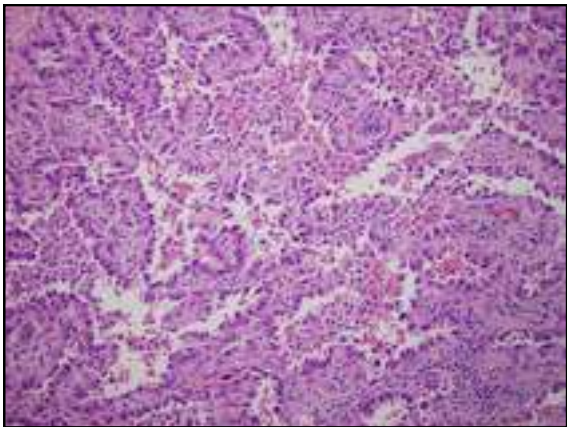
FNA 6/21/13
A (RUL posterior): Adenocarcinoma c/w origin from lung
B (RUL apex): Adenocarcinoma c/w origin from lung

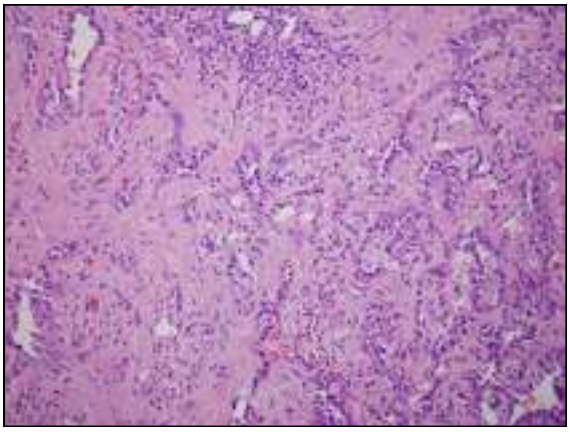
VATS 7/1/13

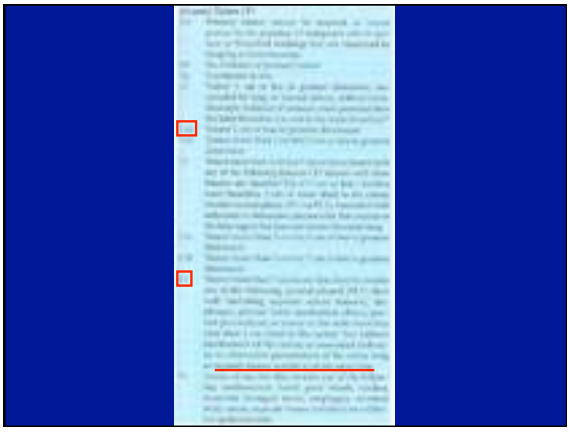
RUL (lobectomy)
Adenocarcinoma, acinar predominant, x4
B3 ("most superior"): 1.5 x 1.2 x 0.7 cm (?FNA: B)
B5: ("inferior to" B3): 0.9 x 0.9 x 0.6 cm
B9: ("posterosuperior"): 1.8 x 1.7 x 0.9 cm (?FNA: A)
B13: 0.6 x 0.4 x 0.4 cm

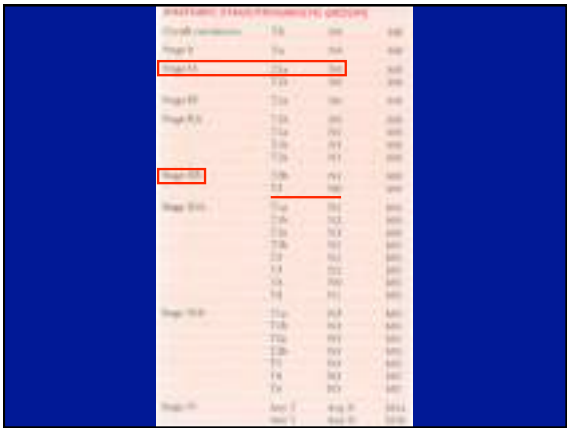
Lymph nodes
R4: 0/"multiple"
Level 7: 0/2
R10: 0/2
R12-14: 0/"multiple"

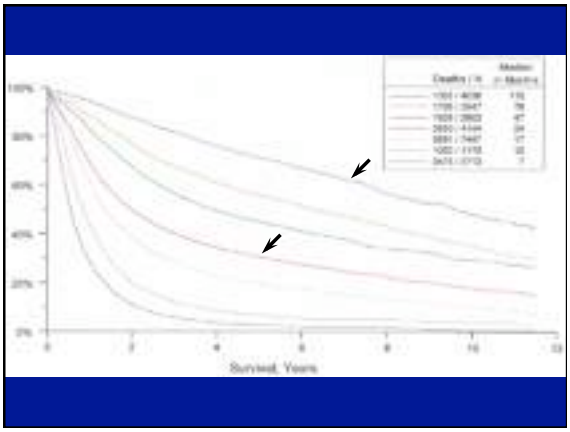


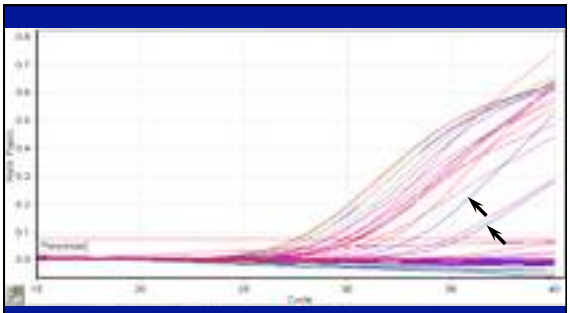




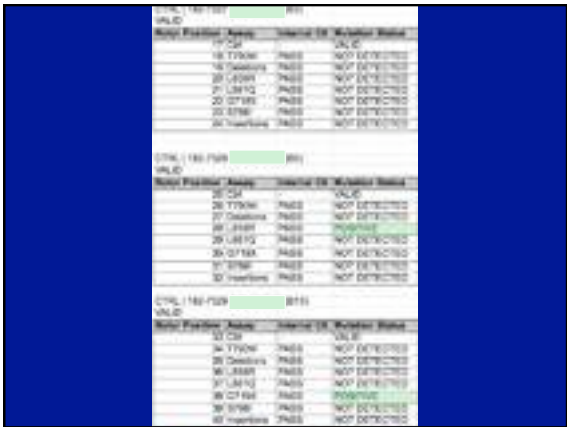


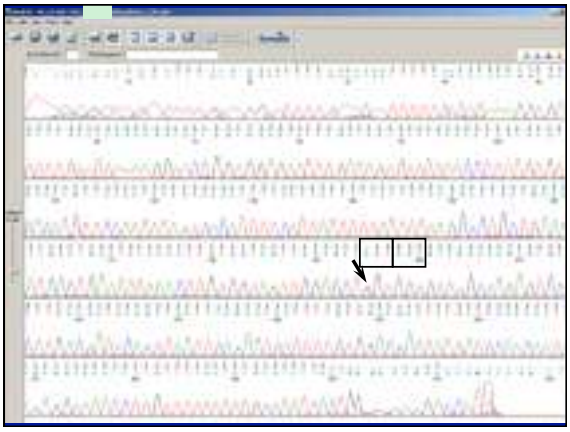


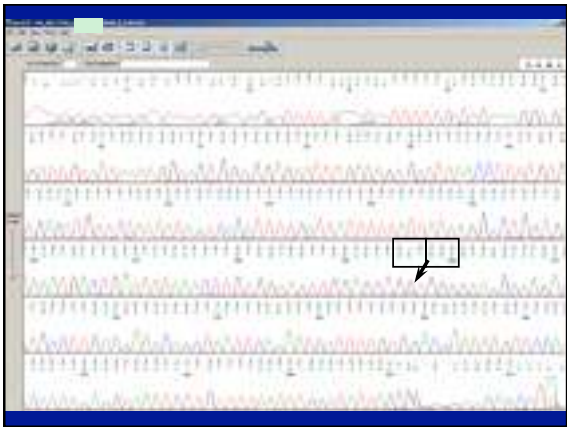




B3: no mutation detected
B5 (L858R): C_T = 33.16
B13 (G719"X"): C_T = 34.84
[Not shown: B9; no mutation detected]







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Case 3: Girard *et al*.

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

Nicolas Girard, MD,* Charuhas Deshpande, MD, PhD,† Christopher Lau, PhD,‡ David Finley, MD,§ Valerie Rusch, MD,§ William Pao, 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"

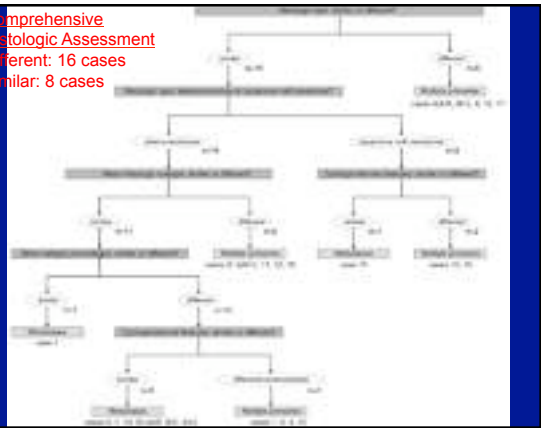
Multiple primary tumors versus metastases
Different: multiple primaries
Similar: metastases

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)

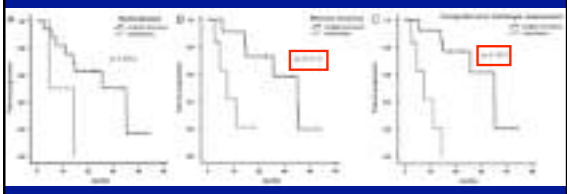
Alternatively based on mutational analysis (4 equivocal pairs)

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.*



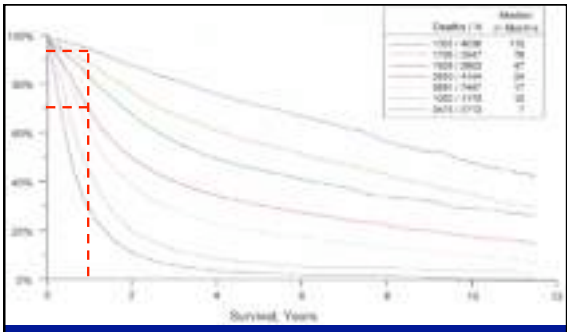
Time to progression
Molecular consensus and comprehensive histologic assessment facilitate distinction between patients with shorter time to progression (metastases) versus longer time to progression (multiple primaries)

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



CT chest 6/5/14
(FNA 6/21/13, VATS 7/1/13)
No evidence of recurrent disease
"Feeling well"

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ROS1 Rearrangements: Bergethon *et al*.

ROS1 Rearrangements Define a Unique Molecular Class of Lung Cancers

Kristin Bergethon, Alice T. Shaw, Sai Hong Ignatius Ou, Ryohei Katayama, Christine M. Lovly, Nathan T. McDonald, Pierre P. Massion, Christine Siwak-Tapp, Adriana Gonzales, Rong Fang, Eugene J. Mark, Julie M. Batten, Huaqun Chen, Keith D. Wilner, Eunice L. Kwak, Jeffrey W. Clark, David P. Carbone, Hongbin Ji, Jeffrey A. Engelman, Mary Mino Kenudson, William Pao, and A. John Iafrate

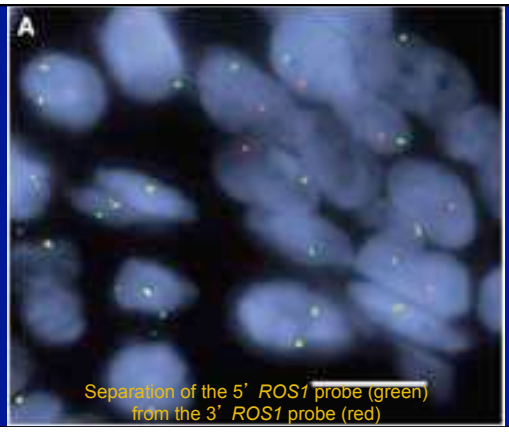
J Clin Oncol 30:863-870

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

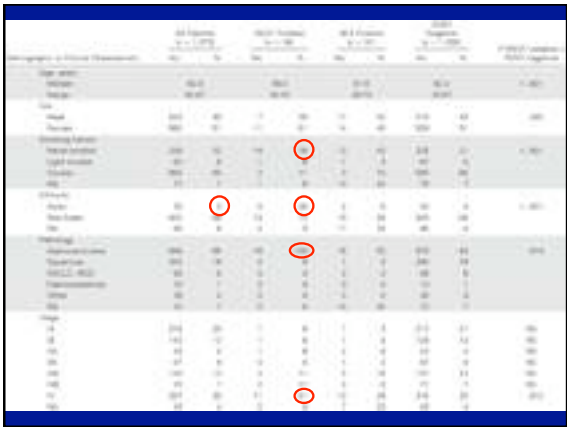


Separation of the 5' *ROS1* probe (green) from the 3' *ROS1* probe (red)

ROS1 Rearrangements: Bergethon *et al.*

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

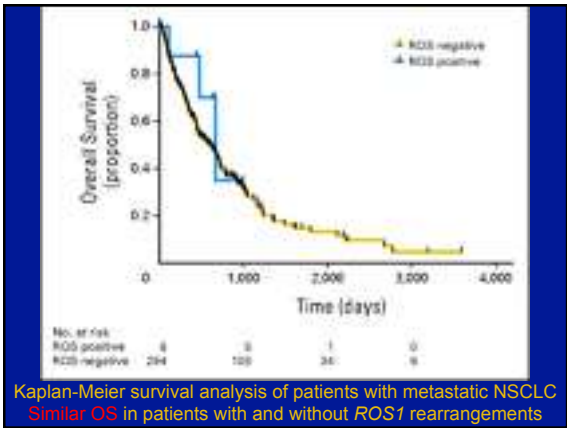
There is an over-representation of Asians and patients presenting with stage IV disease



ROS1 Rearrangements: Bergethon *et al.*

RT-PCR and sequencing to identify the translocation partner

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



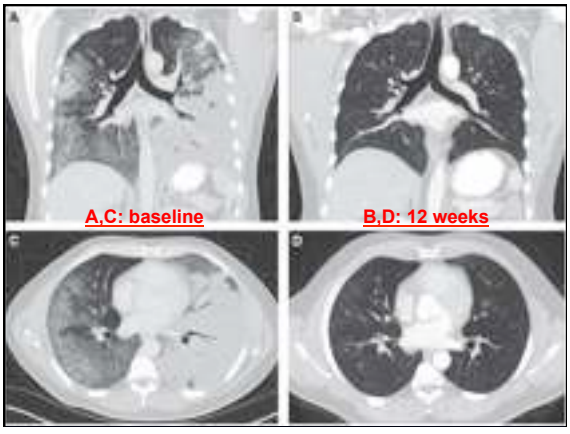
Kaplan-Meier survival analysis of patients with metastatic NSCLC
Similar OS in patients with and without *ROS1* rearrangements

ROS1 Rearrangements: Bergethon *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

Stephania Cardarella[1,2], Atsuko Ogino[1], Mizuki Nishino[2,3], Mohit Butaney[1], Jeanne Shen[2,4], Christine Lydon[1], Varun V. Yeap[1,2], Lynette M. Sholl[2,4], Bruce E. Johnson[1,2,5], and Pasi A. Jänne[1,2,5]

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

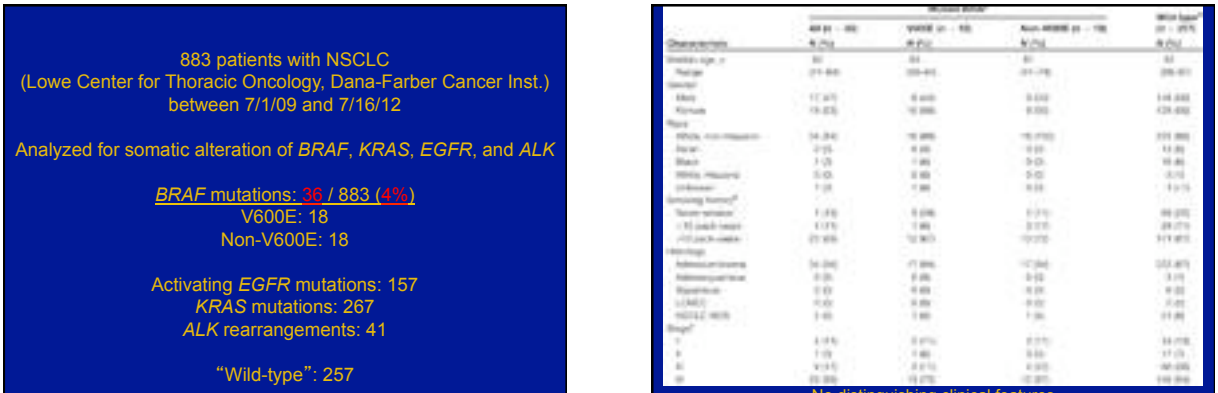
883 patients with NSCLC
(Lowe Center for Thoracic Oncology, Dana-Farber Cancer Inst.)
between 7/1/09 and 7/16/12

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

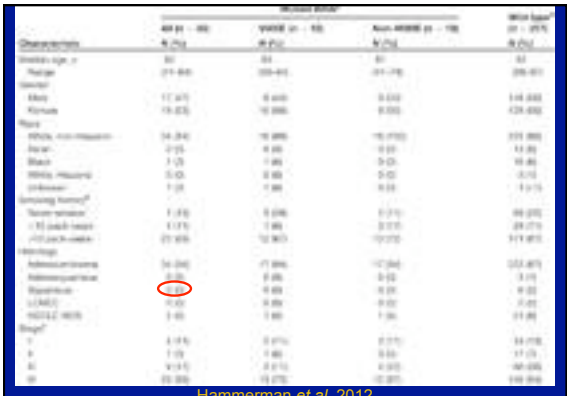
BRAF mutations: 36 / 883 (4%)
V600E: 18
Non-V600E: 18

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

"Wild-type": 257



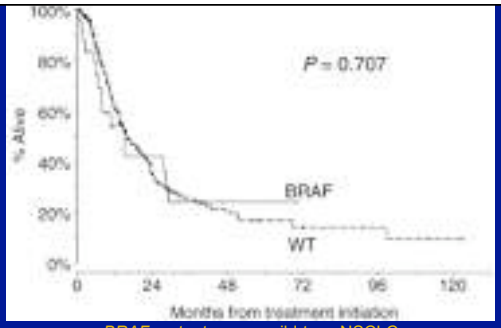
No distinguishing clinical features
between *BRAF*-mutant and wild-type patients



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

Exon	Nucleotide change	Amino acid change	Frequency, N
11	1391G>A	G464E[a]	1
	1391G>T	G464V[b]	1
	1396G>A	G466R	1
	1397G>T	G466V[c]	4
	1406G>C	G469A	2
	1405_1407delGGA	G469del	1
	1406G>T	G469V	1
15	1780G>A	D594N	1
	1781A>G	D594G	2
	1801A>G	K601E	1
	1794_1799dupTAC	T599_V600insT	1
	1799_1801delTGA	V600_K601delinsE	1
	1797>A	V600E[d]	18
	1798G>T	V600L	1

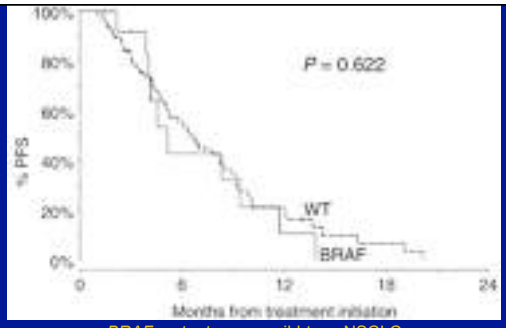
Abbreviations: del, deletion; dup, duplication; ins, insertion.
[a]One patient had both *BRAF* G464E and *KRAS* G12A.
[b]One patient had both *BRAF* G464V and *KRAS* G13C.
[c]One patient had both *BRAF* G466V and *KRAS* G12C.
[d]One patient had both *BRAF* V600E and *PIK3CA* E545K.



BRAF-mutant versus wild-type NSCLC

Patients with stage IV or relapsed metastatic NSCLC (through 9/1/12) on first-line platinum-based combination chemotherapy

Similar response rates (Overall survival)



BRAF-mutant versus wild-type NSCLC

Patients with stage IV or relapsed metastatic NSCLC (through 9/1/12) on first-line platinum-based combination chemotherapy

Similar response rates (Progression-free survival)

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

	Female	Never-Smoker	Asian Heritage	Younger
EGFR	X	X	X	
ALK		X		X
KRAS	X	Smokers		
ROS1		X	X	X
BRAF				

References

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2. Janne PA *et al.* Journal of Clinical Oncology 23 (2005), 3227-3234.
3. Lindeman NI *et al.* Arch Pathol Lab Med 137 (2013), 828-858.
4. Soda M *et al.* Nature 448 (2007), 561-566.
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6. Kobayashi S *et al.* N Engl J Med 352 (2005), 786-792.
7. Gazdar A *et al.* Journal of Thoracic Oncology 9 (2014), 456-463.
8. Girard N *et al.* Am J Surg Pathol 33 (2009), 1752-1764.
9. Bergethon K *et al.* Journal of Clinical Oncology 30 (2012), 863-870.
10. Cardarella S *et al.* Clinical Cancer Research 19 (2013), 4532-4540.
11. Hammerman PS *et al.* Nature 489 (2012), 519-525.