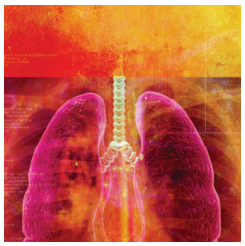


Present and Future Targeted Lung Cancer Therapy: Beginning the End of Nihilism

CHEST 2013
October 26 - 31
Chicago, Illinois

MORNING
EDUCATIONAL
SYMPOSIUM

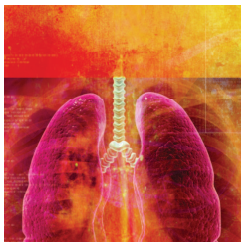
Agenda

5:30–5:35 AM	**Welcome and Introduction** Chair: Douglas A. Arenberg, MD, FCCP
5:35–5:50 AM	**Review of Patient Case Presentation / Collection of Benchmark Outcomes Data** Douglas A. Arenberg, MD, FCCP
5:50–6:10 AM	**Pulmonologists and Multidisciplinary Care Now and in the Future** Douglas A. Arenberg, MD, FCCP
6:10–6:30 AM	**Demystifying the Role of Targeted Therapy for Lung Cancer: When, for Whom, and Where Are We Going?** Johann C. Brandes, MD, PhD
6:30–6:50 AM	**What Do Pathologists Do With Your Biopsy?** Carol Farver, MD
6:50–7:00 AM	**Re-Review of Patient Case Presentation / Collection of Post-Education Outcomes Data** Douglas A. Arenberg, MD, FCCP

Learning Objectives

- Describe the pulmonologist's role in multidisciplinary diagnosis, staging, and molecular characterization of lung cancer
- Describe lung cancer biomarker tests and their importance for individualized therapy
- Describe how pathologists process and analyze lung biopsies for biomarkers

Present and Future Targeted Lung Cancer Therapy: Beginning the End of Nihilism



Case

Douglas A. Arenberg, MD, FCCP
University of Michigan Health System
Ann Arbor, Michigan

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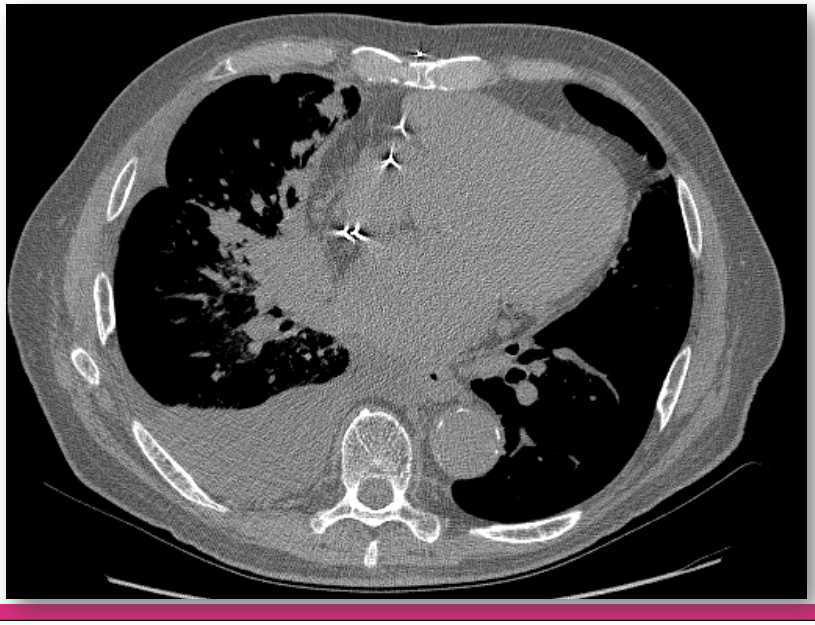
Case

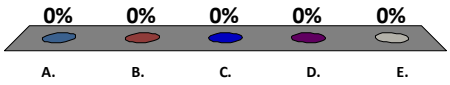
- A 58-year-old woman with a remote 12 pack-year tobacco history presents with recent onset of dyspnea and a CXR showing a RUL mass
  - PMH: Mild knee arthritis, hypertension controlled without meds, exercises regularly
- CT shows a RUL mass with a probable endobronchial component
- PET shows
  - RUL mass
  - Non-enlarged FDG-avid right hilar (10R) and right paratracheal (4R) nodes
  - Moderate-sized pleural effusion

CT Shows…



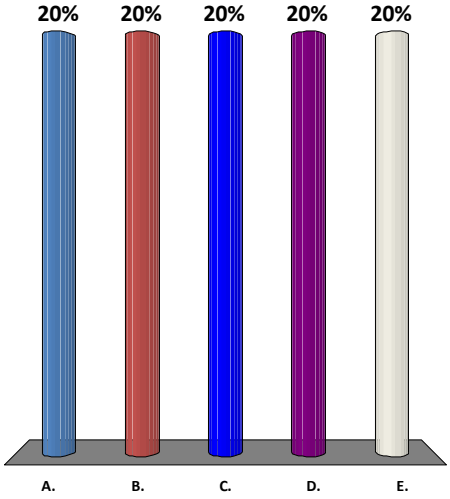
Next Step?

A. EBUS biopsy of the mediastinal nodes
B. Mediastinoscopy
C. Head CT with contrast
D. Bronchoscopy to biopsy the upper lobe mass
E. Ultrasound-guided thoracentesis



Which of the following statements is the most accurate regarding "targeted therapy" for lung cancer?

A. Targeted agents are most effective for early disease
B. Erlotinib, an *EGFR* inhibitor, is more effective in combination with standard chemotherapy
C. *KRAS* mutations predict response to targeted TKIs
D. Non-smokers are most likely to respond to targeted *EGFR TKIs*
E. Crizotinib, an *ALK* inhibitor, is only effective for patients with specific activating point mutations in the *ALK* gene



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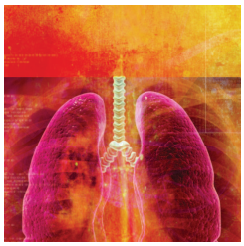

Pulmonologists and Multidisciplinary Care Now and in the Future

University of Michigan Medical School

CHEST 2013
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MORNING EDUCATIONAL SYMPOSIUM

Educational Support

Sponsored by the American College of Chest Physicians.

This educational activity is supported by an educational grant from Boehringer Ingelheim.

This educational activity is supported by an educational grant from Genentech.

Speaker

Douglas A. Arenberg, MD, FCCP
University of Michigan Health System
Ann Arbor, Michigan

Faculty Disclosure

The ACCP remains strongly committed to providing the best available evidence-based clinical information to participants of this educational activity and requires an open disclosure of any relevant financial relationships that create a conflict of interest. It is not the intent of the ACCP to disqualify anyone from participating in this educational activity, but to resolve any conflicts of interest that may arise from financial relationships with commercial interests. All conflicts of interest are reviewed by the educational activity course director/chair, the Education Committee, and/or the Conflict of Interest Subcommittee to ensure that such situations are properly evaluated and, if necessary, resolved. The ACCP educational standards pertaining to conflict of interest are intended to maintain the professional autonomy of the clinical experts inherent in promoting a balanced presentation of science. Through our review process, all ACCP CME activities are ensured of independent, objective, scientifically balanced presentations of information. Disclosure of any or no relevant financial relationships will be made available on-site during all educational activities.

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Douglas A. Arenberg, MD, FCCP

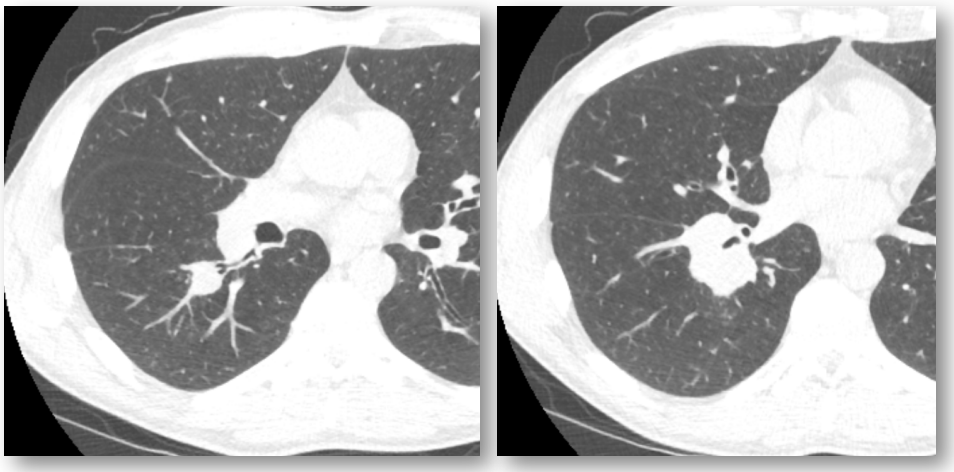
Learning Objective

- Describe the pulmonologist's role in multidisciplinary staging, diagnosis, and molecular characterization of lung cancer

Outline

- Short case and 2 ARS questions
- Case conclusion
- Mechanisms to ensure
  - Team communication
  - Adequate biopsy sample collection
- Conclusion/future prospects
- Repeat 2 ARS questions

52-year-old with cough and hemoptysis, tobacco smoker, ROS: weight loss



Would You…

A. Get a CT guided biopsy of the lung mass
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C. Refer patient for neoadjuvant chemoradiation followed by surgery
D. Do a bronchoscopy to biopsy the mass
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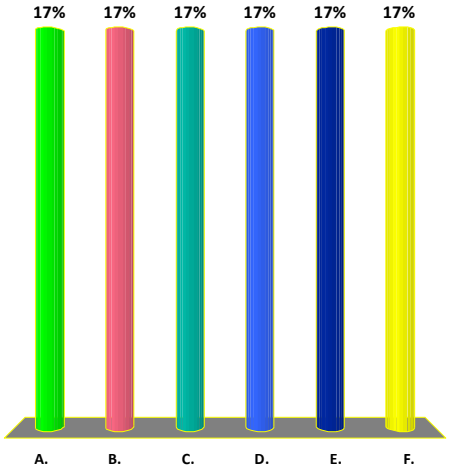
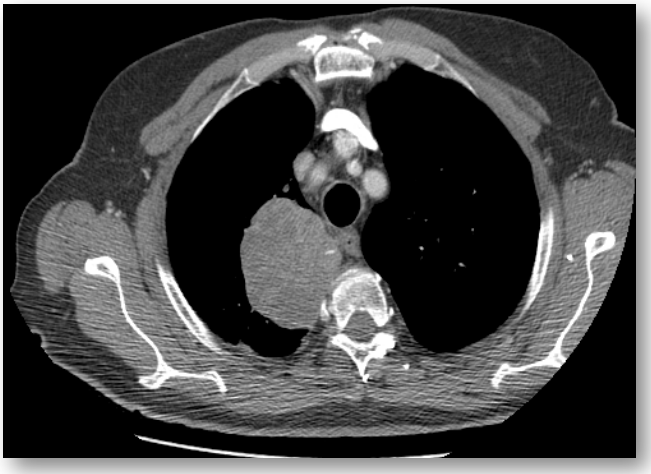
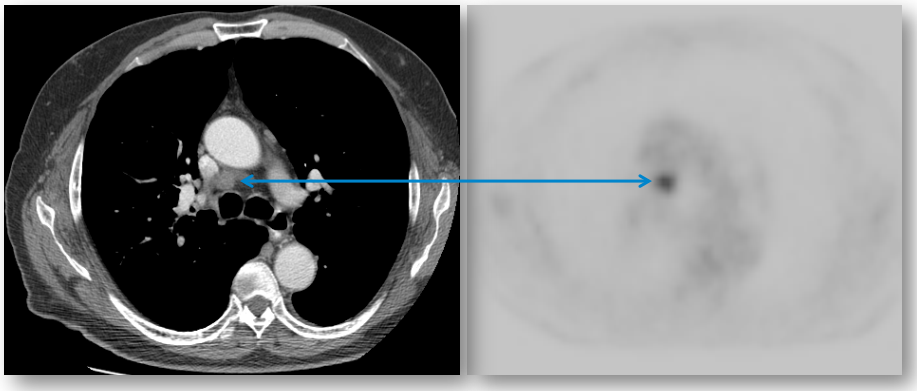
F. Refer patient for surgery



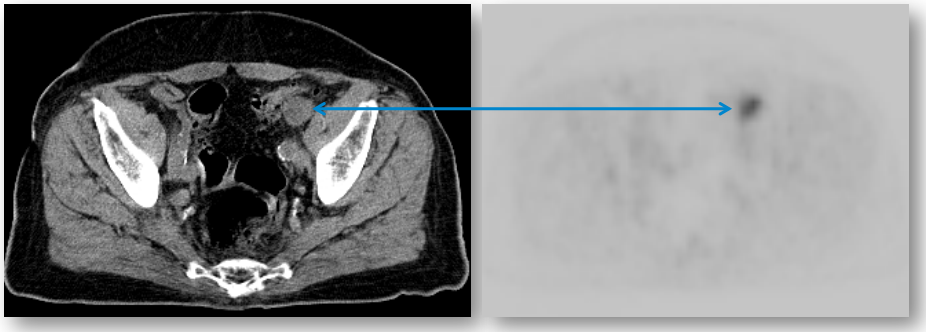
44-year-old, incidental mass discovered on pre-employment physical. Never smoked. Had coughed up some blood recently



44-year-old with incidental RUL mass, PET scan shows enlarged, FDG-avid right paratracheal node

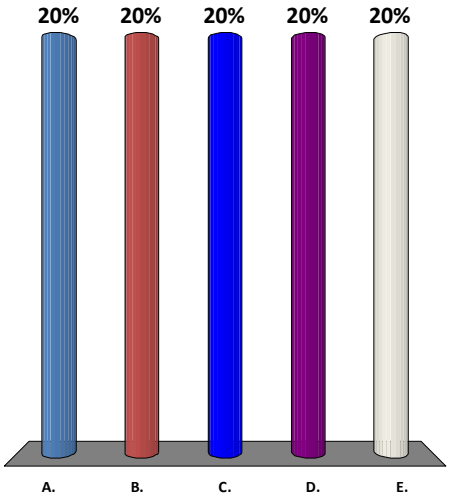


…and an enlarged FDG avid pelvic lymph node



The next step in the evaluation should be…

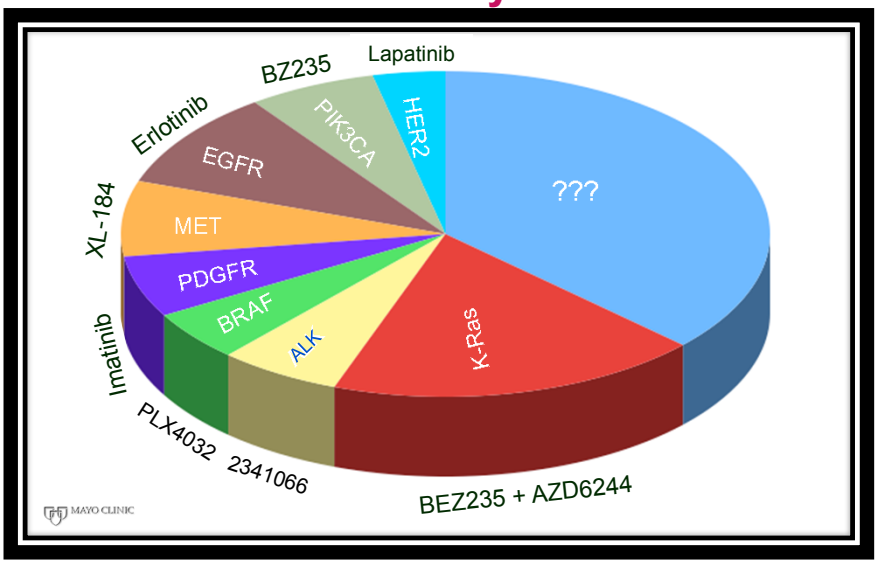
A. Biopsy the lung mass and send for EGFR sequencing
B. Refer patient for neoadjuvant chemoradiation followed by surgery
C. Biopsy the pelvic node
D. Biopsy the mediastinal node
E. Refer patient for systemic chemotherapy only



"Self…What is Individualized Therapy?"

- Recognition that disease pathogenesis and pace, as well as response to (and toxicity from) treatment differ from patient to patient
- Implies the existence of an array of treatment options that can be used either alone or in combination to achieve the best outcomes

Individualized Therapy "The Sexy…"



Non Sexy…

Physiologic stage →

Anatomic Stage ↓

Anatomic	Resectable	Unresectable
I	Surgery	*Biopsy ➢ EBRT ➢ SBRT ➢ RFA ➢Other (Cryo, wedge/ brachy)
II	Surgery ➢ Adjuvant chemotherapy	
	PS 0~2	PS ~2-4
III	*Biopsy Definitive chemo-XRT	*Biopsy Palliative RT Chemo if feasible
IV	*Biopsy Palliative chemo CNS/skeletal XRT	*Biopsy Palliative… ➢ "Chemotherapy" ➢ Radiation

Curative intent

*Always biopsy the most "stage informative" lesion

Why Do We Need Accurate Staging?

- 43,912 patients with lung cancer
  - Pretreatment staging investigations from SEER database
  - CT alone in 77% of patients
  - 21% had a CT and a PET or PET/CT scan
  - Only 2% had a CT, a PET scan, *and* an invasive staging procedure
    - ➢ Bronch with TBNA, EBUS, mediastinoscopy

Farjah F, et al. *J Thorac Oncol*. 2009;4(3):355-363.

Multimodal Mediastinal Staging and Survival

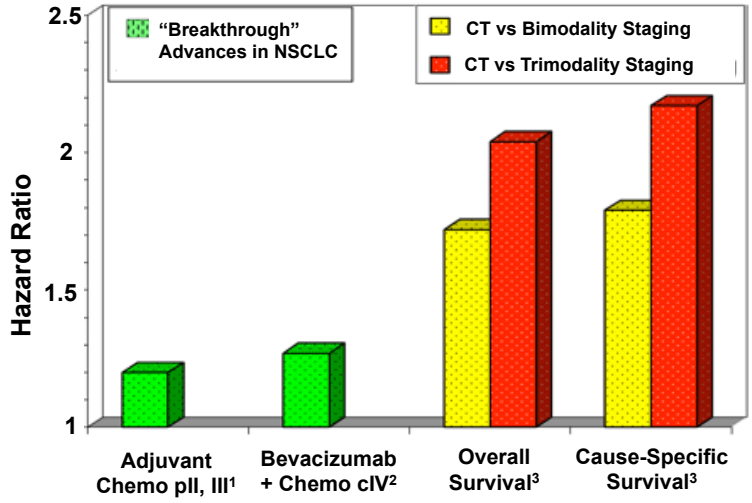
	Overall survival Hazard ratio (99% CI)	Lung cancer cause-specific survival Hazard ratio (99% CI)
Bi- vs. single modality	0.58 (0.56–0.60)	0.56 (0.54–0.58)
Tri- vs. single modality	0.49 (0.45–0.54)	0.46 (0.42–0.52)
Tri- vs. bi-modality	0.85 (0.77–0.93)	0.83 (0.74–0.93)

"Single" = CT only, "Bi" = CT and PET, "Tri-" = CT, PET, and biopsy

Patients who had more thorough staging investigation were almost half as likely to die of lung cancer

Farjah F, et al. *J Thorac Oncol*. 2009;4(3):355-363.

Survival Benefit of Staging Compared With Major Therapeutic Breakthroughs

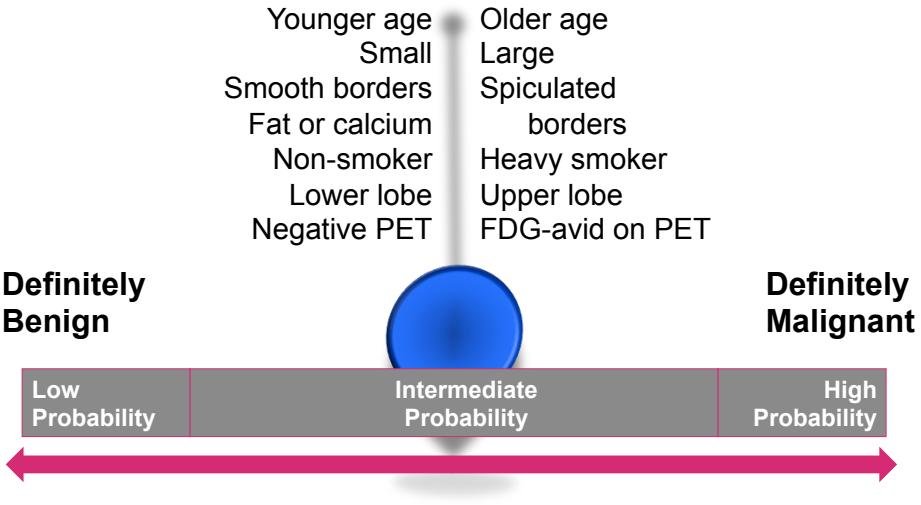


1. Pignon JP, et al. *J Clin Oncol*. 2006;24(18S):Abstract 7008.
2. Sandler A, et al. *N Eng J Med*. 2006;355:2542-2550.
3. Farjah F, et al. *J Thorac Oncol*. 2009;4(3):355-363.

Take Home Lesson?

If you want to make an impact,
do the ordinary things extraordinarily well

Approach to the Patient with a Nodule



What Do We Do With This "Probability"?

Fleischner Zone

PET scan zone "Is this more or less likely to be cancer?"

PET scan zone "This is cancer. What stage is it?"

Definitely Benign

Definitely Malignant

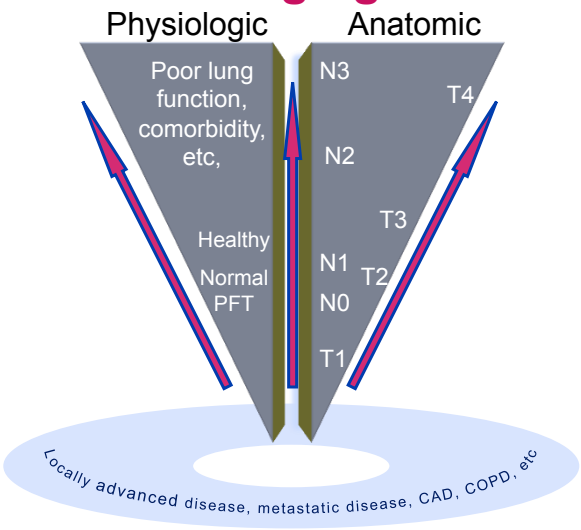
Low Probability	Intermediate Probability	High Probability

PET Scan

- PET-CT is the Swiss Army knife of "oncopulmonology"
  - Diagnosis, nodal, *and* distant staging
- *Not* the equivalent of a biopsy
  - Many false positives
  - Use PET-CT as a "road map" to the best biopsy

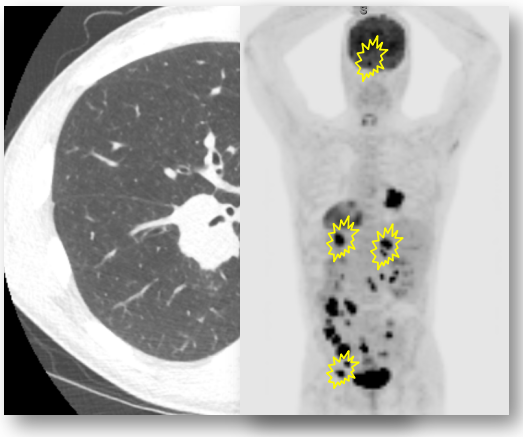
- Most stage informative lesion should be biopsied
  - Exceptions?

Staging



Barriers to surgical resection

What to Biopsy?



A PET scan is ***NOT*** a biopsy. It is a road map that tells you the best place to biopsy.

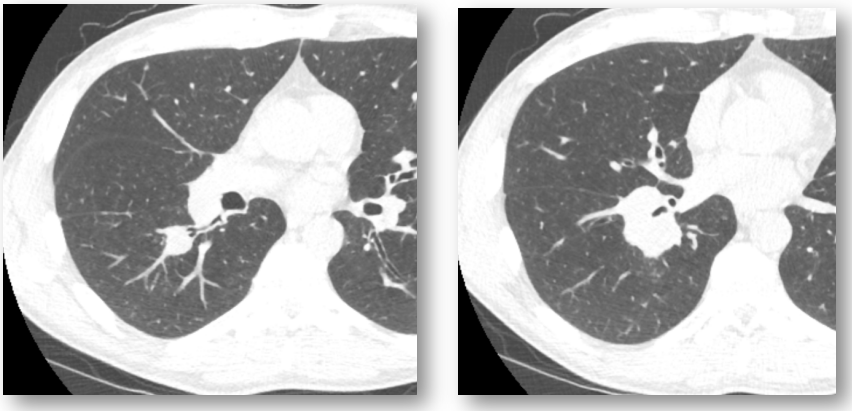
How to Biopsy: Can you Find Targeted Mutations on Small Biopsy?

Reference	Methods	% Adequate	
Nakajima. *Chest.* 2007;132:597.	46 paraffin-embedded samples, EGFR exons 19 and 21. Retrospective	43/43 (100%)	
Garcia-Olive. *ERJ.* 2010;35:391.	Prospective 36 patients with adenocarcinoma or NSCLC NOS referred for staging with EBUS	26/36 (72%)	Small nodes
Schuurbiers. *JTO.* 2010:5(10):1664.	35 patients over 4 years. Smears/cell blocks with > 40% tumor cells	27/35 (77%)	2.9 ± 1.1 (range: 1–5) passes/site
Kang Y. (ATS 2011 abstract)	N = 145, FFPE DNA extraction and PCR	137/145 (94%)	TBBx, and EBUS
van Eijk. *PLoS One.* 2011;6(3): e17791.	43 pts with both cytological and histological tumor tissue; allele-specific qRT-PCR in node AND tumor	43/43 (100%)	All nodal specimens matched primary tumor
Billah. *Cancer Cytopath.* 2011;119(2): 111-117.	209 cytology specimens. 99 EBUS, 67 (CT)-guided FNA, 27 effusions, 16 other FNA	Only 6.2% of specimens were inadequate	CT-FNA, EBUS, and Effusions

What Do These Studies Tell Us About Our Role in an Era of Targeted Therapy?

- "Just a diagnosis" is no longer good enough (and never was)…
  - Proper individualized care starts (and often ends) with accurate staging
- When obtaining cytologic specimens or small biopsies…
  - Know what your oncologist, surgeon, and pathologist want
  - A multidisciplinary team that spans from the pulmonologist to the pathologist to the oncologist

52-year-old with cough and hemoptysis, tobacco smoker, ROS: weight loss



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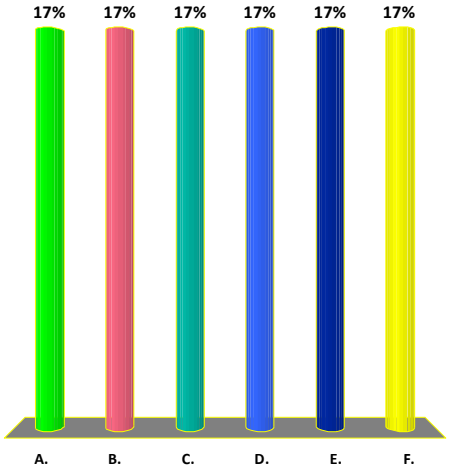

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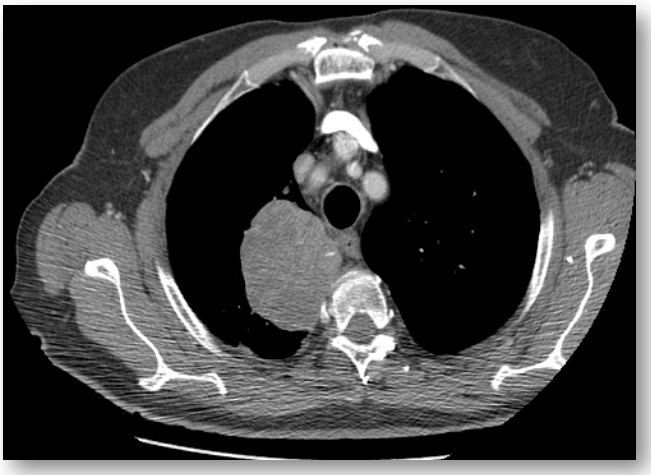

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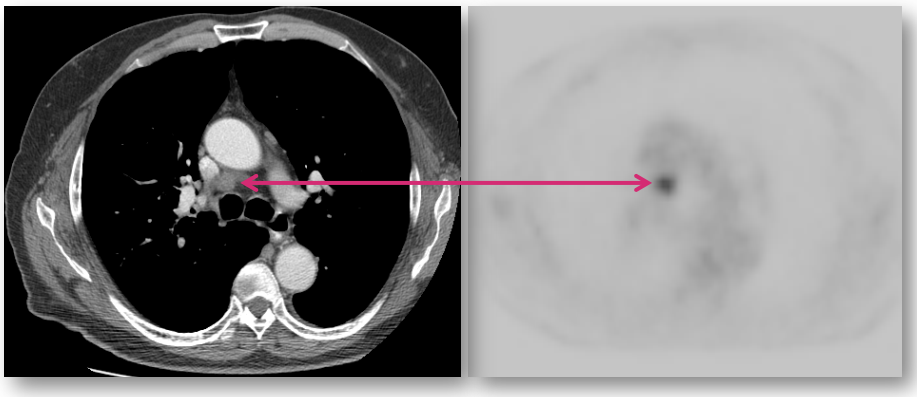

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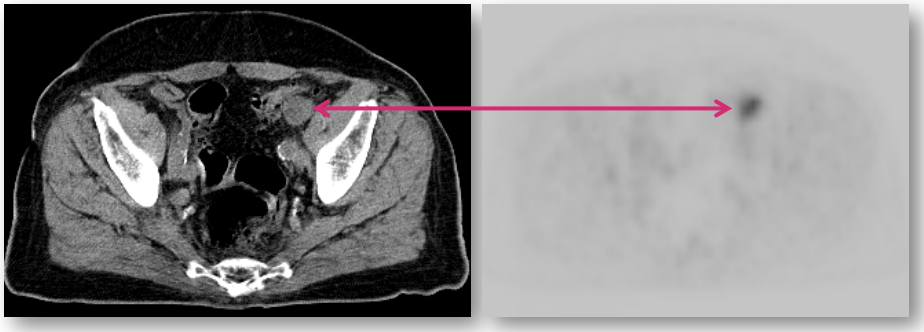

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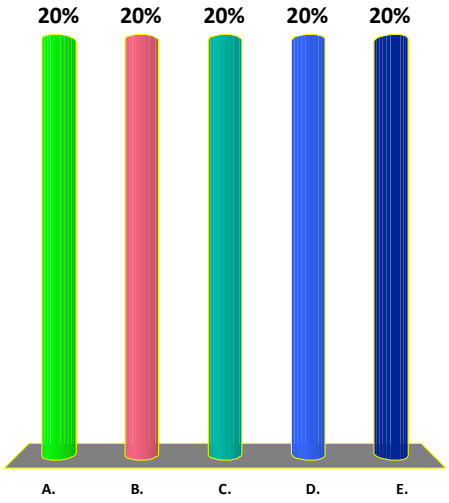

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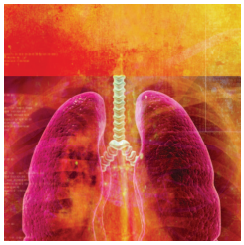

Demystifying the Role of Targeted Therapy for Lung Cancer: When, for Whom, and Where Are We Going?

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Speaker

Johann C. Brandes, MD, PhD
Atlanta VAMC
Emory University
Atlanta, Georgia

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Johann C. Brandes, MD, PhD

Learning Objective

- Describe lung cancer biomarker tests and their importance for individualized therapy

Molecularly Targeted Therapy

- **Targeted therapy** blocks the growth of cancer cells by interfering with specific pathways needed for carcinogenesis rather than by broadly interfering with rapidly dividing cells (eg, with traditional chemotherapy)

Defining the Target

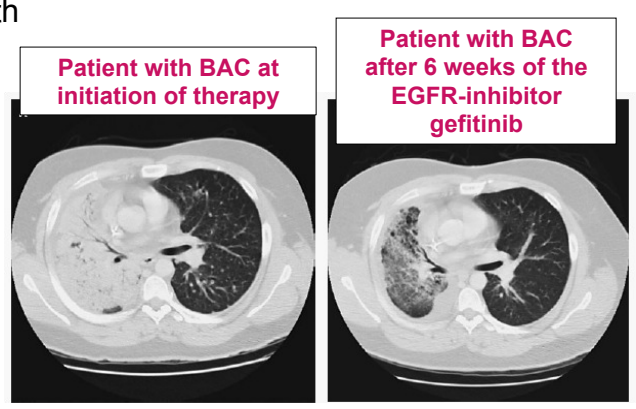
- Is the molecular target one of many active pathways in a particular lung cancer?

  Or

- Is a tumor dependent on the activation of a single molecular pathway ('oncogene addiction')

"Oncogene Addiction"

- Definition: dependence of a cancer cell on one overactive gene or pathway for the cell's survival and growth



Lynch TJ, et al. *N Engl J Med*. 2004;350(121):2129-2139.

Focus of this Presentation

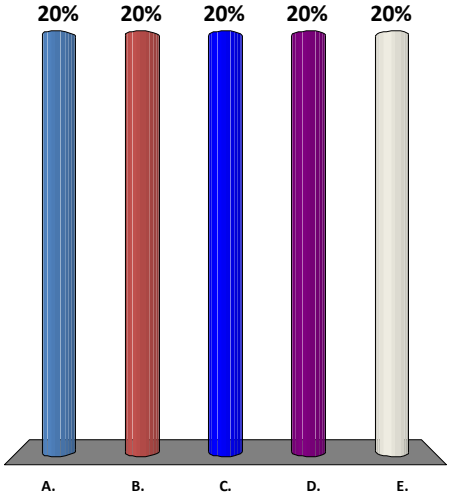
1. Established targets for which FDA-approved therapies exist
2. Emerging targets under clinical evaluation
3. Strategies to overcome resistance to established targeted therapies

Case presentation

- A 39 yo woman presents with SOB and back pain
  - No significant PMH
  - Never smoker
- Physical exam
  - Absent breath sounds over the right hemithorax
  - Dullness to percussion
  - Point tenderness over T8
- CXR: large right side pleural effusion
- PET scan
  - 3 cm RUL mass
  - Large pleural effusion
  - FDG-avid focus in T8

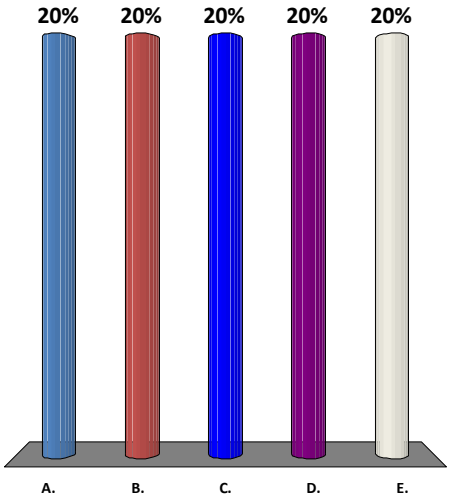
Cytology of pleural cells reveals "metastatic cancer, consistent with NSCLC." What would you do next ?

A. Start chemotherapy with bevacizumab, carboplatin and paclitaxel
B. Start chemotherapy with carboplatin and paclitaxel
C. Start first-line therapy with erlotinib or gefitinib (the patient is a never-smoker)
D. Request histologic sybtyping (squamous-, adeno-, large cell cancer, etc) and mutational analyses if result is non-squamous
E. Request *EGFR* mutational analysis

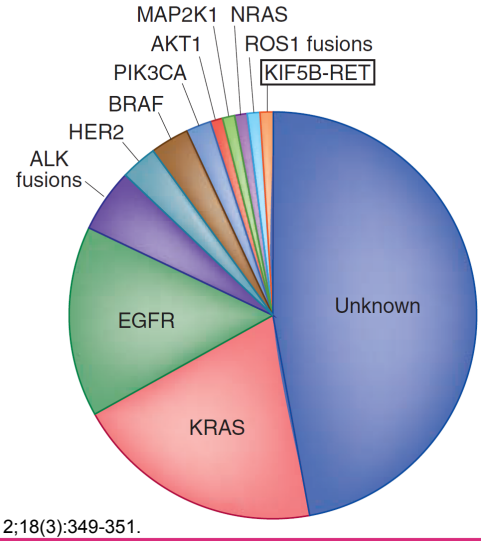


Further analysis of the biopsy specimen reveals adeno-carcinoma with an *EGFR* (L858R) mutation. What is the best treatment for this patient?

A. Multi-agent, platinum-based chemotherapy with bevacizumab
B. Therapy with EGFR-TKIs such as erlotinib or gefitinib
C. Do **NOT** use EGFR-TKIs since the L858R mutation confers resistance to these agents
D. Withhold treatment with EGFR-TKIs pending *K-RAS* results
E. Use crizotinib if first-line EGFR-TKIs fail



Molecular Subsets of Lung Adenocarcinoma



Pao W, et al. *Nat Med*. 2012;18(3):349-351.

Lung Cancer Mutation Consortium (LCMC)

- NCI-sponsored initiative of 14 centers around the country
- **Goal**: to analyze frequency of 10 driver mutations in lung adenocarcinomas by sequencing (8) and FISH (2) in 1000 patients

http://www.golcmc.com/. Accessed Sept 2013.

FISH = fluorescence in situ hybridization.

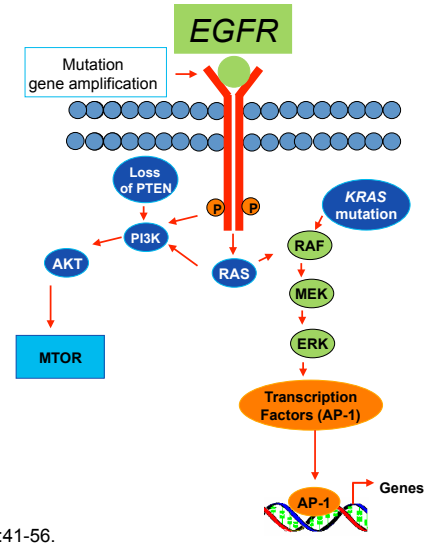
A Multicenter Effort to Identify Driver Mutations and Employ Targeted Therapy in Patients with Lung Adenocarcinomas: The Lung Cancer Mutation Consortium (LCMC)

- *KRAS, EGFR, HER2, BRAF, PIK3CA, AKT1*, *MEK1*, and *NRAS* mutations by multiplexed next-gen sequencing assays
- MET amplifications and ALK translocations by FISH
- 1,102 patients enrolled, 1,007 tested for at least one alteration, 733 tested for all 10 genes
- 60% women, 34% never-smokers
- Median OS
  - 264 patients with driver mutation and targeted therapy: 3.5 years
  - 313 patients with a driver mutation without targeted therapy: 2.4 years
  - 361 patients without driver: 2.1 years ($P < 0.0001$)

Johnson BE, et al. *J Clin Oncol*. 2013;31(suppl) Abstr 8019.

Oncogenic Pathways in NSCLC

- *EGFR* is overexpressed in 40–50% of all NSCLC
- *EGFR* mutations occur in about 10% of all patients with adenocarcinoma and are rare in other subtypes
- *KRAS* mutations occur in 20–30% of all adenocarcinomas
- In mouse models, both *EGFR* mutations and *KRAS* mutations lead to oncogene addiction
- *EGFR* and *KRAS* mutations are mutually exclusive



Adapted from Tiwari D, et al. *Ther Adv Respir Dis*. 2012;6:41-56.

Studies of First Line *EGFR-TKI* Therapy in *EGFR* Mutated NSCLC

Study	No. patients	Treatment arm	Control arm	Stage	Median PFS	Median overall survival	Indication	Study phase	Citation
IPASS	1,217	Gefitinib	Carboplatin, paclitaxel	IIIB/IV	5.7 months vs. 5.8 months; HR for progression for EGFR mutated patients 0.48; HR for progression for EGFR unmutated patients 2.84	18.6 vs 17.3 months	First-line	III	Mok (*NEJM* 2009)
WJTOG3405	177 (M+)	Gefitinib	Cisplatin, docetaxel	IIIB/IV	9.2 vs. 6.3 months ($P < 0.001$)	Data not mature yet	First-line	III	Mitsudomi (*NEJM* 2010)
	203 (M+)	Gefitinib	Carboplatin, paclitaxel	IIIB/IV	10.8 vs 5.4 months (HR 0.3, $P < 0.001$)	30.5 vs 20.6 months (p = NS)	First-line	III	Maemondo (*NEJM* 2010)
OPTIMAL	165 (M+)	Erlotinib	Carboplatin/ Gemcitabine	IIIB/IV	13.6 vs 4.6 months (HR 0.16, $P < 0.001$)		First-line	III	Zhou (*Lancet* 2011)
EURTAC	153 (M+)	Erlotinib	Platinum based chemotherapy	IIIB/IV	9.4 vs 5.2 months ($P < 0.001$)	22.9 vs 18.8 months (p = NS)	First-line	III	Rosell (*Lancet* 2012)
LUX-LUNG-3	345 (M+)	Afatinib	Cisplatin/ pemetrexed	IIIB/IV	11.1 vs 6.9 months ($P < 0.001$)		First-line	III	Yang (*ASCO* 2012)

Crizotinib versus Chemotherapy in Advanced *ALK*-Positive Lung Cancer

Alice T. Shaw, M.D., Ph.D., Dong-Wan Kim, M.D., Ph.D., Kazuhiko Nakagawa, M.D., Ph.D., Takashi Seto, M.D., Lucio Crinó, M.D., Myung-Ju Ahn, M.D., Tommaso De Pas, M.D., Benjamin Besse, M.D., Ph.D., Benjamin J. Solomon, M.B., B.S., Ph.D., Fiona Blackhall, M.D., Ph.D., Yi-Long Wu, M.D., Michael Thomas, M.D., Kenneth J. O'Byrne, M.D., Denis Moro-Sibilot, M.D., D. Ross Camidge, M.D., Ph.D., Tony Mok, M.D., Vera Hirsh, M.D., Gregory J. Riely, M.D., Ph.D., Shrividya Iyer, Ph.D., Vanessa Tassell, B.S., Anna Polli, B.S., Keith D. Wilner, Ph.D., and Pasi A. Jänne, M.D., Ph.D.

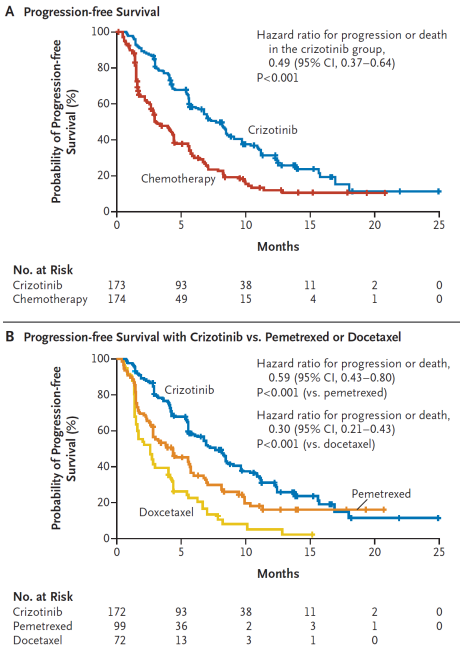
- Phase 3 open-label study
- 1:1 randomization
  - Crizotinib (250 mg bid)
  - Chemotherapy with pemetrexed or docetaxel
- 4,967 patients screened; 347 were randomized
- Primary endpoint: PFS
- Secondary endpoints: response rates, OS, toxicity, patient reported outcomes

Shaw AT, et al. *N Engl J Med*. 2013;368(25):2385-2394.

Crizotinib vs Chemotherapy

Objective response rates:
65% vs. 20%, $P < 0.001$

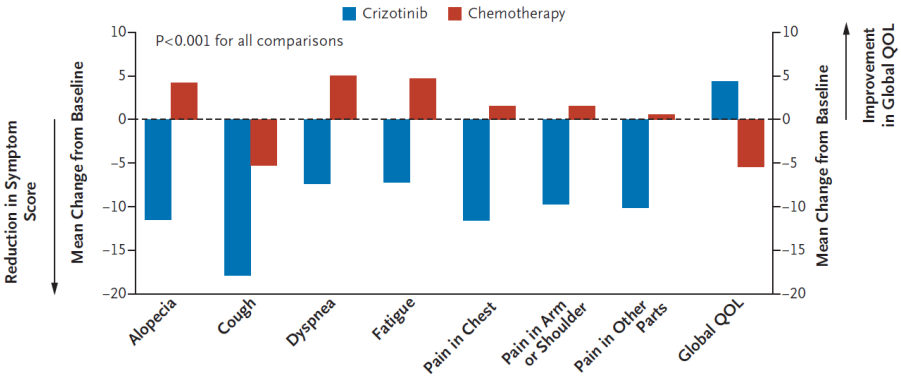
Crizotinib LFT abnormalities:
38% (16% grade III and IV)



Shaw AT, et al. *N Engl J Med*. 2013;368(25):2385-2394.

Patient-Reported Outcomes

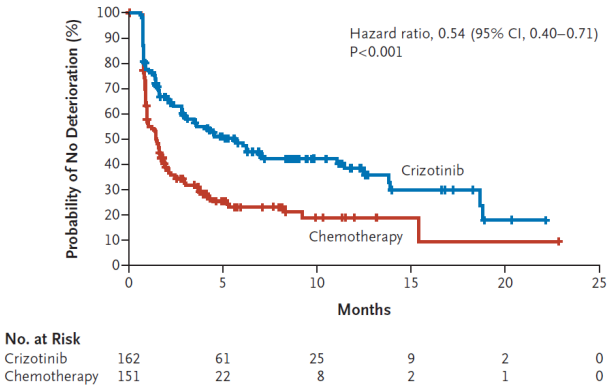
Symptoms and Global QOL



Shaw AT, et al. *N Engl J Med*. 2013;368(25):2385-2394.

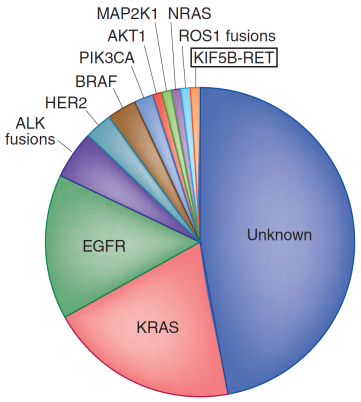
Patient-Reported Outcomes

Composite Lung Cancer Symptom Endpoint



Shaw AT, et al. *N Engl J Med*. 2013;368(25):2385-2394.

Emerging Targets



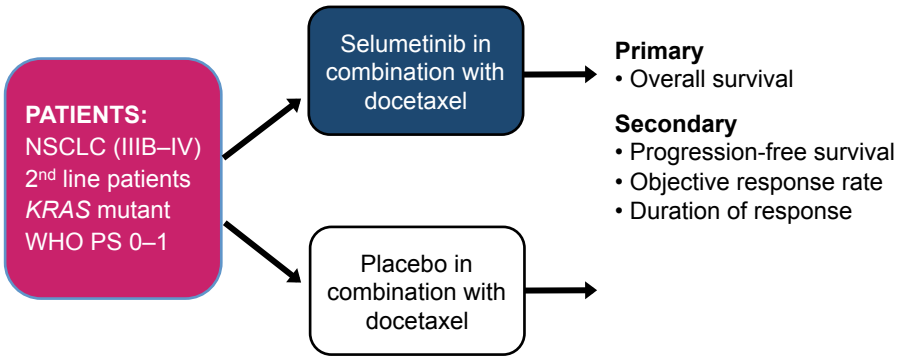
Target	Drug
K-ras	Selumetinib
B-raf (V600E)	Dabrafenib
Her-2	Afatinib
Mek	Trametinib
N-raf	Trametinib
PI3KCa	PKM120
RET fusions	Cabozantenib
ROS-1 fusions	Crizotinib
B-raf (non-V600E)	Trametinib

Pao W, et al. *Nat Med*. 2012;18(3):349-351.
Kris MG, et al. *J Clin Oncol*. 2011;29(suppl)Abstr CRA7506.

Targeting *K-RAS* Mutations: A Formidable Challenge

- 20–30% of adenocarcinomas
- Possibly adverse predictive factor for response to conventional chemotherapy
- All attempts to target *K-RAS* mutant lung cancers have failed so far

Randomized Phase II Trial of MEK-inhibitor Selumetinib (AZD6224) vs. Chemotherapy



http://www.clinicaltrials.gov/ct2/show/NCT00890825?term=Selumetinib+docetaxel&rank=5. Accessed Sept 2013.

Results

- 87 patients with *K-RAS* mutations randomized
  - OS: 9.4 vs 5.6 months ($P = 0.2$)
  - RR: 37% vs 0% ($P < 0.001$)
  - PFS: 5.3 vs 2.1 months (P - 0.01)

http://www.clinicaltrials.gov/ct2/show/NCT00890825?term=Selumetinib+docetaxel&rank=5. Accessed Sept 2013.

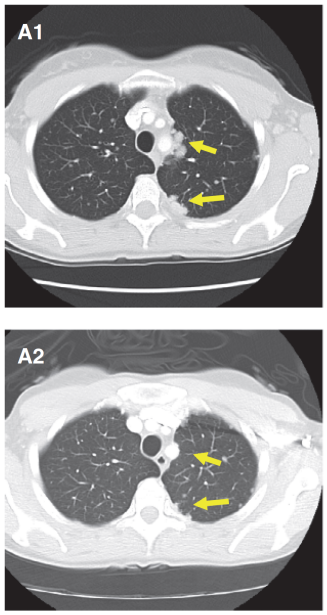
Interim Results of Phase II Study BRF113928 of Dabrafenib in *BRAF* V600E Mutation–Positive Non-Small Cell Lung Cancer (NSCLC) Patients

- Single-arm, 2-stage, phase 2 study
- Stage IV *BRAF* V600E mutation–positive NSCLC patients who failed at least 1 line of chemotherapy
- 17 patients enrolled
  - 12 men
  - 13 former smokers
- Primary endpoint: ORR
- Outcomes: 12 patients evaluable for response: 7 PR, 1 SD, 4 PD
- Duration of response in patients with PR
  - 2 patients progressed (29 and 49 weeks)
  - 3 patients responding (6+ to 24+ weeks)
- Adverse events: decreased appetite, nausea, fatigue, dyspnea, nausea; grade 4 SAE: 1 patient with hemorrhage

Planchard D, et al. *J Clin Oncol.* 2013;31(suppl) Abstr 8009.

Cabozantinib in RET-Fusion Positive NSCLC

- Initial results from a phase 2 trial
- 3 patients treated so far
- 2 responses

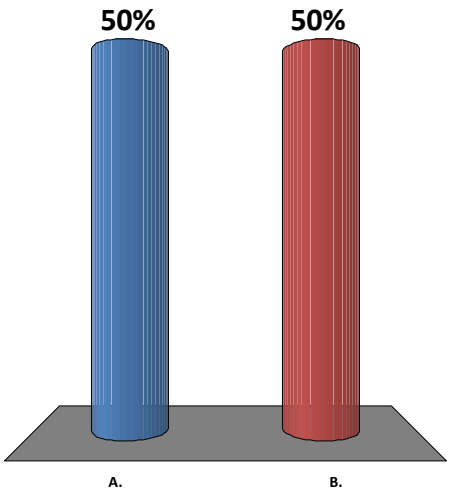


Drilon A, et al. *Cancer Discov*. 2013;3(6):630-635.

Should EGFR-TKI-resistant tumors be re-biopsied?

A. YES. Re-biopsy may determine the appropriate management with standard chemotherapy regimens in a subset of patients

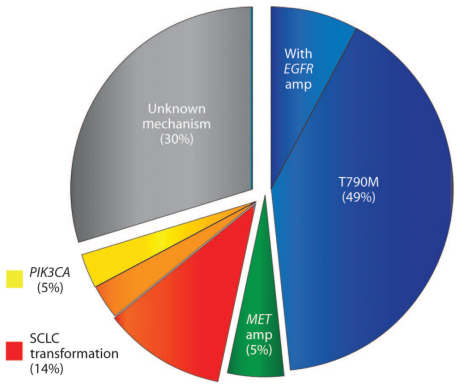
B. NO. Evolution of the tumor is extremely rare and repeated mutation analysis will not yield useful information



Genotypic and Histological Evolution of Lung Cancers Acquiring Resistance to EGFR Inhibitors

Lecia V. Sequist,[1,2*†] Belinda A. Waltman,[2*] Dora Dias-Santagata,[2,3*] Subba Digumarthy,[2,4] Alexa B. Turke,[1,2] Panos Fidias,[1,2] Kristin Bergethon,[3] Alice T. Shaw,[1,2] Scott Gettinger,[5] Arjola K. Cosper,[1] Sara Akhavanfard,[2,3] Rebecca S. Heist,[1,2] Jennifer Temel,[1,2] James G. Christensen,[6] John C. Wain,[1,2,7] Thomas J. Lynch,[5] Kathy Vernovsky,[1] Eugene J. Mark,[2,3] Michael Lanuti,[1,2,7] A. John Iafrate,[2,3] Mari Mino-Kenudson,[2,3] Jeffrey A. Engelman[1,2†]

- 37 patients with acquired resistance to erlotinib or gefitinib
- Biopsy tissue before and after treatment with EGFR TKI was available



Sequist LV, et al. *Sci Transl Med*. 2011;3(75):75ra26.

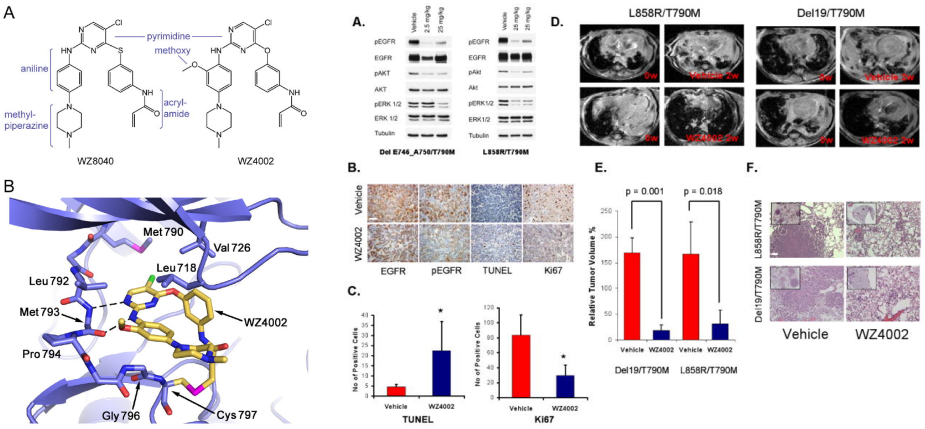
Role of Second-Line Irreversible *EGFR* Inhibitors in Overcoming *EGFR-TKI* Resistance

- Afatinib (BIBW2992) Lux-Lung-1
  - 585 patients progressed after platinum-based chemotherapy and erlotinib, failed to reach primary endpoint (improvement in OS), but a PFS benefit was observed (3.3 vs 1.1 months)
- Neratinib (irreversible panErb Inhibitor) Phase 2 results
  - 3% RR in 167 patients (91 *EGFR* mutated after erlotinib, 48 *EGFR* wt after erlotinib, 28 TKI naive)

Hirsh V. *Curr Oncol*. 2010;17(6):7-8.
Majem M, et al. *Clin Transl Oncol*. 2013;15(5):343-357.

Novel mutant-selective EGFR kinase inhibitors against EGFR T790M

Wenjun Zhou[1,2]*, Dalia Ercan[3,4]*, Liang Chen[3,4]*, Cai-Hong Yun[1,2]*, Danan Li[3,4], Marzia Capelletti[3,4], Alexis B. Cortot[3,4], Lucian Chirieac[5], Roxana E. Iacob[6,7], Robert Padera[5], John R. Engen[6,7], Kwok-Kin Wong[3,4,8,9], Michael J. Eck[1,2], Nathanael S. Gray[1,2] & Pasi A. Jänne[3,4,8]



Zhou W, et al. *Nature*. 2009;462(7276):1070-1074.

Conclusions

- Erlotinib and crizotinib are very effective therapies in oncogene-addicted NSCLC
- Novel targets and targeted therapies are evolving rapidly
- High-quality biopsies are key to enable molecular testing
- Talk to your oncologist and pathologist about tissue allocation
- Do not use too much tissue for IHC
- The correct classification of resistance mechanisms requires re-biopsy
- No data exist on the efficacy of targeted therapy in stage I-III NSCLC

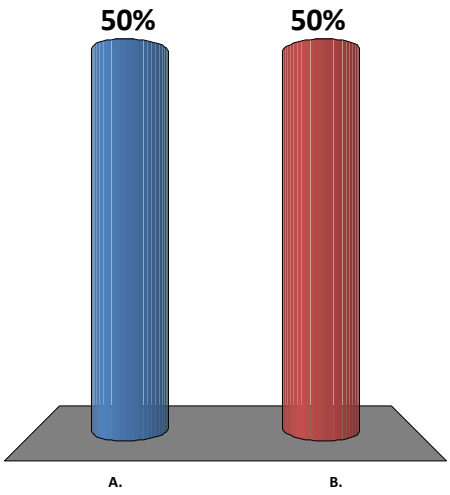
Case presentation

- A 39 yo woman presents with SOB and back pain
  - No significant PMH
  - Never smoker
- Physical exam
  - Absent breath sounds over the right hemithorax
  - Dullness to percussion
  - Point tenderness over T8
- CXR: large right side pleural effusion
- PET scan
  - 3 cm RUL mass
  - Large pleural effusion
  - FDG-avid focus in T8

Should EGFR-TKI-resistant tumors be re-biopsied?

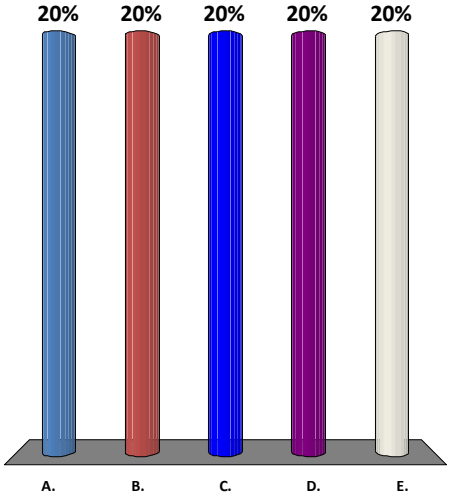
A. YES. Re-biopsy may determine the appropriate management with standard chemotherapy regimens in a subset of patients

B. NO. Evolution of the tumor is extremely rare and repeated mutation analysis will not yield useful information



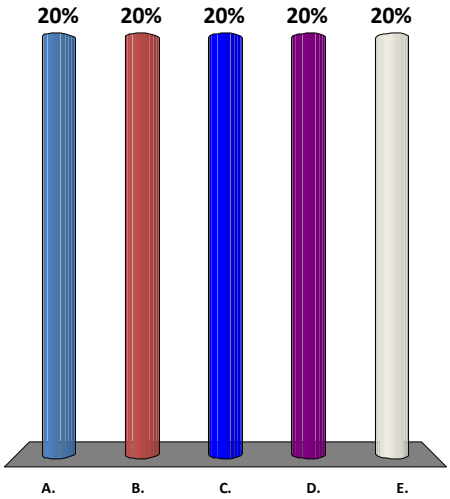
Cytology of pleural cells reveals "metastatic cancer, consistent with NSCLC." What would you do next ?

A. Start chemotherapy with bevacizumab, carboplatin and paclitaxel
B. Start chemotherapy with carboplatin and paclitaxel
C. Start first-line therapy with erlotinib or gefitinib (the patient is a never-smoker)
D. Request histologic sybtyping (squamous-, adeno-, large cell cancer, etc) and mutational analyses if result is non-squamous
E. Request *EGFR* mutational analysis

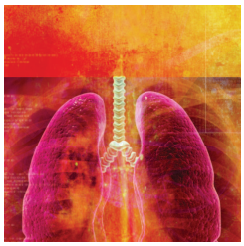


Further analysis of the biopsy specimen reveals adeno-carcinoma with an *EGFR* (L858R) mutation. What is the best treatment for this patient?

A. Multi-agent, platinum-based chemotherapy with bevacizumab
B. Therapy with EGFR-TKIs such as erlotinib or gefitinib
C. Do **NOT** use EGFR-TKIs since the L858R mutation confers resistance to these agents
D. Withhold treatment with EGFR-TKIs pending *K-RAS* results
E. Use crizotinib if first-line EGFR-TKIs fail



Present and Future Targeted Lung Cancer Therapy: Beginning the End of Nihilism



What Do Pathologists Do With Your Biopsy?

CHEST 2013
October 26 - 31
Chicago, Illinois

MORNING
EDUCATIONAL
SYMPOSIUM

Educational Support

Sponsored by the American College of Chest Physicians.

This educational activity is supported by an educational grant from Boehringer Ingelheim.

This educational activity is supported by an educational grant from Genentech.

Speaker

Carol Farver, MD
Pulmonary Pathology
Pathology and Laboratory Medicine Institute
Cleveland Clinic
Cleveland, Ohio

Faculty Disclosure

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The following faculty member of this educational activity has disclosed to the ACCP that no potential conflict of interest exists with any respective company/organization, and this should be communicated to the participants of this educational activity:
Carol Farver, MD

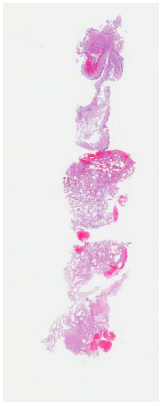
Learning Objective

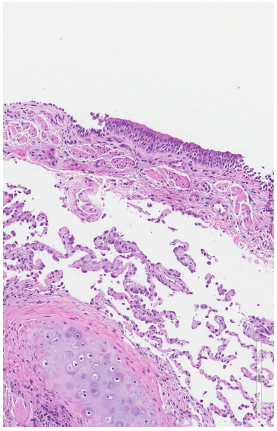
- Describe how pathologists process and analyze lung biopsies for biomarkers
  - Understand what happens to the biopsy tissue after the procedure
  - Discuss the definition of biopsy adequacy for morphology and biomarkers
  - Review the questions clinicians should ask prior to, at the time of, and after the biopsy procedure to optimize handling of the tissue for diagnosis and therapy

Biopsy Procedures

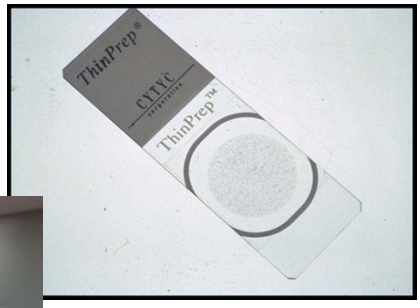
- Bronchoscopic tissue biopsy
  - Primary lung lesions
    - Tissue biopsy
    - Bronchoalveolar lavage fluid/brush
- Fine needle aspiration/biopsy
  - Distant metastases
  - Endobronchial ultrasound guided staging fine needle aspiration/biopsy (EBUS)

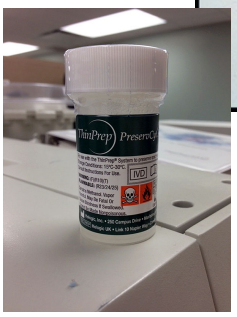
Bronchoscopy Tissue Biopsy



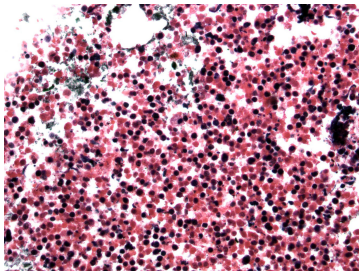


FNAB ThinPrep Slides

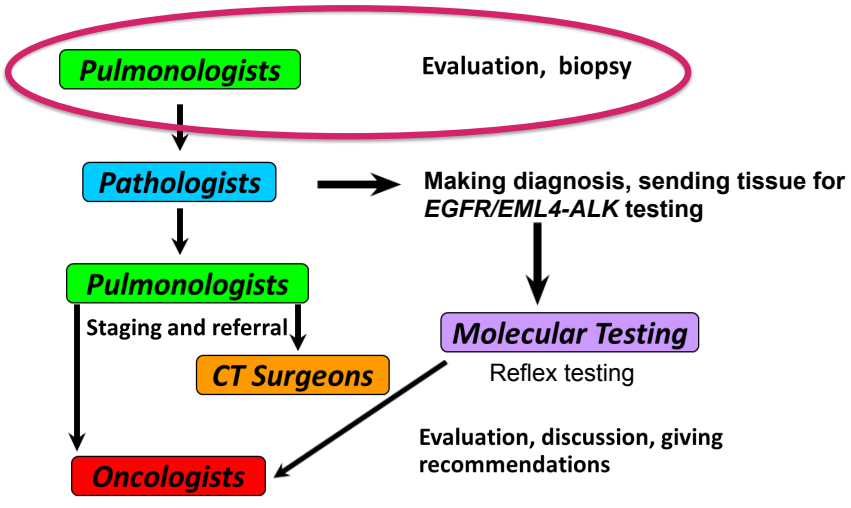




FNAB Cell Block



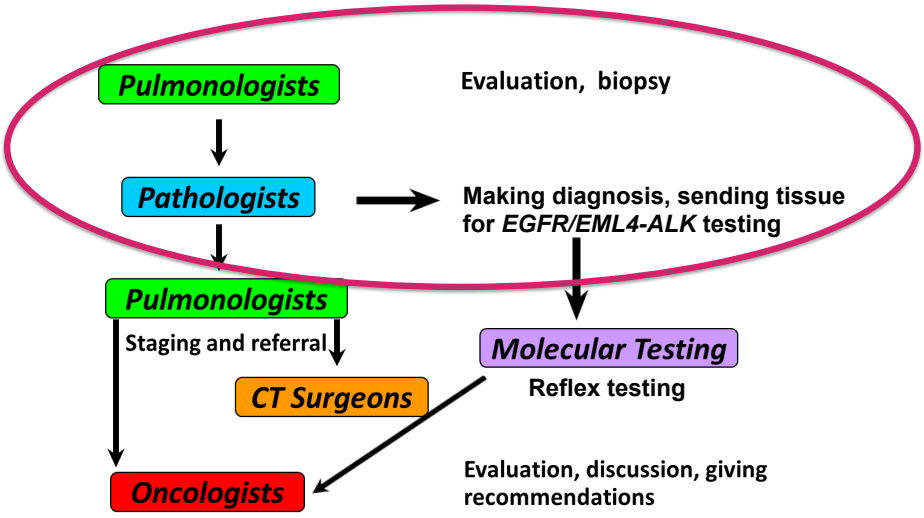
Patient Encounter Flow Chart for Morphology and Molecular Markers



Information Your Pathologist Needs Before the Biopsy Procedure

- Reason for procuring tissue
  - Diagnosis and molecular markers
  - Molecular markers only
    - *EGFR, EML4-ALK, KRAS*, other
  - Diagnosis only
- Clinical history
- Imaging studies

Patient Encounter Flow Chart for Morphology and Molecular Markers



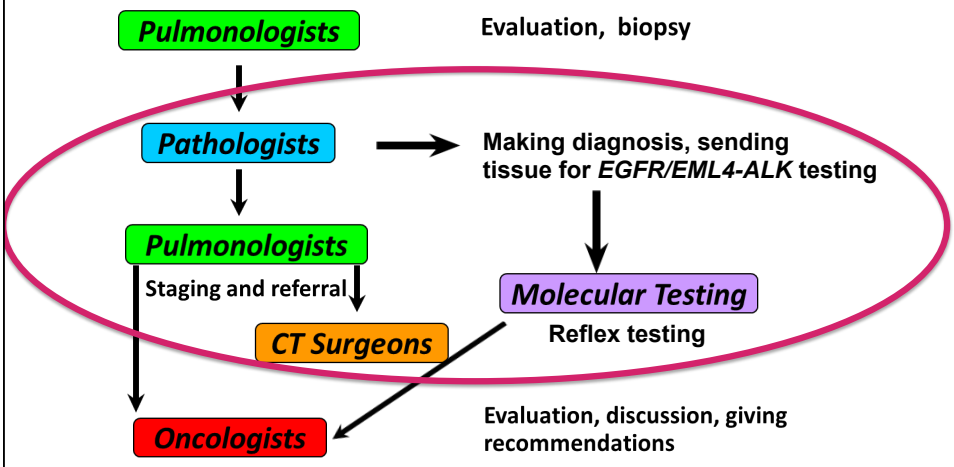
Information Your Pathologist Needs During the Biopsy Procedure

- Location of biopsy
  - Lung
  - Lymph nodes
  - Distant site
- Size
- Imaging characteristics (do you think it is +)

Adequacy Assessment

- Needle is in the correct location
- Sufficient tissue for diagnosis
- Sufficient tissue for molecular markers

Patient Encounter Flow Chart for Morphology and Molecular Markers

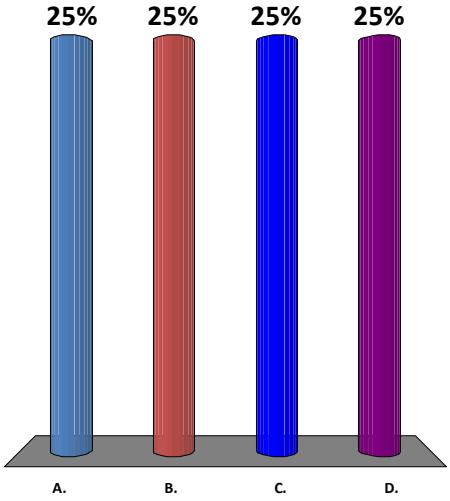


Information Your Pathologist Needs After the Biopsy Procedure

- Clinical history
  - Imaging studies
  - History of malignancy (lung or other)
  - History of therapy
    - Radiation, chemotherapy
- Previous molecular testing performed
  - When?
  - Where?

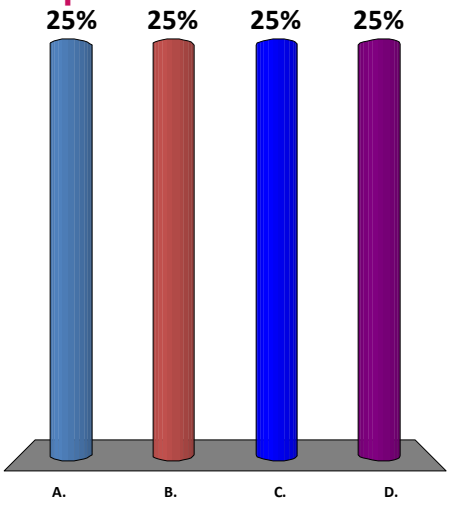
Lung biopsy specimens with morphology of an NSCLC, not otherwise specified, should be evaluated for tumor differentiation using which of the following antibodies?

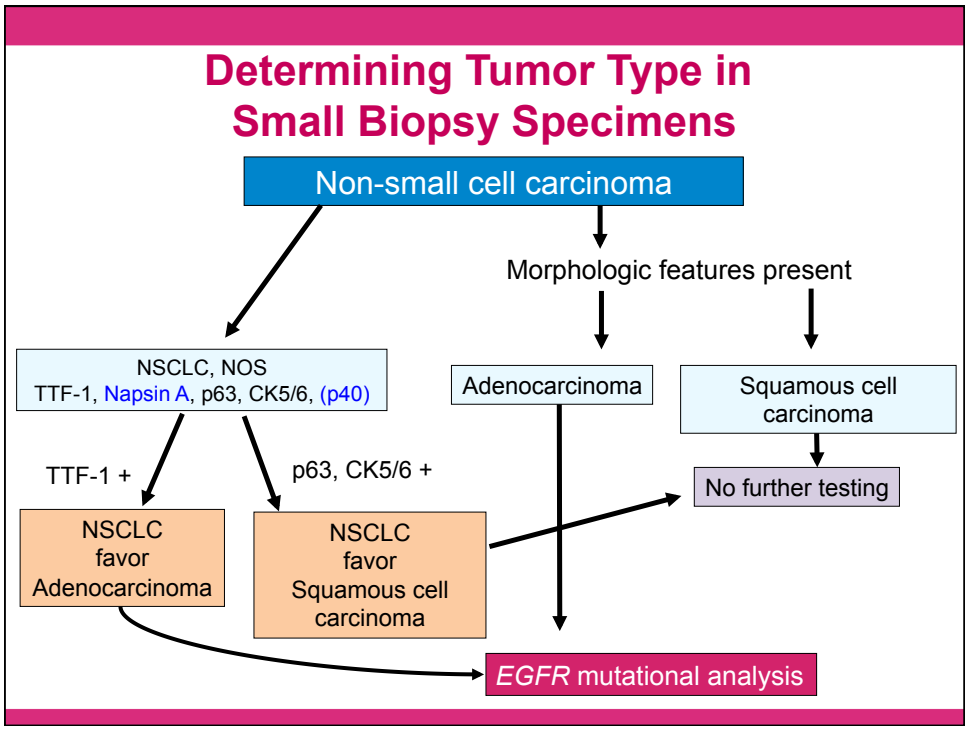
A. TTF-1
B. p63
C. CK5/6
D. All of the above

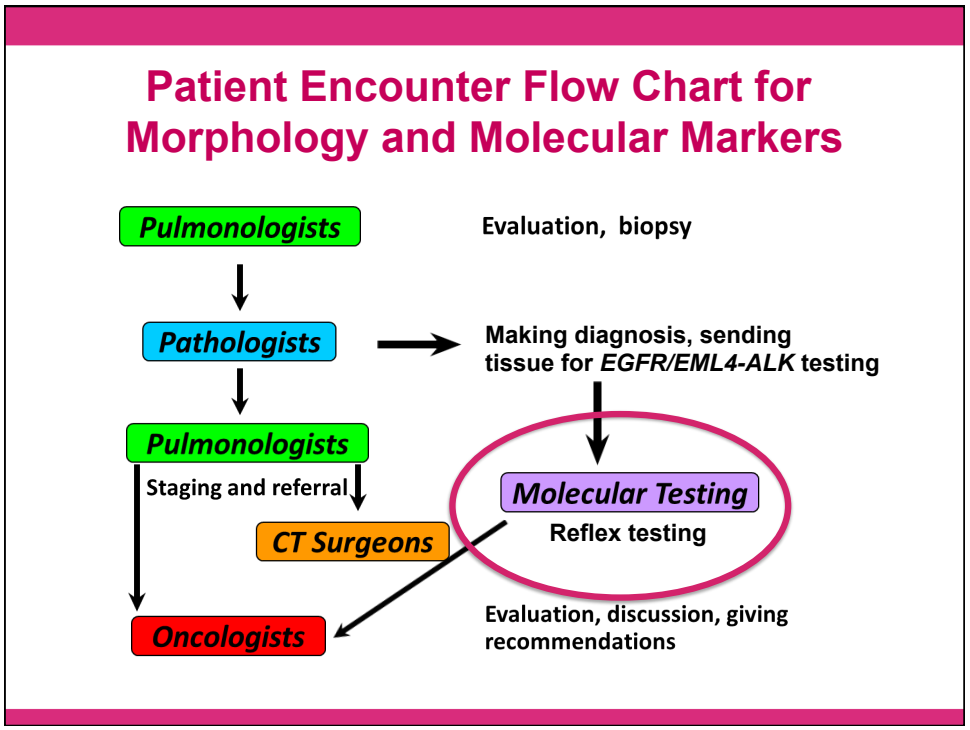


The most reliable method for testing lung cancer for the *EML4-ALK* fusion protein is:

A. Immunohistochemistry
B. Fluorescent in-situ hybridization (FISH)
C. Microbiological cultures
D. Polymerase chain reaction mutational analysis




Determining Tumor Type in Small Biopsy Specimens
Non-small cell carcinoma
Morphologic features present
NSCLC, NOS
TTF-1, Napsin A, p63, CK5/6, (p40)
Adenocarcinoma
Squamous cell carcinoma
TTF-1 +
p63, CK5/6 +
No further testing
NSCLC favor Adenocarcinoma
NSCLC favor Squamous cell carcinoma
EGFR mutational analysis


Patient Encounter Flow Chart for Morphology and Molecular Markers
Pulmonologists
Evaluation, biopsy
Pathologists
Making diagnosis, sending tissue for EGFR/EML4-ALK testing
Pulmonologists
Staging and referral
Molecular Testing
Reflex testing
CT Surgeons
Oncologists
Evaluation, discussion, giving recommendations

The Journal of Molecular Diagnostics, Vol. 15, No. 4, July 2013

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See related Guest Editorial on page 413.

SPECIAL ARTICLE

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

Neal I. Lindeman,* Philip T. Cagle,† Mary Beth Beasley,‡ Dhananjay Arun Chitale,§ Sanja Dacic,¶ Giuseppe Giaccone,‖ Robert Brian Jenkins,** David J. Kwiatkowski,†† Juan-Sebastian Saldivar,‡‡ Jeremy Squire,§§ Erik Thunnissen,¶¶ and Marc Ladanyi‖‖

Lindeman NI, et al. *J Molecular Diag.* 2013;15:415-453.

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

- *EGFR* and *ALK* testing:
  - Should be performed on all biopsies where adenocarcinoma cannot be completely excluded
  - Primary or metastatic tumors are equally suitable for testing
  - Should be done on all advanced staged lesions and recurrent lesions

Lindeman NI, et al. *J Molecular Diag.* 2013;15:415-453.

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

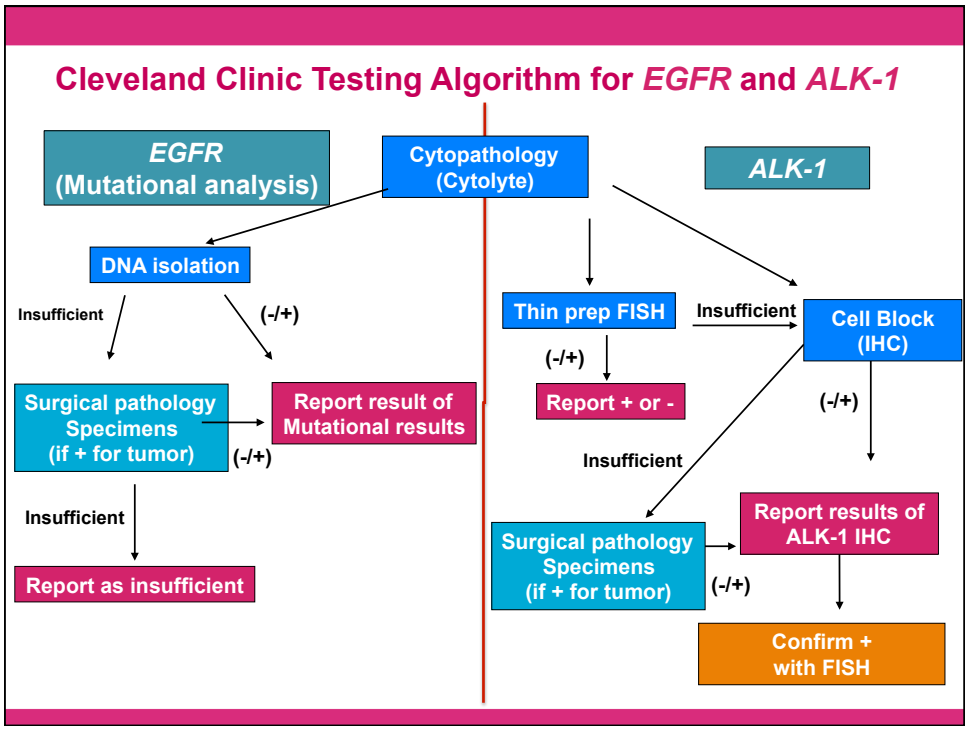
- *ALK* rearrangement testing should be ordered at the time of diagnosis for patients with advanced-stage disease who are suitable for therapy or at the time of recurrence or for disease progression for patients that presented with lower-stage disease
- *EGFR* and *ALK* testing should be prioritized over other proposed molecular markers in lung adenocarcinoma

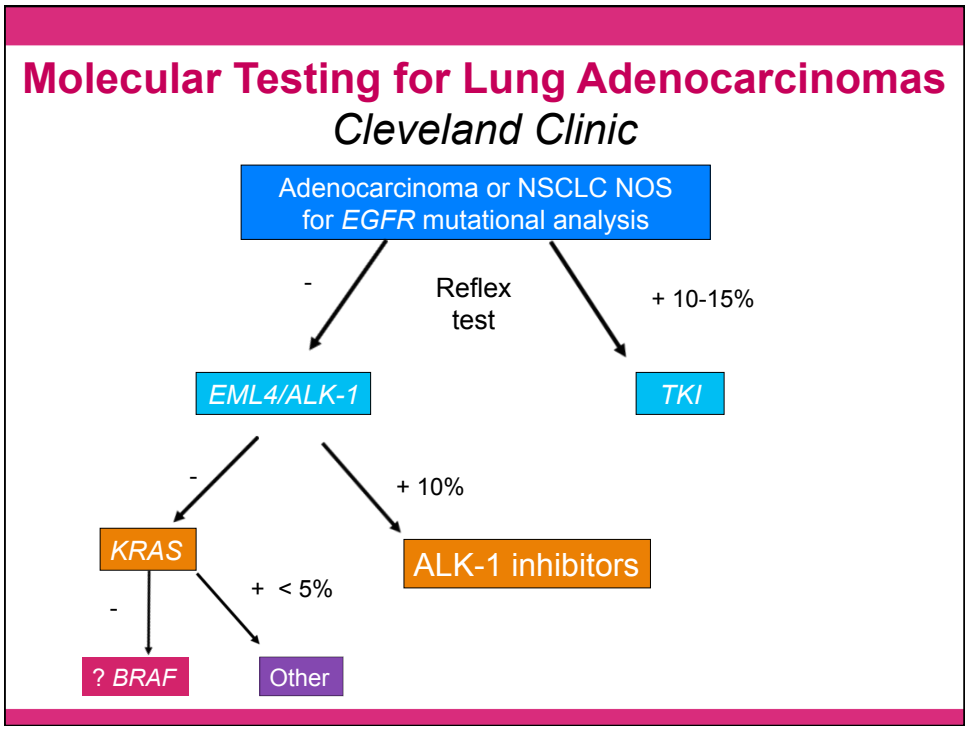
Lindeman NI, et al. *J Molecular Diag.* 2013;15:415-453.

College of American Pathologists, International Association for the Study of Lung Cancer, and Association of Molecular Pathology
Expert Consensus Opinion

- In the setting of multiple primary tumors, each tumor should be tested
- *EGFR* and *ALK* testing for patients presenting with Stage I, II, III disease is encouraged but the decision can be made locally
- Results should be available within 2 weeks (10 working days) of receiving specimen
- Pathologists should determine the adequacy of specimens for *EGFR* testing by assessing cancer cell content and DNA quantity and quality

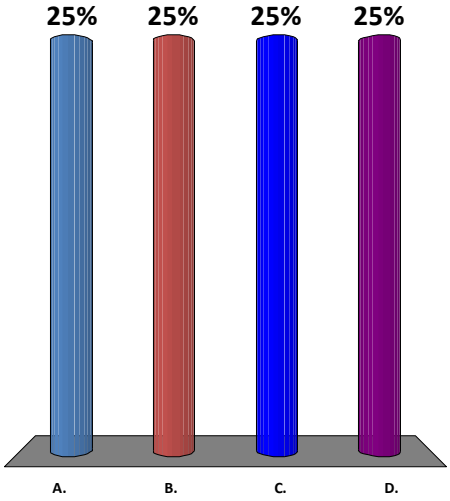
Lindeman NI, et al. *J Molecular Diag.* 2013;15:415-453.


Cleveland Clinic Testing Algorithm for EGFR and ALK-1
EGFR (Mutational analysis)
Cytopathology (Cytolyte)
ALK-1
DNA isolation
Insufficient
(-/+)
Surgical pathology Specimens (if + for tumor)
Report result of Mutational results
(-/+)
Insufficient
Report as insufficient
Thin prep FISH
Insufficient
Cell Block (IHC)
(-/+)
Report + or -
(-/+)
Insufficient
Surgical pathology Specimens (if + for tumor)
Report results of ALK-1 IHC
(-/+)
Confirm + with FISH


Molecular Testing for Lung Adenocarcinomas
Cleveland Clinic
Adenocarcinoma or NSCLC NOS for EGFR mutational analysis
-
Reflex test
+ 10-15%
EML4/ALK-1
TKI
-
+ 10%
KRAS
ALK-1 inhibitors
+ < 5%
-
? BRAF
Other

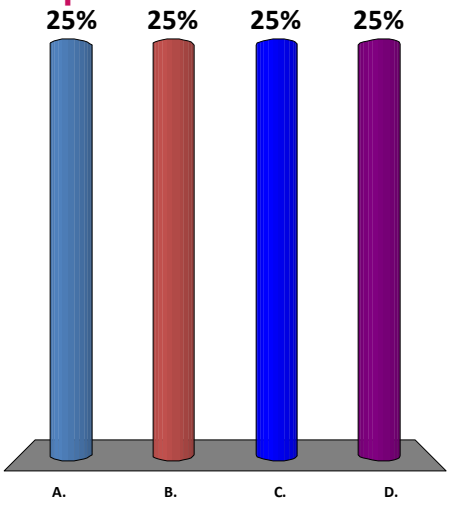
Lung biopsy specimens with morphology of an NSCLC, not otherwise specified, should be evaluated for tumor differentiation using which of the following antibodies?

A. TTF-1
B. p63
C. CK5/6
➡ D. All of the above



The most reliable method for testing lung cancer for the *EML4-ALK* fusion protein is:

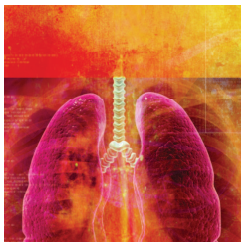
A. Immunohistochemistry
➡ B. Fluorescent in-situ hybridization (FISH)
C. Microbiological cultures
D. Polymerase chain reaction mutational analysis



Summary

- Tissue for NSCLC should be evaluated for evidence of adenocarcinoma/squamous cell carcinoma differentiation using immunohistochemistry
- Biopsy specimens where adenocarcinoma differentiation cannot be definitively excluded should be sent for *EGFR/ ALK-1* testing in the appropriate clinical setting
- Optimal tissue use of both cytology and pathology specimens is critical for diagnosis and therapy in these specimens

Present and Future Targeted Lung Cancer Therapy: Beginning the End of Nihilism



Case

Douglas A. Arenberg, MD, FCCP
University of Michigan Health System
Ann Arbor, Michigan

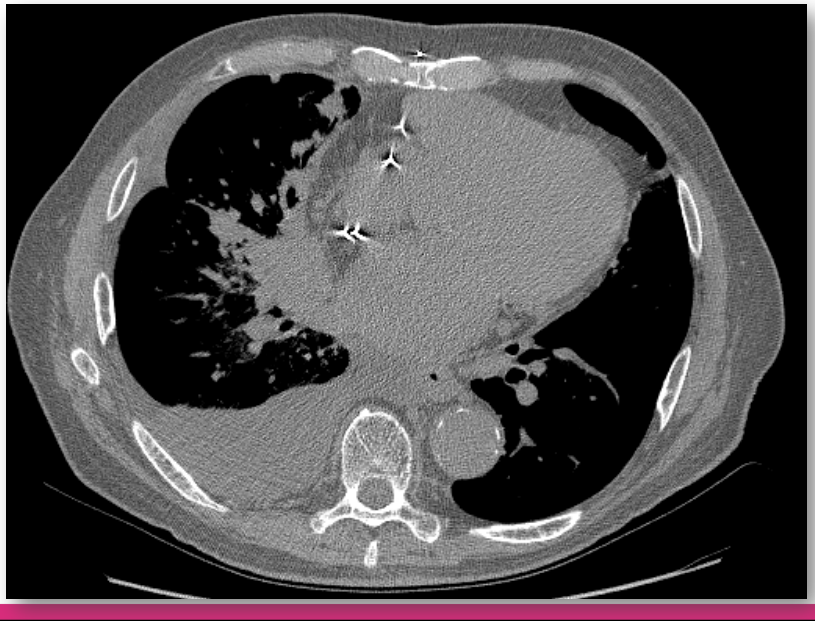
CHEST 2013
October 26 - 31
Chicago, Illinois

MORNING
EDUCATIONAL
SYMPOSIUM

Case

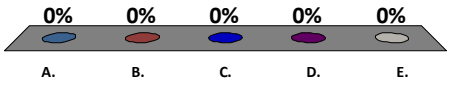
- A 58-year-old woman with a remote 12 pack-year tobacco history presents with recent onset of dyspnea and a CXR showing a RUL mass
  - PMH: Mild knee arthritis, hypertension controlled without meds, exercises regularly
- CT shows a RUL mass with a probable endobronchial component
- PET shows
  - RUL mass
  - Non-enlarged FDG-avid right hilar (10R) and right paratracheal (4R) nodes
  - Moderate-sized pleural effusion

CT Shows…



Next Step?

A. EBUS biopsy of the mediastinal nodes
B. Mediastinoscopy
C. Head CT with contrast
D. Bronchoscopy to biopsy the upper lobe mass
E. Ultrasound-guided thoracentesis



Which of the following statements is the most accurate regarding "targeted therapy" for lung cancer?

A. Targeted agents are most effective for early disease
B. Erlotinib, an *EGFR* inhibitor, is more effective in combination with standard chemotherapy
C. *KRAS* mutations predict response to targeted TKIs
D. Non-smokers are most likely to respond to targeted *EGFR TKIs*
E. Crizotinib, an *ALK* inhibitor, is only effective for patients with specific activating point mutations in the *ALK* gene