Approach to Lung Cancer Screening and Staging in 2011

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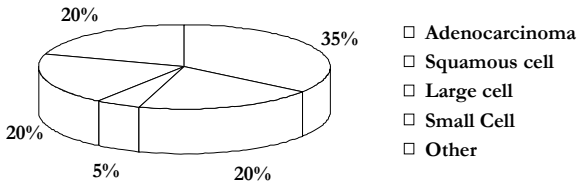
Lung Cancer Statistics

- **Greatest cause of cancer deaths worldwide**
- **Greatest cause of cancer deaths in U.S.**
  - ✓**200,00 new cases in 2010**
  - ✓**165,000 deaths 12% of cancer cases, 29% of cancer deaths**
  - ✓**~13% in never smokers (>22,000 cases)**
- **More than 85% of all patients with lung cancer have a smoking history yet only 20% of smokers acquire lung cancer**

Learning Objectives

- **Review the epidemiology of lung cancer**
- **Discuss controversies in lung cancer screening**
- **New lung cancer staging guidelines**
- **Discuss options for staging**



Challenges in Lung Cancer Diagnosis and Treatment

- How do we screen for lung cancer?
- How do we identify "early disease"?
- Are we staging patients correctly?
- Identifying new therapeutic targets
- Further characterizing the molecular heterogeneity in lung cancer
- Clinically relevant biomarkers (sputum, blood, CT, tumor?)
- Is lung cancer in non-smokers a different disease?

Keys to Successful Lung Cancer Screening

Case

- 60 year old male present to your clinic to enquire about being "screened" for lung cancer
- 60 pack year smoker
- HTN, DM
- Fam hx: CAD
- Exam: nonfocal
- How would you advise this patient?

Keys to Successful Lung Cancer Screening

- Sensitive

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- Lack of overdiagnosis
- Minimal morbidity

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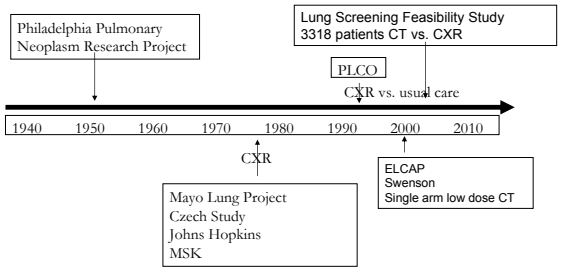
- Cost effective
- Decrease mortality
- Lack of overdiagnosis

Historical Perspective on Lung Cancer Screening

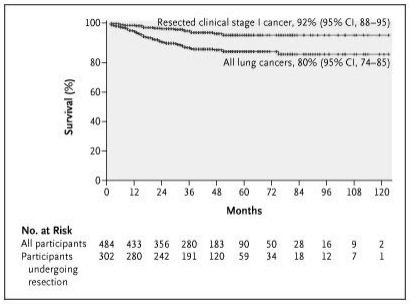


International Early Lung Cancer Action Project

- **Based on ELCAP**
- **Prospective, international, multi-institutional study**
- **31,567 patients at high risk for lung cancer screened**
  - ✓**Azumi Health Care Program, Japan**
    - **3,087 (10%) current or former smokers**
    - **3,299 (10%) non-smokers**
- **Criteria for enrollment varied by institution**
- **27,456 annual screens (second or later?)**

I-ELCAP Investigators. NEJM 2006; 355:1763-1771.

Sounds Good Right?



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- What was the course of those with positive screening but no biopsy?

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- No comparison group
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- Survival versus mortality
- No comment as to how many biopsies done outside protocol
- What was the course of those with positive screening but no biopsy?
- 10 year survival estimated to be 88% but median follow-up was 40 months

November 2010: Lung cancer trial results show mortality benefit with low-dose CT:

Twenty percent fewer lung cancer deaths seen among those who were screened with low-dose spiral CT than with chest X-ray

- Important caveats (positives)
  - ✓ Prospective randomized nature of study
  - ✓ 6.9% reduction in all cause mortality
  - ✓ No universal protocol for follow-up of positive CT scan so likely to be reproducible in community

Important caveats (negatives)

- ✓ Actual study has NOT been published
- ✓ Reduction in deaths in a target group (ages 55-74) so extrapolation not possible
- ✓ Small number of lung cancer deaths (LDCT 354 vs. 442 CXR)
- ✓ Cost analysis

NLST

NLST
National Lung Screening Trial
National Cancer Institute

- Randomized CXR versus low-dose helical CT scan
- Initially screening followed by annual for two years
- 53,564 participants
- Ages 55-74
- Heavy smoker or former smoker
- Asymptomatic
- No prior cancer
- Powered to detect 20% reduction in mortality

NELSON

NELSON
Nederlands-Leuvens Longkanker Screenings Onderzoek

- Launched in 2003
- 16,000 patients
- Screening by MDCT versus no screening
- Years 1, 2 and 4
- Volumetric nodule assessment
- Powered to detect mortality reduction of 20%

Should we be screening?

- Currently not recommended by any organization
- Awaiting final publications
- Further long term analysis of risk/benefit
- Cost analysis
- Individualized discussion with patient

Treatment "First Principles"

- Diagnosis
  - ✓Adequate biopsy sample (bronchoscopy versus CT guided biopsy)
- Stage
  - ✓Stage determines treatment
- Treatment
  - ✓In NSCLC, surgery is the cornerstone of treatment
  - ✓In SCLC, chemotherapy is the cornerstone

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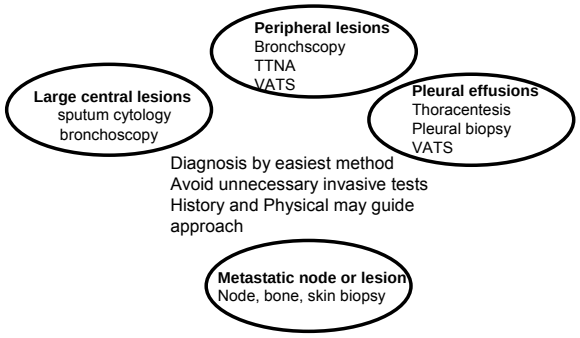
Lung Cancer Diagnostic Strategies: Principles



Traditional Staging

Traditional Staging

Primary tumor → CXR, CT Scan, Bronchoscopy, VATS, Thoracentesis, CT guided Bx → OR Path

Mediastinal nodes → CT Scan, PET, Mediastinoscopy

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Primary tumor → CXR, CT Scan, Bronchoscopy, VATS, Thoracentesis, CT guided Bx → OR Path

Mediastinal nodes → CT Scan, PET, Mediastinoscopy

Distant Mets → CT Scan (through adrenals), PET, Bone scan

5-year survival by TNM status in NSCLC

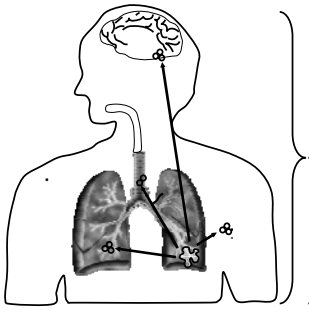
Stage	TNM classification	5-year survival (%)
IA	T1N0M0	61
IB	T2N0M0	38
IIA	T1N1M0	34
IIB	T2N1M0 or T3N0M0	24
IIIA	T1-3N2M0 orT3N1M0	13
IIIB	$T4N_{any}M0$ or $T_{any}N3M0$	5
IV	$T_{any}N_{any}M1$	1

Mountain 1997

New Staging System

- Based on 81,105 cases from around the world
- Between 1990-2000
- Cases: 41% surgery only, chemotherapy only in 23%, radiation only in 11%
- Staging in T,N M status was based on overall SURVIVAL. This is based on pathological stage if possible.
- Validated in terms 1990-1995 compared to 1995-2000, training set versus validation set.

SCLC stages

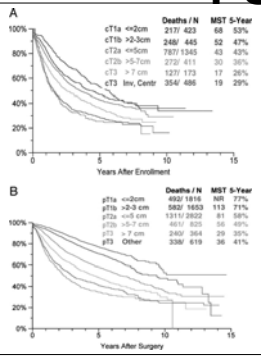


Extensive
Tumour not confined to hemithorax of origin
Distant metastasis

Limited
Tumour confined to hemithorax of origin and/or the mediastinum and supraclavicular nodes

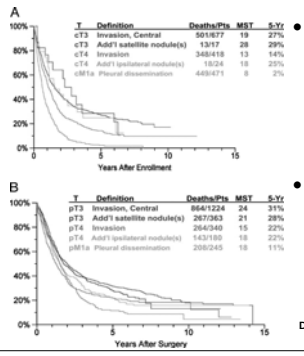
PDQ Guidelines 2000

New Staging According to T Status



- A primary lesion of 7cm or greater is essentially like a T3 tumor that invades mediastinal pleura, diaphragm
- All lesions between 0-3 cm are not the same

New Staging According to Additional Nodules, Invasion



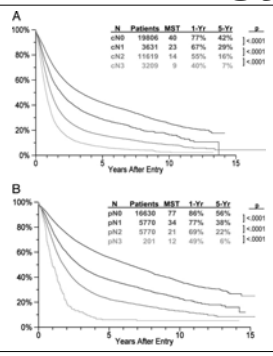
- **Separate nodules in the same lobe are like a T3 primary lesion. That could be IIB instead of IIIB**
- **Additional nodule in different ipsilateral lobe is like T4 so IIIA**

Detterbeck F C et al. Chest 2009;136:260-271

What about small cell?

- **12,000 cases in new cohort**
- **349 surgically resected**
- **Evaluated according to TNM and correlated with survival**

New Staging According to N Status



- **No changes have been made**

Current Controversies in Nodal Staging

- **What test should be performed following negative CT of mediastinum?**
- **Does a negative PET obviate the need for mediastinoscopy?**
- **What is the best modality for comprehensive sampling of mediastinal nodes?**
- **Should we factor in nodal characteristics when staging?**
- **How many nodes should be sampled at the time of mediastinoscopy?**
- **How should re-staging be done following induction chemotherapy?**

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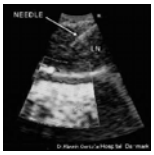
Real time EBUS

- Diagnostic yield 93% (470/502)
- PPV 100%, NPV 11%
- Duration 12.5min
- Accessible stations 2, 3, 4, 7, 10, 11
- Subaortic and paraesophageal nodes not accessible
- Surgical diagnosis recommended in negative biopsies



Herth et al. Thorax 2006; 61:795-798

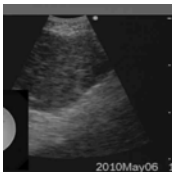
Transbronchial Needle Aspiration (Wang)

- Early 80s
- Hilar and mediastinal nodes
- Sensitivity 36%, Specificity of 98% with blind TBNA*
- Low risk
- Underutilized

* Holty, J-E C, et al., Thorax, 2005

Endobronchial Ultrasound

- Visualize tracheobronchial wall and surrounding structures
- Color doppler for vessel identification
- Can identify multilayer structure of tracheobronchial wall, determine extent of tracheobronchial wall involvement for surgical excision

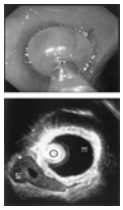


- Mediastinal lymph node biopsy, staging of cancer specially non-surgical N2 N3 staging
- Decrease surgical interventions

Falcone et al. Respiration. 2003; 70:179-94

EBUS

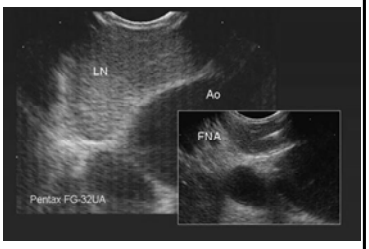
- N=242
- Successful lymphoid access 86% (n=207)
- Diagnostic yield 71% (n=170)
- Surgical procedure in Non-diagnostic: n=70
- Non-diagnostic (lymphocyte neg) 14% (n=35)
  - ✓ Malignancy (27/35)
- Non-diagnostic lymphocyte positive:
  - ✓ No additional diagnosis
- Average duration 5.7m



Herth et al. Chest 2003; 123:604-607

EUS

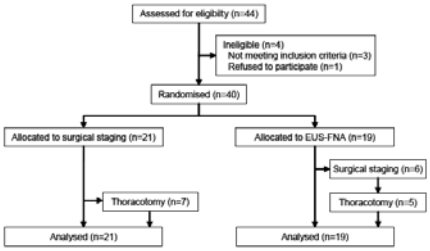
- Limited to posterior and middle mediastinal nodes
- Nodes as little as 3mm
- May also detect positive nodes when CT negative
- May detect celiac node involvement
- Can complement medistinoscopy (Annema, JAMA, 2005)



EBUS

Study	Patients	Sensitivity	Specificity	Mediastinoscopy
Krasnik et al, 2003	11 with 15 lymph nodes			No
Yasufuku et al, 2004	70	95.7%	100%	Yes
Rintoul et al, 2005	18	85%	100%	Yes
Herth FJ et al, 2006	502	94%	100%	Yes

EUS vs. Mediastinoscopy

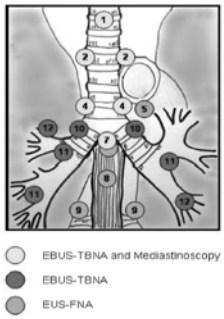


For patients
allocated to EUS-FNA, surgical staging was needed in 32% (P<0.001).
The sensitivity to detect malignant lymph node invasion was 93% (95% CI 66-99) for EUS-FNA and 73% (95% CI 39-93) for surgical staging (P=0.29).

Tourney, et al 2007

Combining EBUS/TBNA and EUS

- Should complement each other to increase yield
- Studies ongoing



Yasufuku, K. et al., 2006

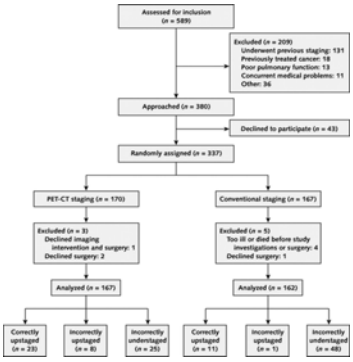
PET Scan: Distant Mets

- ~10% of patients have enlarged adrenal at time of presentation: 2/3 benign adrenal adenomas
  - ✓ 35-45% will have detectable extra-thoracic spread at the time of diagnosis
  - ✓ Most common brain, bones, liver and adrenal glands in that order
  - ✓ PET scan may be useful in detecting adrenal, bone, liver mets

PET Scan

- Based on differences in metabolism of tissues
- 18 F-fluoro-2-deoxy-D-glucose (FDG)
- Standardization Uptake Value (SUV):index of glucose utilization of a lesion
- Abnormal: SUV>2.5 or uptake greater than background activity of the mediastinum

PET is a double edged sword



Maziak D E et al. Ann Intern Med 2009;151:221-228

PET Scan: Pitfalls

- **False positives: metabolically active infectious or inflammatory lesions: Rheumatoid nodules, TB, fungal granulomas, lipoid pneumonia, talc, infarction**
- **Verification bias:Lauer, M.S.. Et al. *Archives of Internal Medicine* 2007**
- **False negatives**
  - ✓ **Tumors with low activity: BAC, carcinoid, well–differentiated adenocarcinomas, renal cell and testicular carcinomas, necrotic tumors**
  - ✓ **Lesions <1 cm (occasionally can detect 8-10mm)**
  - ✓ **Elevated serum glucose**
  - ✓ **Not accurate for brain lesions**
  - ✓ **Careful with small lesions**

  Limited anatomic resolution

Mediastinal Node Disease

Study	Patients	Techniques	Sens	Spec
Antoch	**27**	**PET/CT**	**89**	**94**
		PET	**89**	**89**
		CT	**70**	**59**
Shim	**50**	**PET/CT**	**85**	**84**
		CT	**70**	**69**
Halpern	**36**	**PET/CT**	**60**	**85**
		PET	**50**	**77**

Antoch, et al. *Radiology*, 2003
Shim, et al. *Radiology*, 2005
Ha;pern, et al. *Chest*, 2005

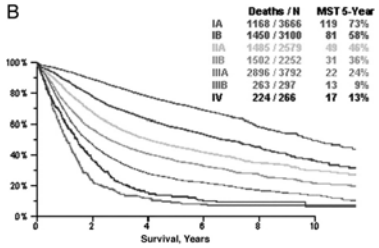
PET Scan: Current Recommendations

- **Chest 2007**
  - ✓**Patients who are candidates for surgery should have a whole body FDG-PET to evaluate the mediastinum**
  - ✓**Abnormal FDG-Pet scan findings should be followed by mediastinal sampling**
  - ✓**Early studies suggest that PET scan may identify 10-20% of non-CNS metastatic disease not detected by standard methods**

PET caveats

- **Keep in mind causes of false negatives and false positives**
- **A suspicious nodule with an SUV of 0-2.5 still has a 24% chance of being malignant**
- **Negative PET in the mediastinum does not obviate the need for mediastinal sampling**
- **PET increasingly being used to assess response/survival**

Overall Survival in New Staging System



Future for Staging

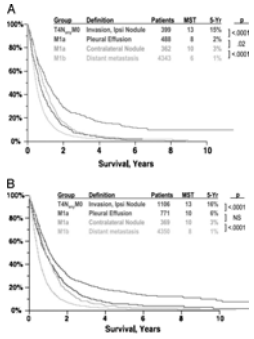
- **Increased use of EBUS/TBNA and EUS as first line in suspected mediastinal involvement**
- **Including molecular markers in initial pathological evaluation**
- **Mediastinal Ultrasonography**
- **Transcervical Extended Mediastinal Lymphadenectomy**

Stage groups according to TNM descriptor and subgroups

T/M	Subgroup	N0	N1	N2	N3
T1	T1a	Ia	IIa	IIIa	IIIb
	T1b	Ia	IIa	IIIa	IIIb
T2	T2a	Ib	IIa	IIIa	IIIb
	T2b	IIa	IIb	IIIa	IIIb
T3	T3 $_{>7}$	IIb	IIIa	IIIa	IIIb
	T3 $_{Inv}$	IIb	IIIa	IIIa	IIIb
	T3 $_{Satell}$	IIb	IIIa	IIIa	IIIb
T4	T4 $_{Inv}$	IIIa	IIIa	IIIb	IIIb
	T4 $_{Ipsi\ Nod}$	IIIa	IIIa	IIIb	IIIb
M1	M1a $_{Contra\ Nod}$	IV	IV	IV	IV
	M1a $_{Pl\ Disem}$	IV	IV	IV	IV
	M1b	IV	IV	IV	IV

Detterbeck F C et al. Chest 2009;136:260-271

New Staging According to M Status



- **Two distinct M groups M1a and 1b**
- **Remember ipsilateral nodule is no longer considered M1**
- **M1a is pleural involvement or contralateral nodule**

Lung Cancer 2011
Towards an individualized approach

Gregory A. Otterson, MD

The Ohio State University

Comprehensive Cancer Center

Chemotherapy plateau

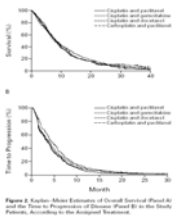
The New England Journal of Medicine

COMPARISON OF FOUR CHEMOTHERAPY REGIMENS FOR ADVANCED NON–SMALL-CELL LUNG CANCER

JOAN H. SCHILLER, M.D., DAVID HARRINGTON, PH.D., CHANDRA P. BELANI, M.D., COREY LANGER, M.D., ALAN SANDLER, M.D., JAMES KROOK, M.D., JUNMING ZHU, PH.D., AND DAVID H. JOHNSON, M.D., FOR THE EASTERN COOPERATIVE ONCOLOGY GROUP

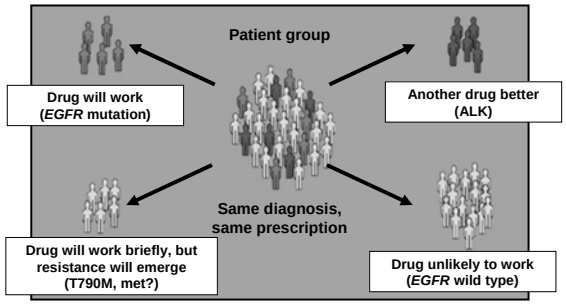
Stratification Variables
Performance status: 0 or 1 vs. 2
Weight loss in previous 6 mo: <5% vs. ≥5%
Disease stage: IIIB vs. IV or recurrent disease
Presence or absence of brain metastases

Regimens
Cisplatin plus paclitaxel
paclitaxel, 135 mg/m² over 24-hr period on day 1
cisplatin, 75 mg/m² on day 2
3-wk cycle
Cisplatin plus gemcitabine
gemcitabine, 1000 mg/m² on days 1, 8, and 15
cisplatin, 100 mg/m² on day 1
4-wk cycle
Cisplatin plus docetaxel
docetaxel, 75 mg/m² on day 1
cisplatin, 75 mg/m² on day 1
3-wk cycle
Carboplatin plus paclitaxel
paclitaxel, 225 mg/m² over 3-hr period on day 1
carboplatin, AUC 6.0 mg/ml/min on day 1
3-wk cycle



NEJM 2002;346:92-8

The Promise of Genotype-Directed Therapy



Phase III Trial of Bevacizumab in NSCLC—ECOG 4599

Eligibility:
- Nonsquamous NSCLC
- No Hx of hemoptysis
- No CNS metastases

PC
Paclitaxel 200 mg/m²
Carboplatin AUC = 6
(q3w) × 6 cycles

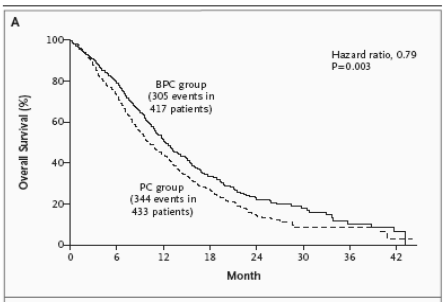
No crossover to bevacizumab permitted

PCB
PC × 6 cycles
+
Bevacizumab
(15 mg/kg q3w) to PD

Stratification variables:
- RT vs no RT
- Stage IIIB or IV vs recurrent
- Wt loss <5% vs ≥5%
- Measurable vs nonmeasurable

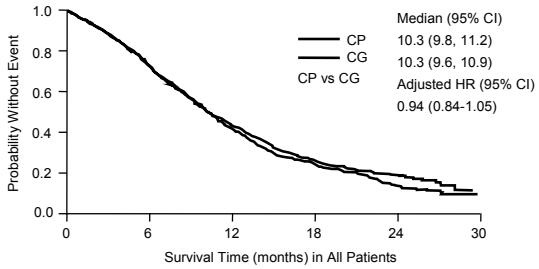
Bevacizumab: recombinant humanized MAb to VEGF-A
Hx = history; RT = radiation therapy; AUC = area under the curve.
Sandler et al. ASCO, 2005. Abstract LBA4 and oral presentation.

E4599: Bevacizumab in NSCLC—Overall Survival



PC = paclitaxel/carboplatin; PCB = PC + bevacizumab; HR = hazard ratio.
NEJM December 14, 2006; 355;2542-50

Overall Survival



Patients at Risk					
CP 862	598	341	146	45	0
CG 863	590	327	139	34	0

Scagliotti G et al. *JCO July 2008, 26:3543-3551*

Histology Matters - Study Design

- Stage IIIB/IV NSCLC
- PS 0 - 1
- No prior chemo
- Randomization: gender, PS, stage, histo vs cyto dx, brain mets

R

Pemetrexed 500 mg/m^2 + Cisplatin 75 mg/m^2 day 1

Primary objective: overall survival

15% non-inferiority margin (HR 1.17)

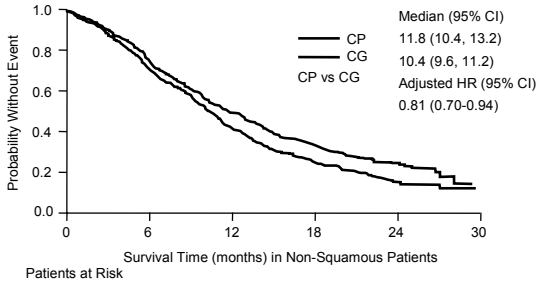
N+ 1700 patients (final analysis when 1190 deaths have occurred; power 80%)

Gemcitabine 1250 mg/m^2 + Cisplatin 75 mg/m^2 day 1; Gemcitabine 1250 mg/m^2 day 8

- B12, folate, and dexamethasone given in both arms
- Preplanned secondary analysis

Scagliotti G et al. *JCO July 2008, 26:3543-3551*

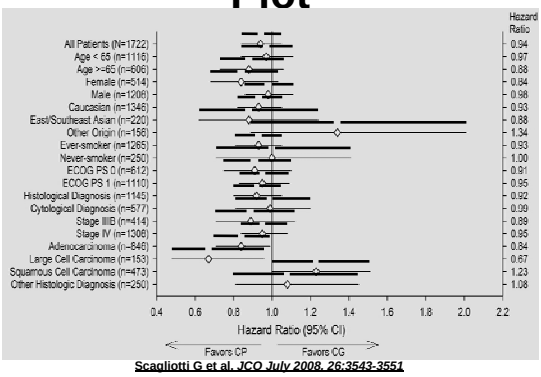
Overall Survival in Patients With Adenocarcinoma or Large Cell Ca



Patients at Risk					
CP 512	369	235	109	36	0
CG 488	334	188	80	21	0

Scagliotti G et al. *JCO July 2008, 26:3543-3551*

Subgroup Analyses Forest Plot

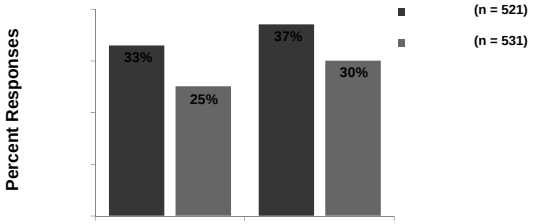


Scagliotti G et al. *JCO July 2008. 26:3543-3551*

Primary Endpoint Results Objective Responses – All Histologies

Response Ratio = 1.31
(1.082 – 1.593)
P = 0.005

Response Ratio = 1.26
(1.060 – 1.496)
P = 0.008



Socinski, et al, ASCO 2010

Phase III *nab*-P/C vs P/C Study Design

Chemo-naive
PS 0-1
Stage IIIb/IV
NSCLC
N = 1,050

→ **1:1**

→ ***nab*-Paclitaxel 100 mg/m² d1, 8 15**
Carboplatin AUC 6 d1
No Premedication
n = 525

→ **Paclitaxel 200 mg/m² d1**
Carboplatin AUC 6 d1
With Premedication of Dexamethasone + Antihistamines
n = 525

Stratification factors:

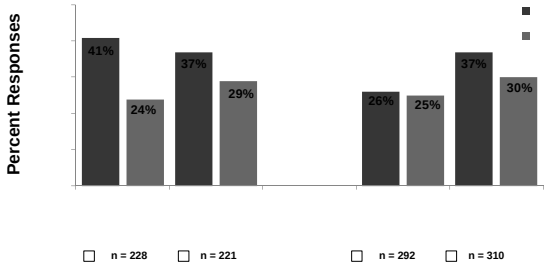
- Stage (IIIb vs IV)
- Age (<70 vs >70)
- Sex
- Histology (squamous vs nonsquamous)
- Geographic region

Socinski, et al, ASCO 2010

Objective Responses by Histology*

Squamous — *P* < 0.001 — *P* = 0.060

Nonsquamous — *P* = 0.808 — *P* = 0.069



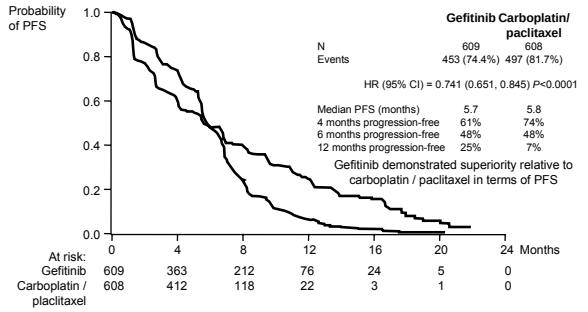
Socinski, et al, ASCO 2010

* Not a pre-specified endpoint

Histology Matters

- **Adenocarcinoma**
  - ✓ **Bevacizumab added to carboplatin and paclitaxel adds to response, PFR, OS**
  - ✓ **Pemetrexed is superior to gemcitabine when combined with cisplatin**
- **Squamous carcinomas**
  - ✓ **Bevacizumab has intolerable toxicity in this population (hemoptysis)**
  - ✓ **Pemetrexed is inferior to gemcitabine when combined with cisplatin**
  - ✓ **Nab-paclitaxel seems to offer a superior response rate (PFS and OS still pending) to solvent paclitaxel**

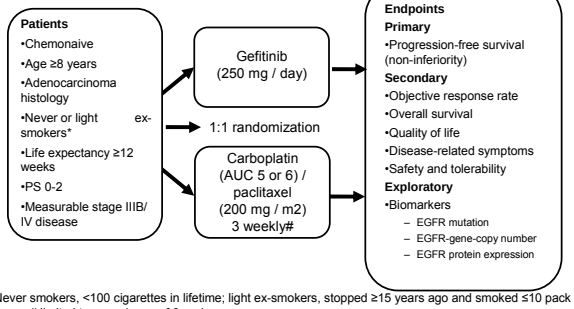
Progression-Free Survival in ITT Population



Primary Cox analysis with covariates
HR <1 implies a lower risk of progression on gefitnib

NEJM 361:947, Sept 3 2009

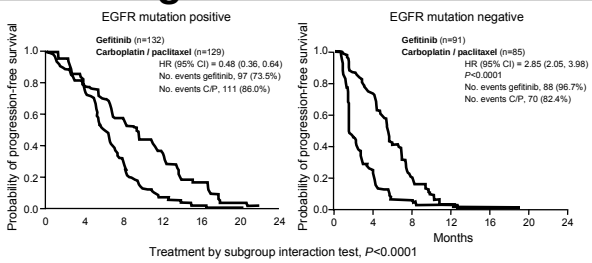
IPASS: Study Design



* Never smokers, <100 cigarettes in lifetime; light ex-smokers, stopped ≥15 years ago and smoked ≤10 pack years; # limited to a maximum of 6 cycles
Carboplatin / paclitaxel was offered to gefitinib patients upon progression
PS, performance status; EGFR, epidermal growth factor receptor

NEJM 361:947, Sept 3 2009

Progression-Free Survival in EGFR Mutation Positive and Negative Patients

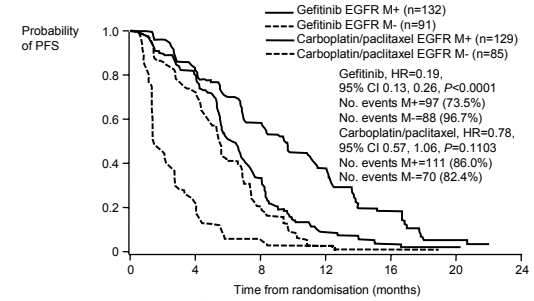


Treatment by subgroup interaction test, *P*<0.0001

ITT population
Cox analysis with covariates

NEJM 361:947, Sept 3 2009

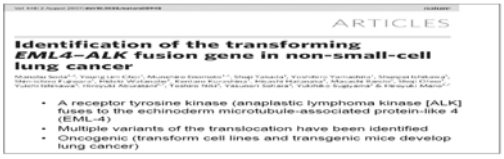
Comparison of PFS by Mutation Status Within Treatment Arms



Hazard ratio <1 implies a lower risk of progression in the M+ group than in the M-group
M+, mutation positive; M-, mutation negative

NEJM 361:947, Sept 3 2009

New Molecular Targets/Biomarkers?



ARTICLES

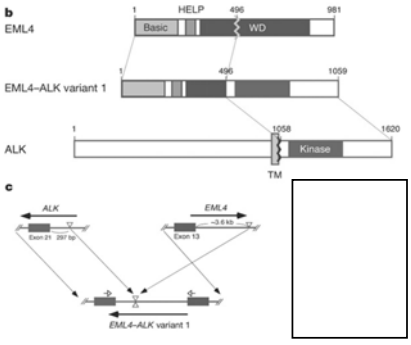
Identification of the transforming *EML4–ALK* fusion gene in non-small-cell lung cancer

- A receptor tyrosine kinase (anaplastic lymphoma kinase [ALK] fuses to the echinoderm microtubule-associated protein-like 4 (EML-4)
- Multiple variants of the translocation have been identified
- Oncogenic (transform cell lines and transgenic mice develop lung cancer)

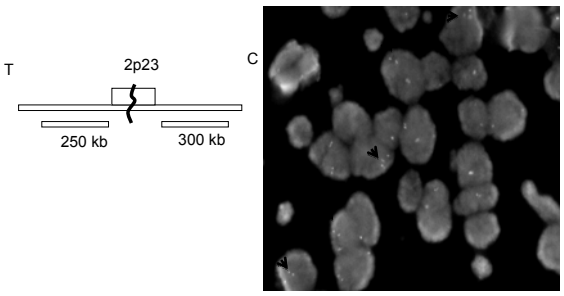
Nature 2007;448:561-6

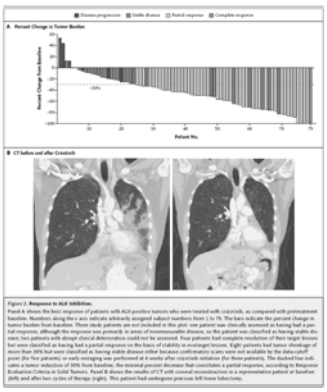
EGFR Mutation Positive Patients

- **TKI 1st line better than chemotherapy wrt OR% and PFS**
- **Confirmatory randomized trial from Europe is pending**
- **Until then, non-smokers or light smokers with adenocarcinoma should be tested for EGFR mutation status in order to make 1st line treatment decisions**
- **If mutation status is not known, chemotherapy is appropriate 1st line therapy**



2009 OSU Molecular Pathology (John Zhao)





NEJM 2010;363:1693-703

Rapid Translation to Clinic

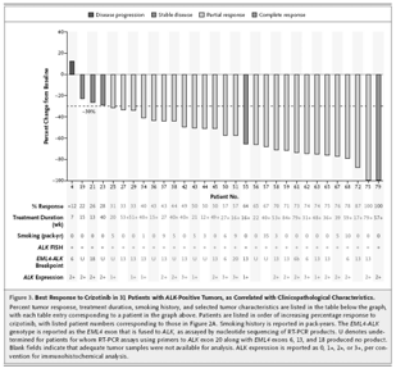
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 28, 2010 VOL. 363 NO. 18

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., Ryan B. 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., Daniel B. Costa, M.D., Ph.D., Mardelia Varella-Garcia, Ph.D., Woo-Ho Kim, M.D., Thomas J. Lynch, M.D., Panos Fidias, M.D., Hannah Stubbs, M.S., Jeffrey A. Engelman, M.D., Ph.D., Lecia V. Sequist, M.D., M.P.H., WeiWei Tan, Ph.D., Leena Gandhi, M.D., Ph.D., Mari Mino-Kenudson, M.D., Greg C. 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., Ravi 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.

NEJM 2010;363:1693-703



NEJM 2010;363:1693-703

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

EML4-ALK Mutations in Lung Cancer That Confer Resistance to ALK Inhibitors

Young Lim Choi, M.D., Ph.D., Manabu Soda, M.D., Ph.D., Yoshihiro Yamashita, M.D., Ph.D., Toshihide Ueno, Ph.D., Junpei Takashima, M.D., Takahiro Nakajima, M.D., Ph.D., Yasushi Yatabe, M.D., Ph.D., Kengo Takeuchi, M.D., Ph.D., Toru Hamada, M.D., Hidenori Haruta, M.D., Ph.D., Yuichi Ishikawa, M.D., Ph.D., Hideki Kimura, M.D., Ph.D., Tetsuya Mitsudomi, M.D., Ph.D., Yoshiro Tanio, M.D., Ph.D., and Hiroyuki Mano, M.D., Ph.D., for the ALK Lung Cancer Study Group

NEJM 2010;363:1734-9

Who are these patients?

Demographic		Patients (#)
Median Age in years		**59 years (Range 29 – 85 years old)**
Gender	**Women**	**8**
	Men	**11**
Tobacco Use	**Never smokers**	**7**
	Light smokers (less than 10 pack years)	**5**
	Smokers (> 10 pk yrs) or Unknown	**7**

OSU Experience with ALK (+) NSCLC

283 NSCLC patients

Screened for KRAS/EGFR mutation over 12 month period

202 patients

negative for EGFR or KRAS mutation

30 patients

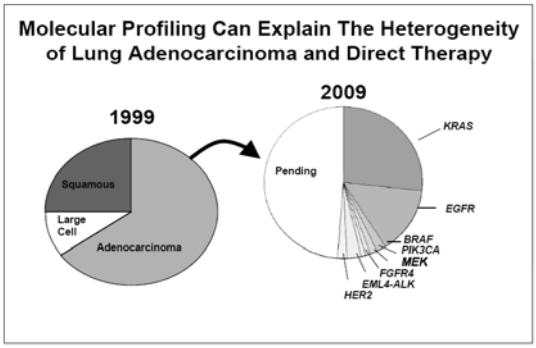
positive for ALK translocation

Who are these patients?

Demographic		Number of patients
Histology	**Adenocarcinoma**	**14**
	Adenosquamous	**3**
	Squamous cell	**1**
	Small cell	**1**
Treatment	**Platinum-based chemotherapy**	**18**
	Pemetrexed	**3**
	Other single-agent chemotherapy	**1**
	Erlotinib	**8**
	ALK inhibitor clinical trial	**2**
Average Survival	**31.1 months**	**Outliers: 5 patients with survival > 5 years with metastatic disease (63-84 months)**

Interesting Findings

- Percentage of screened patients positive for ALK translocation: 16%
- Histology:
  - ✓Squamous/adenosquamous
  - ✓Small cell lung cancer
- Survival Trends
  - ✓Several patients with prolonged survival (> 5 years)
  - ✓3 patients with prolonged response to single agent pemetrexed (13-36 cycles)
  - ✓1 patient with prolonged response to single agent paclitaxel (37 cycles)



Ongoing ALK related projects

- FISH versus IHC analysis of ALK positivity
- ALK tyrosine kinase inhibitor clinical trials:
  - ✓OSU 09090: Phase 2, Open-label Single Arm Study of the Efficacy and Safety of PF-02341066 in Patients with Advanced Non-small Cell Lung Cancer Harboring a Translocation or Inversion Involving the Anaplastic Lymphoma Kinase (ALK) Gene Locus
  - ✓OSU 09081: Phase 3, randomized, open-label study of the efficacy and safety of PF-02341066 versus standard of care chemotherapy (pemetrexed or docetaxel) in patients with advanced non-small cell cancer (NSCLC) harboring a translocation or inversion event involving the Anaplastic lymphoma kinase (ALK) gene locus

Conclusions

- One size fits all is inappropriate
- Biomarker directed therapy is here
- NSCLC ~170,000 pts per year
  - ✓ Non-Squamous (~70% or ~120,000)
  - ✓ Mutant EGFR (~10% or ~17,000)
  - ✓ Mutant KRAS (~25% of Adenos or ~ 34,000)
  - ✓ ALK Translocated (~4% or ~ 8,000)
- CML ~5,000 pts per year
- GIST ~3,500-5,000 pts per year