Approach to Lung Cancer Screening and Staging in 2011

Patrick Nana-Sinkam, MD

The Ohio State University Medical Center

Learning Objectives

- **Review the epidemiology of lung cancer**

- **Discuss controversies in lung cancer screening**

- **New lung cancer staging guidelines**

- **Discuss options for staging**

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**

20%   35%

20%

5%   20%

☐ Adenocarcinoma
☐ Squamous cell
☐ Large cell
☐ Small Cell
☐ Other
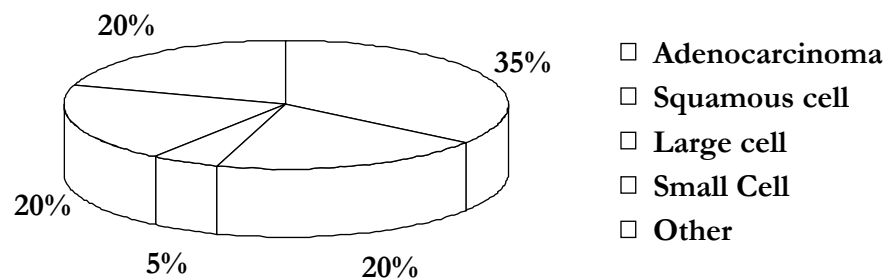
Challenges in Lung Cancer Diagnosis and Treatment

- 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?

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

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- **Sensitive**

Keys to Successful Lung Cancer Screening

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- **High incidence and prevalence**

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- **Diagnose early treatable disease**

Keys to Successful Lung Cancer Screening

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- Diagnose early treatable disease
- Decrease number of patients with late disease

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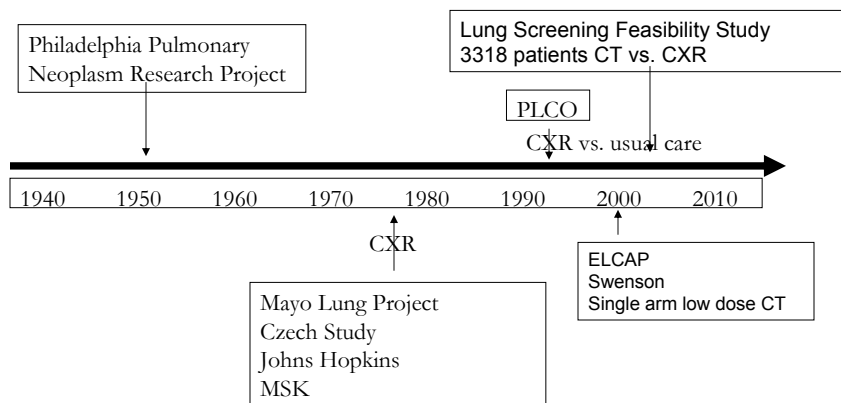- Cost effective
- Decrease mortality

Keys to Successful Lung Cancer Screening

- Sensitive
- High incidence and prevalence
- Diagnose early treatable disease
- Decrease number of patients with late disease
- Cost effective
- Decrease mortality
- Lack of overdiagnosis

Keys to Successful Lung Cancer Screening

- **Sensitive**
- **High incidence and prevalence**
- **Diagnose early treatable disease**
- **Decrease number of patients with late disease**
- **Cost effective**
- **Decrease mortality**
- **Lack of overdiagnosis**
- **Minimal morbidity**

Historical Perspective on Lung Cancer Screening

Philadelphia Pulmonary Neoplasm Research Project

Lung Screening Feasibility Study
3318 patients CT vs. CXR

PLCO
CXR vs. usual care

1940   1950   1960   1970   1980   1990   2000   2010

CXR

Mayo Lung Project
Czech Study
Johns Hopkins
MSK

ELCAP
Swenson
Single arm low dose CT

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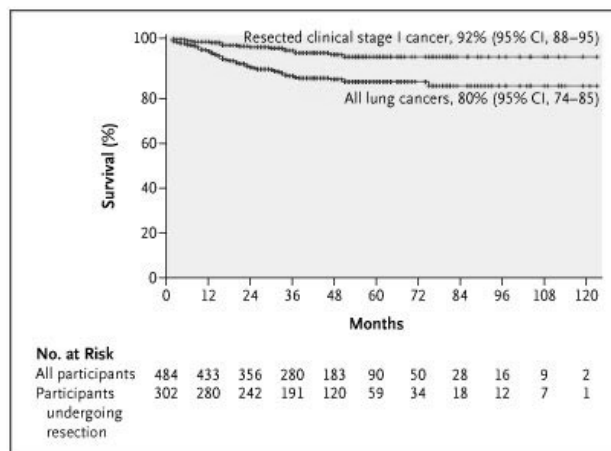
I-ELCAP Investigators. NEJM 2006; 355:1763-1771.

Sounds Good Right?

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

Sounds Good Right?

- No comparison group
- Lead time bias
- 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

NLST

- 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

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**

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**
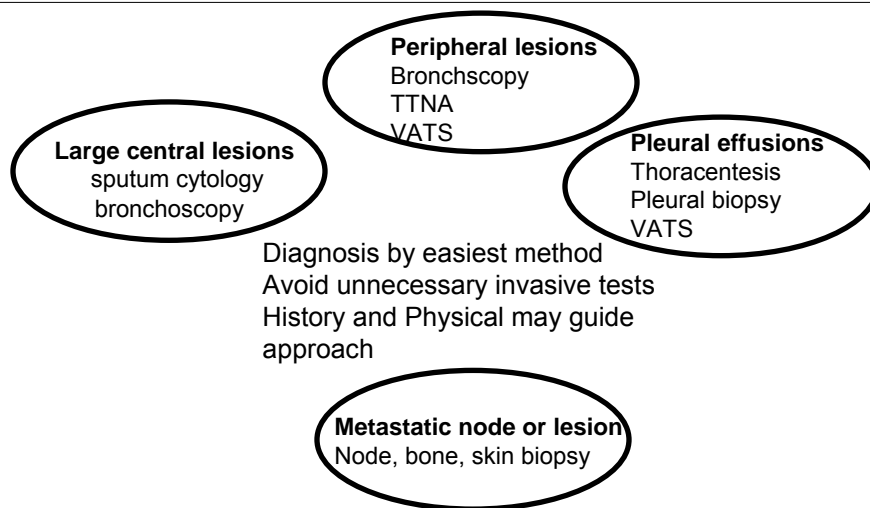- **Individualized discussion with patient**

Learning Objectives

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- **New lung cancer staging guidelines**
- **Discuss options for staging**
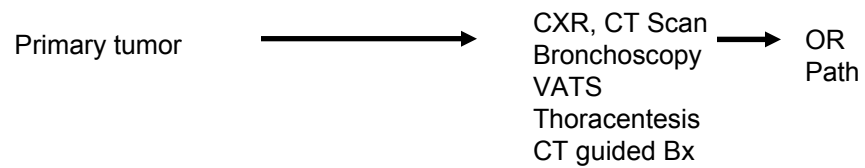
Treatment "First Principles"

- **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**

Lung Cancer Diagnostic Strategies: Principles

Peripheral lesions
Bronchscopy
TTNA
VATS

Large central lesions
sputum cytology
bronchoscopy

Pleural effusions
Thoracentesis
Pleural biopsy
VATS

Diagnosis by easiest method
Avoid unnecessary invasive tests
History and Physical may guide approach

Metastatic node or lesion
Node, bone, skin biopsy

Traditional Staging

Traditional Staging

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

Traditional Staging

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

Mediastinal nodes   →   CT Scan, PET
Mediastinoscopy

Distant Mets   →   CT Scan
(through
adrenals),
PET
Bone scan
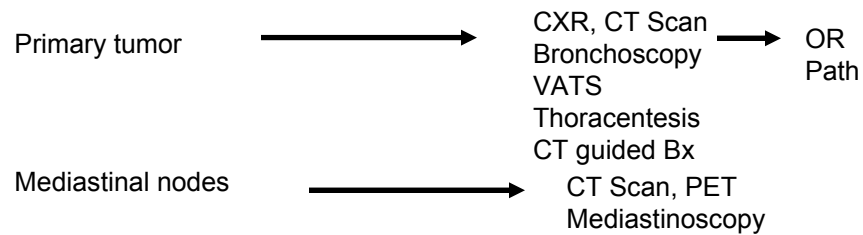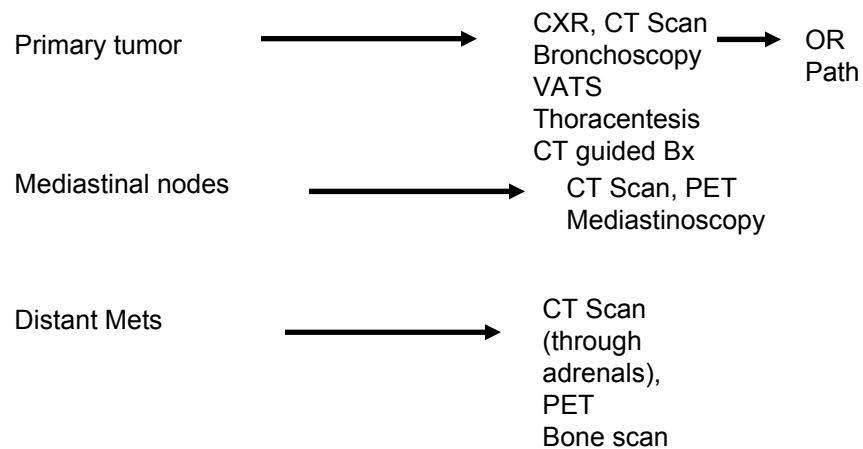
5-year survival by TNM status in NSCLC

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

SCLC stages
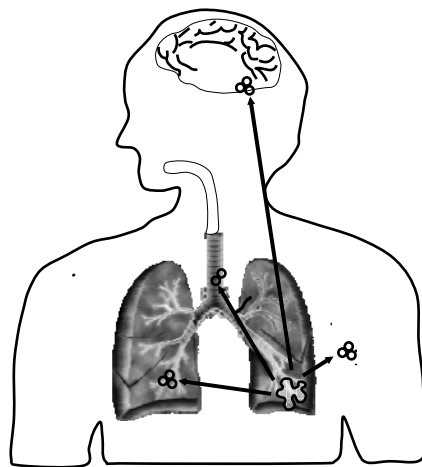
Extensive
Tumour not confined to hemithorax of origin
Distant metastasis

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

PDQ Guidelines 2000

New Staging 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.

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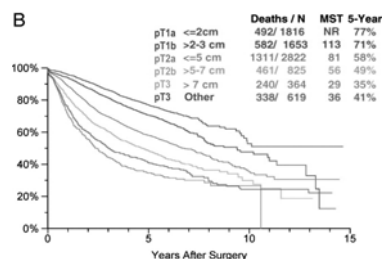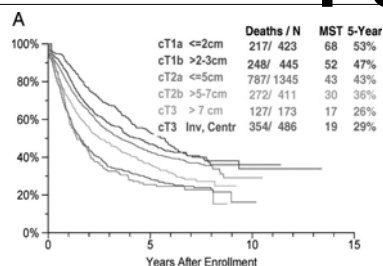
- A primary lesion of 7cm or greater is essentially like a T3 tumor that invades mediastinal pleura, diaphragm
- All lesions between 0-3 cm are not the same

New Staging According to Additional Nodules, Invasion

A

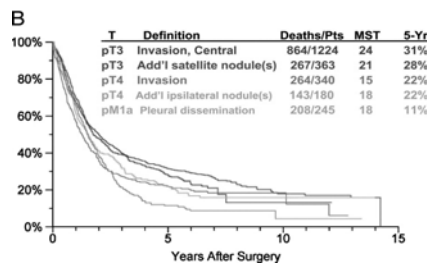| T	Definition	Deaths/Pts	MST	5-Yr
cT3	Invasion, Central	501/677	19	27%
cT3	Add'l satellite nodule(s)	13/17	28	29%
cT4	Invasion	348/418	13	14%
cT4	Add'l ipsilateral nodule(s)	18/24	18	25%
cM1a	Pleural dissemination	449/471	8	2%

B

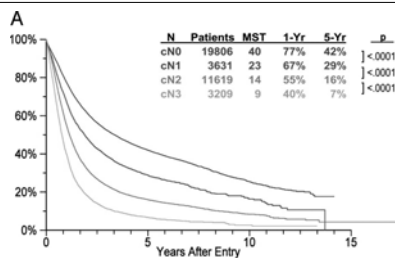| T	Definition	Deaths/Pts	MST	5-Yr
pT3	Invasion, Central	864/1224	24	31%
pT3	Add'l satellite nodule(s)	267/363	21	28%
pT4	Invasion	264/340	15	22%
pT4	Add'l ipsilateral nodule(s)	143/180	18	22%
pM1a	Pleural dissemination	208/245	18	11%

- 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

New Staging According to N Status

A

N	Patients	MST	1-Yr	5-Yr	p
cN0	19806	40	77%	42%	]<.0001
cN1	3631	23	67%	29%	]<.0001
cN2	11619	14	55%	16%	]<.0001
cN3	3209	9	40%	7%	

B

N	Patients	MST	1-Yr	5-Yr	p
pN0	16630	77	86%	56%	]<.0001
pN1	5770	34	77%	38%	]<.0001
pN2	5770	21	69%	22%	]<.0001
pN3	201	12	49%	6%	

- No changes have been made
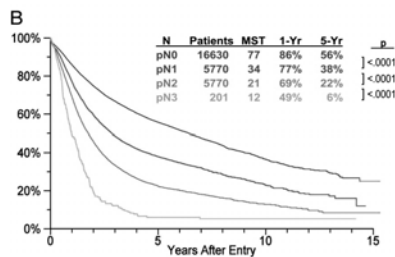
What about small cell?

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

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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Transbronchial Needle Aspiration (Wang)

- **Early 80s**
- **Hilar and mediastinal nodes**
- **Sensitivity 36%, Specificity of 98% with blind TBNA***
- **Low risk**
- **Underutilized**
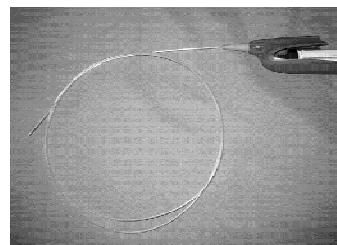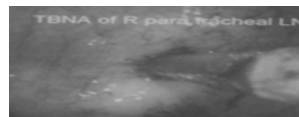
* Holty, J-E C, et al., Thorax, 2005

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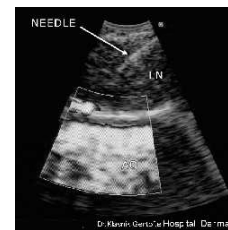
Herth et al. Thorax 2006; 61:795-798

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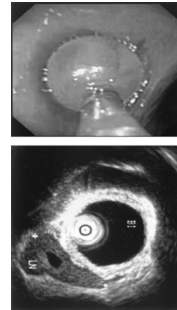
Herth et al. Chest 2003; 123:604-607

EBUS

Study	Patients	Sensitivity	Specificity	Mediastin oscopy
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

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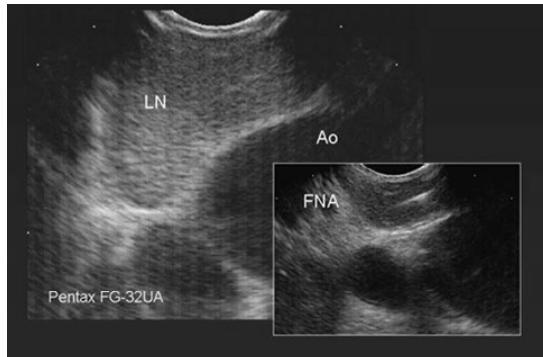
EUS vs. Mediastinoscopy
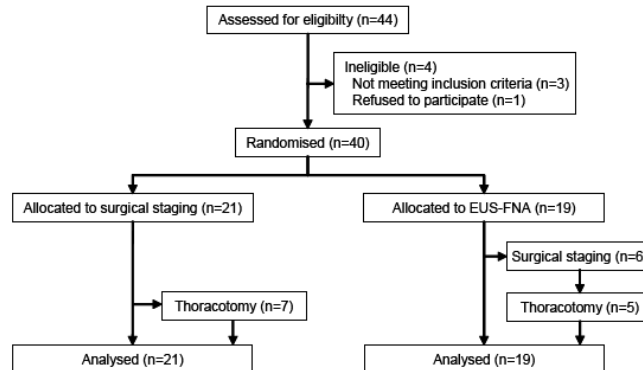
For patients
allocated to EUS-FNA, surgical staging was needed in 32% (P<0.001).
The sensitivity to detect malignant lymph node invasion was 93% (95% CI 66-99) for
EUS-FNA and 73% (95% CI 39-93) for surgical staging (P=0.29).

Tourney, et al 2007

Combining EBUS/TBNA and EUS

- **Should complement each other to increase yield**
- **Studies ongoing**
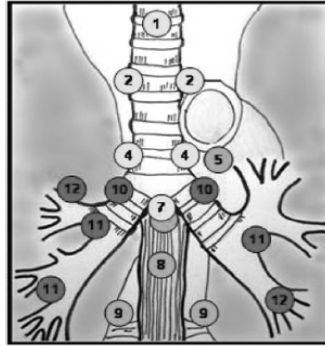
EBUS-TBNA and Mediastinoscopy
EBUS-TBNA
EUS-FNA

Yasufuku, K. et al., 2006

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 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

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PET is a double edged sword
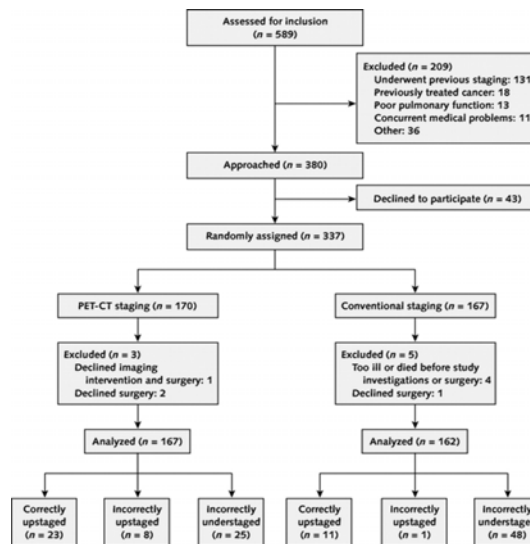
Maziak D E et al. Ann Intern Med 2009;151:221-228

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**

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**

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 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

	Deaths / N	MST	5-Year
IA	1168 / 3666	119	73%
IB	1450 / 3100	81	58%
IIA	1485 / 2579	49	46%
IIB	1502 / 2252	31	36%
IIIA	2896 / 3792	22	24%
IIIB	263 / 297	13	9%
IV	224 / 266	17	13%
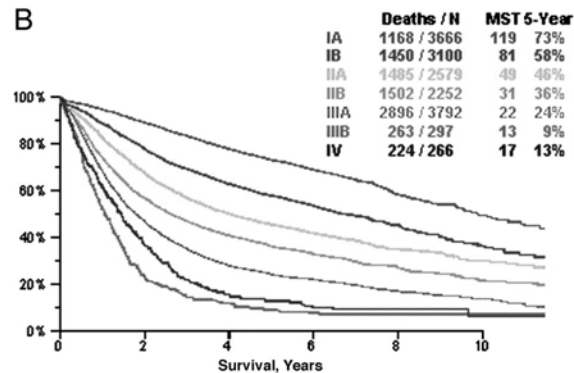
Stage groups according to TNM descriptor and subgroups

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

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**

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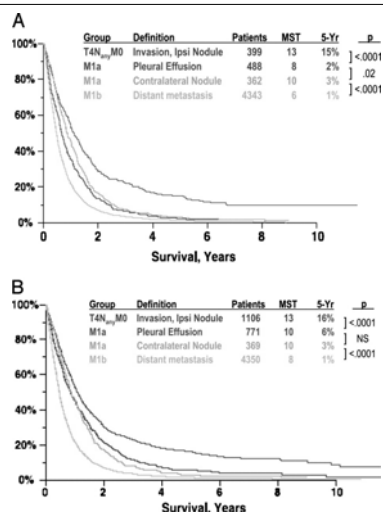
- **Two distinct M groups M1a and 1b**
- **Remember ipsilateral nodule is no longer considered M1**
- **M1a is pleural involvement or contralateral nodule**

Lung Cancer 2011
Towards an individualized approach

Gregory A. Otterson, MD

The Ohio State University

Comprehensive Cancer Center

The Promise of Genotype-Directed Therapy
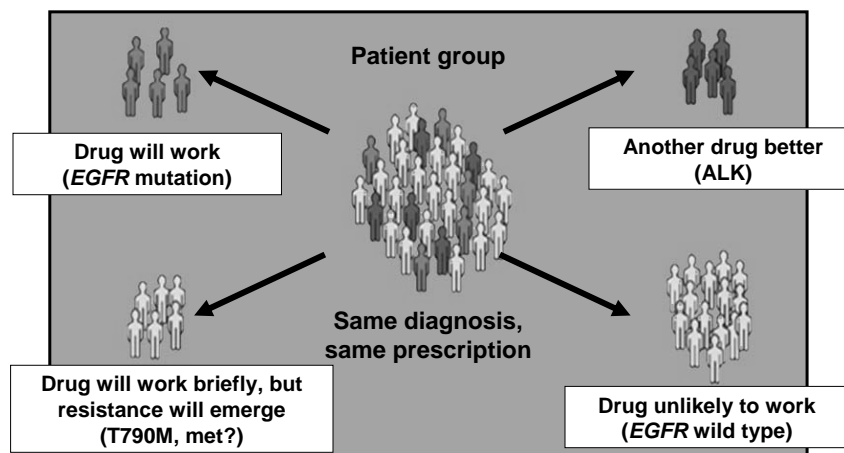
Chemotherapy plateau

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
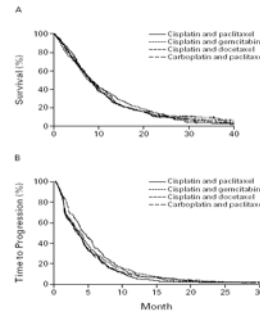
Figure 2. Kaplan–Meier Estimates of Overall Survival (Panel A) and the Time to Progression of Disease (Panel B) in the Study Patients, According to the Assigned Treatment.

NEJM 2002;346:92-8

Phase III Trial of Bevacizumab in NSCLC—ECOG 4599

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

No crossover to bevacizumab permitted

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

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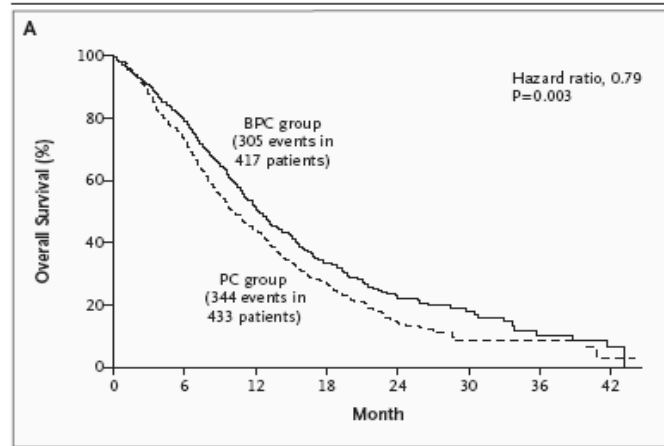
PC = paclitaxel/carboplatin; PCB = PC + bevacizumab; HR = hazard ratio.
NEJM December 14, 2006; 355;2542-50

Histology Matters - Study Design

- Stage IIIB/IV NSCLC
- PS 0 - 1
- No prior chemo
- <u>Randomization</u>: 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

Median (95% CI)

CP 10.3 (9.8, 11.2)

CG 10.3 (9.6, 10.9)

CP vs CG

Adjusted HR (95% CI)

0.94 (0.84-1.05)

Probability Without Event

Survival Time (months) in All Patients
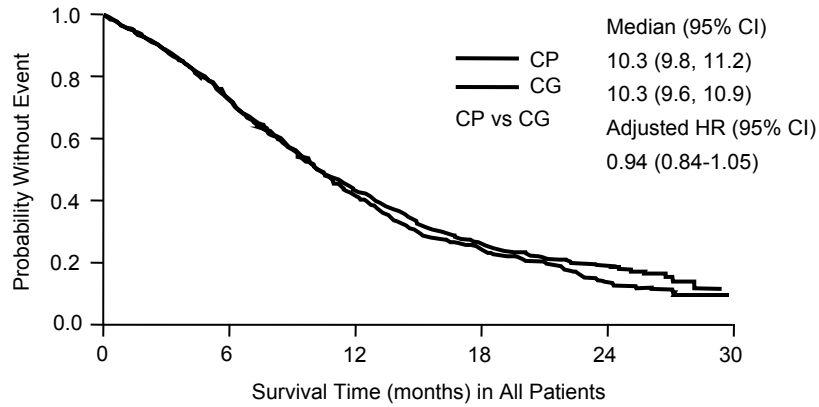
Patients at Risk

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

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

Overall Survival in Patients With Adenocarcinoma or Large Cell Ca

Median (95% CI)

CP 11.8 (10.4, 13.2)

CG 10.4 (9.6, 11.2)

CP vs CG

Adjusted HR (95% CI)

0.81 (0.70-0.94)

Probability Without Event

Survival Time (months) in Non-Squamous Patients
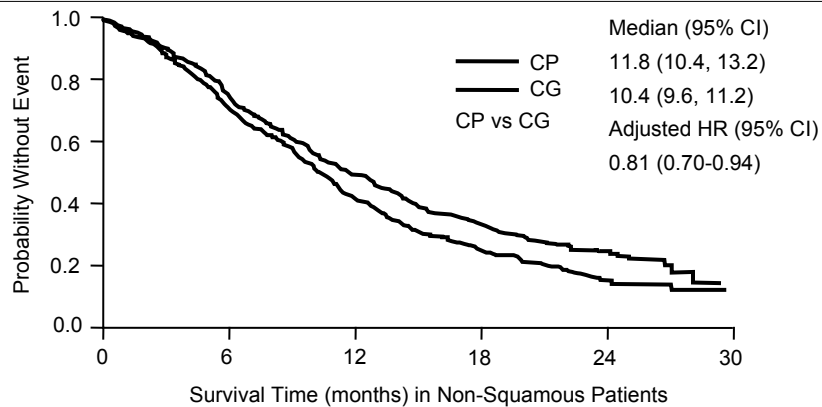
Patients at Risk

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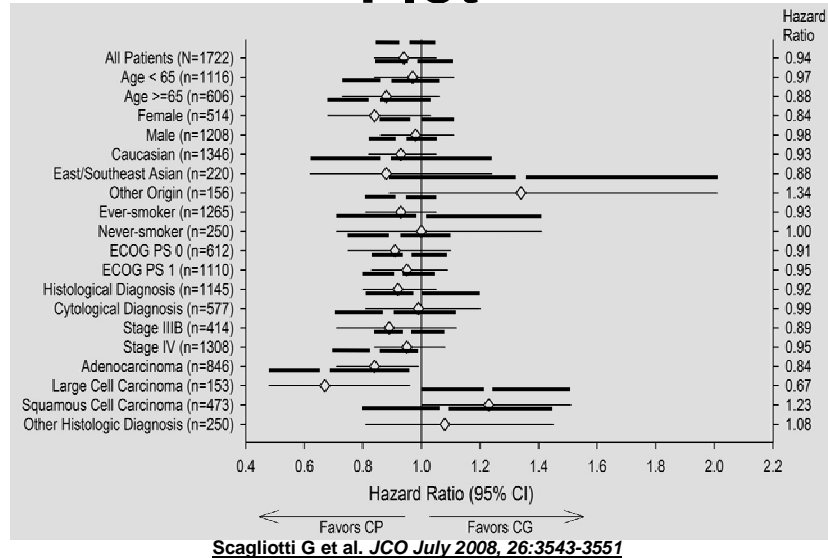
Phase III *nab*-P/C vs P/C Study Design

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

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

(n = 521)

(n = 531)

Percent Responses

33%

25%

37%

30%
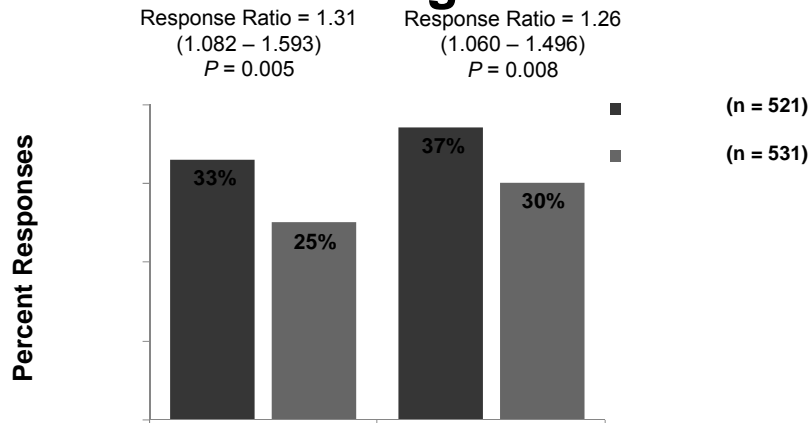
Socinski, et al, ASCO 2010

Objective Responses by Histology*

Squamous		Nonsquamous	
P < 0.001	*P* = 0.060	*P* = 0.808	*P* = 0.069

Percent Responses

41%

24%

37%

29%

26%

25%

37%

30%

n = 228   n = 221   n = 292   n = 310
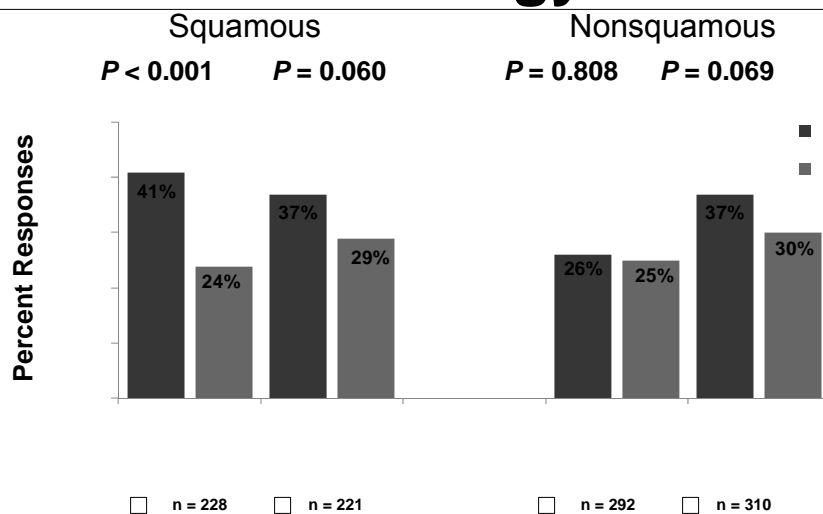
Socinski, et al, ASCO 2010

* 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**

IPASS: Study Design

Patients
- Chemonaive
- Age ≥8 years
- Adenocarcinoma histology
- Never or light ex-smokers*
- Life expectancy ≥12 weeks
- PS 0-2
- Measurable stage IIIB/ IV disease

Gefitinib
(250 mg / day)

1:1 randomization

Carboplatin
(AUC 5 or 6) /
paclitaxel
(200 mg / m2)
3 weekly#

Endpoints
Primary
- Progression-free survival (non-inferiority)

Secondary
- Objective response rate
- Overall survival
- Quality of life
- Disease-related symptoms
- Safety and tolerability

Exploratory
- Biomarkers
  - EGFR mutation
  - EGFR-gene-copy number
  - EGFR protein expression

* 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 ITT Population

Probability of PFS

	Gefitinib	Carboplatin/ paclitaxel
N	609	608
Events	453 (74.4%)	497 (81.7%)

HR (95% CI) = 0.741 (0.651, 0.845) *P*<0.0001

Median PFS (months)	5.7	5.8
4 months progression-free	61%	74%
6 months progression-free	48%	48%
12 months progression-free	25%	7%

Gefitinib demonstrated superiority relative to carboplatin / paclitaxel in terms of PFS

At risk:

	0	4	8	12	16	20	24	Months
Gefitinib	609	363	212	76	24	5	0	
Carboplatin / placlitaxel	608	412	118	22	3	1	0	

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

NEJM 361:947, Sept 3 2009

Progression-Free Survival in EGFR Mutation Positive and Negative Patients

EGFR mutation positive

Probability of progression-free survival

Gefitinib (n=132)
Carboplatin / paclitaxel (n=129)
HR (95% CI) = 0.48 (0.36, 0.64)
No. events gefitinib, 97 (73.5%)
No. events C/P, 111 (86.0%)

EGFR mutation negative

Probability of progression-free survival

Gefitinib (n=91)
Carboplatin / paclitaxel (n=85)
HR (95% CI) = 2.85 (2.05, 3.98)
P<0.0001
No. events gefitinib, 88 (96.7%)
No. events C/P, 70 (82.4%)

Months

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

Probability of PFS

Gefitinib EGFR M+ (n=132)
Gefitinib EGFR M- (n=91)
Carboplatin/paclitaxel EGFR M+ (n=129)
Carboplatin/paclitaxel EGFR M- (n=85)

Gefitinib, HR=0.19,
95% CI 0.13, 0.26, *P*<0.0001
No. events M+=97 (73.5%)
No. events M-=88 (96.7%)
Carboplatin/paclitaxel, HR=0.78,
95% CI 0.57, 1.06, *P*=0.1103
No. events M+=111 (86.0%)
No. events M-=70 (82.4%)

Time from randomisation (months)
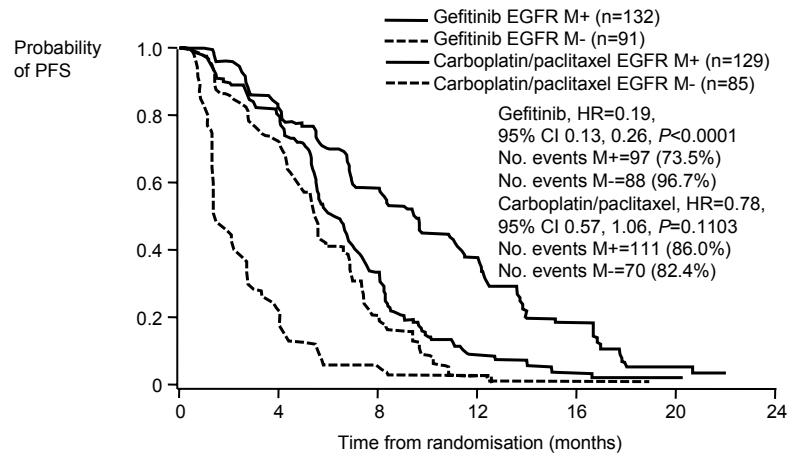
Hazard ratio <1 implies a lower risk of progression in the M+ group than in the M-group
M+, mutation positive; M-, mutation negative

NEJM 361:947, Sept 3 2009

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**

New Molecular Targets/Biomarkers?

ARTICLES

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

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

- 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
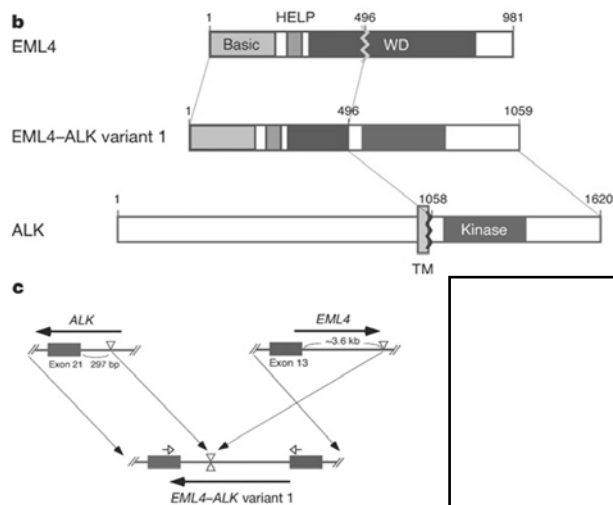
2009 OSU Molecular Pathology (John Zhao)

T   2p23   C

250 kb   300 kb
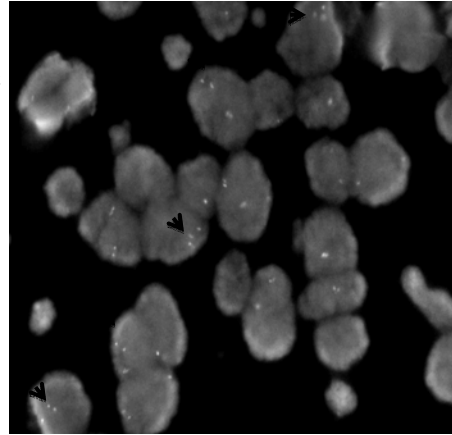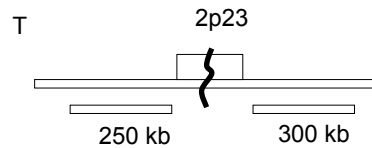
Rapid Translation to Clinic

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., 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., Daniel B. Costa, M.D., Ph.D.,
Marileila 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

Figure 2. Response to ALK Inhibition.

Panel A shows the best response of patients with ALK-positive tumors who were treated with crizotinib, as compared with pretreatment baseline. Numbers along the x axis indicate arbitrarily assigned subject numbers from 1 to 79. The bars indicate the percent change in tumor burden from baseline. Three study patients are not included in this plot: one patient was clinically assessed as having had a partial response, although the response was primarily in areas of nonmeasurable disease, so the patient was classified as having stable disease; two patients with abrupt clinical deterioration could not be assessed. Four patients had complete resolution of their target lesions but were classified as having had a partial response on the basis of stability in nontarget lesions. Eight patients had tumor shrinkage of more than 30% but were classified as having stable disease either because confirmatory scans were not available by the data-cutoff point (for five patients) or early restaging was performed at 6 weeks after crizotinib initiation (for three patients). The dashed line indicates a tumor reduction of 30% from baseline, the minimal percent decrease that constitutes a partial response, according to Response Evaluation Criteria in Solid Tumors. Panel B shows the results of CT with coronal reconstruction in a representative patient at baseline (left) and after two cycles of therapy (right). This patient had undergone previous left lower lobectomy.

Figure 3. Best Response to Crizotinib in 31 Patients with ALK-Positive Tumors, as Correlated with Clinicopathological Characteristics.

Percent tumor response, treatment duration, smoking history, and selected tumor characteristics are listed in the table below the graph, with each table entry corresponding to a patient in the graph above. Patients are listed in order of increasing percentage response to crizotinib, with listed patient numbers corresponding to those in Figure 2A. Smoking history is reported in pack-years. The EML4-ALK genotype is reported as the EML4 exon that is fused to ALK, as assayed by nucleotide sequencing of RT-PCR products. U denotes undetermined for patients for whom RT-PCR assays using primers to ALK exon 20 along with EML4 exons 6, 13, and 18 produced no product. Blank fields indicate that adequate tumor samples were not available for analysis. ALK expression is reported as 0, 1+, 2+, or 3+, per convention for immunohistochemical analysis.

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

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		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

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**

Molecular Profiling Can Explain The Heterogeneity of Lung Adenocarcinoma and Direct Therapy
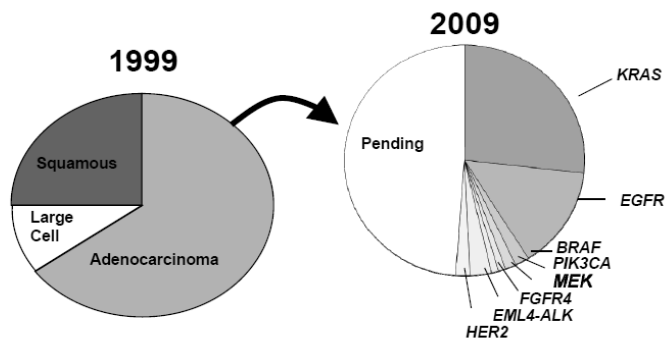
Conclusions

- **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**