

Peri-Operative Therapy for Stages I –III NSCLC: Should We Use Different Approaches For Smokers and Never Smokers?

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Perioperative Therapy in Stages I-III NSCLC
Introduction

- Outcomes in stages I-III NSCLC
- Differences: Smokers vs. Never Smokers
- Multimodality Therapy for Stages I-III 2010
- Dilemmas
 - Local: Surgery vs. Radiation
 - Systemic: Induction vs. Adjuvant Chemotherapy
 - Radiation: Induction Chemotherapy-RT vs. PORT
- How can we apply advances quickly to the perioperative setting?

Perioperative Therapy in Stages I-III NSCLC
Disclosure

I was born a medical oncologist but was raised by thoracic surgeons

**Revised Lung Cancer Staging System
Does "Good Prognosis" Lung Cancer Exist?**

			5 Year Survival	5 Year Survival
T Stage (all N0M0)	Primary Size	N	Clinical Stage	Pathological Stage
T1a	≤ 2 cm	1816	53%	77% ←
T1b	> 2-3 cm	1563	47%	71%
T2a	> 3-5 cm	2822	43%	58%
T2b	> 5-7 cm	825	36%	49%
T2c	>7	364	26%	35%

Rami-Porta R, et al. *J Thorac Oncol* 2007;2(7):593-602.

**Revised Lung Cancer Staging System
Does "Good Prognosis" Lung Cancer Exist?
Nodal Spread**

	N	5 Year Survival Pathological Stage
N1 – Single Node	798	48% ←
N1 – Multiple Nodes	173	35%
N2 – Single Node	740	34%
N2 – Multiple Nodes	281	20%

Rami-Porta R, et al. *J Thorac Oncol* 2007;2(7):593-602.

**Perioperative Therapy in Stages I-III NSCLC
Prognostic Factors in NSCLC**

There is no "good prognosis lung cancer"

23% of patients with tumors less than 2 cm (Stage T1aN0M0 in the revised staging) are dead at 5 years. **All** patients with breast cancer with this risk are recommended additional therapy with primary treatment.

Who is a Never Smoker?

- **Never Smoker**
 - Less than 100 lifetime cigarettes
- **Former Smoker**
 - Stopped smoking cigarettes more than one year ago
- **Current Smoker**
 - Smoking now or stopped smoking cigarettes less than one year ago

Terms to Avoid: Smoker, Non-Smoker

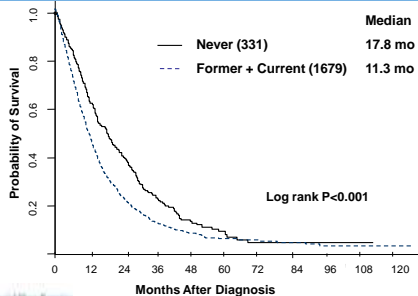
Estimated US Cancer Cases 2010

New Cases	Primary Site
22,000	Lung Cancer in Never Smokers (The 13th Most Common Cancer)
21,800	Brain
21,650	Ovarian
21,500	Stomach
21,370	Liver
19,900	Myeloma
16,500	Esophagus
10,390	Soft Tissue (Includes 3000 GIST)
4800	Chronic Myeloid Leukemia

Cancer Facts & Figures 2010, American Cancer Society

Pack Years of Smoking and Survival in Advanced Lung Cancer

Overall Survival Never Smokers vs. Former + Current Smokers

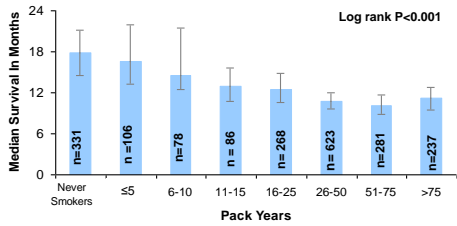


Memorial Sloan-Kettering
Cancer Center

Janjigian YY, et al. Cancer 2010;116(3):670-675.

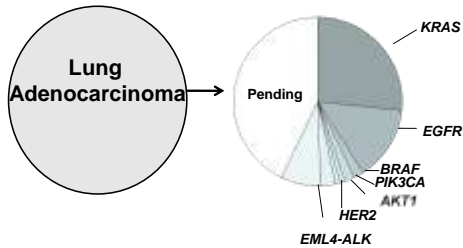
Pack Years of Smoking and Survival in Advanced Lung Cancer

Median Survival by Pack Years of Cigarette Smoking

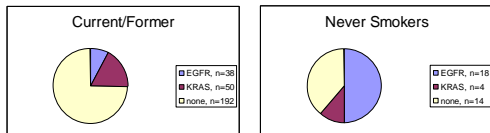


Janjigian YY, et al. Cancer 2010;116(3):670-675.

Molecular Profiling Explains The Heterogeneity of Lung Adenocarcinoma and Defines Targets for Therapy

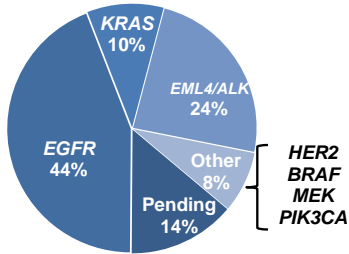


Adenocarcinomas from Never Smokers and Current/Former Smokers Have a Different Molecular Profile



Marks JL, et al. J Thorac Oncol 2008;3(2):111-116.

Molecular Alterations in Lung Adenocarcinoma in Never Smokers (22,000/yr)



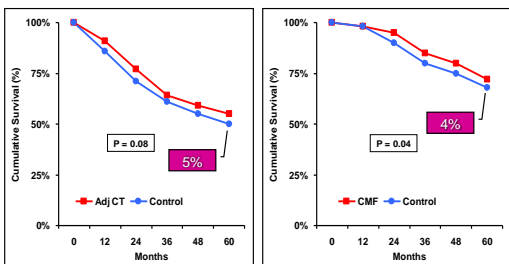
Pham D, et al. *J Clin Oncol* 2006;24(11):1700-1704.
 Shaw AT, et al. *J Clin Oncol* 2009;27(26):4247-4253.
 Riely GJ, et al. *Clin Cancer Res* 2008;14:5731-5734.

NSCLC Adjuvant Trials Post 1995 Meta-Analysis Survival With Adjuvant Chemotherapy

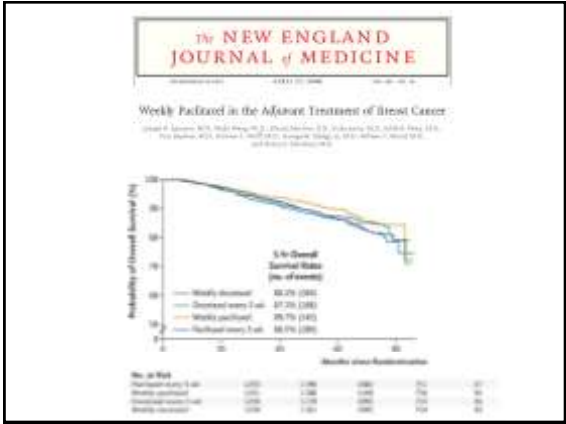
	# Pts	↑ 5 yr (%)	HR	95% CI	p
Meta95	1394	5	0.87	0.74-1.02	0.08
	1209	3	0.96	0.81-1.13	0.59
	1867	4	0.86	0.76-0.98	0.03
	482	15	0.70	0.52-0.92	0.01
	344	2	0.80	0.60-1.07	0.10
	840	8	0.79	0.66-0.95	0.01
Meta07	4584	4	0.89	0.82-0.96	0.005

Scagliotti GV, et al. *J Natl Cancer Inst* 2003; 95:1453-61; Arriagada R, et al. *N Engl J Med* 2004;350:351-60;
 Winton T, et al. *N Engl J Med* 2005;352:2589-2597; Strauss GM, et al. *J Clin Oncol* 2006;24(18s), Abstract 7007;
 Douillard J-Y, et al. *Lancet Oncol* 2006;7:719-727.

Comparing Breast & NSCLC Impact of Adjuvant Chemotherapy



Lung Cancer: Stewart LA, et al. *BMJ* 1995;311:899-909. Bonadonna G, et al. *N Engl J Med* 1995;332:901-906.



ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY

2007 Recommendations for Adjuvant Treatment of Stages I-IIIa NSCLC: Adjuvant Cisplatin-Based Chemotherapy

- Stage IA: Adjuvant chemotherapy is not recommended.
- Stage IB: Adjuvant cisplatin-based chemotherapy is not recommended for routine use.
- Stage IIA: Adjuvant cisplatin-based chemotherapy is recommended.
- Stage IIB: Adjuvant cisplatin-based chemotherapy is recommended.
- Stage IIIA: Adjuvant cisplatin-based chemotherapy is recommended.

◆ The use of adjuvant chemotherapy regimens that include alkylating agents is not recommended as these agents have been found to be detrimental to survival.

◆ Recommendations apply only to completely resected tumors.

ASCO American Society of Clinical Oncology 2007

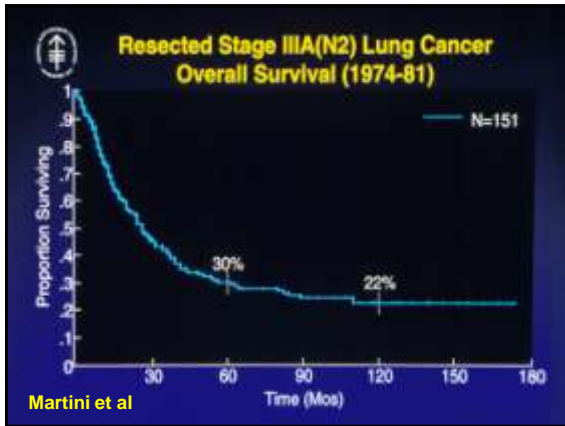
ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY

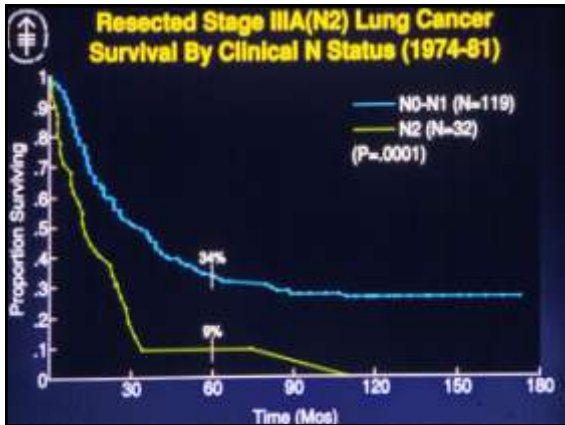
2007 Recommendations for Adjuvant Treatment of Stages I-IIIa NSCLC: Adjuvant Radiotherapy

- Stages IA/B and IIA/B: Adjuvant radiation is not recommended.
- Stage IIIA: Adjuvant radiation therapy is not recommended for routine use because of the lack of prospective, randomized clinical trial data evaluating its efficacy. A clinical trial is underway to determine the advisability of its routine use.

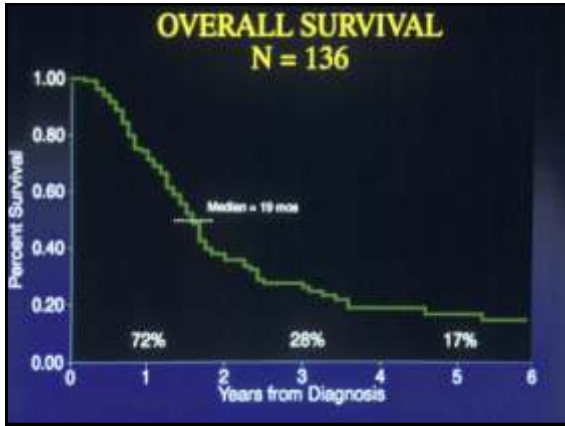
◆ Recommendations apply only to completely resected tumors.

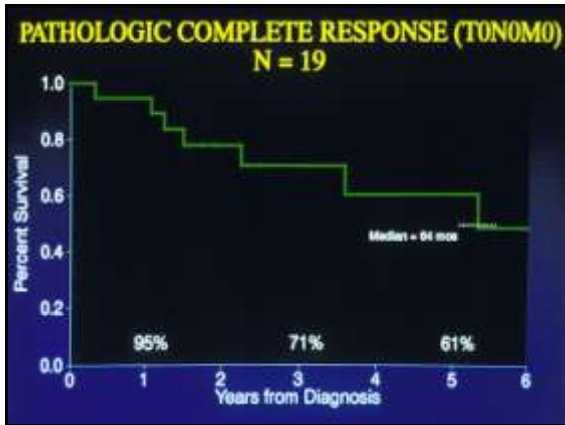
ASCO American Society of Clinical Oncology 2007











Preoperative Chemotherapy Response and Resectability (IIB/IIIA)

	<u>Median</u>	<u>Range</u>
Overall response rate	71%	32-88%
Complete response rate	6%	0-10%
Resection rate	58%	39-77%
Pathologic CR rate	5%	0-16%

8 trials, 424 patients

Preoperative Chemotherapy Survival (IIB/IIIA)

	<u>Median</u>	<u>Range</u>
Median	21 mo	12-64 mo
Proportion surviving		
1 year	71%	63-83%
2 years	42%	28-60%
3 years	28%	23-56%
4 years	22%	20-34%
5 years	26%	17-34%

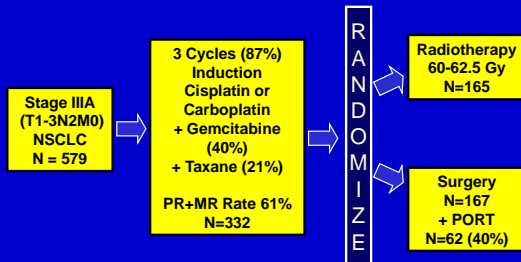
8 trials, 429 patients

Concurrent Chemoradiation in Stage III NSCLC US Cooperative Group Phase III Trials: 1994-2006

Study	Years	Chemoradiation Regimen	Patients	Median Survival	3 year survival
RTOG 9410	94-98	Cisplatin +Vinblastine/XRT	200	17 mo	25%
SWOG 0023	01-04	Cisplatin +Etop/XRT→Docetaxel	125	35 mo	50%
HOG LUN 01-24	02-06	Cisplatin +Etop/XRT→Docetaxel	73	22 mo	27%
HOG LUN 01-24	02-06	Cisplatin +Etop/XRT	74	24 mo	28%

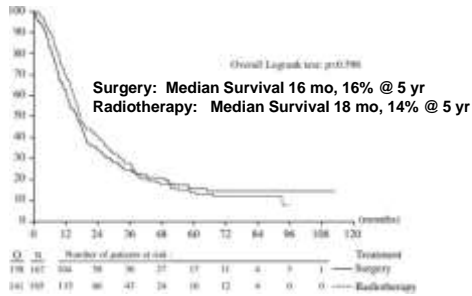
Curran WJ, et al. *Proc Am Soc Clin Oncol* 2003;22:621a; Kelly K, et al. *J Clin Oncol* 2005;23(16S):Abstract 7058; Hanna N, et al. *J Clin Oncol* 2005;23(16S): Abstract 7512.

EORTC-LCG: Resection vs. Radiotherapy After Induction Chemotherapy in Stage IIIA-N2 NSCLC



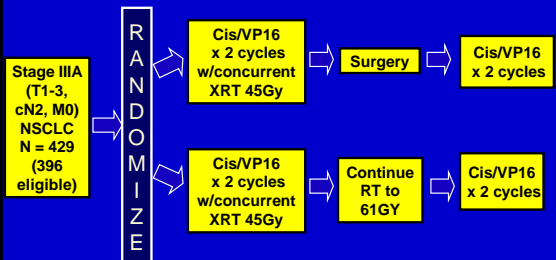
van Meerbeek JP, et al. *J Natl Cancer Inst* 2007;99:442-450.

EORTC-LCG: Resection vs. Radiotherapy After Induction Chemotherapy in Stage IIIA-N2 NSCLC



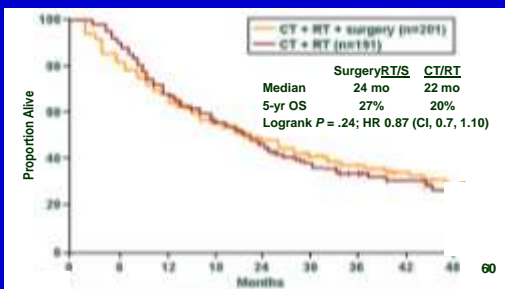
van Meerbeek JP, et al. *J Natl Cancer Inst* 2007;99:442-450.

INT 0139: Definitive CT/RT vs. Induction CT/RT → Surgery for Stage IIIA NSCLC



Albain KS, et al. *J Clin Oncol* 2005;23(16S):Abstract 7014.

INT 0139: Overall Survival Surgery vs.. RT



Albain KS, et al. *J Clin Oncol* 2005;23(16S):Abstract 7014.

INT 0139: Deaths on Treatment

Death	Surgery (n=202)	RT (n=194)
Total	8%	2% (during or after consolidation)
During induction	0	0
30 d post-op	5%	---

Surgery Arm

Type of surgery	Total #	Deaths
Wedge	3	0
Lobectomy	98	1 (1%)
Pneumonectomy	54	14 (26%)

Albain KS, et al. *J Clin Oncol* 2005;23(16S):Abstract 7014.

INT 0139: Results In "Lobectomy" and "Pneumonectomy" Patients

Pneumonectomy "Matched"	Surgery	RT
Median Overall Survival	19 mo	29 mo
3-yr survival	36%	45%
5-yr survival	22%	24%
# Dead	38	42

Lobectomy "Matched"	Surgery	RT
Median Overall Survival	34 mo	22 mo
5-yr survival	36%	18%
# Dead	57	74

Albain KS, et al. *J Clin Oncol* 2005;23(16S):Abstract 7014.

Multimodality Therapy in Stage IIIA NSCLC

Dilemma - Local: Surgery vs. Radiation Factors Favoring Surgery

- Gold Standard Local Control
- Gold Standard Staging
- *In vivo* chemosensitivity testing possible during induction and for adjuvant use
- "Resistant" Tumor Tissue Available
- Better Approach for Large Primaries
- Post treatment surveillance easier

Multimodality Therapy in Stage IIIA NSCLC

**Dilemma - Local: Surgery vs. Radiation
Factors Favoring Radiation**

- Decreased early mortality, especially in patients requiring pneumonectomy
- More available
- Better choice at a “low volume” surgery center

Multimodality Therapy in Stage IIIA NSCLC

**Dilemma - Systemic: Induction vs. Adjuvant
Chemotherapy
Factors Favoring Induction Chemotherapy**

- Attacks micrometastases at earliest time
- Better drug delivery and tolerability
- Ability to assess sensitivity of agents used in induction and adjuvant settings
- Time to identify patients with unsuspected metastases and comorbidities before local therapy given

Multimodality Therapy in Stage IIIA NSCLC

**Dilemma - Systemic: Induction vs. Adjuvant
Chemotherapy
Factors Favoring Adjuvant Chemotherapy**

- Patients precisely staged
- Ample tumor tissue available to tailor or target therapy

Multimodality Therapy in Stage IIIA NSCLC
**Dilemma - Radiation: Induction
 Chemotherapy-RT vs. PORT**
Factors Favoring Induction Chemotherapy-RT

- Potential to improve local control and survival over chemotherapy plus surgery plus PORT. No data to show these benefits. More toxicity with concomitant.

Multimodality Therapy in Stage IIIA NSCLC
**Dilemma - Radiation: Induction Chemotherapy-RT
 vs. PORT**
Factors Favoring Post-Op RT (PORT)

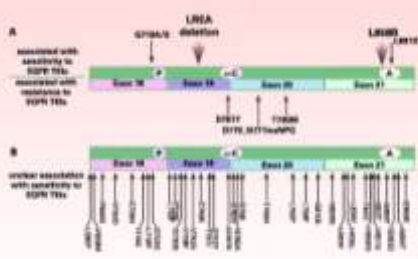
- Improved local control over no PORT
- Decreased size of RT fields
- Patients precisely staged
- Decreased morbidity compared to concomitant Chemotherapy-RT
- ANITA Trial and SEER data suggest survival improvement in stage IIIA cohort who received PORT

**Effect of PORT on Survival - 7465 Patients
 SEER Database: 1988-2002**

	5 Year Survival Univariate	Overall Survival Multivariate
N0 Radiotherapy Observation n = 1305	31% 41% <i>P</i> < 0.0001	HR 1.18 HR 1.00 <i>P</i> = 0.0435
N1 Radiotherapy Observation n = 4173	30% 34% <i>P</i> = 0.0006	HR 1.10 HR 1.00 <i>P</i> = 0.0196
N2 Radiotherapy Observation n = 1987	27% 20% <i>P</i> = 0.0036	HR 0.86 HR 1.00 <i>P</i> = 0.0077

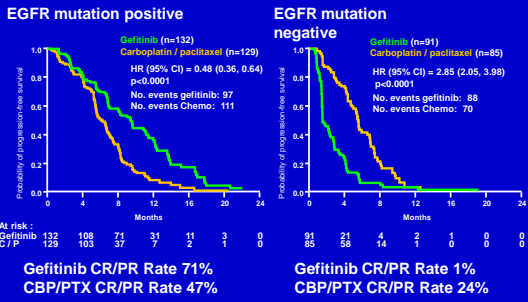
Lally BE. *J Clin Oncol* 2006;24:2998-3006.

EGFR Mutations with Both Sensitivity and Resistance



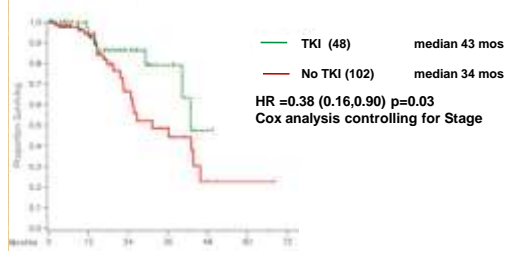
Riely GJ, et al. *Clin Cancer Res* 2006;12:7232-7241.

IPASS: Results in EGFR Mutation Positive and Negative Patients (All Asian, 94% Never Smokers)



Mok T, et al. *Proc ESMO* 2008. Abstract LBA1.

Disease-Free Survival in Stage I-III Lung Adenocarcinoma with EGFR mutation MSK Series- Cox Multivariable Analysis



Janjigian YY, et al. *J Clin Oncol* 2009;27(15s). Abstract 7523.

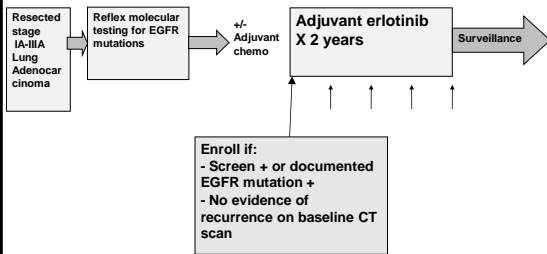
A Phase II trial of Adjuvant Erlotinib in Patients with Resected, Early Stage Non-Small Cell Lung Cancer with Confirmed Mutations in the Epidermal Growth Factor Receptor



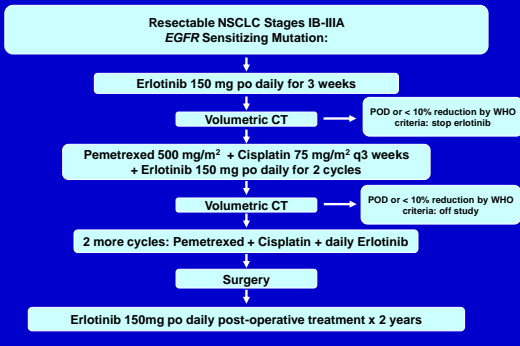
MGH: Lecia Sequist
MSKCC: Jerry Azzoli

Adjuvant Erlotinib in EGFR Mutation + Patients

Design



ECON Pre- and Post-Op Therapy Trial Erlotinib and Chemotherapy for Operable NSCLC



ECOG 4599: Phase III Trial of Chemotherapy +/- Bevacizumab in NSCLC

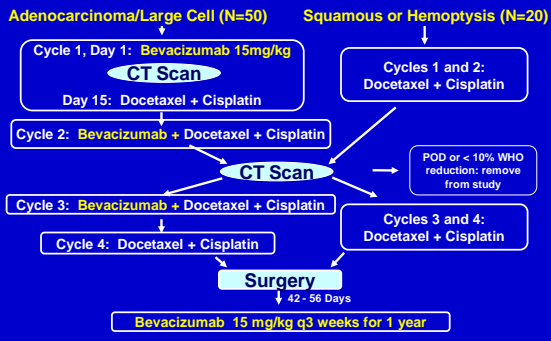
- Randomized phase III trial in 878 patients – JUL 01- APR 04
- No prior therapy for stage IIIB/IV non-squamous NSCLC

	Carboplatin -plus-Paclitaxel Only	Bevacizumab (15mg/kg) + Carboplatin -plus- Paclitaxel	<i>p</i>
Entered	444	434	
CR/PR Rate	15%	35%	<0.001
1 Yr Survival	44%	51%	
2 Yr Survival	15%	23%	
Median Survival	10.3 months	12.3 months	0.007

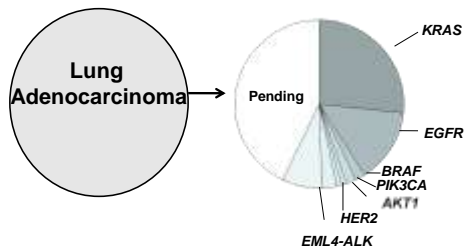
Sandler A, et al. *N Engl J Med* 2006;355:2542-2550.

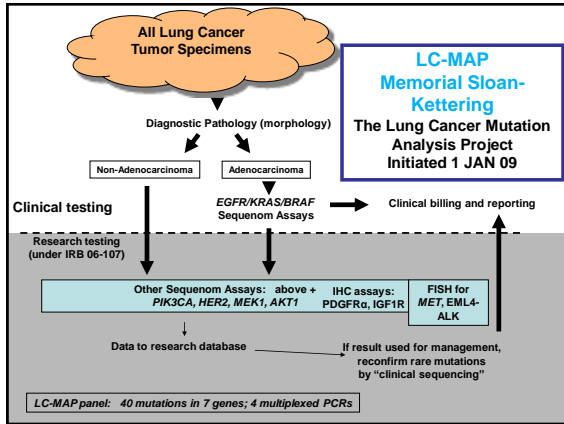
BEACON Pre- and Post-Therapy Trial

Bevacizumab And Chemotherapy for Operable NSCLC (IB-IIIa)



Molecular Profiling Explains The Heterogeneity of Lung Adenocarcinoma and Defines Targets for Therapy





Memorial Sloan-Kettering Mutations Identified in LC-MAP

MSKCC 1 JAN - 30 JUN 09	
N = 301	
KRAS	72
EGFR	63
EML4-ALK	22
BRAF	1
PIK3CA	4
HER2	0
MEK1	0
AKT1	0

Using *EGFR* and *KRAS* Mutations and ERCC1 Expression to Select Therapy MSK Adjuvant Treatment Assignment 2009

	<i>EGFR</i> Mutation	<i>KRAS</i> Mutation	<i>EGFR</i> and <i>KRAS</i> WILDTYPE
ERCC1 Positive	(3% of patients) vinorelbine + docetaxel, followed by clinical trial of erlotinib	(7% of patients) vinorelbine + docetaxel, followed by clinical trial of KRAS vaccine - RASVAX	(25% of patients) vinorelbine + docetaxel
ERCC1 Negative	(7% of patients) vinorelbine + cisplatin, followed by clinical trial of erlotinib	(13% of patients) vinorelbine + docetaxel, followed by clinical trial of KRAS vaccine RASVAX	(45% of patients) vinorelbine + cisplatin (Plan to open ECOG 1505 to use PEM/CIS)

Azzoli CG, et al. *J Thorac Oncol* 2008;3(2):111-116.

Perioperative Therapy for Stages I-III

Conclusions

- Never smoking status imparts a better prognosis and higher likelihood of an *EGFR* mutation
- Multimodality therapy is the standard of care for clinical stages IB-III NSCLC. Cure is possible
- Systemic therapy should always be considered because of the high risk of deadly systemic relapse
- Agents with response and survival improvements in stage IV should be quickly “moved-up”
- While surgery and radiation are equally effective local therapies, surgery has many advantages
- Induction use identifies active agents both for individual patients and drug development
