

Integration of Targeted Therapies in Early Stage Non-Small Cell Lung Cancer

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Integration of Targeted Therapies in Early Stage NSCLC

Introduction

- **Outcomes and therapy of stages I-III NSCLC**
- **Opportunities to add new agents: erlotinib/gefitinib and bevacizumab to improve survival and curability**
- **Adjuvant and Neoadjuvant Approaches**

Integration of Targeted Therapies in Early Stage NSCLC

Financial Disclosure

- **Consulting Fees**
 - SanofiAventis
 - AstraZeneca
 - Bristol-Myers Squibb
 - Imclone

Integration of Targeted Therapies in Early Stage NSCLC
Additional Disclosure

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

USA Lung Cancer New Cases by Stage: 2008

	Patients
NON-SMALL CELL	187,000
Stage I	37,000
Stage II	13,000
Stage IIIA	50,000
Stage IIIB (limited)	10,000
Stage IV-IIIB	75,000
SMALL CELL	28,000
Limited	11,000
Extensive	17,000

Revised Lung Cancer Staging System

Does “Good Prognosis” Lung Cancer Exist?

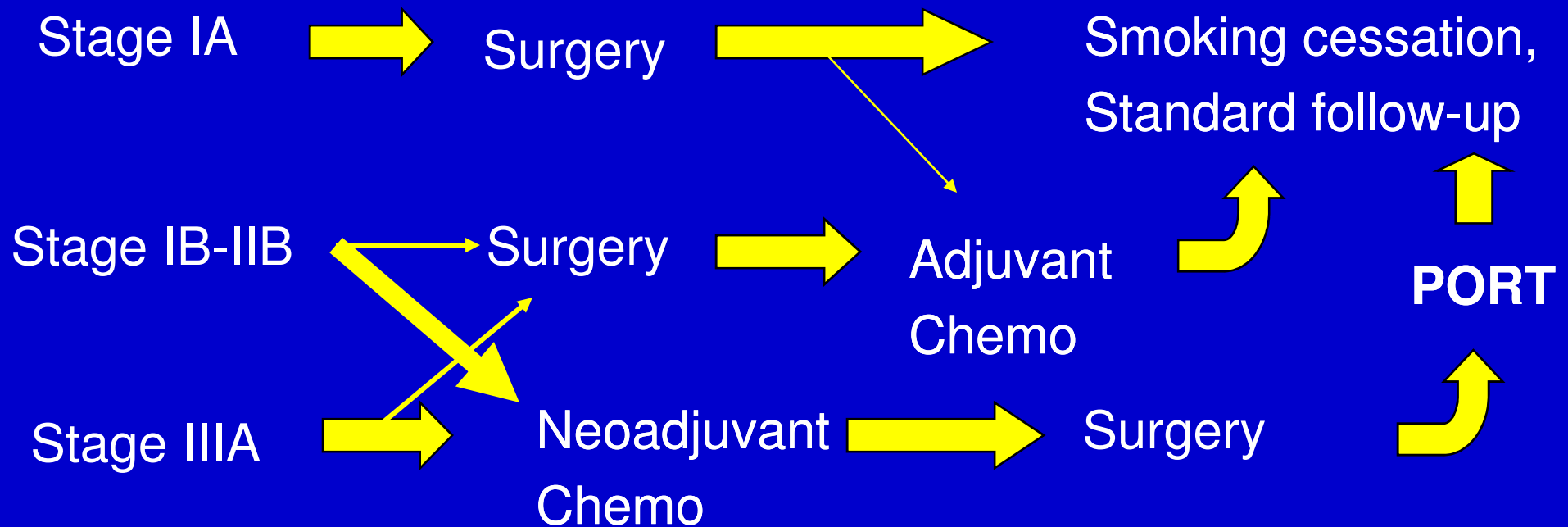
			5 Year Survival	5 Year Survival
T Stage (all N0M0)	Primary Size	N	Clinical Stage	Pathological Stage
T1a	≤ 2 cm	1816	53%	77% ←
T1b	> 2-3 cm	1563	47%	71%
T2a	> 3-5 cm	2822	43%	58%
T2b	> 5-7 cm	825	36%	49%
T2c	>7	364	26%	35%

Integration of Targeted Therapies in Early Stage NSCLC

There is no such thing as “good prognosis lung cancer”

- **23% of patients with tumors less than 2 cm (Stage T1_aN0M0) in the revised staging) are dead at 5 years**
- **We recommend that all patients with breast cancer with this risk of death be considered for additional therapy after primary treatment**

Resectable NSCLC Management at MSK



Neoadjuvant chemo options:

1. MVP(100)
2. cis(75-100) + docetaxel
3. cis(75-100) + gemcitabine
4. cis(75-100) + pemetrexed
5. protocol

Adjuvant chemo options:

1. cis(100) + vinorelbine (BR.10, Winton et al)
2. erlotinib for *EGFR* mutation (+) patients
3. protocol

Integration of Targeted Therapies in Early Stage NSCLC

Opportunities:

Drugs Improving Response and Survival in Stage IV

- **Erlotinib**
- **Gefitinib**
- **Bevacizumab**
- **Cetuximab**

Prospective Trials Correlating Response with *EGFR* Mutations

	N	Agent	Response Rate	Exon 19	Exon 21
Inoue 2006	16	Gefitinib	75%	67%	86%
Cappuzzo 2007	23	Gefitinib	65%	NR	NR
Paz-Ares 2006	38	Erlotinib	82%	95%	67%
Sequist 2007	26	Gefitinib	62%	59%	78%
Kris 2007	21	Gefitinib	81%	90%	70%
Mok 2008	132	Gefitinib	71%	NA	NA

Survival Improvement in Never Smoking Patients Treated in Placebo-Controlled Trials of Gefitinib or Erlotinib

Trial (Year)	Regimens Compared	Number of Never Smokers (Percent of Total)	Hazard Ratio (95% CI)
ISEL (2005)	Gefitinib: Placebo	372 (22%)	0.67 (0.5 to 0.9)
BR.21 (2004)	Erlotinib: Placebo	146 (20%)	0.4 (0.3 to 0.6)






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 NEJM 2006

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	3	0.83	0.64-1.08	0.12
	840	8	0.79	0.66-0.95	0.01
Meta06	4584	4	0.89	0.82-0.96	0.005

JNCI 03; NEJM 04; NEJM 05; J Clin Oncol 08; Lancet Oncol 06

The NEW ENGLAND JOURNAL of MEDICINE

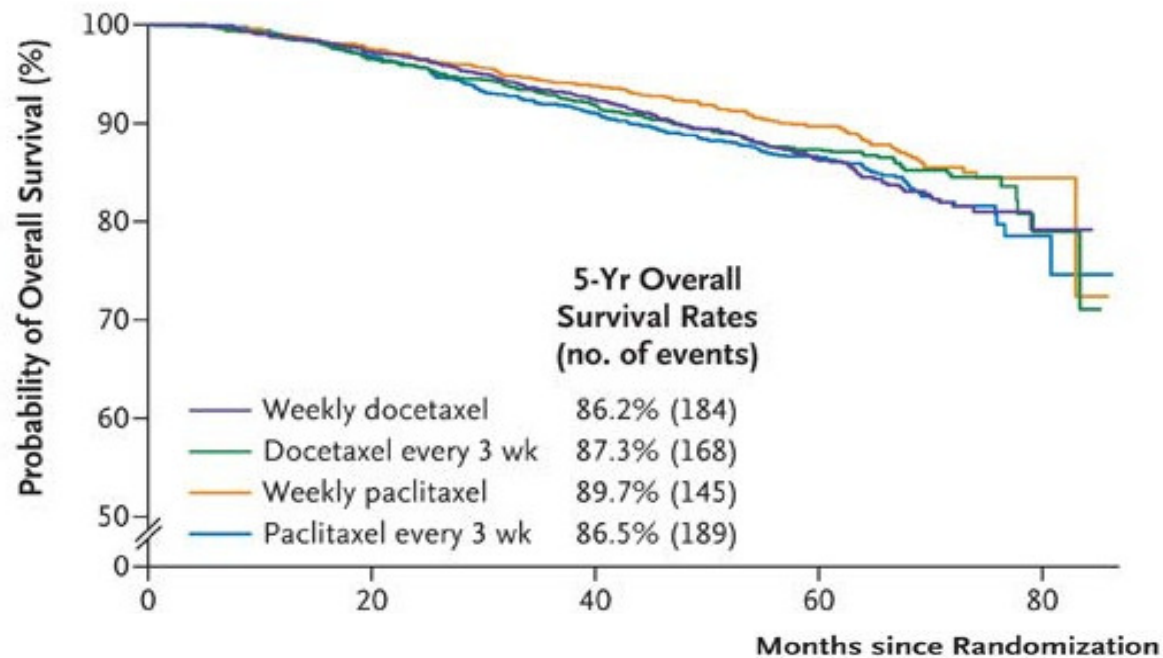
ESTABLISHED IN 1812

APRIL 17, 2008

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Weekly Paclitaxel in the Adjuvant Treatment of Breast Cancer

Joseph A. Sparano, M.D., Molin Wang, Ph.D., Silvana Martino, D.O., Vicky Jones, M.D., Edith A. Perez, M.D.,
Tom Saphner, M.D., Antonio C. Wolff, M.D., George W. Sledge, Jr., M.D., William C. Wood, M.D.,
and Nancy E. Davidson, M.D.



No. at Risk

Paclitaxel every 3 wk	1253	1196	1082	751	27
Weekly paclitaxel	1231	1188	1100	756	36
Docetaxel every 3 wk	1236	1178	1095	733	36
Weekly docetaxel	1230	1181	1092	734	30

E1505: Phase III Adjuvant Chemotherapy ± Bevacizumab

Eligibility

- Resected IB (>4cm) – IIIA
- ≥ lobectomy
- No previous chemotherapy
- No planned XRT
- No CVA/TIA
- No ATE in 12 months

N = 1500

R
A
N
D
O
M
-
I
Z
E

Chemotherapy* x 4 cycles

Chemotherapy* x 4 cycles +
bevacizumab x 1 year

- Cisplatin and vinorelbine
- Cisplatin and docetaxel
- Cisplatin and gemcitabine
- Cisplatin and pemetrexed

Primary endpoint: overall survival

**Secondary endpoints: disease-free survival, safety
[bleeding and arterial thromboembolic events (ATEs)]**

Using *EGFR* and *KRAS* Mutations and ERCC1 Expression to Select Therapy

MSK Adjuvant Treatment Assignment 2008

	<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 <i>KRAS</i> vaccine - RASVAX	(25% of patients) vinorelbine + docetaxel
ERCC1 Negative	(7% of patients) vinorelbine + cisplatin, followed by clinical trial of erlotinib	(13% of patients) vinorelbine + cisplatin, followed by clinical trial of <i>KRAS</i> vaccine RASVAX	(45% of patients) vinorelbine + cisplatin

Azzoli J Thorac Oncol 2008

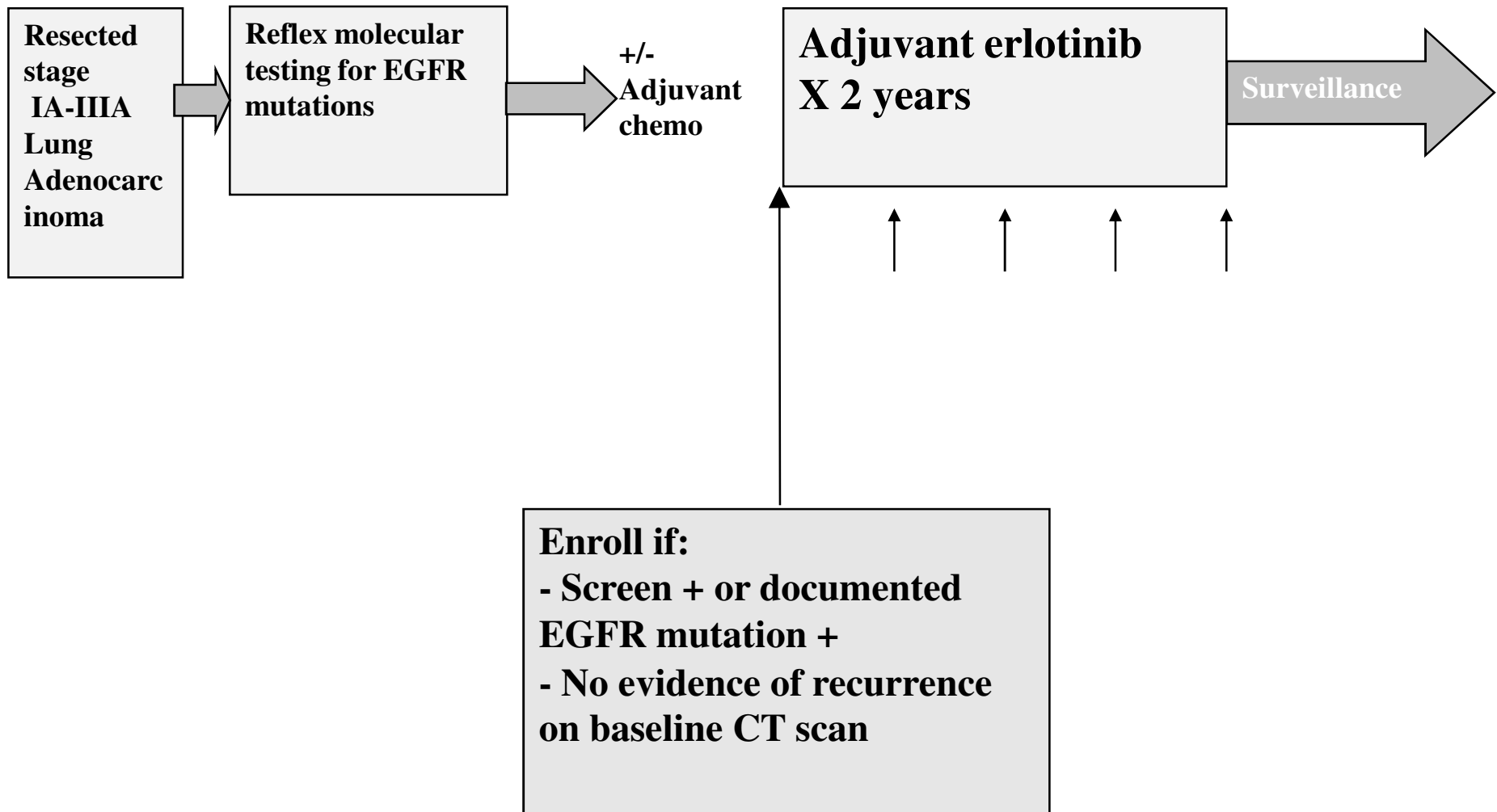
A Phase II trial of Adjuvant Erlotinib in Patients with Resected, Early Stage Non-Small Cell Lung Cancer with Confirmed Mutations in the Epidermal Growth Factor Receptor



Memorial Sloan-Kettering
Cancer Center

Adjuvant Erlotinib

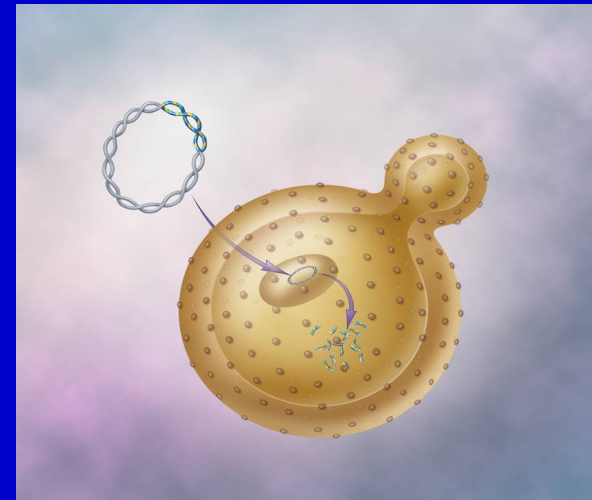
Schema



KRAS vaccine (GI 4000, RASVAX)

Recombinant *S. cerevisiae* yeast with mutant KRAS

- codon 61 glutamine to arginine [Q61R]
- codon 61 glutamine to leucine [Q61L]



PLUS

- codon 12 glycine to valine [G12V] = GI-4014
- codon 12 glycine to cysteine [G12C] = GI-4015
- codon 12 glycine to aspartate [G12D] = GI-4016

KRAS Vaccine (RASVAX)

Phase II Trial:

Stage I-IIIB NSCLC treated with curative intent

KRAS mutations: G12C, G12V, G12D

Mutation-specific GI-4000 vaccination (G12C,V, or D)

Injections: weekly X3 then monthly X3 then every 3 months for 3 years

Endpoints:

KRAS-specific CD4+,CD8+ T

Lymphocyte proliferation assays

Chromium release assays

Antibody titers by ELISA

NCIC CTG BR.19

Closed: 502/1160

Completely
resected
Stage IB - IIIA
NSCLC

Stratify:

Histology

Chemo

RT

Gender

R
A
N
D
O
M
I
Z
E

Observation alone

Gefitinib 250 mg/day
x 2 years

Randomized Double-Blind Trial In Adjuvant NSCLC with Tarceva (RaDIANT)

N=945

IB – IIIA

EGFR +

IHC or FISH

Stratify:

Histology

Gender, Age

Smoking Hx

Chemo

R
A
N
D
O
M
I
Z
E

Placebo

Erlotinib 150 mg/day

x 2 years

Primary Endpoint: Disease-Free Survival

S0720-Pharmacogenomic-based adjuvant therapy (Stage I (>2 cm) or IB. PI: G Bepler

	Low ERCC1 (< 66)	High ERCC1 (> 66)
Low RRM1 (< 40.5)	Gemcitabine + Cisplatin	Gemcitabine + Cisplatin
High RRM1 (> 40.5)	Gemcitabine + Cisplatin	Observation

NSCLC Adjuvant Therapy 2009

- Actual results *at least* comparable to breast and colon cancer – relative results better
- There is no such thing as a “good prognosis” NSCLC. 23% of pT1a patients are dead at 5 years
- 80% drug delivery a good benchmark
- Tissue available – our best chance to personalize
- No proven option other than cisplatin which is contraindicated in most patients
- Despite opportunities for biology-based care and the ability to cure, a neglected area of research

PREOPERATIVE CHEMOTHERAPY - TREATMENT PLAN -

2-3 Cycles of Chemotherapy



SURGERY



2 Cycles of Chemotherapy



**Mediastinal Irradiation
If tumor in resected N2 nodes**

Integration of Targeted Therapies in Early Stage NSCLC 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 before local therapy given**
- **Time to identify patients with unrecognized comorbidities before local therapy given**

***EGFR* Mutations and Gefitinib Sensitivity**

04-071 Study Plan

**cStage I or II NSCLC
BAC Features and/or
<15 pack year Smoker
Measurable Lesion
Operable and Resectable**

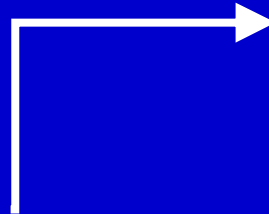
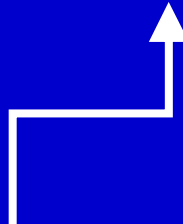
**Chest CT
Needle Biopsy for
EGFR Mutation
Testing in
Exons 18-24**

Repeat Chest CT

**Gefitinib 250 mg
PO daily for at
least 21 days**

**Surgery
Repeat *EGFR*
Mutation Testing in
Exons 18-24
Tumor Banking**

**Continue Gefitinib for
2 years if CT
Response or *EGFR*
exon 19 or 21 Mutation
Present**



EGFR Mutations and Gefitinib Sensitivity

Results: Primary Study Endpoint

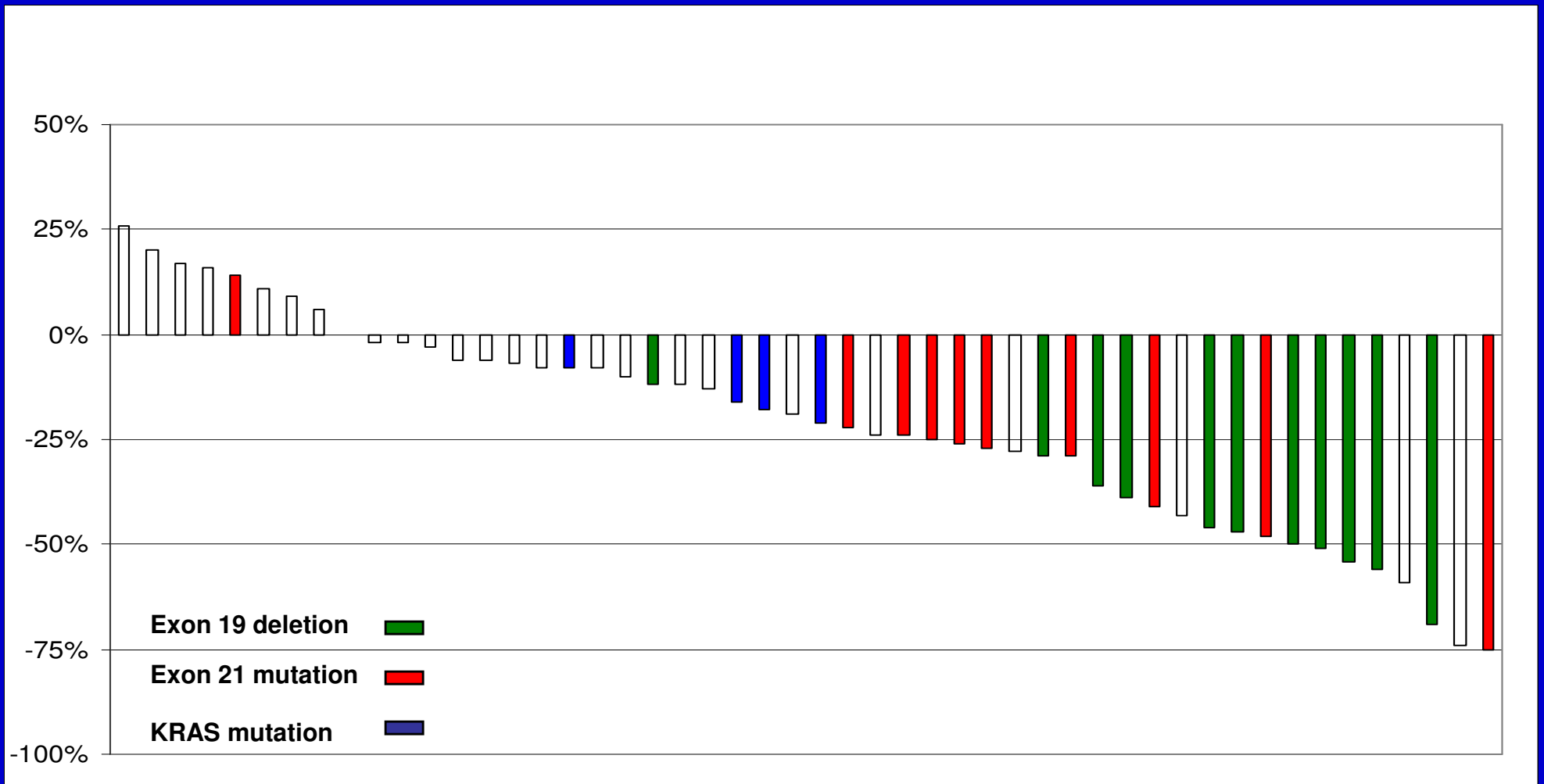
Planned Enrollment: 50
Completed Study: 50

Final Results	<i>EGFR</i> Exon 19 or 21 Mutation	<i>EGFR</i> Wild Type *
Response	17 (81%)	4 (14%)
No Response	4	25

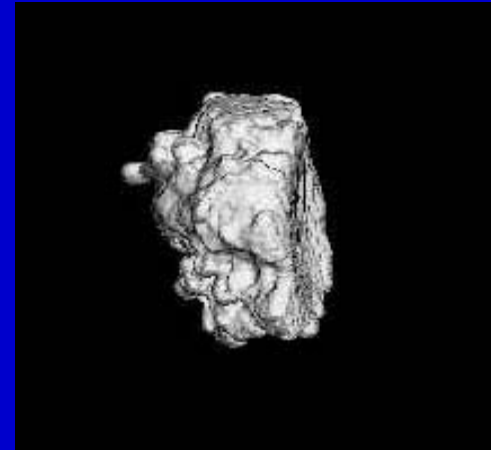
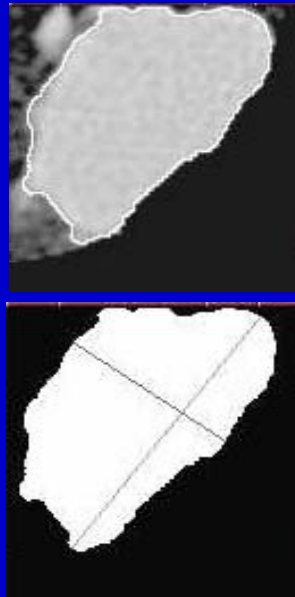
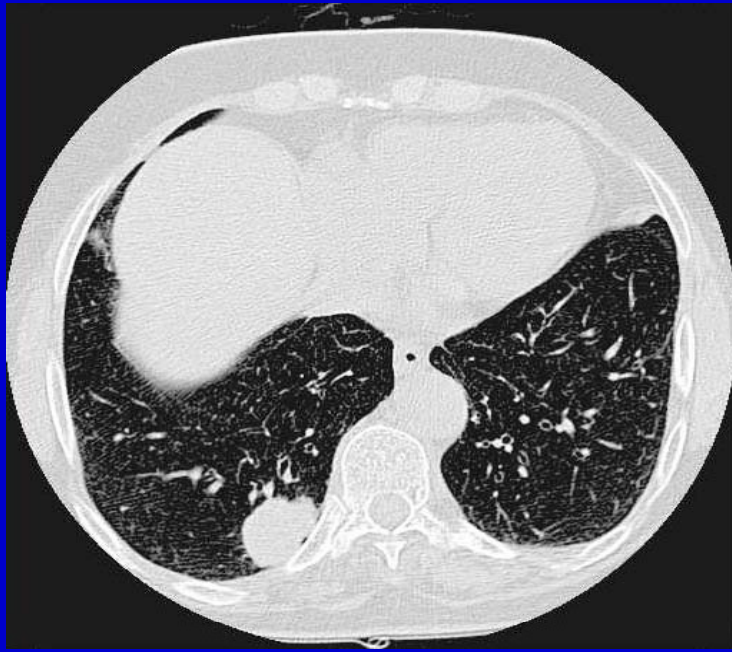
* No mutation in *EGFR* exons 18-24

Fisher's exact test: two tailed P value < 0.0001

EGFR Mutations and Gefitinib Sensitivity Response with Gefitinib after 21 days WHO (Bidimensional) Criteria

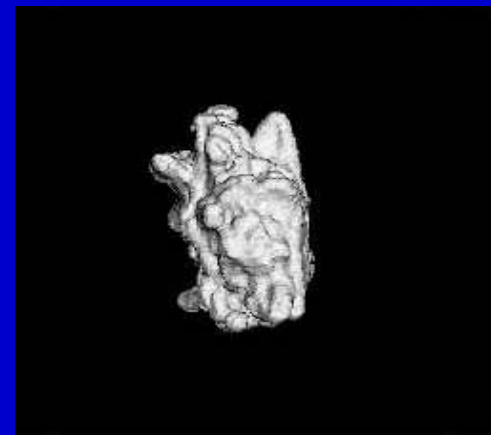


Patient with *EGFR* exon 19 mutation



Pre-Gefitinib

Long axis = 36 mm
Short axis = 21 mm
Area = 540 mm²
Volume = 12692 mm³



After Gefitinib

Long axis = 26 mm
Short axis = 18 mm
Area = 328 mm²
Volume = 7243 mm³

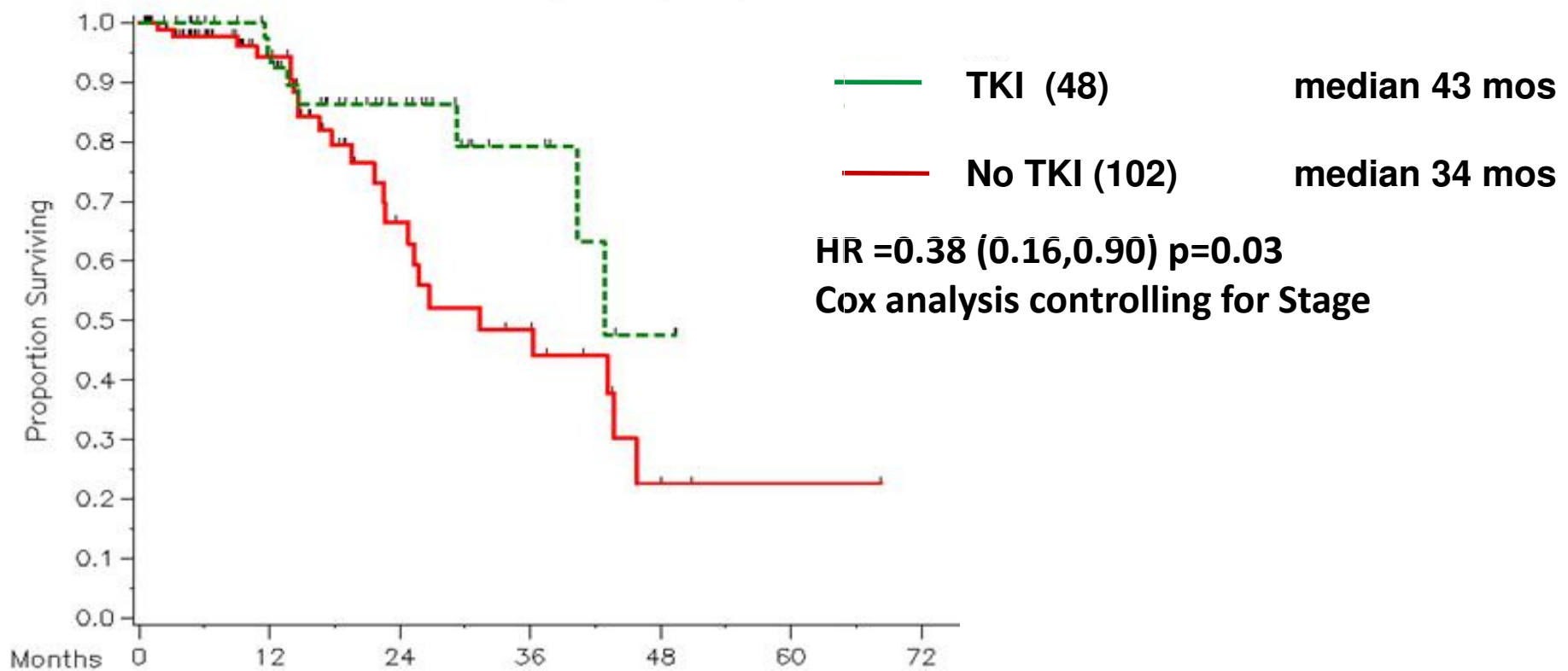
***EGFR* Mutations and Gefitinib Sensitivity**

04-071 Results

- In this ongoing study, there is a 67% difference in the proportion of *EGFR* exon 19 and 21 mutations in patients with “response” and “no response” following gefitinib
- A short trial of preoperative gefitinib can determine chemosensitivity to tailor adjuvant therapy to individual patients

Disease-Free Survival in Stage I-III Lung Adenocarcinoma with EGFR mutation

MSK Series- Cox Multivariable Analysis



Janjigian Proc ASCO 2009 (Submitted)

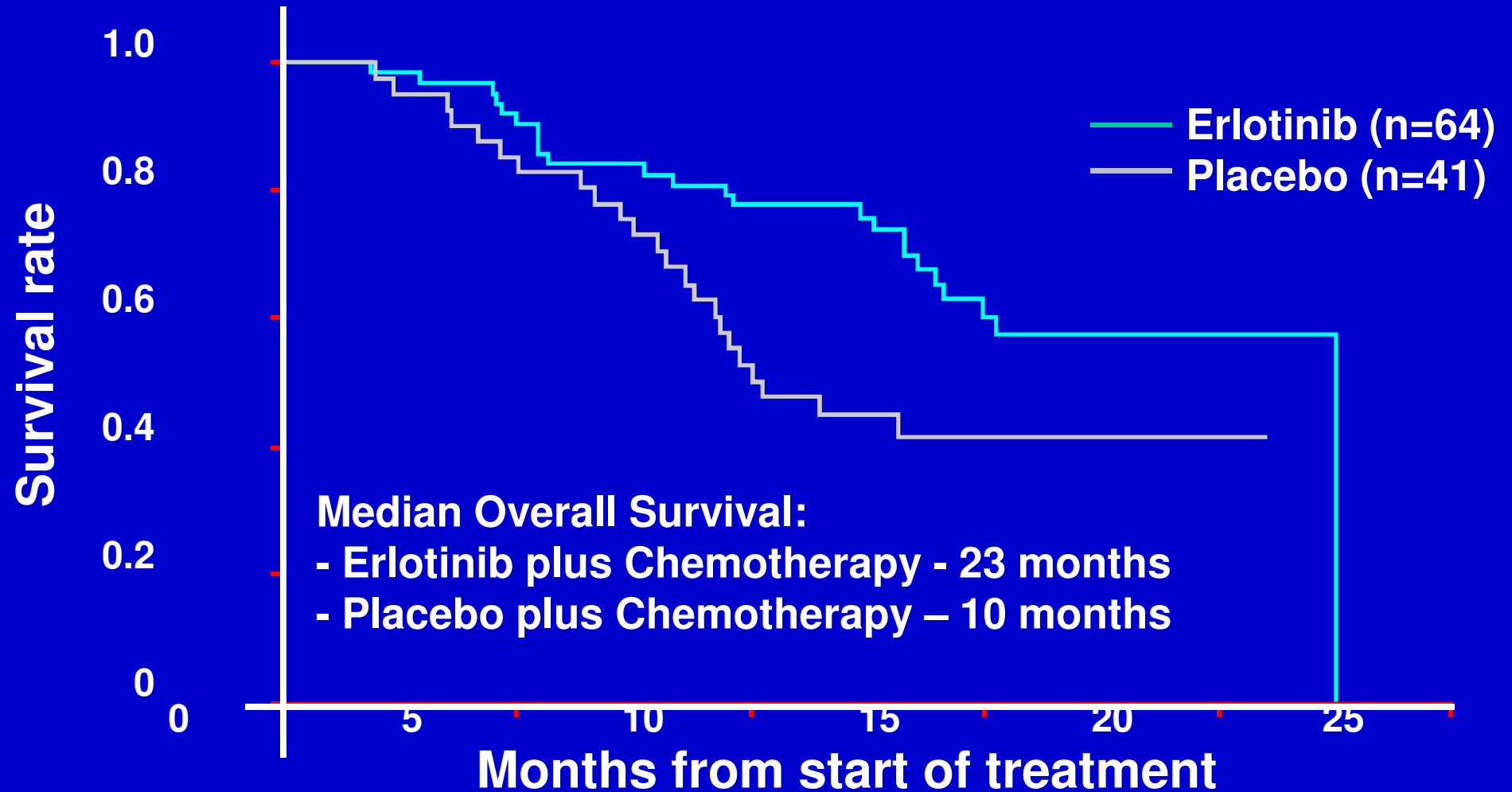
Smoking History and EGFR TKI Sensitivity

Author	Agent (Patients)	Response Rate Never Smokers	Response Rate Current/Former	Difference
Miller 2004	Gefitinib (MSKCC)	36%	8%	28%
Cohen 2003	Gefitinib (IDEAL2)	29%	5%	24%
Fukuoka 2003	Gefitinib (Japan)	33%	9%	24%
Takano 2004	Gefitinib (Japan)	63%	18%	45%
Han 2005	Gefitinib (Korea)	33%	15%	18%
Shepherd 2004	Erlotinib (CBR.21)	25%	4%	21%
ISEL 2005	Gefitinib (ISEL)	18%	5%	13%

Incidence of EGFR Mutations by Number of Pack Years of Cigarette Smoking

Number of pack years	Number of patients with <i>EGFR</i> mutations		
0 (n=67)	34 (51%)	CI 38.4-63.5%	
1-5 (n=19)	7 (37%)	CI 17.2-61.4%	p=0.31
6-10 (n=22)	10 (46%)	CI 25.1-67.3%	p=0.81
11-15 (n=10)	3 (30%)	CI 8.1-64.6%	p=0.31
16-25 (n=22)	2 (9%)	CI 1.6-30.6%	p<0.005
26-50 (n=67)	6 (9%)	CI 3.7-19.1%	p<0.005
51-75 (n=30)	3 (10%)	CI 2.6-27.7%	p<0.005
>75 (n=28)	0 (0%)	CI 0-15%	p<0.005

TRIBUTE: Chemotherapy \pm Erlotinib Survival in Never Smokers with NSCLC



Herbst J Clin Oncol 2005

ECON Pre- and Post-Op Therapy Trial

Erlotinib and Chemotherapy for Operable NSCLC

Resectable NSCLC Stage IB-IIIa:
Adenocarcinoma with ≤ 15 pack-year smoking history and/or features of BAC

Erlotinib 150 mg po daily for 3 weeks

Volumetric CT

POD or $< 10\%$ reduction by WHO criteria: stop erlotinib

Pemetrexed 500 mg/m² + Cisplatin 75 mg/m² q3 weeks
+ Erlotinib 150 mg po daily for 2 cycles

Volumetric CT

POD or $< 10\%$ reduction by WHO criteria: off study

2 more cycles: Pemetrexed + Cisplatin + daily Erlotinib

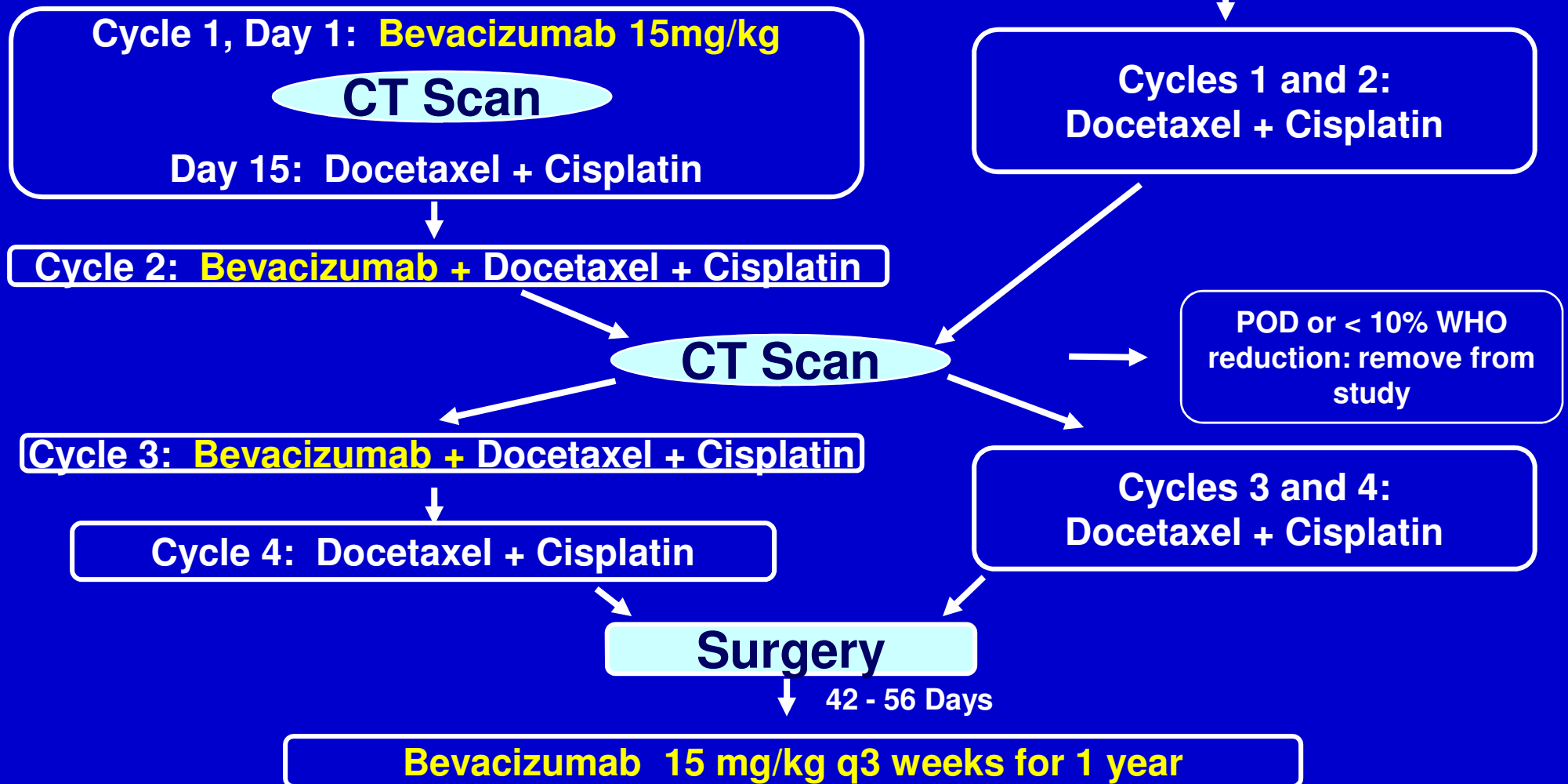
Surgery

Erlotinib 150mg po daily post-operative treatment x 2 years

BEACON Pre- and Post-Op Therapy Trial

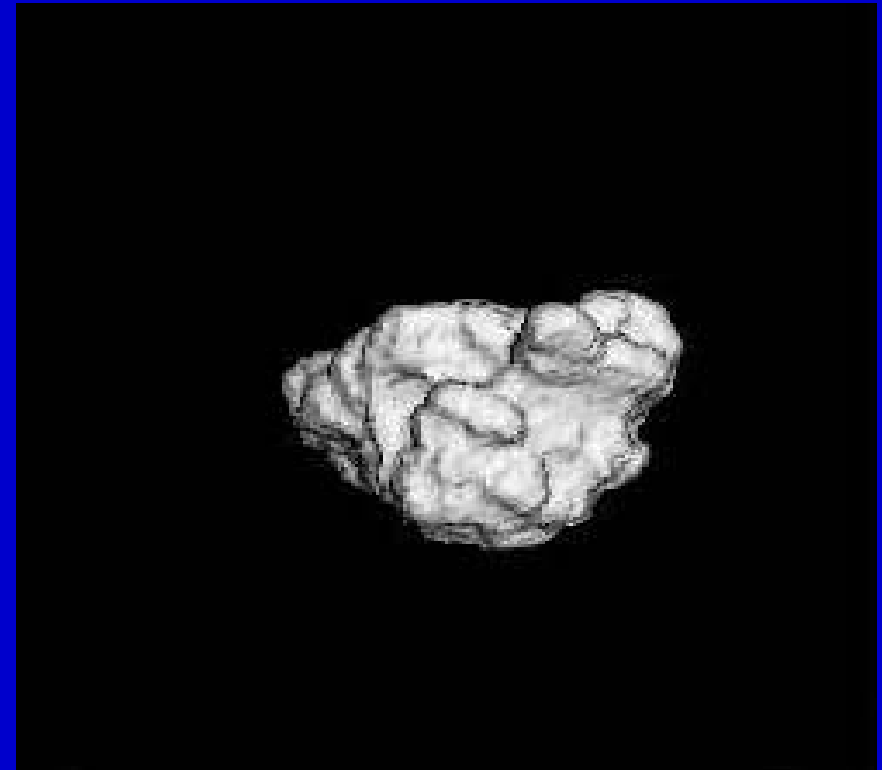
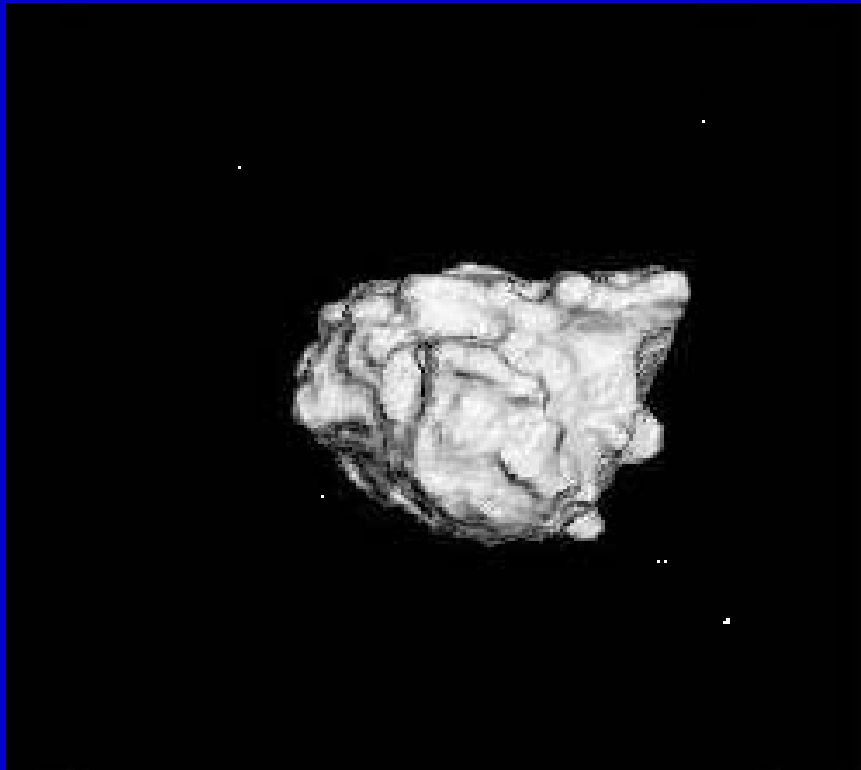
BEvacizumab And Chemotherapy for Operable NSCLC (IB-III A)

Non-Squamous (N=50) **Squamous or Central Tumor (N=20)**



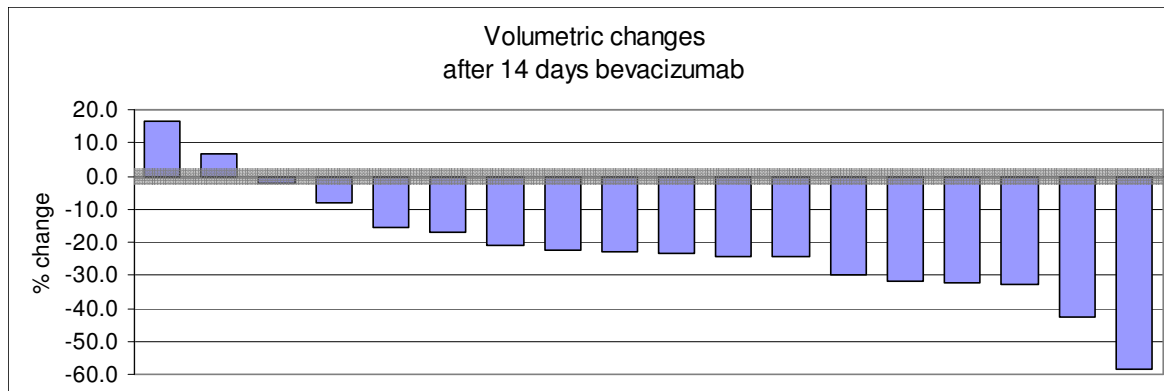
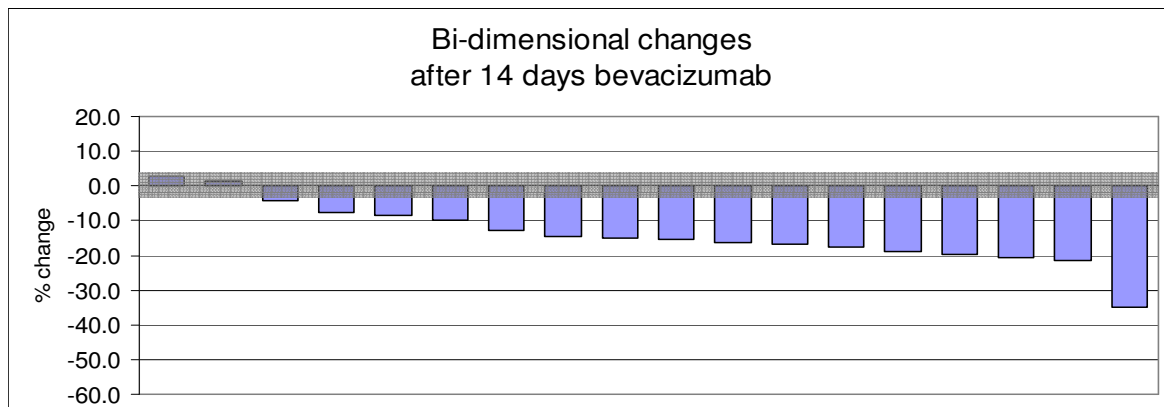
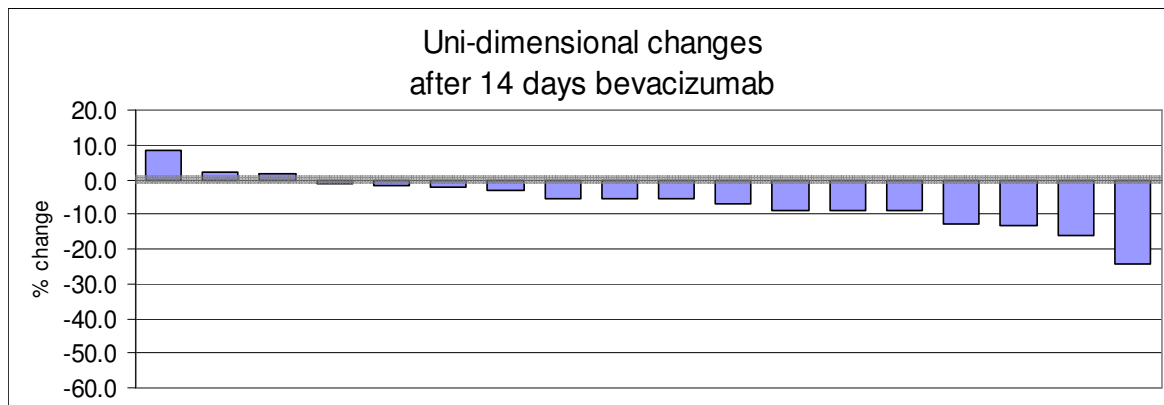
Pre-bevacizumab

2 weeks post-bevacizumab



% change	RECIST	Bidimensional	3D volumetric
	+ 8%	-21%	-32%

Changes in Lesion Size After 14 Days of Bevacizumab



James Proc IASLC 2007

All Lung Cancer
Tumor
Specimens

Diagnostic Pathology

Non-Adenocarcinoma

Adenocarcinoma

EGFR/KRAS
mutation testing

Clinical billing
and reporting

Clinically indicated
Research testing
(using IRB #06-107)

Sequenom Assays: *PIK3CA, HER2, HRAS, BRAF, NRAS, MEK1, AKT1, EGFR, KRAS* + IHC assay: PDGFR α + FISH: MET, ALK

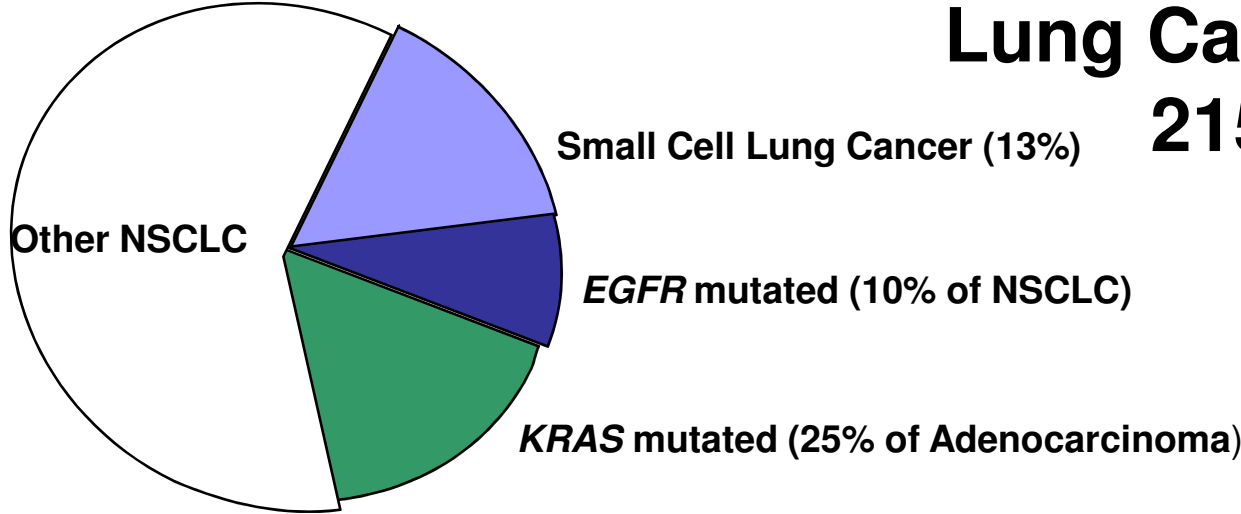
Data to CRDB and
patient record

If result used for management,
reconfirm by "clinical sequencing"

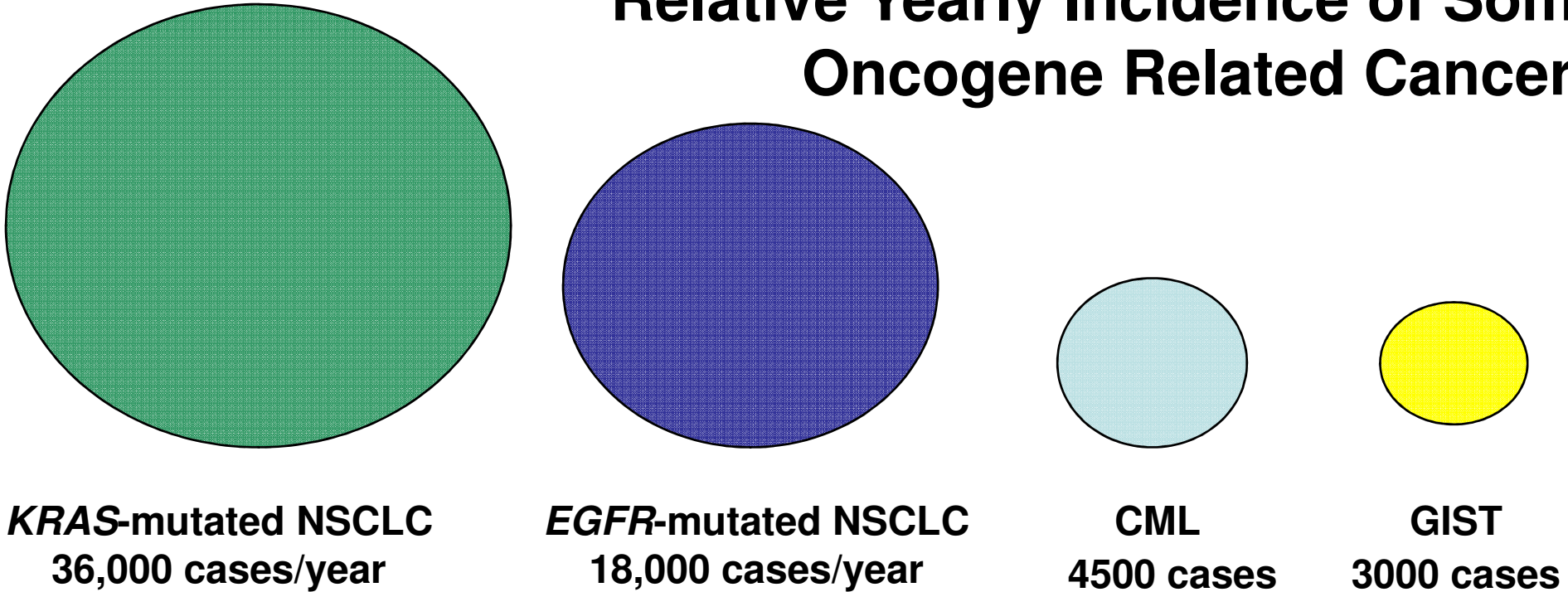
Routine
MSKCC
Lung Cancer
Molecular
Profiling

Lung Cancer 2008 – USA

215,000 New Cases



Relative Yearly Incidence of Some Oncogene Related Cancers



Integration of Targeted Therapies in Early Stage NSCLC

Conclusions

- **Multimodality therapy is the standard of care for clinical stages IB-III NSCLC. Cure is possible**
- **Systemic therapy should 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 both surgery and radiation are effective local treatments, there are many advantages to surgery**
- **Advances in systemic therapy will change staging, require tissue pretreatment, & improve outcomes**

MSKCC Adjuvant and Neoadjuvant Studies for NSCLC

Neoadjuvant

For all patients with resectable Stage I – III NSCLC

BEACON (05-052)

For high-risk stage IB-III A,
≥ 15 pack-year smoker

ECON (07-103)

For high-risk stage IB-III B,
< 15 pack-year smoker

Adjuvant

For all patients with R0 resected IB – IIIB NSCLC not enrolled in ECON or BEACON

VIN-DOC (07-022)

ERCC1 Positive *or* ineligible for cisplatin
Phase II vinorelbine, docetaxel, bevacizumab
Endpoint: vinorelbine delivery

ERCC1 Negative *and* eligible for cisplatin
Cisplatin plus vinorelbine (BR.10 – Winton et al)

Consolidation

IA - IIIB NSCLC, not enrolled in ECON or BEACON, who have completed all therapy

POSTER (08-154)

EGFR mutation +
Phase II erlotinib trial
Endpoint: erlotinib delivery

RASVAX (06-102)

KRAS mutation +
Ph 2 GI-4000 trial
Endpoint: mutation specific immune response

