

Exploring Personalized Therapy for First Line Treatment of Advanced Non-Small Cell Lung Cancer (NSCLC)



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Conflicts of Interest

- In the past 12 months, I have been compensated for serving as a consultant for the following:
 - Genentech
 - Glaxo Smithkline
 - Astellas
 - Synta
 - Imclone

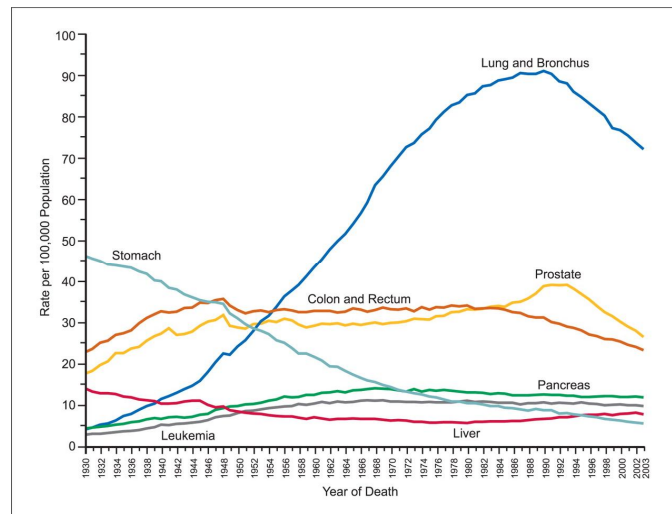
Outline

- Lung cancer basics
- Standard options for first line therapy
- Role of targeted agents
- Molecular selection

Lung Cancer

- Approximately 220,000 new cases are diagnosed each year in the US
- The incidence of small cell lung cancer is decreasing
- NSCLC accounts for 85%
- Almost 50% of the patients with NSCLC present at an advanced stage of the disease

Annual Age-adjusted Cancer Death Rates

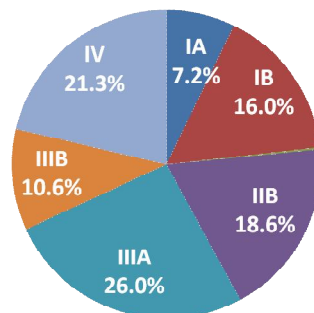


From Jemal, A. et al.
CA Cancer J Clin 2007;57:43-66.

NSCLC

- 80-90% of patients have history of smoking cigarettes
- Includes a variety of histological subtypes
 - Adenocarcinoma
 - Squamous cell carcinoma
 - Large cell carcinoma
 - Bronchioloalveolar carcinoma (BAC)
 - NOS ("Not otherwise specified")

Stage at Diagnosis



NSCLC: Treatment by Stage

- Stage I-III are considered surgically resectable
- Chemotherapy is beneficial for stages IB, II and IIIA after surgery
- For stage III disease, if surgery is not feasible, combination of chemotherapy and radiation is recommended
- Systemic therapy is the mainstay of treatment for advanced stage disease

Advanced Stage Disease

- Presence of malignant pleural or pericardial effusion
- Metastatic involvement of contralateral lung or other extrathoracic sites

Treatment of Advanced NSCLC

Chemotherapy

- Cisplatin
- Carboplatin

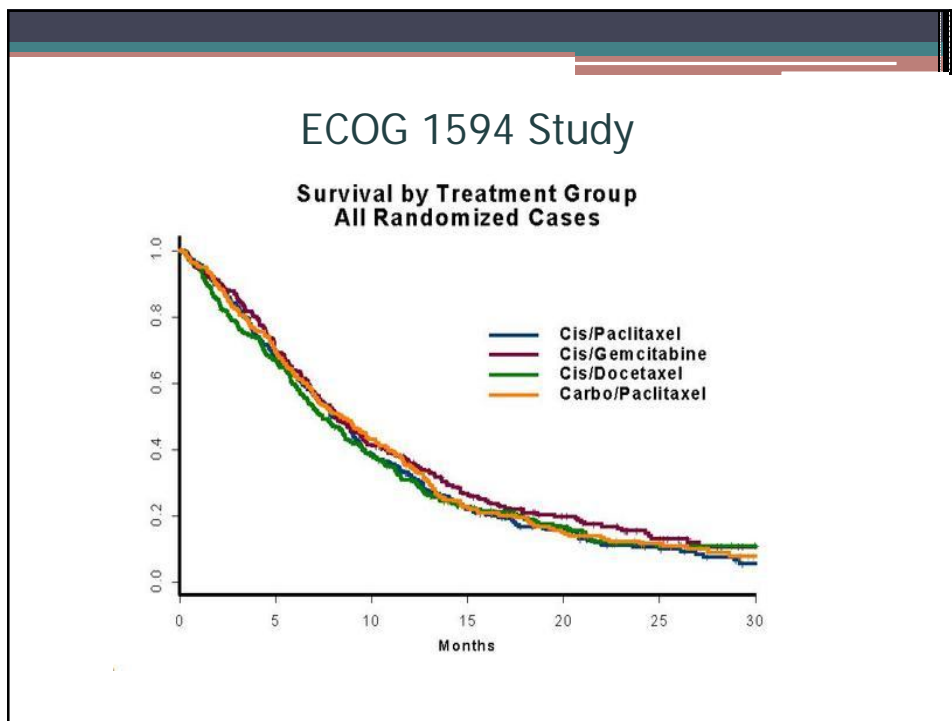
- Paclitaxel (Taxol)
- Docetaxel (Taxotere)
- Gemcitabine (Gemzar)
- Pemetrexed (Alimta)
- Vinorelbine (Navelbine)

Targeted Therapy

- Bevacizumab (Avastin)
- Cetuximab (Erbix)
- Erlotinib (Tarceva)
- Gefitinib* (Iressa)

Evolution of Chemotherapy for Advanced NSCLC

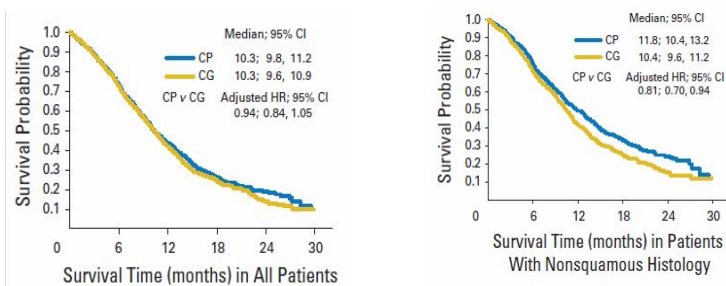
- 1980's
 - Effectiveness of platinum compounds is established
- 1990's
 - Combination of platinum with a new agent is proven superior to platinum alone
- 2000's
 - Plateau reached with two-drug combinations
 - Targeted agents enter the treatment arena



Selection of Therapy

- Since many regimens with comparable benefits were available, treatment for an individual patient was based on:
 - Side effects profile of the medication
 - Patient's functional status
 - Pre-existing medical conditions
 - Ease of schedule
 - Patient choice

Pemetrexed (Alimta): A New Chemotherapeutic Agent



Scagliotti et al, J Clin Oncol, 2008

Pemetrexed (Alimta): Indications

- Approved for treatment of NSCLC in the following settings
 - First line therapy
 - Maintenance therapy
 - Second line therapy
 - A very well tolerated chemotherapy agent
- Not for use in:
 - Squamous histology
 - Patients with severe renal dysfunction

Overcoming NSCLC Treatment Plateau

- Improving therapeutic regimens
 - Novel cytotoxic and targeted agents
 - Optimization of current regimens/modalities
- Individualizing therapy
 - No more “one size fits all” approach for advanced NSCLC
 - Recent data indicate that specific patient characteristics may predict response and outcome to therapy
 - Treatment selection based on
 - Tumor histology
 - Biomarker expression

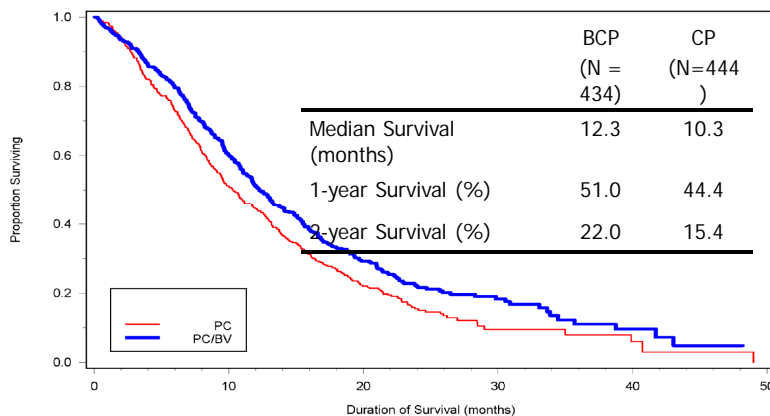
Targeted Therapies: Limited Initial Success

TARGET	AGENT	CT	OUTCOME
EGFR	gefitinib	PC	No benefit
	erlotinib	PC	No benefit
MMP's	AG3340	PC	No benefit
	BMS275291	PC	No benefit
FT (ras)	lonafarnib	PC	No benefit
PKC α	ISIS 3521	PC	No benefit
RXR	Bexarotene	PC	No benefit

Anti-Angiogenic Therapy

- Tumors require new blood supply to grow and metastasize
- Interruption of blood supply can cause regression of cancer
- Treatments targeted against VEGF, an important mediator of new blood vessel formation have proven to be beneficial
 - Bevacizumab (Avastin)
 - Other new agents under clinical testing

ECOG 4599: Avastin Improves Survival

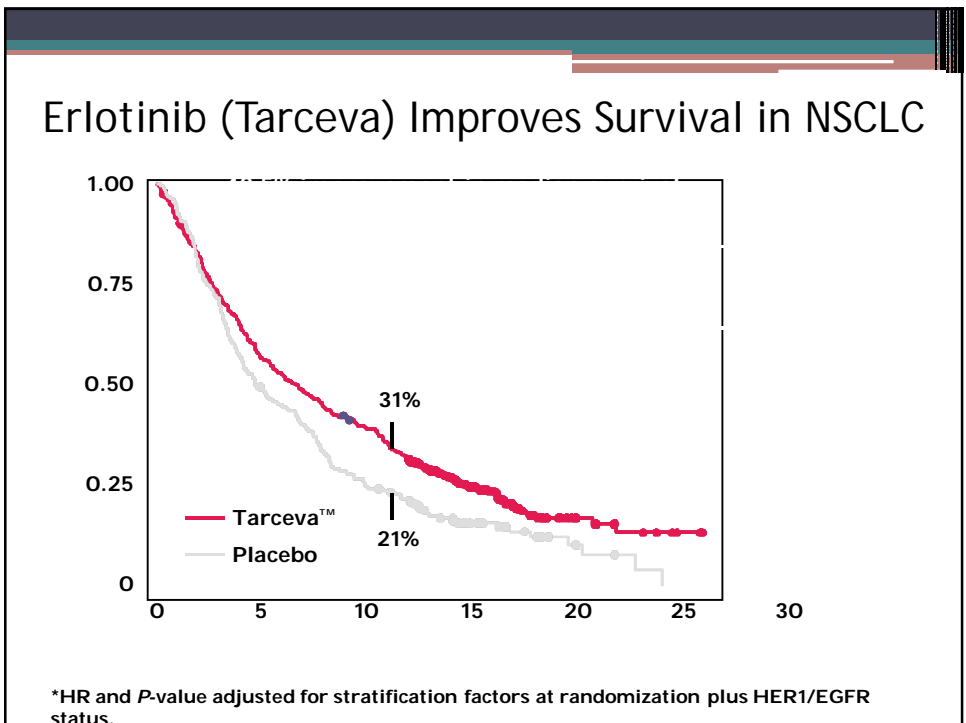
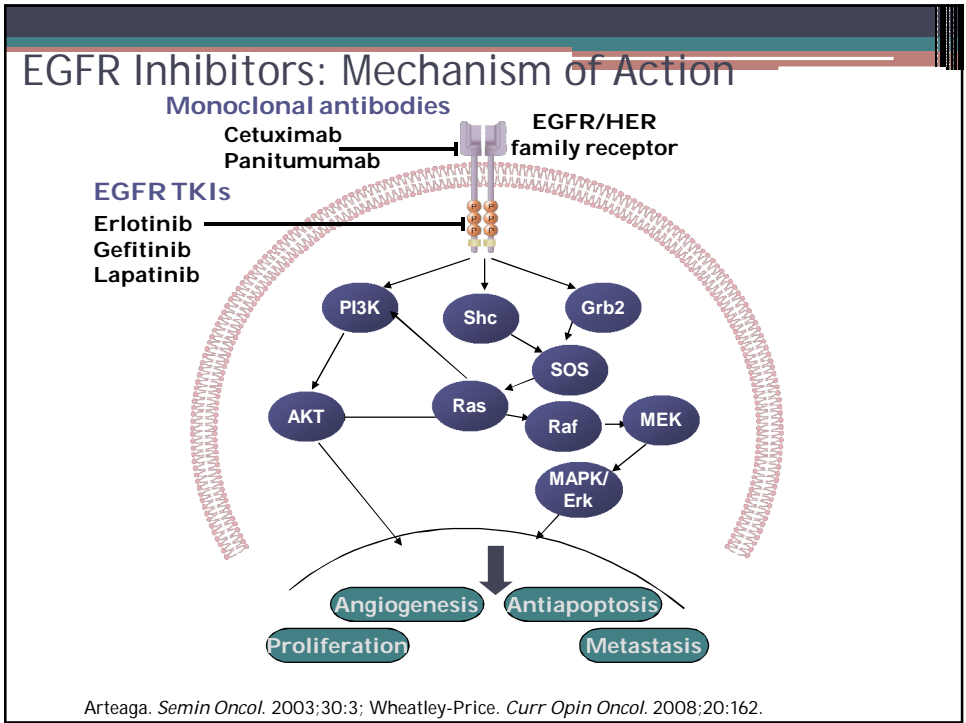


Avastin: Not for All

- Higher risk of bleeding and suppression of bone marrow
- Not recommended in:
 - Squamous histology
 - Patients with recent arterial blood clots
 - Uncontrolled high blood pressure
- Higher risk of side effects with increasing age

Targeting EGFR

- The epidermal growth factor receptor (EGFR) pathway is critical for cancer cells
- Interruption of EGFR has become a proven strategy for the treatment of a variety of cancers
- This pathway is important for Non-small cell lung cancer



Tarceva: Who Benefits from Therapy?

- Clinical benefit is noted across a broad group of patients
- However, robust responses are seen in:
 - Women
 - Adenocarcinoma histology
 - Never-smokers (less than 100 cigarettes)
 - Asian ethnicity
- Why do these groups do well?

EGFR Mutation

The NEW ENGLAND
JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 20, 2004 VOL. 350 NO. 21

Activating Mutations in the Epidermal Growth Factor
Receptor Underlying Responsiveness of Non-Small-Cell
Lung Cancer to Gefitinib

Thomas J. Lynch, M.D., Daphne W. Bell, Ph.D., Raffaella Sordella, Ph.D., Saraida Gurubhagavatula, M.D.,
Ross A. Okimoto, B.S., Brian W. Brannigan, B.A., Patricia L. Harris, M.S., Sara M. Haegert, B.A.,
Jeffrey G. Supko, Ph.D., Frank G. Haluska, M.D., Ph.D., David N. Louis, M.D., David C. Christiani, M.D.,
Jeff Settleman, Ph.D., and Daniel A. Haber, M.D., Ph.D.

Science**express**

Report

EGFR Mutations in Lung Cancer: Correlation with Clinical Response to Gefitinib Therapy

J. Guillermo Paez,^{1,2*} Pasi A. Jänne,^{1,2*} Jeffrey C. Lee,^{1,3*} Sean Tracy,¹ Heidi Greulich,^{1,2} Stacey Gabriel,⁴
Paula Herman,¹ Frederic J. Kaye,⁵ Neal Lindeman,⁶ Titus J. Boggon,^{1,3} Katsuhiko Naoki,¹ Hidefumi Sasaki,⁷
Yoshitaka Fujii,⁷ Michael J. Eck,^{1,3} William R. Sellers,^{1,2,4†} Bruce E. Johnson,^{1,2†} Matthew Meyerson^{1,3,4†}

Who has an EGFR Mutation?

- Women (Approximately 20%)
- Asian ethnicity (30-40%)
- Never-smokers (40%)
- Adenocarcinoma histology (20%)

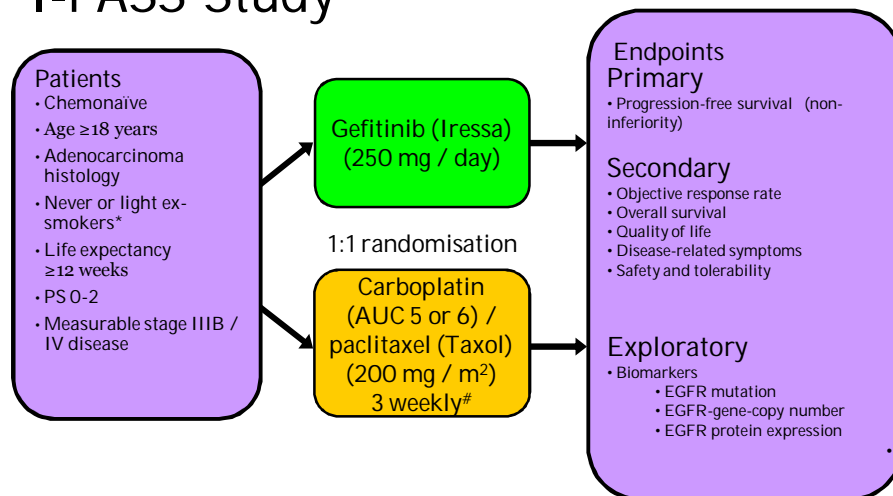
Who Should be Tested for EGFR Mutation?

- The test is commercially available
- Can add an additional cost
- It could take 2-4 weeks to get the results of the test
- It is not practicable to obtain the test in everyone
- Never-smokers, adenocarcinoma, Asians and women are tested for EGFR mutation

Is it Good to Have an EGFR Mutation?

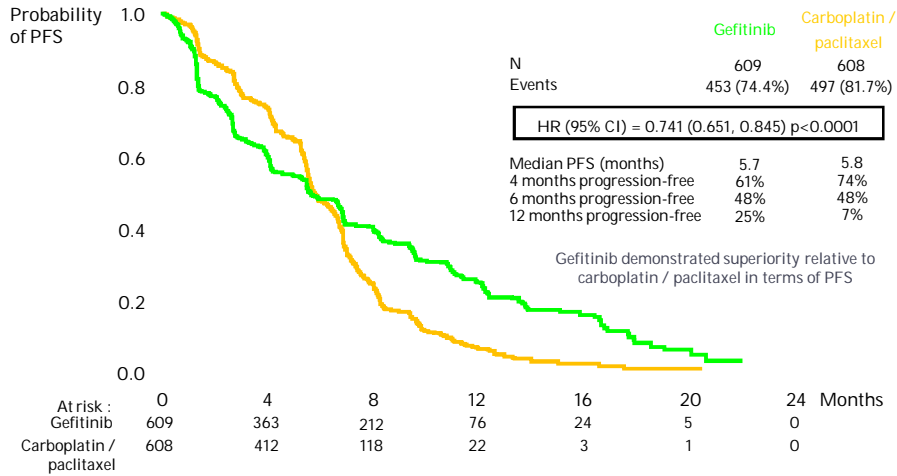
- Yes
- Erlotinib works very well in patients with EGFR mutation
 - Response rate of 60-80%
 - Survival duration of > 2 years
- Even chemotherapy works better in patients with EGFR mutation

I-PASS Study



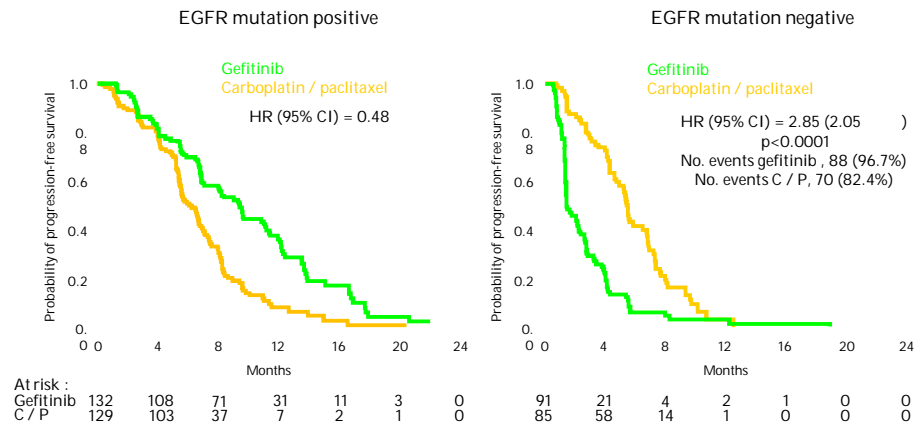
*Never smokers, <100 cigarettes in lifetime; light ex-smokers, stopped ≥15 years ago and smoked ≤10 pack years; #limited to a maximum of 6 cycles
 Carboplatin / paclitaxel was offered to gefitinib patients upon progression
 PS, performance status; EGFR, epidermal growth factor receptor

Progression-free survival



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

Progression-free survival in EGFR mutation positive and negative patients



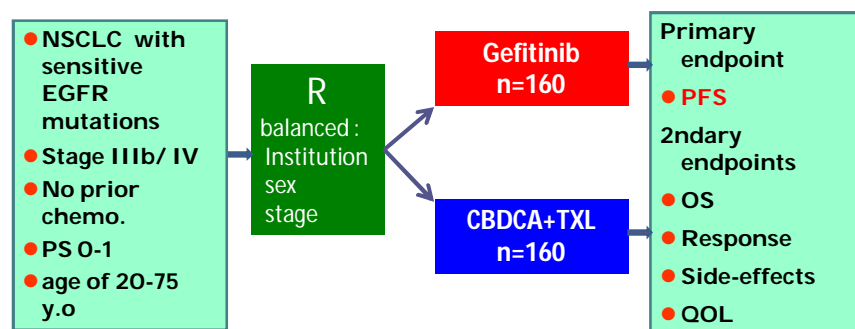
Treatment by subgroup interaction test, p<0.0001

ITT population
Cox analysis with covariates

IPASS Study: Implications

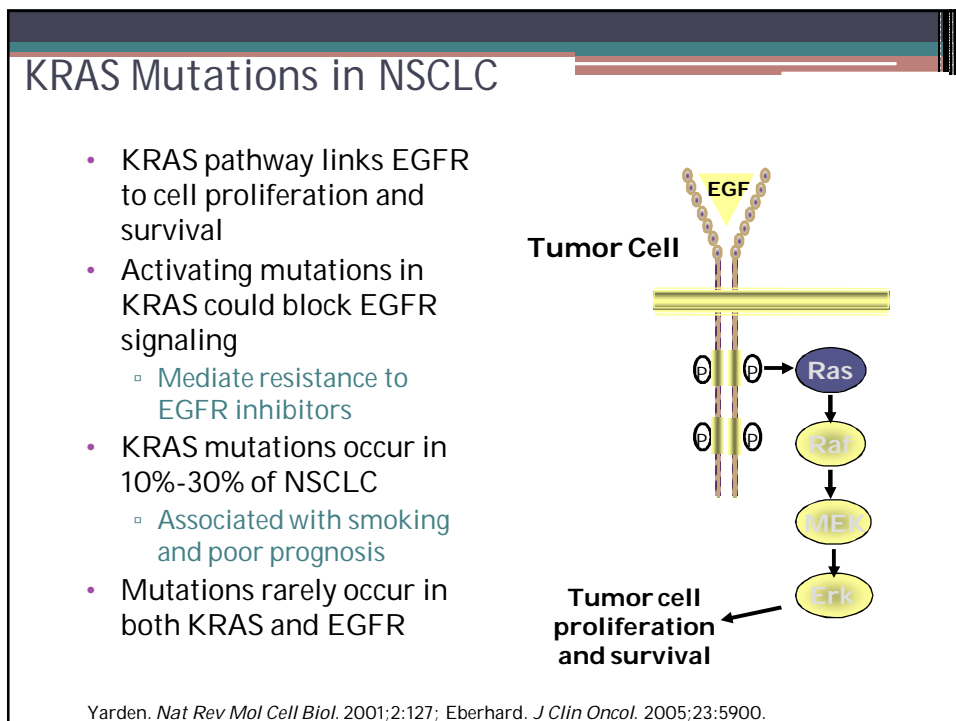
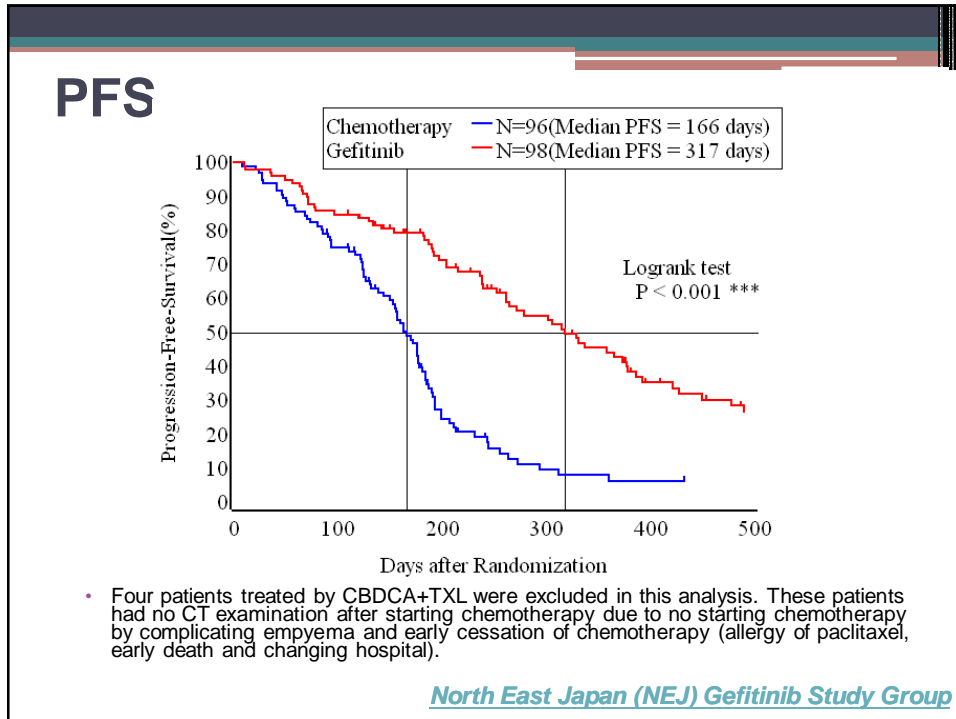
- Molecular selection is a major determinant of outcome with EGFR inhibitors
- EGFR inhibition is superior to chemotherapy in patients with mutated EGFR
- Screening for EGFR mutation if EGFR inhibitors are considered for first line therapy
- Overall survival was not different
 - This means that benefit with EGFR inhibitors in preserved regardless of use in either first line or second line therapy

NEJ002 Study

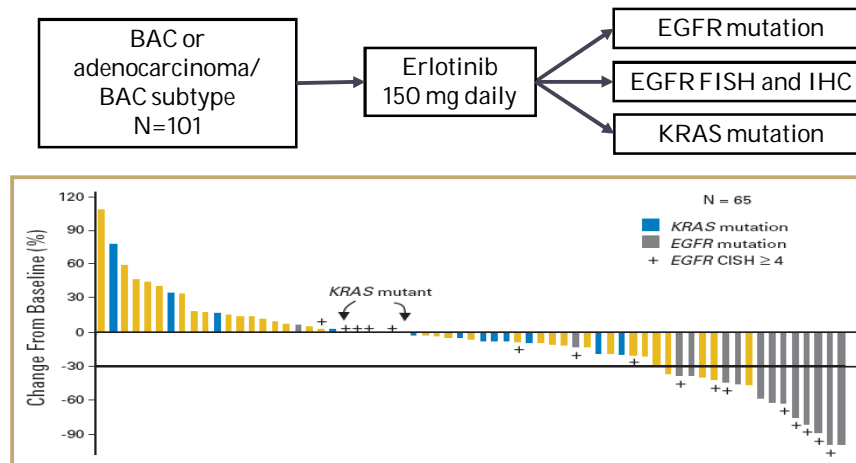


- The sample size was calculated to be 320 in total (alpha=5%, power=80%) to confirm the superiority of Arm A (hazard ratio = 0.69).
- An interim analysis to investigate PFS was planned 4 months after 200 pts were entered .

North East Japan (NEJ) Gefitinib Study Group



Effect of KRAS on Response to Erlotinib



Several patients with KRAS mutation have stable disease or even minor responses (which very likely correlate with modest clinical benefit)

Miller. *J Clin Oncol*. 2008;26:1472.

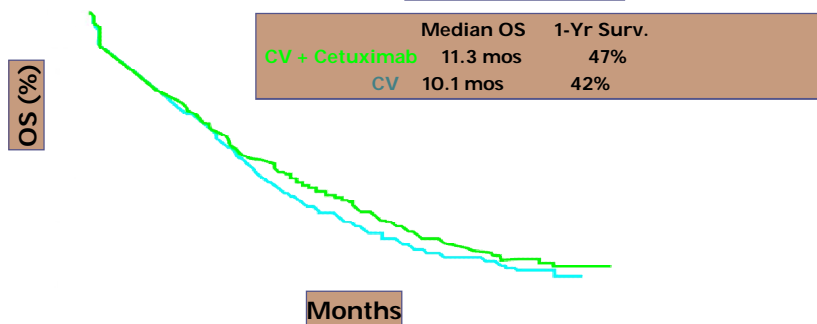
Why do Tumors Become Resistant to EGFR Inhibitors?

- Tumors develop secondary mutations after sustained exposure to EGFR inhibitors
- Tumors develop alternate pathways to overcome EGFR inhibition
- New agents are being tested for patients with secondary resistance to erlotinib (Tarceva)

Antibodies Against EGFR

- These agents block the external surface of the receptor
 - Cetuximab (Erbix)
 - Panitumumab (Vectibix)

Erbix (Cetuximab) Improves Survival



	CV + Cetuximab	CV	P
RR	36%	29%	0.012
PFS	4.8 mos	4.8 mos	NS
TTF	4.2 mos	3.7 mos	0.015

No difference in survival between adenocarcinoma and SCC in Caucasians

TTF=time to treatment failure.

Pirker. ASCO. 2008 (abstr 3).

Cetuximab (Erbix): Current Status

- Not currently approved by the FDA
- The benefit was modest, but was present in squamous and adenocarcinoma
- Has demonstrated promising results when given in combination with radiation therapy for patients with inoperable, locally advanced NSCLC

EML-4/ALK Translocation

- A molecular abnormality reported recently
- Present in 3-4% of all cases of NSCLC
- Patients likely to have this:
 - Never-smokers
 - Younger patients
 - Males
 - Adenocarcinoma (with signet cell features)

Why is This Relevant Today?

- A new drug that blocks this pathway is under clinical testing (Pfizer)
- It has demonstrated responses in 65% of patients with this molecular abnormality
- Not available outside of a clinical trial

Clinical Trials

- The only way new treatment advances are brought to routine practice is by conducting clinical trials
- Only about 3-4% of adults with cancer are treated on clinical trials
- If we doubled the number of patients enrolled on trials, the time to discovery of new medicines can be cut to half
- Several common myths hinder patient from entering trials

What Role Can you Play?

- Continue to be champions for lung cancer research
- Be advocates for smoking cessation
- Educate children against taking up cigarette smoking
- Support family members and friends

In Closing

- Treatment of NSCLC is moving from an empiric approach to individualized approaches
- The landscape of NSCLC is changing rapidly

Acknowledgements

- Patients and families
- Dr. Jack West
 - I have known him for several years and have first-hand knowledge of his passion for advancing Cancer Education
- Physicians, researchers and other allied staff that dedicate their time and efforts
- The Internet

We depend on your support to continue GRACE educational programs like these.

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