
Never-Smokers with Lung Cancer: A Compelling Story for a Distinct Disease



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In Memory of Zhuan Mike Chen

A never-smoking victim of lung cancer who fought not only for himself but to improve our understanding and treatment for others facing this disease

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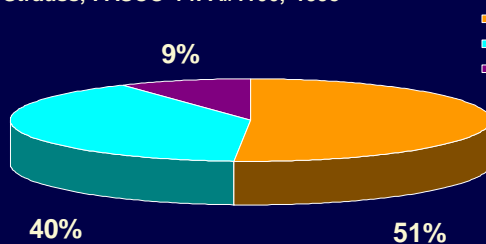
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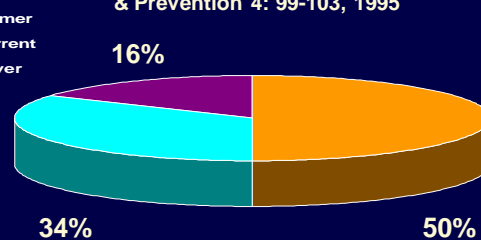
Smoking Status at Time of Diagnosis

- Never-smoker: <100 cigarettes lifetime
- Prior smoker: quit > 1 year before Dx
- Current smoker: ongoing or quit < 1 yr before Dx

Strauss, PASCO 14: A#1106, 1995



Spitz: Cancer, Epidemiol, Biomarkers, & Prevention 4: 99-103, 1995

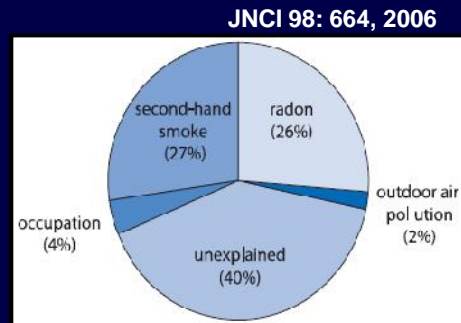


~20-25,000 new cases in US each year



Never-Smokers with Lung Cancer

- Seen in up to 1/3 of lung cancer cases in Asia
- Disproportionately seen in women, unlike lung cancer in general
- Overwhelmingly adenocarcinoma, often bronchioloalveolar carcinoma (BAC) or adeno/BAC
- Among never-smokers, environmental tobacco smoke (passive exposure), radon, occupational exposures, cooking oils, and often “unknown” factors are considered as contributing causes
- Much remains unknown about underlying causes of lung cancer among never-smokers



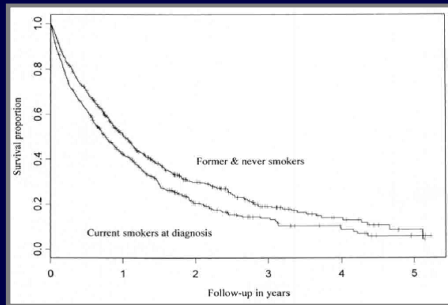
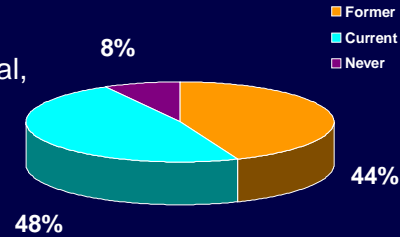
Comparison of Gene Expression in Smoker vs. Non-Smoker Adenocarcinomas

- Malignant and non-malignant tissue from 6 smoker and 6 NS lung adenocarcinomas
- **4x** as many genes changed between non-tumor and tumor lung in NS than in smokers
- This suggests that adenoCa evolves very locally in NS but as a field effect in smokers
 - non-involved lung in smokers looks more like smoker tumor than like NS lung
- Small numbers, but provocative



Smoking and Lung Cancer Survival: Multivariate Analysis

- 1155 pts, Henry Ford Hosp., 1995-1998
- Smoking assoc'd w/worse lung cancer survival, but also
 - Higher comorbidities
 - Worse nutrition
 - Less treatment...



Significant difference in survival, even with analysis separating effect of smoking status compared with other correlated variables.

Tammemagi, Chest 2004



Improved Survival in AdenoCa NSCLC Among Never-Smokers vs. Current Smokers

- Moffitt experience, 132 NS vs. 522 current smokers w/adeno NSCLC
- More women in NS group (78% vs. 54%, $p < 0.0001$)
- BAC seen in 24% of non-smokers, 10% of smokers with adenoCa
- Significantly superior survival in NS
 - Overall surv at 5 years: 23% vs. 16% ($p = 0.004$)
 - Cancer-specific survival at 5 years: 28% vs. 22% ($p = 0.018$)
- Remains significant in multivariate analysis

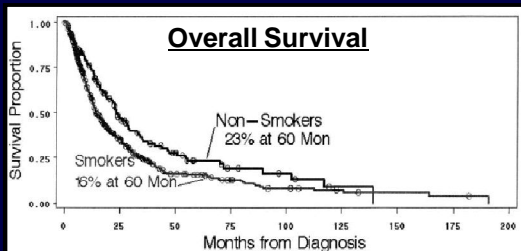


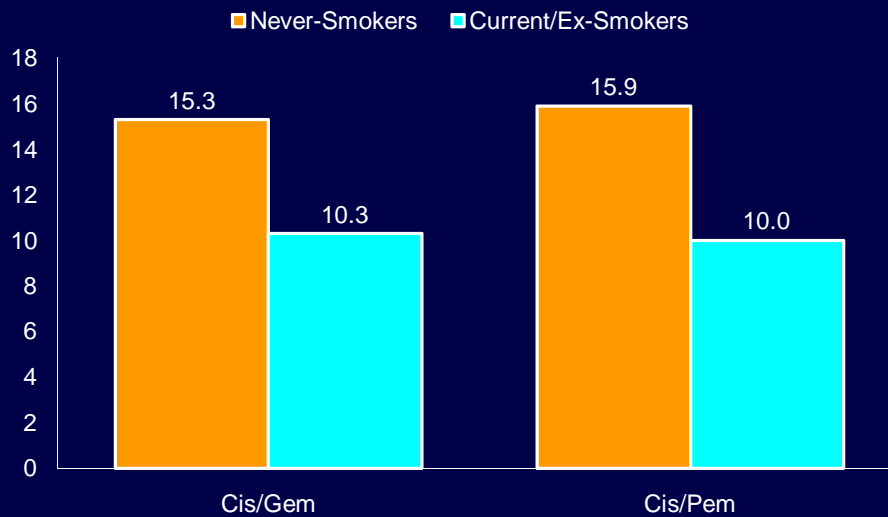
Table 2—Multivariate Analyses of Factors Related to Overall Survival

Variables	p Value	Hazard Ratio	95% Confidence Interval
Male vs female gender	0.0185	1.255	1.039-1.515
Current vs never-smokers	0.0246	1.325	1.037-1.693
Increasing stage	< 0.0001	1.559	1.635-2.051

Nordquist, Chest 2004, 126: 347-351



Longer Survival with Chemo for Never-Smokers: Cisplatin/Gemcitabine vs. Cisplatin/Pemetrexed



Scagliotti, J Clin Oncol 2008



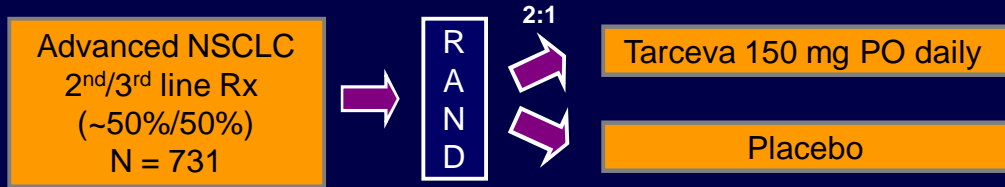
Clinical Factors Predicting Gefitinib Sensitivity: MSKCC Single Agent Data

- 1997-2002, 139 Pts, 21 Partial Responses (15%)
- **Univariate Prognostic Factors**
 - **Never Smokers** vs Former/Current –36% vs 8%, $p < 0.001$
 - AdenoCa vs Other Histologies -21% vs 0%, $p < 0.001$
 - Bronchioloalveolar vs Other AdenoCa –37% vs 15%, $p < 0.001$
 - Female Gender -19% vs 8%, $p = 0.14$
- **Multivariate Prognostic Factors**
 - **Never Smokers** vs Former/Current ($p = 0.005$)
 - Bronchioloalveolar vs Other AdenoCa ($p = 0.007$)

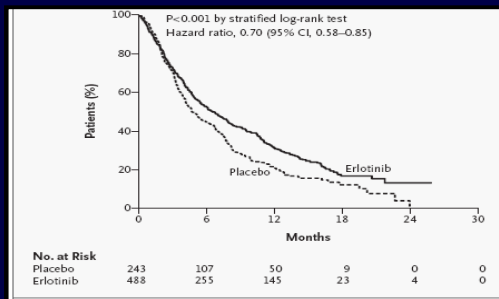
Miller, J Clin Oncol 2004



NCI Canada BR.21 Erlotinib (Tarceva) vs. Placebo in Adv. NSCLC



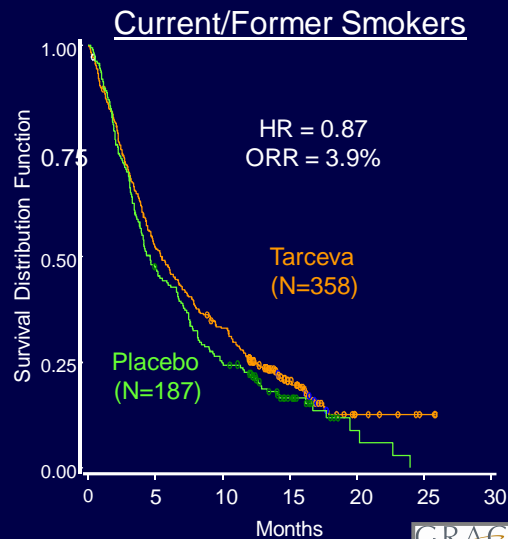
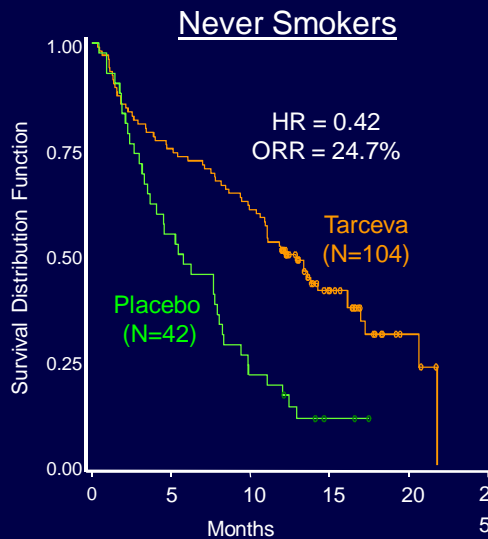
Overall Survival



Shepherd,
NEJM 2005



BR.21 (Erlotinib vs. Placebo, 2nd/3rd Line): Survival Benefit by Smoking Status



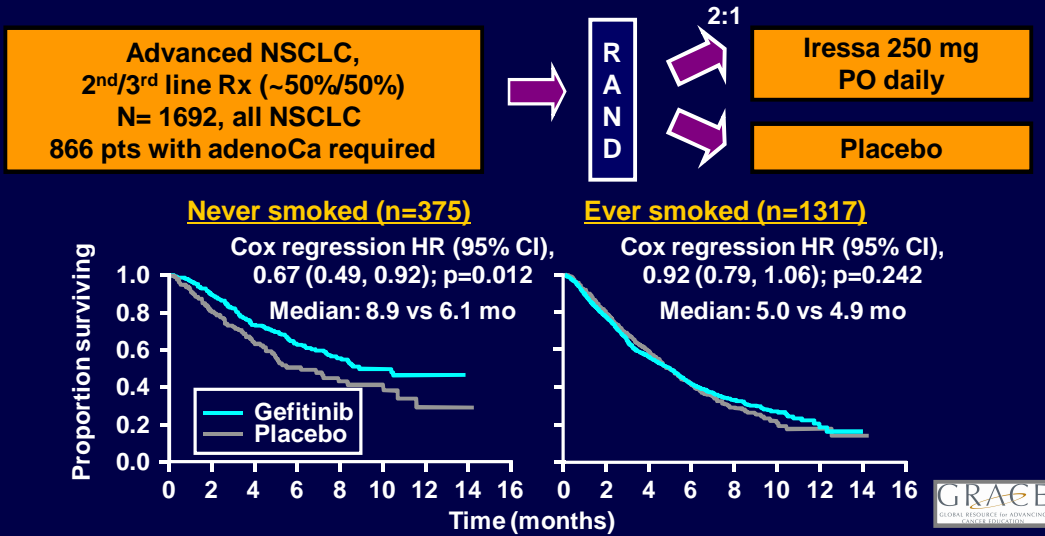
OSI Pharmaceuticals, Data on File



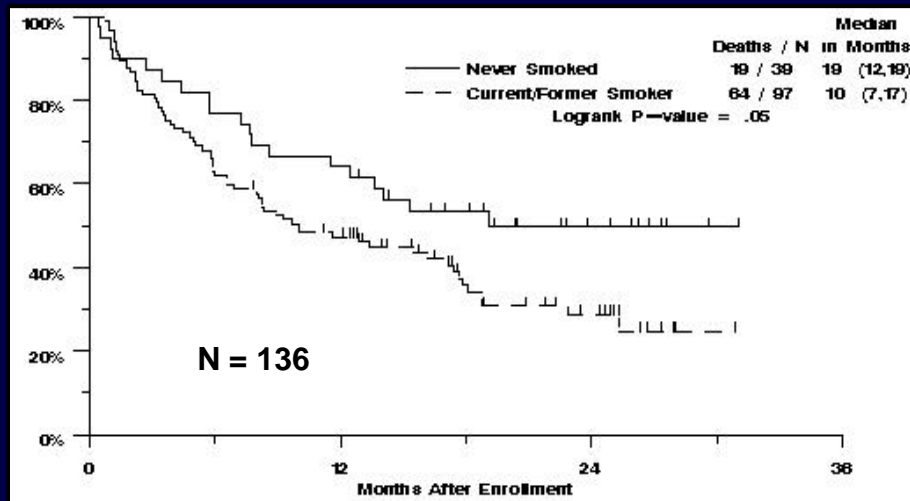
Gefitinib (Iressa) in Pre-Treated Advanced NSCLC: Outcome by Smoking Status

Thatcher, Lancet 2005

Iressa Survival Eval. in Lung Cancer (ISEL) Trial



S0126: Gefitinib (Iressa) in Advanced BAC, Overall Survival by Smoking Status



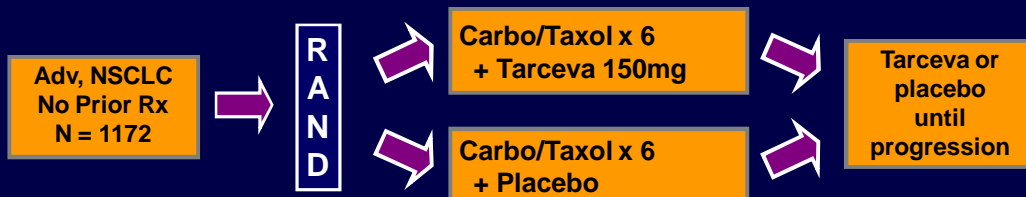
West, J Clin Oncol 2006

Phase II Trial of Erlotinib (Tarceva) in BAC: Clinical Variables

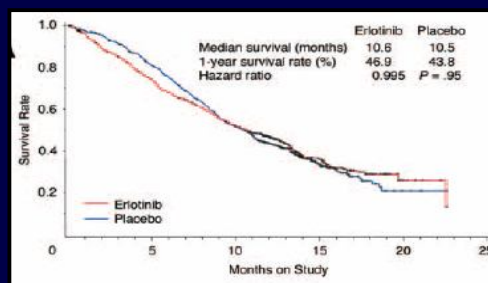
Variable	Resp. Rate
Non-Smokers	45%
Former/CurrentSmokers	18%
Women	27%
Men	17%
No rash	0%
Rash	35%
Chemo-naive	21%
Prior Chemo	35%
Pure BAC	11%
Other BAC	29%

Kris, PASCO 2004

TRIBUTE Trial: Chemo +/- Erlotinib in First-Line Advanced NSCLC



Overall Survival

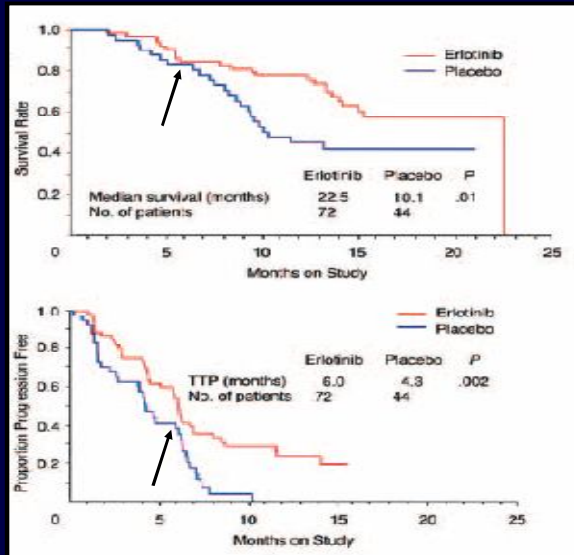


Herbst,
J Clin Oncol 2005

TRIBUTE Trial (Chemo +/- Erlotinib) in First-Line NSCLC: Non-Smokers

Overall Survival

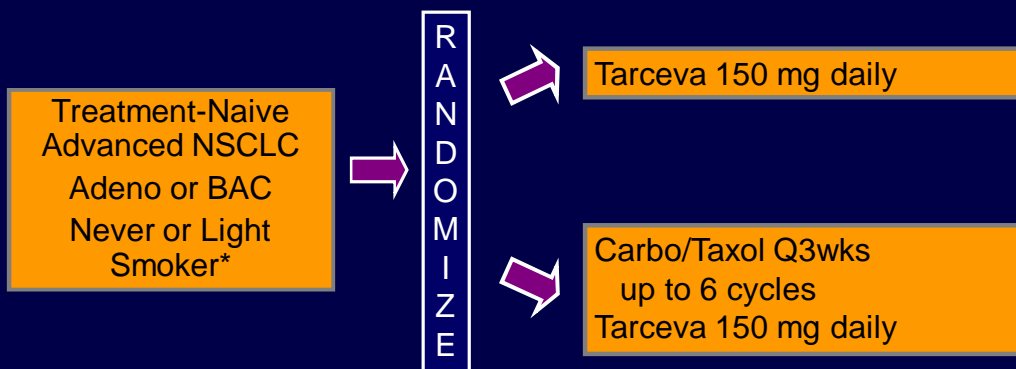
Progression-Free Survival



Herbst, JCO 2005, 23; 5892-5299

CALGB 30406: Randomized Phase II in Never or Light Smokers (Ongoing)

Principal Investigator – Pasi Jänne



Patients continue Tarceva until disease progression

*never smoker: ≤ 100 cigarettes/lifetime; "light" former smoker: quit ≥ 1 year ago and ≤ 10 pack years

Conclusions on Never-Smokers with Lung Cancer

- Distinct epidemiologic profile for non-smokers with lung cancer
 - Disproportionately Asian populations, women > men
- Distinct pathologic and molecular profile for non-smokers with lung cancer
 - Most commonly adenocarcinoma, BAC
 - typically genetically simpler cancer than in smokers
- Distinct clinical outcomes for non-smokers with lung cancer
 - Longer survival overall, with standard chemotherapy, & targeted therapies
- EGFR-TKIs clearly separates never-smokers
 - Subset with greatest benefit in positive trials
 - Subset with significant benefit in negative trials
 - Seen with both Tarceva & Iressa; single agent trials & combinations w/chemo
- Increasing number of studies for never-smokers
- **KEY QUESTION:** Is never-smoking status the central variable or correlated with molecular variable(s) that drives different biological behavior?



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www.CancerGrace.org/lung/

- GRACE members can leave comments and questions at

www.tinyurl.com/GRACENSLungCA

