5 Minute JournalClub

Key ASCO Presentations
Issue 7, 2010

First-Line Erlotinib with or without Chemotherapy for Never or Light Smokers with Advanced Non-Small Cell Lung Cancer (NSCLC)

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CME INFORMATION

OVERVIEW OF ACTIVITY

Each year, thousands of clinicians and basic scientists sojourn to the American Society of Clinical Oncology (ASCO) Annual Meeting to learn about recent clinical advances that yield alterations in state-of-the-art management for all tumor types. Attracting tens of thousands of attendees from every corner of the globe to both unveil and digest the latest research, ASCO is unmatched in attendance and clinical relevance. Results presented from ongoing trials lead to the emergence of new therapeutic agents and changes in the indications for existing treatments across all cancer medicine. Despite the importance of the conference, the demands of routine practice often limit the amount of time oncology clinicians can realistically dedicate to travel and learning. To bridge the gap between research and patient care, this CME activity will deliver a serial review of the key presentations from the ASCO Annual Meeting and expert perspectives on how these new evidence-based concepts can be applied to routine clinical care. This activity will assist medical oncologists and other cancer clinicians in the formulation of optimal clinical management strategies for patients with diverse forms of cancer.

LEARNING OBJECTIVE

- Compare and contrast the value of EGFR mutation status versus former smoking status in the accurate identification of patients likely to benefit from first-line EGFR tyrosine kinase inhibitor therapy, with or without concurrent chemotherapy.

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FACULTY — The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process:

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Advisory Committee: Amgen Inc, AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, Lilly USA LLC; Consulting Agreements: Amgen Inc, AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, Genentech BioOncology, Lilly USA LLC, SynDevRx Inc; Paid Research: Amgen Inc, AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, Genentech BioOncology, Geron, Novartis Pharmaceuticals Corporation, Oncothyreon, OSI Oncology, Sanofi-Aventis.

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Data and Safety Monitoring Board: Bayer HealthCare Pharmaceuticals; Paid Research: Abraxis BioScience, Celgene Corporation, Genentech BioOncology, GlaxoSmithKline, Lilly USA LLC, Pfizer Inc; Speakers Bureau: Genentech BioOncology, GlaxoSmithKline, Lilly USA LLC, Sanofi-Aventis.

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To go directly to the slides and commentary, **click here**.

Last Friday we hosted our annual daylong lung cancer Think Tank with seven renowned investigators, co-chaired by Tom Lynch (be on the lookout for the highlights audio program). One of the main objectives of this closed "recording session" was to review data sets from Chicago, and this dizzying scientific chat included discussion of the following work profiled in the enclosed slide sets:

1. **Crizotinib in patients with EML4-ALK mutations**
An update of the stunning Phase I-II data first presented at ASCO '09 included impressive waterfall plots in which almost all patients had reduced tumor sizes with this not-yet available agent. Approximately four to five percent of patients harbor this newly described translocation that fits the classic oncogene addiction model, and at the Think Tank Dr Lynch described one such individual from his practice who entered this study with substantial symptomatic tumor burden and is still in response two years later. All in attendance agreed on the urgency of making this agent available and of standardizing and disseminating the assay technology, but the faculty was unsure how long this will actually take.

2. **EGFR TKIs versus chemotherapy for patients with EGFR mutations**
A CALGB trial in first-line *metastatic* disease reinforced recent study results clearly demonstrating that a TKI without chemo is preferred for these patients. In contrast, the confusing and incomplete **BR19 trial** suggested the possibility that in the *adjuvant* setting, not only would EGFR TKIs not be beneficial, but for very much unknown reasons they could also be detrimental. Specifically because of this and one prior Stage III data set, there was a strong sentiment among the Think Tank investigators not to use these agents as adjuvant therapy outside a protocol setting.

By the end of this amazing day, it was apparent that a new tissue-based algorithm for systemic treatment of advanced non-small cell lung cancer was on the table. Specifically, the faculty endorsed the baseline evaluation for patients with adequate tumor specimens for EGFR and EML4-ALK mutations and maybe K-ras, which might be predictive of benefit with sorafenib. For patients with needle biopsies without the necessary tumor quantity to conduct these assays, the decision regarding rebiopsy must be individualized based on smoking history, site of disease and performance status. Ed Kim, who first reported his landmark "BATTLE" trial at AACR — followed by

more data from Roy Herbst at ASCO — cautioned that core biopsies by interventional radiology are much more likely to yield adequate tissue than those obtained by bronchoscopy. After hearing MD Anderson coinvestigator John Heymach comment on the unprecedented translational data in BATTLE, it was clear this was the future paradigm of lung cancer research.

3. **Palliative (supportive) care extends survival in the advanced disease setting**
In what some view as the biggest surprise of ASCO, a Harvard randomized trial demonstrated marked OS increases for patients who visited a palliative care specialist about once a month. Dr Lynch had a number of patients in this study and believes the benefits were primarily the result of better management of depression, anxiety and "existential angst." All agreed that "If this was a drug, we'd use it." How to get this advance to patients is unclear.

4. **Older patients may benefit from doublet chemotherapy in first-line advanced disease**
This **plenary presentation** confirmed an emerging theme within oncology: Older patients who can safely tolerate standard therapy derive the same benefits as younger patients.

Next up on our final ASCO issue of 5-Minute Journal Club: GI cancers and a provocative study in pancreatic cancer.

Neil Love, MD
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This program is supported by educational grants from Bristol-Myers Squibb Company, Celgene Corporation, Genentech BioOncology and Millennium Pharmaceuticals Inc.

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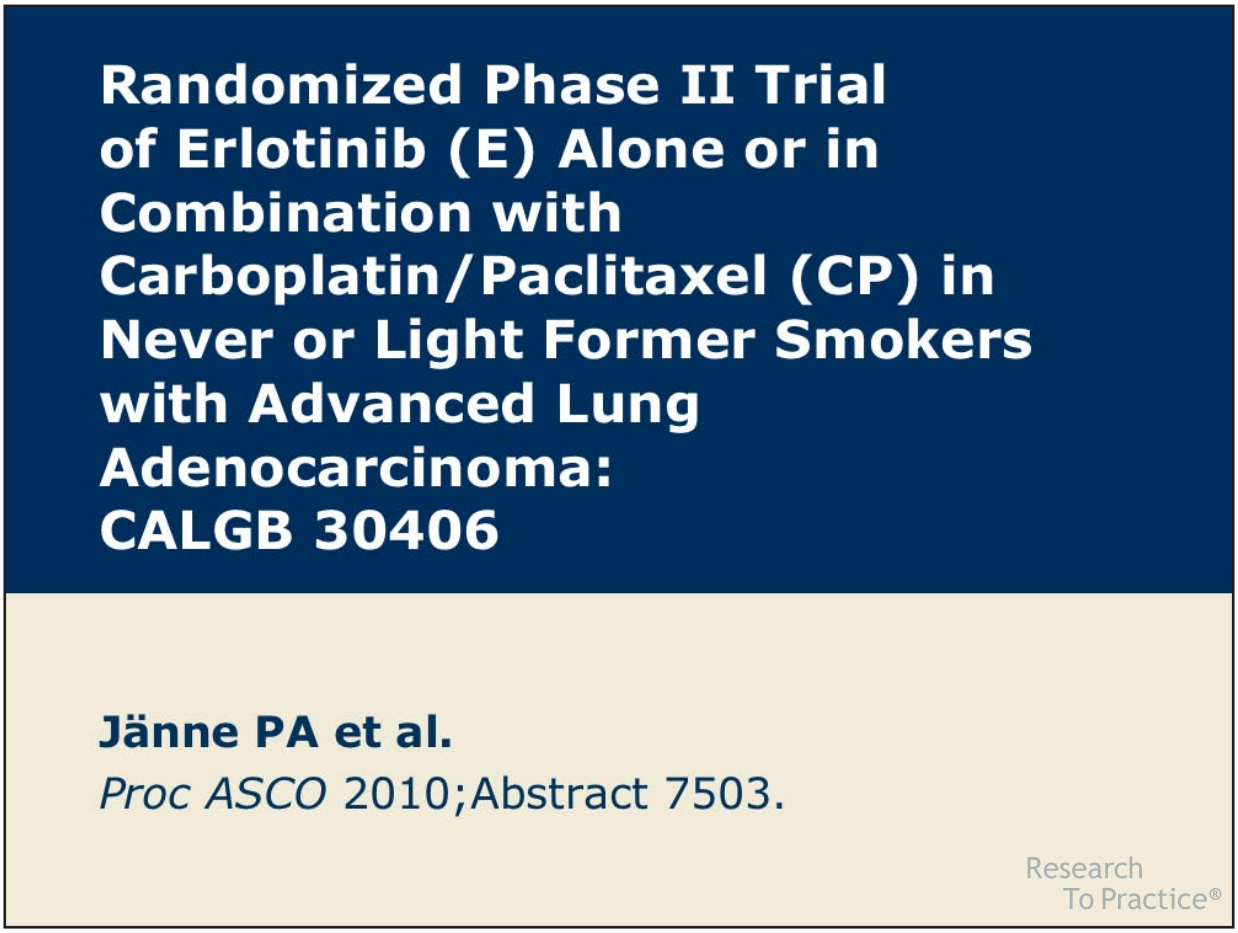
First-Line Erlotinib with or without Chemotherapy for Never or Light Smokers with Advanced Non-Small Cell Lung Cancer (NSCLC)

Presentation discussed in this issue

Jänne PA et al. **Randomized phase II trial of erlotinib (E) alone or in combination with carboplatin/paclitaxel (CP) in never or light former smokers with advanced lung adenocarcinoma: CALGB 30406.** *Proc ASCO* 2010;**Abstract 7503**.

Slides from a presentation at ASCO 2010 and transcribed comments from recent interviews with Roy S Herbst, MD, PhD (6/23/10), Corey J Langer, MD (7/2/10) and Mark A Socinski, MD (6/4/10)



Introduction

- The efficacy of EGFR tyrosine kinase inhibitors (TKIs) in non-small cell lung cancer (NSCLC) is greatest in patients with EGFR mutations.
- Single-agent activity of EGFR TKIs in EGFR mutation-positive NSCLC (*NEJM* 2009;361:947; *NEJM* 2009;361:958)
  - 1st-line response rate (RR): 60-80%
  - 1st-line progression-free survival (PFS): 10-14 months
- Gefitinib is superior to 1st-line chemotherapy in nonsmokers or former light smokers in East Asia (*NEJM* 2009;361:947).
- In never smokers, the addition of erlotinib (E) to chemotherapy resulted in improvement in survival, time to progression and RR in advanced NSCLC (*JCO* 2005;23:5892).
- **Current study objective:**
  - Evaluate erlotinib alone or in combination with chemotherapy as first-line therapy for never or former light smokers with advanced adenocarcinoma of the lung.

Jänne PA et al. *Proc ASCO* 2010;Abstract 7503.

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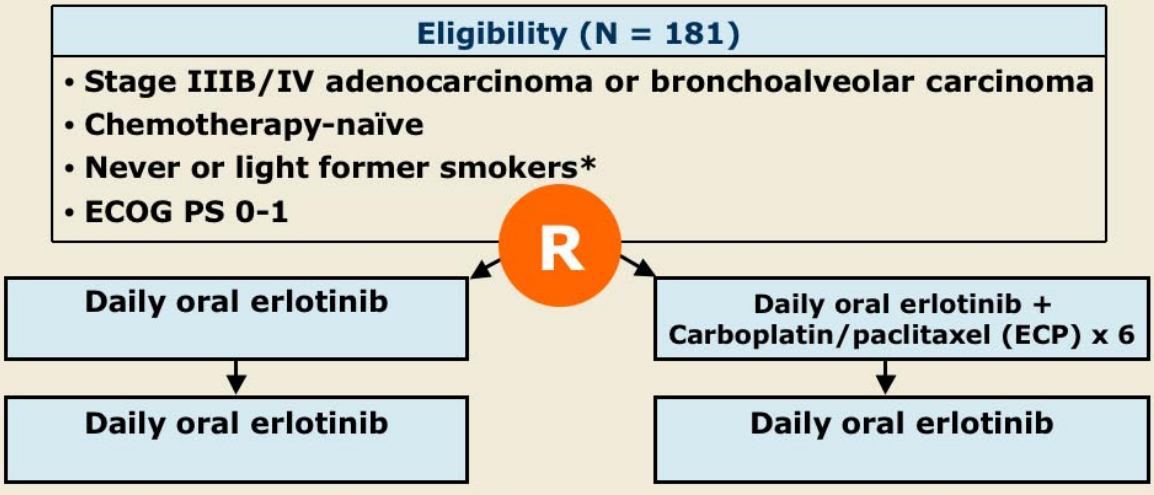
Study Design



* Never smoker: <100 cigarettes/lifetime; light former smoker: quit >1 year ago and smoked <10 pack years

Jänne PA et al. *Proc ASCO* 2010;Abstract 7503.

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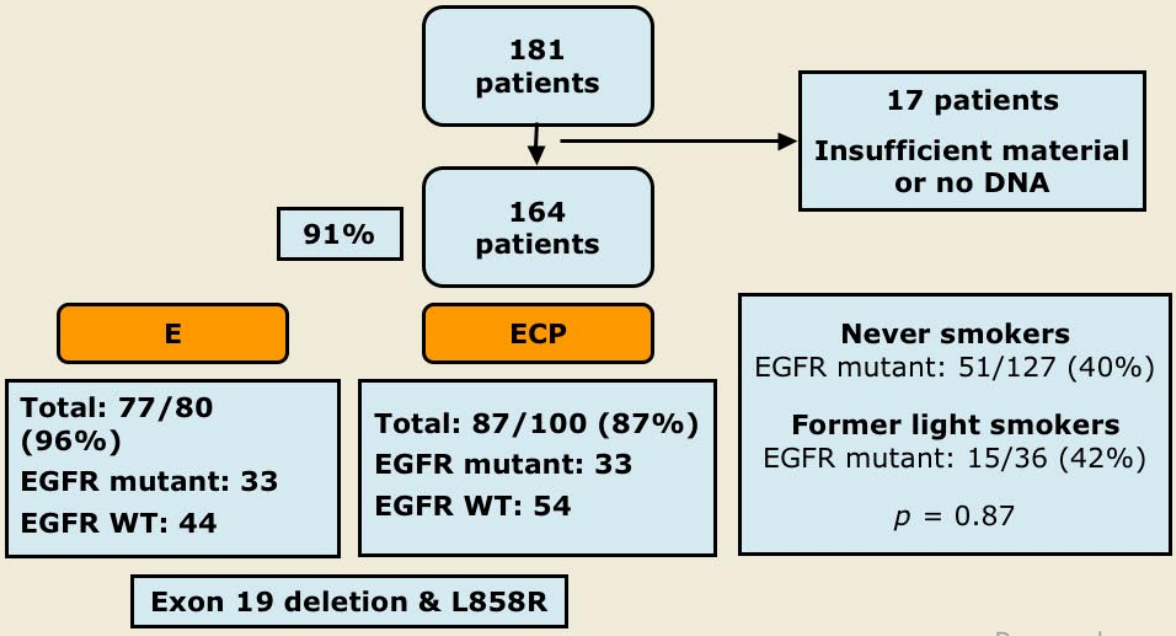
Tumor Genotyping Analyses



Jänne PA et al. *Proc ASCO* 2010;Abstract 7503.

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Efficacy Analyses by Treatment and EGFR Mutation Status

Endpoint	E	ECP
Progression-free survival (n = 81, 100)	6.7 mo	6.6 mo
EGFR mutant vs wild type*	15.7 vs 2.7 mo $p < 0.0001$	17.2 vs 4.8 mo $p < 0.0001$
Overall survival (n = 81, 100)	24.3 mo	19.6 mo
EGFR mutant vs wild type*	31.3 vs 18.1 mo $p = 0.0093$	39.0 vs 13.7 mo $p = 0.0012$
Response rate (n = 81, 100)	35%	48%
EGFR mutant vs wild type*	67% vs 9% $p < 0.0001$	73% vs 33% $p = 0.0004$

* E arm: n = 33 EGFR mutant, n = 44 EGFR wild type; ECP arm: n = 33 EGFR mutant, n = 54 EGFR wild type

Response evaluation every 2 cycles (6 weeks)

Jänne PA et al. *Proc ASCO* 2010;Abstract 7503.

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Grade 3/4 Adverse Events

Adverse Event (AE)	E (n = 81)	ECP (n = 100)
Hematologic - any	1/0	29/20
Anemia Neutropenia Febrile neutropenia Thrombocytopenia	0/0 0/0 0/0 0/0	6/0 24/17 7/3 1/4
Non-hematologic - any	18/2	38/12
Rash Diarrhea Fatigue Nausea/vomiting	6/0 4/0 1/0 1/0	10/0 6/0 16/1 7/0
Dose reductions	23%	27%
Death on study	3 (4%)	2 (2%)

Jänne PA et al. *Proc ASCO* 2010;Abstract 7503.

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Conclusions

- E and ECP yield similar outcomes in a predominantly Caucasian never smoker population of patients with NSCLC.
  - PFS = 6.6 and 6.7 mo, respectively
  - OS = 24.3 and 19.6 mo, respectively
- EGFR mutations identify patients most likely to benefit (PFS, OS, RR) from E or ECP.
- E is better tolerated than ECP.
- EGFR TKIs alone remain an acceptable first-line therapy for patients with advanced EGFR mutant NSCLC.

Jänne PA et al. *Proc ASCO* 2010;Abstract 7503.

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Investigator comment on the results of CALGB-30406: Erlotinib versus erlotinib/carboplatin/paclitaxel in never or light smokers with advanced NSCLC

As enthusiastic as we were about the IPASS data, I believe the average community oncologist wondered whether that study in an Asian population applied to US patients. Our CALGB data with mostly Caucasian, US patients largely mirrors the IPASS experience.

The rate of EGFR mutations in IPASS was 60 percent, and in the CALGB study it was 40 percent for never smokers, so a little less. However, when a molecular marker predicts for very high response and survival rates in 40 percent of your patients, then it's worth looking for that marker. These study results reinforce the concept that we should be carefully considering whom we need to test for the EGFR mutation and whether we have enough tissue or whether we should rebiopsy the tumor. The impact of this once-a-day oral EGFR TKI can be fantastic in the right patients.

Interview with Mark A Socinski, MD, June 4, 2010

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Investigator comment on the results of CALGB-30406: Erlotinib versus erlotinib/carboplatin/paclitaxel in never or light smokers with advanced NSCLC

This study was actually derived from my own work with the TRIBUTE trial, which demonstrated no improvement from adding an EGFR inhibitor to carboplatin/paclitaxel in unselected patients. However, for never smokers the median survival improved from 10.1 to 22.5 months. Today we realize that those were patients with EGFR mutations, which had not been identified when we reported.

In the current study never or former light smokers received erlotinib with or without chemotherapy. There was no difference in progression-free or overall survival in patients overall who received erlotinib alone versus the combination. The same appears to be true for patients with EGFR mutations, although those groups cannot be compared directly.

Patients who received chemotherapy and erlotinib obviously experienced more toxicity, especially anemia, neutropenia, febrile neutropenia and thrombocytopenia. So for light or never smokers, used as a surrogate for EGFR mutations, one would probably use erlotinib alone because there is no additional benefit from the addition of chemotherapy.

Interview with Roy S Herbst, MD, PhD, June 23, 2010

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Investigator comment on the results of CALGB-30406: Erlotinib versus erlotinib/carboplatin/paclitaxel in never or light smokers with advanced NSCLC

This study was based on the post hoc observation from the TRIBUTE trial, in which a subgroup of never smokers who were about 22 percent of the total population had a marvelous survival benefit, on the order of 22.5 months with the addition of the EGFR inhibitor to chemotherapy versus 10.1 months with placebo.

My one quibble with the CALGB study is that they didn't have a true control arm. Everybody received erlotinib, either alone or combined with chemotherapy. Nevertheless, patients with an EGFR mutation and advanced NSCLC who received chemotherapy with erlotinib fared quite well, with a median overall survival of 39 months. For those who received single-agent erlotinib, it was approximately 31 months. Dr Pasi Janne glossed over this difference, and the question remains: Should we administer erlotinib alone to patients with an EGFR mutation or should we interdigitate it with standard chemotherapy? Certainly the trial did not address this issue, because it made no direct comparison of outcome in patients with EGFR mutations who received erlotinib alone versus chemotherapy/erlotinib. Nonetheless, this was an excellent study, which actually mandated tissue collection.

Interview with Corey J Langer, MD, July 2, 2010