5 Minute JournalClub

Key ASCO Presentations
Issue 7, 2010

NCIC CTG BR.19: Gefitinib Therapy for Patients with Completely Resected 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 OBJECTIVES

- Evaluate the efficacy and tolerability of gefitinib monotherapy in patients with completely resected Stage IB to IIIA NSCLC.
- Describe the relationship between K-ras or EGFR mutation status and overall survival following post-operative treatment with gefitinib or placebo.

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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:

Roy S Herbst, MD, PhD
Professor of Medicine
Chief, Section of Thoracic Medical Oncology
Department of Thoracic/Head and Neck Medical Oncology
Barnhart Family Distinguished Professor in Targeted Therapies
The University of Texas MD Anderson Cancer Center
Houston, Texas

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.

Lecia V Sequist, MD, MPH
Assistant Professor of Medicine, Harvard Medical School
Center for Thoracic Cancers, Massachusetts General Hospital Cancer Center
Boston, Massachusetts

Advisory Committee: Bristol-Myers Squibb Company; Consulting Agreement: Telik Inc.

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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
Research To Practice
Miami, Florida

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

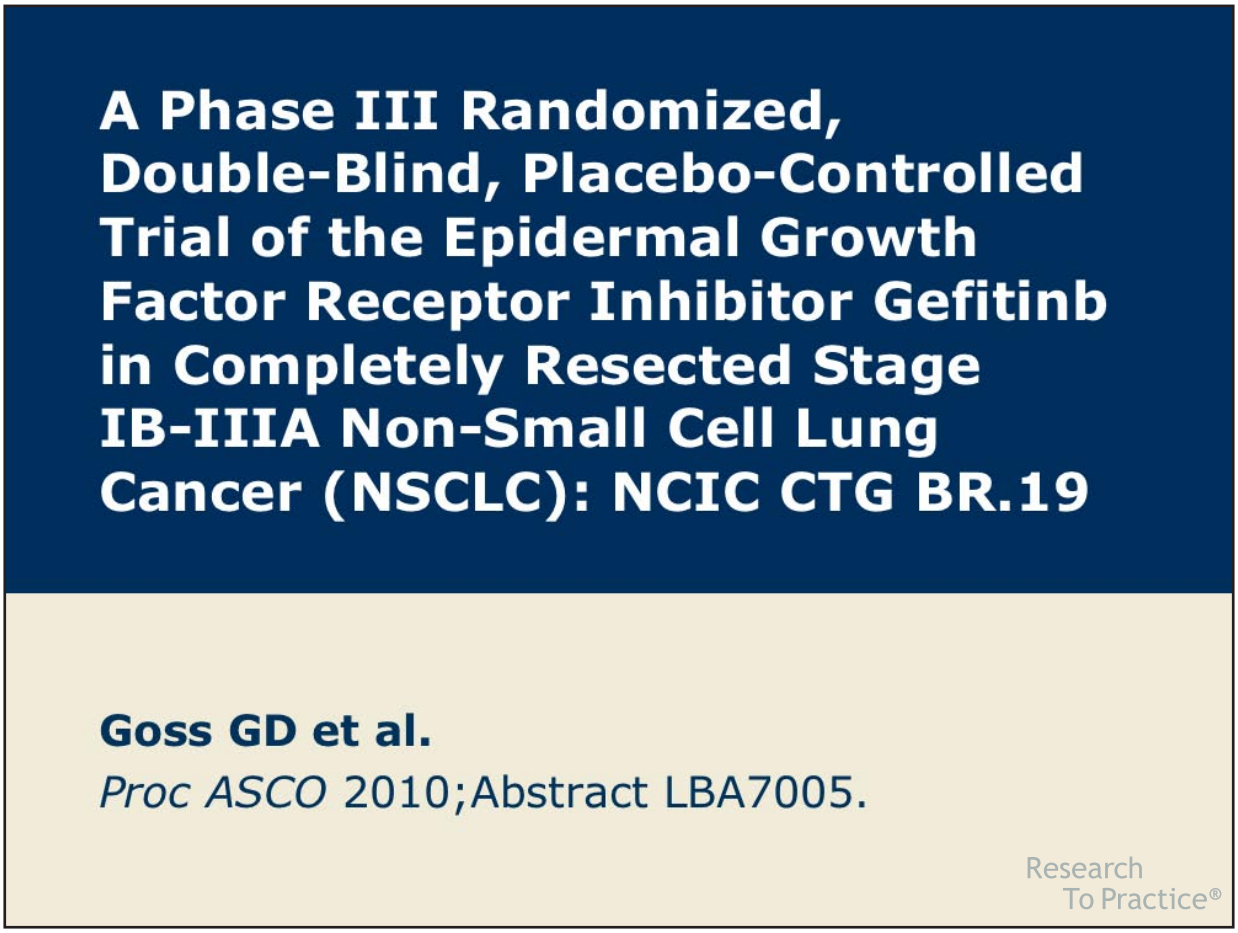
Research To Practice
One Biscayne Tower
2 South Biscayne Boulevard, Suite 3600
Miami, FL 33131

NCIC CTG BR.19: Gefitinib Therapy for Patients with Completely Resected Non-Small Cell Lung Cancer (NSCLC)

Presentation discussed in this issue

Goss GD et al. **A Phase III randomized, double-blind, placebo-controlled trial of the epidermal growth factor inhibitor gefitinib in completely resected Stage IB-IIIA non-small cell lung cancer (NSCLC): NCIC CTG BR.19.** *Proc ASCO* 2010;**Abstract LBA7005**.

Slides from a presentation ASCO 2010 and transcribed comments from recent interviews with Roy S Herbst, MD, PhD (6/23/10) and Lecia V Sequist, MD, MPH (6/18/10)



Introduction

- A 2002 meta-analysis from 52 randomized trials revealed a five percent improvement in survival at five years with adjuvant chemotherapy for patients with completely resected NSCLC (*BMJ* 1995;311:899).
- Gefitinib, an EGFR tyrosine kinase inhibitor, demonstrated activity in monotherapy trials for patients with advanced NSCLC (*Proc Am Assoc Cancer Res* 2001;42:630A).
- **Current study objectives:**
  - To investigate the efficacy and tolerability of oral gefitinib in patients with completely resected NSCLC.
  - To confirm the prognostic and predictive significance of KRAS mutation, EGFR gene expression and EGFR mutation.

Goss GD et al. *Proc ASCO* 2010;Abstract LBA7005.

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Trial Schema

Accrual: 503 (Closed)[1]

Eligibility

Resected IB, II and IIIA NSCLC ECOG PS 0-2

R

Gefitinib (n = 251) daily x 2 years

Placebo (n = 252) daily x 2 years

[1] In April 2005, accrual was closed early due to the inferiority of gefitinib arm.

Patients were stratified by stage, histology, post-operative radiation, sex and adjuvant chemotherapy.

Goss GD et al. *Proc ASCO* 2010;Abstract LBA7005.

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Overall Survival and Disease-Free Survival

	Gefitinib (n = 251)	Placebo (n = 252)	Hazard Ratio	*p*-value
Median overall survival (OS)	5.1 years	Not reached	1.23	0.136
Median disease-free survival (DFS)	4.2 years	Not reached	1.22	0.152

Multivariate analysis

- **Age ≥65 years and tumor size ≥4 cm (p = 0.0003) were significantly associated with shorter survival.**
- **Gefitinib remained not significant, but there was a trend suggesting it may be harmful (p = 0.097).**

Goss GD et al. *Proc ASCO* 2010;Abstract LBA7005.

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Exploratory Biomarker Analyses: Overall Survival (Placebo Arm)

Patient Group (n)	Hazard Ratio	*p*-value
KRAS mutant vs wild-type (n = 53, 128)	1.12	0.662
EGFR mutant vs wild-type (n = 40, 145)	1.06	0.830
EGFR FISH High polysomy vs low copy (n = 59, 104) Amplified vs low copy (n = 15, 104)	 0.94 1.26	0.77

KRAS and EGFR mutation status and EGFR copy number are not prognostic for overall survival.

Goss GD et al. *Proc ASCO* 2010;Abstract LBA7005.

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Exploratory Biomarker Analyses: Overall Survival (Gefitinib vs Placebo Arm)

Patient Group (n)	Hazard Ratio	*p*-value
KRAS		
Wild-type (n = 254)	1.13	0.512
Mutant (n = 96)	1.51	0.163
EGFR		
Wild-type (n = 281)	1.21	0.301
Mutant (n = 76)	1.58	0.160
EGFR FISH		
Low copy (n = 205)	1.38	0.13
High copy (n = 134)	1.25	0.38
Amplified only	1.22	0.69

KRAS and EGFR mutations and EGFR copy number are not predictive for a trend towards improvement in survival nor an overall survival benefit in response to gefitinib.

Goss GD et al. *Proc ASCO* 2010;Abstract LBA7005.

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Selected Grade 3/4 Adverse Events

	Gefitinib (n = 249)		Placebo (n = 243)	
Adverse Event	**Grade 3 (%)**	**Grade 4 (%)**	**Grade 3 (%)**	**Grade 4 (%)**
Dehydration	2 (<1)	0	1 (<1)	0
Diarrhea	3 (2)	0	2 (<1)	0
Dyspnea	7 (3)	3 (2)	9 (4)	1 (<1)
Infection - Other	4 (2)	0	3 (1)	0
Nausea	2 (<1)	0	0	0
Pneumonitis	1 (<1)	2 (<1)	3 (1)	0

Goss GD et al. *Proc ASCO* 2010;Abstract LBA7005.

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Conclusions

- Gefitinib was well tolerated.
- Gefitinib did not improve DFS and OS in patients with completely resected early stage NSCLC in this underpowered study.
- KRAS mutation status, EGFR by FISH or EGFR sensitizing mutation status were neither prognostic nor predictive of survival in exploratory analysis.
- A targeted agent that improves OS in NSCLC in the adjuvant setting has yet to be demonstrated.
- Currently, the treatment of choice for patients in good performance is chemotherapy.
- The results of the RADIANT trial of adjuvant erlotinib are awaited (NCT00373425).

Goss GD et al. *Proc ASCO* 2010;Abstract LBA7005; www.clinicaltrials.gov.

Investigator comment on the results of NCIC-CTG BR.19: A Phase III study of adjuvant gefitinib in NSCLC

SWOG-S0023 evaluated chemoradiation therapy followed by maintenance gefitinib versus placebo, and that study was halted because patients who received maintenance gefitinib actually fared worse than those who received placebo.

This is a similar study in earlier, Stage I to IIIA disease, in which patients received adjuvant chemotherapy and then either gefitinib or placebo. They had enrolled about 500 patients when SWOG-S0023 was completed, and this study was stopped because of that negative result. It was the right decision because, for whatever reason, the patients who received gefitinib fared no better and actually are trending a little worse in terms of overall survival.

Even though gefitinib was well tolerated, there is no benefit from gefitinib in patients with resected lung cancer. In exploratory analyses of K-ras and EGFR mutations and EGFR FISH, none were predictive for outcome.

Another ongoing study, RADIANT, is evaluating adjuvant erlotinib. Based on these results, I would not bet the house on the outcomes of that study. For whatever reason, adjuvant EGFR TKIs will not be beneficial in unselected patients.

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

Investigator comment on the results of NCIC-CTG BR.19: A Phase III study of adjuvant gefitinib in NSCLC

Nobody quite knows what to make of the results from this study. In 2005, the ISEL study of second- and third-line gefitinib versus placebo and the SWOG study of maintenance gefitinib versus placebo were negative, and the BR.19 investigators decided to shut their trial down before completing the planned accrual.

After several years of follow-up, BR.19 was presented, but it was difficult to discern how many patients received gefitinib and the duration of treatment. The bottom line was that no survival difference was evident between those who received adjuvant gefitinib and those who received placebo. Of most concern, there was a trend toward possible harm from gefitinib, which was observed to be consistent across different subgroups, including those with an EGFR mutation. It's not entirely clear what might cause this apparent detriment, but it's consistent with the SWOG study.

We are now awaiting the results of the RADIANT trial, which is evaluating adjuvant erlotinib versus placebo, but instead of taking "all-comers," it requires patients to be positive for EGFR overexpression by either immunohistochemistry or FISH. So hopefully in two years we will have an answer, but I would be especially interested to see the results in patients with EGFR mutations.

Interview with Lecia V Sequist, MD, MPH, June 18, 2010