5 Minute JournalClub

SPECIAL EDITION
Issue 1, 2011

Studies in Advanced NSCLC of Maintenance Pemetrexed and Erlotinib and of BIBW 2992 or MetMAb Targeted Therapy for Acquired Resistance to Erlotinib and Gefitinib

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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 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 diverse forms of cancer.

LEARNING OBJECTIVES

- Communicate the benefits of continued pemetrexed maintenance therapy to appropriately selected patients with advanced-stage NSCLC.
- Recall emerging efficacy and safety data with combined therapies targeting the EGFR signaling pathway in patients with advanced NSCLC, and consider their potential role in the care of patients with EGFR activating mutations.

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This CME activity contains slides and edited commentary. To receive credit, the participant should review the slide presentations, read the commentary, complete the Post-test with a score of 75% or better and fill out the Educational Assessment and Credit Form located on our website at ResearchToPractice.com/5MJCASCO2011/Lung/CME.

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Edward S Kim, MD
Associate Professor of Medicine
Chief, Section of Head and Neck Medical Oncology
Director, Clinical Research Operations
Department of Thoracic/Head and Neck Medical Oncology
The University of Texas MD Anderson Cancer Center
Houston, Texas

Advisory Committee: Bayer HealthCare Pharmaceuticals, Onyx Pharmaceuticals Inc; Consulting Agreements: Bayer HealthCare Pharmaceuticals, Boehringer Ingelheim Pharmaceuticals Inc, Onyx Pharmaceuticals Inc; Paid Research: Genentech BioOncology, Lilly USA LLC, OSI Oncology.

Thomas J Lynch Jr, MD
Jonathan and Richard Sackler Professor of Internal Medicine
Director, Yale Cancer Center
Physician-in-Chief, Smilow Cancer Hospital at Yale New Haven
New Haven, Connecticut

Board of Directors: Infinity Pharmaceuticals Inc; Consulting Agreements: Boehringer Ingelheim Pharmaceuticals Inc, SuperGen Inc; Stock Ownership: Biogen Idec, Infinity Pharmaceuticals Inc.

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To go directly to the slides and investigator commentary for the featured abstracts, **click here**.

The electric pace of oncology in 2011 means that most busy practitioners barely have time to read abstracts, let alone dive into journal articles and watch or attend meeting presentations. Addressing that challenge, this latest experiment in cancer education attempts to provide our quickest take possible on the most memorable presentations from ASCO 2011. This first issue focuses on solid tumors (hematologic cancers will be coming next week), and for each of the presentations summarized below we have created a brief, clickable slide set reviewing the most essential findings and providing the perspectives of clinical investigators (presented on the last slide of each set). Here we go:

1. Vemurafenib and ipilimumab in melanoma

Two plenary papers on Phase III trials with these agents showed important survival benefits (**ab LBA4** and **LBA5**). The findings and recent FDA approval of both of these agents heighten the importance of BRAF V600E mutation testing and create a challenging choice between these two interesting novel compounds as first-line therapy for patients with tumors harboring these mutations.

2. GI cancers: Adjuvant imatinib in GIST; neoadjuvant treatment of rectal cancer

Another compelling plenary paper (**ab LBA1**) reported a trial in patients with high-risk GIST revealing that 3 years of adjuvant imatinib resulted in much better PFS and OS than 1 year. Importantly, in both groups relapses started occurring 6 months after the discontinuation of treatment, suggesting the need for longer-duration or perhaps indefinite imatinib.

Also in GI cancer, 2 trials (**ab 3503 and 3504**) addressed a couple of old, lingering questions in terms of the choice of chemotherapy to pair with radiation therapy in rectal cancer. Bottom line: There doesn't seem to be a current role for neoadjuvant oxaliplatin, and it's pretty challenging to think of a good reason to use 5-FU instead of capecitabine.

3. Important Phase I-II studies on novel agents
In our nominee for most exciting ASCO data set (**ab 4516**), the Met/VEGFR2 TKI cabozantinib (formerly XL 184) in prostate cancer produced some of the most stunning outcomes seen in this or any other solid tumor, including dramatic improvements evident on bone scans often associated with major symptom palliation.

A close second to the cabozantinib paper (**ab 7525**) and one that kept the faculty at our recent lung cancer Think Tank buzzing demonstrated that pan-EGFR blockade with the irreversible TKI afatinib combined with cetuximab resulted in significant responses in patients with advanced NSCLC resistant to an EGFR TKI, including those with T790M mutations.

Another encouraging NSCLC paper (**ab 7505**) evaluated the monoclonal antibody MetMAb and demonstrated improved PFS in the 52% of patients with Met overexpression.

4. Iniparib in triple-negative breast cancer
We all knew it was coming, but the biggest downer of the meeting (**ab 1007**) was the pretty much negative study — presented by the diminutive genius Joyce O'Shaughnessy — of iniparib plus chemo in advanced TNBC. These disappointing findings left many scratching their heads and have forced researchers back to the drawing board in an attempt to figure out why this putative PARP inhibitor worked in the Phase II but not the Phase III setting.

5. Reinforcement of the new lung adenocarcinoma advanced-disease paradigm
The PARAMOUNT trial (**ab CRA7510**) again supported the role of some type of maintenance strategy after first-line chemo with or without bev, this time the "continuation" of pemetrexed, and while we await Phase III data from the related PointBreak trial, pem/carbo with or without bev followed by pem and/or bev maintenance are commonly employed nonprotocol approaches.

In a similar vein, the EURTAC study (**ab 7503**) again demonstrated that for patients with EGFR mutation-positive advanced lung cancer, an EGFR TKI results in better short-term outcomes than chemo.

6. Bevacizumab with chemotherapy in breast and ovarian cancer
Two neoadjuvant breast trials (**ab LBA1005 and 1006**) demonstrated more path CRs with bev, and a reanalysis of the RIBBON 2 trial evaluating this anti-angiogenic agent in the second-line setting revealed a doubling of response rates for patients with triple-negative disease (**ab 1010**).

In recurrent ovarian cancer, chemo plus bev with bev maintenance until progression resulted in longer PFS (**ab LBA5007**), and more follow-up from the ICON7 "adjuvant" trial (**ab LBA5006**) continued to show a slowing of disease progression with chemo/bev followed by bev maintenance. However, as yet no impact on survival has been observed. What this means in both cancers outside a protocol setting and from a regulatory/reimbursement perspective continues to be vociferously debated.

Next up on our condensed ASCO highlights reel: Liquid tumor snippets.

Neil Love, MD
Research To Practice
Miami, Florida

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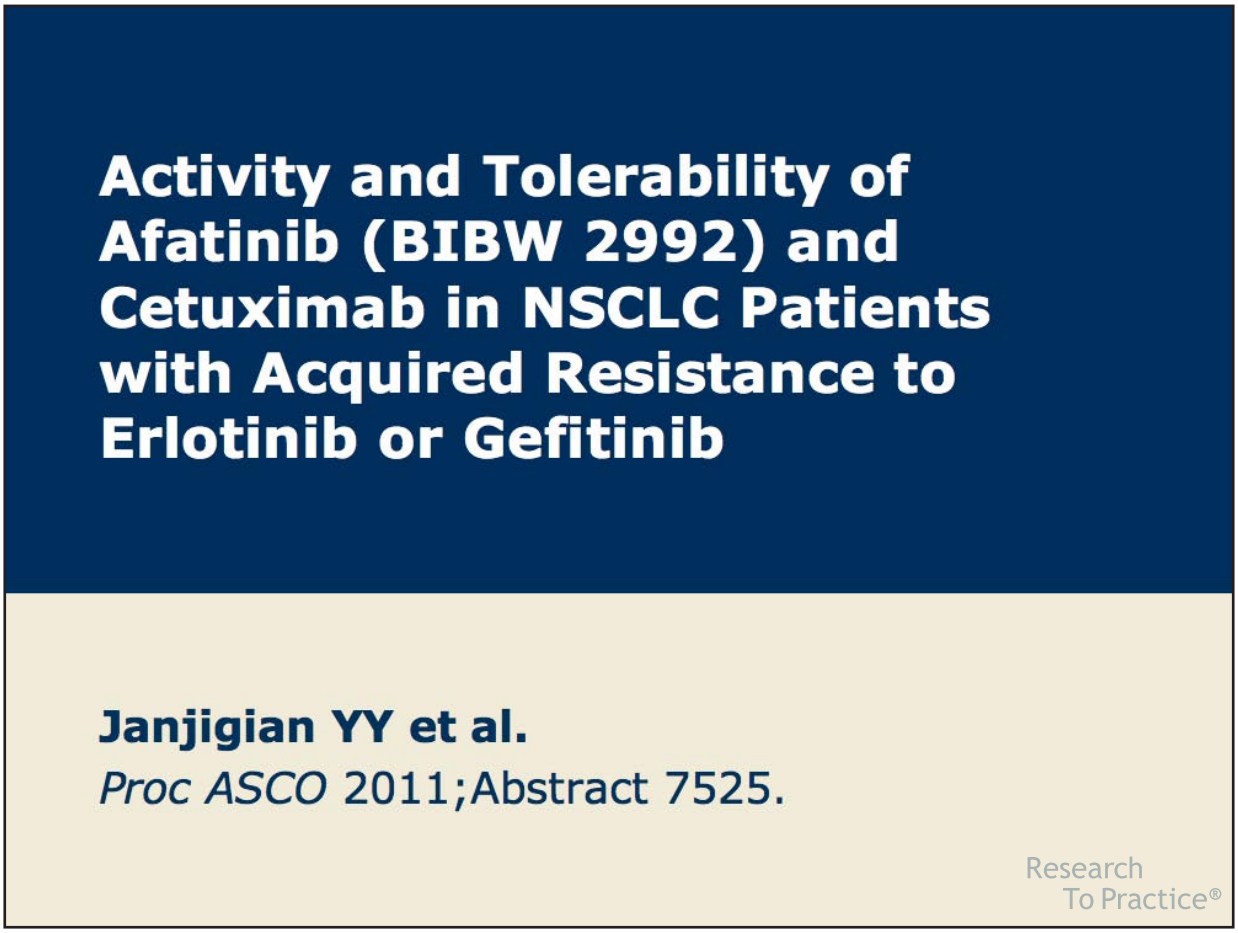
Research To Practice
One Biscayne Tower
2 South Biscayne Boulevard, Suite 3600
Miami, FL 33131

Studies in Advanced NSCLC of Maintenance Pemetrexed and Erlotinib and of BIBW 2992 or MetMAb Targeted Therapy for Acquired Resistance to Erlotinib and Gefitinib

Presentation discussed in this issue

Janjigian YY et al. **Activity and tolerability of afatinib (BIBW 2992) and cetuximab in NSCLC patients with acquired resistance to erlotinib or gefitinib.** *Proc ASCO* 2011;**Abstract 7525**.

Slides from a presentation at ASCO 2011 and comments from Thomas J Lynch Jr, MD



Introduction

- Patients with NSCLC and sensitizing EGFR mutations will develop acquired resistance (AR) to EGFR tyrosine kinase inhibitors (TKIs) and lose their initial responses to these agents.
- AR is associated with a second site mutation within exon 20 of the EGFR gene, T790M, in more than 50% of cases.
- Currently, no therapeutic agents have proven effective in the treatment of AR.
- Preclinical data in a transgenic T790M mouse model have demonstrated that combined EGFR targeting with cetuximab and the HER family targeted agent afatinib induces near complete responses.

Janjigian YY et al. *Proc ASCO* 2011;Abstract 7525.

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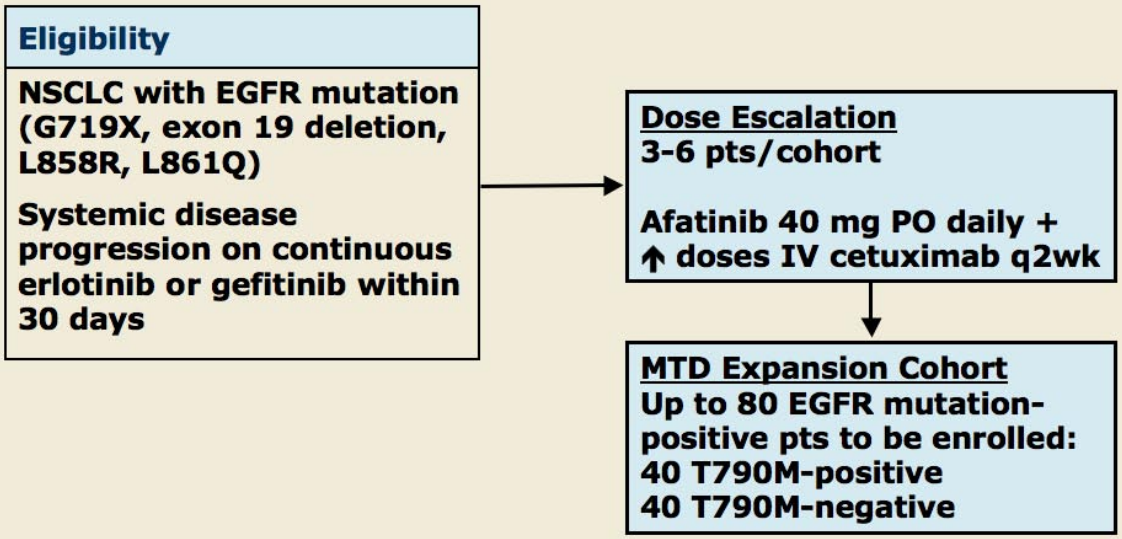
Phase Ib Study of Afatinib + Cetuximab for Patients with NSCLC and Acquired Resistance to EGFR TKIs



Janjigian YY et al. *Proc ASCO* 2011;Abstract 7525.

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Best Response at MTD by EGFR Mutation Status

	T790M-positive	T790M-negative	T790M unknown	No EGFR mutation	Total
Total treated	27	15	3	2	47
Evaluable for efficacy	26	14	3	2	45
Best response, n (%)					
Any PR	13 (50)	8 (57)	2 (67)	—	23 (51)
Confirmed PR	9 (35)	7 (50)	2 (67)	—	18 (40)
Clinical response (any PR + SD)	24 (92)	13 (93)	3 (100)	2 (100)	42 (93)
Progression of disease	2 (8)	1 (7)	—	—	3 (7)

MTD = Afatinib 40 mg daily + cetuximab 500 mg/m^2 q2wk

Janjigian YY et al. *Proc ASCO* 2011;Abstract 7525.

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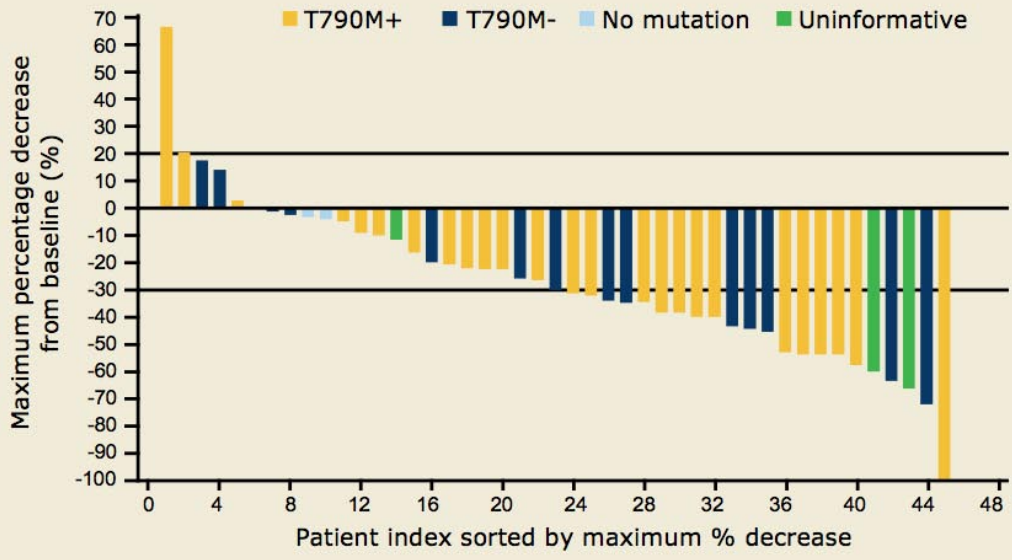
Best Response at MTD by EGFR Mutation Status



With permission from Janjigian YY et al. *Proc ASCO* 2011;Abstract 7525.

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Select Adverse Events at MTD (n = 47)

Adverse event, n (%)	All grades	Grade ≥3
Rash	42 (89)	3 (6)
Diarrhea	35 (74)	3 (6)
Dyspnea	13 (28)	3 (6)
Xerosis	27 (57)	1 (2)
Nausea/vomiting	35 (74)	1 (2)
Paronychia	14 (30)	1 (2)
Dermatitis acneiform	10 (21)	1 (2)

Adverse events observed in >20% of patients.

Janjigian YY et al. *Proc ASCO* 2011;Abstract 7525.

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Conclusions

- The recommended Phase II dose (MTD) is afatinib 40 mg daily and cetuximab 500 mg/m^2 every 2 weeks.
- Most patients in this study (>90%) derived clinical benefit from afatinib + cetuximab.
- Objective responses were observed in T790M mutation-positive and negative tumors.
- These data suggest that EGFR mutation-positive NSCLC with acquired resistance to erlotinib and gefitinib continues to depend on EGFR signaling.

Janjigian YY et al. *Proc ASCO* 2011;Abstract 7525.

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Investigator Commentary: Afatinib with Cetuximab for Patients with NSCLC and EGFR Acquired Resistance

Probably the most promising combination in this setting of EGFR acquired resistance is afatinib, or BIBW 2992, with cetuximab for patients who have T790M acquired resistance. The data presented at ASCO this year suggested a significant response rate with this combination. This study is based on some terrific early mouse work, which was published by William Pao and Katerina Politi at Memorial Sloan-Kettering in 2009. Their results suggested that although neither afatinib nor cetuximab seemed to do much as single agents, their combination produced profound results in genetically engineered mouse models of resistance that carry T790M. It was quite encouraging to see this activity now confirmed in patients. We are eager to see what the duration of benefit is in this setting.

These data bring up an important issue, which is that in targeted therapy we need to move toward bringing these combinations up front earlier in the treatment of lung cancer.

Thomas J Lynch Jr, MD

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