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

For more visit ResearchToPractice.com/5MJCASCO2011

Research To Practice®

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.

ACCREDITATION STATEMENT

Research To Practice is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

CREDIT DESIGNATION STATEMENT

Research To Practice designates this enduring material for a maximum of 1.25 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

HOW TO USE THIS CME ACTIVITY

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.

CONTENT VALIDATION AND DISCLOSURES

Research To Practice (RTP) is committed to providing its participants with high-quality, unbiased and state-of-the-art education. We assess potential conflicts of interest with faculty, planners and managers of CME activities. Real or apparent conflicts of interest are identified and resolved through a conflict of interest resolution process. In addition, all activity content is reviewed by both a member of the RTP scientific staff and an external, independent physician reviewer for fair balance, scientific objectivity of studies referenced and patient care recommendations.

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:

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.

EDITOR — Dr Love is president and CEO of Research To Practice, which receives funds in the form of educational grants to develop CME activities from the following commercial interests: Allos Therapeutics, Amgen Inc, Astellas Pharma Global Development Inc, Bayer HealthCare Pharmaceuticals/Onyx Pharmaceuticals Inc, Biogen Idec, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Cephalon Inc, Daiichi Sankyo Inc, Dendreon Corporation, Eisai Inc, EMD Serono Inc, Genentech BioOncology, Genomic Health Inc, ImClone Systems, a wholly owned subsidiary of Eli Lilly and Company, Lilly USA LLC, Millennium: The Takeda Oncology Company, Mundipharma International Limited, Myriad Genetics Inc, Novartis Pharmaceuticals Corporation, OSI Oncology, Sanofi and Seattle Genetics.

RESEARCH TO PRACTICE STAFF AND EXTERNAL REVIEWERS — The scientific staff and reviewers for Research To Practice have no real or apparent conflicts of interest to disclose.

This educational activity contains discussion of published and/or investigational uses of agents that are not indicated by the Food and Drug Administration. Research To Practice does not recommend the use of any agent outside of the labeled indications. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications and warnings. The opinions expressed are those of the presenters and are not to be construed as those of the publisher or grantors.

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

Last review date: September 2011
Expiration date: September 2012

5 MinuteJournalClub

SPECIAL EDITION
Issue 1, 2011

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

Research To Practice is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Research To Practice designates this enduring material for a maximum of 5.25 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

This activity is supported by educational grants from Bristol-Myers Squibb Company, Celgene Corporation and Genentech BioOncology.

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

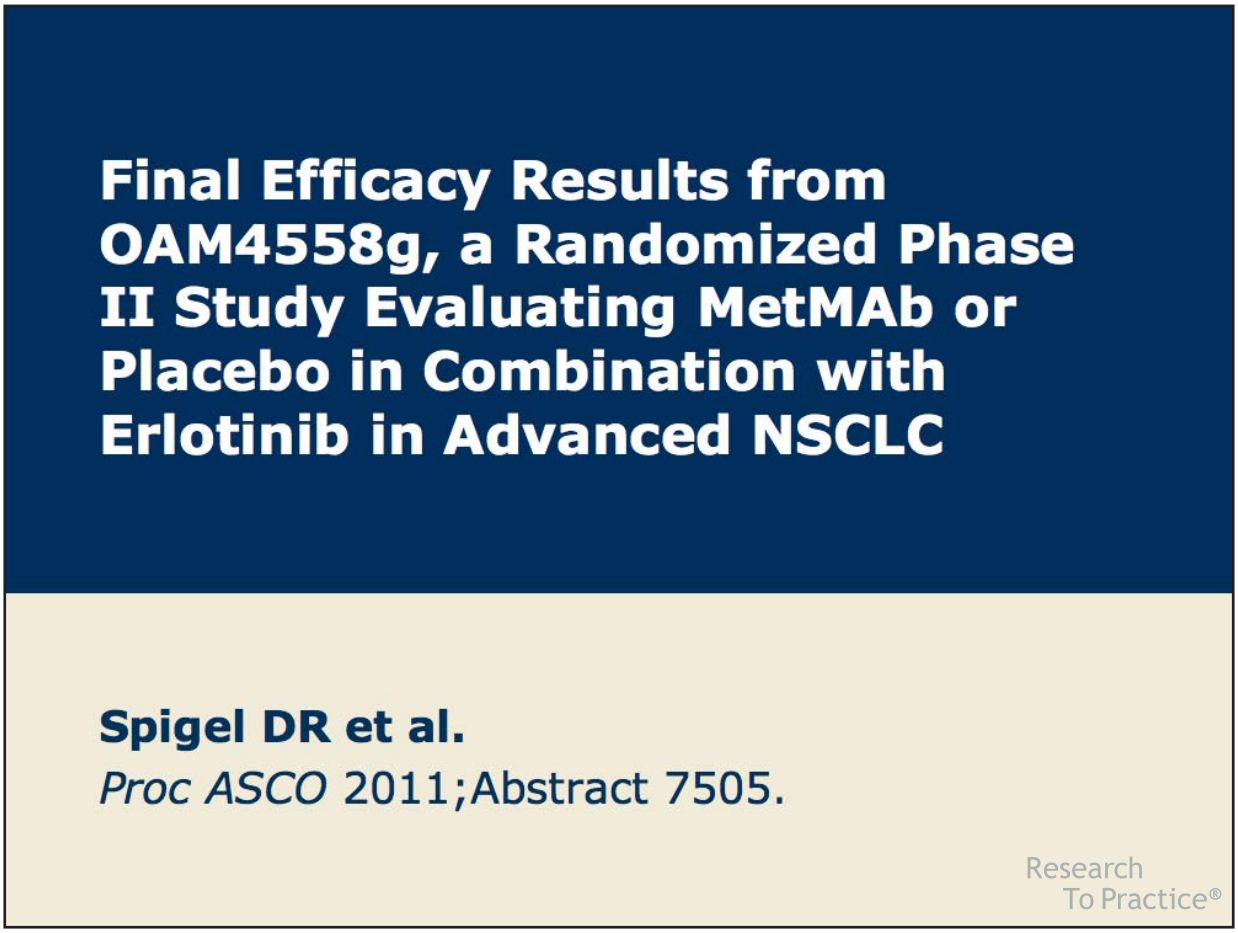
This email was sent to you by Dr Neil Love and Research To Practice. To unsubscribe to future email requests and announcements, **click here**. To unsubscribe from all email communications, including CME/CNE activities sent by Research To Practice, **click here**. To update your information on our current distribution lists, **click here**.

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

Spigel DR et al. **Final efficacy results from OAM4558g, a randomized phase II study evaluating MetMAb or placebo in combination with erlotinib in advanced NSCLC.** *Proc ASCO* 2011;**Abstract 7505**.

Slides from a presentation at ASCO 2011 and comments from Edward S Kim, MD



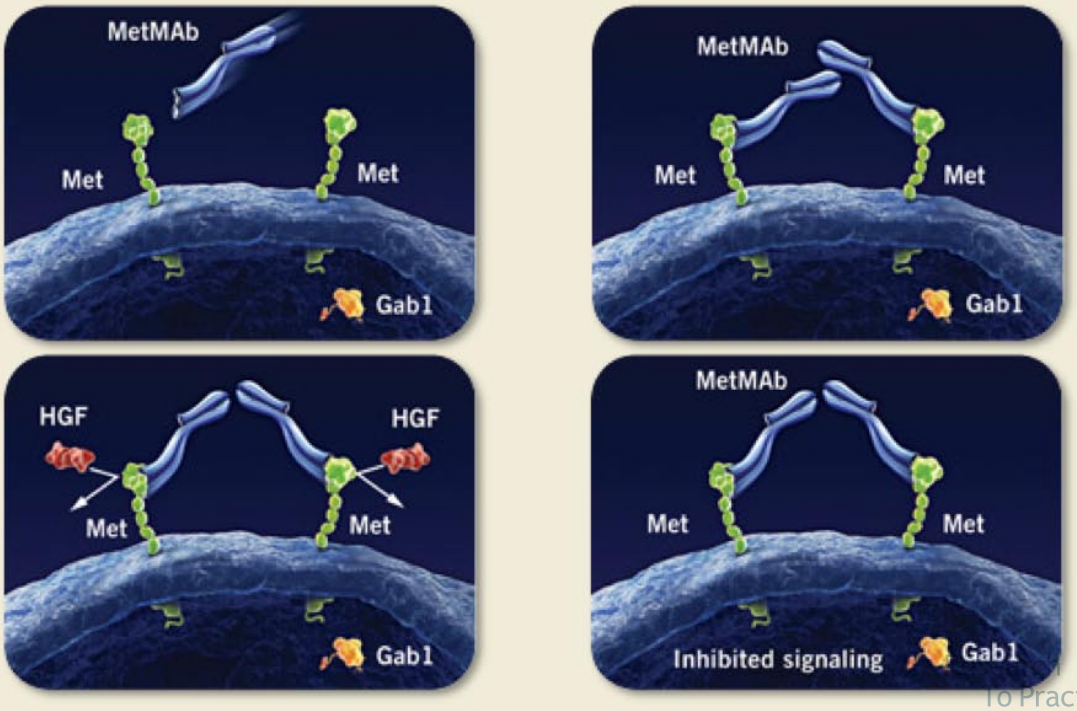
Introduction

- Met overexpression is associated with a worse prognosis in many cancers including NSCLC.
- Met activation is associated with resistance to the EGFR tyrosine kinase inhibitors (TKIs) erlotinib and gefitinib in patients with activating mutations in EGFR (Engelman *Science* 2007).
- MetMAb is a monovalent antibody targeted against c-MET.
- Preclinical data in mouse NSCLC tumor model suggest that inhibiting both Met and EGFR with MetMAb and erlotinib, respectively, is superior to inhibiting either alone (*Proc AACR* 2008;Abstract 1336).

Spigel DR et al. *Proc ASCO* 2011;Abstract 7505.

Research
To Practice®

MetMAb Mechanism of Action



To Practice®

OAM4558g: A Phase II Study of Erlotinib ± MetMAb in Advanced NSCLC

Eligibility (N = 137)

Stage IIIB/IV NSCLC

One or two prior lines of therapy for NSCLC

Tissue sample required

R

MetMAb
15 mg/kg IV q3wks
+
Erlotinib
150 mg daily
(n = 69)

Placebo
IV q3wks
+
Erlotinib
150 mg daily
(n = 68)

Coprimary endpoints:

1. *PFS in Met diagnostic positive patients (defined as ≥50% tumor cells with moderate or strong staining intensity by IHC)*
2. *PFS in overall ITT population*

27 patients on placebo arm were administered MetMAb upon disease progression.

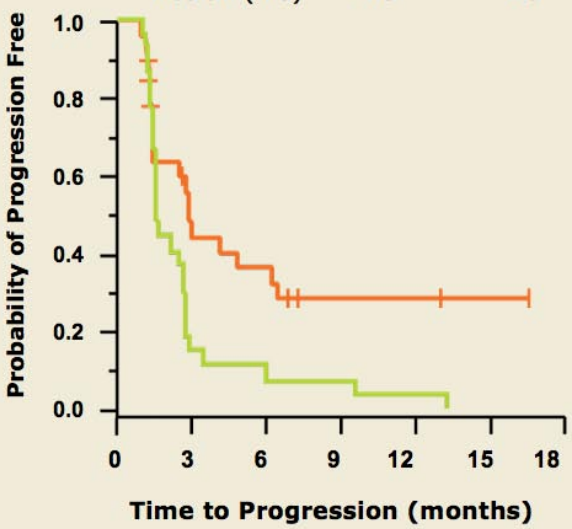
Research To Practice®

Spigel DR et al. *Proc ASCO* 2011;Abstract 7505.

Efficacy in Met Diagnostic Positive Patients

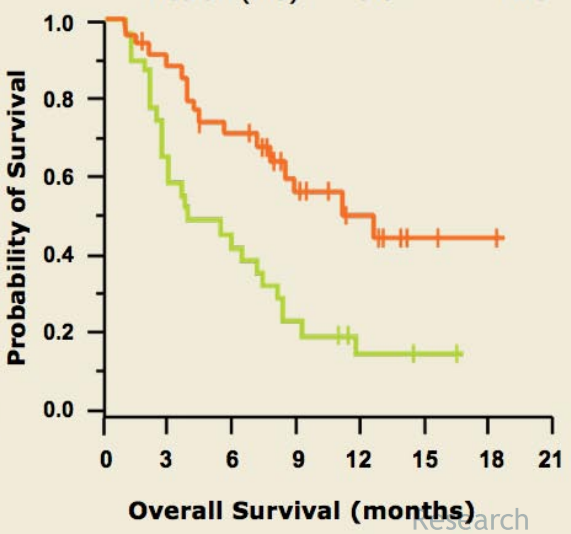
PFS: HR = 0.53, *p* = 0.04

	Placebo + erlotinib	MetMAb + erlotinib
Median (mo)	1.5	2.9



OS: HR = 0.37, *p* = 0.002

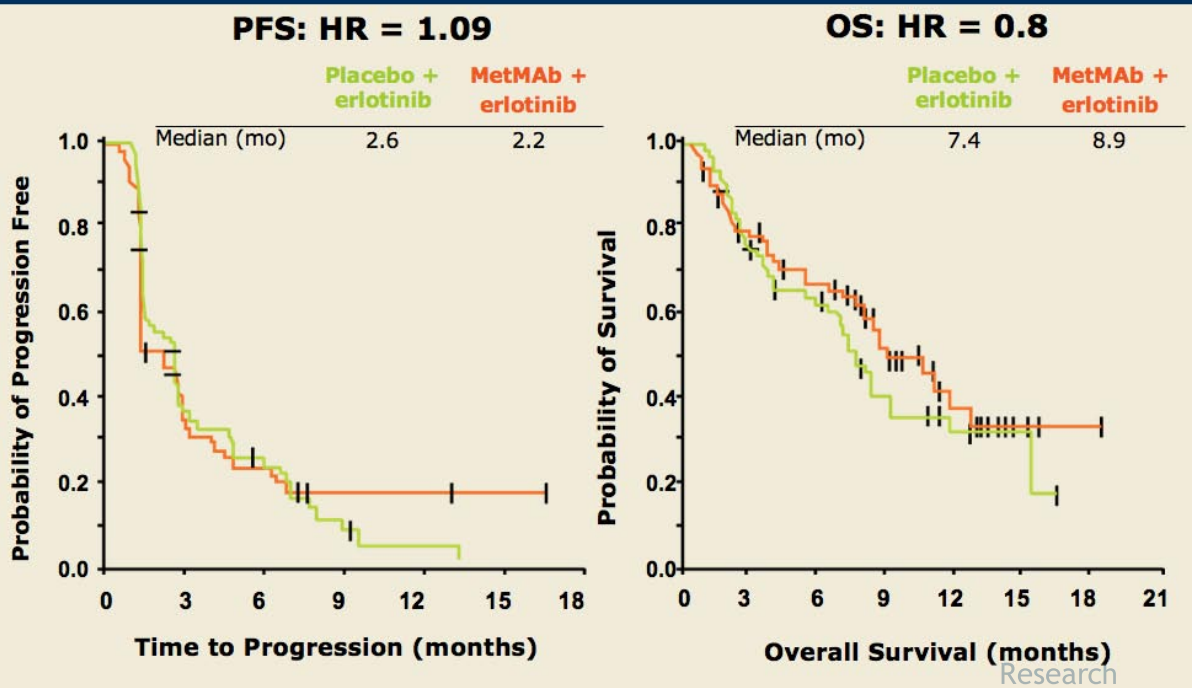
	Placebo + erlotinib	MetMAb + erlotinib
Median (mo)	3.8	12.6



Research To Practice®

With permission from Spigel DR et al. *Proc ASCO* 2011;Abstract 7505.

Efficacy in ITT Population



With permission from Spigel DR et al. *Proc ASCO* 2011;Abstract 7505.

Research To Practice®

Select Adverse Events in Met Diagnostic Positive Patients

Adverse Event*	Placebo + Erlotinib (n = 31)	MetMAb + Erlotinib (n = 35)
Rash	61.3%	62.9%
Diarrhea	41.9%	51.4%
Fatigue	38.7%	45.7%
Nausea	29.0%	37.1%
Peripheral edema	**6.5%**	**22.9%**
Vomiting	16.1%	5.7%

* Adverse events reported in ≥10% of patients

Spigel DR et al. *Proc ASCO* 2011;Abstract 7505.

Research To Practice®

Conclusions

- In patients with NSCLC and positive c-MET IHC, the addition of MetMAb to erlotinib resulted in a twofold reduction in the risk of progression (HR = 0.53, p = 0.04) and a near-threefold reduction in the risk of death (HR = 0.37, p = 0.002).
- EGFR mutation or FISH status does not drive the benefit from MetMAb (data not shown).
- MetMAb + erlotinib was well tolerated and no new significant safety findings were reported.

Spigel DR et al. *Proc ASCO* 2011;Abstract 7505.

Research To Practice®

Investigator Commentary: MetMAb + Erlotinib for the Treatment of Advanced NSCLC

This was an interesting Phase II study using erlotinib as the standard approach in a second- and third-line population of patients and comparing them to patients receiving erlotinib with the Met-targeted antibody MetMAb. A nice aspect of this study was that the authors wanted to evaluate patients who had Met positivity versus those who were negative using a predefined IHC-type scoring. Fifty-two percent of patients were diagnosed as Met-positive in the study.

Results with the half of the patients who were Met positive are encouraging. Overall survival of these patients receiving MetMAb with erlotinib was more than 12 months compared to 3.5 months in patients receiving erlotinib alone. The hazard ratio for overall survival was 0.37. Almost a doubling of progression-free survival (PFS) with a hazard ratio of 0.53 was observed. In the overall population, however, PFS did not favor MetMAb with erlotinib, and the hazard ratio for overall survival was 0.8. Studies like these where there is a targeted agent and a test to define the molecular characteristics of a patient population make us more excited. A Phase III trial with this agent is actively being planned.

Edward S Kim, MD