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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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.

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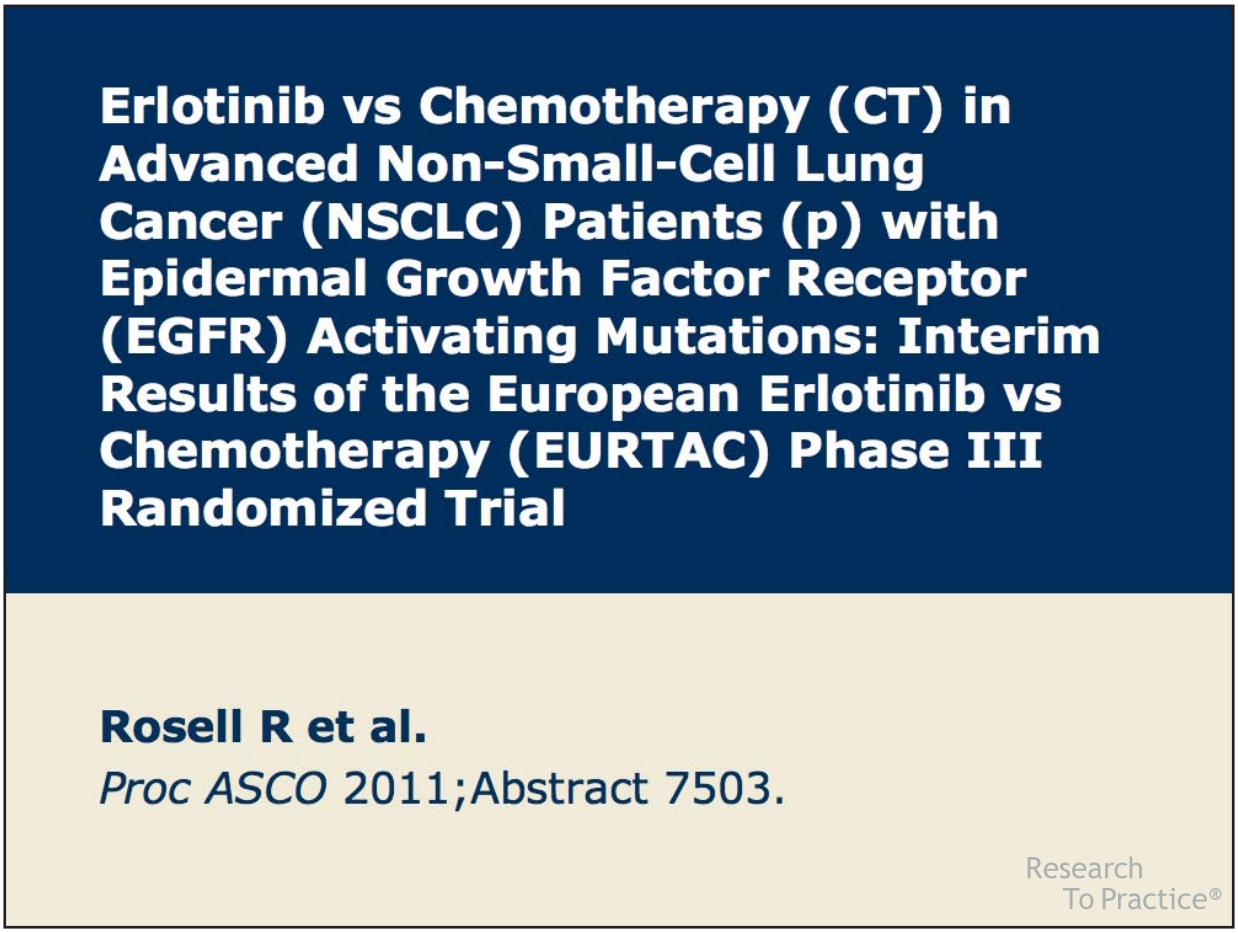
Studies in Advanced NSCLC of Maintenance Pemetrexed and Erlotinib and of BIBW 2992 or MetMAb Targeted Therapy for Acquired Resistance to Erlotinib and Gefitinib

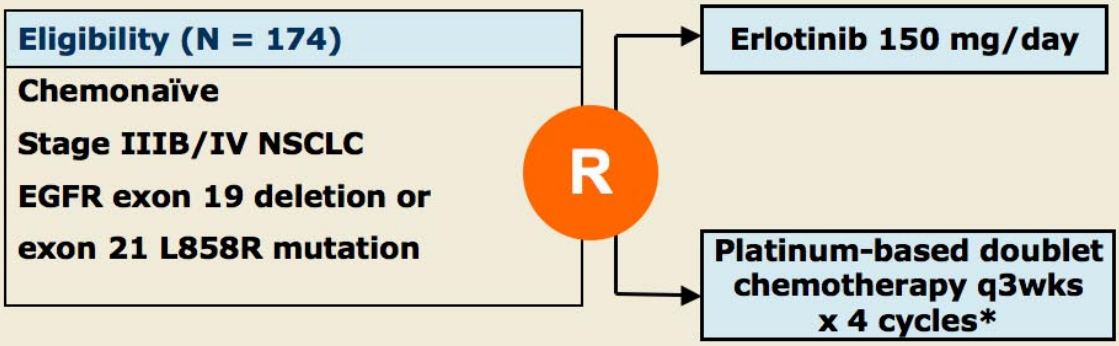
Presentation discussed in this issue

Rosell R et al. **Erlotinib versus chemotherapy (CT) in advanced non-small cell lung cancer (NSCLC) patients (p) with epidermal growth factor receptor (EGFR) mutations: Interim results of the European Erlotinib versus Chemotherapy (EURTAC) phase III randomized trial.** *Proc ASCO* 2011;**Abstract 7503**.

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



EURTAC Phase III Study Design



**Cisplatin/docetaxel, cisplatin/gemcitabine, carboplatin/docetaxel or carboplatin/gemcitabine*

Rosell R et al. *Proc ASCO* 2011;Abstract 7503.

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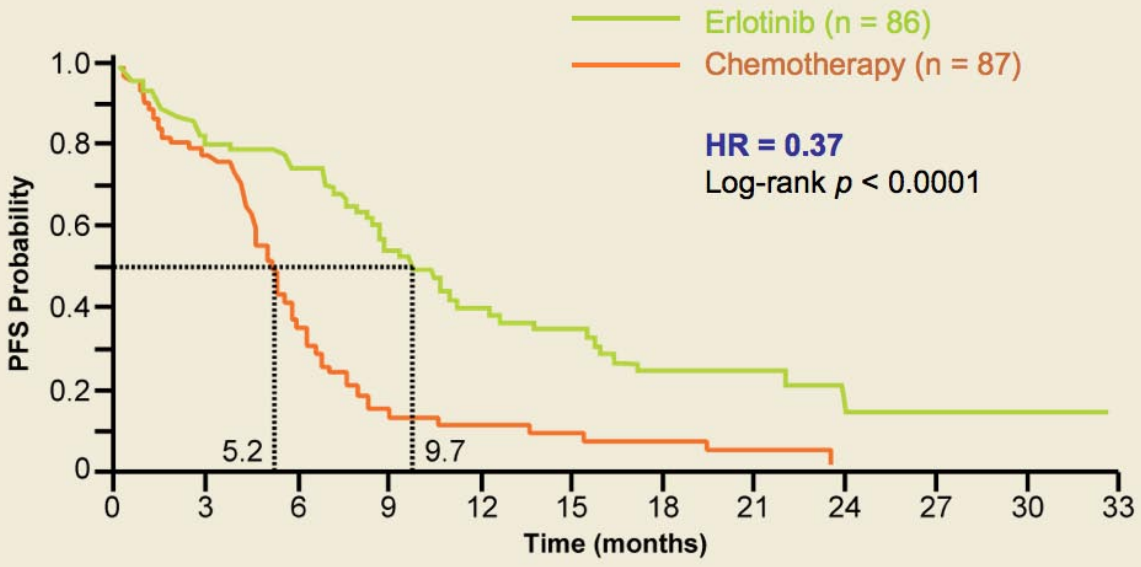
Primary Endpoint: PFS in ITT Population (Updated Analysis January 26, 2011)



With permission from Rosell R et al. *Proc ASCO* 2011;Abstract 7503.

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Best Overall Response in ITT Population (Updated Analysis January 26, 2011)

Clinical parameter	Erlotinib (n = 86)	Chemotherapy (n = 87)
Best overall response rate	58%	15%
Complete response	2%	0%
Partial response	56%	15%
Disease control rate	79%	66%

Rosell R et al. *Proc ASCO* 2011;Abstract 7503.

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Select Adverse Events (Interim Analysis August 2, 2010)

Adverse event	Erlotinib (n = 75)*		Chemotherapy (n = 74)*	
	All Grades	Grade 3/4	All Grades	Grade 3/4
Neutropenia	0	0	36%	22%
Thrombocytopenia	1%	0	12%	12%
Anemia	11%	1%	46%	4%
ALT elevation	80%	5%	72%	0
Rash	80%	9%	3%	0
Diarrhea	57%	4%	19%	0

* Safety population included only those patients who received at least one dose of study treatment

Rosell R et al. *Proc ASCO* 2011;Abstract 7503.

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Conclusions

- EURTAC met its primary PFS endpoint at the interim analysis.
- Study results confirm significant PFS benefit of first-line erlotinib over standard chemotherapy for patients with EGFR mutation-positive NSCLC:
  - 63% reduction in risk of progression or death (HR = 0.37)
- Overall survival data are immature (data not shown).
- The tolerability of erlotinib was consistent with previous studies.

Rosell R et al. *Proc ASCO* 2011;Abstract 7503.

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Erlotinib Can Be Considered as a Standard First-Line Therapy for Patients with EGFR Mutation

Study	Response rate	PFS
EURTAC	58% vs 15%	9.7 vs 5.2 mo (HR = 0.37)
OPTIMAL	83% vs 36%	13.1 vs 4.6 mo (HR = 0.16)
NEJ002	74% vs 31%	10.8 vs 5.4 mo (HR = 0.30)
WJTOG 3405	62% vs 31%	9.2 vs 6.3 mo (HR = 0.49)

Mok T. *Proc ASCO* 2011;Discussant.

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Investigator Commentary: First-Line Erlotinib for Patients with EGFR-Mutated NSCLC

The EURTAC study was a large prospective study in which patients were tested for classical EGFR mutations in exons 19 and 21 and received front-line erlotinib or platinum-based doublets. An update of the study was presented at ASCO, and it continued to show an impressive hazard ratio of 0.37 for the primary endpoint of progression-free survival (PFS). No update was provided on overall survival, but we can now say that in the Western and Asian populations those patients who harbor EGFR mutations in their tumors benefit from the PFS and quality-of-life standpoints by starting with an EGFR TKI up front.

I believe it is important to obtain tissue up front when we diagnose patients because several tests, including the ALK and EGFR mutation tests, can now make a meaningful difference to a patient who undergoes treatment up front. In an ideal world, we would like to test every patient, but we consider smoking status and histology when thinking about patients eligible for mutation testing. If someone does have nonsquamous lung cancer, specifically an adenocarcinoma, regardless of their smoking history, we should try and test that patient.

Edward S Kim, MD