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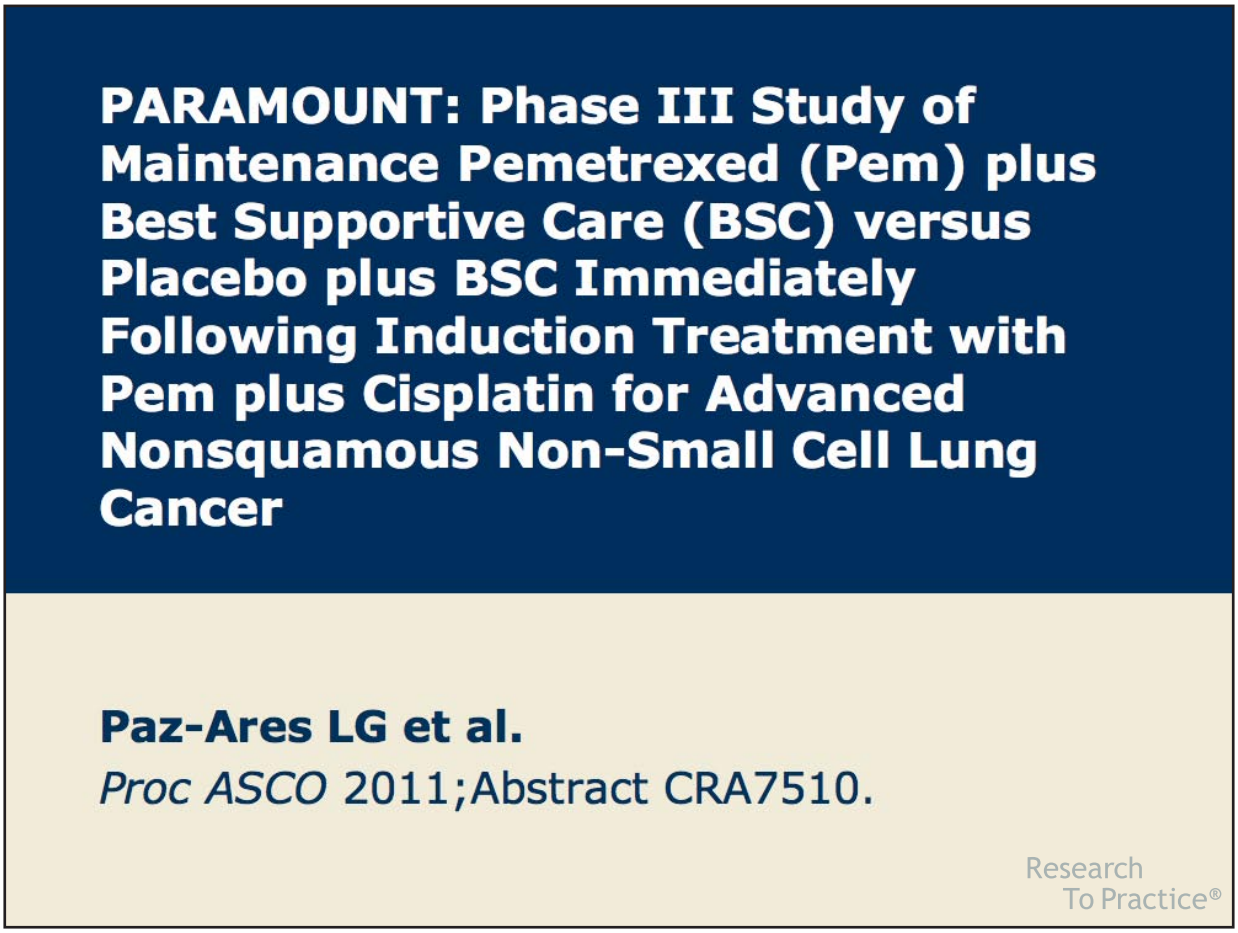
Studies in Advanced NSCLC of Maintenance Pemetrexed and Erlotinib and of BIBW 2992 or MetMAb Targeted Therapy for Acquired Resistance to Erlotinib and Gefitinib

Presentation discussed in this issue

Paz-Ares L et al. **PARAMOUNT: Phase III study of maintenance pemetrexed (pem) plus best supportive care (BSC) versus placebo plus BSC immediately following induction treatment with pem plus cisplatin for advanced nonsquamous non-small cell lung cancer (NSCLC).** *Proc ASCO* 2011;**Abstract CRA7510**.

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



Maintenance Therapy: Continuation vs Switch

- Continuation maintenance
  - Continual suppression of malignancy will be more effective than intermittent use
- Switch maintenance (planned sequential)
  - Transition to proven second-line therapy before the emergence of resistance
  - Early use assures exposure to second-line therapy (ie, "no one falls off the cliff")

Edelman MJ. *Proc ASCO* 2011;Discussant.

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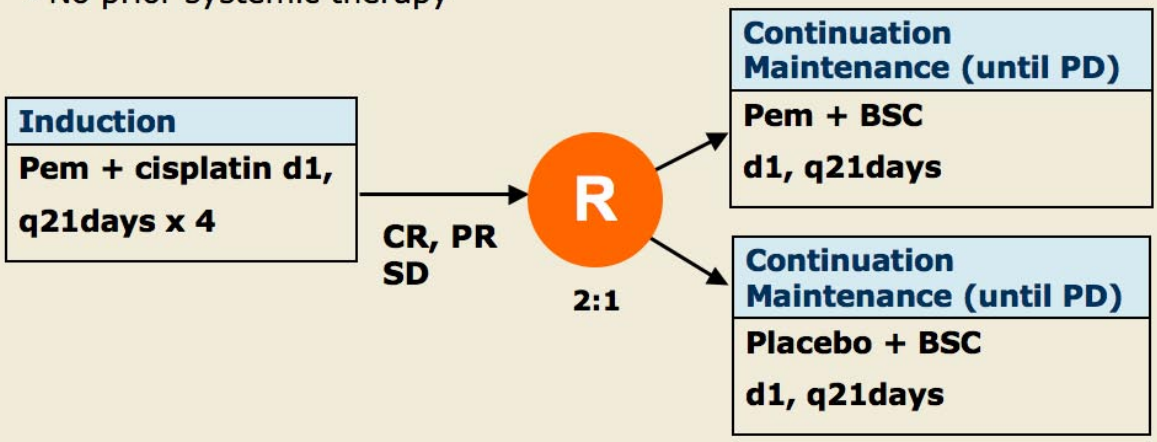
PARAMOUNT Phase III Study of Pemetrexed Continuation Maintenance

Patient Eligibility:

- Nonsquamous NSCLC
- No prior systemic therapy



Paz-Ares LG et al. *Proc ASCO* 2011;Abstract CRA7510.

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Progression-Free Survival (PFS) from Maintenance: Independent Review

	Pem + BSC (n = 316)	Placebo + BSC (n = 156)
Median PFS* (months)	3.9	2.6
	Hazard ratio: 0.64, p = 0.0002	

* 88% of patients were independently reviewed (472/539).

Paz-Ares LG et al. *Proc ASCO* 2011;Abstract CRA7510.

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Tumor Response* from Maintenance Independent Review

	Pemetrexed (n = 316)	Placebo (n = 156)	*p*-value
Response rate	9 (2.8%)	1 (0.6%)	0.176
Complete response	0	0	
Partial response	9 (2.8%)	1 (0.6%)	
Stable disease	218 (69.0%)	92 (59.0%)	—
Disease control rate	227 (71.8%)	93 (59.6%)	0.009

*Response represents a further tumor reduction from the baseline response to induction therapy.

Paz-Ares LG et al. *Proc ASCO* 2011;Abstract CRA7510.

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Select Grade 3 and 4 Drug-Related Toxicities

Adverse event	Pemetrexed (n = 359)	Placebo (n = 180)
Fatigue*	4.2%	0.6%
Anemia*	4.5%	0.6%
Neutropenia*	3.6%	0
Leukopenia	1.7%	0
Sensory neuropathy	0.3%	0.6%
Mucositis/stomatitis	0.3%	0
ALT (SGPT)	0.3%	0

*Statistically significant between arms ($p \leq 0.05$)

Paz-Ares LG et al. *Proc ASCO* 2011;Abstract CRA7510.

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Conclusions

- The trial met its primary PFS endpoint as pemetrexed maintenance therapy resulted in a significant benefit compared to placebo for patients with advanced nonsquamous NSCLC (3.9 mo vs 2.6 mo; HR = 0.64).
- Pemetrexed maintenance was well tolerated.
- Mature OS data are pending.

Paz-Ares LG et al. *Proc ASCO* 2011;Abstract CRA7510.

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Investigator Commentary: Continuation Maintenance with Pemetrexed for Advanced Nonsquamous NSCLC

The main question of the PARAMOUNT trial was how effective would continuation maintenance be with pemetrexed. The progression-free survival results were consistent with their previous reports. Although they remained statistically significant, they were not as dramatic. I believe these results can be used by community oncologists as validation that you can start with a pemetrexed-based doublet with platinum up front and then continue the pemetrexed as maintenance. Some will argue that continuation maintenance is not as effective as switch maintenance, and this is a topic that will remain debatable in the future.

The important message from PARAMOUNT is that pemetrexed maintenance is safe to administer and the PFS benefit is maintained. It is an acceptable standard in addition to other regimens that clinicians use to treat patients. I personally was not a big believer in maintenance therapy, but I do use it now. Continuing to treat a patient with a therapeutic agent seems to help.

Edward S Kim, MD

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