Lung Cancer™ UPDATE

Conversations with Oncology Investigators

Bridging the Gap between Research and Patient Care

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SPECIAL ISSUE
Proceedings from a Clinical Investigator Think Tank



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Lung Cancer Update
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OVERVIEW OF ACTIVITY

Lung cancer is increasingly being recognized as a heterogeneous group of tumors. Not long ago, it was clinically sufficient to make a differentiation between small cell lung cancer and non-small cell lung cancer (NSCLC). Published results from recent trials have led to the approval of 3 different agents for NSCLC in the maintenance setting, with only 1 of these being for the broad population of patients with NSCLC. Individualized treatment decisions are increasingly driven by genetic biomarkers in addition to histological subtype and patient-specific characteristics. Determining which treatment approach is most appropriate in a given case requires careful consideration of patient characteristics, biomarkers and available health-system resources. Oncology clinicians must possess a clear understanding of the benefits and risks of each of the various available options and how best to integrate the emerging data and agents into the therapeutic algorithm. To bridge the gap between research and patient care, this activity is designed to expose oncology clinicians to the available peer-reviewed evidence and expert perspectives that can be translated into strategies for optimal patient care.

LEARNING OBJECTIVES

- Apply the results of emerging clinical research to the current and future treatment of NSCLC.
- Identify patients with metastatic NSCLC who may experience incremental benefit from maintenance biologic therapy and/or chemotherapy.
- Use biomarkers, clinical characteristics and tumor histology to select individualized front-line treatment approaches for patients with NSCLC.
- Educate appropriately selected patients about the benefits and risks of combination chemotherapy with bevacizumab or cetuximab.
- Recognize the effects of NSCLC tumor-specific mutations on prognosis and/or response to treatment with EGFR inhibitors.
- Recall the scientific rationale for investigational agents demonstrating promising activity in NSCLC, and distinguish how they may enhance existing therapeutic standards.
- Formulate an evidence-based treatment approach to adjuvant chemotherapy for NSCLC that recognizes the toxicities of different doublet regimens.
- Recall the scientific rationale for ongoing investigation of novel agents or therapeutic approaches in lung cancer, and counsel appropriately selected patients about study participation.

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TREATMENT OF EGFR WILD-TYPE, ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC)

FIRST-LINE AND MAINTENANCE THERAPY

DR BELANI: For patients with EGFR wild-type disease and nonsquamous cell histology — bevacizumab-eligible patients — we administer the ECOG-E4599 regimen of carboplatin/paclitaxel and bevacizumab, followed by maintenance bevacizumab if the patient has stable or responsive disease.

Alternatively, if a patient is not eligible to receive bevacizumab, we use the combination of carboplatin and pemetrexed. If these patients have responsive or stable disease, they go on to receive continuation maintenance pemetrexed, based on recently presented data from the PARAMOUNT trial.

In that trial, patients initially received the combination of cisplatin and pemetrexed. Patients were then stratified based on initial treatment response and were randomly assigned in a 2-to-1 fashion to single-agent pemetrexed or placebo.

An improvement in progression-free survival (PFS) was reported with maintenance pemetrexed as assessed by the investigators and by independent review. Survival data are not yet mature. The overall incidence of toxicity with maintenance therapy was minimal. The common toxicities were fatigue and neutropenia, and occasional other side effects occurred (Paz-Ares 2011; [1.1]).

DR LANGER: I tend to agree with Dr Belani. We administer a platinum-based combination, although increasingly we're using pemetrexed whether patients are eligible for bevacizumab or not.

Many of us have adopted what we call the Patel-Hensing regimen of carboplatin/pemetrexed and bevacizumab. Both pemetrexed and bevacizumab are continued as maintenance on this regimen (Patel 2009).

DR SOCINSKI: The PointBreak study is comparing 4 cycles of carboplatin/paclitaxel/bevacizumab followed by maintenance bevacizumab to the Patel-Hensing regimen (1.2). This trial has closed to accrual, and we may see initial results at ASCO 2012.

DR HEYMACH: One of the interesting facets of the PointBreak study is that 2 different questions are embedded in the study design. One question addresses treatment in the up-front setting, and the other is in the maintenance setting.

Another trial — ECOG-E5508 — is evaluating induction carboplatin/paclitaxel/bevacizumab followed by maintenance therapy with pemetrexed alone, bevacizumab alone or the combination (1.2). This in an important study in combination with PointBreak because these trials will help us isolate the importance of pemetrexed, bevacizumab or the combination in the maintenance setting.

DR LOVE: Tom, were you surprised by the PARAMOUNT study results?

DR LYNCH: I thought the magic of the JMEN trial was switch maintenance to pemetrexed for patients who had not received this agent in the

1.1

PARAMOUNT: A Phase III Study of Maintenance Pemetrexed (Pem) with Best Supportive Care (BSC) versus Placebo with BSC Immediately After Induction Treatment with Pem and Cisplatin for Advanced Nonsquamous Non-Small Cell Lung Cancer

Efficacy — Independent review*	Pem + BSC (n = 316)	Placebo + BSC (n = 156)	Hazard ratio	*p*-value
Median progression-free survival	3.9 mo	2.6 mo	0.64	0.0002

Select Grade 3 or 4 adverse events	Pem (n = 359)	Placebo (n = 180)
Anemia†	4.5%	0.6%
Fatigue†	4.2%	0.6%
Neutropenia†	3.6%	0%
Leukopenia	1.7%	0%

* 88% of patient cases were independently reviewed (472/539)
† Statistically significant between arms ($p \leq 0.05$)

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

initial induction doublet (Ciuleanu 2009), so I was a bit surprised by the PARAMOUNT study results. I thought that it would always make more sense to use pemetrexed maintenance after you first used a taxane or gemcitabine.

DR LILENBAUM: Perhaps another way to ask this question is to ask whether this is unique to pemetrexed or whether it's a paradigm shift that can be applied to other agents once you drop carboplatin or the platinum agent and simply continue with the second agent.

DR SOCINSKI: The interesting contrast between the JMEN and PARAMOUNT studies is that when you evaluate who benefited from switch maintenance in the JMEN trial, it was mostly the patients with stable disease, whereas in the PARAMOUNT study, the patients who tended to benefit were the ones who experienced a response.

So maybe that's telling us that the sensitivity early on should dictate whether or not we should practice continuation maintenance or switch maintenance.

SECOND- AND LATER-LINE THERAPY

DR LOVE: What options are available once a patient experiences disease progression?

DR LANGER: One option for bevacizumab-eligible patients is entering the Phase III AvaALL trial. Patients must have gone through initial treatment with 4 to 6 cycles of a bevacizumab-containing combination and then have started bevacizumab maintenance therapy, so we are selecting out patients who have already demonstrated benefits with bevacizumab.

Patients are then randomly assigned to a standard second-line treatment alone or with bevacizumab. In this study, continuation of bevacizumab

1.2

Key Trials of Maintenance Therapy in Advanced Non-Small Cell Lung Cancer

Identifier	Eligibility	Target accrual	Randomization
PointBreak	• Stage IIIB/IV • Measurable disease • No prior treatment • No predominant squamous cell • No CNS disease	900	• Pemetrexed/carboplatin/bevacizumab → pemetrexed/bevacizumab • Paclitaxel/carboplatin/bevacizumab → bevacizumab
ECOG-E5508	• Stage IIIB/IV • Measurable disease • Predominantly nonsquamous • No brain metastases	1,282	• **Induction:** - Paclitaxel/carboplatin/bevacizumab • **Maintenance:** - Bevacizumab - Pemetrexed - Pemetrexed/bevacizumab

www.clinicaltrials.gov. Accessed November 2011.

beyond disease progression can go on to a third- and even fourth-line treatment (1.3).

DR HEYMACH: Concern exists regarding whether tumors adapt and whether in some fashion they may activate alternate pathways that help them grow faster. So I believe this is an important study.

We recently published a study in which we followed plasma cytokines in patients who received bevacizumab for colorectal cancer. As patients became resistant, we observed a whole set of angiogenic factors, including basic FGF, HGF and PDGF rising before these tumors progressed (Kopetz 2010). So you can imagine that if you release the holds on angiogenesis, these tumors may become "revved up."

A consistent observation in studies with VEGF inhibitors has been that PFS can be prolonged, but it's much more difficult to prolong overall survival (OS). A great example of this is the BeTa study led by Roy Herbst, recently published in *The Lancet* (Herbst 2011; [1.4]).

This study evaluated erlotinib with bevacizumab versus erlotinib in the second-line setting. The authors reported a significant prolongation in PFS. The hazard ratio was on the order of 0.62, so a 38% reduction in the likelihood of disease progression was seen but with absolutely no difference whatsoever in OS. This raised the specter that you may be affecting postprogression survival when you discontinue bevacizumab.

NOVEL CYTOTOXIC AGENTS

DR LOVE: Mark, would you summarize the updated data that you presented at ASCO 2011 on nanoparticle albumin-bound (*nab*) paclitaxel as first-line therapy for advanced NSCLC?

DR SOCINSKI: At ASCO last year I presented the initial results on the

primary endpoint of this randomized Phase III trial, which compared carboplatin/paclitaxel at standard doses administered every 3 weeks to a regimen of carboplatin every 3 weeks with *nab* paclitaxel at 100 mg/m^2 weekly. The overall response rate for carboplatin/paclitaxel was 25%, which we would all say is par for the course, and it was 33% for carboplatin/*nab* paclitaxel.

One of the stratification factors was histology, squamous versus nonsquamous. For patients with squamous cell NSCLC, the objective response rate was 24% with carboplatin/paclitaxel versus 41% with carboplatin/*nab* paclitaxel — with virtually no difference in objective response rate in the nonsquamous population (Socinski 2010; [1.5]).

At this year's ASCO, we presented the PFS and OS data, and no statistically significant benefit was observed in either. Now, in case you're a real optimist, the hazard ratio was 0.91 in favor of the *nab* paclitaxel arm, but it was not statistically significant.

When you specifically evaluate the squamous population, in whom we reported a significant benefit in response rate, you find that the hazard ratio for PFS dropped down to about 0.88, but again it was not statistically significant for PFS or OS.

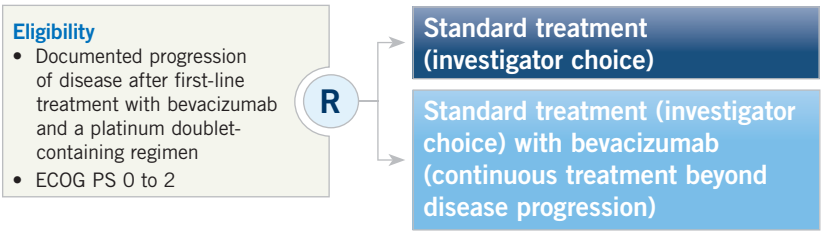
Interestingly, one of the other stratification factors was age. A subset

1.3

AvaALL: A Phase IIIb Trial of Standard Treatment with or without Bevacizumab Therapy Beyond Disease Progression for Patients with Nonsquamous Non-Small Cell Lung Cancer

Protocol IDs: MO22097, NCT01351415

Target Accrual: 600 (Open)



www.clinicaltrials.gov. Accessed November 2011.

1.4

BeTa Study: Efficacy of Second-Line Erlotinib with or without Bevacizumab in Advanced Non-Small Cell Lung Cancer

	Erlotinib + bevacizumab (n = 319)	Erlotinib + placebo (n = 317)	Hazard ratio	*p*-value
Median overall survival	9.3 mo	9.2 mo	0.97	0.7583
Median PFS	3.4 mo	1.7 mo	0.62	NR

PFS = progression-free survival; NR = not reported

Herbst RS et al. *Lancet* 2011;377(9780):1846-54.

analysis by age reported a remarkable difference in OS for the patients older than age 70. The median survival on the carboplatin/paclitaxel arm was approximately 11 months, and on the *nab* paclitaxel arm it was 19 months. That was not expected. We don't have a good explanation for that difference, but that's what the data show (Socinski 2011; [1.5]).

DR LOVE: What role does *nab* paclitaxel play in lung cancer clinical practice based on these data?

DR LYNCH: I envision 2 possibilities for *nab* paclitaxel. One is it may be a better agent for patients with squamous cell carcinoma based on Mark's preliminary evidence.

The second place it might provide a benefit is when we are using chemotherapy with immunomodulatory monoclonal antibodies, because you don't want dexamethasone administered when you're trying to stimulate T-cell mobilization. In that circumstance, avoiding steroids is a big advantage. That's another scenario in which I consider *nab* paclitaxel.

DR SOCINSKI: I believe *nab* paclitaxel creates a better option for many patients. The median age of a lung cancer patient is 70. Some patients have baseline neuropathy or have issues with steroids.

An advantage in infusion time also exists. I administer *nab* paclitaxel for 10 to 15 minutes versus the conventional paclitaxel 3- to 4-hour infusion schedule.

The rate of neuropathy was also lower with *nab* paclitaxel in our trial. Now, none of us believe that *nab* paclitaxel is less neuropathic. It probably has more to do with the schedule rather than the nature of the molecule. ■

1.5

Efficacy of Carboplatin/*Nab* Paclitaxel versus Carboplatin/Paclitaxel as First-Line Therapy for Advanced Non-Small Cell Lung Cancer

Response rate by histological subtype[1]	Carboplatin/ paclitaxel	Carboplatin/ *nab* paclitaxel	Response ratio*	*p*-value
All patients (n = 531; 521)	25%	33%	1.31	0.005
Squamous (n = 221; 228)	24%	41%	—	<0.001
Nonsquamous (n = 310; 292)	25%	26%	—	0.808
Survival by histological subtype and age[2]	**Carboplatin/ paclitaxel**	**Carboplatin/ *nab* paclitaxel**	**Hazard ratio**	***p*-value**
Median PFS — all patients (n = 531, 521)	5.9 mo	6.3 mo	0.902	0.214
Squamous (n = 221, 229)	5.7 mo	5.6 mo	0.865	0.245
Nonsquamous (n = 310, 292)	6.5 mo	6.9 mo	0.933	0.532
Median OS — all patients (n = 531, 521)	11.2 mo	12.1 mo	0.922	0.271
Age ≥70 years (n = 82, 74)	10.4 mo	19.9 mo	0.583	0.009

* Response ratio >1 favors *nab* paclitaxel; PFS = progression-free survival; OS = overall survival

[1] Socinski MA et al. *Proc ASCO* 2010;**Abstract LBA7511**.
[2] Socinski MA et al. *Proc ASCO* 2011;**Abstract 7551**.

SELECT PUBLICATIONS

Ciuleanu T et al. **Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: A randomised, double-blind, phase 3 study.** *Lancet* 2009;374(9699):1432-40.

Herbst RS et al. **Efficacy of bevacizumab plus erlotinib versus erlotinib alone in advanced non-small-cell lung cancer after failure of standard first-line chemotherapy (BeTa): A double-blind, placebo-controlled, phase 3 trial.** *Lancet* 2011;377(9780):1846-54.

Kopetz S et al. **Phase II trial of infusional fluorouracil, irinotecan, and bevacizumab for metastatic colorectal cancer: Efficacy and circulating angiogenic biomarkers associated with therapeutic resistance.** *J Clin Oncol* 2010;28(3):453-9.

Patel JD et al. **Phase II study of pemetrexed and carboplatin plus bevacizumab with maintenance pemetrexed and bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer.** *J Clin Oncol* 2009;27(20):3284-9.

Paz-Ares LG 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**.

Socinski M et al. **Survival results of a randomized, phase III trial of *nab*-paclitaxel and carboplatin compared with Cremophor-based paclitaxel and carboplatin as first-line therapy in advanced non-small cell lung cancer.** *Proc ASCO* 2011;**Abstract 7551**.

Socinski MA et al. **Results of a randomized, phase III trial of *nab*-paclitaxel (*nab*-P) and carboplatin (C) compared with Cremophor-based paclitaxel (P) and carboplatin as first-line therapy in advanced non-small cell lung cancer (NSCLC).** *Proc ASCO* 2010;**Abstract LBA7511**.

MANAGEMENT OF EGFR MUTATION-POSITIVE, ADVANCED NSCLC

FIRST-LINE THERAPY

DR LOVE: What is your approach to a patient with unknown EGFR mutation status whose disease is responding to chemotherapy/bevacizumab who is then found to have an EGFR mutation?

DR LYNCH: We know from work performed by Lecia Sequist that the response rate to tyrosine kinase inhibitors (TKIs) is quite good in first-, second- and third-line treatment of EGFR mutation-positive disease (Sequist 2008). So for a patient who is responding to chemotherapy/bevacizumab, I would continue with the bevacizumab and then immediately start erlotinib upon disease progression. I wouldn't fault someone who decided instead of administering bevacizumab maintenance to administer erlotinib maintenance. I believe that's also perfectly rational. In this setting you want to aim for the most mileage possible.

DR LOVE: Would you discuss the EURTAC study results reported at ASCO 2011 and contrast them with results from other trials of first-line therapy for advanced EGFR-mutant NSCLC?

DR LYNCH: One of the big questions after Tony Mok's publication on the IPASS study was whether the benefit of gefitinib compared to carboplatin/paclitaxel was related somehow to the fact that this was an Asian population

(Mok 2009). Many people thought the benefit was related to geography and ethnicity more than biology and science. They argued that something was different about the Asian population and questioned whether the IPASS results were generalizable to a Caucasian population.

I believe what's positive about the EURTAC study is that it provides additional evidence that the presence or absence of a mutation should drive therapy, as opposed to ethnicity. The EURTAC study was presented by Rafael Rosell at ASCO 2011. Twelve hundred patients were screened for EGFR mutations. The authors identified 174 patients with EGFR mutations. Those patients were randomly assigned to receive erlotinib or platinum-based chemotherapy.

The response rate was 15% with chemotherapy versus 58% with erlotinib. PFS was dramatically prolonged from 5.2 months to 9.7 months, and median survival was slightly prolonged, although not statistically significant. It's unclear whether a survival benefit will be seen, as those results are still immature (Rosell 2011; [2.1]).

The key points are that EURTAC confirmed the results of the IPASS study by showing a clear response rate and PFS benefit and confirmed the principle that for patients who have EGFR mutations, initial therapy with a TKI is associated with a clinical benefit in the form of an improved response rate and improved PFS. The presence or absence of an EGFR mutation should drive treatment, not ethnicity or geography.

DR LOVE: What role does cetuximab play in the first-line setting?

DR LYNCH: This question comes down to whether cetuximab should be approved by the FDA for NSCLC. I believe cetuximab is an active agent in lung cancer. However, we need to know which patients will benefit because it's not without toxicity.

Robert Pirker presented an intriguing study at IASLC 2011 on patients who received cetuximab on the FLEX study. One of the benefits of the FLEX study was that it required immunohistochemistry testing as a condition for enrolling. The report at IASLC this year focused specifically on H-score, which is a quantitative

2.1

EURTAC: A Phase III Trial of First-Line Erlotinib versus Chemotherapy for Patients with Advanced Non-Small Cell Lung Cancer with EGFR Activating Mutations

	Erlotinib (n = 86)	Chemotherapy (n = 87)	Hazard ratio	*p*-value
Median progression-free survival	9.7 mo	5.2 mo	0.37	<0.0001
Median overall survival	22.9 mo	18.8 mo	0.80	0.42
Best overall response rate	58%	15%	—	—
Complete response rate	2%	0%	—	—
Partial response rate	56%	15%	—	—
Disease control rate	79%	66%	—	—

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

measure that can evaluate the degree of membrane staining with EGFR. The cutoff number appears to be 200 — if your H-score is greater than 200, you intensely stain for EGFR. This occurred in approximately one third of the patients.

Those patients with an H-score greater than 200 appeared to have a much more substantial survival benefit (Pirker 2011; [2.2]). The median survival for those patients was approximately 2 to 3 months longer, not just 1 month longer as reported in the overall population (Pirker 2009). More importantly, patients with an H-score less than 200 did not have a survival benefit. I find that incredibly intriguing.

2.2

EGFR Expression as a Predictor of Survival for First-Line Chemotherapy (CT) with Cetuximab (Cet) in Patients with Advanced Non-Small Cell Lung Cancer on the FLEX Study

	ITT population		Low EGFR expression		High EGFR expression	
	CT (n = 568)	**CT + cet** (n = 557)	**CT** (n = 399)	**CT + cet** (n = 377)	**CT** (n = 167)	**CT + cet** (n = 178)
Median overall survival	10.1 mo	11.3 mo	10.3 mo	9.8 mo	9.6 mo	12.0 mo
	HR = 0.87; $p = 0.044$		HR = 0.99; $p = 0.88$		HR = 0.73; $p = 0.011$	

"Conclusion: The addition of cetuximab to first-line CT substantially prolonged OS in patients with advanced NSCLC and high tumor EGFR expression. EGFR expression is a disease-related biomarker that may facilitate the optimization of first-line CT plus cetuximab by tailoring treatment to those patients most likely to derive a clinically meaningful benefit."

Pirker R. et al. *Proc IASLC* 2011;**Abstract 1557**.

ACQUIRED RESISTANCE AND NOVEL STRATEGIES FOR TARGETING THE EGFR PATHWAY

DR LOVE: What are your thoughts on the recent report describing activity of the combination of afatinib and cetuximab in patients with NSCLC and acquired resistance to erlotinib or gefitinib?

DR LYNCH: The setting in which afatinib will have a huge effect is when used in combination with cetuximab. This combination is by far our best current regimen for a patient with secondary resistance to erlotinib. Response rates appear quite robust with the combination of cetuximab and afatinib (Janjigian 2011; [2.3]). My prediction is that the combination will be approved within the next 12 to 24 months.

DR LOVE: Vince, you were involved with the Phase II study of combination afatinib/cetuximab. Would you go through some of the clinical data that have been observed with this combination in EGFR TKI-resistant NSCLC?

DR MILLER: We reported an overall confirmed response rate of 40% for patients who'd experienced disease progression within 30 days on an EGFR TKI alone or an EGFR TKI with chemotherapy (2.3). The water-

2.3

Activity of Afatinib and Cetuximab in Patients with Advanced Non-Small Cell Lung Cancer with Acquired Resistance to Erlotinib or Gefitinib

Best response	**T790M-positive** (n = 26)	**T790M-negative** (n = 14)	**T790M unknown** (n = 3)	**No EGFR mutation** (n = 2)
Any partial response (PR)	50%	57%	67%	—
Confirmed PR	35%	50%	67%	—
Stable disease (SD)	42%	36%	33%	—
Clinical response (any PR + SD)	92%	93%	100%	100%

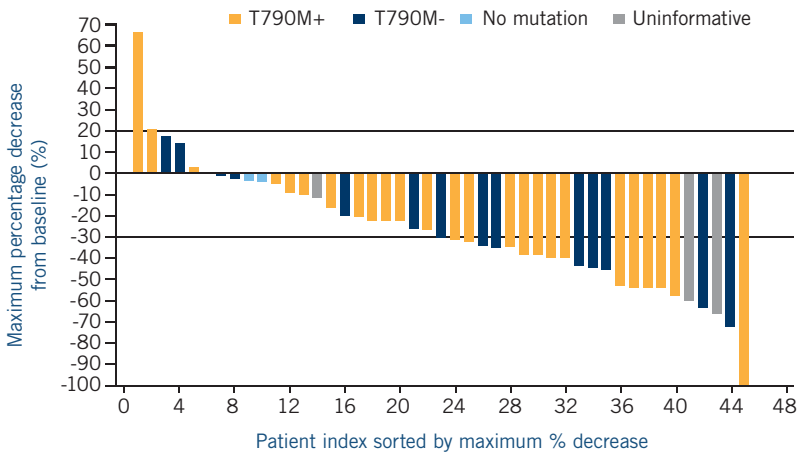
Select adverse events at MTD (n = 47)	All grades	Grade ≥3
Rash	89%	6%
Diarrhea	74%	6%
Fatigue	47%	4%
Dyspnea	28%	8%
Dermatitis acneiform	21%	2%

MTD = maximum tolerated dose

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

2.4

Best Response at Maximum Tolerated Dose to Afatinib/Cetuximab for Patients with Advanced Non-Small Cell Lung Cancer and Resistance to an EGFR Tyrosine Kinase Inhibitor



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

fall plot was impressive (Janjigian 2011; [2.4]).

DR LOVE: Has afatinib been used as first-line therapy for EGFR-mutant NSCLC?

DR MILLER: A fairly mature body of data exists on administering afatinib up front for treatment of disease with EGFR-sensitizing mutations. Response rates and median PFS are similar to the median with erlotinib.

DR LOVE: Is it possible to ascertain whether the efficacy is the same for patients with versus without T790M mutations at this point?

DR MILLER: It appears to be similar, as we've observed great responses in both patient groups (2.3).

DR LYNCH: The combination appears good for any type of acquired resistance, as far as we can tell now. Maybe MET would be different, but the acquired resistance phenotype is not limited to T790M alone, which then begs the question, should this combination be first-line therapy? I've seen some movement in the area of a first-line trial moving forward.

DR LANGER: We have an identified patient population with a mutation that becomes resistant. We had, up until now, no standard therapy in this setting. I hope that the afatinib/cetuximab combination can somehow obtain formal approval without going through the machinations of Phase III testing.

DR BELANI: I believe the need for our community oncologists to obtain biopsies and order these tests is the most important message here. We now have a select group of patients who will benefit from select therapy.

CONTINUATION OR REINITIATION OF EGFR TKI THERAPY

DR LOVE: What are your thoughts on rechallenging with erlotinib patients with advanced EGFR-mutant NSCLC who experience disease progression who have had prior treatment with erlotinib?

DR LYNCH: You often see nice responses in patients with EGFR mutations who are rechallenged with erlotinib after 1 year. For patients who don't have EGFR mutations, I wouldn't rechallenge with erlotinib. I would move on to another agent at that point.

DR LOVE: Vince, what are your thoughts on continuation of an EGFR TKI alone or with another agent at disease progression?

DR MILLER: I believe EGFR TKI therapy does remain an integral part of care. It may be that with some strategies one can transiently interrupt the TKI, in which case the proportion of the second site mutation can drop.

Chemotherapy comes in and has a nice result, and then you resume the TKI in the sensitive population. Or it may be that a subset of patients exists who fare best continuing on EGFR TKI therapy.

DR LILENBAUM: I believe those are the 2 main strategies. Until recently, I would have continued the TKI and added some form of chemotherapy for a patient with a known mutation or a robust, durable response to the TKI without molecular information.

I have recently shifted away from this approach. Now, in the absence of a clinical trial, I typically take the patient off TKI therapy, administer chemotherapy and then restart TKI therapy after completion of chemotherapy.

TARGETING MET IN NSCLC

DR LOVE: Would you discuss the results from the Phase II study evaluating MetMAb in combination with erlotinib for advanced NSCLC?

DR SEQUIST: MetMAb is an antibody that inhibits HGF-mediated activation of the MET receptor tyrosine kinase. A randomized Phase II study presented at ASCO evaluated MetMAb with erlotinib as second- and third-line treatment for NSCLC of any histology.

A key point was that patients had to have adequate tissue available to enter the trial so that a number of correlative analyses could be performed, which turned out to be quite revealing. Patients were randomly assigned to receive erlotinib and placebo or erlotinib and MetMAb.

The bottom line from this study was that when all the patients in the intent-to-treat population were evaluated, no huge advantage was evident. But when you viewed the available patient tissue and evaluated the MET expression by IHC, you found that patients were carefully parsed into a MET-positive and a MET-negative group.

In the MET-positive group, the combination of MetMAb and erlotinib performed quite well. In contrast, in the MET-negative group the combination of MetMAb and erlotinib appeared harmful compared to erlotinib alone (Spigel 2011; [2.5]). So this is an interesting biomarker that predicted both benefit and harm.

DR LYNCH: I was a bit surprised by some of the findings here, in that I thought MET inhibition would work best in patients with EGFR mutations because we believe MET is a potential mechanism of resistance and an alternative mechanism of signaling and activating PI3 kinase. But it seems as though this benefit may be even larger in patients who don't have EGFR mutations. So the most important part of this presentation to me was the confirmation that the

2.5 **OAM4558g: A Phase II Trial of Erlotinib (E) with or without MetMAb as Second- or Third-Line Therapy for Advanced Non-Small Cell Lung Cancer**

	Patients with positive c-MET immunohistochemistry			
	E + MetMAb	E + placebo	Hazard ratio	*p*-value
Median progression-free survival	2.9 mo	1.5 mo	0.53	0.04
Median overall survival	12.6 mo	3.8 mo	0.37	0.002
	Patients with negative c-MET immunohistochemistry			
Median progression-free survival	1.4 mo	2.7 mo	1.82	0.06
Median overall survival	8.1 mo	15.3 mo	1.78	0.16

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

2.6

Phase II Trial of the Oral c-MET Inhibitor Tivantinib (T) in Combination with Erlotinib (E) for Patients with Previously Treated, EGFR Inhibitor-Naïve Advanced Non-Small Cell Lung Cancer

Median progression-free survival	E + T	E + placebo	Hazard ratio	*p*-value
ITT population (n = 84, 83)	3.8 mo	2.3 mo	0.81	0.24
Nonsquamous population (n = 58, 59)	NR	NR	0.71	0.12
K-ras mutation cohort (n = 10, 5)	NR	NR	0.18	0.006

ITT = intent to treat; NR = not reported

Sequist LV et al. *J Clin Oncol* 2011;29(24):3307-15.

2.7

MARQUEE: A Phase III Trial of Erlotinib with ARQ 197 (Tivantinib) versus Erlotinib with Placebo for Patients with Previously Treated, Locally Advanced or Metastatic Nonsquamous Non-Small Cell Lung Cancer (NSCLC)

Protocol ID: NCT01244191 **Target Accrual:** 988 (Open)

Eligibility

- Nonsquamous NSCLC
- Disease progression on 1 to 2 lines of chemotherapy (1 of which must be a platinum doublet)

R

- Erlotinib PO qd + tivantinib PO BID
- Erlotinib PO qd + placebo PO BID

Sandler A et al. *Proc ASCO* 2011;**Abstract TPS217**; **www.clinicaltrials.gov**, November 2011.

benefit appears not to be necessarily related only to EGFR mutations in this setting. I would argue that we're seeing a combination effect here. Perhaps adding MetMAb or tivantinib to cetuximab and afatinib will become our 3-drug backbone at some point. The advantage of monoclonal antibodies is that they're cleaner than TKIs and are more likely to be well tolerated than a combination of multiple TKIs.

DR LOVE: Lecia, would you also discuss your results with ARQ 197, now called tivantinib, in combination with erlotinib in previously treated NSCLC?

DR SEQUIST: This agent is a TKI that blocks MET. We recently published results from a Phase II study that evaluated erlotinib with tivantinib versus erlotinib with placebo as second- and third-line therapy for NSCLC. When we parsed out the different groups, it appeared as though most of the benefit with the combination treatment occurred in the patients with nonsquamous disease. An intriguing, albeit small, subset of patients with K-ras mutations fared exceptionally well with erlotinib and tivantinib (Sequist 2011; [2.6]).

The overall results of the trial are now being followed up on in the randomized Phase III MARQUEE trial, which is evaluating the combination of erlotinib and tivantinib compared to erlotinib alone in patients with nonsquamous NSCLC.

Patients who have experienced disease progression after 1 or 2 prior lines of chemotherapy are randomly assigned in a 1-to-1 fashion to tivantinib/erlotinib or placebo/erlotinib. Patients are being stratified according to EGFR mutation and K-ras mutation status, and tissue is being collected for various analyses of MET status (Sandler 2011; [2.7]).

DR LOVE: Tom, where do you believe these strategies are heading?

DR LYNCH: I believe that neither of them will be home runs themselves. Two antibodies will be more specific and have less overlapping toxicity, which is advantageous. If the K-ras story pans out, then tivantinib will be a significant agent. ■

SELECT PUBLICATIONS

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**.

Mok TS et al. **Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma.** *N Engl J Med* 2009;361(10):947-57.

Pirker R et al. **Epidermal growth factor receptor (EGFR) expression as a predictor of survival for first-line chemotherapy plus cetuximab in FLEX study patients with advanced non-small cell lung cancer (NSCLC).** *Proc IASLC* 2011;**Abstract 1557**.

Pirker R et al. **Cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer (FLEX): An open-label randomised phase III trial.** *Lancet* 2009;373(9674):1525-31.

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**.

Sequist LV et al. **Randomized phase II study of erlotinib plus tivantinib versus erlotinib plus placebo in previously treated non-small-cell lung cancer.** *J Clin Oncol* 2011;29(24):3307-15.

Sequist LV, Lynch TJ. **EGFR tyrosine kinase inhibitors in lung cancer: An evolving story.** *Annu Rev Med* 2008;59:429-42.

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**.

ADJUVANT CHEMOTHERAPY FOR NSCLC

DR LOVE: In general, what is your preferred adjuvant regimen for patients with early-stage NSCLC?

DR HEYMACH: For disease with nonsquamous cell histology, I would typically administer cisplatin and pemetrexed. We tend to stick with cisplatin-based regimens, with the exception of patients with Stage IB disease greater than 4 centimeters. You can make an argument for using carboplatin and paclitaxel in that setting based on the CALGB-9633 data (Strauss 2008). So given a patient with poor performance status and Stage IB disease with a larger tumor who desires adjuvant therapy, I'll treat with carboplatin and paclitaxel. I prefer docetaxel and cisplatin for

3.1

TREAT: A Phase II Trial on Refinement of Early-Stage Non-Small Cell Lung Cancer Adjuvant Chemotherapy with Cisplatin/Pemetrexed (CPx) versus Cisplatin/Vinorelbine (CVb)

	CPx (n = 67)	**CVb** (n = 65)	*p*-value
Clinical feasibility rate*	95.5%	75.4%	0.001
Delivery of absolute intended dose	74.6%	20.0%	<0.0001
Grade 3 or 4 hematologic toxicity	10.0%	74.0%	<0.001

* Primary endpoint. Secondary efficacy endpoints not yet reported — awaiting longer follow-up

Kreuter M et al. *Proc ASCO* 2011;**Abstract 7002**.

patients with good performance status and squamous cell histology.

DR SOCINSKI: For disease with nonsquamous cell histology, I administer cisplatin/pemetrexed. In the case of squamous cell histology, I offer a choice of cisplatin/docetaxel or cisplatin/gemcitabine.

DR LANGER: We're administering more cisplatin/pemetrexed now since the Scagliotti data were reported (Scagliotti 2008). It's interesting how we had extrapolated data from the advanced disease setting to the adjuvant setting without data to justify it in the adjuvant setting directly.

At ASCO 2011, the TREAT analysis compared pemetrexed/cisplatin to cisplatin/vinorelbine, which we could conventionally call the standard adjuvant regimen for early-stage NSCLC.

The cisplatin/pemetrexed regimen was clearly superior to cisplatin/vinorelbine from the standpoints of feasibility, toxicity and treatment delivery. The investigators found it challenging to deliver all 4 cycles of cisplatin/vinorelbine on this trial (Kreuter 2011; [3.1]). Whether those results will translate into a long-term PFS or OS advantage remains to be seen.

Also at ASCO this year was a poster on the ongoing Phase III ECOG-E1505 trial evaluating adjuvant cisplatin-based chemotherapy with or without bevacizumab for completely resected early-stage NSCLC. That trial protocol was amended to allow the cisplatin/pemetrexed regimen. The poster at ASCO reported on basic demographics of patients enrolled to date and distribution of regimens. About 16% of patients on the ECOG-E1505 study have now received the cisplatin/pemetrexed regimen. The predominant regimen, as I would have predicted, is cisplatin/docetaxel (Wakelee 2011). ■

SELECT PUBLICATIONS

Scagliotti GV et al. **Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer.** *J Clin Oncol* 2008;26(21):3543-51.

Strauss GM et al. **Adjuvant paclitaxel plus carboplatin compared with observation in stage IB non-small-cell lung cancer: CALGB 9633 with the Cancer and Leukemia Group B, Radiation Therapy Oncology Group, and North Central Cancer Treatment Group study groups.** *J Clin Oncol* 2008;26(31):5043-51.

Wakelee HA et al. **Interim report of on-study demographics and toxicity from E1505, a phase III randomized trial of adjuvant (adj) chemotherapy (chemo) with or without bevacizumab (B) for completely resected early-stage non-small cell lung cancer (NSCLC).** *Proc ASCO* 2011;**Abstract 7013**.

MANAGEMENT OF SMALL CELL LUNG CANCER

DR LOVE: What is your take on the data presented at ASCO 2011 on the Phase III ACT-1 trial evaluating amrubicin versus topotecan as second-line therapy for small cell lung cancer (SCLC)?

DR LANGER: By way of background, amrubicin has been approved for several years in Japan. It is clearly active both in chemosensitive and chemorefractory SCLC. In Phase II studies, it has produced higher response rates and generally better PFS than topotecan (Kimura 2011).

ACT-1 is a huge Phase III trial with a 2-to-1 randomization of amrubicin versus standard full-dose topotecan. Patients with both chemorefractory and chemosensitive disease were enrolled. Amrubicin was clearly superior with respect to response rate and PFS with a trend toward an OS advantage. Both arms performed better than historic controls.

Typically, median survival is 3 or 4 months for patients with chemorefractory SCLC. Here it was about 5½ to 6 months, which remains dismal but better than what we've seen in the past.

In a subset analysis of the chemorefractory group, a borderline statistically significant advantage was observed in survival with a *p*-value just less than 0.05. Most of that benefit seemed to be toward the tail of the survival curves, beyond the median (Jotte 2011; [4.1]). ■

4.1

ACT-1: A Phase III Trial of Amrubicin versus Topotecan as Second-Line Treatment for Small Cell Lung Cancer

	Amrubicin (n = 424)	Topotecan (n = 213)	Hazard ratio	*p*-value
Median overall survival (ITT population)	7.5 mo	7.8 mo	0.880	0.1701
Chemotherapy-refractory cohort (n = 199, 96)	6.2 mo	5.7 mo	0.766	0.0469
Median progression-free survival	4.1 mo	3.5 mo	0.802	0.0182
Overall response rate	31.1%	16.9%	—	0.0001

Jotte R et al. *Proc ASCO* 2011;**Abstract 7000**.

SELECT PUBLICATIONS

Jotte R et al. **Randomized phase III trial of amrubicin versus topotecan (Topo) as second-line treatment for small cell lung cancer (SCLC).** *Proc ASCO* 2011;**Abstract 7000**.

Kimura T et al. **Review of the management of relapsed small-cell lung cancer with amrubicin hydrochloride.** *Clin Med Insights Oncol* 2011;5:23-34.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **In the Phase II TREAT trial of adjuvant chemotherapy for patients with early-stage NSCLC, treatment with cisplatin/vinorelbine resulted in similar levels of clinical feasibility, treatment delivery and toxicity when compared to cisplatin/pemetrexed.**
   a. True
   b. False

2. **The Phase III ECOG-E1505 trial is evaluating adjuvant chemotherapy with or without _____ for patients with completely resected early-stage NSCLC.**
   a. Bevacizumab
   b. Erlotinib
   c. Pemetrexed
   d. All of the above

3. **Which of the following trials is evaluating the use of maintenance therapy for patients with advanced NSCLC?**
   a. PointBreak
   b. PARAMOUNT
   c. ECOG-E5508
   d. All of the above

4. **In the Phase III BeTa trial, evaluating erlotinib with or without bevacizumab as second-line therapy for advanced NSCLC, which endpoint was significantly improved with the addition of bevacizumab?**
   a. PFS
   b. OS
   c. Both a and b
   d. None of the above

5. **Carboplatin/*nab* paclitaxel has demonstrated an improvement in response rates in the _____ subtype of NSCLC when compared to standard carboplatin/paclitaxel.**
   a. Squamous
   b. Nonsquamous
   c. Both a and b

6. **The Phase III EURTAC trial of erlotinib versus chemotherapy for patients with advanced NSCLC and EGFR activating mutations reported statistically significant improvements in _____ for patients receiving erlotinib.**
   a. Median PFS
   b. Median OS
   c. Overall response rate
   d. Both a and c

7. **In a Phase II trial of afatinib with cetuximab for patients with NSCLC and acquired resistance to erlotinib or gefitinib, investigators reported confirmed responses in _____.**
   a. T790M mutation-positive disease
   b. T790M mutation-negative disease
   c. Both of the above
   d. None of the above

8. **The addition of MetMAb to erlotinib resulted in improved PFS and OS among patients with c-MET-positive NSCLC in the second-line setting.**
   a. True
   b. False

9. **The Phase III MARQUEE trial is evaluating erlotinib with tivantinib for patients with _____ locally advanced or metastatic NSCLC.**
   a. Previously treated
   b. Previously untreated

10. **The Phase III ACT-1 trial of amrubicin versus topotecan as second-line treatment for SCLC reported statistically significant improvements in _____ for patients who received amrubicin.**
    a. Overall response rate
    b. PFS
    c. OS
    d. Both a and b
    e. All of the above

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Lung Cancer Update — Think Tank Issue 1, 2011

Research To Practice is committed to providing valuable continuing education for oncology clinicians, and your input is critical to helping us achieve this important goal. Please take the time to assess the activity you just completed, with the assurance that your answers and suggestions are strictly confidential.

PART 1 — Please tell us about your experience with this educational activity

How would you characterize your level of knowledge on the following topics?

4 = Excellent 3 = Good 2 = Adequate 1 = Suboptimal

	BEFORE	AFTER
Phase III AvaALL study of continuous bevacizumab beyond disease progression in advanced nonsquamous NSCLC	4 3 2 1	4 3 2 1
Results of the EURTAC study: Erlotinib versus chemotherapy in advanced, EGFR-mutant NSCLC	4 3 2 1	4 3 2 1
PointBreak trial: Pemetrexed/carboplatin/bevacizumab followed by maintenance pemetrexed/bevacizumab versus the ECOG-E4599 regimen for Stage IIIB/IV nonsquamous NSCLC	4 3 2 1	4 3 2 1
PARAMOUNT study results with maintenance pemetrexed after cisplatin/pemetrexed for advanced nonsquamous NSCLC	4 3 2 1	4 3 2 1
Quantitative EGFR expression level as a predictor of benefit from first-line cetuximab with chemotherapy in the FLEX trial	4 3 2 1	4 3 2 1
Activity of afatinib/cetuximab in patients with NSCLC and acquired resistance to erlotinib or gefitinib	4 3 2 1	4 3 2 1
Results of studies combining MetMAb or ARQ 197 with erlotinib for advanced NSCLC	4 3 2 1	4 3 2 1
Results of a Phase III study of carboplatin with *nab* paclitaxel compared to standard-formulation paclitaxel as first-line therapy in advanced NSCLC	4 3 2 1	4 3 2 1

Was the activity evidence based, fair, balanced and free from commercial bias?

☐ Yes ☐ No If no, please explain: .....

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☐ This activity validated my current practice; no changes will be made
☐ Create/revise protocols, policies and/or procedures
☐ Change the management and/or treatment of my patients
☐ Other (please explain): .....

The content of this activity matched my current (or potential) scope of practice.

☐ Yes ☐ No If no, please explain: .....

Please respond to the following learning objectives (LOs) by circling the appropriate selection:

4 = Yes 3 = Will consider 2 = No 1 = Already doing N/M = LO not met N/A = Not applicable

As a result of this activity, I will be able to:

- Apply the results of emerging clinical research to the current and future treatment of NSCLC. . . . . 4 3 2 1 N/M N/A
- Identify patients with metastatic NSCLC who may experience incremental benefit from maintenance biologic therapy and/or chemotherapy . . . . . 4 3 2 1 N/M N/A
- Use biomarkers, clinical characteristics and tumor histology to select individualized front-line treatment approaches for patients with NSCLC. . . . . 4 3 2 1 N/M N/A
- Educate appropriately selected patients about the benefits and risks of combination chemotherapy with bevacizumab or cetuximab. . . . . 4 3 2 1 N/M N/A
- Recognize the effects of NSCLC tumor-specific mutations on prognosis and/or response to treatment with EGFR inhibitors. . . . . 4 3 2 1 N/M N/A

- Recall the scientific rationale for investigational agents demonstrating promising activity in NSCLC, and distinguish how they may enhance existing therapeutic standards. . . . . 4 3 2 1 N/M N/A
- Formulate an evidence-based treatment approach to adjuvant chemotherapy for NSCLC that recognizes the toxicities of different doublet regimens. . . . . 4 3 2 1 N/M N/A
- Recall the scientific rationale for ongoing investigation of novel agents or therapeutic approaches in lung cancer, and counsel appropriately selected patients about study participation. . . . . 4 3 2 1 N/M N/A

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PART 2 — Please tell us about the faculty and moderator for this educational activity

4 = Excellent 3 = Good 2 = Adequate 1 = Suboptimal

Faculty	Knowledge of subject matter	Effectiveness as an educator
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John Heymach, MD, PhD	4 3 2 1	4 3 2 1
Corey J Langer, MD	4 3 2 1	4 3 2 1
Rogerio C Lilenbaum, MD	4 3 2 1	4 3 2 1
Thomas J Lynch Jr, MD	4 3 2 1	4 3 2 1
Vincent A Miller, MD	4 3 2 1	4 3 2 1
Lecia V Sequist, MD, MPH	4 3 2 1	4 3 2 1
Mark A Socinski, MD	4 3 2 1	4 3 2 1
Moderator	**Knowledge of subject matter**	**Effectiveness as an educator**
Neil Love, MD	4 3 2 1	4 3 2 1

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Lung Cancer™ UPDATE

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