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"

CME Certified

Lung Cancer Update
A Continuing Medical Education Audio Series

STATEMENT OF NEED/TARGET AUDIENCE

Lung cancer is the leading cause of cancer mortality in the United States in both men and women, resulting in more deaths than breast, prostate, colon and pancreatic cancer combined. Progress in the screening, prevention and treatment of this disease has been modest, and about 85 percent of patients who develop lung cancer will die from it. In addition, a sense of therapeutic nihilism has pervaded the medical community in the past. Chemotherapy, surgery and radiation therapy have had a modest effect on patient outcomes; however, recent improvements have been seen in time to progression and survival in lung cancer clinical trials. Published results from ongoing clinical trials lead to the continuous emergence of new therapeutic agents and changes in the indications for existing treatments. In order to offer optimal patient care — including the option of clinical trial participation — the practicing medical oncologist must be well informed of these advances. To bridge the gap between research and patient care, *Lung Cancer Update* uses discussions with leading oncology investigators. By providing access to the latest research developments and expert perspectives, this CME program assists these physicians in the formulation of up-to-date clinical management strategies.

GLOBAL LEARNING OBJECTIVES

- Critically evaluate the clinical implications of emerging clinical trial data in lung cancer treatment, and incorporate these data into management strategies in the adjuvant, neoadjuvant, locally advanced and metastatic settings.
- Counsel appropriately selected patients about the availability of ongoing clinical trials.
- Develop and explain a management strategy for treatment of elderly patients and those with poor performance status in the adjuvant, neoadjuvant, locally advanced and metastatic settings.
- Integrate emerging data on utilization of targeted molecular therapies and molecular and genetic assays in the development of individual management strategies for patients with lung cancer.
- Counsel patients with localized primary lung cancer about the risks and benefits of adjuvant chemotherapy.
- Identify the impact of smoking-related comorbidities on the treatment of patients with lung cancer and integrate smoking cessation into the management strategy for these patients.

PURPOSE OF THIS ISSUE OF *LUNG CANCER UPDATE*

The purpose of this special edition of *Lung Cancer Update* is to support these global objectives by offering the perspectives of Drs Curran, Greco, Hanna, Kim, Langer, Lynch, Miller, Pass, Sandler, Schiller and Socinski on the integration of emerging clinical research data into the management of lung cancer.

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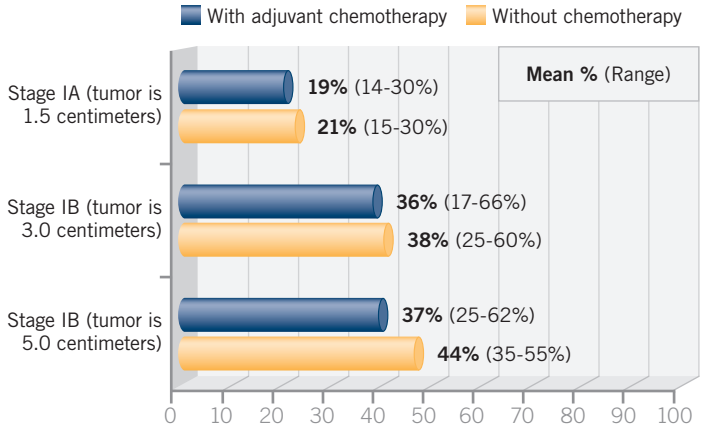
FACULTY POLL QUESTION 1

The following patients (age 60 and in good health) ask you to estimate their risk of relapse with and without adjuvant chemotherapy. How would you respond?



n = 9

SOURCE: Survey of Think Tank Participants, July 12, 2007, Miami, Florida.

Select Excerpts from the Discussion

Track 15

DR LOVE: Ed, how do you approach the choice of an adjuvant chemotherapy regimen?

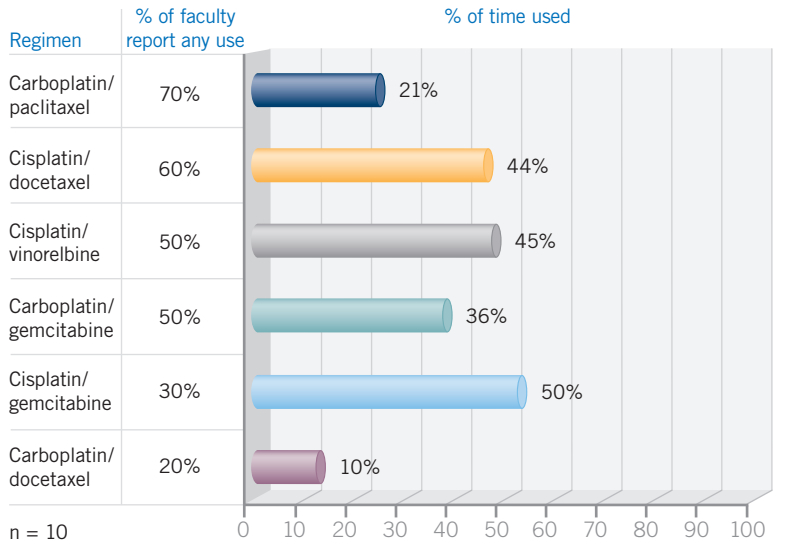
DR KIM: I generally use cisplatin-based therapy. I use cisplatin/docetaxel 60 to 70 percent of the time and cisplatin/vinorelbine 30 to 40 percent of the time.

DR LOVE: Nasser?

DR HANNA: I use docetaxel/cisplatin. The logic behind that is docetaxel is a slightly superior drug compared to vinorelbine in the metastatic setting, and vinorelbine is the drug for which we have the most data in the adjuvant setting. I extrapolate that docetaxel will be more effective in the adjuvant

FACULTY POLL QUESTION 2

When you use adjuvant chemotherapy off protocol, which regimens do you tend to use? (Check all that apply)



SOURCE: Survey of Think Tank Participants, July 12, 2007, Miami, Florida.

setting. However, I have no qualms with colleagues using cisplatin/vinorelbine or other regimens from the trials.

DR LYNCH: I agree with Nasser. I answered the question as 90 percent cisplatin/docetaxel and 10 percent cisplatin/gemcitabine. However, if I see a 69-year-old patient six weeks postoperatively with a creatinine level of 1.7 mg/dL who doesn't look so great, I would likely use carboplatin/paclitaxel.

Tracks 21-22

DR LOVE: Joan, can you discuss ECOG-E1505, which randomly assigns patients to adjuvant therapy with a cisplatin-based regimen with or without bevacizumab (1.1)?

DR SCHILLER: ECOG-E1505 is a Phase III trial for patients with selected Stage IB to IIIA NSCLC, who will be randomly assigned to four cycles of chemotherapy versus four cycles of chemotherapy and up to one year of bevacizumab. To some degree, the chemotherapy will be "dealer's choice." The referring physician can choose among cisplatin/gemcitabine, cisplatin/docetaxel and cisplatin/vinorelbine.

1.1

Phase III Study of Adjuvant Chemotherapy with or without Bevacizumab for Patients with Completely Resected Stage IB-IIIA NSCLC

Protocol ID: ECOG-E1505
Target Accrual: 1,500

* Patients are stratified according to type of chemotherapy, stage, histology and gender.

Eligibility

- Stage IB (≥4 cm) to IIIA
- Resection within the past six to 12 weeks
- ECOG performance status 0-1
- No history of CVA or TIA
- History of MI or angina acceptable if no evidence of active disease within the past 12 months

Study Contact

Heather Wakelee, MD, Protocol Chair
Tel: 650-723-9094; 800-756-9000

SOURCE: NCI Physician Data Query, August 2007.

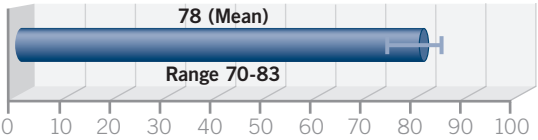
Eligible patients will have Stage IB to IIIA disease, with eligible IB tumors measuring greater than four centimeters in size. The reason for that is based on a subset analysis CALGB conducted of their adjuvant study, in which patients with larger Stage IB tumors were the ones who seemed to benefit (Strauss 2006). We'll apply the typical bevacizumab exclusion criteria. Patients will be allowed to have had squamous cell carcinoma, however, because the disease will be removed. It is hoped that the histology will not be important if the tumor is not there.

DR GRECO: I believe the scientific aspects of the study are good, but we see a lot of arbitrary thinking about which adjuvant regimens we should use. People have strong feelings about cisplatin, and although I prefer to be more lenient with the type of chemotherapy allowed, many purists are designing the studies.

DR SANDLER: I agree. The study was originally for all patients with Stage IB to IIIA disease. Then the CALGB update reported on this 4-cm concept, and the NCI was adamant that we use the 4-cm cutoff. So we're using the 4-cm cutoff based on retrospective data from the CALGB-9633 study, which used paclitaxel/carboplatin (Strauss 2006), but they won't allow paclitaxel/carboplatin in the E1505 study, which has been the only regimen to report survival data with bevacizumab (Sandler 2006).

FACULTY POLL QUESTION 3

What was the age of the oldest patient to whom you have administered adjuvant chemotherapy?



n = 10

SOURCE: Survey of Think Tank Participants, July 12, 2007, Miami, Florida.

DR SOCINSKI: I believe patients will balk not at the randomization between chemotherapy with or without bevacizumab but at receiving bevacizumab for a year. I speak with a lot of patients about adjuvant therapy — it usually is three or four cycles, and then they're done. Now you have the patient who is postthoracotomy thinking about treatment that is either nine weeks or 12 months.

Track 51

DR LOVE: Tom, our faculty has treated patients between 70 and 83 years of age with adjuvant chemotherapy. What are your thoughts?

DR LYNCH: I believe that is a reasonable range. I don't believe it's wrong if you have an 83-year-old woman without other medical problems. It's difficult to imagine she has lung cancer with no other medical problems, but if that's the case, it's reasonable to treat someone regardless of age. The catch is that there are very few patients who fit this description exactly. In general, we do consider age as a factor. Early eighties is probably as high as one should go.

DR SOCINSKI: When you use adjuvant therapy in older patients, what are you using? My practice has been to use cisplatin for all patients when I can, but we know cisplatin is a more toxic drug in the elderly. I was the one who used adjuvant therapy in the 83-year-old, and I used carboplatin/paclitaxel. ■

SELECT PUBLICATIONS

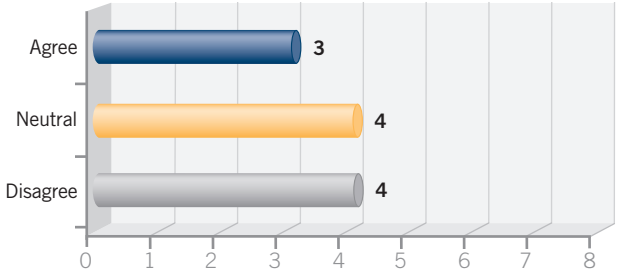
Azzoli CG et al. **A phase II tolerability study of cisplatin plus docetaxel as adjuvant chemotherapy for resected non-small cell lung cancer.** *J Thorac Oncol* 2007;2(7):638-44. **Abstract**

Sandler A et al. **Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer.** *N Engl J Med* 2006;355(24):2542-50. **Abstract**

Strauss GM et al. **Adjuvant chemotherapy in stage IB non-small cell lung cancer (NSCLC): Update of Cancer and Leukemia Group B (CALGB) protocol 9633.** *Proc ASCO* 2006;**Abstract 7007**.

FACULTY POLL QUESTION 4

Over the next few years, it will be shown that bevacizumab is a useful addition to chemoradiation therapy for locally advanced NSCLC.



n = 11

SOURCE: Survey of Think Tank Participants, July 12, 2007, Miami, Florida.

Select Excerpts from the Discussion

Track 37

DR LOVE: Wally, can you discuss the clinical trial strategies incorporating bevacizumab with chemoradiation therapy for Stage III disease?

DR CURRAN: In SWOG-S0533, bevacizumab is introduced to a SWOG-S9504 core concurrently and after chemoradiation therapy either on day one or 15 (2.1). The patients are stratified by risk for hemoptysis, based on squamous-cell histology, history of hemoptysis and evidence of bulky disease. Mark Socinski has an investigator-initiated trial also evaluating bevacizumab with chemoradiation therapy.

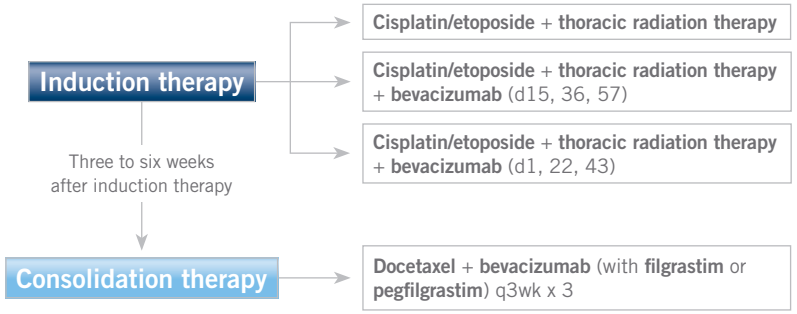
Preclinical data suggest that VEGF inhibition can sensitize tumor cells to radiation therapy and chemoradiation therapy (Jain 2001). We have to be aware of competing toxicity — the greatest risk is of a tremendous antitumor response that may result in a catastrophic local effect.

DR LOVE: I didn't realize that, historically, when only chemoradiation therapy

2.1

Multicenter Pilot Trial of Cisplatin/Etoposide/Radiation Therapy Followed by Consolidation Docetaxel and Bevacizumab in Three Cohorts of Patients with Inoperable, Locally Advanced Stage III NSCLC

Protocol ID: SWOG-S0533
Target Accrual: 182 (Open)
Trial Start Date: June 15, 2006



Primary Endpoints
Frequency and severity of toxicity

Secondary Endpoints
Progression-free survival, overall survival and response

Stratification
High versus low risk

Eligibility
- Stage IIIA (N2) disease meeting the following criteria:
  - N2 mediastinal lymph nodes must be multiple or bulky on CT scan or x-ray so that the patient is not a candidate for induction chemotherapy or chemoradiation therapy followed by surgical resection
- Stage IIIB disease with histologically or radiographically confirmed positive N3 nodes
- T4 lesions of any size that invade the mediastinum, heart, great vessels, trachea, esophagus, vertebral body or cranium

SOURCE: NCI Physician Data Query, October 2007.

was used, you initially saw tracheoesophageal (TE) fistulas because of tumor response.

DR CURRAN: It even existed in the radiation therapy–alone era. My elders taught me that if you have patients with esophageal or tracheal involvement, use a lower radiation dose per fraction so as not to have such a rapid response as to develop a fatal TE fistula. We need to figure out how to conduct these new trials where we integrate three modalities providing us with a response.

Tracks 39-42

DR LOVE: Nasser, what's your view of the clinical implications of the HOG trial you presented at ASCO this year (Hanna 2007; [2.2])?

2.2

HOG LUN 01-24: Progression-Free and Overall Survival with Cisplatin/Etoposide and Concurrent Chest Radiation Therapy (XRT) with or without Consolidation Docetaxel for Patients with Inoperable Stage III NSCLC

	Cisplatin/etoposide/XRT → observation	Cisplatin/etoposide/XRT → docetaxel	*p*-value
Progression-free survival (median)	12.9 mo	12.3 mo	0.941
Overall survival (median)	24.1 mo	21.5 mo	0.940

SOURCE: Hanna NH et al. *Proc ASCO* 2007;**Abstract 7512**.

DR HANNA: The important, larger picture with HOG LUN 01-24 is that we previously had no randomized trial to support consolidation docetaxel, and now our current randomized trial does not add support to its use (Hanna 2007).

DR GRECO: I agree with Nasser that we really had no randomized data to support what I call the "SWOG factor," which may have inhibited our understanding of how to treat unresectable Stage III disease, because more and more patients were receiving that therapy in an ad hoc fashion, without the Phase III data. HOG LUN 01-24 suggests that the majority of patients don't benefit from that approach, although some still may.

DR LOVE: Corey, does HOG LUN 01-24 essentially end the use of consolidation therapy?

DR LANGER: I don't believe consolidation therapy is dead. We need to evaluate other drugs — preferably other targeted agents, particularly if we figure out through molecular correlative studies who is more likely to respond to the drugs. The blind shotgun approach probably doesn't work here.

DR LOVE: What are some of the innovative concepts you believe are worth pursuing for patients with Stage III disease, Nasser?

DR HANNA: Whether the anti-angiogenics will work well with chemoradiation therapy is still not known. The bottom line is that the biologics must be used in a targeted patient population. It is not one size fits all. We may identify a subset of patients who should receive targeted agents, but the majority may not benefit, except for anti-angiogenics, which could be the exception. ■

SELECT PUBLICATIONS

Hanna NH et al. **Phase III trial of cisplatin (P) plus etoposide (E) plus concurrent chest radiation (XRT) with or without consolidation docetaxel (D) in patients (pts) with inoperable stage III non-small cell lung cancer (NSCLC): HOG LUN 01-24/USO-023.** *Proc ASCO* 2007;**Abstract 7512**.

Jain RK. **Normalizing tumor vasculature with antiangiogenic therapy: A new paradigm for combination therapy**. *Nat Med* 2001;7(9):987-9. **Abstract**

3.1 **AVAiL Trial: Progression-Free Survival (PFS) After Cisplatin/Gemcitabine with or without Bevacizumab in Chemotherapy-Naïve Patients with Advanced or Recurrent NSCLC**

	Median PFS	Hazard ratio	*p*-value
Cisplatin/gemcitabine + placebo	6.1 months	Reference	Reference
Cisplatin/gemcitabine + bevacizumab 7.5 mg/kg	6.7 months	0.75	0.0026
Cisplatin/gemcitabine + bevacizumab 15 mg/kg	6.5 months	0.82	0.0301

SOURCE: Manegold C et al. *Proc ASCO* 2007;**Abstract LBA7514**.

Select Excerpts from the Discussion

Track 4

DR KIM: The AVAiL trial was evaluating cisplatin/gemcitabine, with two different doses of bevacizumab (versus placebo) — 7.5 mg/kg and 15 mg/kg — which were grouped for the final analysis (Manegold 2007; [3.1]).

The primary endpoint of the study was progression-free survival, and it was not powered for overall survival.

The study was positive for the addition of bevacizumab at the 7.5-mg/kg and 15-mg/kg doses compared to placebo. I should note that 15 mg/kg is the established dose of bevacizumab in NSCLC currently.

We knew everyone would start comparing the two doses of bevacizumab — however, this trial was not powered to show that difference directly.

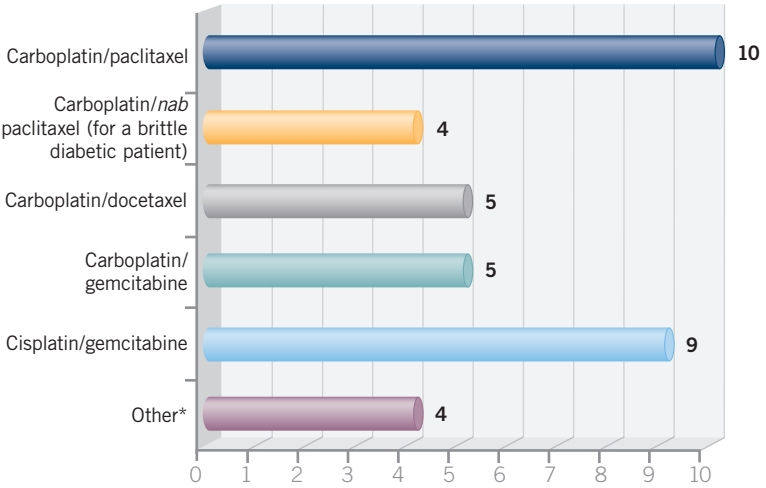
We don't have overall survival data yet.

The importance of the AVAiL study is that it is the second positive Phase III trial with bevacizumab in front-line NSCLC. It supports the use of bevacizumab in the first-line setting with chemotherapy.

Obvious benefit was seen with both of the doses of bevacizumab — the standard 15-mg/kg dose and the lower dose of 7.5 mg/kg.

FACULTY POLL QUESTION 5

Which of the following agents do you believe are reasonable to combine with bevacizumab in first-line management of metastatic disease? (Check all that apply)



n = 10

* Cisplatin with paclitaxel or docetaxel, cisplatin with vinorelbine, carboplatin with pemetrexed

SOURCE: Survey of Think Tank Participants, July 12, 2007, Miami, Florida.

DR LYNCH: The good news from the AVAiL trial is that the study was positive and both doses are safe. I believe it's reasonable to continue to administer 15 mg/kg. The AVAiL trial also demonstrated that bevacizumab can be given safely with a nonpaclitaxel-containing regimen.

A slight increase was seen in the rate of hypertension with the 15-mg/kg dose compared to 7.5 mg/kg.

However, most importantly, the toxicities we're most worried about — hemoptysis and bleeding — were similar between the two arms (Manegold 2007). Safety-wise, people can feel comfortable with either dose of bevacizumab.

DR LOVE: Joan, one of the first questions that came up after this presentation was, what about the dose of bevacizumab in the adjuvant study, ECOG-E1505?

DR SCHILLER: Because all of the data we have in terms of survival are with the 15-mg/kg dose, that's the dose we will use going forward.

3.2

ECOG-E4599: Efficacy of the Addition of Bevacizumab (B) to Paclitaxel (P) and Carboplatin (C) in Previously Untreated Metastatic Nonsquamous NSCLC

Endpoint	PC (n = 433)	PCB (n = 417)	HR (95% CI)	*p*-value
Median OS	10.3 months	12.3 months	0.79 (0.67-0.92)	0.003
Two-year OS	15%	23%	—	—
Median PFS	4.5 months	6.2 months	0.66 (0.57-0.77)	<0.001
Overall response	15%	35%	—	<0.001

HR = hazard ratio; OS = overall survival; PFS = progression-free survival

SOURCE: Sandler A et al. *N Engl J Med* 2006a;355(24):2542-50. **Abstract**

Track 6

DR LOVE: Alan, we are interested in your perception of the AVAiL trial results because of your involvement with ECOG-E4599.

DR SANDLER: The AVAiL study provides more supportive evidence that bevacizumab has activity in NSCLC when administered with chemotherapy, in this case a cisplatin-based regimen (Manegold 2007). It was designed to evaluate time to progression, and it met its endpoint. It was not designed specifically to evaluate the two different doses.

ECOG-E4599 is the only study that has shown a survival advantage, and the dose of bevacizumab was 15 mg/kg (Sandler 2006a; [3.2]). That's the dose that has the best level of evidence.

The AVAiL trial also demonstrated that the toxicity with bevacizumab was similar to what was seen in ECOG-E4599. The incidence of bleeding was about the same, maybe a bit lower. Hypertension was roughly the same, or perhaps a bit higher. Within the AVAiL trial, the incidence of some of the noncritical toxicities was a little higher with the higher dose. For example, proteinuria and hypertension may have been more dose related, but the severe toxicities were roughly similar across both bevacizumab arms (Manegold 2007).

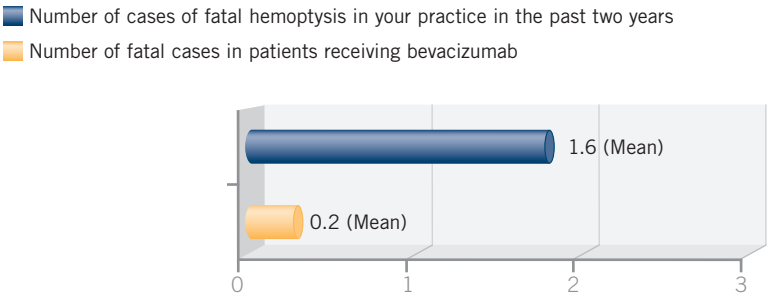
Tracks 7, 10

DR LOVE: Ed, which chemotherapy agents do you tend to combine with bevacizumab in metastatic disease?

DR KIM: I believe any one of these regimens with carboplatin or cisplatin is reasonable with 15 mg/kg of bevacizumab. We have enough safety data. At our

FACULTY POLL QUESTION 6

Use of Bevacizumab in Clinical Practice



n = 9

SOURCE: Survey of Think Tank Participants, July 12, 2007, Miami, Florida.

institution, we try to enroll in a study first. If that's not possible, I wrote the trial with carboplatin/docetaxel/bevacizumab, and that's been my preference off protocol. However, I believe either taxane is reasonable.

DR LOVE: Vince, how are you approaching these questions off study — the dose of bevacizumab and the choice of chemotherapeutic agent?

DR MILLER: I continue to use 15 mg/kg of bevacizumab, but I've homed in more on a platinum/taxane doublet until we have survival data from the AVAiL study.

DR GRECO: A purist would say that only paclitaxel and carboplatin should be used. In my opinion, any of the chemotherapy regimens thought to be equivalent in advanced NSCLC and that have Phase II safety data are reasonable to use with bevacizumab.

Track 11

DR LOVE: Do you believe bevacizumab-related hemoptysis is associated with tumor response?

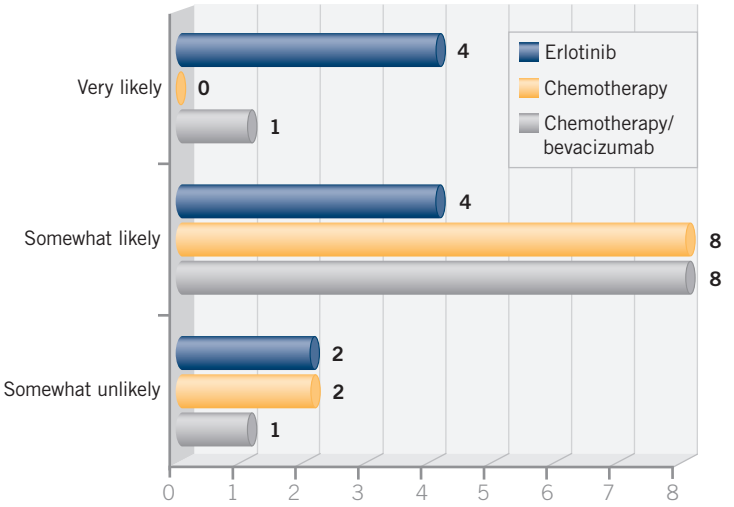
DR LYNCH: I would say yes — it is associated with a response. The only problem is that some people bleed in the first or second cycle.

DR LOVE: Let's say you see a patient who starts to have a rapid response that is cavitary. How will you react?

DR LYNCH: I recently received an email from a colleague who showed me

FACULTY POLL QUESTION 7

A 60-year-old woman with NSCLC who is a lifelong nonsmoker presents with symptomatic metastatic disease to the bone. She asks you what the likelihood is of the following therapies providing symptomatic relief for at least three months. How would you respond?



n = 10

SOURCE: Survey of Think Tank Participants, July 12, 2007, Miami, Florida.

a beautiful response to carboplatin/paclitaxel/bevacizumab. It had become completely cavitary. He asked me, "Tom, what do I do now?" I said, "Keep going. That's what you're aiming for."

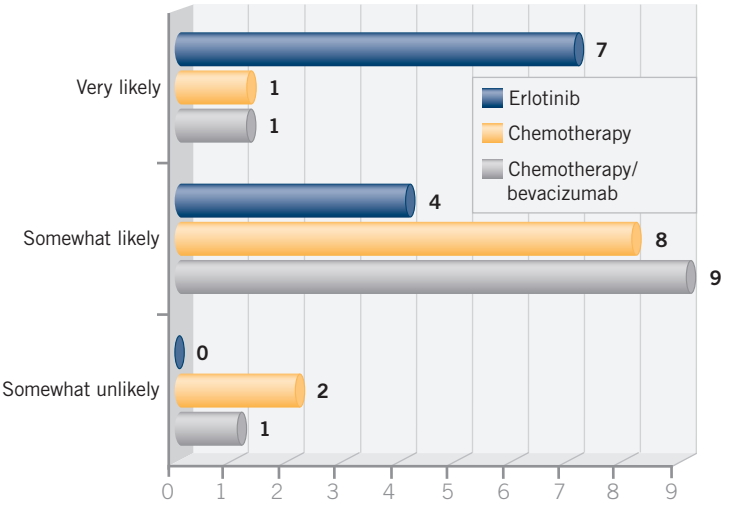
This doctor consulted with three other doctors, took the patient off the study, radiated the lung and put the patient on maintenance bevacizumab afterward. The presence of the cavitation led this doctor to use radiation therapy. I'm curious how other people would handle that large cavitary response.

DR CURRAN: Intuitively it makes sense that it could work because radiation therapy has a hemostatic effect. There are even trials now in which a small dose of radiation is administered prior to the bevacizumab for patients thought to be at high risk — those with squamous histology, central disease, a history of hemoptysis or some other endobronchial disease.

DR SCHILLER: In ECOG-E4599, we retrospectively evaluated any factors that would predict for fatal bleeds. The only one that stood out was pretreatment cavitation (Sandler 2006b).

FACULTY POLL QUESTION 8

A 60-year-old woman with NSCLC presents with exon 19 mutation and symptomatic metastatic disease to the bone. She asks you what the likelihood is of the following therapies providing symptomatic relief for at least three months. How would you respond?



n = 11

SOURCE: Survey of Think Tank Participants, July 12, 2007, Miami, Florida.

DR SANDLER: Remember, the numbers are small. We combined the Phase II study with ECOG-E4599, and the overall number of significant pulmonary hemorrhages was relatively small (Sandler 2006b).

Track 12

DR HANNA: I believe the central location of the tumor is a big risk factor. I do not administer bevacizumab to patients with Stage III disease who have central cavitary lesions. At this point, even if we radiate these tumors ahead of time, we don't know if it will make a difference.

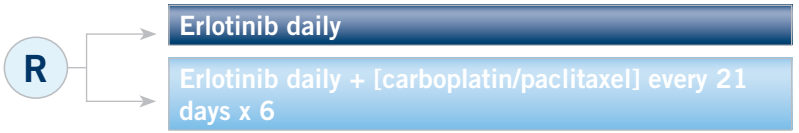
If it's mediastinal lymphadenopathy, location doesn't worry me. If the tumor is bulky and located next to the pulmonary artery, that worries me.

DR SANDLER: Looking back at the clinical studies, location has never been an issue. Is it the proximity to a vessel or bronchus that might be more important in terms of causing bleeding and hemoptysis? None of that has been borne out. You're nervous when it's central, but we forge ahead.

3.3

Phase II Randomized Trial of Erlotinib with or without Carboplatin/ Paclitaxel in Patients with Chemotherapy-Naïve Stage IIIB/IV NSCLC

Protocol ID: CALGB-30406
Target Accrual: 180 (Open)



Select Eligibility Criteria

- Adenocarcinoma
- Stage IIIB/IV
- Nonsmoker or former light smoker

Study Contacts

Cancer and Leukemia Group B
Pasi Janne, MD, PhD
Tel: 617-632-6076
Vincent Miller, MD
Tel: 212-639-7243

SOURCE: NCI Physician Data Query, August 2007.

DR LYNCH: The AVAiL study did not find any relationship to location. I believe that centrality won't be a big concern.

Tracks 28, 31

DR LOVE: If you have a patient who is a lifelong nonsmoker and has symptomatic metastatic disease, what is the likelihood that she's going to derive pain relief from antitumor therapy? Most of you thought she would be likely to obtain pain relief from erlotinib but not as likely with chemotherapy. Vince, does that mean that in these situations you would consider erlotinib as first-line therapy?

DR MILLER: I tend to use erlotinib more either as first-line or third-line therapy. I'm driven by either the mutation status or clinical factors to incorporate erlotinib into therapy early on. If patients have favorable profiles (ie, a mutation that confers a 75 percent positive predictive value for response), they live a long time. It's simply a matter of time until we establish a survival benefit for patients with mutations, but we need the trials to be completed.

DR KIM: We don't perform mutation testing on everyone, but when we see patients with these clinical factors — never smokers or adenocarcinoma with BAC features — I use the standard option of chemotherapy/bevacizumab. The second aspect would be to consider the nonstandard therapy — erlotinib.

DR GRECO: Patients need to be selected out. For those presenting in the first-line setting who are nonsmokers, my choice would be erlotinib.

3.4 **Novel Paclitaxel Formulation: *Nab* Paclitaxel (Abraxane®)**

"ABI-007…is a novel, biologically interactive, nanometer-sized albumin-bound paclitaxel particle initially developed to avoid the toxicities associated with polyethylated castor oil. It is the first of a new class of anticancer agents that incorporate albumin particle technology and exploit the unique properties of albumin, a natural carrier of lipophilic molecules in humans.

Administered as a colloidal suspension of 130 nanometer particles, ABI-007 allows the safe infusion of significantly higher doses of paclitaxel than the doses used with standard paclitaxel therapy, with shorter infusion schedules (30 minutes v 3 hours, respectively) and no premedication."

SOURCE: Gradishar WJ et al. *J Clin Oncol* 2005;23(31):7794-803. **Abstract**

With the mutations, the rate of benefit is even higher. We can identify a group of patients, clinically, who are likely to respond. I won't use first-line erlotinib with the majority of patients who have FISH-negative disease, have no mutations or have been smoking heavily and have RAS mutations.

DR SOCINSKI: I believe erlotinib is an important drug for never smokers. If they don't want to enroll on CALGB-30406 (3.3), I tend to treat never smokers with four cycles of chemotherapy and bevacizumab followed by immediate erlotinib.

Track 43

DR LOVE: What is the potential role of nanoparticle albumin-bound (*nab*) paclitaxel in lung cancer treatment?

DR GRECO: It has a different type of neurotoxicity that usually abates. It's less toxic and easier to use than the standard paclitaxel formulation (3.4), and the breast cancer data are impressive. We don't have definitive data in lung cancer yet, but there will be a Phase III trial comparing *nab* paclitaxel to standard paclitaxel. This agent may not be superior, but the toxicity advantages could be important.

DR LOVE: If it turns out that the efficacy is the same but there's less neurotoxicity than with Cremophor-based paclitaxel, would that be enough for you?

DR GRECO: It would be enough for me. It's already on the market and used in breast cancer. I believe there are a number of circumstances in which less neurotoxicity — for alcoholics, diabetics and others — is an advantage.

Track 45

DR LOVE: Vince, can you discuss where we are with vandetanib (ZD6474; [3.5])?

3.5

Phase II Randomized Trial of Vandetanib with Docetaxel in Patients with Previously Treated NSCLC

	Vandetanib 300 mg + docetaxel (n = 44)	Vandetanib 100 mg + docetaxel (n = 42)	Placebo + docetaxel (n = 41)
Progression-free survival (PFS)			
Median PFS	17.0 weeks	18.7 weeks	12.0 weeks
HR vs placebo + docetaxel	0.83	0.64	—
95% confidence interval	0.50-1.36	0.38-1.05	—
Partial response rate	18%	26%	12%
Overall survival (OS)			
Median OS	7.9 months	13.1 months	13.4 months
HR vs placebo + docetaxel	1.28	0.91	—
95% confidence interval	0.78-2.10	0.55-1.52	—

HR = hazard ratio

SOURCE: Heymach JV et al. *J Clin Oncol* 2007;25(27):4270-7. **Abstract**

DR MILLER: There are Phase III trials searching for benefits (3.6). It's a biologically active drug. In patients who have failed erlotinib, one trial is comparing vandetanib to supportive care. Another trial is comparing it to erlotinib after progression on chemotherapy. A third trial is evaluating docetaxel with vandetanib as a second-line regimen versus docetaxel alone.

DR LOVE: If you had to guess which strategy would be the most effective with vandetanib, what would you hypothesize?

DR LYNCH: I believe the placebo-controlled trials will most likely be positive. However, we've made little progress in standard second-line therapy for lung cancer, so I'd love to see the docetaxel combination study show benefit. ■

SELECT PUBLICATIONS

Ardizzoni A et al; CISCA (CISplatin versus CArboplatin) Meta-analysis Group. **Cisplatin-versus carboplatin-based chemotherapy in first-line treatment of advanced non-small-cell lung cancer: An individual patient data meta-analysis.** *J Natl Cancer Inst* 2007;99(11):847-57. **Abstract**

Arnold AM et al; National Cancer Institute of Canada Clinical Trials Group Study BR.20. **Phase II study of vandetanib or placebo in small-cell lung cancer patients after complete or partial response to induction chemotherapy with or without radiation therapy: National Cancer Institute of Canada Clinical Trials Group Study BR.20.** *J Clin Oncol* 2007;25(27):4278-84. **Abstract**

Cappuzzo F. **Should every lung cancer patient be tested for EGFR mutation?** *Expert Opin Ther Targets* 2006;10(6):789-91. **Abstract**

Clark GM et al; National Cancer Institute of Canada Clinical Trials Group. **Smoking history and epidermal growth factor receptor expression as predictors of survival benefit from erlotinib for patients with non-small-cell lung cancer in the National Cancer Institute of Canada Clinical Trials Group study BR.21.** *Clin Lung Cancer* 2006;7(6):389-94. **Abstract**

3.6

Ongoing Phase III Randomized Trials of Vandetanib (ZD6474) in Locally Advanced or Metastatic NSCLC

Protocol ID	Target accrual	Randomization	Setting	Start date
D4200C00032	1,240	Vandetanib + docetaxel Docetaxel	2nd line	3/2006
D4200C00057	1,150	Vandetanib Erlotinib	2nd, 3rd line	8/2006
D4200C00044	930	Vandetanib + BSC BSC	Post-EGFR TKI failure	11/2006
D4200C00036	508	Vandetanib + pemetrexed Pemetrexed	2nd line	1/2007

SOURCE: **www.clinicaltrials.gov**, October 2007.

Gradishar WJ et al. **Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer.** *J Clin Oncol* 2005;23(31):7794-803. **Abstract**

Gridelli C et al. **Cisplatin plus gemcitabine or vinorelbine for elderly patients with advanced non small-cell lung cancer: The MILES-2P studies.** *J Clin Oncol* 2007;25(29):4663-9. **Abstract**

Hawkins MJ et al. **Study of three weekly *nab*-paclitaxel regimens in combination with carboplatin as first-line therapy in advanced non-small cell lung cancer (NSCLC).** *Proc ASCO* 2007;**Abstract 7659**.

Herbst RS et al. **Phase II study of efficacy and safety of bevacizumab in combination with chemotherapy or erlotinib compared with chemotherapy alone for treatment of recurrent or refractory non small-cell lung cancer.** *J Clin Oncol* 2007;25(30):4743-50. **Abstract**

Heymach JV et al. **Randomized, placebo-controlled phase II study of vandetanib plus docetaxel in previously treated non small-cell lung cancer.** *J Clin Oncol* 2007;25(27):4270-7. **Abstract**

Manegold C et al. **Randomised, double-blind multicentre phase III study of bevacizumab in combination with cisplatin and gemcitabine in chemotherapy-naïve patients with advanced or recurrent non-squamous non-small cell lung cancer (NSCLC): BO17704.** *Proc ASCO* 2007;**Abstract LBA7514**.

Sandler A et al. **Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer.** *N Engl J Med* 2006a;355(24):2542-50. **Abstract**

Sandler AB et al. **Retrospective study of clinical and radiographic risk factors associated with early onset, severe pulmonary hemorrhage in bevacizumab-treated patients with advanced non-small cell lung cancer (NSCLC).** *Proc ASCO* 2006b;**Abstract 7068**.

Sequist LV et al. **Molecular predictors of response to epidermal growth factor receptor antagonists in non-small-cell lung cancer.** *J Clin Oncol* 2007;25(5):587-95. **Abstract**

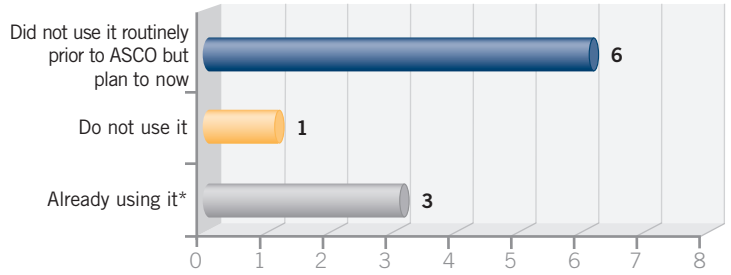
Tsao MS et al. **Erlotinib in lung cancer — Molecular and clinical predictors of outcome.** *N Engl J Med* 2005;353(2):133-44. **Abstract**

SECTION 4

Prophylactic Cranial Irradiation (PCI) for Extensive-Stage Small Cell Lung Cancer (SCLC)

FACULTY POLL QUESTION 9

How have you used PCI in extensive-disease small cell lung cancer in a clinical setting?



n = 10

* Years of use (mean) = 20 (range 10-30)

SOURCE: Survey of Think Tank Participants, July 12, 2007, Miami, Florida.

Select Excerpts from the Discussion

Tracks 1-2

DR LOVE: Wally, can you discuss the implications of the EORTC-08993 trial that evaluated the impact of PCI on the reduction of symptomatic brain metastases for patients with extensive-disease SCLC who responded to chemotherapy (Slotman 2007; [4.1])?

DR CURRAN: My concern with this study is that the patients did not undergo meticulous restaging, including brain scans at baseline. At the recent RTOG meeting, we discussed the possibility that these patients were being treated for subclinical brain metastases. I am not comfortable with a randomized trial in which you don't evaluate the brain before you treat it. I have to assume there's a 10 to 25 percent risk of subclinical disease. Also, their definition of chemotherapy response to continue on to the randomization was not particularly rigorous.

The positive results are an interesting observation, but it is not up to American

4.1

EORTC Randomized Trial of Prophylactic Cranial Irradiation (PCI) versus No PCI in Extensive-Disease SCLC After Response to Chemotherapy

Endpoints	PCI (n = 143)	Control (n = 143)	Hazard ratio (95% CI), *p*-value
One-year symptomatic brain metastases	14.6%	40.4%	0.27 (0.16-0.44), $p < 0.001$
Six-month failure-free survival	23.4%	15.5%	0.76 (0.59-0.96), $p = 0.02$
One-year overall survival	27.1%	13.3%	0.68 (0.52-0.88), $p = 0.003$

SOURCE: Slotman B et al. *Proc ASCO* 2007;**Abstract 4**.

clinical research standards. The magnitude of survival benefit is puzzling. How can the survival benefit be greater than in limited disease?

DR HANNA: I agree with Wally about the criticism that they should have obtained baseline brain imaging studies on all patients. However, if the patient met certain criteria that raised suspicion of brain metastases, they did require baseline brain imaging. They didn't tell us how many patients had undergone baseline brain imaging, which would have been useful. There was also an imbalance in the proportion of patients who had other sites of metastases, presumably liver and adrenal, which was worse in the observation arm.

The problem I have isn't that the study is not provocative and we probably ought to be doing it for some patients; it's that the author's conclusion was PCI is now the standard practice for all patients with extensive-stage SCLC who are responding. If you have a patient with liver and adrenal metastases that has some response to initial chemotherapy, it's ridiculous to use PCI.

DR LOVE: Describe the patient whom you would treat with PCI.

DR HANNA: I would use it with the patient who is free of bulky liver, adrenal or bone metastases or the patient who has an excellent response to chemotherapy and based on clinical intuition is going to survive for a while. Those are the patients who will suffer from symptomatic brain metastases.

DR GRECO: I believe selected patients can benefit, and this study would support that. Most studies — even the large trials — don't tell us about individual patients. You use that information in the context of the patient you see in your office that day. You don't just say, "This study showed a survival benefit, so I'm going to use this therapy for every patient with extensive-stage SCLC." ■

SELECT PUBLICATION

Slotman B et al. **A randomized trial of prophylactic cranial irradiation (PCI) versus no PCI in extensive disease small cell lung cancer after a response to chemotherapy (EORTC 08993-22993).** *Proc ASCO* 2007;**Abstract 4**.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **The Phase III randomized trial ECOG-E4599 demonstrated that the addition of bevacizumab to carboplatin/paclitaxel improved overall and progression-free survival in patients with advanced NSCLC.**
   a. True
   b. False

2. **Following retrospective analysis of the ECOG-E4599 trial data, which of the following factors was found to be attributed to the pulmonary hemorrhage associated with bevacizumab?**
   a. Age
   b. Prior chemoradiation
   c. Cavitation

3. **Which doses of bevacizumab were evaluated in the AVAiL trial?**
   a. 2.5 mg/kg
   b. 7.5 mg/kg
   c. 15 mg/kg
   d. Both a and b
   e. Both b and c

4. **Results from the AVAiL trial concluded that both doses of bevacizumab when combined with cisplatin/gemcitabine significantly improved progression-free survival and response rate.**
   a. True
   b. False

5. **Which dose(s) of bevacizumab is being evaluated in the adjuvant study ECOG-E1505?**
   a. 2.5 mg/kg
   b. 7.5 mg/kg
   c. 15 mg/kg
   d. Both a and b
   e. Both b and c

6. **ECOG-E1505 will evaluate the efficacy of bevacizumab in combination with _____ in the adjuvant setting.**
   a. Cisplatin-based therapy
   b. Carboplatin-based therapy
   c. Both a and b
   d. None of the above

7. **Clinical trials suggest that patients with NSCLC are more likely to respond to treatment with erlotinib based upon which of the following?**
   a. Gender
   b. Ethnicity
   c. Nonsmoking status
   d. All of the above

8. **Which of the following are benefits of *nab* paclitaxel over paclitaxel?**
   a. Shorter infusion time
   b. Lack of premedication requirement
   c. Less neurotoxicity
   d. All of the above

9. **Based on results from EORTC-08993, prophylactic cranial irradiation significantly reduces the risk of symptomatic brain metastases and significantly improves both disease-free and overall survival in patients with extensive-stage SCLC.**
   a. True
   b. False

Post-test answer key: 1a, 2c, 3e, 4a, 5c, 6a, 7d, 8d, 9a

EVALUATION FORM

Lung Cancer Update — Think Tank Issue 1, 2007

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GLOBAL LEARNING OBJECTIVES

To what extent does this issue of *LCU* address the following global learning objectives?

- Critically evaluate the clinical implications of emerging clinical trial data in lung cancer treatment, and incorporate these data into management strategies in the adjuvant, neoadjuvant, locally advanced and metastatic settings. . . . . 5 4 3 2 1 N/A
- Counsel appropriately selected patients about the availability of ongoing clinical trials. . . . . 5 4 3 2 1 N/A
- Develop and explain a management strategy for treatment of elderly patients and those with poor performance status in the adjuvant, neoadjuvant, locally advanced and metastatic settings. . . . . 5 4 3 2 1 N/A
- Integrate emerging data on utilization of targeted molecular therapies and molecular and genetic assays in the development of individual management strategies for patients with lung cancer. . . . . 5 4 3 2 1 N/A
- Counsel patients with localized primary lung cancer about the risks and benefits of adjuvant chemotherapy. . . . . 5 4 3 2 1 N/A
- Identify the impact of smoking-related comorbidities on the treatment of patients with lung cancer and integrate smoking cessation into the management strategy for these patients. . . . . 5 4 3 2 1 N/A

OVERALL EFFECTIVENESS OF THE FACULTY MEMBERS

To what extent do you feel the faculty members' comments were helpful or not helpful?

. . . . . .

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Objectives were related to overall purpose/goal(s) of activity.	5	4	3	2	1	N/A
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Will influence how I practice.	5	4	3	2	1	N/A
Will help me improve patient care.	5	4	3	2	1	N/A
Stimulated my intellectual curiosity.	5	4	3	2	1	N/A
Overall quality of material.	5	4	3	2	1	N/A
Overall, the activity met my expectations.	5	4	3	2	1	N/A
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Which of the modules did you find particularly relevant to your practice? Please elaborate on what about the topics and comments was helpful to you.

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LCUTT107

Lung Cancer™ UPDATE

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