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Patterns of Care in Medical Oncology

Management of Lung Cancer in the Adjuvant and Metastatic Settings

Adjuvant Therapy of Non-Small Cell Lung Cancer

Treatment of Stage III Non-Small Cell Lung Cancer

Treatment of Metastatic Non-Small Cell Lung Cancer

Treatment of Small Cell Lung Cancer

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A Survey Comparing Practices of Lung Cancer Clinical Investigators and General Oncologists

CME Certified

FROM THE PUBLISHERS OF:

Breast Cancer® UPDATE · Colorectal Cancer™ UPDATE · Lung Cancer™ UPDATE · Non-Hodgkin's Lymphoma™ UPDATE · Prostate Cancer™ UPDATE · Renal Cell Cancer™ UPDATE

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PowerPoint files of the graphics contained in this document can be downloaded at **www.PatternsOfCare.com**.

Continuing Medical Education (CME) Information

STATEMENT OF NEED/TARGET AUDIENCE

It is important for practicing oncologists to be aware of similarities and differences between his or her practice patterns, those of others in community practice and those of lung cancer clinical investigators. It is also important for oncologists to recognize that heterogeneity exists in the oncology community, especially in clinical situations for which there is suboptimal research evidence.

This program focuses on the self-described practice patterns of randomly selected medical oncologists on a variety of key clinical issues in cancer. Also included are clinical investigator commentary and references addressing these issues. This CME program will provide medical oncologists with information on national cancer patterns of care to assist with the development of clinical management strategies.

GLOBAL LEARNING OBJECTIVES FOR THE *PATTERNS OF CARE* SERIES

- Compare and contrast the management strategies of community oncologists and cancer clinical investigators for the treatment of lung cancer in the adjuvant, locally advanced and metastatic settings.
- Discuss cancer management issues for which relative agreement and heterogeneity exist in patterns of care.
- Counsel cancer patients about multiple acceptable treatment options when they exist.

PURPOSE OF THIS ISSUE

The purpose of this issue of *Patterns of Care* is to support these objectives by comparing the perspectives of 150 randomly selected community medical oncologists with 21 thoracic oncology specialists and to offer in-depth commentary from faculty regarding their practice patterns in the management of lung cancer.

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COMMERCIAL SUPPORT

This program is supported by education grants from Genentech BioOncology/OSI Pharmaceuticals Inc and Sanofi-Aventis.

PHARMACEUTICAL AGENTS DISCUSSED IN THIS PROGRAM

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Financial disclosures for other oncologists quoted in this issue may be found in the cited CME pieces of origin.

COMMENTS IN THIS MONOGRAPH

To highlight the practice issues presented in this survey, a number of excerpts are included from CME publications. For financial disclosures of authors, please refer to the original publications. Audio programs from Research To Practice can be accessed at **www.LungCancerUpdate.com**.

ABOUT THIS SURVEY

This survey was completed in August 2007 by 150 community-based medical oncologists and 21 oncologists who specialize in lung cancer management (see list on page 3) in the United States. The community-based oncologists were randomly selected from a proprietary mail list used by Research To Practice for distribution of its CME programs, and the specialists included physicians who have participated in education programs with Research To Practice and others referred for this project.

Clinical Investigators Completing the Survey (August 2007)

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Editor's Note: Patterns of care or recipe for disaster?

The enclosed results from a survey of 150 randomly selected US-based medical oncologists and 21 lung cancer clinical investigators illustrate the current integration of clinical research findings into daily patient care.

As with all studies of this type, one can tease out interesting variations in how physicians approach common and not-so-common management scenarios.

Clearly there have been a number of major recent changes in the treatment of non-small cell lung cancer, most notably the evolution of adjuvant chemotherapy and the new role of biologics — specifically bevacizumab and erlotinib — in the management of advanced disease.

Even better, as we have seen in many other major solid tumor types, ongoing clinical trials are attempting to evaluate these and other targeted interventions at earlier stages of disease with the hope that other therapeutic home runs on par with adjuvant trastuzumab in breast cancer are on the horizon for lung cancer.

Unfortunately, an equally valid view of lung cancer practice patterns is that our available interventions are woefully inadequate in the face of this brutal disease.

It is almost impossible to comprehend that in spite of these and other therapies, ***almost 160,000*** people die of lung cancer every year in the US alone. (See figure below).

Comparing this apocalyptic statistic to breast cancer — where incidence rates are almost identical, but 42,000 lives are lost each year — we must acknowledge that our current diagnostic, therapeutic and technologic advances have pretty much failed to meaningfully address this profound public health disaster.

Have we become desensitized to what is going on here? Has the smoking connection made it OK to blame the patients and therefore ignore the human toll of this disease? I am tired of hearing the whining about smoking. Yes, most lung cancers are theoretically preventable — just like heart disease — but let's get real here.

The ads and PR campaigns targeting teenagers to prevent this addiction are critical, long overdue and inadequately funded, but tens of millions of people have already quit smoking and remain at high risk to die of this disease in the next few years.

At our recent lung cancer think tank, my co-chair, Tom Lynch, voiced concern that our current understanding of lung cancer is prerudimentary at best and concluded that available resources should be poured into the laboratory to go back to the basics to figure out what this disease is all about.

Tom's suggestion couldn't be more apropos because the truth is that a therapeutic platform in which 75 percent of patients are dead in a couple of years reflects patterns of care that just don't work.

— Neil Love, MD
DrNeilLove@ResearchToPractice.com
October 11, 2007

A SNAPSHOT OF CAUSES OF DEATH IN THE UNITED STATES

Annual overall mortality: Most common causes

Age	All ages	<25 yrs	25-34 yrs	35-44 yrs	45-54 yrs	55-64 yrs	65-74 yrs	75-84 yrs	85+ yrs
All causes	2,448,288	73,512	41,300	89,461	176,781	262,519	413,497	703,024	687,852
Heart disease	685,089	2,022	3,250	13,600	37,732	65,060	107,263	207,331	248,796
Cancer	556,902	3,194	3,741	15,509	49,843	95,692	141,248	167,617	80,046
Cerebrovascular disease	157,689	437	583	2,460	6,127	9,946	20,708	52,847	64,579
Chronic respiratory disease*	126,382	395	282	950	3,537	12,077	29,919	49,286	29,934
Accidents	109,277	20,552	12,541	16,766	15,837	9,170	8,081	13,108	13,146

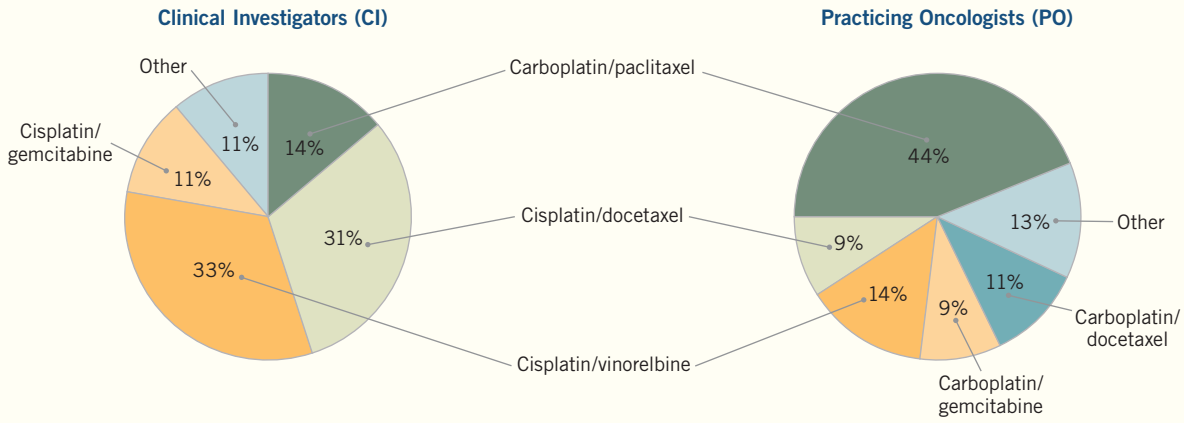
Annual cancer mortality: Most common tumor types

Age	All ages	<25 yrs	25-34 yrs	35-44 yrs	45-54 yrs	55-64 yrs	65-74 yrs	75-84 yrs	85+ yrs
All cancers	556,902	3,194	3,741	15,509	49,843	95,692	141,248	167,617	80,046
Lung	158,086	29	154	2,478	12,374	30,956	49,386	48,619	14,088
Colon/rectum/anus	55,958	44	291	1,315	4,442	8,304	12,934	17,331	11,296
Lymphoid/hematopoietic	55,679	1,169	865	1,728	3,785	7,471	12,885	18,442	9,334
Breast	42,000	16	407	2,716	6,365	8,267	8,338	9,644	6,245
Pancreas	30,777	11	60	548	2,540	5,320	8,104	9,708	4,486
Prostate	29,554	2	1	25	418	2,074	6,033	12,284	8,717

SOURCES: Hoyert DL et al. National Vital Statistics Reports 2006;54(13):1-26; Office of Statistics and Programming, Centers for Disease Control and Prevention. Data Source: NCHS, National Vital Statistics System; * Lower respiratory disease

FIGURE 1

Approximately what percent of the time do you use the following adjuvant non-small cell lung cancer (NSCLC) chemotherapy regimens?



Lung Cancer Update 2007 (1)

DR CHANDRA P BELANI: Adjuvant therapy has become the standard for patients with resected non-small cell lung cancer. After 2005, it was the standard for patients with Stage IB to IIIA disease. Recently we have developed a brewing controversy regarding whether we should administer adjuvant therapy to patients with Stage IB disease.

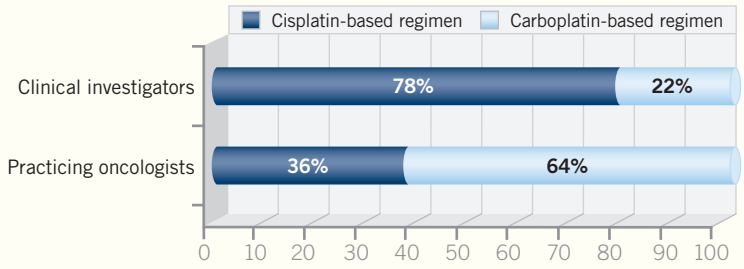
One issue in the controversy is whether or not it was carboplatin that caused the failure of the carboplatin and paclitaxel regimen for patients with Stage IB disease in CALGB-9633. At long-term follow-up, the data failed to show an improvement in overall survival because the hazard ratio fell from 0.62 to 0.80 and the *p*-value was no longer significant. As a word of caution: This was a small trial, and it is still not completed. In general, considering the results of the other clinical trials, the JBR.10 study, the IALT study and the ANITA trial, adjuvant chemotherapy did play a role in Stage IB disease, but in those trials the chemotherapy was cisplatin based.

The CALGB-9633 trial has shown in a subset analysis that among patients who have tumors greater than four centimeters, a benefit still exists. But again, we may be reading too much into these subset analyses, which were not clear endpoints of these clinical studies.

In the clinical setting, for Stage IB disease, I offer chemotherapy to patients, informing them that in a small subset it has shown a benefit and in another subset it has not shown a benefit. I let the patient decide whether he or she wants to receive adjuvant chemotherapy. If the tumor is greater than four centimeters in size, then I usually suggest that the patient receive it.

FIGURE 2

Approximate percentage of the time the following platinum-based chemotherapy regimens for adjuvant treatment of NSCLC are utilized:



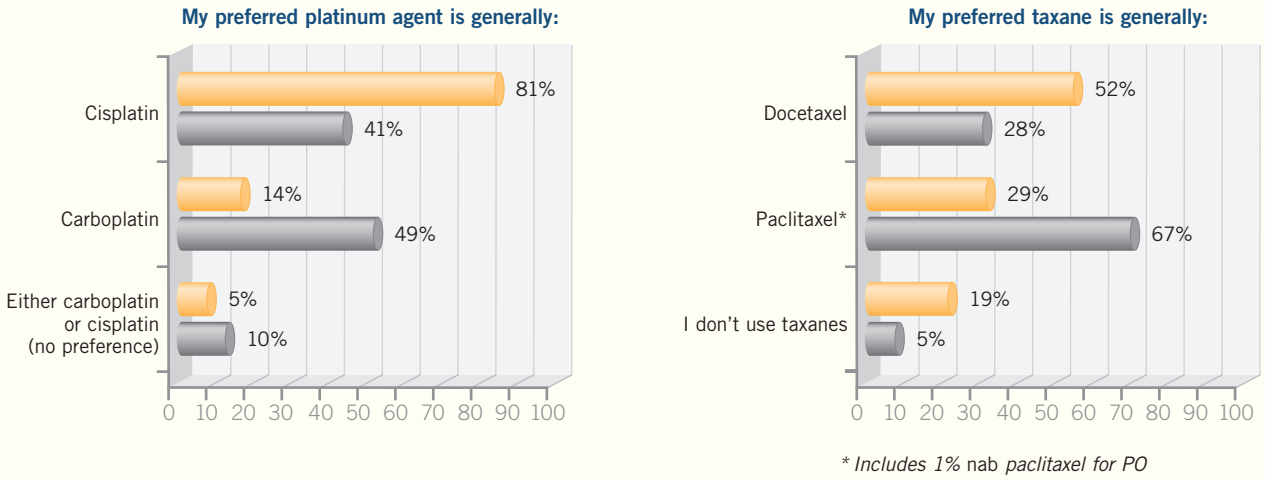
Lung Cancer Update 2007 (4)

DR MARTIN J EDELMAN: I believe the weight of data supports a cisplatin-based adjuvant regimen. If one wants to be completely data driven, cisplatin/vinorelbine is probably the most validated regimen out there, but it's difficult to administer. In Stage IV disease, cisplatin/docetaxel is at least as good — possibly even superior — and probably better tolerated than cisplatin/vinorelbine, so I consider that a reasonable regimen.

If somebody told me that he or she intended to administer cisplatin/vinorelbine, I would not argue about it.

FIGURE 3

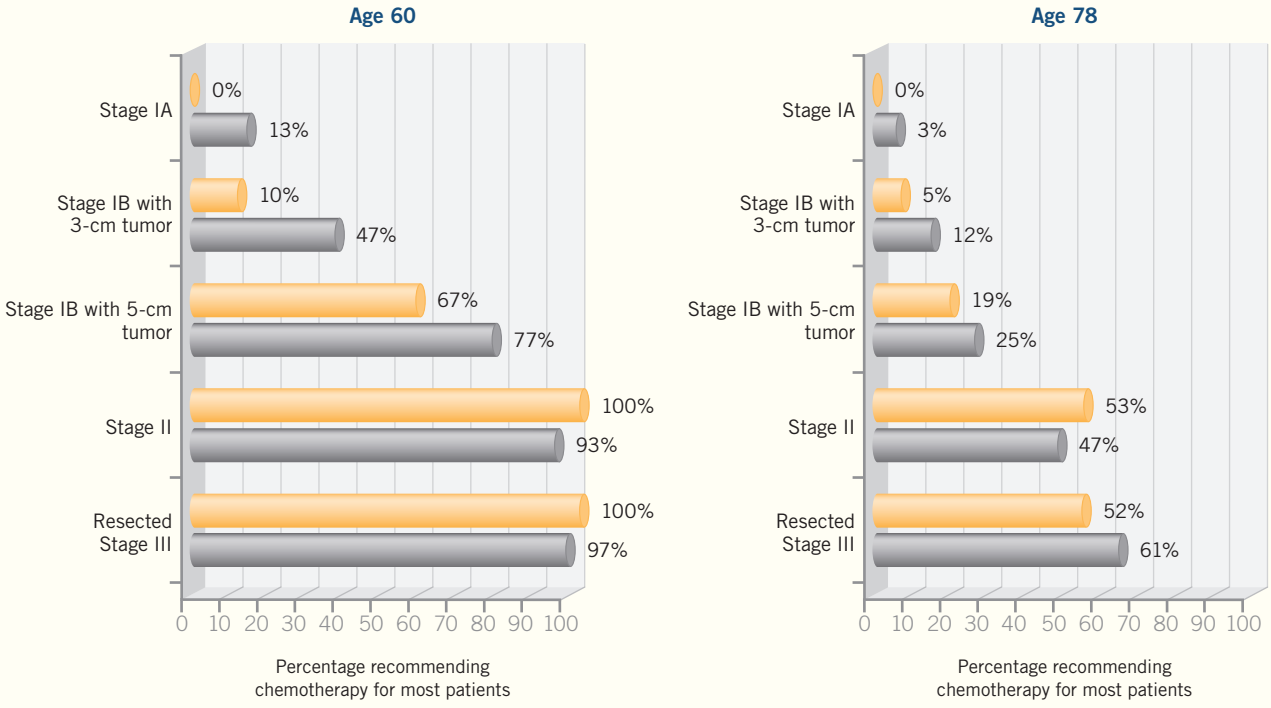
*When recommending adjuvant chemotherapy for NSCLC, which is your **preferred** agent?*



** Includes 1% nab paclitaxel for PO*

FIGURE 4

Would you generally recommend adjuvant chemotherapy for patients with PS 0 or 1 in the following scenarios?



The combination of cisplatin/gemcitabine is also a reasonable approach. I believe the crucial drug in this regimen is the platinum agent.

However, despite all the arguments, I believe carboplatin/paclitaxel is also reasonable. It has been pointed out that to conduct an adequately powered study of patients with Stage IB disease, you'd have to enroll about 2,000 patients.

So the CALGB carboplatin/paclitaxel study that showed an improvement in

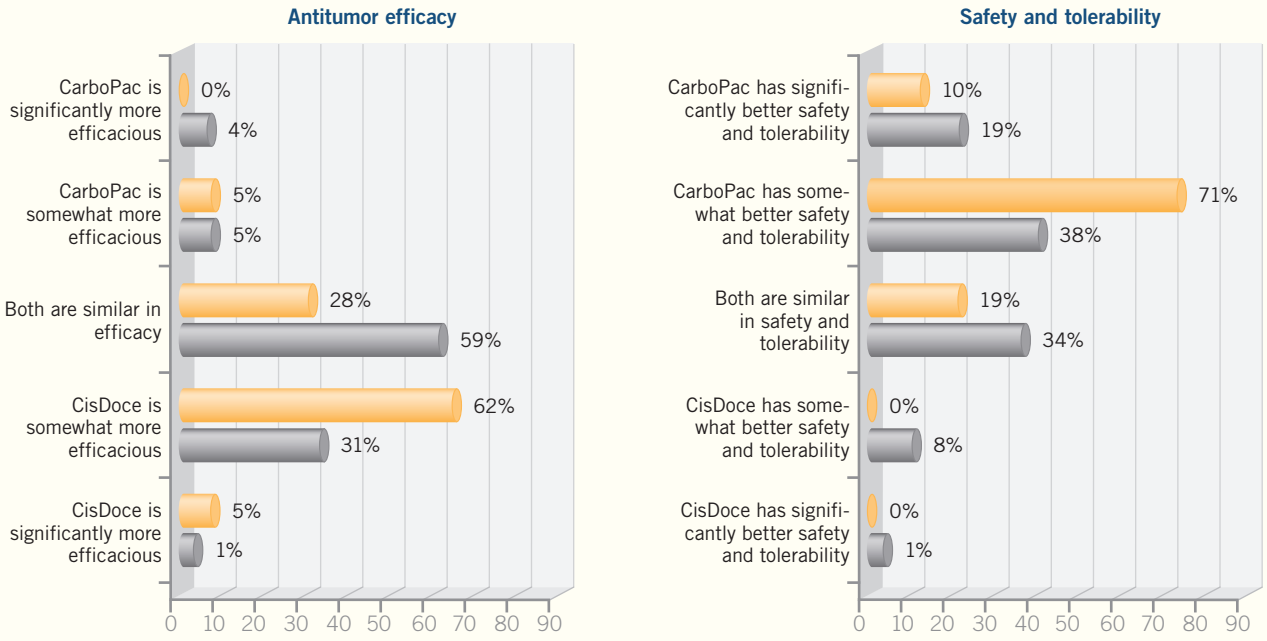
Text continued on page 8

CLINICAL INVESTIGATORS (CI) PRACTICING ONCOLOGISTS (PO)

FIGURE 5

A 60-year-old patient is to receive adjuvant chemotherapy for Stage II adenocarcinoma of the lung. In this setting, how would you compare the following regimens?

Carboplatin/paclitaxel (CarboPac) to cisplatin/docetaxel (CisDoce)



Carboplatin/paclitaxel (CarboPac) to cisplatin/gemcitabine (CisGem)

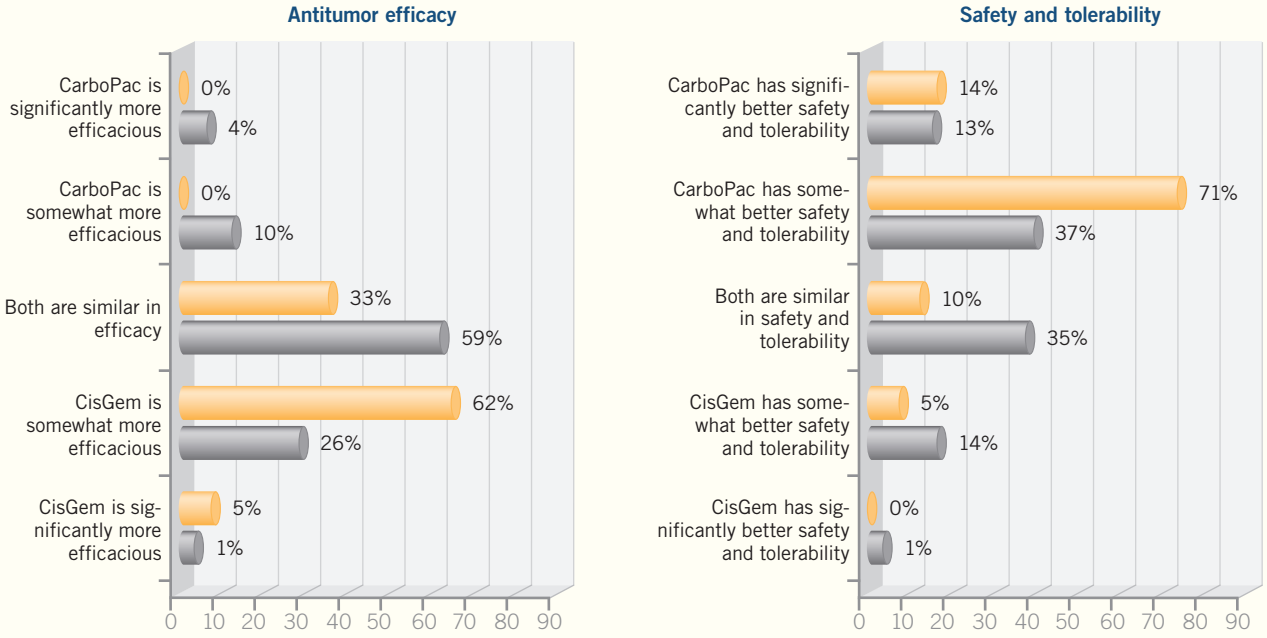
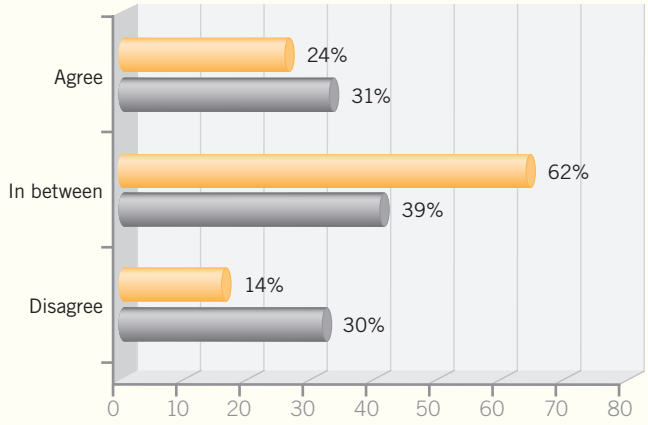


FIGURE 6

Neoadjuvant chemotherapy alone for localized NSCLC is a reasonable alternative to postoperative adjuvant therapy alone with regard to overall long-term clinical outcome.



progression-free survival in Stage IB disease was probably underpowered.

If you consider the subgroup of patients with tumors measuring four centimeters, you see that those patients clearly fared better. I don't believe carboplatin/paclitaxel is inactive in this setting — occasionally we do use that combination.

Why? We use it because some patients simply cannot tolerate cisplatin-based therapy. It is not unusual for us to start with a cisplatin-based therapy and then switch the patient after one or two cycles because he or she cannot tolerate it. So for their final couple of cycles, these patients are treated with a carboplatin-based therapy.

Interview, July 2007

DR NASSER H HANNA: I use cisplatin-based adjuvant therapy, unless the patient has a contraindication for cisplatin. If a patient has modest renal insufficiency, I'll administer carboplatin. I believe the general practice in the oncology community is to use carboplatin-based therapy. However, I think little difference in outcome is likely to appear.

We had a clue about that from ASCO 2007, when Milleron presented an early analysis of a neoadjuvant trial. He indicated that a regimen of carboplatin/paclitaxel resulted in the same degree of success as cisplatin/gemcitabine — in terms of complete resection rate, response rate and percent necrosis — suggesting that a carboplatin-based neoadjuvant regimen may be as good as cisplatin. We don't have any survival data on that study yet.

I generally combine docetaxel with cisplatin. The majority of data we have from the adjuvant setting is with cisplatin/vinorelbine. But multiple trials have been conducted comparing cisplatin/docetaxel to cisplatin/vinorelbine or single-agent docetaxel to single-agent vinorelbine, in which docetaxel is a more active and effective agent.

Lung Cancer Update 2007 (3)

DR MARK A SOCINSKI: We are currently conducting a Phase II study evaluating docetaxel and carboplatin in the adjuvant setting.

We previously conducted a feasibility study of that combination, and our endpoint was to determine whether we could deliver four cycles of therapy within 12 weeks to more than 80 percent of the patients.

The study included 72 patients and showed that 80 percent of them were able to receive four cycles. We allowed patients to receive growth factor support, and approximately one third of the patients received growth factors at some point during the four cycles.

No treatment-related deaths occurred. Our conclusion was that this is a feasible regimen for the patient whom you consider not to be a good candidate for a cisplatin-based approach. The Phase II safety data suggest that you can use that regimen. The data in our trial were similar to what the CALGB showed with carboplatin and paclitaxel.

Lung Cancer Update Think Tank 2007

DR THOMAS J LYNCH: My use of neoadjuvant therapy has declined over the years.

I had a lot more enthusiasm for it before we had evidence that adjuvant therapy had benefit. The only patients for whom I tend to think of neoadjuvant therapy now are those with bulky N2 disease, for whom we will administer neoadjuvant chemotherapy up front and proceed to surgery.

Adjuvant therapy has completely changed the dimension of neoadjuvant therapy. I don't see a great advantage to neoadjuvant therapy over adjuvant therapy for Stage I and Stage II disease. Even for patients with resectable Stage IIIA disease, neoadjuvant therapy is questionable at that point.

Lung Cancer Update Think Tank 2007

DR HANNA: I can think of a couple of patients for whom we have used preoperative therapy recently.

Some patients have lost weight, and you become nervous about moving them to surgery up front, but you believe the disease is still curable radiographically — bulky N2 disease — and ultimately, you know they will require both surgery and chemotherapy. So you administer a few courses of chemotherapy and allow the disease to declare itself.

Lung Cancer Update 2006 (4)

DR VINCENT A MILLER: We now have several markers that can predict benefit from EGFR TKIs in the metastatic setting, which can be determined in any patient — such as smoking history, ethnicity and pathology — and some in

FIGURE 7

What is the role of erlotinib after resection of Stage II NSCLC in the following?

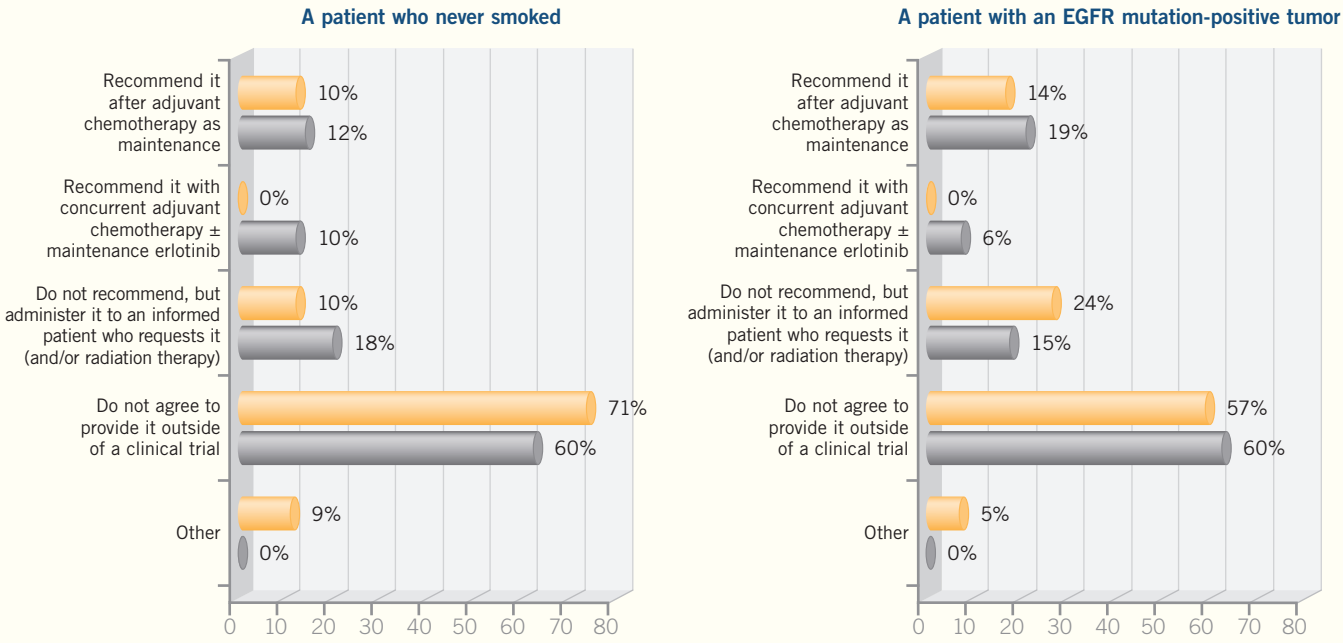
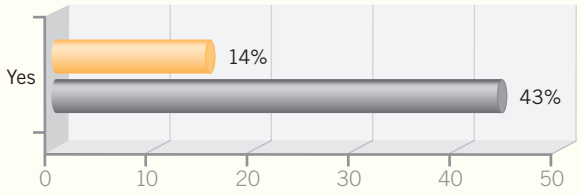


FIGURE 8

Would you recommend erlotinib (with or without adjuvant chemotherapy) as postoperative treatment for a 61-year-old woman with Stage II pure bronchoalveolar carcinoma?



the molecular arena.

In the arena of clinical variables, factors include never smoking, adenocarcinomas and Asian ethnicity. I believe a history of never smoking is the most powerful predictor of benefit.

ASCO 2006 was important in terms of reporting some prospective trials of EGFR tyrosine kinase inhibitors in patients known to have EGFR mutations. The lowest response rate in prospectively identified patients with mutations was about 65 percent, and it went up to about 85 or 90 percent. So a patient has about a 75 or 80 percent chance of having a response if he or she has an EGFR mutation. That is pretty good compared to what we had two or three years ago and even compared to what we have in other commonly studied diseases that are driven by diagnostic testing.

In our trial for patients with bronchoalveolar cancer — presented at ASCO 2006 — we had some patients with an EGFR mutation and a high EGFR copy number. Their response rate was 90 percent and their median survival was about three years with erlotinib.

The response rate for patients without an EGFR mutation and with an EGFR copy number lower than four was four percent, and their median survival was only 15 months. Those are pretty powerful predictors for a difference in clinical outcome.

Lung Cancer Update Think Tank 2006

DR HARVEY I PASS: For the patient who is a never smoker or has an EGFR mutation, I have to say that I can't, off trial, dissuade him or her from adjuvant erlotinib because it makes sense to me.

Obviously, the trial must be performed to answer the clinical question: If we compare erlotinib with the best adjuvant chemotherapy regimens, is that the way to go? I believe we're talking about a selected population. In that situation, I can't go against the patient who has read

FIGURE 9

RADIANT: A Randomized Phase III Study of Erlotinib with or without Adjuvant Chemotherapy in NSCLC Patients with EGFR-Positive Tumors

Protocol IDs: OSI-774-302, NCT00373425
Target accrual: 945

Eligibility

- Stage IB-IIIA NSCLC
- Complete removal of tumor by surgery
- Primary tumor tissue from surgery must be EGFR-positive by certain tests
- No tumors with mixed histology of NSCLC and SCLC
- No prior radiation therapy for NSCLC
- No history of poorly controlled gastrointestinal disorders
- Four cycles of adjuvant chemotherapy allowed prior to randomization

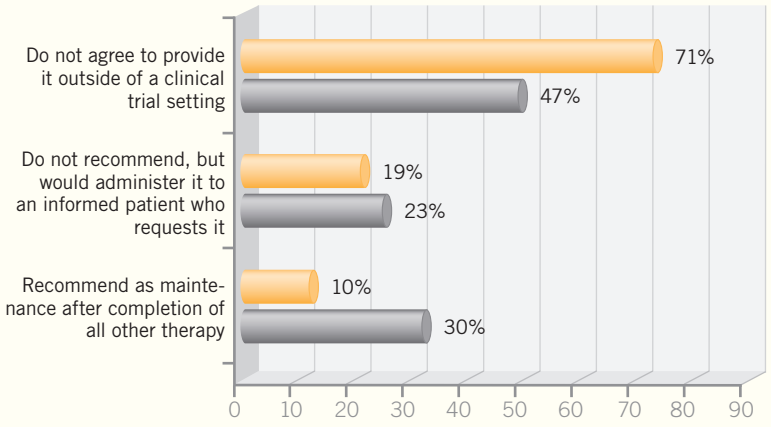
Study Contact

OSIP Medical Information
Tel: 800-572-1932, ext 7821

SOURCE: NCI Physician Data Query, September 2007.

FIGURE 10

What is the role of erlotinib for a never smoker with unresectable NSCLC after definitive chemoradiation therapy?



all the data and wants to go that route.

DR LYNCH: I've softened on this issue. I believe for patients who have mutation-positive disease, you need to have a detailed discussion with them. They're not going to be able to wait for the Phase III trials to be conducted, and obviously, I endorse the concept of Phase III trials. However, for that patient with mutation-positive disease, I have a long discussion with them, and I don't believe it's crazy to consider adding erlotinib after chemotherapy.

Lung Cancer Update 2007 (3)

DR BRUCE E JOHNSON: The adjuvant setting is more complicated, and it will be a long time before we know how to use assays for EGFR and incorporate them into the therapeutic algorithm. The trial currently being planned will evaluate patients with the epidermal growth factor present either by immunohistochemistry receptor or by fluorescence in situ hybridization.

After surgical resection, those patients who are believed to benefit from chemotherapy will receive adjuvant therapy. If the tumor is EGFR-positive by immunohistochemistry or fluorescence in situ hybridization, those patients will be randomly assigned to receive erlotinib versus placebo (Figure 9).

That trial will take several years to accrue the patients, and because it's in patients with relatively early-stage disease, we will have to wait for three to five years from the time the last person is enrolled to see the survival information. So we don't know that just yet.

The other part that's embedded within that trial is that those patients will also be studied for other determinants of benefit, including the mutations of the epidermal growth factor receptor.

The amount of tumor tissue available for these adjuvant studies is obviously much greater than in studies of patients with advanced disease, with whom we're typically working with needle aspirations or bronchoscopic biopsies.

Lung Cancer Update 2007 (3)

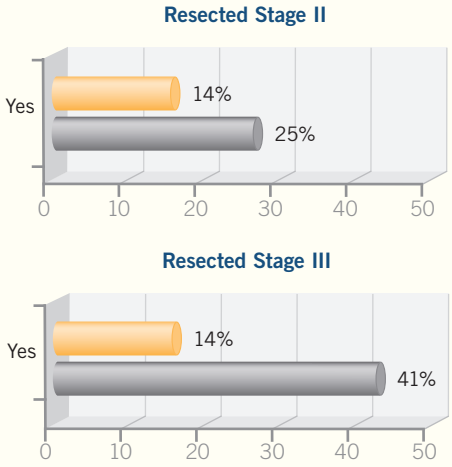
DR SOCINSKI: In the absence of data and in the wake of SWOG-S0023, in which the use of an EGFR TKI after chemoradiation therapy showed a decreased survival rate, I have been conservative in my approach. I administer adjuvant chemotherapy — I have not yet administered adjuvant erlotinib or gefitinib.

There is an outstanding prematurely stopped trial by the NCI of Canada, in which adjuvant gefitinib was studied in unselected patients. It was closed before it met its accrual goal, and we don't have any information yet.

We currently have an adjuvant trial, RADIANT (Figure 9), which selects patients with EGFR-positive disease by immunohistochemistry or FISH

FIGURE 11

Cost and reimbursement issues aside, would you consider including bevacizumab as adjuvant treatment for a young, otherwise-healthy, well-informed patient with NSCLC who requests it?



analysis, in which you can administer chemotherapy or not. Then they're randomly assigned to a placebo or erlotinib. Until we see data from that trial, I have not used it as a recommended treatment in the adjuvant setting.

Lung Cancer Update 2007 (2)

DR COREY J LANGER: In the ECOG-E4599 first-line advanced NSCLC study, the addition of bevacizumab to paclitaxel/carboplatin demonstrated a two-month improvement in median overall survival and about a six to eight percent improvement in one- and two-year survival. It also showed more toxicity, particularly pulmonary hemorrhage.

In the bevacizumab/paclitaxel/carboplatin arm, 15 treatment-related deaths occurred out of 305 patients. Not all were related to hemorrhage — some were from neutropenic fever or other causes.

In the control group, two treatment-related deaths occurred out of 344 patients. So, although we excluded patients with squamous histology, brain metastases, ongoing thromboembolic phenomena, anticoagulation use or antecedent hemoptysis, we still saw a heightened treatment-related death rate.

I believe many of those concerns are going to fall by the wayside in the adjuvant trial. The tumors have been resected. By definition, these patients have no residual tumor in the chest. Ideally, they should not have pulmonary hemorrhage.

Lung Cancer Update 2006 (3)

DR EDWARD S KIM: Bevacizumab works well in the metastatic setting, so there is a rationale to move our best metastatic regimen to adjuvant therapy.

With bevacizumab, you need to consider the problems that could occur in a postoperative setting. We have to derive that from the colon trials. We're not sure if there will be any wound dehiscence in lung cancer patients who have had surgery.

Lung Cancer Update 2007 (3)

DR HEATHER A WAKELEE: We activated the ECOG-E1505 (Figure 12) study recently and are more comfortable than ever with our choice of regimens that investigators can select: cisplatin/gemcitabine, cisplatin/vinorelbine and cisplatin/docetaxel, all with and without bevacizumab.

At this point, we're still sticking with the 15-mg/kg dose of bevacizumab because that's the dose for which we have known survival benefit in the metastatic setting. The bevacizumab is administered at the 15-mg/kg dosing every three weeks starting with the first cycle of chemotherapy and then continuing for one year.

We are limiting patients with Stage IB disease to those whose tumors are four centimeters or larger. We know from subset analyses of the larger adjuvant trials that patients with Stage IB disease don't seem to benefit overall. The CALGB IB trial was statistically negative overall, but those whose tumors were four centimeters or larger did show a survival benefit. That's why we came up with the 4-cm cutoff.

At this point we're not limiting to any specific non-small cell histology. We're also not excluding patients receiving anticoagulation.

Based on the safety data that have emerged in colorectal cancer — and now hints that have emerged in the AVAiL study — patients who have had any sort of stroke or transient ischemic attack are excluded. Patients who have had any other arterial thrombotic events within six months — such as myocardial infarction — are also excluded.

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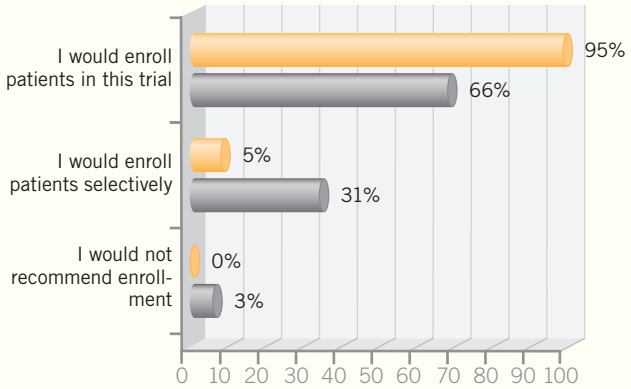
FIGURE 12

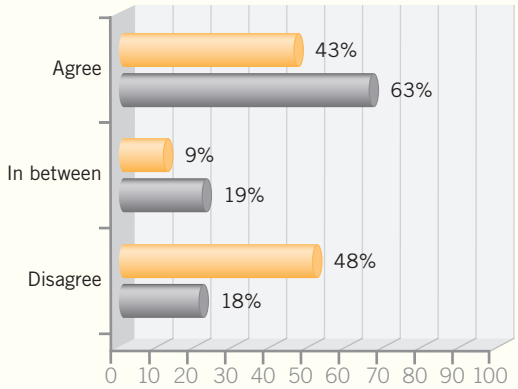
The following questions apply to the planned ECOG-E1505 trial, a Phase III trial randomly assigning patients with resected Stage IB (>4 cm) to IIIA NSCLC to adjuvant chemotherapy alone or adjuvant chemotherapy with 1 year of bevacizumab (see figure below). All histologies are eligible, including squamous cell, and patients can receive 1 of the following 3 chemotherapy regimens:

- *Cisplatin/vinorelbine*
- *Cisplatin/docetaxel*
- *Cisplatin/gemcitabine*

How would you feel about enrolling patients in this trial?



This trial should have included carboplatin/paclitaxel as one of the adjuvant chemotherapy regimens.



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

R

Chemotherapy

Adjuvant chemotherapy (**vinorelbine** + **cisplatin** OR **docetaxel** + **cisplatin** OR **gemcitabine** + **cisplatin**)

Chemotherapy + bevacizumab

Adjuvant chemotherapy with **bevacizumab** (chemotherapy as described above with **bevacizumab** on d1 q3wk x 1y)

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

Eligibility

- 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, October 2007.

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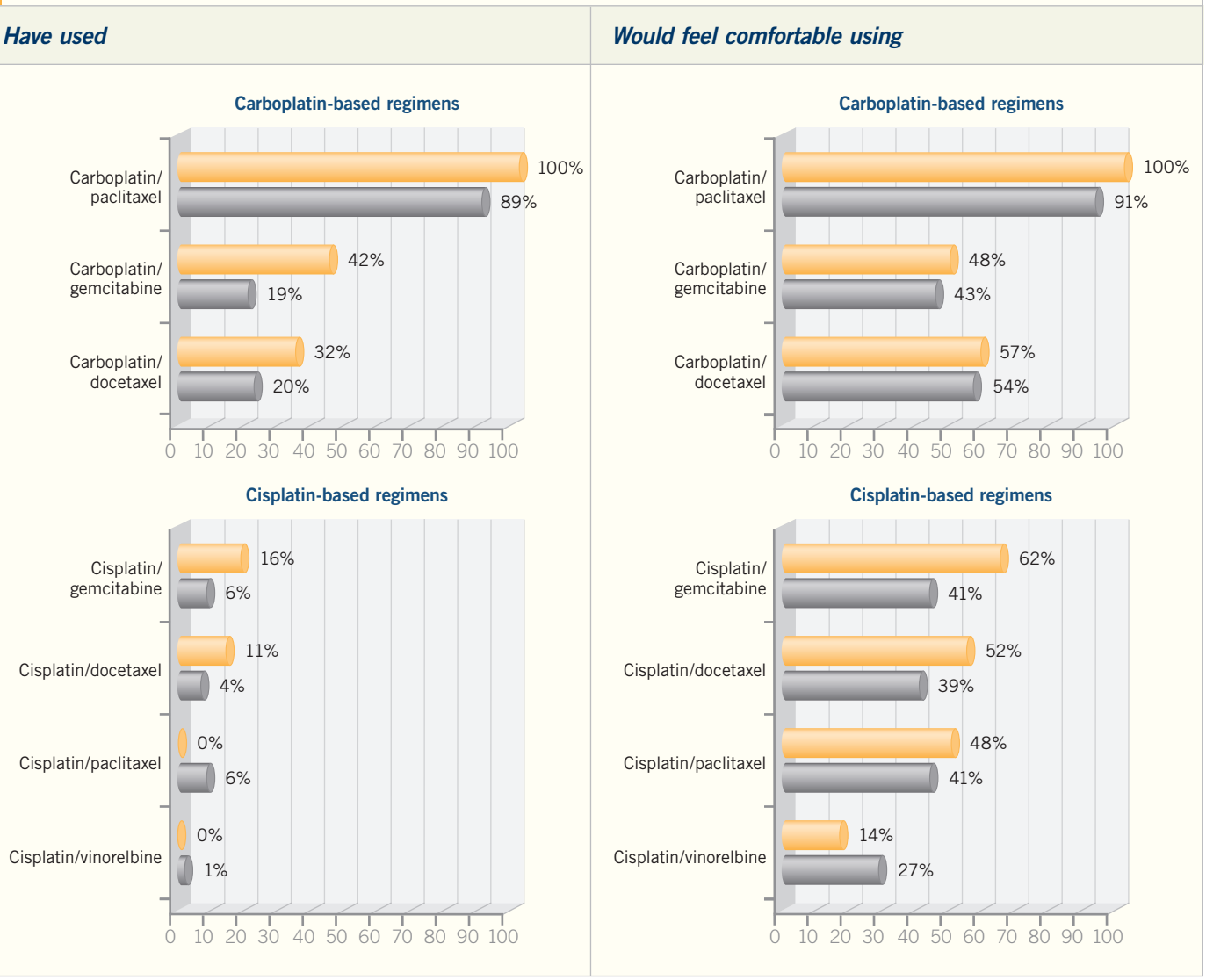
FIGURE 13

Which of the following therapies have you used or would you feel comfortable using with bevacizumab in the treatment of NSCLC? (May have more than one response)



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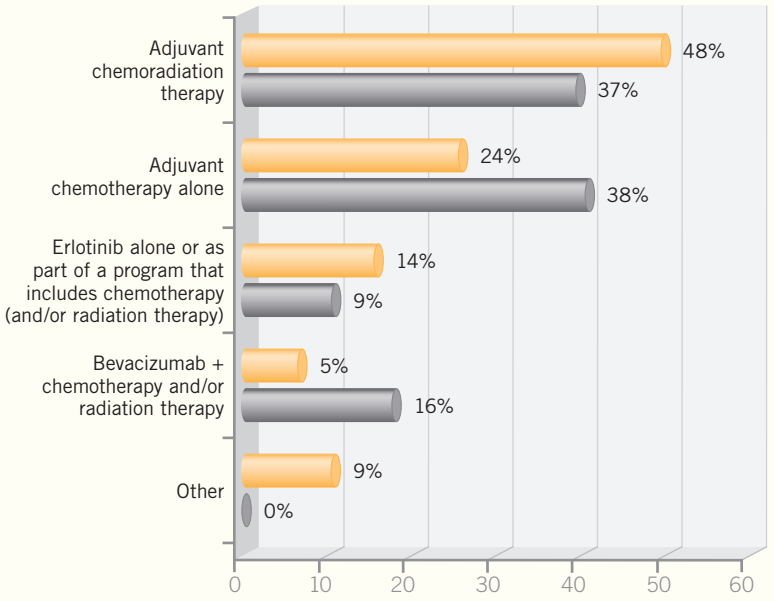
Tomizawa Y et al. **A phase I dose escalation study of biweekly gemcitabine and carboplatin in completely resected stage IB-IIIA nonsmall cell lung cancer.** *Am J Clin Oncol* 2007;30(5):498-502. **Abstract**

Winton T et al. **Vinorelbine plus cisplatin vs observation in resected non-small-cell lung cancer.** *N Engl J Med* 2005;352(25):2589-97. **Abstract**

Winton TL et al. **A prospective randomised trial of adjuvant vinorelbine (VIN) and cisplatin (CIS) in completely resected stage IB and II non small cell lung cancer (NSCLC) Intergroup JBR.10.** *Proc ASCO* 2004;**Abstract 7018**.

FIGURE 14

If cost and reimbursement were not issues, which adjuvant therapy would you recommend off protocol for a 60-year-old nonsmoker with a good performance status and good lung function whom you are seeing postoperatively after complete resection (with negative margins) of pathologic Stage IIIA (T1-2, N2) nonsquamous NSCLC, assuming the patient has no medical contraindications to any of the treatment choices?



Lung Cancer Update 2006 (4)

DR PASS: The question of how to treat Stage IIIA lung cancer has been a vexing one. A number of studies have been performed using induction therapy for Stage IIIA nodal disease, two of which, despite very small accrual, were highly touted for the positive survival advantage seen among patients who received induction cisplatin-based therapy.

By the same token, Phase II trials studying the combination of chemotherapy and radiation therapy resulted in a randomized trial that evaluated whether induction chemoradiation therapy was better than definitive chemoradiation therapy without surgery for Stage IIIA disease.

The RTOG-9309 study presented by Dr Kathy Albain at ASCO 2003 appeared to suggest that surgery after induction chemoradiation therapy was not any better than definitive chemoradiation therapy, although it was associated with a trend toward improved progression-free survival.

If you evaluate the data carefully, however, you notice a high mortality rate for patients who underwent pneumonectomy. The overall operative mortality rate was seven percent, but the operative mortality rate in patients requiring pneumonectomy was 14 percent.

A subsequent unplanned analysis of the trial was presented by Dr Albain at a follow-up ASCO 2005 meeting, in which the authors carefully matched patients treated with definitive chemoradiation therapy to patients with lobectomies and not pneumonectomies.

Sure enough, they found a fairly dramatic survival advantage in the lobectomy-only group favoring combined chemoradiation therapy with surgery.

Lung Cancer Update 2007 (4)

DR HANNA: In 2003, SWOG published results from the SWOG-S9504 Phase II trial. The study included 83 patients with Stage IIIB disease who were treated with cisplatin/etoposide for two cycles concurrently with 61 Gray of radiation, followed by three cycles of consolidation docetaxel.

The median survival time was 26 months. This patient population should have had a median survival time of about 13 months with Stage IIIB and chemoradiation treatment only. Instead, they had a five-year survival of 29 percent. Historically, that group should have had a five-year survival of five, seven, eight percent.

This engendered a lot of enthusiasm and became a de facto standard for many physicians, based upon a single, relatively small Phase II trial. We sought to confirm that this strategy was effective. We did a randomized Phase III study that included patients with both Stage IIIA and Stage IIIB disease.

A total of 243 patients entered our trial. All patients received cisplatin/etoposide and concurrent radiation with 59.4 Gray. Then, after a rest period of four to eight weeks — and as long as they had not progressed and remained eligible — patients were randomly assigned to either three cycles of docetaxel consolidation or observation.

We reported several provocative findings. No difference in progression-free survival between the two randomized arms was seen, and there was no difference in median survival, three-year survival or overall survival. The *p*-value was 0.9. The curves were completely superimposable.

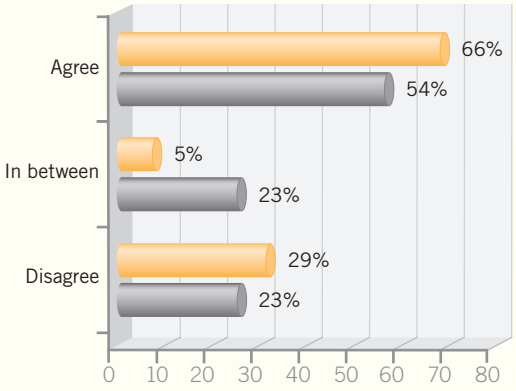
Lung Cancer Update 2007 (3)

DR WAKELEE: The Hoosier Oncology Group (HOG) trial, which evaluated

FIGURE 15

For potentially resectable Stage IIIA, N2-positive NSCLC in a patient with a good performance status:

*I would generally recommend **against** surgery if a mediastinoscopy after induction therapy demonstrated residual viable cancer.*



I would consider a high likelihood of the need for pneumonectomy to be a strong contraindication to proceeding with surgery.

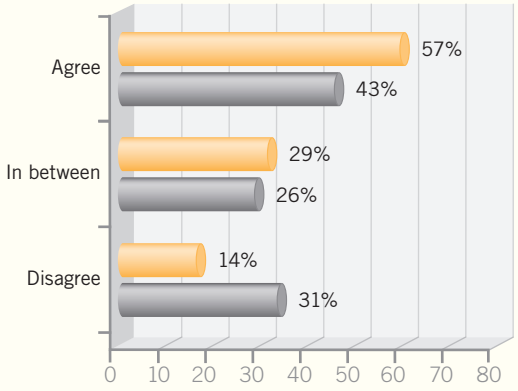
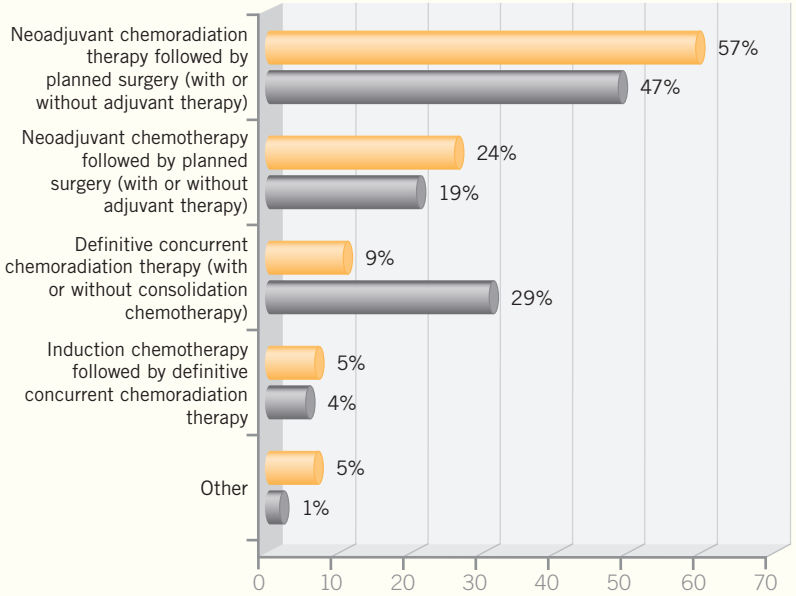


FIGURE 16

For nonbulky Stage IIIA, N2-positive NSCLC in a patient with a good performance status, my most common treatment approach is:



chemotherapy with cisplatin/etoposide and concurrent radiation therapy with or without consolidation chemotherapy for unresectable Stage IIIA and IIIB disease, was the most practice-changing presentation in lung cancer at ASCO. All patients in the study received chemotherapy and radiation therapy, and then they were randomly assigned to either consolidation docetaxel using the standard SWOG-S9504 protocol or nothing. The trial showed no difference in survival between the two arms.

Criticisms include the fact that it was a relatively small study and it was stopped early because of an interim analysis showing that there was no way statistically to obtain a separation of the curves. The study begs the question of what consolidation chemotherapy is achieving in that situation.

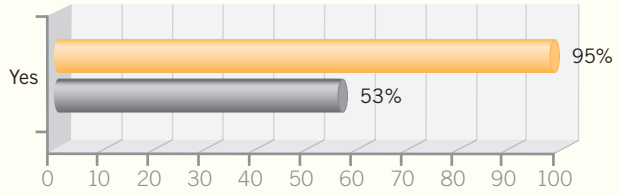
Other studies that evaluated induction chemotherapy with additional chemoradiation therapy in a similar patient population also didn't show any benefit beyond the standard chemoradiation intervention. Again, it's bringing into the forefront this question of what to do with Stage III disease.

For several years, everyone has been comfortable with the SWOG-S9504 regimen. Now we have to question that.

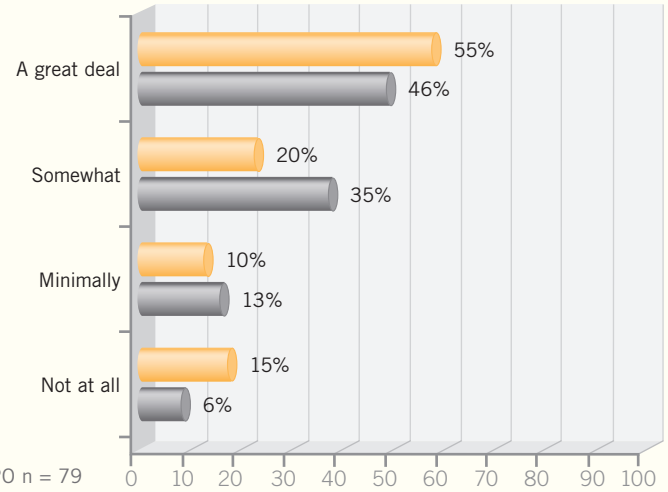
However, I have a hard time believing that two cycles of a platinum doublet with radiation therapy are enough to cure Stage III disease when we know we need more than that to improve survival for earlier stages. I don't believe the question is dead, but I believe we need to move

FIGURE 17

Are you aware of the updated clinical trial results evaluating the safety and efficacy of docetaxel consolidation chemotherapy presented at the 2007 ASCO meeting?

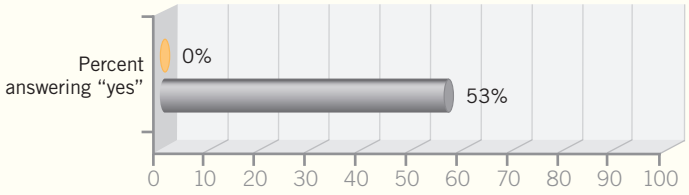


*If yes, to what extent do you believe these results will influence your use of docetaxel consolidation chemotherapy?**

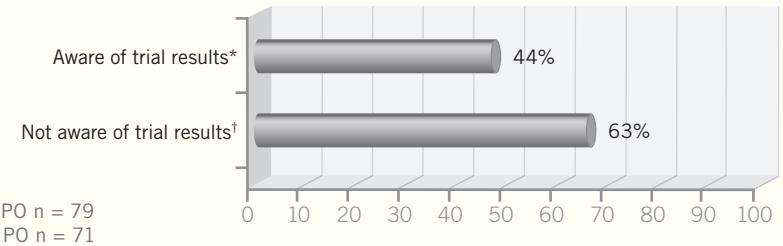


*CI n = 20; PO n = 79

For a patient with unresectable Stage IIIB NSCLC treated with concurrent chemoradiation therapy, would you recommend docetaxel consolidation chemotherapy?



*Percent of practicing oncologists who **would** recommend docetaxel consolidation, based on awareness of updated trial results:*



* PO n = 79
† PO n = 71

away from simply building on S9504.

Many people are still using a weekly carboplatin-based regimen and a taxane with the radiation therapy. To say that we shouldn't administer any chemotherapy after that is a somewhat frightening proposition, considering that these patients are not receiving much chemotherapy at all during the radiation therapy.

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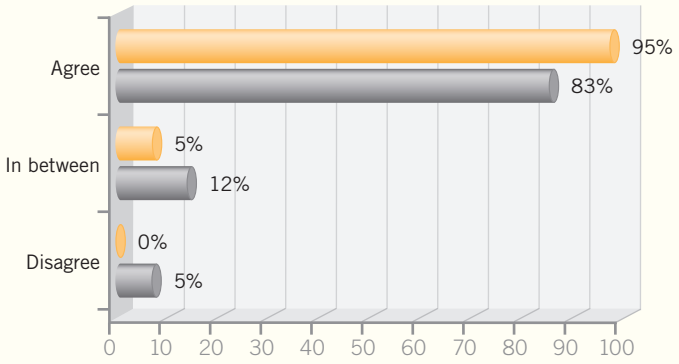
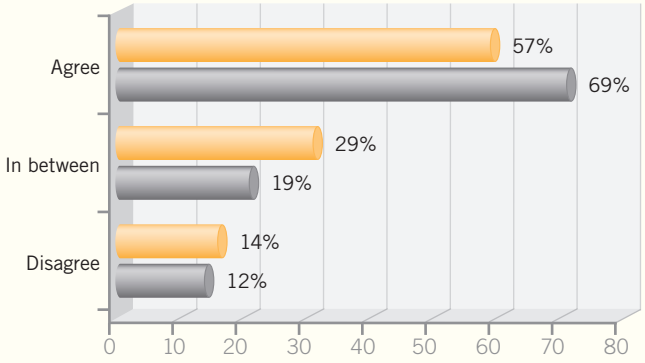
Syrigos KN et al. **Biweekly administration of docetaxel and gemcitabine as adjuvant therapy for stage II and IIIA non-small cell lung cancer: A phase II study.** *Anticancer Res* 2007;27(4C):2887-92. Abstract

FIGURE 18

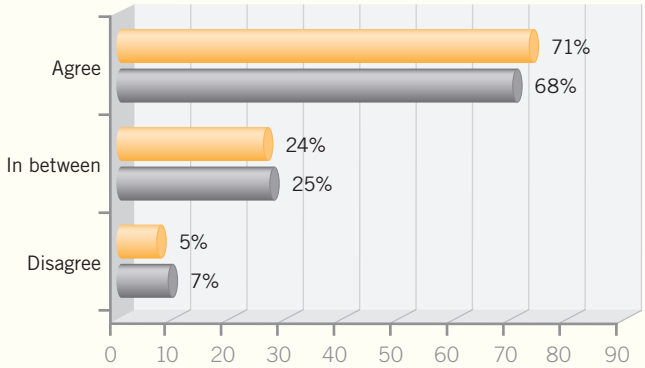
Chemotherapy in combination with bevacizumab is the current standard for the first-line treatment of metastatic NSCLC for patients without contraindications.



Women obtain equal benefit from the addition of bevacizumab to chemotherapy for NSCLC as men.



A significant part of the mechanism of the antitumor action of bevacizumab in NSCLC is improved delivery of chemotherapy to the tumor.



CLINICAL INVESTIGATORS (CI)
PRACTICING ONCOLOGISTS (PO)

Lung Cancer Update 2007 (3)

DR JOHNSON: In terms of our algorithm for the management of metastatic disease in the clinical setting for patients who are not in the EGFR-enriched populations, we follow the Eastern Cooperative Oncology Group (ECOG) algorithm. For patients with adenocarcinoma without brain metastasis, serious cardiovascular or cerebrovascular problems or clotting, we recommend paclitaxel, carboplatin and bevacizumab. For patients with squamous cell carcinoma, brain metastasis or hemoptysis, we administer paclitaxel and carboplatin without bevacizumab. We try to utilize the same drugs off study as we do on study. For patients with a number of comorbidities, we administer a single agent such as vinorelbine.

For patients treated with paclitaxel, carboplatin and bevacizumab, side effects we see include hypertension and an increased risk of clotting, bleeding and proteinuria, which are all manageable. We also see an increased risk of deep venous thrombosis and pulmonary emboli.

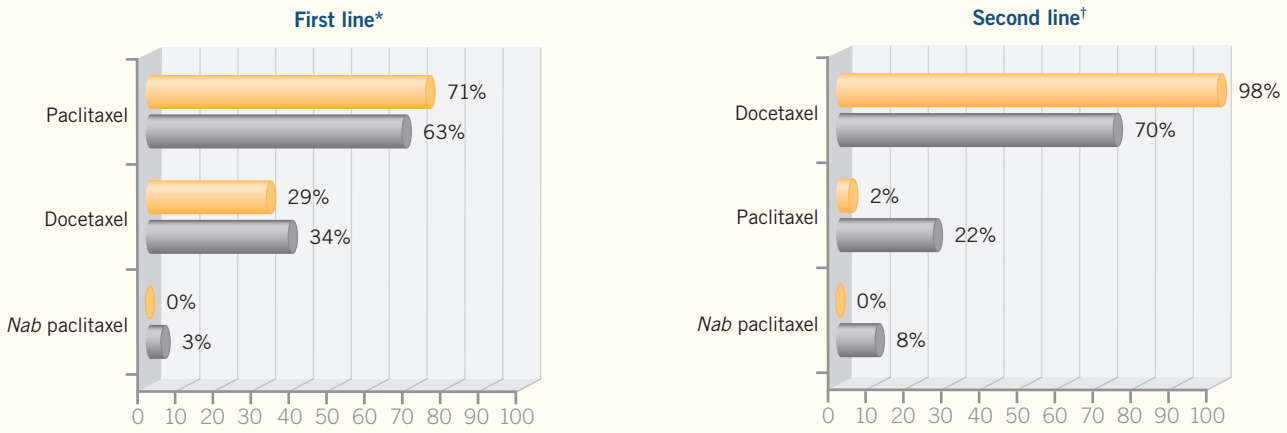
For patients in second-line therapy off study who have been treated with two agents — most commonly carboplatin/paclitaxel in our setting — and have a good response and go off therapy for an extended period, we'll commonly go to docetaxel as second-line therapy. For a patient who shows a mediocre response to initial chemotherapy, we will generally use erlotinib as the second agent. We often use pemetrexed as the third-line agent. For almost everybody off study, we use one of the three approved agents for second-line treatment — pemetrexed, docetaxel or erlotinib.

Lung Cancer Update 2007 (3)

DR WAKELEE: In the setting of first-line metastatic disease, I believe we're

FIGURE 19

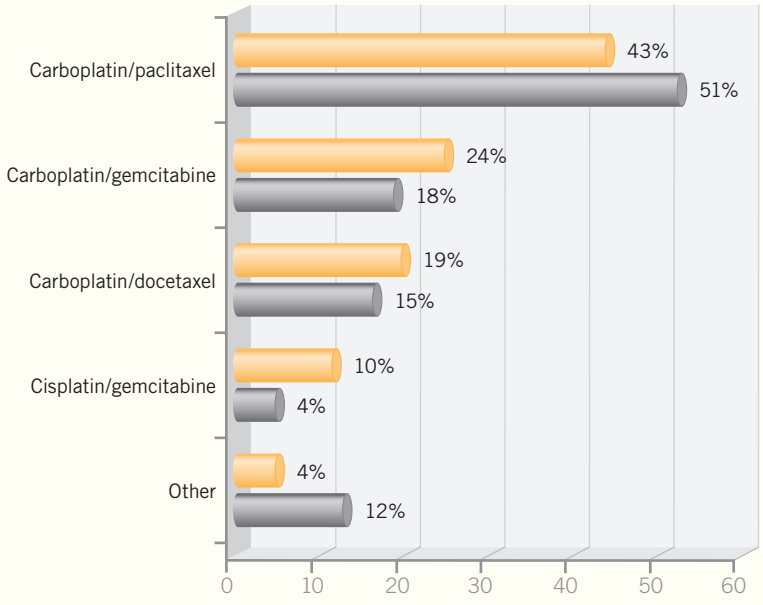
When using a taxane-based regimen in the metastatic setting, what percent of the time do you use the following agents? (Mean)



*CI n = 21; PO n = 149; †CI n = 16; PO n = 139

FIGURE 20

Which doublet chemotherapy regimen is your usual first choice for a patient with metastatic NSCLC and a good performance status?



still left with a platinum doublet, potentially even a nonplatinum doublet, as the chemotherapy base. Additionally, some trials are evaluating carboplatin and pemetrexed as another platinum doublet. It's a reasonable option, and it may be less toxic than some of the other regimens, but it's not better, and you lose an agent that's commonly used in the second line. Is that good or bad? I believe it's a matter of order, and I do not believe it's a huge step forward; it's simply a nice alternative.

For my patients in a nonprotocol setting who are not eligible or for whom I don't want to administer bevacizumab, in the first line I tend to use carboplatin and gemcitabine. I'll also use carboplatin/paclitaxel. It's between those two options, and we discuss the toxicity differences and scheduling differences with each patient. Occasionally I'll use a cisplatin backbone if the patient wants to be extremely aggressive.

Interview, May 2007

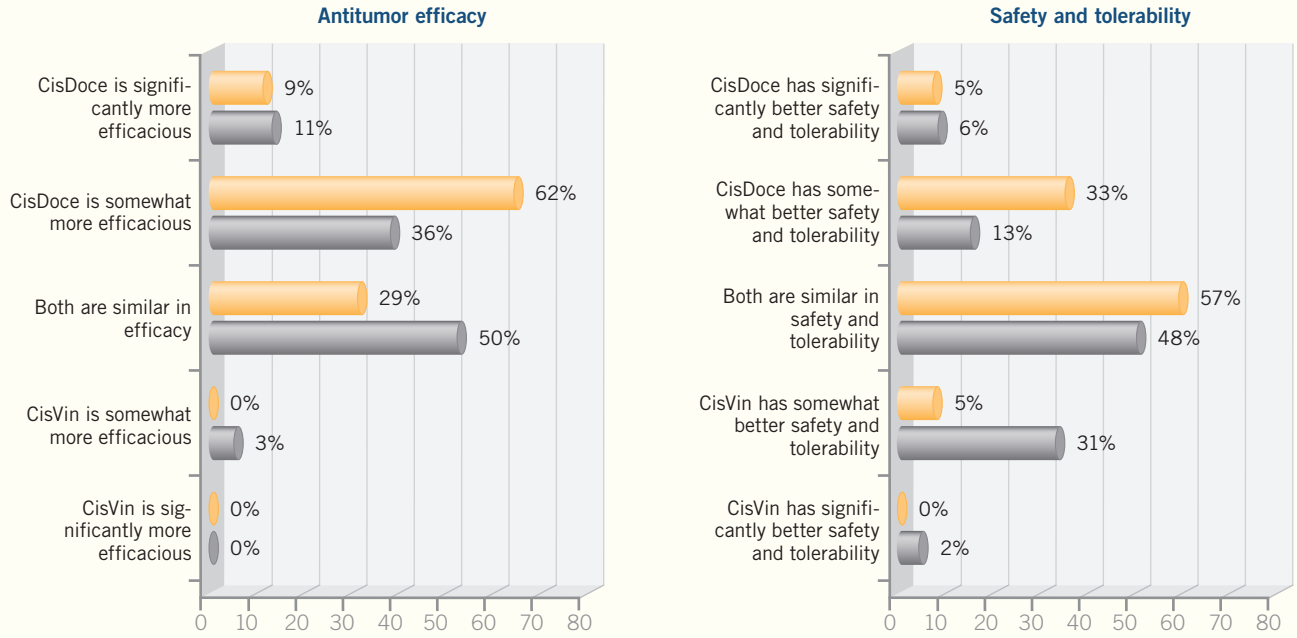
DR ALAN B SANDLER: ECOG-E4599 showed that the addition of bevacizumab to paclitaxel/carboplatin in metastatic disease provided a progression-free survival advantage over that same chemotherapy alone. I believe that bevacizumab and other VEGF-mediated agents or VEGF-directed agents have two distinct mechanisms of action.

First, I believe they have an effect on the tumor itself. Tumors have leaky vasculature, and an anti-angiogenic agent such as bevacizumab appears to help prune some of the newer vasculature, diminishing the leakiness and, therefore, allowing for better drug penetration by decreasing the interstitial fluid pressure in the tumor.

Dr Willett at Harvard showed this

FIGURE 21

A 60-year-old man with a history of smoking and a performance status of 1 presents with metastatic adenocarcinoma of the lung with bone and adrenal involvement. In this setting, how would you compare cisplatin/docetaxel (CisDoce) to cisplatin/vinorelbine (CisVin)?



in patients with rectal cancer, demonstrating decreased interstitial pressure in rectal tumors pre- and postbevacizumab. That's one effect: providing better chemotherapy penetration to the tumor. That would not appear to be as important in the adjuvant setting, in which there is no tumor.

The other effect relates to the concept of eliminating or reducing the development of new vasculature for the initial microscopic and then small tumors, stopping the new blood vessels from forming and turning the cancer into a chronic disease. It's hoped that mechanism will play a major role in the setting of early disease.

Lung Cancer Update 2007 (4)

DR EDELMAN: In the advanced disease setting, I've held fairly closely to the ECOG-E4599 eligibility criteria. We had discussions in which people were concerned because of the neutropenic fever or the hemoptysis seen with the addition of the VEGF inhibitor, but again, viewing this in the aggregate, patients did better with bevacizumab. They lived longer, and so if we have patients who would have been eligible for that study, then we do approach them about the use of bevacizumab.

I have used it pretty much exactly as it was used on E4599. The only difference is that I tend to use less cytotoxic chemotherapy — I use four cycles, not six, and I base that on my belief that the evidence is pretty compelling that pushing the cytotoxics does not aid you after four courses of therapy. I'm an advocate of evidence-based medicine, but here and there one can do an induction. I could certainly be criticized, but I believe it's a reasonable approach and it's well tolerated.

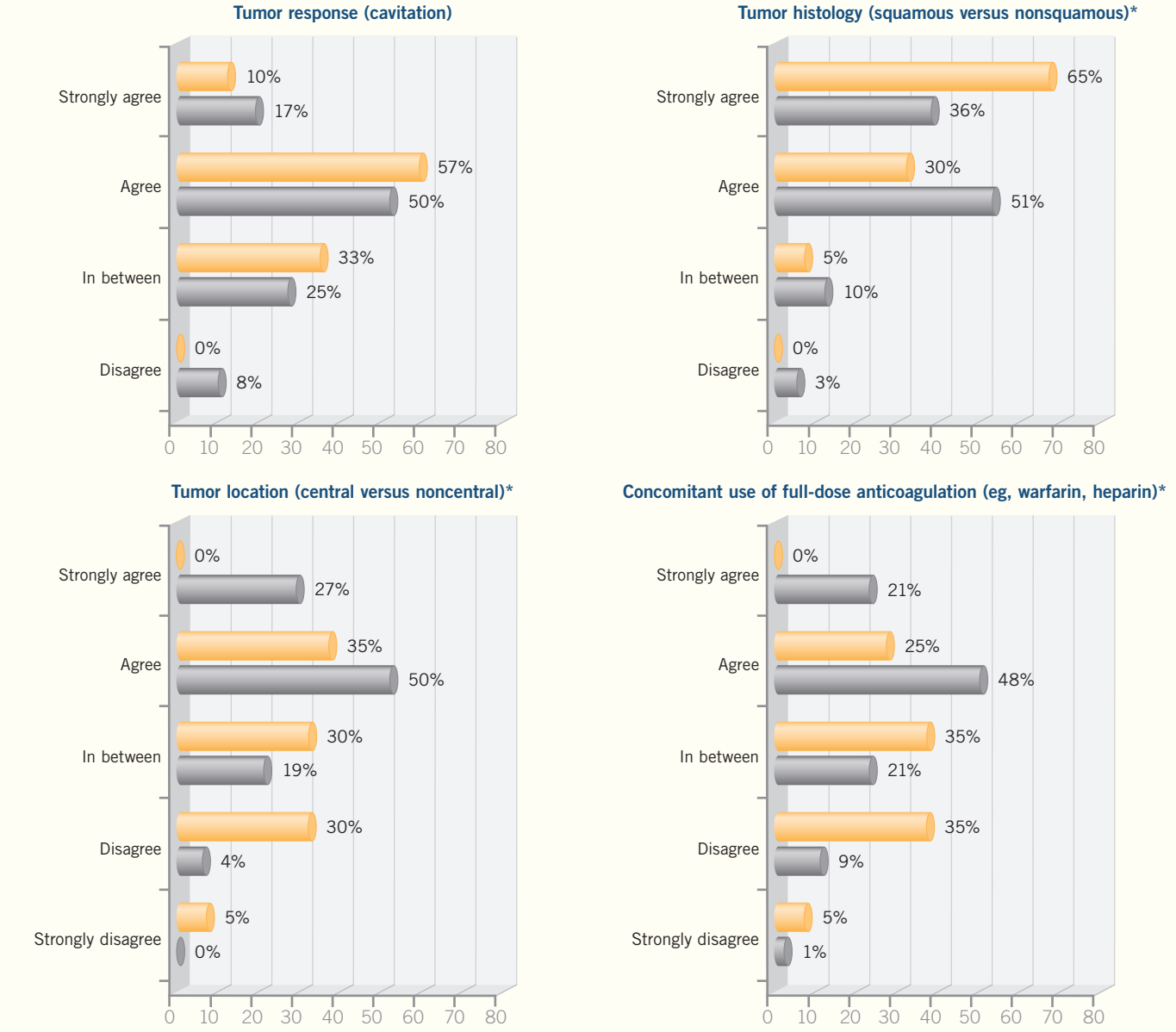
Lung Cancer Update 2007 (2)

DR JOAN H SCHILLER: In ECOG-E4599, our statisticians conducted an unplanned analysis evaluating which subpopulations benefited from bevacizumab and which did not. They reviewed all the predefined stratification factors, and none of these resulted in a difference between whether or not patients were likely to benefit from bevacizumab. A difference did appear between men and women, however, which is puzzling. Both men and women derived a benefit from bevacizumab in terms of response rate and progression-free survival, but for some reason the men seemed to have a longer overall survival rate if they were receiving bevacizumab compared to chemotherapy alone. For the women, the survival appeared to be roughly the same.

Granted, this was a retrospective analysis, and the women did extremely well on the control arm. The median survival for women on the control arm without bevacizumab was more than 13 months compared to a median survival of approximately eight and a half months for the men on the control arm. I don't know why women on our control arm did so well, but that's one reason why we didn't see a benefit.

FIGURE 22

The following are predisposing risk factors for hemoptysis in patients with NSCLC receiving bevacizumab.



*CI n = 20; PO n = 150

One explanation why women on the control arm may have done so well is that they may have received more epidermal growth factor inhibitors. This study was conducted when gefitinib and erlotinib were just coming out. The big news was that women seemed to benefit more than men from those drugs, so it's possible that the women were more likely to receive those drugs than the men, and that's why the women on the control arm performed better.

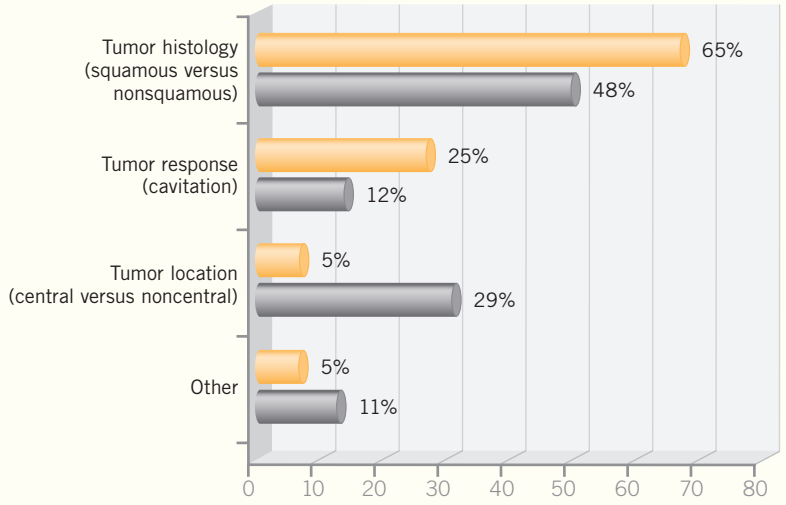
As a practicing oncologist, I have been treating women with lung cancer with bevacizumab, based on the fact that this was not a prospective analysis, and no difference was seen in the colorectal carcinoma data evaluating men versus women. In the breast cancer data, it appears that women are benefiting from bevacizumab. Based on those factors, I've continued to treat women. Moving forward, gender will be a major stratification factor.

Lung Cancer Update 2007 (3)

DR JOHNSON: My experience with the carboplatin/paclitaxel/bevacizumab

FIGURE 23

*Which of the following do you consider the most important predisposing risk factor for hemoptysis in patients with NSCLC receiving bevacizumab?**



*CI n = 20; PO n = 150

regimen is that it does have added toxicity. We have used anti-angiogenic agents for approximately five to seven years, so we have experience with them. The oral pills that are the VEGF II inhibitors share some of the same side effects, which include high blood pressure and increased risk of clotting, bleeding and proteinuria. The side effects are manageable, as with many of the other agents we use. The hypertension is treatable, and we handle most of it ourselves.

The risk of clot is real, however. We see an increased risk of deep venous thrombosis and pulmonary emboli. When you apply the algorithm of limiting this treatment to the adenocarcinomas with no history of hemoptysis, you don't see much of a problem with hemoptysis and with other risks of bleeding, although in the randomized trial it clearly runs around two or three percent. This is true for both the US and European trials, even within that selected population.

In terms of the patients who have bleeds, we've identified squamous cell cancer and a history of hemoptysis as risk factors.

In my experience, one of the differences with the anti-angiogenic agents, and this is true of both bevacizumab and the small-molecule inhibitors of the VEGF receptors, is that these lesions can cavitate. It's different than what we've typically seen with cytotoxic therapy alone. These spherical lesions hollow out in the middle and develop a cavity, which appears to be associated with the development of hemoptysis.

The assumption is that the anti-angiogenic agents block the blood flow to the middle of the tumor, it necroses and you lose some of the structure. The blood vessels can't regrow, and they bleed into it.

In the trials we designed using agents directed against VEGF, we have not held therapy if it's an uncomplicated cavitation. With any hemoptysis an oncologist will obviously stop treatment, but so far we don't have enough evidence to stop treatment for a cavitation.

Lung Cancer Update 2006 (4)

DR SANDLER: We attempted to define prognostic variables for pulmonary hemorrhage in patients who received bevacizumab. It was a case control study in which we combined the data sets from a Phase II study with those from the ECOG-E4599 study and attempted to assess a wide range of prognostic variables to see if one could better define which group of patients was more at risk.

We looked at 22 patients with Grade III or higher pulmonary hemorrhage. Not surprising with the limited number of patients, nothing was statistically significant, but there appeared to be trends for patients with baseline cavitation in their tumors and a history of hemoptysis that predated treatment.

Patients with hemoptysis were not allowed in the study. In ECOG-E4599, it was not specifically written into the study at first, but then one or more patients entered the study who had hemoptysis. After the first 60 or so patients, it was put in specifically as an exclusion criterion.

In our study, we had an independent radiology group examine all the individual CT scans, and tumor size and location did not seem to correlate with pulmonary hemorrhage. We saw a hint that endobronchial disease might be an issue, although that was not statistically significant and it is a very difficult interpretation on a CT scan, and the results were inconsistent across all the CT scans and techniques.

Lung Cancer Update Think Tank 2006

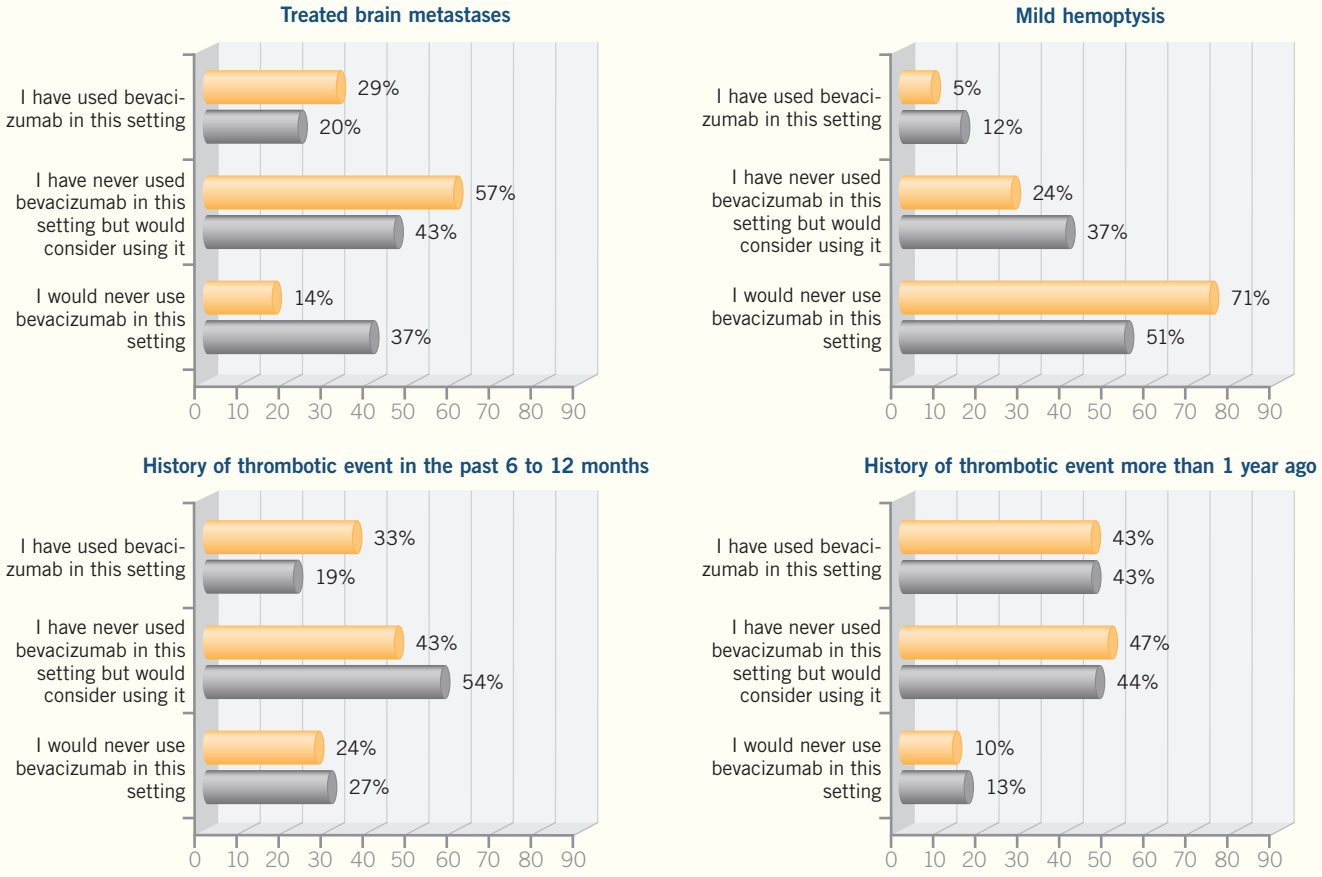
DR LYNCH: We're participating in a trial to answer the question regarding the use of bevacizumab in patients with treated brain metastases.

Patients have their brain lesions radiated first, and then they receive chemotherapy with bevacizumab. Because of the restrictions in eligibility for ECOG-E4599, which did not allow patients with CNS metastases, I believe we have to follow an evidence-based approach, and I have not been using bevacizumab in this setting outside of a protocol.

DR MILLER: We may be amending the current bevacizumab clinical trials to allow patients with previously radiated brain metastases. These contraindications to anti-VEGF therapy have relative

FIGURE 24

What is your feeling regarding the use of bevacizumab outside of a protocol setting in each of the following scenarios?



degrees. Certainly squamous histology and hemoptysis are much more powerful contraindications. This drug is very active in patients with glioblastoma multiforme — huge tumors with lots of edema — and we're undertaking approval strategy trials for those patients. We usually obtain the blessing of a neurologist to use bevacizumab in treated brain metastases, but we certainly have done it.

DR ROY S HERBST: I would wait until more data are available to use bevacizumab in patients with CNS lesions, which I expect will be soon. One trial, called PASSPORT, will determine if you can use chemotherapy with bevacizumab for patients with previously treated brain metastases.

Interview, July 2007

DR HANNA: At ASCO 2007, Christian Manegold presented a randomized Phase III study called the AVAiL trial. Patients with metastatic disease received cisplatin/gemcitabine with a placebo, bevacizumab at 7.5 mg/kg or bevacizumab at 15 mg/kg. The primary endpoint was originally overall survival, but it was amended to progression-free survival.

Both the 7.5 mg/kg and the 15 mg/kg arms had a statistically significant improvement in progression-free survival. Although they were not meant to be compared to one another, the two bevacizumab arms appeared to improve the progression-free survival by just about the same amount.

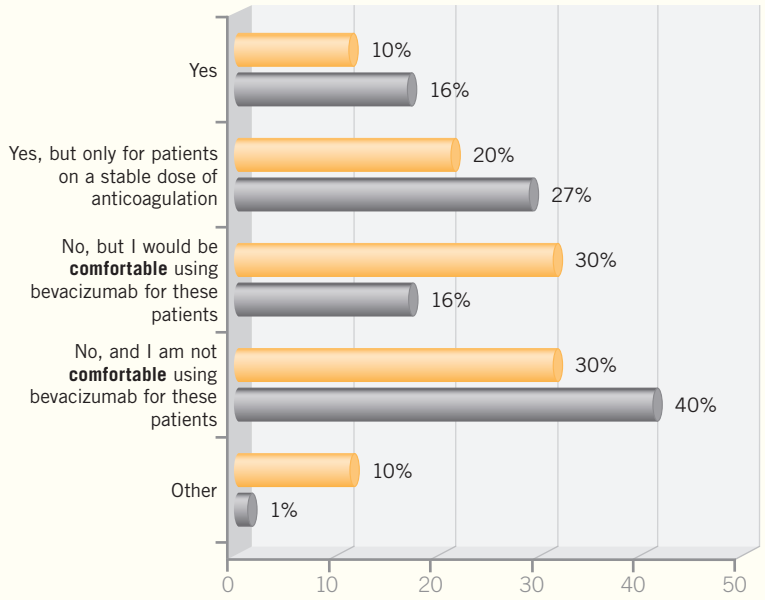
The toxicity profiles of the two dose levels were very similar. The 15 mg/kg dose had a little more bleeding than both the control arm and the 7.5 mg/kg arm. It also had a higher rate of Grade III and IV hypertension. There may have been some slight toxicity disadvantages, with no apparent efficacy advantages with the higher dose.

The incidence of bleeding was low overall. The fear was that the cisplatin/gemcitabine chemotherapy would cause more thrombocytopenia, and when combined with bevacizumab, it might result in some higher-risk bleeding.

The rate of fatal pulmonary hemorrhage was one percent or less on all three arms — that wasn't the concern. It was other Grade III and IV hemorrhages,

FIGURE 25

*Have you used bevacizumab for patients receiving therapeutic anticoagulation?**



*CI n = 20; PO n = 150

which trended a little worse for the 15 mg/kg arm. They didn't assign a *p*-value, so I am not sure whether or not it was statistically different.

Lung Cancer Update 2007 (3)

DR SOCINSKI: As a purist, I'd point out that the AVAiL trial wasn't designed to address the dose question.

The way I interpret AVAiL is that it's a second positive trial evaluating the use of bevacizumab in combination with chemotherapy — in this case, cisplatin/gemcitabine. The regimen appears to be safe, and both the 7.5-mg/kg and the 15-mg/kg doses improved the primary endpoint of progression-free survival. No survival data were presented.

The 7.5-mg/kg dose did not appear to be less toxic, and I have continued to use 15 mg/kg, based on the survival results from ECOG-E4599. I would bet that at least by ASCO 2008, we will see some survival data from the AVAiL trial, and perhaps that will change our minds about the dosing. For right now, in the absence of survival data in that trial, I've continued administering the 15-mg/kg dose.

Lung Cancer Update 2007 (3)

DR WAKELEE: In the United States, carboplatin/paclitaxel with bevacizumab is approved. Given the AVAiL data, gemcitabine/cisplatin with bevacizumab would certainly be a reasonable approach now.

We're conducting an ongoing trial with carboplatin/gemcitabine/bevacizumab. I wouldn't say that regimen is "ready for prime time" — not until we have the toxicity data, given the increased thrombocytopenia and neutropenia with carboplatin/gemcitabine. Substituting docetaxel for paclitaxel is also reasonable because we don't have any toxicity differences that would be of concern.

AVAiL was a European study of gemcitabine and cisplatin with or without bevacizumab. It evaluated two doses of bevacizumab: 7.5 mg/kg or 15 mg/kg. The 15-mg/kg dose was the dose used in the ECOG-E4599 carboplatin/paclitaxel study.

AVAiL demonstrated a statistically significant improvement in progression-free survival — not a big difference, but a real difference statistically — with both the 7.5-mg/kg and the 15-mg/kg doses. The trial wasn't powered to compare 15 mg/kg to 7.5 mg/kg — only both of those doses to placebo. Overall survival data weren't mature yet.

The big question is whether we can get away with using 7.5 mg/kg of bevacizumab. I'm cautious still. We don't have the survival data yet. We have no real way of evaluating any difference between 15 mg/kg and 7.5 mg/kg, even if we could do it statistically. I don't believe it's wrong to consider using 7.5 mg/kg, but I'm not ready to make the change in my practice. Certainly we won't be making a change in the ECOG-E1505 adjuvant trial, in which we're still using the 15-mg/kg dose every three weeks.

Of note, the bleeding risk in the AVAiL trial was lower than expected. They didn't observe any significant CNS hemorrhages, which is an issue that had been raised in ECOG-E4599.

Approximately nine percent of patients on the trial were on therapeutic anticoagulation. This was an exclusion criterion for people going on, but once they were on the trial, if they ended up needing anticoagulation therapy, they were able to stay on the study. There was no increased bleeding for that group either.

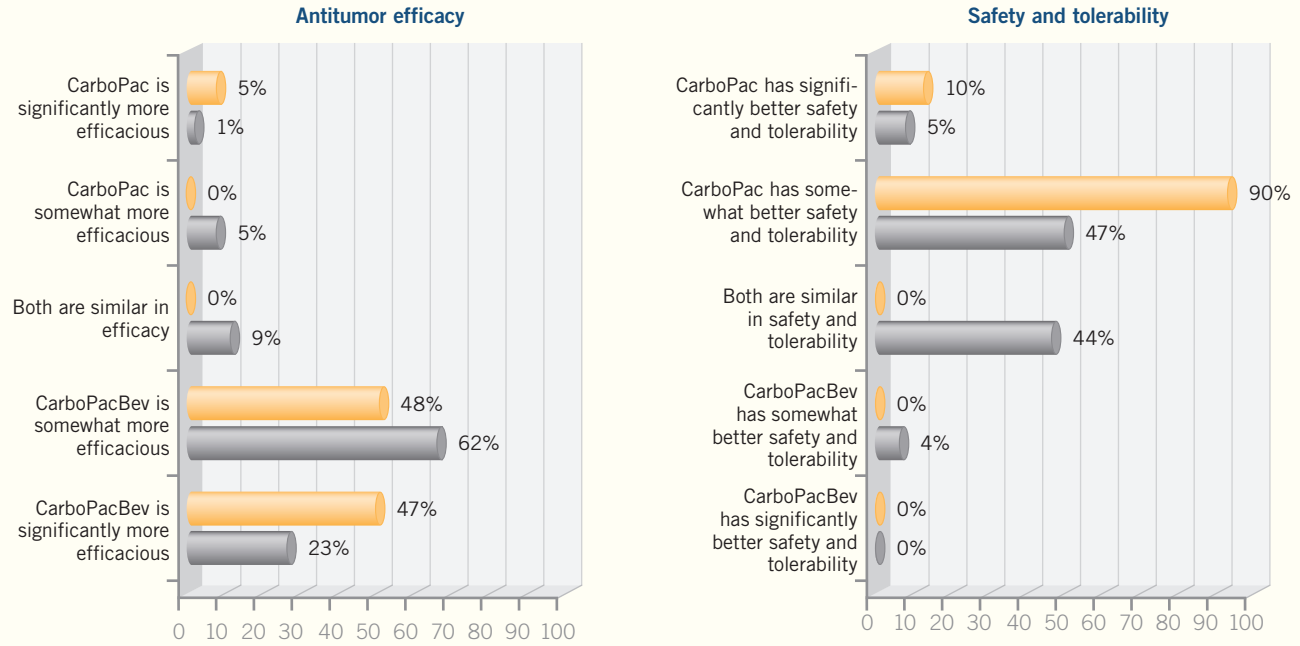
Lung Cancer Update 2007 (3)

DR SOCINSKI: The question that I am asked most frequently by practicing oncologists about metastatic disease is regarding how to approach never smokers. The never smokers represent approximately 10 percent of the population. In my experience, if you use the cutoff of 10 to 15 pack years, the oligosmokers comprise approximately another 10 percent. So one in five patients with lung cancer fall into this category. That's not insignificant when you consider the number of patients with lung cancer.

The one observation I am convinced of in that population is that anti-EGFR therapy seems to be important. The

FIGURE 26

A 65-year-old patient with a history of smoking and a good performance status presents with adenocarcinoma of the lung that has metastasized to the bone and liver. In this setting, how would you compare carboplatin/paclitaxel (CarboPac) to CarboPac and bevacizumab (CarboPacBev)?



question I struggle with regarding the never smokers is that many of them are eligible for bevacizumab. What do you do in that setting? Are they candidates for erlotinib or bevacizumab? What's the role of chemotherapy?

One option is to treat these patients with chemotherapy and bevacizumab and then, as we continue the bevacizumab, perhaps add erlotinib. We have a lot of safety information, and I don't believe we're going to harm patients with that approach.

If patients are not bevacizumab candidates — let's say they have brain metastases — then the question is, should we use chemotherapy followed immediately by a maintenance strategy with erlotinib or chemotherapy with erlotinib or erlotinib alone?

We currently have the CALGB-30406 trial that randomly assigns these patients to erlotinib alone versus carboplatin/paclitaxel with erlotinib. It is exploring two of the three possibilities. You might argue that we should have used four cycles of chemotherapy followed immediately by erlotinib or chemotherapy alone as a control arm, but there are only so many questions you can ask in a randomized Phase II trial to sort out these issues.

Lung Cancer Update Think Tank 2007

DR MILLER: I tend to use erlotinib more either in the first- or third-line setting. I don't have a huge second-line cohort. I'm driven by knowing either the EGFR mutation status or the clinical factors to incorporate erlotinib into therapy early on. If someone has a favorable profile — a 75 percent positive predictive value for a response to erlotinib, for example — those patients live for a long time, and it's only a matter of time until we establish a survival benefit for patients with EGFR mutations, treated in that fashion, rather than with chemotherapy. We need the trials to be conducted, and they're ongoing.

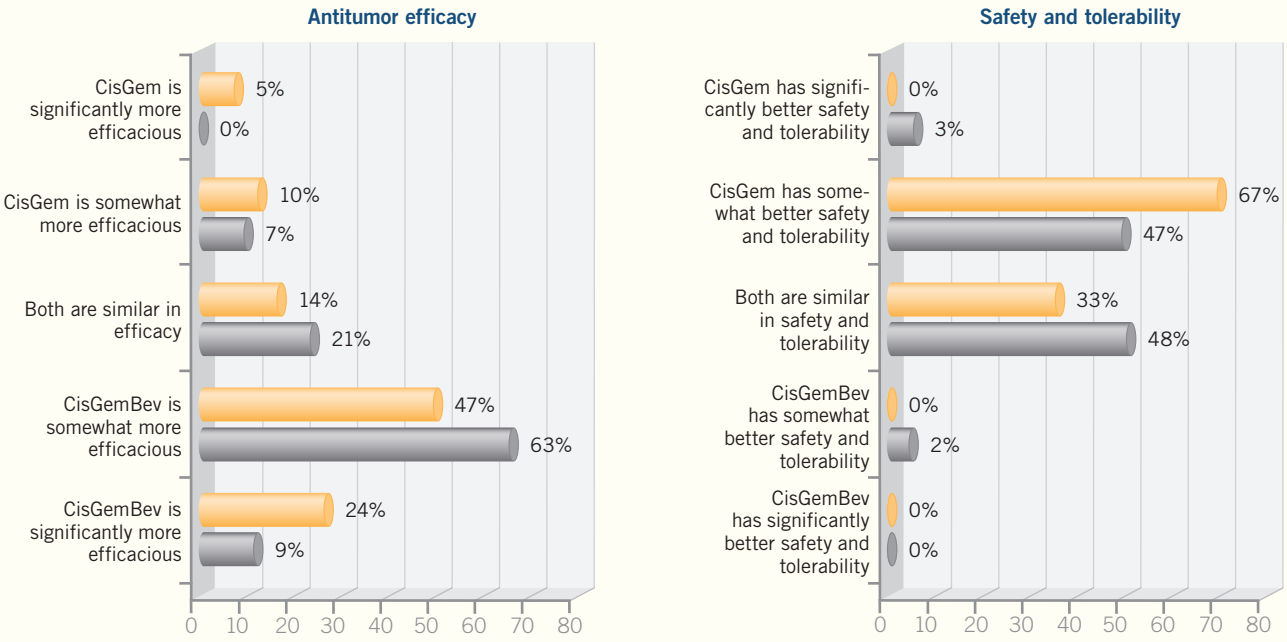
Lung Cancer Update 2007 (3)

DR JOHNSON: We believe it's important to design a clinical trial to ask the question whether patients who have EGFR mutation-positive disease will perform better with front-line EGFR-directed therapy like gefitinib or erlotinib. We believe that for two reasons. One is that time to progression, at least with the axon 19 deletion mutants, is approximately one to one and a half years, which is two to three times longer than with conventional chemotherapy. In addition, the survival with that group in the retrospective studies is approximately three years, and that's in comparison to 10 to 12 months with other protocol groups.

It's important to set up the clinical trials to show that that's the case. However, the process for obtaining the gene sequence is not easy. You need to have 300 to 500 tumor cells, and they have to undergo DNA sequencing, which is currently the approved test. The results of that test take approximately two weeks. People come to the conclusion that we haven't seen the definitive evidence that mutation testing should be

FIGURE 27

A 65-year-old patient with a history of smoking and a good performance status presents with adenocarcinoma of the lung that has metastasized to the bone and liver. In this setting, how would you compare cisplatin/gemcitabine (CisGem) to CisGem and bevacizumab (CisGemBev)?



incorporated in practice.

I believe we need to take the steps to show that is the case. Some of us have been able to integrate it into our practices, and we use it for making decisions regarding whether patients should receive initial treatment with gefitinib or erlotinib.

Lung Cancer Update 2007 (4)

DR WALTER J CURRAN JR: Erlotinib is generally better tolerated, especially compared to doublet-based chemotherapy. If it provides the same palliation and arrest of symptoms you might see with doublet chemotherapy at the start and you have a never smoker or an oligosmoker in a low PS state at diagnosis, perhaps a bit on the elderly side, I would like to have data to support erlotinib as initial treatment for that patient. We don't have the data, but I'm hoping to see it because erlotinib is an option that many patients and families would prefer.

Lung Cancer Update Think Tank 2007

DR KIM: We don't conduct EGFR mutational testing on everyone who walks through the door. But when we see clinical factors predictive of a response to erlotinib, mostly the never smokers or those with adeno-bronchoalveolar features, I offer them the standard option, which would be chemotherapy/bevacizumab. The second aspect would be to consider the nonstandard therapy, erlotinib.

I presented those options to two different patients on the same day. One was a 60-year-old female who was a light smoker, five pack years, in her twenties, and the other one was 30 to 35 years old and a never smoker. Both elected the first-line erlotinib option.

Interview, July 2007

DR HANNA: In approaching a patient with metastatic disease in the clinical setting in the first- and second-line situation, the most important questions are: What is the performance status of the patient? What are the comorbidities? Is the patient losing weight? What's his or her appetite like? If a patient is PS 3 or 4, clearly, the right thing is best supportive care.

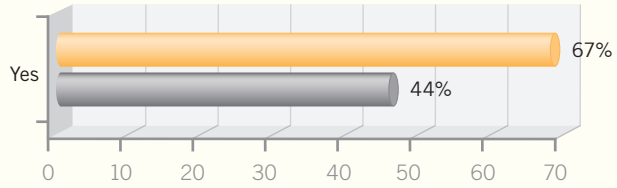
If the patient is PS 2, but in addition is having significant loss of appetite, loss of weight and comorbidities, then I believe the appropriate thing for that patient is best supportive care, unless the patient is a never smoker. Then I would consider single-agent erlotinib.

For patients who are PS 0 or 1 and don't have contraindications to chemotherapy, I believe a platinum-based two-drug regimen is standard. For patients who are bevacizumab eligible, the addition of bevacizumab is reasonable. That would include patients who don't have brain metastases, squamous histology, a history of hemoptysis or uncontrolled hypertension. I treat those patients initially with two courses of chemotherapy and repeat the CT scan. If they appear to be experiencing a clinical benefit, I administer four courses of che-

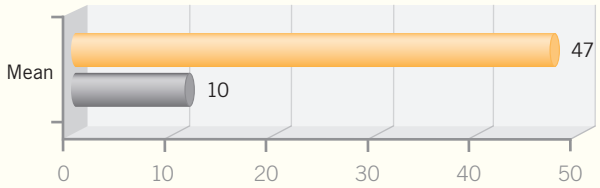
Text continued on page 27

FIGURE 28

Have you ordered the EGFR mutation test for a patient with NSCLC?



*If yes, how many times have you ordered the EGFR mutation test?**



*CI n = 14; PO n = 66

Patient gender plays a role in my decision to utilize erlotinib in the second-line management of advanced NSCLC.

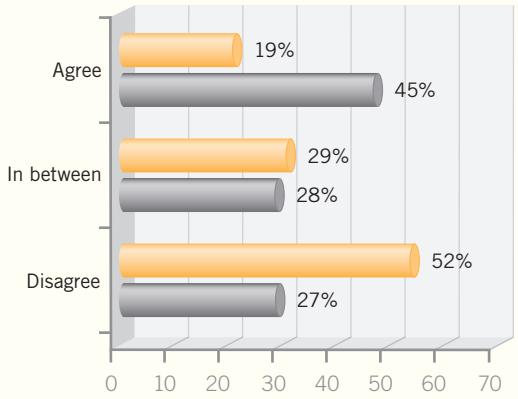
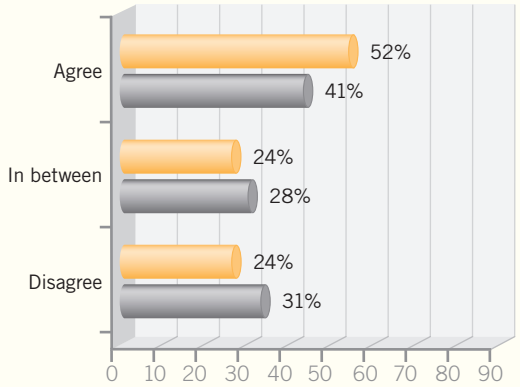
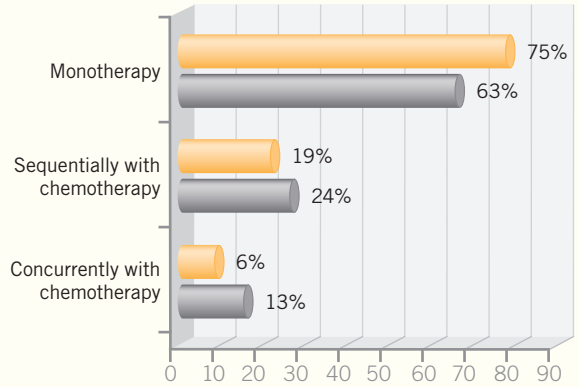


FIGURE 29

A 62-year-old female nonsmoker presents with recurrent NSCLC with mediastinal node involvement and distant metastases to the bone and adrenal gland. She previously received adjuvant carboplatin/paclitaxel and is 2 years from original diagnosis. Erlotinib should be administered as part of her first-line treatment.



*Which of the following best represents the way you utilize erlotinib in metastatic disease?**



*CI n = 16; PO n = 103

FIGURE 30

A 60-year-old female nonsmoker presents with metastatic NSCLC with asymptomatic bone involvement and mutated EGFR status. In this setting, how would you compare first-line erlotinib to carboplatin/paclitaxel (CarboPac)?

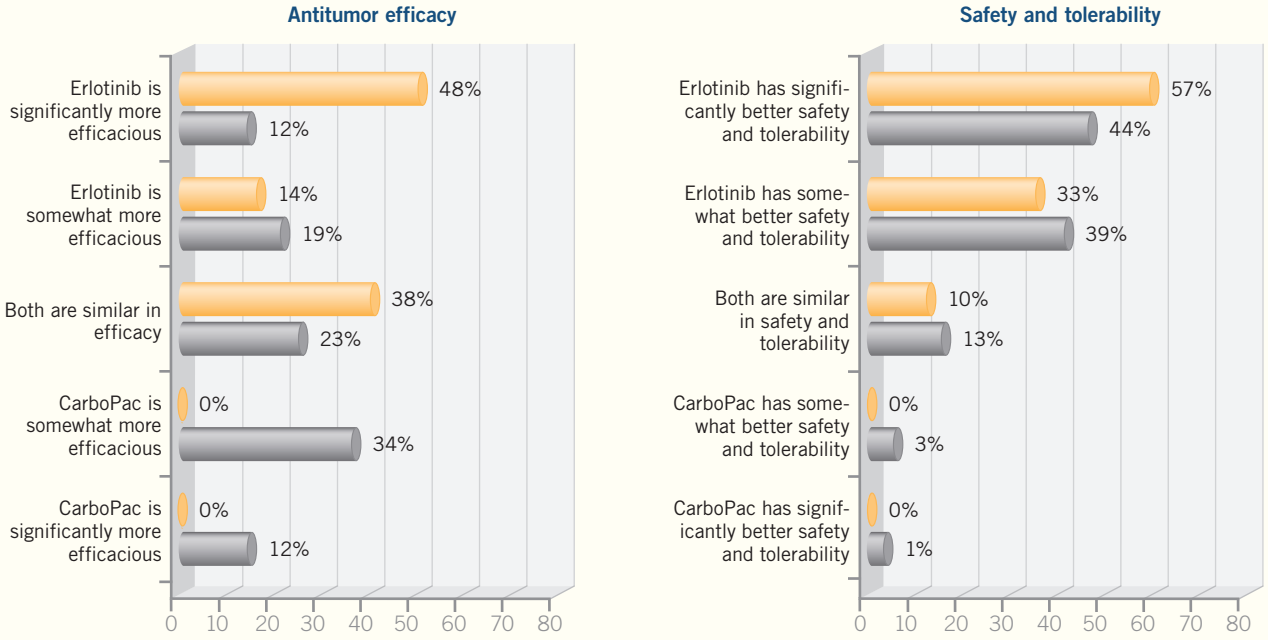
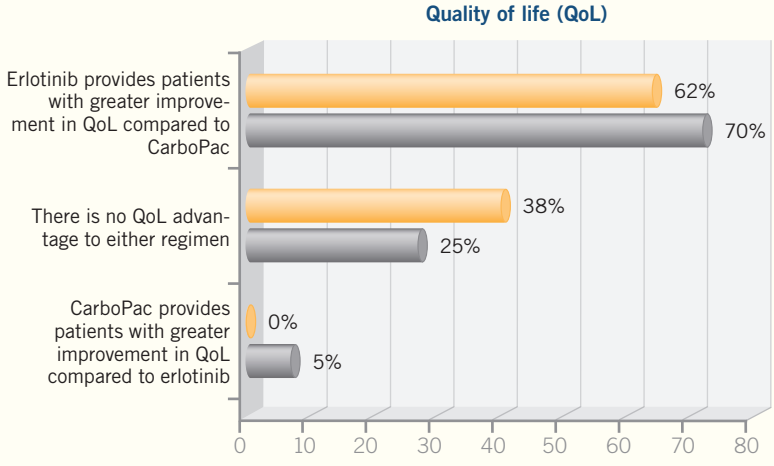


FIGURE 31

A 60-year-old female nonsmoker presents with metastatic NSCLC with asymptomatic bone involvement and mutated EGFR status. In this setting, how would you compare first-line erlotinib to carboplatin/paclitaxel (CarboPac)?



motherapy. Because the ECOG-E4599 study continued patients on bevacizumab, I administer that in maintenance until the time of progression.

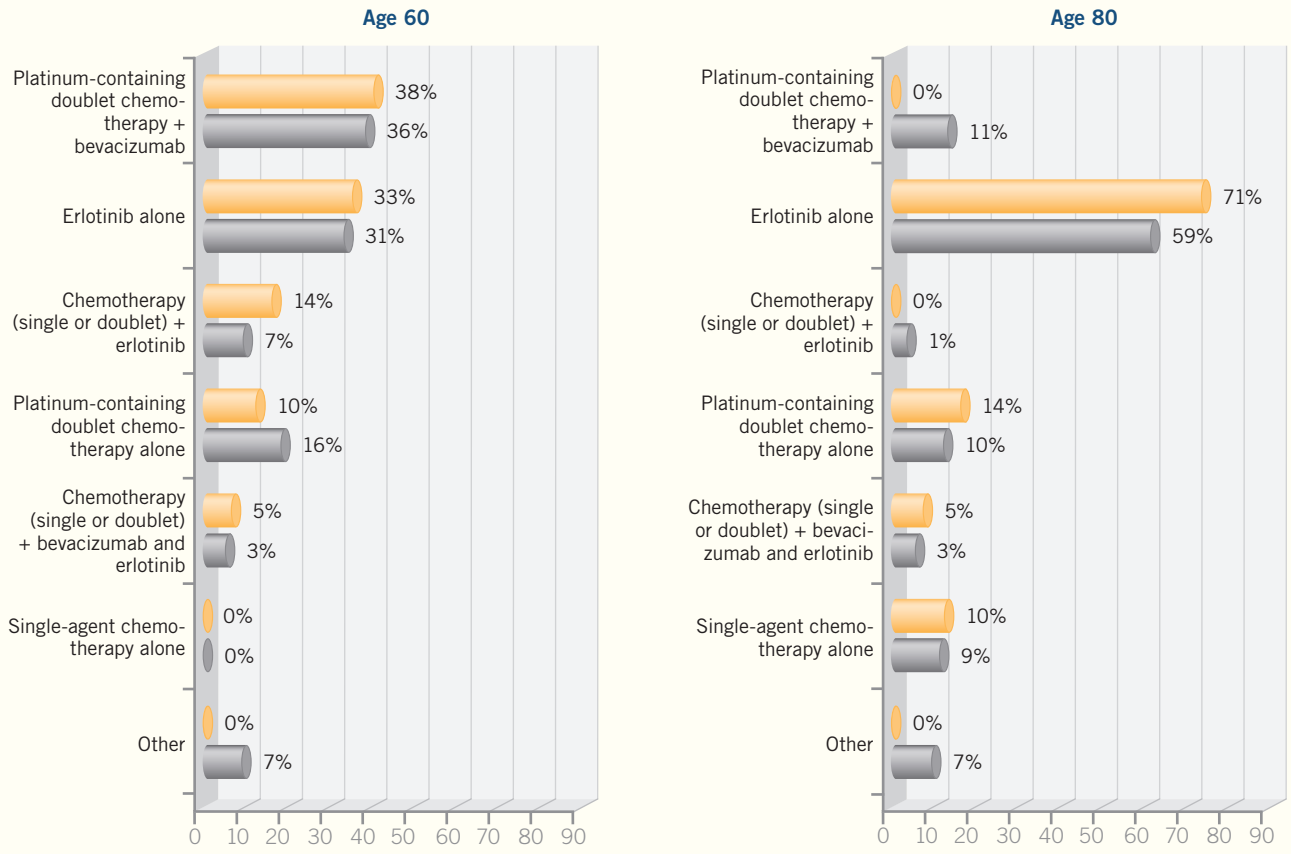
Lung Cancer Update 2007 (4)

DR EDELMAN: I approach PS 2 patients by administering a dose-attenuated, platinum-based regimen. I have found the carboplatin/gemcitabine regimen to be extremely well tolerated. We've used that, either the two drugs by themselves or sequentially, followed by weekly paclitaxel.

This is also well tolerated. I believe there's a fair amount of evidence that says that those who doubt the role of a platinum agent in PS 2 patients should consider repenting: 1) the study that was presented by Obasaju of carboplatin/gemcitabine versus gemcitabine, which showed similar results for the overall population and the PS 2 preplanned subanalysis, and 2) the CALGB study that evaluated carboplatin/paclitaxel

FIGURE 32

A female nonsmoker presents with de novo metastatic, pure bronchoalveolar carcinoma with bone and adrenal involvement. She has a good performance status and good renal function and wants to be aggressive with treatment. Which treatment would you most likely recommend if the patient was:



versus paclitaxel, which showed that if anything, the PS 2 patients probably see the most dramatic degree of benefit from the addition of a platinum agent.

Why is that, and why do we have this significant split? I believe it's because PS 2 is a heterogeneous group. There are three groups of patients who end up what we call, in our simplistic way, PS 2. There are those whose performance status has decreased as a consequence of their disease. We all see patients who come in, and they have their families who say, "This guy was working, doing manual labor four weeks ago," and they say, "Yeah, now it's a pain to get up and walk around." Reasonably, they're still walking around, doing normal activities, but they're too fatigued or they're weak and they've lost weight. That's one group. Those are the disease-result PS 2s.

You have a second group that's been PS 2 for 20 years. They have comorbidities. They never get out of bed to begin with. That's another bunch, and then you also have frail individuals. We all know this type of patient, the little old lady who looks as if she's going to get blown away in the next wind storm, and they have poor muscle mass — they're doing fine until suddenly they're not. I think those latter two groups, the ones who have significant comorbidities and the frail patients, tend not to do well when they receive a two-drug regimen because, for one reason or another, it aggravates their preexisting comorbidity.

Lung Cancer Update 2007 (3)

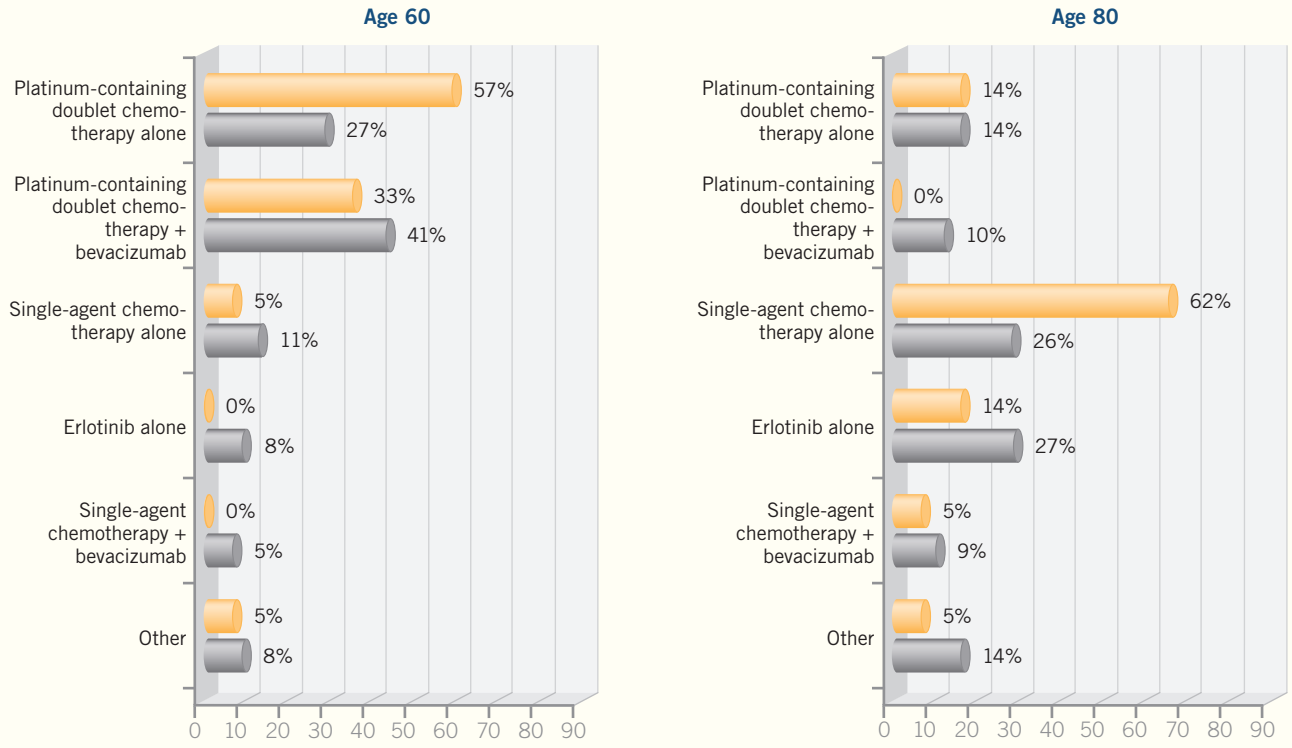
DR SOCINSKI: There was a very interesting trial presented at ASCO this year designed to evaluate the administration of immediate maintenance docetaxel following four cycles of first-line doublet chemotherapy versus second-line docetaxel per the standard approach, which is to wait until time of progression. Their ability to deliver second-line therapy was much higher in the immediate group than in the delayed group. We know if you let the natural history of this disease play out, things happen and patients who are good candidates for treatment become marginal- or no-treatment candidates, based on declining performance status and disease-related symptoms.

Text continued on page 30

FIGURE 33

What would be your most likely recommendation for a patient with de novo metastatic NSCLC if the patient was:

Previously functioning normally and is now PS 2 due to tumor-related symptoms



Previously functioning poorly as a result of COPD, with current PS 2 due to comorbidities apparently unrelated to the tumor

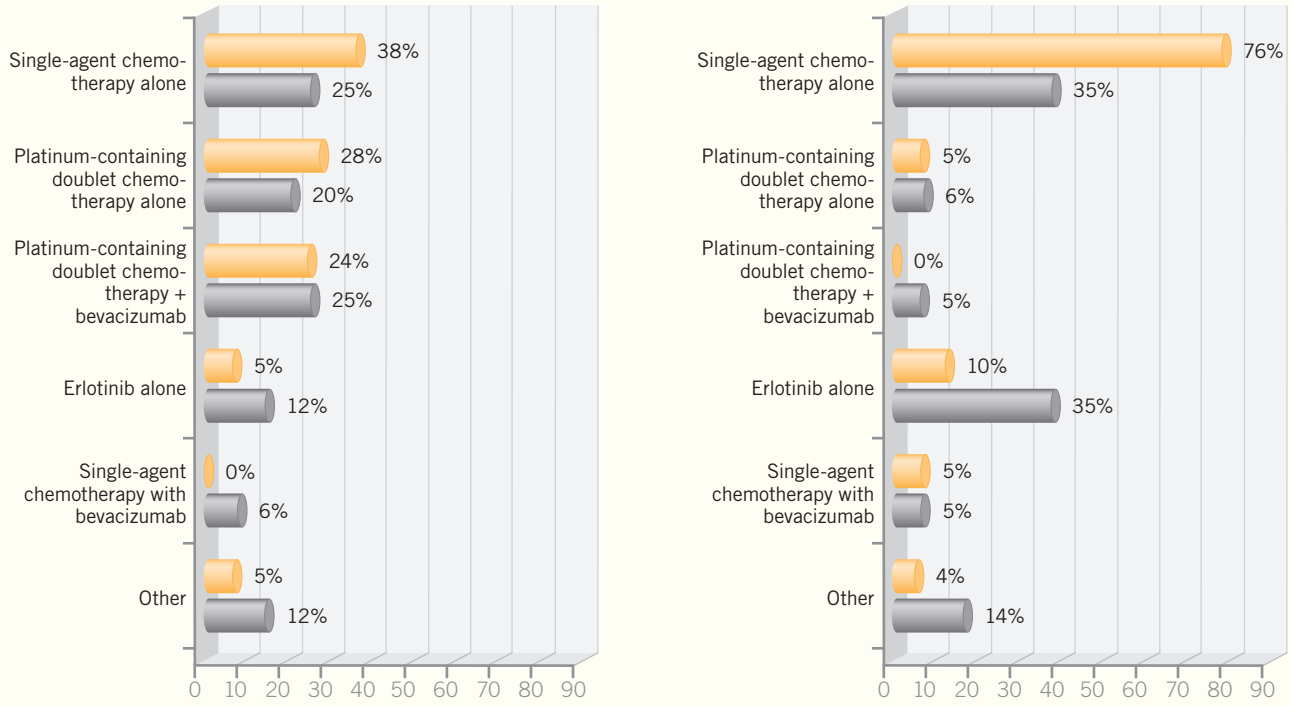
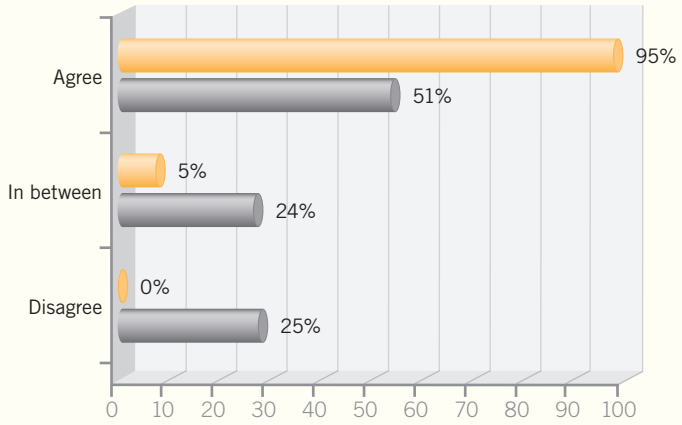
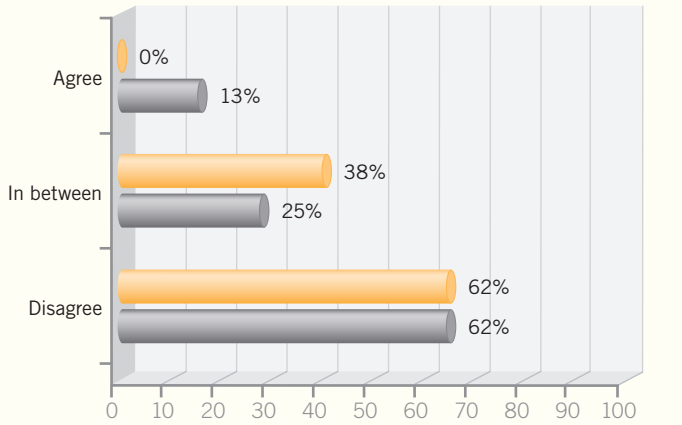


FIGURE 34

For patients who demonstrate stable disease after 6 cycles of chemotherapy with bevacizumab, I continue bevacizumab as maintenance therapy.



A patient with Stage IV NSCLC and a good performance status who has stable disease following 4 cycles of carboplatin/gemcitabine chemotherapy should receive maintenance docetaxel chemotherapy.



We know that second-line therapy works, but it can only be effective if you can administer it to the patient. So, post-ASCO 2007, this raised the question in my mind: How do you follow patients after four to six cycles of first-line chemotherapy? What triggers you to institute second-line therapy? I do not consider myself an overtester so I do not perform a lot of x-rays and CT scans while following patients, but I do see them every four to six weeks. I can tell a lot just by their appetite, pain level and chest x-ray. But I tend to think that obviously, you're not going to benefit patients with second-line therapy if they end up not being good treatment candidates.

This trial also suggested that the time to disease progression was improved with immediate docetaxel rather than waiting until disease progression to institute second-line chemotherapy. There was a trend toward improved survival in this setting. We know that second-line therapy improves survival, but if you don't receive it, you're not going to live longer.

Lung Cancer Update 2007 (1)

DR RONALD B NATALE: A major study was presented by Roy Herbst at ASCO 2006 evaluating the combination of bevacizumab and erlotinib in the second-line setting. This was an unselected group of patients, and the objective response rate was close to 25 percent, which is considerably higher than the 10 percent or so objective response rate one would expect with erlotinib alone.

That was encouraging and has led to a definitive randomized Phase III trial in which I am participating, and in fact, I am one of the major accruers to the BETA (bevacizumab and Tarceva®) study. This is a randomized trial in the second-line setting in which all patients receive erlotinib and then either placebo or bevacizumab every three weeks. That study will answer the question as to whether the combination confers a benefit.

Lung Cancer Update 2007 (3)

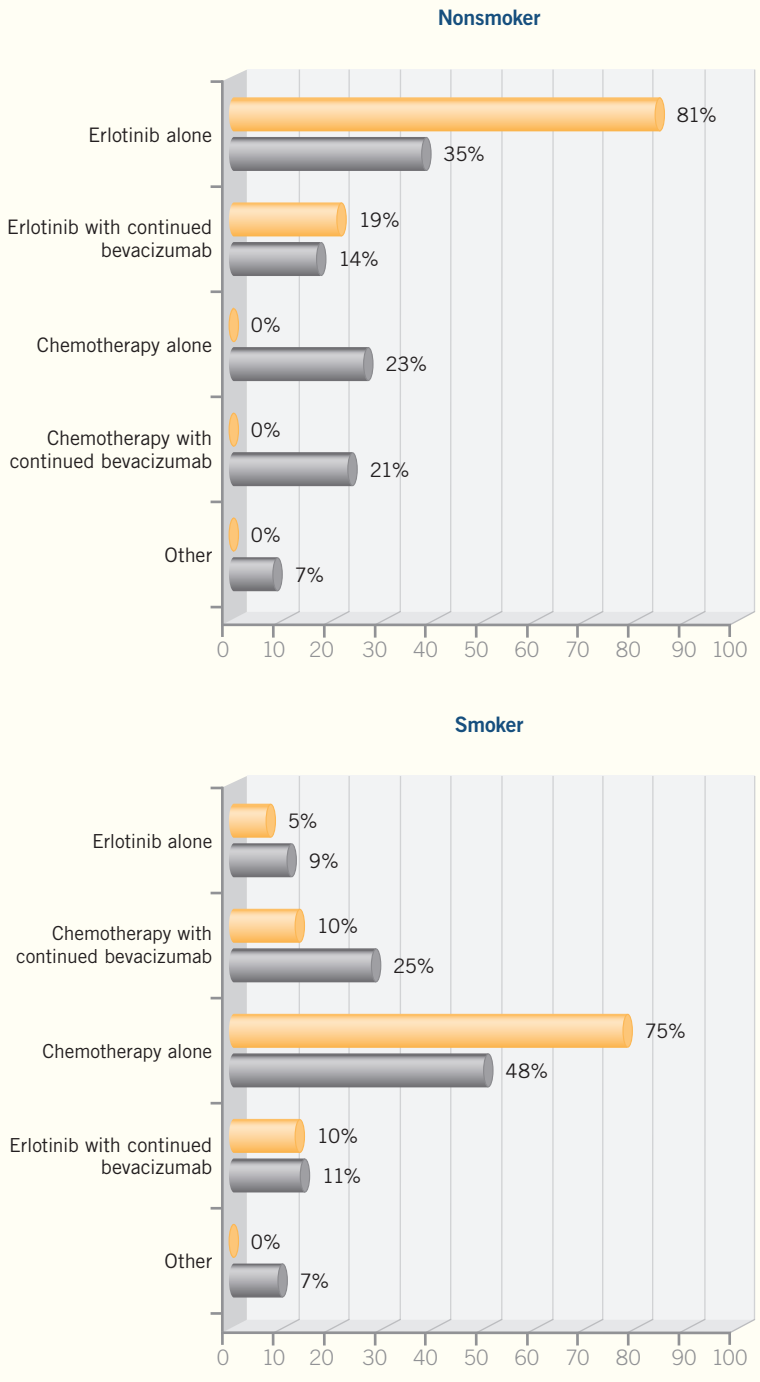
DR SOCINSKI: The attractiveness of combining erlotinib and bevacizumab is that they target two new, validated pathways. Each agent has been shown to improve survival. It's a novel targeted approach that breaks away from some of the traditional toxicities we have with regular chemotherapy. It makes biologic sense to combine them.

The initial data we had from MD Anderson and Vanderbilt were encouraging, and a randomized Phase II trial suggested that bevacizumab added to chemotherapy or erlotinib was better than chemotherapy alone. It also suggested that the combination of erlotinib and bevacizumab appeared as good, with less toxicity, than the chemotherapy/bevacizumab arm. The bevacizumab/erlotinib combination opens up the possibility that some patients may be better served with a noncytotoxic approach.

I believe the jury is still out on that issue. Phase III trials are ongoing that will answer the question about combination bevacizumab/erlotinib. We also have to remember that we may be able to identify with various biomarkers patients

FIGURE 35

A 60-year-old patient has an excellent response to carboplatin/paclitaxel/bevacizumab as first-line therapy for metastatic disease and is continued on bevacizumab. At 16 months, the patient develops slow but definite disease progression. Outside a protocol setting, the following patients should be offered which treatment?



who, at least from the erlotinib point of view, may be the best candidates for that approach.

SELECT PUBLICATIONS

Clark GM et al. **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

Fehrenbacher L et al. **A phase II, multicenter, randomized clinical trial to evaluate the efficacy and safety of bevacizumab in combination with either chemotherapy (docetaxel or pemetrexed) or erlotinib hydrochloride compared with chemotherapy alone for treatment of recurrent or refractory non-small cell lung cancer.** *Proc ASCO* 2006;Abstract 7062.

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 I/II trial evaluating the anti-vascular endothelial growth factor monoclonal antibody bevacizumab in combination with the HER-1/epidermal growth factor receptor tyrosine kinase inhibitor erlotinib for patients with recurrent non-small-cell lung cancer.** *J Clin Oncol* 2005a;23(11):2544-55. Abstract

Herbst RS et al. **TRIBUTE: A phase III trial of erlotinib hydrochloride (OSI-774) combined with carboplatin and paclitaxel chemotherapy in advanced non-small-cell lung cancer.** *J Clin Oncol* 2005b;23(25):5892-9. Abstract

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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.

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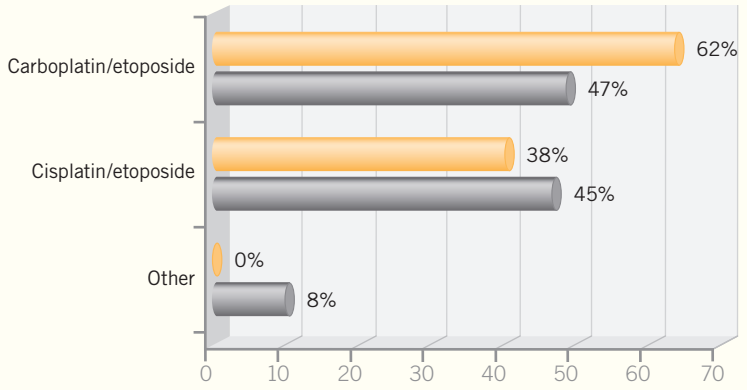
Sandler A et al. **Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer.** *N Engl J Med* 2006;355(24):2542-50. Abstract

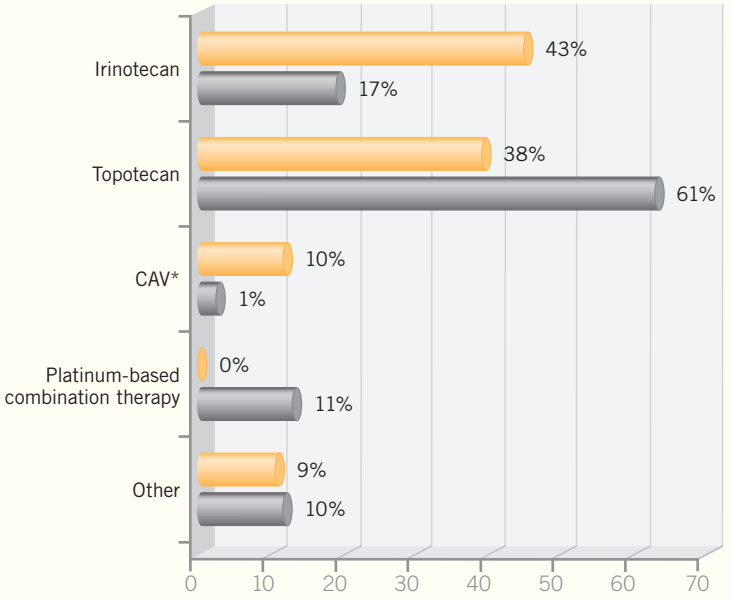
Sandler A et al. **Randomized phase II/III trial of paclitaxel (P) plus carboplatin (C) with or without bevacizumab (NSC #704865) in patients with advanced non-squamous cell lung cancer (NSCLC): An Eastern Cooperative Oncology Group (ECOG) Trial — E4599.** *Proc ASCO* 2005;Abstract 4.

FIGURE 36

For extensive-stage small cell lung cancer, in general, what is your recommended chemotherapy regimen?



A 60-year-old woman with extensive-stage small cell lung cancer has a partial response to carboplatin/etoposide chemotherapy. Four months later, she starts to show progression of disease and her performance status is still adequate for her to tolerate chemotherapy. Which would be your likely second-line treatment of choice?



* CAV = cyclophosphamide, doxorubicin and vincristine

Lung Cancer Update 2006 (3)

DR HANNA: The Japanese Cooperative Oncology Group (JCOG) reported a positive Phase III study in small cell lung cancer (SCLC) four years ago evaluating the combination of irinotecan and cisplatin compared to a control arm of etoposide and cisplatin, and the etoposide and cisplatin arm performed as you would expect. The irinotecan arm was statistically superior. The study was meant to accrue approximately 225 patients, but the Data Safety Monitoring Committee stopped the study early, according to the statistical design, based on the positive findings. So only 150 patients were accrued.

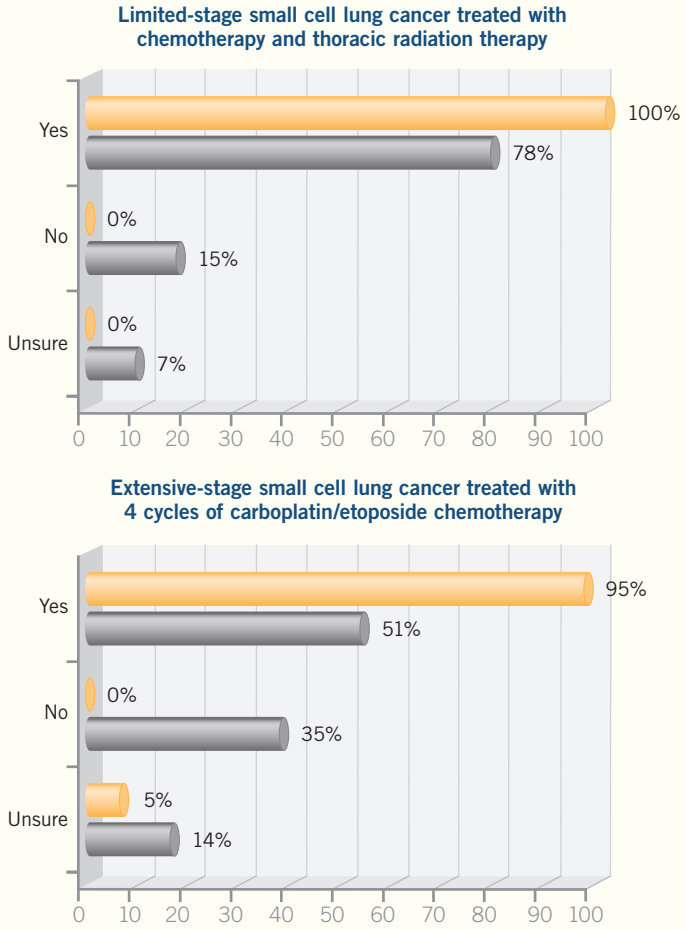
We set out to either confirm or refute those data in a largely US patient population. We used cisplatin and etoposide as our control arm. We modified the dose and schedule of the irinotecan arm. Thirty percent of the patients on the JCOG trial never received their day-15 irinotecan. We were hoping to make an every four-week regimen an every three-week regimen, and therefore, you would intensify the dose.

We also sought to take advantage of the synergism between irinotecan and cisplatin, so we split the dose. When you administer cisplatin at its full dose and irinotecan at its full dose, you see quite a bit of nausea and vomiting. So the hope was, by splitting the dose, it would be more tolerable.

I was lucky enough to present the data at ASCO last year. It involved approximately 330 patients. It was a two-to-one randomization. Approximately 220 patients received irinotecan and cisplatin, which represents three times the number of patients who received irinotecan on the JCOG trial. Unfortunately, we weren't able to replicate the data. The efficacy parameters were all the same. The median survival was approximately nine and a half months to 10 months on both arms. The one-year survival was the same on both. The differences between the regimens were largely in terms of

FIGURE 37

Would you generally recommend prophylactic cranial irradiation for a 60-year-old woman with good performance status and small cell lung cancer who has a good partial response to her treatment under the following circumstances?



the toxicities. The etoposide arm caused more neutropenia and more neutropenic infection. The irinotecan arm caused more diarrhea and mucositis and dehydration. So it is a trade-off of side effects. You have to think about the individual patient. You have to determine which side-effect profile you should consider for your individual patient.

The Southwest Oncology Group is replicating the JCOG regimen. Both arms of the SWOG-S0124 study are identical to the arms of the JCOG study. It's a much larger trial than the JCOG trial, larger than our trial, with more than 500 patients. I understand that its accrual is quite good. If it's a matter of our changing the dose and schedule of the irinotecan arm, and that was why it was not superior, then the Southwest Oncology Group study should show us that.

Lung Cancer Update 2006 (4)

DR THOMAS E STINCHCOMBE: We're interested in investigating *nab* paclitaxel in patients with small cell lung cancer. In our Phase I trial, we saw some nice responses in patients who had been previously treated for SCLC. The advantage of the combination of carboplatin and *nab* paclitaxel for patients with SCLC would be a reduction in febrile neutropenia. Our current regimen of cisplatin/irinotecan is associated with a significant incidence of febrile neutropenia of approximately five percent. If we could administer carboplatin/*nab* paclitaxel every three weeks, it would be a significant improvement in terms of patient convenience over cisplatin/etoposide or carboplatin/etoposide on days one through three.

Cancer Conference Update 2007 (3)

DR KIM: Brain metastases are a big problem in SCLC. A meta-analysis published in 1998 suggested a decreased risk of brain metastases and an improvement in survival with radiation therapy. This was predominantly in limited-stage SCLC with some extensive-stage small cell disease.

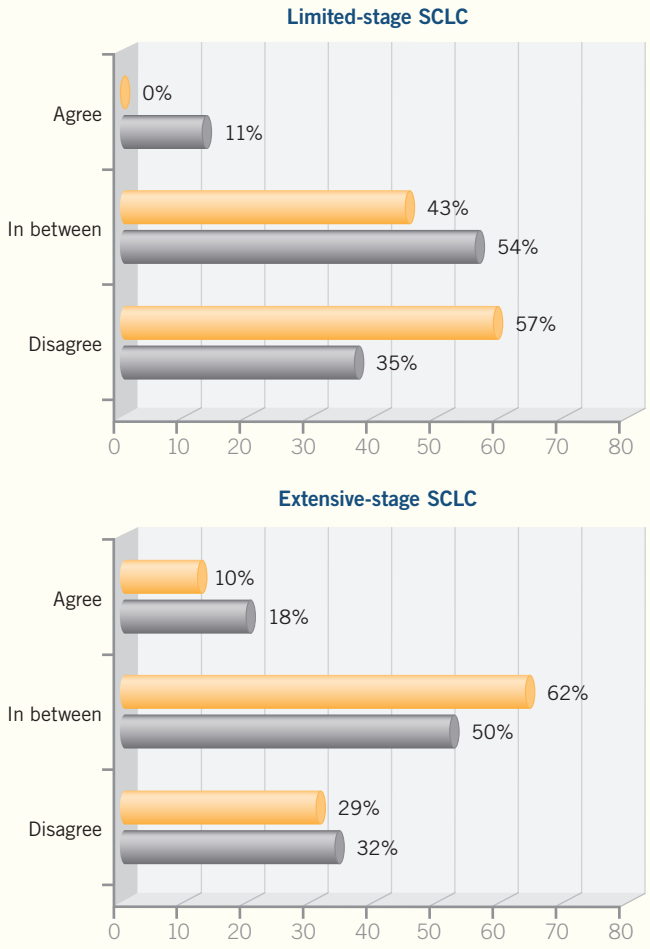
The EORTC study that was presented at ASCO 2007 on the use of prophylactic cranial irradiation (PCI) in extensive-stage SCLC was interesting. I believe we have to take the data with a grain of salt in that they show some proof of concept but, again, we have to tailor the data to our patients in practice. This study focused on extensive-disease SCLC. Four to six cycles of therapy were administered up front. They called this induction therapy but, in fact, it is the routine therapy we administer for extensive disease. The patients, if they experienced any response — and this response was gauged by the investigators or the treating physicians, it was not based on RECIST — were then randomly assigned to receive PCI. The PCI varied between 20 and 30 Gray in a one-week or two-week time frame, or no PCI.

Randomization occurred within five weeks of completing the chemotherapy, and then patients were required to start the PCI within six weeks of completing the chemotherapy.

The primary endpoint was to demonstrate a reduction in risk of developing symptomatic brain metastases, and the key word here is "symptomatic." That goes with the spirit of the entire study

FIGURE 38

Bevacizumab will eventually have a role in the treatment of:



— patients were responding. They may have been symptomatically responding, feeling better. It's a palliative situation.

There was not a mandated staging of the brain at baseline, which can obviously be quite problematic. We had a list of eligibility criteria, by which the patient had to have one or more of the listed symptoms in order to require an imaging test, either a CT or an MRI. We don't know what would have happened if they had all undergone imaging — some of those people might have had gross disease already but been asymptomatic.

The numbers were quite positive. The hazard ratio for development of symptomatic metastases was 0.27. It's nearly a 75 percent reduction, which was a very favorable outcome. One-year survival was approximately double with PCI and was reported as 27 percent versus 13.3 percent. Failure-free survival was 23.4 versus 15.5 percent. And again, some stratification issues that were different regarding the amount of extrathoracic disease and extracranial disease existed in the two cohorts. So I don't believe, definitively, that we can say one way or another that every patient who responds to chemotherapy should receive PCI. I don't believe that this is that kind of study. But for providing a proof of principle, it validates the concept that administering PCI to patients with extensive-stage SCLC and good chemotherapy responses may be justifiable.

Lung Cancer Update 2007 (1)

DR BELANI: When you compare SCLC to non-small cell, you don't see the same patient numbers and morbidity and mortality. But if you compare it to other tumors, then it's a significant disease. There is not enough research on it. Among all lung cancers, the numbers have dropped from 20 percent to 13 percent. Most of them are being treated in the community because the response rate with standard treatments is high enough that these patients don't show up for a research study. Therefore, it will be difficult to compare experimental regimens to the standard regimen in the front-line setting. We need to develop select markers for select patients in the second-line and recurrent disease settings and take them to the front-line setting. I believe bevacizumab is one of a class of VEGF-targeted compounds that still should be evaluated in SCLC.

Lung Cancer Update 2007 (2)

DR SCHILLER: ECOG completed a Phase II trial in extensive-stage SCLC, which was platinum/etoposide and bevacizumab. It was a one-arm trial that had only 68 patients. It met its first safety endpoint, and the study itself was completed approximately six months ago. There were no unusual toxicities and, specifically, there was a lack of hemoptysis. We are planning to move forward with the randomized Phase III study of cisplatin/etoposide with or without bevacizumab in extensive-stage disease through ECOG.

SELECT PUBLICATIONS

Hanna NH et al. **Randomized, phase III trial comparing irinotecan/cisplatin with etoposide/cisplatin in patients with previously untreated, extensive-stage small cell lung cancer.** *J Clin Oncol* 2006;24(13):2038-43. Abstract

Noda K et al. **Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer.** *N Engl J Med* 2002;346(2):85-91. Abstract

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.

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

- Compare and contrast the management strategies of community oncologists and cancer clinical investigators for the treatment of lung cancer in the adjuvant, locally advanced and metastatic settings. 5 4 3 2 1
- Discuss cancer management issues for which relative agreement and heterogeneity exist in patterns of care. 5 4 3 2 1
- Counsel cancer patients about multiple acceptable treatment options when they exist. 5 4 3 2 1

OVERALL EFFECTIVENESS OF THE ACTIVITY

Objectives were related to overall purpose/goal(s) of activity. 5 4 3 2 1

Related to my practice needs. 5 4 3 2 1

Will influence how I practice 5 4 3 2 1

Will help me improve patient care 5 4 3 2 1

Stimulated my intellectual curiosity 5 4 3 2 1

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Patterns of Care in Medical Oncology

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