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Lung Cancer™ UPDATE

Conversations with Oncology Investigators

Bridging the Gap between Research and Patient Care

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STATEMENT OF NEED/TARGET AUDIENCE

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

GLOBAL LEARNING OBJECTIVES

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

PURPOSE OF THIS ISSUE OF *LUNG CANCER UPDATE*

The purpose of Issue 4 of *Lung Cancer Update* is to support these global objectives by offering the perspectives of Drs Sandler, Miller, Pass and Stinchcombe on the integration of emerging clinical research data into the management of lung cancer.

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UPCOMING EDUCATIONAL EVENTS

48th Annual Meeting of the American Society for Therapeutic Radiology and Oncology
November 5-9, 2006
Philadelphia, Pennsylvania
Event website: **astro.org**

Chemotherapy Foundation Symposium
Innovative Cancer Therapy for Tomorrow
November 8-11, 2006
New York, New York
Event website: **mssm.edu/tcf**

Fifth Annual British Thoracic Oncology Group (BTOG) Meeting
January 24-27, 2007
Dublin, Ireland
Event website: **btog.org**

2007 Society of Surgical Oncology Annual Cancer Symposium
March 15-18, 2007
Washington, DC
Event website: **surgonc.org**

American Association for Cancer Research Annual Meeting
April 14-18, 2007
Los Angeles, California
Event website: **aacr.org**

ASCO 2007 Annual Meeting
June 1-5, 2007
Chicago, Illinois
Event website: **asco.org**

INTERVIEW

Alan B Sandler, MD

Dr Sandler is Associate Professor of Medicine, Medical Director of Thoracic Oncology and Director of the Vanderbilt-Ingram Cancer Center Affiliate Network Program at Vanderbilt University Medical Center's Division of Hematology/Oncology in Nashville, Tennessee.

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Select Excerpts from the Interview

Track 8

DR LOVE: When you presented the data from ECOG-E4599 in 2005 (Sandler 2005), one of your concluding comments was that first-line carboplatin, paclitaxel and bevacizumab is a new standard of care for NSCLC patients who would have been eligible for the study. Do you still feel that way?

DR SANDLER: Yes. My specific quote was that this combination in the nonsquamous-cell population included in ECOG-E4599 was the new ECOG reference standard. I certainly would acknowledge that some toxicity associated with the regimen appears greater than with chemotherapy alone, but the benefits that were seen with respect to all the outcomes, including survival, outweigh the risks.

We did not specifically look at quality of life in the study, but it appears that other nonspecific toxicities, such as fatigue, were not increased and that quality of life in fact improved, because in virtually every other study that has shown an improvement in survival, quality of life has been better.

DR LOVE: The trial stipulated that bevacizumab would be continued alone after the chemotherapy until the disease progresses. Do you do that in your practice?

DR SANDLER: Yes, that is exactly what I do. I follow the intent and guidelines of ECOG-E4599. The potential benefit of the maintenance portion of the bevacizumab has been widely recognized.

I no longer have any patients actively being treated on ECOG-E4599. I do have one patient who went between a year and a half and a year and three quarters and was on a maintenance dose of bevacizumab, and I have some other patients who had gone not quite that far.

Track 4

DR LOVE: Can you discuss the data that you presented at ASCO 2006 on pulmonary hemorrhage in patients treated with bevacizumab in the study?

DR SANDLER: We submitted a poster that attempted to define prognostic variables for pulmonary hemorrhage (Sandler 2006). 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.

DR LOVE: Hemoptysis wasn't allowed in the study, correct?

DR SANDLER: Correct. 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.

DR LOVE: Oncologists are interested in whether location — peripheral versus proximal — was a factor, and I would also be interested in whether a correlation appeared with tumor bulk.

DR SANDLER: We observed size using three centimeters as a cutoff, and it did not seem to correlate. We noted location, but when radiologists look at what they define as central tumors, it really encompasses a wide range of tumors because I believe their definition is anything that's more than two centimeters away from the pleural reflection.

In our study, we had an independent radiology group examine all the individual CAT scans — so they were all independently reviewed — and size and location did not seem to matter. 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 CAT scan, and the results were inconsistent across all the CAT scans and techniques.

Track 9

DR LOVE: Can you update us on the erlotinib/bevacizumab combination data that were presented at ASCO?

DR SANDLER: The combination of erlotinib and bevacizumab involves the inhibition of the EGFR pathway along with angiogenesis and was based on a Phase I and II study conducted by Dr Roy Herbst at MD Anderson and my colleagues and me at Vanderbilt, in which we had 40 patients with previously treated nonsquamous-cell, non-small cell lung cancer.

We saw a 20 percent response rate, a roughly seven-month progression-free survival and a 12.5-month median survival (Sandler 2004), but because it was a Phase I/II limited-institution study, a subsequent larger-scale randomized Phase II study was conducted that involved 120 patients and was presented at ASCO (Fehrenbacher 2006).

This study had three arms: Bevacizumab in combination with either chemotherapy (docetaxel or pemetrexed) or erlotinib compared with chemotherapy alone. An improvement in progression-free survival favored the two bevacizumab arms. It was three months on the chemotherapy alone arm and roughly four and a half months on the two bevacizumab arms — 4.4 months with erlotinib and 4.8 months with chemotherapy (1.1).

Track 10

DR LOVE: Would it be correct to say that you observed the same results by adding erlotinib to bevacizumab as with adding chemotherapy to bevacizumab? You would expect fewer side effects with the double biologic therapy than with chemotherapy and bevacizumab.

DR SANDLER: That's an interesting point, and that is my take on this study. It's another example that the addition of bevacizumab to chemotherapy or, in this case, a biologic, an EGFR tyrosine kinase (TK) inhibitor, such as erlotinib, showed benefit when compared to chemotherapy alone. That's the first point.

The second point is that it now provides evidence that a nonchemotherapy-based approach in the second-line setting consisting of erlotinib and bevacizumab might prove to be equivalent to chemotherapy.

A large Phase III study of more than 600 patients is evaluating erlotinib alone versus erlotinib and bevacizumab in the second-line setting (OSI3364g).

1.1

Phase II Randomized Study Comparing Chemotherapy (Docetaxel or Pemetrexed) with or without Bevacizumab and Erlotinib/Bevacizumab as Second-Line Therapy for NSCLC

Parameter	Chemotherapy alone (n = 41)	Chemotherapy + bevacizumab (n = 40)	Erlotinib + bevacizumab (n = 39)
Progression-free survival			
Median	3.0 months	4.8 months	4.4 months
Six-month rate	21.5%	30.5%	33.6%
Adjusted hazard ratio (95% CI)*	NA	0.66 (0.38-1.16)	0.72 (0.42-1.23)
Unadjusted hazard ratio (95% CI)	NA	0.78 (0.47-1.30)	0.76 (0.45-1.28)
Overall survival			
Six-month rate	62.4%	72.1%	78.3%
Response rate			
CR/PR	12.2%	12.5%	17.9%
CR/PR/SD	39.0%	52.5%	51.3%

* Adjusted by randomization stratification factors (ECOG performance status, smoking history)

CR = complete response; PR = partial response; SD = stable disease

SOURCE: Fehrenbacher L et al. *Proc ASCO* 2006;**Abstract 7062**.

DR LOVE: From the practical or clinical perspective of a physician in practice, what are the implications of these data?

DR SANDLER: That's another very good question. We do not have official randomized Phase III data for the biologic doublet, but we certainly have enough evidence — more evidence than we have for chemotherapy in the third-, fourth- and fifth-line settings, which we are all guilty of administering.

In clinical practice, this combination would be a bit of a reach at this point. It would be intriguing for those patients who are selected for the use of erlotinib — nonsmokers, Asian patients, patients with EGFR mutations, FISH-positive cases, et cetera.

In our Phase I/II study there was a hint that this combination was working in patients with and without EGFR mutations, smokers and nonsmokers. That has not been broken out yet for the randomized Phase II study, but it's possible that the combination may allow for the use of the EGFR agent in a broader range of patients.

DR LOVE: What is seen in terms of side effects and toxicity with this biologic doublet, both in terms of data and your own clinical experience?

DR SANDLER: No surprises have occurred in toxicity (1.2). We're seeing rash, minimal diarrhea associated with the EGFR TK inhibitor, some proteinuria and hypertension related to bevacizumab. Three deaths related to pulmonary hemorrhage occurred on the study — two on the chemotherapy/bevacizumab arm and one on the erlotinib/bevacizumab arm (Fehrenbacher 2006).

1.2

Phase II Randomized Study Comparing Chemotherapy (Docetaxel or Pemetrexed) with or without Bevacizumab and Erlotinib/Bevacizumab as Second-Line Therapy for NSCLC

Parameter	Chemotherapy alone (n = 41)	Chemotherapy + bevacizumab (n = 40)	Erlotinib + bevacizumab (n = 39)
Drug discontinuation due to an adverse event (AE)	24%	25%	10%
Serious AEs	54%	40%	33%
Grade V drug-related AEs	5%	8%	3%

SOURCE: Fehrenbacher L et al. *Proc ASCO* 2006;**Abstract 7062**.

Track 12

DR LOVE: I want to get your take on a couple of new developments in lung cancer clinical research. What are your thoughts about ZD6474, or vandetanib?

DR SANDLER: ZD6474 is an oral agent that has both EGFR and VEGF TK inhibition, and it has been involved in two randomized Phase II studies (1.3).

Ron Natale presented a study of ZD6474 compared to gefitinib and demonstrated an improvement in time to progression with ZD6474 (Natale 2006).

John Heymach from MD Anderson presented another study evaluating docetaxel with or without ZD6474, which also showed an improvement in time to progression with the combination, favoring a lower dose in that setting (Heymach 2006).

DR LOVE: Is ZD6474 sort of the oral tyrosine kinase inhibitor version of your doublet of erlotinib and bevacizumab?

DR SANDLER: Correct, that's the theory.

The interesting aspect is that apparently, depending on the dose, you may see one effect over the other. At 100 mg, the effect appears to be more of an antiangiogenic one, and that may explain why in combination with chemotherapy the lower dose seems to be better, but the higher dose when used on its own, which has both effects, seems to be better than the lower dose.

DR LOVE: Where do you think we will be heading with this agent? Will we be using it in clinical practice in the near future, and if so, where and how?

DR SANDLER: Randomized Phase III studies are now going forward. If the results are positive, it will become a player in the treatment of metastatic non-small cell lung cancer.

1.3

ZD6474 (Vandetanib) in Treatment of Patients with Advanced Non-Small Cell Lung Cancer Previously Treated with Platinum-Based Chemotherapy

	ZD6474* (n = 83)	Gefitinib* (n = 85)	Docetaxel + placebo† (n = 41)	Docetaxel + ZD6474 100 mg† (n = 42)	Docetaxel + ZD6474 300 mg† (n = 44)
Median PFS	11.0 wks	8.1 wks	12.0 wks	18.7 wks	17.0 wks
Hazard ratio (95% CI)	0.69 (0.50-0.96)		NA	0.64 (0.38-1.05)	0.83 (0.50-1.36)
p-value*	0.025		NA	0.074	0.416

SOURCES: * Natale RB et al. *Proc ASCO* 2006;**Abstract 7000**; † Heymach JV et al. *Proc ASCO* 2006;**Abstract 7016**.

SELECT PUBLICATIONS

Brahmer JR et al. **ECOG 4599 phase III trial of carboplatin and paclitaxel ± bevacizumab: Subset analysis of survival by gender.** *Proc ASCO* 2006;**Abstract 7036**.

Dowlati A et al. **Prospective correlative assessment of biomarkers in E4599 randomized phase II/III trial of carboplatin and paclitaxel ± bevacizumab in advanced non-small cell lung cancer (NSCLC).** *Proc ASCO* 2006;**Abstract 7027**.

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**.

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* 2005;23(11):2544-55. **Abstract**

Heymach JV et al. **A phase II trial of ZD6474 plus docetaxel in patients with previously treated NSCLC: Follow-up results.** *Proc ASCO* 2006;**Abstract 7016**.

Jain RK. **Normalization of tumor vasculature: An emerging concept in antiangiogenic therapy.** *Science* 2005;307(5706):58-62. **Abstract**

Johnson DH et al. **Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer.** *J Clin Oncol* 2004;22(11):2184-91. **Abstract**

Natale RB et al. **ZD6474 versus gefitinib in patients with advanced NSCLC: Final results from a two-part, double-blind, randomized phase II trial.** *Proc ASCO* 2006;**Abstract 7000**.

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

Sandler AB 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 non-small cell lung cancer (NSCLC): An Eastern Cooperative Oncology Group (ECOG) trial — E4599.** *Proc ASCO* 2005;**Abstract 4**.

Sandler AB et al. **Phase I/II trial evaluating the anti-VEGF MAb bevacizumab in combination with erlotinib, a HER1/EGFR-TK inhibitor, for patients with recurrent non-small cell lung cancer.** *Proc ASCO* 2004;**Abstract 2000**.

INTERVIEW

Vincent A Miller, MD

Dr Miller is Associate Attending Physician in Thoracic Oncology Service at Memorial Sloan-Kettering Cancer Center in New York, New York.

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Track 2

DR LOVE: Can you discuss the predictors of response to the TKIs in patients with non-small cell lung cancer?

DR MILLER: We now have several markers that can be determined in any patient — such as smoking history, ethnicity and pathology — and some in

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 TKIs 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 (Miller 2006; Asahina 2006; Paz-Ares 2006; Sutani 2006; Sunaga 2006).

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 (Miller 2006). Those are pretty powerful predictors for a difference in clinical outcome with two tests.

Track 8

DR LOVE: What is your approach to first-line therapy in the metastatic setting for nonsmokers or those with less than a 15 pack-year history who quit smoking 30 years ago?

DR MILLER: For a never smoker and in the context of the Phase III data with bevacizumab (Sandler 2005), I am still moved by the experience in the TRIBUTE study. In that trial, we conducted a prospective subgroup analysis of 72 never smokers who received erlotinib with chemotherapy and 44 never smokers who received placebo with chemotherapy (Herbst 2005).

We saw nearly a 2.5-fold difference in median survival: 10 months for the control group, which was not significantly different from the survival for the whole study group, and 22.5 months for the group that received erlotinib with chemotherapy (Herbst 2005; [2.1]). Even in the most ambitious Phase II study from a single institution, I don't believe we have ever seen a nearly two-year median survival in untreated patients with metastatic lung cancer.

Given those data and having had a good experience with that regimen for my patients, I believe this is clearly an effective treatment for the majority of these individuals. They are not cured, and we don't want to lose sight of the fact that we have a tremendous amount of work to do, but it is a palpable step forward in their therapy.

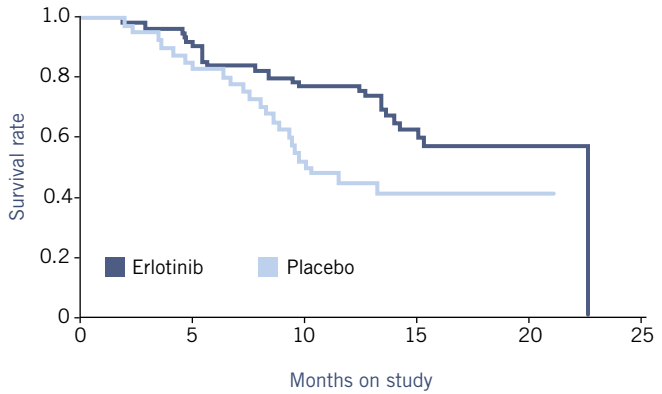
DR LOVE: How would you integrate chemotherapy and erlotinib in terms of timing?

DR MILLER: In the metastatic setting, I tend to start the chemotherapy with erlotinib. I try to use it the same way we did in the TRIBUTE trial (Herbst 2005) because without any clear biologic indication otherwise that's where we have our best clinical results.

When you use erlotinib in that type of population, with a high frequency of EGFR mutations, you tend to induce apoptosis in the tumor cells. Therefore, you may not have an inhibitory or negative interaction between the chemotherapy and erlotinib. This has been demonstrated in cell lines.

2.1

Overall Survival for Never Smokers in the TRIBUTE Trial: Erlotinib or Placebo, Combined with Carboplatin and Paclitaxel



	Erlotinib	Placebo	*p*-value
Median survival (months)	22.5	10.1	0.01
Number of patients	72	44	—

SOURCE: Herbst RS et al; TRIBUTE Investigator Group. **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* 2005;23(25):5892-9. Reprinted with permission from the American Society of Clinical Oncology. **Abstract**

Track 9

DR LOVE: How long do you use chemotherapy, and how long do you use erlotinib?

DR MILLER: I use up to six cycles of chemotherapy with erlotinib. Then I put the patient on erlotinib maintenance until progression. One of the abstracts we presented at ASCO 2006 addressed the question of management for patients with great responses to erlotinib followed by progression.

Should erlotinib be continued or stopped? There is a raging debate on this with trastuzumab in breast cancer. Our data were fairly provocative that it may be beneficial to continue erlotinib. The rate of progression appeared

greater among patients off erlotinib than among those on erlotinib (Riely 2006).

We evaluated patients who either had a known EGFR mutation or had been on erlotinib or gefitinib for at least six months (ie, surrogates for benefit from the drug) and who then experienced documented progression. We obtained a CAT scan and a PET scan. We stopped the erlotinib, and we obtained the same scans three weeks later (Riely 2006).

Then we restarted the erlotinib and repeated the CAT scan and PET scan three weeks later. Hence we had paired data at baseline, off erlotinib and back on erlotinib. We also had careful correlation of clinical symptoms (Riely 2006).

We were impressed by the worsening symptomatology in that relatively short time period. Seven out of 10 patients felt worse when they had stopped receiving erlotinib, and then when they resumed the erlotinib, seven out of 10 patients either stabilized or felt better.

Also, a suggestion was observed on the CAT and PET scans, particularly the PET scan, that some of the lesions flared and then quieted down when patients went back on the TKI (Riely 2006).

Track 10

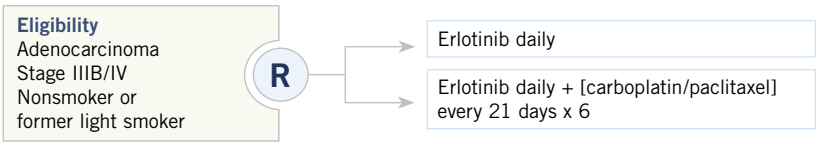
DR LOVE: Can you discuss some of the current ongoing clinical trials evaluating erlotinib?

DR MILLER: One of the studies we are leading in CALGB is a randomized Phase II trial (CALGB-30406; [2.2]). This trial will compare chemotherapy

2.2

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

Protocol IDs: CALGB-30406, NCT00126581
Target Accrual: 180 (Open)



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

SOURCE: NCI Physician Data Query, August 2006.

and erlotinib versus erlotinib alone, and each of those will be compared to historical controls from the TRIBUTE trial (Herbst 2005).

We want to see if erlotinib alone looks as good as carboplatin/paclitaxel in the never-smoking population from the TRIBUTE trial. Will these patients have a 10-month median survival? We also want to see if the other group (chemotherapy with erlotinib) maintains the 23-month median survival that we saw for the never smokers in the TRIBUTE trial.

Every patient on the trial must have adequate tissue for EGFR sequencing. We want to accrue enough patients with EGFR mutations to observe whether there's a differential benefit between patients with an EGFR mutation and the oligosmokers at large.

Maybe chemotherapy with erlotinib is better for the oligosmokers at large, but erlotinib alone looks as good as the combination for the patients with mutations.

SELECT PUBLICATIONS

Asahina H et al. **A phase II study of gefitinib as a first-line therapy for advanced non-small cell lung cancers with epidermal growth factor receptor (EGFR) gene mutations.** *Proc ASCO* 2006;**Abstract 13014**.

Fossella F et al. **Randomized, multinational, phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small-cell lung cancer: The TAX 326 study group.** *J Clin Oncol* 2003;21(16):3016-24. **Abstract**

Herbst RS et al; TRIBUTE Investigator Group. **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* 2005;23(25):5892-9. **Abstract**

Miller VA et al. **EGFR mutation and copy number, EGFR protein expression and KRAS mutation as predictors of outcome with erlotinib in bronchioloalveolar cell carcinoma (BAC): Results of a prospective phase II trial.** Presentation. *Proc ASCO* 2006;**Abstract 7003**.

Paz-Ares L et al. **A prospective phase II trial of erlotinib in advanced non-small cell lung cancer (NSCLC) patients (p) with mutations in the tyrosine kinase (TK) domain of the epidermal growth factor receptor (EGFR).** *Proc ASCO* 2006;**Abstract 7020**.

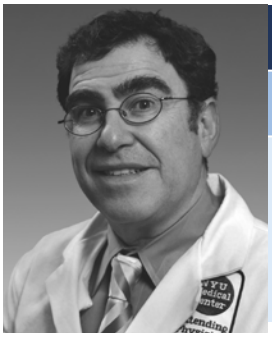
Riely GJ et al. **Prospective FDG-PET and CT assessment of discontinuation of erlotinib (E) or gefitinib (G) in patients with EGFR TKI sensitive non-small cell lung cancer (NSCLC) who subsequently progress radiographically on E or G ("acquired resistance") followed by re-initiation of E or G and the subsequent addition of everolimus (RAD001).** *Proc ASCO* 2006;**Abstract 7065**.

Sandler AB 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 non-small cell lung cancer (NSCLC): An Eastern Cooperative Oncology Group (ECOG) Trial — E4599.** *Proc ASCO* 2005;**Abstract 4**.

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

Sunaga N et al. **Phase II study of the efficacy of gefitinib in patients with non-small cell lung cancer with the EGFR mutations.** *Proc ASCO* 2006;**Abstract 7183**.

Sutani A et al. **Phase II study of gefitinib for non-small cell lung cancer (NSCLC) patients with epidermal growth factor receptor (EGFR) gene mutations detected by PNA-LNA PCR clamp.** *Proc ASCO* 2006;**Abstract 7076**.



INTERVIEW

Harvey I Pass, MD

Dr Pass is Professor of Cardiothoracic Surgery and Surgery and Chief of the Division of Thoracic Surgery and Thoracic Oncology in the Department of Cardiothoracic Surgery at NYU School of Medicine and NCI Cancer Center in New York, New York.

Tracks 1-11

Track 1 Introduction

Track 2 Induction chemotherapy with or without radiation therapy for Stage IIIA NSCLC

Track 3 Clinical management of Stage IIIA disease

Track 4 Mortality of right versus left pneumonectomy

Track 5 Impact of surgical volume on outcomes

Track 6 Potential complications of preoperative radiation therapy and chemotherapy

Track 7 RTOG-0412: Neoadjuvant cisplatin/docetaxel with or without thoracic conformal radiation therapy followed by surgical resection and docetaxel for Stage IIIA NSCLC

Track 8 Surgeon's perspective on adjuvant chemotherapy for Stage IA/B disease

Track 9 Incorporation of novel targeted agents into induction and adjuvant clinical trials

Track 10 Use of PET in clinical practice

Track 11 Evolving surgical technologies in the diagnosis and treatment of lung cancer

Select Excerpts from the Interview

Track 2

DR LOVE: Can you provide an overview of the clinical and research issues involved in the management of Stage IIIA non-small cell lung cancer?

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 appeared to suggest that surgery after induction chemoradiation therapy was not any better than definitive chemoradiation therapy, although it was associated with a trend in improved progression-free survival (Albain 2005; [3.1]).

If you look at the data carefully, however, you notice a high mortality rate for patients who underwent pneumonectomy. The overall operative mortality rate was seven percent, of which the operative mortality rate due to pneumonectomies was 14 percent. One of the reasons for the pneumonectomies was that the trial design was not stratified by lymph node size.

A subsequent unplanned analysis of the trial was presented by Dr Albain at a follow-up ASCO 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 group (3.2).

The next trial, RTOG-0412, was then planned to ask a new question: What is the role of radiation therapy in Stage IIIA disease?

To avoid the pneumonectomy issue, the trial was designed to carefully stratify nodal disease into microscopic or clinically apparent disease and also to indicate by mediastinoscopy the number of stations involved. Essentially, this was to ensure against including patients with bulkier disease in this trial.

Although this trial has brought some controversy, the role of radiation therapy is an important issue because we still do not know whether induction chemotherapy alone or induction chemoradiation therapy is better.

3.1

RTOG-9309: Phase III Randomized Trial Comparing Chemoradiotherapy with or without Surgical Resection in Patients with Stage IIIA (pN2) NSCLC

	Chemo-radiotherapy + surgery (n = 202)	Chemo-radiotherapy alone (n = 194)	Hazard/ odds ratio (95% CI)	*p*-value
Median progression-free survival (PFS)	12.8 months	10.5 months	0.77 (0.62-0.96)	0.017
Five-year PFS	22.4%	11.1%	—	—
Median overall survival	23.6 months	22.2 months	0.87 (0.70-1.10)	0.24
Five-year overall survival	27.2%	20.3%	0.63 (0.36-1.10)	0.10

CI = confidence interval

SOURCE: Albain KS et al. Presentation. ASCO 2005;**Abstract 7014**.

3.2

RTOG-9309: Exploratory Survival Analysis According to Type of Surgery

	Pneumonectomy		Lobectomy	
	Chemo/XRT + surgery (n = 51)	Chemo/XRT alone* (n = 51)	Chemo/XRT + surgery (n = 90)	Chemo/XRT alone* (n = 90)
Median survival	19 months	29 months	34 months	22 months
Five-year overall survival	22%	24%	36%	18%
p-value (log-rank)	NS		0.002	

* Patients on the chemoradiotherapy + surgery arm were matched with those on the chemoradiotherapy alone arm for four prestudy factors (Karnofsky performance status, age, sex and T stage)

Chemo/XRT = chemoradiotherapy; NS = not significant

SOURCE: Albain KS et al. Presentation. ASCO 2005;**Abstract 7014**.

Track 7

DR LOVE: Could you talk more about the design of the RTOG-0412 trial you are co-chairing?

DR PASS: The study is designed to enroll approximately 580 patients to try to show a 10 percent increase in survival for patients treated with induction chemoradiation therapy over those treated with induction chemotherapy alone (3.3).

This trial involves multiple types of treatment, and all patients are treated surgically, so patients don't feel that they are losing out by not having surgery. However, we truly don't know whether the response rate or long-term survival is different between the induction chemoradiation group and the induction chemotherapy group.

We are also offering a new chemotherapy regimen in the trial. The advantage of our trial is that it will be easier to sell to patients because they will all be treated surgically.

In addition, the surgery will be made safer by defining disease that is amenable to lobectomy, which allows for less resection. If a patient needs a pneumonectomy, we will allow it, but we're trying to decrease the number of pneumonectomies.

DR LOVE: Can you talk about the chemotherapy regimen that's used and why it was chosen?

DR PASS: The cisplatin/docetaxel induction regimen was the one used by Dr Betticher in the Swiss Trials, which showed promising response rates and intermediate five-year survival rates (Betticher 2006).

This combination was followed up at the IASLC meeting, and the outcomes held up and were similar to the Roth or Rosell numbers we had from before.

The issue, therefore, became whether this new regimen could be combined with radiation therapy. We combined these regimens but reduced the doses to make them more compatible.

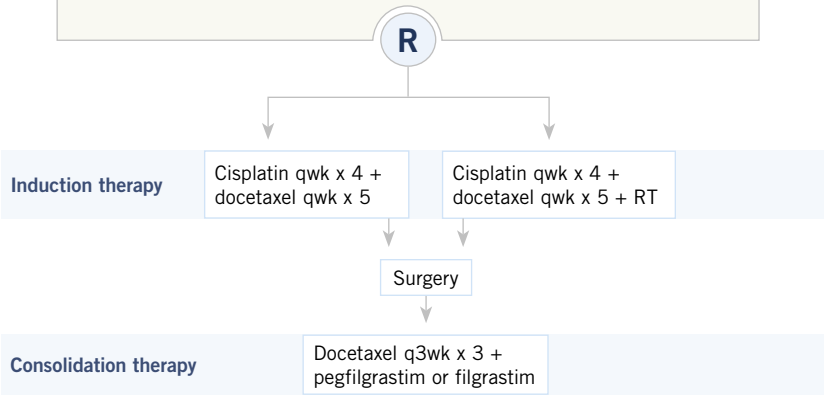
3.3

Phase III Study Comparing Neoadjuvant Cisplatin and Docetaxel with or without Thoracic Conformal Radiation Therapy Followed by Surgical Resection and Docetaxel

Protocol IDs: RTOG-0412, NCT00113386, CALGB-RTOG-0412, ECOG-RTOG-0412, NCCTG-RTOG-0412, SWOG-S0332
Target Accrual: 574 (Open)

Eligibility
- Stage IIIA non-small cell lung cancer
- Resectable disease

Stratification
- T1 versus T2-3
- Involved mediastinal lymph nodes (1 versus ≥2 versus not evaluable)
- Nodal micrometastases versus clinically involved nodes



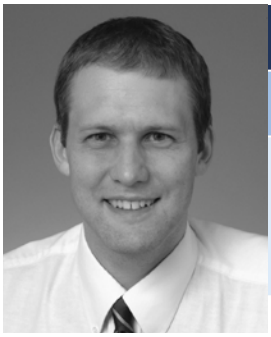
Study Contact:
Radiation Therapy Oncology Group
Maria Werner-Wasik, MD
Tel: 215-955-7679

SOURCE: NCI Physician Data Query, September 2006.

SELECT PUBLICATIONS

Albain KS et al. **Phase III study of concurrent chemotherapy and radiotherapy (CT/RT) vs CT/RT followed by surgical resection for Stage IIIA (PN2) non-small cell lung cancer (NSCLC): Outcomes update of North American Intergroup 0139 (RTOG 9309).** *Proc ASCO* 2005;**Abstract 7014**.

Betticher DC et al; Swiss Group for Clinical Cancer Research (SAKK). **Prognostic factors affecting long-term outcomes in patients with resected stage IIIA pN2 non-small-cell lung cancer: 5-year follow-up of a phase II study.** *Br J Cancer* 2006;94(8):1099-106. **Abstract**



INTERVIEW

Thomas E Stinchcombe, MD

Dr Stinchcombe is Clinical Assistant Professor in the Department of Hematology/Oncology of the Multidisciplinary Thoracic Oncology Program at the University of North Carolina in Chapel Hill, North Carolina.

Tracks 1-12

Track 1 Introduction

Track 2 Clinical trial experience with nanoparticle albumin-bound (*nab*) paclitaxel in lung cancer

Track 3 Potential clinical advantages of *nab* paclitaxel for lung cancer

Track 4 Resolution of neuropathy with *nab* versus standard paclitaxel formulation

Track 5 Scheduling of *nab* paclitaxel in the treatment of lung cancer

Track 6 Clinical development of *nab* paclitaxel for lung cancer

Track 7 CALGB-9633 trial of adjuvant carboplatin/paclitaxel for Stage IB disease

Track 8 Clinical trial experience with adjuvant carboplatin/docetaxel

Track 9 Incorporating bevacizumab into adjuvant clinical trials

Track 10 Clinical questions in the treatment of Stage III NSCLC

Track 11 Incorporating multikinase inhibitors into lung cancer clinical trials

Track 12 Side effects and tolerability of sunitinib in patients with lung cancer

Select Excerpts from the Interview

Track 2

DR LOVE: Can you review the available clinical research information on *nab* paclitaxel for patients with lung cancer?

DR STINCHCOMBE: We have some significant Phase II trials. One study, presented by Mike Hawkins, used carboplatin in combination with *nab* paclitaxel. It was a cohort design in which approximately 25 patients were enrolled sequentially in each cohort with the dose of *nab* paclitaxel escalating from 225 to 340 mg/m^2 every three weeks (Hawkins 2006).

All cohorts showed an overall response rate of approximately 29 percent, and an additional 15 percent of patients had stable disease (4.1). The combination of carboplatin and *nab* paclitaxel appeared to be relatively well tolerated. Particularly, the rate of myelosuppression was low (Hawkins 2006).

In addition, a single-agent *nab* paclitaxel trial for patients with an ECOG

performance status of zero or one was published in the *Annals of Oncology* by Dr Mark Green. That trial showed a median progression-free survival of approximately six months and a median survival of approximately 11 months (Green 2006; [4.2]).

That's significant because that's the progression-free and overall survival we generally see with double-agent chemotherapy regimens. These are promising data.

4.1

Dose-Escalation Trial of *Nab* Paclitaxel Followed by Carboplatin as First-Line Therapy in Patients with Advanced Stage NSCLC

Nab paclitaxel dose (q3wk)	Overall response rate + unconfirmed responses	Stable disease ≥16 weeks
225 mg/m^2 (n = 25)	40%	24%
260 mg/m^2 (n = 25)	24%	24%
300 mg/m^2 (n = 22)	23%	9%
340 mg/m^2 (n = 22)	27%	0%
All doses (n = 94)	29%	15%

SOURCE: Hawkins MJ et al. *Proc ASCO* 2006;**Abstract 7132**.

4.2

Single-Agent *Nab* Paclitaxel as First-Line Therapy in Patients with Advanced Stage NSCLC

	Nab paclitaxel 260 mg/m^2 q3wk (n = 43)
Overall response rate	16.3%
Disease control rate	48.8%
Median time to progression	6 months
Median survival	11 months
One-year disease-free survival	13%
One-year survival	45%

SOURCE: Green MR et al. *Ann Oncol* 2006;17(8):1263-8. **Abstract**

Track 3

DR LOVE: Can you talk about the potential clinical advantages of *nab* paclitaxel?

DR STINCHCOMBE: The Phase III trial for patients with breast cancer showed a lower rate of Grade IV neutropenia with *nab* paclitaxel, which was statistically significant (Gradishar 2006).

Obviously, patients with lung cancer often have cardiopulmonary disease. Because febrile neutropenia could be potentially life threatening, a lower rate

of myelosuppression would be a significant advantage.

We are also intrigued by the increased efficacy in the breast cancer literature, and we want to see if that may exist in non-small cell lung cancer.

The other avenue we're interested in exploring is that of the patient with small cell lung cancer. In our Phase I trial, we saw some nice responses in patients who had been previously treated for small cell lung cancer. The advantage of the combination of carboplatin and *nab* paclitaxel for patients with small cell lung cancer would be a reduction in febrile neutropenia.

4.3

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

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

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

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

Our current regimen of cisplatin/irinotecan has a significant incidence of febrile neutropenia of approximately five percent. If we can administer carboplatin/*nab* paclitaxel every three weeks, it would be a significant improvement over cisplatin/etoposide or carboplatin/etoposide on days one through three, in terms of patient convenience.

DR LOVE: How much of an advantage is the avoidance of premedications and allergic reactions with *nab* paclitaxel?

DR STINCHCOMBE: That's a significant advantage. We know hypersensitivity reactions occur with the standard formulation of paclitaxel in about three percent of patients. This can be a significant event, and it can be life threatening.

Premedications also make it somewhat cumbersome in that some patients have diabetes and develop hyperglycemia related to the dexamethasone. Also, the standard formulation of paclitaxel requires a three-hour infusion, whereas *nab* paclitaxel only requires a 30-minute infusion (4.3). *Nab* paclitaxel could make the visit more efficient for the patient.

Track 5

DR LOVE: Where do you see clinical research heading with *nab* paclitaxel in lung cancer?

DR STINCHCOMBE: *Nab* paclitaxel may be studied in several areas of development in non-small cell and small cell lung cancer.

Interest has arisen in performing a Phase III trial comparing it to the standard formulation of paclitaxel to determine whether it may be superior. That probably would be done in combination with carboplatin. It may be superior in terms of efficacy or toxicity, which would be a valuable step forward.

A current Phase II trial evaluating carboplatin, *nab* paclitaxel and bevacizumab is headed by Craig Reynolds. ECOG-E4599 showed a statistically significant increase in the incidence of neutropenia with carboplatin, paclitaxel and bevacizumab (Sandler 2005).

I personally don't believe it was a clinically significant difference, but the combination of carboplatin, *nab* paclitaxel and bevacizumab may reduce the risk.

If we're going to develop a platinum-based combination with bevacizumab, a multitargeted TKI and potentially a fourth agent, we need to minimize the toxicity with our platinum platform so we don't have an increased rate of neutropenia or other complications.

Therefore, if we were to develop a four-drug therapy for non-small cell lung cancer, it might benefit us to have a taxane that is better tolerated, with less myelosuppression.

SELECT PUBLICATIONS

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

Green MR et al. **Abraxane®, a novel Cremophor®-free, albumin-bound particle form of paclitaxel for the treatment of advanced non-small-cell lung cancer.** *Ann Oncol* 2006;17(8):1263-8. **Abstract**

Hawkins MJ et al. **Dose escalation study of *nab*-paclitaxel followed by carboplatin as first line therapy in advanced non-small cell lung cancer (NSCLC).** *Proc ASCO* 2006;**Abstract 7132**.

Herbst RS, Sandler AB. **Non-small cell lung cancer and antiangiogenic therapy: What can be expected of bevacizumab?** *Oncologist* 2004;9(Suppl 1):19-26. **Abstract**

Sandler AB 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 non-small cell lung cancer (NSCLC): An Eastern Cooperative Oncology Group (ECOG) Trial — E4599.** *Proc ASCO* 2005;**Abstract 4**.

Sparreboom A et al. **Comparative preclinical and clinical pharmacokinetics of a Cremophor-free, nanoparticle albumin-bound paclitaxel (ABI-007) and paclitaxel formulated in Cremophor (Taxol).** *Clin Cancer Res* 2005;11(11):4136-43. **Abstract**

Stinchcombe TE et al. **Preliminary results of phase I trial of carboplatin (CP) in combination with ABI-007 administered weekly or every 3 weeks in patients (pts) with solid tumors.** San Antonio Breast Cancer Symposium 2005;**Abstract 1092**.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **A Phase II randomized study demonstrated that erlotinib/bevacizumab was at least as efficacious as second-line therapy in terms of progression-free and overall survival as chemotherapy with bevacizumab in patients with non-small cell lung cancer.**
   a. True
   b. False
2. **ZD6474 (vandetanib) is an oral _____ __ tyrosine kinase inhibitor.**
   a. EGFR
   b. VEGF
   c. Both a and b
3. **ZD6474 demonstrated improvements in progression-free survival compared to gefitinib in patients with advanced non-small cell lung cancer previously treated with platinum-containing chemotherapy.**
   a. True
   b. False
4. **Which of the following clinical parameters may be a predictor of response to the TKIs?**
   a. Smoking history
   b. Ethnicity
   c. Pathology
   d. All of the above
   e. None of the above
5. **According to the TRIBUTE trial, the addition of erlotinib to chemotherapy for the treatment of patients with metastatic non-small cell lung cancer who had never smoked significantly improved median overall survival.**
   a. True
   b. False
6. **In RTOG-0412, comparing neoadjuvant chemotherapy to chemoradiation therapy followed by surgical resection and docetaxel, the induction chemotherapy regimen is _____.**
   a. Carboplatin/paclitaxel
   b. Cisplatin/vinorelbine
   c. Cisplatin/docetaxel
7. **In a Phase II trial of single-agent *nab* paclitaxel as first-line therapy in patients with advanced non-small cell lung cancer, the median survival was approximately _____ months.**
   a. Six
   b. Eleven
   c. Fifteen
   d. Twenty
   e. None of the above
8. **According to a Phase III trial for patients with metastatic breast cancer, which of the following are potential clinical advantages of *nab* paclitaxel over the standard formulation of paclitaxel?**
   a. Less neutropenia
   b. Higher response rate
   c. Longer time to tumor progression
   d. All of the above
   e. None of the above
9. **The standard formulation of paclitaxel requires a three-hour infusion, and *nab* paclitaxel requires only a 30-minute infusion without steroid premedication.**
   a. True
   b. False
10. **Results from an unplanned analysis of the RTOG-9309 trial indicated a survival advantage associated with which surgical approach combined with chemoradiotherapy?**
    a. Pneumonectomy
    b. Lobectomy

Post-test answer key: 1a, 2c, 3a, 4d, 5a, 6c, 7b, 8d, 9a, 10b

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Lung Cancer Update — Issue 4, 2006

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

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Faculty	Knowledge of subject matter	Effectiveness as an educator
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Vincent A Miller, MD	5 4 3 2 1	5 4 3 2 1
Harvey I Pass, MD	5 4 3 2 1	5 4 3 2 1
Thomas E Stinchcombe, MD	5 4 3 2 1	5 4 3 2 1

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LCU406

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