A Phase I Study of Gefitinib with Concurrent Dose-Escalated Weekly Docetaxel and Conformal Three-Dimensional Thoracic Radiation Followed by Consolidative Docetaxel and Maintenance Gefitinib for Patients with Stage III Non-small Cell Lung Cancer

Brian Center, MD, William Jeffrey Petty, MD, Diandra Ayala, BS, William H. Hinson, PhD, James Lovato, MS, James Capellari, MD, Timothy Oaks, MD, Antonius A. Miller, MD, and Arthur William Blackstock, MD

Background: Concurrent radiation and chemotherapy is the standard of care for good performance status patients with stage III non-small cell lung cancer. Locoregional control remains a significant factor relating to poor outcome. Preclinical and early clinical data suggest that docetaxel and gefitinib have radiosensitizing activity. This study sought to define the maximum tolerated dose of weekly docetaxel that could be given with daily gefitinib and concurrent thoracic radiation therapy.

Patients and Materials: Patients with histologically confirmed, inoperable stage III non-small cell lung cancer and good performance status (Eastern Cooperative Oncology Group 0–1) were eligible for this study. Patients received three-dimensional conformal thoracic radiation to a dose of 70 Gy concurrently with oral gefitinib at a dose of 250 mg daily and intravenous, weekly docetaxel at escalating doses from 15 to 30 mg/m^2 in cohorts of patients. Patients were given a 2-week rest period after the concurrent therapy, during which they received only gefitinib. After the 2-week rest period, patients received consolidation chemotherapy with docetaxel 75 mg/m^2 given every 21 days for two cycles. Maintenance gefitinib was continued until disease progression or study completion.

Results: Sixteen patients were enrolled on the study between December 2003 and April 2007 with the following characteristics: median age, 64 years (range 43–79 years); M/F: 9/7; and performance status 0/1, 1/15. Dose-limiting pulmonary toxicity and esophagitis were encountered at a weekly docetaxel dose of 25 mg/m^2, resulting in a maximum tolerated dose of 20 mg/m^2/wk. Overall, grade 3/4 hematologic toxicity was observed in 27% of patients. Grade 3/4 esophageal and pulmonary toxicities were reported in 27% and 20% of patients, respectively. The overall response rate was 46%, and the median survival for all patients was 21 months.

Conclusions: Concurrent thoracic radiation with weekly docetaxel and daily gefitinib is feasible but results in moderate toxicity. For further studies, the recommended weekly docetaxel dose for this chemoradiation regimen is 20 mg/m^2.

Key Words: Chemoradiation, Lung cancer, Epidermal growth factor receptor, Pulmonary toxicity.

(*J Thorac Oncol.* 2010;5: 69–74)

Despite advances in chemotherapy, radiation therapy, and surgery, the overall 5-year survival for patients with locally advanced non-small cell lung cancer (NSCLC) remains less than 15%.[1] The inability to achieve locoregional control is a significant factor in the poor outcome for these patients. With radiation alone, more than half of patients relapse within the chest.[2] Improvements in locoregional control and overall survival have been suggested by multiple phase II[3–6] and randomized phase III trials[7–10] using combined modality therapy. Based on these studies, the current standard of care in the United States for advanced, unresectable NSCLC is concurrent chemotherapy and thoracic radiation.[11]

The semisynthetic taxane, docetaxel, has been shown to have considerable activity as a first or second-line agent in NSCLC.[12] Of particular interest for combined modality treatment, docetaxel acts as a radiosensitizer through its induction of a G2/M phase cell cycle arrest. This phase of the cell cycle is known to be the most radiosensitive, with a relative sensitivity 2.5 times greater than that of G1/S.[13] Contributing to its synergy with radiation, docetaxel is also cytotoxic in the S phase, the most radioresistant part of the cell cycle.[13,14] Recent biologic studies have also revealed an important function of taxanes in the phosphorylation of antiapoptotic protein bcl-2.[15,16] This may further enhance radiation cyto-

Department of Radiation Oncology, Wake Forest University School of Medicine, Winston Salem, North Carolina.

Disclosure: Dr. Blackstock received clinical research funding from Merck, Sanofi Aventis, OSI Pharmaceuticals, AstraZeneca, Genentech and Eli Lilly. He has served on advisory boards for Sanofi Aventis, Eli Lilly and Genentech. William Jeffrey Petty receives clinical research funding from OSI Pharmaceuticals.

Address for correspondence: Arthur W. Blackstock, MD, Department of Radiation Oncology, Wake Forest University, Medical Center Boulevard, Winston-Salem, NC 27516. E-mail: ablackst@wfubmc.edu

ISSN: 1556-0864/10/0501-0069

toxicity by abrogating the immortalizing function of anti-apoptotic proteins.

Gefitinib is a small molecule tyrosine kinase inhibitor, which inhibits epidermal growth factor receptor (EGFR) signaling by blocking the intracellular adenosine triphosphate-binding site.[17] Blockade of EGFR function improves the outcomes of patients with metastatic NSCLC. The utility of these drugs for treating patients with stage III disease has not been adequately studied. There is preclinical evidence that demonstrates that EGFR blockade potentiates the antitumor efficacy of radiation.[18,19] This mechanism of radiosensitivity is poorly understood. EGFR inhibition may render tumor cells more susceptible to radiation-induced apoptosis by inhibiting cell repair from sublethal and lethal radiation damage. In a proof-of-principle clinical trial, EGFR inhibition has been shown to decrease cyclin D1 protein expression and reduce the percentage of lung cancer cells in the radioresistant S-phase of the cell cycle by inducing G1 arrest.[20] A recently published phase III trial demonstrated a local control benefit and an overall survival benefit when the EGFR antibody, cetuximab, was combined with radiation therapy in patients with advanced head and neck cancer.[21]

At the time when this study was initiated, preclinical evidence demonstrated the potent radiation sensitizing activity of docetaxel, and emerging data suggested that EGFR directed therapies might also potentiate radiation. Therefore, we sought to define the maximum tolerated dose (MTD) of weekly docetaxel that could be given with daily gefitinib and concurrent thoracic radiation in a phase I study. The reported MTD for docetaxel (alone) given with concurrent thoracic radiation is in the range of 20 mg/m^2 and 30 mg/m^2, resulting in our rationale for starting at a dose of 15 mg/m^2 in our trial.[22–24] It should be noted that this study, as a secondary end point, did attempt to discern prospectively, the tumor EGFR and Kras mutation status before patient enrollment. Because most of patients were diagnosed with a fine needle biopsy, the material available for analysis was most often insufficient.

PATIENTS AND METHODS

Eligibility

Patients with histologically or cytologically documented stage IIIA/IIIB NSCLC deemed to be unresectable or inoperable were eligible. Patients with involvement of the scalene, supraclavicular, contralateral hilar nodes, cytologically positive pleural effusions, or patients who had received prior chemotherapy or radiation therapy for NSCLC were not eligible. Additional inclusion criteria included patient age >18 years, Eastern Cooperative Oncology Group Performance Status 0 to 1, adequate bone marrow function (granulocytes $\geq$1500/μl, platelets $\geq$100,000/μl, and hemoglobin >8.0 g/dl), adequate kidney function (serum creatinine <1.5 $\times$ upper limit of normal), adequate liver function (bilirubin <1.5 mg/dl, aspartate aminotransferase [serum glutamic oxaloacetic transaminase] <2 $\times$ upper limit of normal), and adequate lung function (forced expiratory volume in 1 second $\geq$1.2 liters). Patients were excluded if $\geq$2 weeks had elapsed since formal exploratory thoracotomy. Treatment with a nonapproved or investigational drug within 30 days of the initiation of treatment or prior use of EGFR targeting drugs disqualified patients from the study. Patients with currently active malignancy other than nonmelanoma skin cancer were considered ineligible, with the exception of those that had completed therapy, and were considered to be less than a 30% risk of relapse per their physicians.

Any patients with a history of severe hypersensitivity reaction to docetaxel or other drugs formulated with polysorbate 80, and those with known severe hypersensitivity to gefitinib or any excipients of that product were also excluded. Patients with evidence of severe or uncontrolled systemic disease, any other significant clinical disorder, or laboratory finding determined to be a contraindication to participation in the trial were excluded. Similarly, criteria for exclusion extended to any patient demonstrating a $\geq$ grade 1 neuropathy, irrespective of etiology, and any patient with evidence of clinically active interstitial lung disease. Concomitant use of phenytoin, carbamazepine, rifampicin, barbiturates, or St. John's Wort was also a reason for exclusion from the study.

All patients signed informed consent forms that were approved by the Institutional Review Board at the Wake Forest University Baptist Medical Center.

Treatment Schema

The complete 15-week treatment course consisted of a 7-week concurrent chemoradiation phase, followed by a 2-week rest period and subsequent 6-week consolidation phase. During the chemoradiation phase, patients received daily (M-F) radiation to a total dose of 70 Gy, oral administration of gefitinib at 250 mg/d, and docetaxel 15 to 30 mg/m^2 administered once per week IV over 30 minutes. During the 2-week rest period, patients received only the 250 mg of gefitinib per day. During the consolidation chemotherapy phase, patients continued gefitinib at 250 mg and received docetaxel 75 mg/m^2 administered IV over 60 minutes every 3 weeks for two cycles. The dose of docetaxel during the chemoradiation was increased in a stepwise fashion in increments of 5 mg/m^2 from a starting dose of 15 mg/m^2 based on dose-limiting toxicities (DLT) encountered at the previous dose level. Three patients in a dose cohort had to have completed the complete course of chemoradiation therapy before escalation to the next dose level. Intrapatient dose escalation was not permitted. If two of the three patients in a cohort experienced DLT, it was determined that the MTD had been exceeded, and the preceding dose level was declared the MTD. If one patient of the initial three experienced DLT, then the dose level was expanded to a minimum of six patients. If two or more of these six patients experienced DLT, it was determined that the MTD was exceeded, and the preceding dose level was declared the MTD.

DLT was defined as any of the following: grade $\geq$4 neutropenia, grade $\geq$3 thrombocytopenia, and grade $\geq$3 nonhematologic toxicity that resulted in a >7 day interruption of therapy. The Common Terminology Criteria for Adverse Events, version 3.0, of the NCI were used.

Radiation Guidelines

All patients were treated with 3D conformal treatment planning. The specific design and configuration of the fields

were individualized based on the volume and location of the disease. Treatment volumes were based on preoperative computed tomography scans of the thorax. The gross tumor volume (GTV) consisted of the primary tumor and any involved lymph nodes as determined by radiologic criteria of >1.0 cm short axis, central necrosis, or positron emission tomography positivity. Clinical target volume 1 (CTV1) included the GTV plus 1.0 cm margin, with the exception of the interface of the primary lesion and normal pulmonary parenchyma, where it was a minimum of 0.5 cm. Elective treatment of next echelon lymph nodes was permitted for inclusion in CTV1. CTV2 included only the GTV plus a 1.0 cm margin, except at the interface of the lesion and pulmonary parenchyma where it was 0.5 cm. Planning target volumes 1 and 2 (PTV1 and PTV2) were 1.0 cm expansions on the CTV1 and CTV2, respectively. PTV1 received 40 Gy in 2 Gy daily fractions >4 weeks, subsequently PTV2 received 30 Gy in 2 Gy daily fractions for 3 weeks. In all instances, the entire PTV was encompassed within the 95% isodose surface and no more than 10% of the volume within this isodose surface receiving greater than 110% of the prescription dose as evaluated by dose volume histogram. Although the maximum point dose for the spinal cord could not exceed 49 Gy, there were no V_{20} (percent lung allowed to receive ≥20 Gy in the composite radiation portals) dose constraint requirements. The total lung volume was defined as the volume of both lungs (combined pair organ) minus the GTV.

Chemotherapy Guidelines

During concurrent chemoradiation, the docetaxel dose was reduced by 50% if the granulocyte count was 500 to 999/μl or platelet count was 50,000 to 74,999/μl on the day of planned treatment. Treatment was omitted for granulocyte count <500/μl or platelet count <50,000/μl. The radiation was continued if the docetaxel was held; however, if a cessation of radiation therapy was warranted, then both gefitinib and docetaxel were held for the remainder of the concurrent phase of the treatment.

During the consolidation phase, if the granulocyte count was <1500/μl or the platelet count was <100,000/μl on the scheduled day of administration, therapy was delayed for 1 week for count recovery. The docetaxel dose was reduced by 25% in subsequent cycles for a granulocyte nadir count <500/μl or a platelet nadir count <25,000/μl for 7 days or more or for febrile neutropenia (defined as ANC <500 and two measurements of $T \geq 38.2°C$ [100.8°F]).

Throughout the study, patients received gefitinib at a dose of 250 mg PO daily until disease progression or study closure.

Statistical Considerations

The statistical analysis was performed at the Wake Forest University Comprehensive Cancer Center. The frequency and severity of all side effects and toxicities were tabulated and analyzed using categorical techniques. Although understanding the limitations of a phase I trial, Kaplan-Meier methods were used to estimate the time to progression and survival distributions, and response was determined using the RECIST.[25]

RESULTS

Patient Characteristics

Between December 3, 2003, and April 24, 2007, 16 eligible patients were enrolled. One patient received docetaxel at a lower dose level than outlined in the study and was deemed not evaluable for toxicity. Another patient had no repeat computed tomography and was therefore not evaluable for response. The pretreatment characteristics of the patients are listed in Table 1. The median age was 63.6 years (range 43–79 years), and all except one patient had a performance status of 1.

Toxicity

Tables 2 and 3 summarize the grade 3 to 5 treatment-related toxicities observed during the combined modality part of the study. At our starting dose of 15 mg/m^2, grade IV neutropenia and grade III pulmonary toxicities were observed in the same patient, allowing us to continue our dose escalation. Although there were no >7-day interruptions in treatment during the chemoradiation, two patients were unable to complete the planned 70 Gy, stopping at 62 Gy and 66 Gy, respectively, for toxicity. Two patients missed the week 4 dose of concurrent chemotherapy, whereas two additional patients missed the week 5 and week 7 dosing, respectively, for toxicity. Unacceptable DLT were encountered at the 25 mg/m^2 docetaxel dose level. Of the four patients entered at the 25 mg/m^2 dose level, one experienced a fatal radiation-related pneumonitis, the second experienced an uneventful grade 3 diarrhea, whereas the third patient had grade 3 esophagitis that resulted in a greater than 7-day hospital admission. This same patient at the 25 mg/m^2 dose level also experienced a grade 4 neutropenia.

Two patients suffered fatal pulmonary toxicities that were at least possibly due to treatment. As described above, a patient at the 25 mg/m^2 experienced what clinically and radiographically appeared to be a radiation-related pneumonitis. The second patient at the 20 mg/m^2 dose level developed grade 4 hypoxia that ultimately progressed to a grade 5 event. The review of the radiologic studies suggested that this was a bilateral, diffuse interstitial process most consistent with the known pulmonary toxicity described for gefitinib. The third fatal pulmonary event was observed, but after a careful clinical and radiographic review by independent phy-

TABLE 1. Patient Characteristics

N	16
Age (yr), median (range)	63.6 (43–79)
Race, *N* (%)	
White	12 (75)
Black	4 (25)
Sex, *N* (%)	
Female	7 (44)
Male	9 (56)
Performance status, *N* (%)	
0	1 (6)
1	15 (94)

TABLE 2. Treatment-Related Hematologic Toxicity[a]

Docetaxel Dose (mg/m^2)	Neutropenia Grade			Thrombocytopenia Grade			Anemia Grade			Neutropenic Fever Grade		
	3	4	5	3	4	5	3	4	5	3	4	5
15	0	1	0	0	0	0	0	0	0	1	0	0
20	1	0	0	0	0	0	1	0	0	0	0	0
25	0	1	0	0	0	0	0	0	0	1	0	0

[a] Represents the highest grade toxicity experienced by a patient within each category/column.

TABLE 3. Treatment-Related Nonhematologic Toxicity[a]

Docetaxel Dose (mg/m^2)	Pulmonary Grade			Esophagitis Grade			Diarrhea Grade		
	3	4	5	3	4	5	3	4	5
15	1	0	0	0	0	0	0	0	0
20	0	0	1	1	0	0	0	0	0
25	0	0	1	2	0	0	1	0	0

[a] Represents the highest grade toxicity experienced by a patient within each category/column.

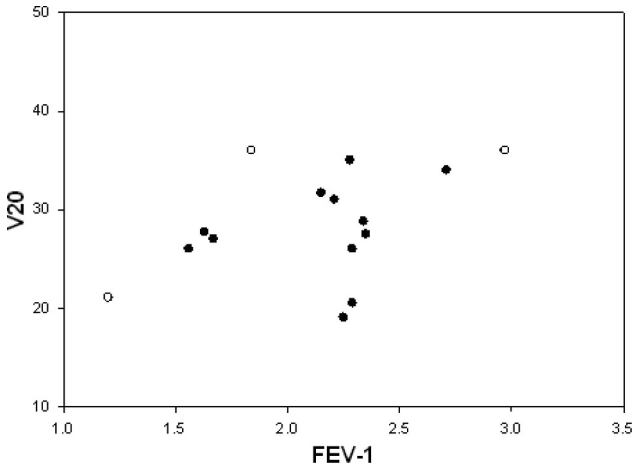

FIGURE 1. Patients experiencing an acute ≥ grade III radiation pneumonitis are represented by the open circles. FEV-1, forced expiratory volume in 1 second. Pneumonitis was defined by National Cancer Institute CTC version 3.0. V_{20} reflects percent lung receiving ≥20 Gy.

TABLE 4. Response to All Therapy Including the Consolidation Chemotherapy

Docetaxel Dose (mg/m^2)	No. of Patients	Not Evaluable	Progressive Disease	Stable	Partial Response	Complete Response
15	6	0	2	3	0	1
20	6	1[a]	0	2	3	0
25	4	0	0	1	2	1

[a] The predefined imaging to assess response was not performed.

sicians, this was deemed to have been the result of an unrelated pulmonary infection. Overall, grade 3 to 5 pulmonary toxicities were observed in 20% of patients—the pulmonary and V_{20} parameters are outlined in Figure 1.

In general, the hematologic toxicity was modest, with grade 3 to 4 events observed in 27% of patients. Two patients experienced grade 4 neutropenia: one patient at the 15 mg/m^2 dose level and the other at the 25 mg/m^2 dose level, respectively.

Survival

Although the primary end point of this study was to determine the docetaxel MTD when given with current thoracic radiation and gefitinib chemotherapy, best response to therapy is shown in Table 4. The overall median survival for all patients was 21.0 months (95% confidence interval 5.1—not reached). The median progression-free survival was 7.1 months (95% CI: 5.1–10.8).

DISCUSSION

At the time this phase I trial was initiated, the preclinical rationale for this treatment strategy was compelling, and the results from the SWOG S0023[26] trial of maintenance gefitinib and the HOG[27] consolidation docetaxel trial were unavailable. Although this study did attempt, unsuccessfully, to discern the EGFR/Kras mutation status in all tumors treated, the emerging clinical studies of patients with specific genetic mutations benefiting when treated with EGFR tyrosine kinase inhibitor were also unavailable.

The results from other phase I/II trials, which have incorporated concurrent EGFR inhibition with chemoradiation, have demonstrated similar results to those seen in this study.[11,28,29] Unfortunately, these additional trials of chemoradiation with gefitinib did not prospectively select patients based on the tumor EGFR or Kras mutation status. In this trial, we have determined that the MTD in unselected patients receiving weekly docetaxel when given concurrent with 70 Gy conformal thoracic radiation and daily gefitinib is 20 mg/m^2. The DLTs seem related to the potent radiosensitizing effects of this combination. Although hematologic toxicities were not uncommon, they were manageable and self-limiting. The most frequent and significant toxicities were pulmonary and esophageal.

Other investigators who have attempted to incorporate EGFR tyrosine kinase inhibitors into conventional chemoradiation regimens have also reported moderate toxicity. In a study reported by Stinchcombe et al.,[11] 23 unselected patients received induction carboplatin, paclitaxel, and irinotecan, followed by 74 Gy thoracic radiation with concurrent gefitinib, carboplatin, and paclitaxel, and then maintenance gefitinib. Grade 3 esophagitis was significant and observed in 20% of patients. The authors also report a median progression free survival of 9 months and a median overall survival of 16 months, which is comparable to our findings. In a second study from Choong et al.,[28] 34 patients were randomized to two different conventional platinum-based chemoradiation therapies with the addition of concurrent daily erlotinib. Grade 3 esophagitis was observed in 26% of patients and a median survival of 10 months and 14 months for the two respective cohorts was observed. Although the investigators assessed tu-

mors for EGFR status by immunohistochemistry or fluorescence in situ hybridization post hoc, patients with EGFR positive tumors showed no significant overall survival benefit.

The Cancer and Leukemia Group B (CALGB) has reported phase II results with induction paclitaxel and carboplatin followed by either 66 Gy thoracic radiation with gefitinib in the defined "poor risk" patients or 66 Gy thoracic radiation with gefitinib, carboplatin, and paclitaxel in the defined "good risk" patients.[29] In both arms, maintenance gefitinib was continued after chemoradiation. Interestingly, the "poor risk" patients who received only gefitinib concurrent with radiation performed better with a median progression-free survival of 11.5 months and a median overall survival of 19 months compared with the "good risk" patients who received both chemotherapy and gefitinib concurrently with thoracic radiation and had a median progression-free survival of 9.2 months and a median overall survival of 12 months. *EGFR* gene amplification, EGFR mutation, and K-*ras* status were not accounted for in the CALGB study. Although differences in treatement-related toxicities were observed, it is possible that imbalances in tumor molecular profiles contributed to differences in outcome.[30]

The interaction of EGFR inhibitors with radiation sensitizing chemotherapy may be antagonistic. This concept is supported by preclinical data, which have investigated the sequence dependence of cytotoxic chemotherapy and EGFR inhibitors.[31–33] Several clinical studies in patients with metastatic NSCLC have demonstrated a lack of benefit when chemotherapy is combined with gefitinib or erlotinib.[34–36] The recently reported Iressa Pan-Asia Study demonstrated that for select patient populations, EGFR inhibitors alone may perform as well as combination chemotherapy.[37] Given this result and the results of the CALGB study discussed above, a phase II trial investigating induction chemotherapy followed by concurrent erlotinib (alone) and radiation is currently enrolling.

CONCLUSIONS

Concurrent thoracic radiation with weekly docetaxel and daily gefitinib is feasible with moderate toxicity. The MTD of docetaxel is 20 mg/m^2 when combined with 70 Gy thoracic radiation and gefitinib 250 mg daily.

ACKNOWLEDGMENTS

Supported in part by Sanofi-Aventis U.S. and AstraZeneca.

REFERENCES

1. Jemal A, Siegel R, Ward E, et al. Cancer Statistics, 2008. *CA Cancer J Clin* 2008;58:71–96.
2. Clamon G, Herndon J, Cooper R, et al. Radiosensitization with carboplatin for patients with unresectable stage III non-small-cell lung cancer: a phase III trial of the Cancer and Leukemia Group B and the Eastern Cooperative Oncology Group. *J Clin Oncol* 1999;17:4–11.
3. Choy H, Akerley W, Safran H, et al. Paclitaxel plus carboplatin and concurrent radiation therapy for patients with locally advanced non-small cell lung cancer. *Semin Oncol* 1996;23:117–119.
4. Akerley W, Choy H. Concurrent paclitaxel and thoracic radiation for advanced non-small cell lung cancer. *Lung Cancer* 1995;12(Suppl 2): S107–S115.
5. Socinski MA, Blackstock AW, Bogart JA, et al. Randomized phase II trial of induction chemotherapy followed by concurrent chemotherapy and dose-escalated thoracic conformal radiotherapy (74 Gy) in stage III non-small-cell lung cancer: CALGB 30105. *J Clin Oncol* 2008;26:2457–2463.
6. Blackstock AW, Herndon JE II, Paskett ED, et al. Similar outcomes between African American and non-African American patients with extensive-stage small-cell lung carcinoma: report from the Cancer and Leukemia Group B. *J Clin Oncol* 2006;24:407–412.
7. Curran W, Scott C, Langer C, et al. Phase III comparison of sequential versus concurrent chemoradiation for patients (Pts) with unresectable stage III non small cell lung cancer (NSCLC): initial report of the radiation therapy oncology group (RTOG) 9410. *Proc ASCO* 2000;19:484a.
8. Furuse K, Fukuoka M, Kawahara M, et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non-small-cell lung cancer. *J Clin Oncol* 1999;17:2692–2699.
9. Schaake-Koning C, van den Bogaert W, Dalesio O, et al. Effects of concomitant cisplatin and radiotherapy on inoperable non-small-cell lung cancer. *N Engl J Med* 1992;326:524–530.
10. Jeremic B, Shibamoto Y, Acimovic L, et al. Randomized trial of hyperfractionated radiation therapy with or without concurrent chemotherapy for stage III non-small-cell lung cancer. *J Clin Oncol* 1995;13: 452–458.
11. Stinchcombe TE, Morris DE, Lee CB, et al. Induction chemotherapy with carboplatin, irinotecan, and paclitaxel followed by high dose three-dimension conformal thoracic radiotherapy (74 Gy) with concurrent carboplatin, paclitaxel, and gefitinib in unresectable stage IIIA and stage IIIB non-small cell lung cancer. *J Thorac Oncol* 2008;3:250–257.
12. Miller VA, Kris MG. Docetaxel (taxotere) as a single agent and in combination chemotherapy for the treatment of patients with advanced non-small cell lung cancer. *Semin Oncol* 2000;27:3–10.
13. Hennequin C, Giocanti N, Favaudon V. S-phase specificity of cell killing by docetaxel (taxotere) in synchronised HeLa cells. *Br J Cancer* 1995; 71:1194–1198.
14. Hennequin C, Giocanti N, Favaudon V. Interaction of ionizing radiation with paclitaxel (taxol) and docetaxel (taxotere) in HeLa and SQ20B cells. *Cancer Res* 1996;56:1842–1850.
15. Friedland D, Cohen J, Miller R Jr, et al. A phase II trial of docetaxel (taxotere) in hormone-refractory prostate cancer: correlation of antitumor effect to phosphorylation of Bcl-2. *Semin Oncol* 1999;26:19–23.
16. Miyake H, Hara S, Arakawa S, et al. Overexpression of Bcl-2 regulates sodium butyrate- and/or docetaxel-induced apoptosis in human bladder cancer cells both in vitro and in vivo. *Int J Cancer* 2001;93:26–32.
17. Magne N, Chargari C, Castadot P, et al. The efficacy and toxicity of EGFR in the settings of radiotherapy: focus on published clinical trials. *Eur J Cancer* 2008;44:2133–2143.
18. Bianco C, Bianco R, Tortora G, et al. Antitumor activity of combined treatment of human cancer cells with ionizing radiation and anti-epidermal growth factor receptor monoclonal antibody C225 plus type I protein kinase A antisense oligonucleotide. *Clin Cancer Res* 2000;6:4343–4350.
19. Bonner JA, Raisch KP, Trummell HQ, et al. Enhanced apoptosis with combination C225/radiation treatment serves as the impetus for clinical investigation in head and neck cancers. *J Clin Oncol* 2000;18:47S–53S.
20. Petty WJ, Dragnev KH, Memoli VA, et al. Epidermal growth factor receptor tyrosine kinase inhibition represses cyclin D1 in aerodigestive tract cancers. *Clin Cancer Res* 2004;10:7547–7554.
21. Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. *N Engl J Med* 2006; 354:567–578.
22. Brunsvig PF, Hatlevoll R, Berg R, et al. Weekly docetaxel with concurrent radiotherapy in locally advanced non-small cell lung cancer: a phase I/II study with 5 years' follow-up. *Lung Cancer* 2005;50:97–105.
23. Koukourakis MI, Kourousis C, Kamilaki M, et al. Weekly docetaxel and concomitant boost radiotherapy for non-small cell lung cancer. A phase I/II dose escalation trial. *Eur J Cancer* 1998;34:838–844.
24. Mauer AM, Masters GA, Haraf DJ, et al. Phase I study of docetaxel with concomitant thoracic radiation therapy. *J Clin Oncol* 1998;16:159–164.
25. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000;92:205–216.
26. Kelly K, Chansky K, Gaspar LE, et al. Phase III trial of maintenance gefitinib or placebo after concurrent chemoradiotherapy and docetaxel

consolidation in inoperable stage III non-small-cell lung cancer: SWOG S0023. *J Clin Oncol* 2008;26:2450–2456.
27. Hanna N, Neubauer M, Yiannoutsos C, et al; Hoosier Oncology Group; US Oncology. Phase III study of cisplatin, etoposide, and concurrent chest radiation with or without consolidation docetaxel in patients with inoperable stage III non-small-cell lung cancer: the Hoosier Oncology Group and U.S. Oncology. *J Clin Oncol* 2008;26: 5755–5760.
28. Choong NW, Mauer AM, Haraf DJ, et al. Phase I trial of erlotinib-based multimodality therapy for inoperable stage III non-small cell lung cancer. *J Thorac Oncol* 2008;3:1003–1011.
29. Ready N, Janne P, Herndon II J, et al. Chemoradiotherapy (CRT) and gefitinib (G) in stage III non small cell lung cancer (NSCLC): a CALGB stratified phase II trial. *J Clin Oncol* 2006;24:Abstract 7024.
30. Bhutani M, Pathak AK, Mao L. SWOG S0023: what meets the eye may be only half the truth. *J Clin Oncol* 2008;26:4848–4849; author reply 4850–4841.
31. Azzariti A, Xu JM, Porcelli L, et al. The schedule-dependent enhanced cytotoxic activity of 7-ethyl-10-hydroxy-camptothecin (SN-38) in combination with gefitinib (Iressa, ZD1839). *Biochem Pharmacol* 2004;68: 135–144.
32. Chun PY, Feng FY, Scheurer AM, et al. Synergistic effects of gemcitabine and gefitinib in the treatment of head and neck carcinoma. *Cancer Res* 2006;66:981–988.
33. Xu JM, Azzariti A, Severino M, et al. Characterization of sequence-dependent synergy between ZD1839 ("Iressa") and oxaliplatin. *Biochem Pharmacol* 2003;66:551–563.
34. Giaccone G, Herbst RS, Manegold C, et al. Gefitinib in combination with gemcitabine and cisplatin in advanced non-small-cell lung cancer: a phase III trial—INTACT 1. *J Clin Oncol* 2004;22:777–784.
35. Herbst RS, Giaccone G, Schiller JH, et al. Gefitinib in combination with paclitaxel and carboplatin in advanced non-small-cell lung cancer: a phase III trial–INTACT 2. *J Clin Oncol* 2004;22:785–794.
36. Herbst RS, Prager D, Hermann R, 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;23:5892–5899.
37. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med* 2009;361:947–957.