

FREE CE MONOGRAPH!

ADVANCED
Non-Small Cell Lung Cancer

IMPLEMENTING
TREATMENT
ADVANCES
IN CLINICAL
PRACTICE

Advanced Non-Small Cell Lung Cancer: Implementing Treatment Advances in Clinical Practice

A Continuing Education Monograph for Oncology Nurses.

Editor

Nancy G. Houlihan, RN, MA, AOCN®

Nurse Leader

Division of Ambulatory Services

Memorial Sloan Kettering Cancer Center

New York, NY

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Oncology Education Services, Inc.

125 Enterprise Dr.

Pittsburgh, PA 15275

www.oesweb.com

Publisher **Michele McCorkle, RN, MSN**

Director **Michele Galioto, RN, MSN**

Scientific Writer **Pamela Oestreicher, PhD**

Project Manager **Dana Barkley, BS, MS**

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PROGRAM INFORMATION

Overview

This monograph will discuss available treatment options for advanced non-small cell lung cancer and ways to implement treatment advances to improve patient outcomes. Treatment of advanced lung cancer has significantly progressed over the last decade, leading to improved survival and quality of life for patients. These advances include new treatment guidelines according to stage, development of new chemotherapeutic agents, multi-drug regimens, sequential approaches, investigation into targeted therapies, and improved evidence-based symptom management strategies. The care of patients with lung cancer, the number one cause of death from cancer in the United States, requires a greater understanding of specific patient care needs as newer treatment options become available. This monograph will review stage-appropriate interventions and current treatment guidelines based on research outcomes.

Target Audience

This monograph is intended for oncology nurses interested in learning about the treatment options available for advanced non-small cell lung cancer and how they implement treatment advances to improve patient outcomes.

Educational Objectives

After completing this educational monograph, participants will be able to:

1. Discuss the efficacy of treatment options for advanced non-small cell lung cancer.
2. Discuss strategies to maximize quality of life for those with advanced non-small cell lung cancer.
3. Identify ways to use treatment efficacy data for advanced non-small cell lung cancer to improve patient outcomes in your clinical practice.

Continuing Education Information

This program has been approved for 1.5 contact hours by the Oncology Nursing Society (ONS) Approver Unit. ONS is accredited as an approver of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

ONS's approval of CE credit for this learning program does not imply endorsement of Lilly Oncology, nor does ONS assume responsibility for the educational content of this monograph.

This monograph is an independent study for oncology nurses interested in learning about the treatment options available for advanced non-small cell lung cancer, and how they implement treatment advances to improve patient outcomes.

This independent study also is available on the Internet at www.oesweb.com. If you complete the online post-test for CE credit, you are not eligible to receive CE credit for completing the print post-test and vice-versa.

Editor Biography

Nancy G. Houlihan, RN, MA, AOCN®

Nancy Houlihan has been an oncology nurse for thirty years, most of which have been spent at Memorial Sloan Kettering Cancer Center (MSKCC). At MSKCC, Ms. Houlihan has worked as a Clinical Nurse Specialist for the last twelve years. She has presented at many regional and national programs about lung cancer and related management topics for MSKCC, the Oncology Nursing Society, various pharmaceutical companies, and the masters program in Oncology Nursing at Columbia University. Ms. Houlihan is a member of the national planning committee for Lung Cancer Awareness Week, and the editor of the website www.lungcancer.org.

Ms. Houlihan is the editor and author of *Site-Specific Cancer Series: Lung Cancer*, a recent ONS publication, and she is a regular volunteer speaker for a series of teleconferences on lung cancer for patients and professionals that is sponsored by Cancer Care, Inc. She is on the board of the New York City Chapter of the Oncology Nursing Society, and she was the education chair for two years. Ms. Houlihan also coordinates the New York City Chapter's activities for lung cancer awareness.

Lung cancer is one of the most common of all malignancies and is the leading cause of cancer death worldwide. In 2004, about 174,000 new cases of lung cancer will be diagnosed in the U.S., or about 13% of new cancer diagnoses; about 160,000 patients will die of the disease (Jemal et al., 2004). Of these cases, about 80% will be non-small cell lung cancer (NSCLC), whose primary histological subtypes are adenocarcinoma, squamous cell carcinoma, and large cell carcinoma (Lindsey & Thielvoldt, 1999; National Comprehensive Cancer Network [NCCN], 2004).

Unfortunately, non-small cell lung cancer is associated with a poor prognosis. While surgical resection can produce cures in early stage patients, over 70% of patients are diagnosed with advanced disease. Chemotherapy regimens developed in the past decade have provided modest survival benefits to patients with advanced or recurrent disease, but the five-year survival rate remains only 15% (American Cancer Society [ACS], 2003a). Thus, oncology professionals face special challenges in identifying the most appropriate treatment decisions and in providing acute and supportive care throughout the disease continuum. This monograph will provide an overview of the epidemiology, pathophysiology, prognostic factors, and available treatments for NSCLC. In addition, it will focus on new agents recently approved or in clinical testing for the treatment of advanced NSCLC.

Epidemiology

The incidence of lung cancer is higher in males (86.0 per 100,000) than females (51.4 per 100,000), and it is the leading cause of cancer death in both sexes (Jemal et al., 2004). It causes more deaths each year than prostate, breast, and colorectal cancer combined. Incidence and mortality rates are one-third higher for African Americans than for white Americans.

While the rates of incidence and death have been decreasing slightly in men in recent years, the rates of incidence and death among women are steadily increasing. In 2004, 80,660 women will be diagnosed with lung cancer and 68,510 will die from it. Deaths from lung cancer among women have increased 150% since 1980, and more women die each year from lung cancer than succumb to breast, ovarian, and uterine cancer combined.

The vast majority of lung cancer deaths are preventable; 80% of such deaths in men and 75% in women are estimated

to be attributable to the effects of smoking. Ninety percent of lung cancers are related to smoking (NCCN, 2004). "The risk of lung cancer increases with the number of cigarettes smoked, years of smoking duration, earlier age at onset of smoking, degree of inhalation, tar and nicotine content, the use of unfiltered cigarettes, and passive smoking, and it decreases in proportion to the number of years after smoking cessation" (Ginsberg, Vokes, & Rosenzweig, 2001, p. 926). Other causal agents include occupational exposure to carcinogens, air pollution, radon exposure, and a high-fat diet, although none of these risk factors approaches that of tobacco use. Genetic predisposition may also play a role in some individuals, possibly rendering them less able to defend against the carcinogens in tobacco smoke (Lindsey & Thielvoldt, 1999; NCCN, 2004).

Despite recent advances in diagnostic testing, there are no clinically proven recommendations for screening, even for high-risk populations (Haas, 2003). Screening with chest X-ray, either alone or in combination with sputum cytology, has not been shown to save lives (Haas, 2003), nor has early detection been proven to increase survival (ACS, 2003b). Additionally, current screening tools can produce false positive tests that result in unnecessary invasive procedures, such as percutaneous needle biopsy or thoracotomy. Overdiagnosis, or the diagnosis of a small or indolent tumor that would not have otherwise been clinically significant, may also occur (National Cancer Institute [NCI], 2003a).

Several techniques are currently in clinical trials exploring their efficacy in detecting lung cancer at a treatable stage and, therefore, improving survival. Among the methods under study are standard chest X-ray, helical chest computerized tomography (CT), sputum analysis (including genetic testing for mutations associated with lung cancer), and light fluorescent bronchoscopy (LIFE). The trials exploring these methods will inevitably take many years to complete because survival must be their primary end point (Haas, 2003).

Pathophysiology

Almost all lung cancer arises from pluripotent bronchial epithelial stem cells; normally, such cells differentiate into stratified reserved cells, ciliated goblet columnar cells, neuroendocrine cells, and the pneumocytes that line the alveoli. However, chronic exposure to inhaled substances or carcinogens may alter stem cell development causing a series of hyperplastic, metaplastic, or neoplastic changes, resulting in malignant cell formation and growth (Ginsberg et al., 2001; Houlihan, 2004).

Non-small cell lung cancer subtypes include squamous cell carcinoma, adenocarcinoma, and large cell carcinoma. In squamous cell carcinoma, which represents approximately 29% of lung cancer cases, the squamous cells of the epithelium undergo abnormal growth; this type of NSCLC usually arises centrally, is slower growing, and often remains within the thoracic cavity. Untreated, squamous cell tumors eventually invade and obstruct the bronchial lumen. (Lindsey & Thielvoldt, 1999; Ginsberg et al 2001; Houlihan, 2004). Adenocarcinoma, by contrast, is usually peripheral in origin and frequently metastasizes to distant sites, such as the lymph nodes, adrenal glands, liver, bone, and brain. It is characterized by formation of glands and papillary structures and usually develops in the peripheral airway or bronchoalveolar area (Ginsberg et al., 2001; Lindsey & Thielvoldt, 1999; Houlihan, 2004). Adenocarcinoma is the most common type of lung cancer in North America, accounting for 40% of cases (Ginsberg et al., 2001).

Finally, large cell carcinoma features relatively large cells with prominent nucleoli and morphologic differentiation (Lindsey & Thielvoldt, 1999). This subtype accounts for approximately 15% of all lung cancers; because of more accurate methods of determining tumor histology, many tumors that would have previously been diagnosed as large cell carcinoma can now be more accurately classified as adenocarcinomas or squamous cell carcinomas. As a result, the incidence of large cell carcinomas is decreasing (Ginsberg et al., 2001).

Clinical Presentation and Diagnosis

Approximately 90% of patients with lung cancer present with one or more symptoms at the time of diagnosis; the most common symptoms are cough, shortness of breath, wheezing, and hemoptysis. Seventy-five percent of patients with lung cancer experience coughing, which can easily be mistaken for an upper respiratory infection or symptoms of chronic tobacco use in the absence of other symptoms (Lindsey & Thielvoldt, 1999). Cough may result from tumor obstruction of the main bronchi, while bloody sputum may result from a large tumor that has developed necrotic areas or tumor invasion of adjacent blood vessels (Ginsberg et al., 2001).

The growth of a lung tumor may encroach upon adjacent structures such as the chest wall or mediastinum. For example, apical tumors may result in Pancoast's syndrome, in which lesions involving the intrathoracic nerves cause pain in the shoulder that radiates to the arm (Ginsberg et al., 2001; Lindsey & Thielvoldt, 1999). Tumors that invade the

lymph nodes in the mediastinum can result in malfunction of the diaphragm or vocal cord. Some patients with this type of tumor present with nerve palsy-like symptoms such as hoarseness and dysphagia (Ginsberg et al., 2001).

Compression of the superior vena cava (SVC syndrome) is also possible. In SVC syndrome, the patient presents with swelling in the face, neck, and arms with neck and thoracic vein distension, usually a sign of advanced disease (Lindsey & Thielvoldt, 1999; Houlihan, 2004).

Paraneoplastic syndromes occur in 10% of lung cancer patients. They are caused by tumor cell secretion of specific substances which have an effect on multiple systems of the body including endocrine, neurologic, hematologic, and musculoskeletal. An example includes Hypercalcemia of Malignancy seen in squamous cell carcinoma patients (Haapola, 2000, Tyson, 2004).

Prognostic factors

The most important factors that affect the prognosis of the patient with lung cancer are the stage of the disease at diagnosis and the patient's performance status (Lindsey & Thielvoldt, 1999; Ginsberg et al., 2001). Males, patients over the age of 60, patients who lose more than 10% of body weight due to the disease, and patients with certain molecular markers, such as *ras* proto-oncogene mutations, are also predicted to have a less favorable prognosis (Ginsberg et al., 2001; ACS, 2003b; NCCN, 2004). Overexpression of the epidermal growth factor receptor (EGFR) has also been associated with poor prognosis (Ciardello et al., 2004; Franklin et al., 2002).

Staging

The **TNM**, or American Joint Committee on Cancer (AJCC), system is used to stage NSCLC. **T** is for tumor (size and spread within the lung and in nearby organs); **N** is for lymph node spread; and **M** is for distant metastasis. Information about each aspect is used to calculate the TNM stage, described as the number 0 or Roman numerals I–IV (ACS, 2003b). After the stage of each individual aspect is determined (Table 1), the overall stage can be calculated using the chart in Table 2 (ACS, 2003b). Stage I and II cancers have smaller tumors and limited or no lymph node spread, while stage III cancers involve larger tumors, more extensive lymph node spread, or both. Any patient with distant metastasis, no matter what the extent of the original tumor or lymph node spread, is classified as Stage IV (ACS, 2003b; NCCN, 2004).

TABLE 1. T Stages, N Stages, and M Stages for NSCLC

T stages	
Tis	Cancer is found only in the layer of cells lining the air passages. It has not invaded other lung tissues. This stage is also known as carcinoma in situ.
T1	The cancer is no larger than 3 cm, has not spread to the membranes that surround the lungs (visceral pleura), and does not affect the main branches of the bronchi.
T2	The cancer has one or more of the following features: <ul style="list-style-type: none"> • It is larger than 3 cm • It involves a main bronchus, but is not closer than 2 cm to the point where the trachea branches into the left and right main bronchi • It has spread to the membranes that surround the lungs • The cancer may partially clog the airways, but this has not caused the entire lung to collapse or to develop pneumonia
T3	The cancer has one or more of the following features: <ul style="list-style-type: none"> • Spread to the chest wall, diaphragm, membranes surrounding the space between the two lungs (mediastinal pleura), or membranes of the sac surrounding the heart (parietal pericardium) • Invades a main bronchus and is closer than 2 cm to the point where the trachea branches into the left and right main bronchi, but does not affect this area • Has grown into the airways enough to cause an entire lung to collapse or to cause pneumonia in the entire lung
T4	The cancer has one or more of the following features: <ul style="list-style-type: none"> • Spread to the mediastinum, heart, trachea, esophagus, backbone, or the point where the trachea branches into the left and right main bronchi • Two or more separate tumor nodules are present in the same lobe • There is a fluid containing cancer cells in the space surrounding the lung
N stages	
N0	No spread to lymph nodes
N1	Spread to lymph nodes within the lung and/or located around the area where the bronchus enters the lung (hilar lymph nodes). Metastases affect lymph nodes only on the same side as the cancerous lung.
N2	Spread to lymph nodes around the point where the windpipe branches into the left and right bronchi or to lymph nodes in the mediastinum. Affected lymph nodes are on the same side of the cancerous lung.
N3	Spread to lymph nodes near the collarbone on either side, to hilar lymph nodes, or to mediastinal lymph nodes on the side opposite the cancerous lung.
M stages	
M0	No spread to distant organs or areas. Sites considered distant include other lobes of the lungs, lymph nodes further than those mentioned in N stages, and other organs or tissues such as the liver, bones, or brain.
M1	The cancer has spread distantly.

Note. Adapted from *How is lung cancer staged?* by American Cancer Society, 2003. Retrieved June 2, 2003, from http://www.cancer.org/docroot/CRI/content/CRI_2_4_3X_How_is_lung_cancer_staged_26.asp?sitearea=.

TABLE 2. Stage Grouping for NSCLC

T stage	N stage	M stage	Overall stage
Tis (in situ)	N0	M0	Stage 0
T1	N0	M0	Stage IA
T2	N0	M0	Stage IB
T1	N1	M0	Stage IIA
T2	N1	M0	Stage IIB
T3	N0	M0	Stage IIB
T1	N2	M0	Stage IIIA
T2	N2	M0	Stage IIIA
T3	N1	M0	Stage IIIA
T3	N2	M0	Stage IIIA
Any T	N3	M0	Stage IIIB
T4	Any N	M0	Stage IIIB
Any T	Any N	M1	Stage IV

Note. Adapted from *How is lung cancer staged?* by American Cancer Society, 2003. Retrieved June 2, 2003, from http://www.cancer.org/docroot/CRI/content/CRI_2_4_3X_How_is_lung_cancer_staged_26.asp?sitearea=.

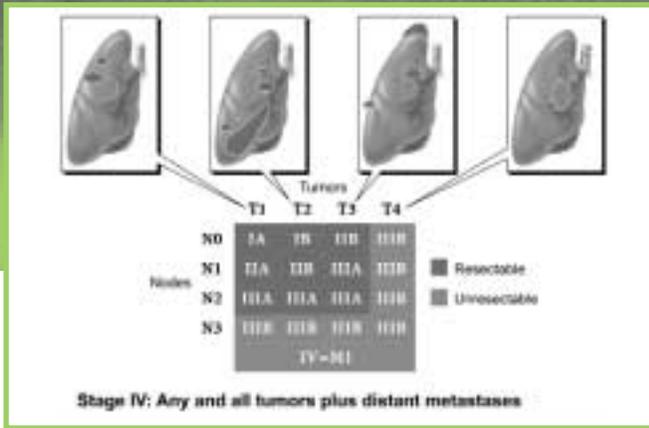


FIGURE 1.
Lung Tumor Staging –
A Graphic Depiction

Morbidity and mortality

Survival rates for NSCLC are disappointingly low unless the disease is discovered in an early stage. However, as shown previously, the majority of patients present with advanced disease, and nearly 45% present with clinically detectable metastasis at the time of diagnosis (Lindsey & Thielvoldt, 1999). Thus, only 15% of patients with lung cancer will survive five years after their diagnosis (ACS, 2003a). Advanced NSCLC is associated with a median survival time of just six to eight months and a one-year survival rate of 10%–20% (Langer et al., 1995). Although 13% of cancer diagnoses in men and 12% in women in 2004 will be of lung cancer, the percentages of cancer deaths that will be caused by the disease are 32% and 25%, respectively (Jemal et al., 2004). Although almost all patients with localized breast cancer and 62% of those with localized colorectal cancer are alive five years after their diagnosis, survival times for patients with NSCLC are more frequently measured in months than years (ACS, 2003a). **Table 3** shows the five-year survival rates associated with various stages of NSCLC (Crawford, Detterbeck, Leopold, & Rivera, 2000).

Comorbidities are common and include emphysema, pneumonia, and weight loss. Patients with NSCLC tend to be older adults; thus, they may also present with cardiac conditions or diabetes.

TABLE 3. Five-Year Survival Rates of NSCLC by Clinical and Pathologic Stages

Clinical stage	5-year survival (%)
IA	61
IB	38
IIA	34
IIB	24
IIIA	13
IIIB	5
IV	1
Pathologic stage	5-year survival (%)
IA	67
IB	57
IIA	55
IIB	39
IIIA	23

Note. Information from *Coordination of Care for the Management of Non-Small Cell Lung Cancer*, by J. Crawford, F. Detterbeck, K.A. Leopold, & M.P. Rivera, 2000, Princeton, NJ: Bristol-Myers Squibb.

It is clear that, due to the low survival rates for NSCLC and the high correlation of the disease with tobacco use, prevention is a key goal. While focus on treatment is important, oncology professionals should also encourage smoking cessation, both in their patients and in the larger community, to reduce the incidence of this deadly disease. Even after diagnosis, it is beneficial for patients to stop smoking and reduce exposure to secondhand smoke, as doing so may improve the success of treatment and prevent potential complications.

Treatments

For patients with stage I or II disease, surgery is the treatment of choice. Patients who have resectable disease but who cannot undergo surgery are usually treated with definitive radiotherapy (Crawford et al., 2000; Lindsey & Thielvoldt, 1999; NCCI, 2004). However, since the disease is usually advanced by the time of diagnosis, surgery is often used in combination with radiation therapy and chemotherapy. Currently, there is no one course of treatment that has shown distinct superiority to others. Thus, there is no standard of care, and therapies should be chosen based upon individual patient characteristics and preferences. Because NSCLC is associated with poorer survival rates than many other cancers, the goals of treatment for advanced disease are often to provide palliation of symptoms and to extend survival rather than cure (**Table 4**).

TABLE 4. Treatment of NSCLC

Stage	Treatment	5-Year Survival
I	Surgical Resection +/- adjuvant chemotherapy or radiation OR Definitive RT for unresectable Patients	70%
II	Surgical Resection adjuvant chemotherapy and/or radiation	50%
III a	Induction Therapy + Surgery	10-30%
III b	Chemotherapy + Radiation	< 10%
IV	Chemotherapy/Palliation	1%

Note. Based on information in *Clinical Practice Guidelines in Oncology™ – Non-Small Cell Lung Cancer*, Version 1.2004, by National Comprehensive Cancer Network (NCCN), 2004. Retrieved July 14, 2004, from http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#site;Lung_Cancer, N.G. Houlihan (ed.), 2004, Pittsburgh, PA: Oncology Nursing Society.

Recent studies suggest that adjuvant chemotherapy for early stage NSCLC can be efficacious. When patients are treated with platinum regimens, survival rates at five years can be as high as 65%. The first large-scale study to support adjuvant chemotherapy for early-stage NSCLC was the International Adjuvant Lung Cancer Trial (IALT), reported in 2003 and published in 2004. It enrolled nearly 1900 patients and demonstrated a clear survival benefit from the addition of adjuvant therapy, with an absolute benefit of 4% at 5 years (LeChevalier, 2004). Other studies include the CALGB 9633 trial, designed to compare adjuvant **carboplatin** (Paraplatin®, Bristol-Myers Squibb, Princeton, NJ)/**paclitaxel** (Taxol®, Bristol-Myers Squibb, Princeton, NJ) to no adjuvant therapy for patients with completely resected stage IB NSCLC. The study demonstrated a marked improvement in overall survival in the treatment group (Winton et al., 2004). The National Cancer Institute of Canada (NCIC) BR10 study randomized patients with resected stage IB and stage II NSCLC to either observation or four cycles of **cisplatin** (Platinol®, Bristol-Myers Squibb, Princeton, NJ)/**vinorelbine** (Navelbine®, GlaxoSmithKline, Research Triangle Park, NC). The regimen was well tolerated with little toxicity. In this case, five-year relapse-free survival was significantly better in treated patients: 61% vs. 48% for observation (Lynch, 2004; Strauss et al., 2004). When these results are taken in the context of the results of studies of chemotherapy in the metastatic setting, some researchers suggest that platinum-based regimens should be considered for average risk patients who have early stage NSCLC (Lynch, 2004).

The emphasis in this monograph, however, will be on treatment for **advanced non-small cell lung cancer** (stage IIIB or IV), the type of NSCLC most frequently diagnosed and offering the least hope for long-term survival. Prior to the 1980s, NSCLC was thought to be relatively unresponsive to chemotherapy. First-generation studies of alkylating agents were actually shown to decrease survival, and chemotherapeutic regimens then available did not show response rates higher than 20% (Thomas, 2003a). Many patients were not treated with chemotherapy during this time, but rather were managed with best supportive care.

During the 1980s, second-generation (early cisplatin-based) regimens demonstrated an improvement over earlier regimens, with a slight prolongation of disease-free survival and amelioration of lung cancer related symptoms (Thomas, 2003a). Response rates ranged from 10%-30% and median survival times from six to eight months, with no long-term survivors (Ginsberg, 2001). These regimens were associated with many side effects and toxicities, which were not well-

TABLE 5. Platinum-Based Regimens

CAP	Cyclophosphamide (Cytoxan®, Bristol-Myers Squibb, Princeton, NJ) Doxorubicin (Doxil®, OrthoBiotech, Raritan, NJ) Cisplatin (Platinol®, Bristol-Myers Squibb, Princeton, NJ)
VdP	Vindesine (Eldinsine®, Eli Lilly Australia Pty Limited, Sydney, AU) Cisplatin
EP	Etoposide (VePesid®, Bristol-Myers Squibb, Princeton, NJ) Cisplatin
EC	Etoposide Carboplatin (Paraplatin®, Bristol-Myers Squibb, Princeton, NJ)
MVP	Mitomycin (Mutamycin®, Bristol-Myers Squibb, Princeton, NJ) Vinblastine (generic) Cisplatin
MIP	Mitomycin Ifosfamide (IFEX/Mesnex® Kit, Bristol-Myers Squibb, Princeton, NJ) Cisplatin

controlled by available means such as effective antiemetics. Thus, with only modest benefits seen, many referring physicians were reluctant to treat advanced-stage patients with chemotherapy because the clinical benefit did not clearly outweigh the risks of treatment.

Third-generation regimens, usually a newer agent in combination with a platinum compound, have had more marked success, with improvements seen in patients with advanced or recurrent disease. Various drug doublets have been extensively evaluated, and phase II trials have often shown response rates greater than 35%. As expected, response rates have been somewhat lower in the large randomized cooperative group trials (15%-28%), with one-year survival rates of 31%-38%. Median survival has been extended from 3.6 to 6.5 months. (Thomas, 2003b). Further, many new regimens do not have the toxicities associated with earlier cisplatin-based regimens. This is related in part to improvements in supportive care, particularly in the management of nausea and vomiting.

Third-generation combinations most often include cisplatin or carboplatin in combination with paclitaxel (Taxol®, Bristol-Myers Squibb, Princeton, NJ), docetaxel (Taxotere®, Aventis, Bridgewater, NJ), vinorelbine (Navelbine®, GlaxoSmithKline, Research Triangle Park, NC), gemcitabine (Gemzar®, Lilly, Indianapolis, IN), or irinotecan (Camptosar®, Pfizer [Pharmacia], New York, NY). In addition, various non-platinum doublets have been studied (Thomas, 2003a). There are four third-generation chemotherapy combinations (Table 6) currently approved by the FDA for treatment of advanced NSCLC: paclitaxel plus cisplatin, vinorelbine plus cisplatin, gemcitabine plus cisplatin (two dosing schedules), and docetaxel plus cisplatin.

TABLE 6. FDA-Approved Regimens for the Treatment of Advanced NSCLC

Paclitaxel 135 mg/m ² over 24 h every three weeks
Cisplatin 75 mg/m ² after paclitaxel every three weeks
Vinorelbine 30 mg/m ² weekly
Cisplatin 120 mg/m ² days 1 and 19, then every six weeks
Gemcitabine 1000 mg/m ² days 1, 8, and 15 every four weeks
Cisplatin 100 mg/m ² after gemcitabine day 1
Gemcitabine 1250 mg/m ² days 1 and 8 every three weeks
Cisplatin 100 mg/m ² after gemcitabine day 1
Docetaxel 75 mg/m ² day 1 every three weeks
Cisplatin 75 mg/m ² day 1 every three weeks

While the FDA-approved regimens all contain cisplatin, carboplatin is frequently substituted. Carboplatin is more consistent than cisplatin in meeting one of the primary goals of treatment for advanced disease: palliation of symptoms. It is important to consider with cisplatin that even when nausea and vomiting are well controlled, it is still associated with potentially life-threatening side effects such as nephrotoxicity and quality-of-life-affecting side effects such as neurotoxicity or ototoxicity (Ginsberg et al., 2001; Miaskowski & Viele, 1999). In addition, the hydration requirements of cisplatin make it inconvenient to administer, particularly in the outpatient setting.

To date, none of the third-generation two-drug combination regimens has shown clear benefits over the others in terms of efficacy or toxicity. The various combinations used in advanced NSCLC include paclitaxel-, docetaxel-, vinorelbine-, gemcitabine-, and irinotecan-based platinum regimens, as well as non-platinum two-drug regimens.

Paclitaxel-based regimens

Combinations containing paclitaxel have been evaluated in a number of clinical trials. In an early multi-institutional registration trial by the Eastern Cooperative Oncology Group (ECOG), the third-generation regimen of paclitaxel plus cisplatin was compared with the second-generation regimen of etoposide plus cisplatin. Five hundred ninety-nine patients who had received no prior chemotherapy were randomized to receive either paclitaxel at one of two different doses (135 mg/m² and 250 mg/m²) or etoposide 100 mg/m² on days 1–3. Both sets of patients received cisplatin 75 mg/m², and both regimens were repeated every three weeks. The paclitaxel group showed a longer median survival (9.9 months versus 7.6 months) and greater one-year survival (38.9% versus 31.8%). This difference was not statistically significant, although the small size of the difference may have been due to longer-than-expected survival times for the etoposide group. Toxicity was higher in the paclitaxel arm, with increased neutropenia at the lower dose and increased myalgias, neurotoxicity, and possibly treatment-related cardiac events in patients receiving the higher dose. Quality of life (QOL) scores, however, were not significantly different in the two arms (Bonomi et al., 2000).

An additional trial comparing paclitaxel 175 mg/m² and

cisplatin 80 mg/m² to cisplatin 100 mg/m² alone in 414 patients with advanced disease showed an advantage for the paclitaxel/cisplatin combination. Patients in the paclitaxel/cisplatin arm of the study had an overall response rate of 26%, while those receiving single-agent cisplatin responded at a rate of 17%. However, the difference in one-year survival was not statistically significant (36% and 30%, respectively) (Thomas, 2003a).

The combination of paclitaxel and carboplatin has also been evaluated extensively in clinical trials. A phase III trial of 444 patients by the Southwest Oncology Group (SWOG) compared paclitaxel and carboplatin to vinorelbine and cisplatin. Paclitaxel 225 mg/m² and carboplatin (area under time versus concentration curve [AUC] = 6 mg/ml/min) were given on day 1 every 21 days, while vinorelbine 25 mg/m² was given weekly, with cisplatin 100 mg/m² on day 1 every 28 days. The regimens had similar efficacy, with response rates of 25% and 28% and one-year survival of 36% and 33%, respectively. Median survival was eight months for both arms. Although the two combinations proved similar in efficacy, the paclitaxel and carboplatin regimen was less toxic, with less grade 3 nausea and grade 4 absolute neutrophil count (ANC). As a result, a greater percentage of the patients receiving paclitaxel and carboplatin (26%) were able to complete the study than those receiving vinorelbine and cisplatin (14.5%) (Kelly, Crowley, Bunn, & Livingston, 1999). Despite the favorable toxicity profile of paclitaxel and carboplatin, patient-scored quality-of-life data was similar for the two regimens. The paclitaxel-carboplatin regimen was also four times as expensive as vinorelbine and cisplatin. Thus, had toxicity differences not been seen, it might be advisable to use the latter regimen. This study, therefore, illustrates the importance of continued pharmaco-economic evaluation in randomized clinical trials. A number of other trials have demonstrated tolerability and efficacy with various paclitaxel-based regimens in the treatment of advanced NSCLC.

Docetaxel-based regimens

Phase II studies of docetaxel plus cisplatin have shown response rates between 32%–48% and median survival of 8–13 months, with the highest response and longest median survival in the highest-dose regimen (100 mg/m² docetaxel and 80 mg/m² cisplatin). The high-dose regimen required concomitant administration of filgrastim in order to prevent cytopenias. Docetaxel/carboplatin regimens have also been examined; in a multicenter phase II study, docetaxel 80 mg/m² and carboplatin (AUC = 6 mg/ml/min) were given

TABLE 7. Summary of gemcitabine/carboplatin trials.

Investigators	Phase	Gem (mg/m ²)	Carbo (AUC)	Eval. Pts.	RR (%)	Median survival (weeks)
28-day schedule						
Carmichael et al., 1997	I/II	1000 d 1, 8, 15	5.2 d 1	13	31 (4/13)	45
Ng et al., 1998	II	1000 d 1, 8, 15	5 d 1	7	0 (0/7)	18.5
Carrato et al., 1998	II	1000 d 1, 8, 15	5 d 1	32	46 (15/32)	38
Jovtis, 1998	II	1000 d 1, 8, 15	5 d 1	33	45 (15/33)	NR
Total				85	40	18.5–45
21-day schedule						
Edelman et al., 1998	II	1000 d 1, 8	5.5 d 1	25	32 (8/25)	44
Illiano et al., 1999	II	800–1200 d 1, 8	5 d 8	26	50 (13/26)	NR
Carrato et al., 1998	II	1000 d 1, 8	5 d 1	43	37 (16/43)	38
Sederholm, 1997	II	1200 d 1, 8	5 d 2	9	37 (16/43)	NR
Total				103	44 (4/9)	38–44

Note. From Langer, C.J., Gandara, D.R., Calver, P., Edelman, M.J., & Ozols, R.F. (1999). Gemcitabine and carboplatin in combination: An update of phase I and phase II studies in non-small cell lung cancer. *Seminars in Oncology*, 26 (1 Suppl. 4), 12–18.

every three weeks, along with oral dexamethasone 8 mg twice a day for days 1-3 of the cycle. Of the 27 evaluable patients, 13 (48%) showed an objective response, including one complete response. This unusually high response rate may be due, in part, to the small size of the trial. Larger, multicenter trials often demonstrate lower response rates and are thought to be more representative of the population as a whole. The regimen was associated with neutropenia (48% of cycles), including febrile neutropenia (9%). Thrombocytopenia and non-hematologic toxicities were generally minor (Belani, 1999).

Results were recently reported for a large, phase III randomized trial evaluating two docetaxel plus platinum combinations and vinorelbine plus cisplatin in previously untreated advanced NSCLC. A slight improvement in median survival was seen for the docetaxel/cisplatin regimen (11.3 months) compared to vinorelbine/cisplatin (10.1 months). Improvements were also seen in response rates as well as one- and two-year survival times. In this trial, results with docetaxel plus carboplatin were similar to those of vinorelbine plus cisplatin. These findings resulted in FDA approval of docetaxel plus cisplatin in the first-line treatment of NSCLC in December 2002 (Fossella et al., 2003).

Vinorelbine-based regimens

Vinorelbine’s activity in NSCLC was demonstrated both as a single agent and in combination with cisplatin in early trials. A SWOG trial of 432 patients (415 evaluable) examined vinorelbine plus cisplatin versus cisplatin alone, with filgrastim administered if necessary for grade 3 or 4 neutropenia. Progression-free (four months versus two months) and overall (eight months versus six months) survivals were longer for patients receiving the combination therapy. One- and two-year survivals also favored vinorelbine plus cisplatin (36% versus 20% and 12% versus 6%, respectively). However, vinorelbine produced greater

toxicity, with 120 episodes of grade 4 neutropenia in the combination arm and only three in the cisplatin-only arm (Wozniak et al., 1998). Similar efficacy was demonstrated in a European multicenter trial comparing vinorelbine plus cisplatin with vinorelbine alone or vindesine plus cisplatin. The combination of vinorelbine plus cisplatin showed superior efficacy, with a 30% response rate as compared to 19% for vindesine plus cisplatin and 14% for vinorelbine alone. Median survival was also longest in the vinorelbine plus cisplatin arm at 40 weeks; vindesine plus cisplatin resulted in median survival of 32 weeks, and single-agent vinorelbine was 31 weeks. However, the two combination regimens were associated with greater toxicity than single-agent vinorelbine; neutropenia was most frequent for patients in the vinorelbine/cisplatin group, and neurotoxicity was most frequent in the vindesine/cisplatin group. The greater tolerability of the vinorelbine-only regimen may make it a viable option for patients who cannot tolerate cisplatin-containing regimens (Le Chevalier et al., 1994).

Phase III trials comparing vinorelbine combinations to other third generation combination have been previously described in the paclitaxel-based regimens and docetaxel-based regimens portions of the monograph.

Gemcitabine-based regimens

As a single agent, gemcitabine has shown activity in NSCLC. An early trial by Anderson et al. (1994) showed that gemcitabine 800 mg/m² or 1000 mg/m² (given on days 0, 7, and 14 of a 28-day cycle) produced partial responses in 16 of 79 evaluable patients (20%), a median survival of seven months, and mild, manageable toxicity. Subsequent trials examined the combination of gemcitabine and cisplatin at various dosing schedules (Thomas, 2003a). In addition, investigators have tested gemcitabine and carboplatin in various combinations. Three- and four-week cycles have been tested in various phase II trials, with response rates

ranging from 30%–50% (Table 7, Langer et al., 1999). The 21-day cycle is associated with less thrombocytopenia, while maintaining similar efficacy to that of the 28-day cycle (Thomas, 2003a). During 2002 and 2003, phase III studies were presented that confirmed the lower toxicity of the 21-day schedule and suggested that gemcitabine with carboplatin on the 21 day regimen is now a standard of treatment in advanced NSCLC. Its relatively low toxicity profile has also led several groups to use it as a platform for combination with newer drugs (Edleman, 2003; Harper, 2003). The regimen has been shown to be a feasible treatment in elderly patients (i.e., >70 yrs.), with improvements seen in symptoms and quality of life (Maestu et al., 2003). Finally, a regimen of gemcitabine with cisplatin has been compared to a regimen of gemcitabine with carboplatin in a phase III randomized trial. The researchers here concluded that the two regimens resulted in similar efficacy and toxicity, but that the carboplatin regimen could be a better option for patients unable to tolerate cisplatin (Zatloukal et al., 2003).

Irinotecan-based regimens

The irinotecan-cisplatin combination has shown promising results, with response rates of up to 75%. However, neutropenia and severe diarrhea can be dose-limiting toxicities. European practice has shown the irinotecan-cisplatin combination to be more effective than vindesine-cisplatin (29% response rate versus 22% in a phase III trial, respectively). Irinotecan plus cisplatin has also been compared to irinotecan alone; the combination produced superior results (43% compared to 21% for single-agent therapy). Because of these results, Japanese cooperative groups have begun to use this combination as a reference regimen in randomized trials (Thomas, 2003a).

Platinum-based regimens: Conclusions

Platinum-based combinations of two drugs have generally proven superior in efficacy to single-agent regimens. While single agents typically result in response rates of 10%-20%, platinum-based combinations can produce rates of 30%-35%, with median survival lengthened by approximately six to eight weeks. There is a modest toxicity increase associated with combination regimens as compared to single agents. For patients who cannot tolerate platinum-containing regimens, single-agent therapy may be a viable option.

When comparing the various two-drug regimens, no single combination has emerged as clearly more efficacious than others, an observation confirmed by ECOG trial 1594. This trial compared four regimens, listed in Table 8. No

statistically significant difference was noted for the primary efficacy endpoints of this trial. The gemcitabine/cisplatin combination, however, showed the best median time to progression, while toxicity (nausea, febrile neutropenia, overall grade 3/4 toxicity) was lower with paclitaxel plus carboplatin. Because there is no clearly superior regimen, no standard for therapy exists; therefore, treatment for NSCLC should be chosen based on the individual patient and his or her preferences. The scheduling of doses is also an important factor in treatment, since it affects synergistic and additive effects, toxicity, and convenience for the patient (Abratt et al., 1998).

TABLE 8. ECOG Trial 1594: Regimens and Efficacy Data

Regimen	Response Rate	Median Survival (months)	One-Year Survival	Time to Progression (months)
Paclitaxel 175 mg/m ² Cisplatin 75 mg/m ²	21%	7.8	31%	3.5
Gemcitabine 1000 mg/m ² d 1,8,15 Cisplatin 100 mg/m ² d1 28-day cycle	21%	8.1	36%	4.5*
Docetaxel 75 mg/m ² Cisplatin 75 mg/m ²	17%	7.4	31%	3.6
Paclitaxel 225 mg/m ² Carboplatin (AUC 6)	15%	8.2	38%	3.3

Note. All regimens are q 3 weeks except where noted.

*Statistically significant difference.

Note. Information from "Phase II and III trials: comparison of four chemotherapy regimens in advanced non small-cell lung cancer (ECOG 1594)", by M.D. Fisher & A. D'Orazio, 2000, *Clinical Lung Cancer*, 2(1), pp. 21-22.

With the exception of hematologic toxicity, carboplatin is better tolerated by patients, with fewer renal, neurologic, and gastrointestinal side effects. Furthermore, carboplatin does not necessitate the use of aggressive hydration and antiemetics seen with cisplatin therapy (Langer, Gandara, Calvert, Edelman, & Ozols, 1999). Thus, combinations with carboplatin may be options for patients who cannot tolerate cisplatin therapy.

Non-platinum combinations

Several non-platinum doublets have been studied in the treatment of NSCLC. Georgoulis et al. (1999) compared docetaxel plus cisplatin with docetaxel plus gemcitabine in 315 patients, with equivalent efficacy and toxicity for both regimens. Interestingly, the cisplatin-containing regimen was more effective in patients with a non-adenocarcinoma, while patients with adenocarcinomas fared better on the docetaxel/gemcitabine regimen. The combination of gemcitabine and paclitaxel has also been examined. In a phase II trial by Hirsh et al. (2003) with gemcitabine 1000 mg/m² and paclitaxel 100 mg/m² weekly, 2 of 40 evaluable patients (5%) had a complete response, while an additional 20 patients (50%) had a partial response. Median survival was 9.8 months, and one-year survival was 35%, with manageable toxicity. Other gemcitabine-based combinations that have been tested include gemcitabine with vinorelbine, vincristine (generic), topotecan (Hycamptin®, GlaxoSmithKline, Research Triangle Park, NC), irinotecan, or high-dose epirubicin (Ellence®, Pfizer [Pharmacia], New York, NY) (Barr, Mirsky, Clinthorne, Bendel, & Smith, 1999; Chen et al., 1999; Thomas, 2003a). The combination of docetaxel and vinorelbine has also been evaluated (Miller, 1999).

Thus far, no non-platinum regimen has shown clear superiority to platinum-containing regimens, though some have shown similar efficacy. Non-platinum regimens also do not show substantially decreased toxicity; however, as more combinations are evaluated, lower-toxicity regimens may emerge. It is also interesting to note the absence of one type of toxicity in particular in the gemcitabine/vinorelbine combination. This doublet does not cause alopecia, a side effect that can be particularly distressing to patients with cancer.

Various recent trials have examined three-drug combinations, such as paclitaxel, carboplatin, and vinorelbine and paclitaxel, carboplatin, and gemcitabine. For example, a trial of sequential paclitaxel, carboplatin, and gemcitabine produced a response in 9 of 28 evaluable patients (32%), with a median survival of 10.8 months (Edelman et al., 1999). The efficacy of triplet regimens is, in general, similar to that of

two-drug regimens; however, triplets are also associated with greater toxicity and cost. Thus, their use should be restricted to the clinical trial setting.

While research on conventional cytotoxic chemotherapy in NSCLC continues, a therapeutic plateau has clearly been reached, and it is unlikely that future investigation using approved agents will uncover a regimen significantly superior to others already in existence. As a result, major improvements in therapy for NSCLC are likely to come from innovative strategies such as novel targeted agents, discussed in detail later in this monograph (Thomas, 2003a).

Second-Line Therapies

Until recently, few patients with advanced NSCLC survived long enough to be good candidates for second-line therapy for progressive or relapsed disease. However, as response rates and toxicities with first-line regimens have improved, second-line therapy has become an important clinical issue (Thomas, 2003a). Various single agents have been investigated as second-line treatment, with mixed results. **Table 9** shows response rate data for various single agents as second-line therapy in advanced disease.

TABLE 9. Single Agents in Second-Line Therapy for Advanced NSCLC

Investigators	Dose/schedule	No. of patients	Overall response rate (%)	Median survival (wks)
Murphy et al., 1994	P 175 mg/m ² 24 hr q 21 d	40	3	18
Socinski & Steagal, 1997	P 140 mg/m ² 96 hr q 21 d	11	0	NR
Hainsworth, Thompson, & Greco, 1995	P 135 or 200 mg/m ² 1 hr q 21 d	26	23	NR
Burris et al., 1993	D 100 mg/m ² q 21 d	35	17	NR
Rinaldi et al., 1994	V 20 mg/m ² /wk	18	0	NR
Nakai et al., 1991	CPT-11 200 mg/m ² q 21–28 d	22	14	NR
Gridelli et al., 1999	G 1000 mg/m ² /wk	30	20	22
Mattson et al., 1999	MTA 500 mg/m ²	22* 22†	8 35	NR NR

Note. P = paclitaxel, D = docetaxel, V = vinorelbine, CPT-11 = irinotecan, G = gemcitabine, MTA = multitargeted antifolate.
 * Patients had failed prior platinum-containing regimen
 † Patients had failed prior non-platinum-containing regimen
 Note. Adapted from "Advances in Chemotherapy," by M. Thomas, 2003. In M. Haas (Ed.), *Contemporary Issues in Lung Cancer*, Boston: Jones & Bartlett, p. 58.

In a trial of docetaxel 75 or 100 mg/m² every three weeks versus 30 mg/m² vinorelbine weekly or ifosfamide 2 g/m² on days 1-3 every three weeks in patients who had received prior platinum-based chemotherapy regimens, single-agent docetaxel proved to have superior efficacy. It should be noted that patients randomized to the non-docetaxel arm were given vinorelbine, with ifosfamide only used in those patients who had previously received vinorelbine. While all three arms of the trial had similar median survival times (5.5-5.7 months), response rates favored docetaxel (11% for the higher dose and 7% for the lower dose versus 1% for either vinorelbine or ifosfamide), as did one-year survival (32%, 32%, and 10%, respectively). However, grade 4 neutropenia and neutropenia-related infection were higher for patients receiving docetaxel, particularly at the higher dose level (Fossella et al., 1999, 2003). Another randomized trial showed a clear benefit for docetaxel over best supportive care, with one-year survival of 37% in patients receiving docetaxel 75 mg/m² versus 12% for those receiving only aggressive symptom management. In addition, significantly fewer patients receiving docetaxel required either opioid or non-opioid interventions for pain (Shepherd et al., 2000). As a result of these trials, docetaxel 75 mg/m² every three weeks has been approved by the FDA as a second-line therapy for NSCLC, and subsequent trials will use this regimen as a reference (Thomas, 2003a).

Pemetrexed (Alimta®, Lilly), a multitargeted antifolate discussed in further detail below, has also shown activity as second-line therapy.

There are several factors that may affect second-line treatment decisions, including the patient's willingness to proceed with additional treatment, the patient's performance status, and whether the patient has persistent side effects from first-line treatment. In general, patients should be reasonably healthy, as medically compromised patients often have difficulty tolerating additional treatment. In patients not considered candidates for standard treatment, weekly single agents and certain non-platinum doublets are well tolerated and are promising options in this setting.

Treating Advanced NSCLC in the Elderly

Nearly 40% of patients with NSCLC are 65 years of age or older, yet only a small percentage of the eligible elderly population are entered in clinical trials. While advanced age has historically been considered an adverse prognostic factor in patients with NSCLC, more recent data shows that this may not be the case. A review of ECOG trial 5592, the paclitaxel registration trial that compared two doses of

paclitaxel in combination with cisplatin to the standard etoposide/cisplatin regimen, showed that, in general, patient characteristics were similar in older and younger patients. Older patients (70 years of age or older) did have a higher incidence of cardiovascular and respiratory comorbidities at enrollment. However, leukopenia and neuropsychiatric toxicities were the only toxicities more commonly experienced in this elderly group. Response rate, time to progression, survival, and quality of life scores were similar in elderly and younger patients (Langer et al., 2000).

A subset analysis of elderly patients has also been reported for ECOG 1594 (Table 8), the four-arm trial evaluating four different third-generation regimens using paclitaxel and cisplatin as the reference arm. Only 20% of enrollees (227 patients) were 70 or older, with 1% (9 patients) age 80 or older. Patients between the ages of 70-80 had equivalent toxicity and efficacy as compared to younger patients, while those 80 or older had substantially worse toxicity and efficacy outcomes (Langer et al., 2003). These analyses suggest that older patients less than 80 years of age with good performance status need not be excluded from standard third-generation therapies.

In an attempt to improve treatment tolerability and define options in elderly patients not considered candidates for platinum-based treatment, non-platinum regimens have been evaluated. The phase III multicenter Italian lung cancer in the elderly study (MILES trial) randomized patients to receive single-agent vinorelbine, single-agent gemcitabine, or the combination of vinorelbine plus gemcitabine. In this trial there was no survival advantage with the combination treatment arm when compared to either single agent vinorelbine or gemcitabine. While patient-scored quality of life was similar in all arms, the combination regimen was observed to be more toxic (Gridelli et al., 2003). In contrast, a second Italian trial of the Southern Italy Cooperative Oncology Group (SICOG) demonstrated improved survival with the combination of gemcitabine plus vinorelbine compared to vinorelbine alone. No significant differences were noted in either hematologic or non-hematologic toxicities (Frasci et al., 2000). Weekly taxanes have also been evaluated with demonstrated efficacy and more favorable tolerability than seen with the standard higher-dose three-week schedule (Hainsworth et al., 2000). Since comorbidities that negatively affect treatment outcomes are more likely to occur in the elderly, the medically compromised patient or the patient with a less than optimal performance status may be best served by monotherapy with gemcitabine, vinorelbine, or a weekly

taxane. To date, few trials have specifically studied treatment in the older, medically compromised patient (Thomas, 2003a), although the Zatloukal et al. (2003) study showed that the elderly can and do benefit from therapy with a combination of gemcitabine and carboplatin.

Novel Approaches to the Treatment of NSCLC

New chemotherapeutics: Folate antagonists.

Several folate antagonists, such as methotrexate (Trexall®, Barr Laboratories, Pomona, NY), fluorouracil, and edatrexate, have been investigated in NSCLC. These agents work by blocking the active site of dihydrofolate reductase (DHFR), an enzyme that reduces folic acid to its biologically active form. In doing so, folate antagonists keep folic acid in an inactive state, thus compromising the formation of nucleotides. As a result, DNA and RNA formation and, ultimately, cell growth are disrupted (“Folate Antagonists,” 2003). These older agents, while having demonstrated activity in a number of cancers, have been found to be relatively inactive in NSCLC. It has been postulated that this lack of effect is because these agents target only thymidylate synthase, an enzyme that is frequently overexpressed in NSCLC, such that antifolates are unable to inhibit formation of the undesirable protein (Postmus & Green, 1999).

Pemetrexed

Pemetrexed (Alimta®, MTA, LY231514, Eli Lilly and Company, Indianapolis, IN) is an agent with multiple enzymatic targets in the folate pathway. Because it inhibits multiple targets, pemetrexed may be able to overcome drug resistance coming from overexpression of a single enzyme in the pathway (Figure 2). It was approved in February 2004, in combination with cisplatin, for the treatment of

patients with malignant pleural mesothelioma whose disease is either unresectable or who are otherwise not candidates for curative surgery. It has shown promising activity in NSCLC, and it received accelerated FDA approval in August 2004 for second-line treatment of NSCLC. Accelerated approval means that the manufacturer (Eli Lilly) must continue phase III trials and provide additional data to the FDA as it becomes available.

Pemetrexed Clinical Trials

Phase II trials of pemetrexed as a single agent have shown response rates of 14%-23%; combinations with cisplatin, gemcitabine, and other agents have been investigated as well (Postmus & Green, 1999). One phase II trial evaluating the combination of pemetrexed plus gemcitabine produced a response rate of less than 25%, while phase II trials combining pemetrexed with cisplatin resulted in response rates of 39%-45% (Ettinger, 2002; Manegold et al., 2000).

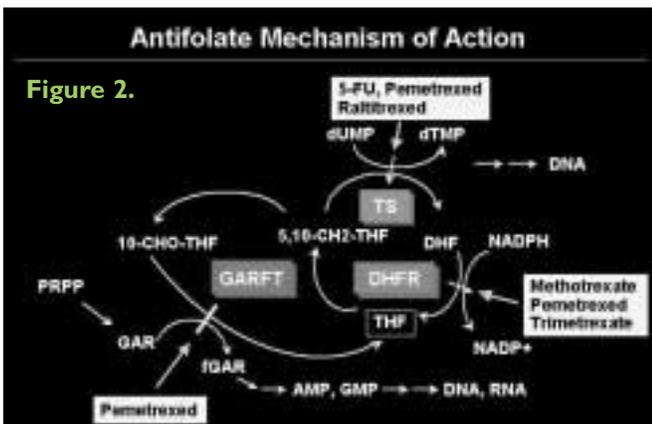
An important phase III trial of pemetrexed compared to docetaxel in 571 patients with recurrent disease was reported in 2003 and published in 2004 (Hanna et al.). This was the largest phase III trial (prior to its publication date) of pretreated patients with advanced NSCLC. In this study, patients were stratified by:

- ECOG performance status 0/1 vs. 2
- Stage III vs. IV
- Number of prior chemotherapy regimens
- Best response to prior chemotherapy
- Time elapsed since last chemotherapy
- Prior platinum
- Prior taxane
- Homocysteine level
- Center

Patients were randomized to two arms:

1. Pemetrexed 500 mg/m² IV q 3 wks (n=283). Folic acid 350-1000 mcg daily + vitamin B12 1,000 mcg q 9 wks; dexamethasone 4 mg bid on day -1, day 0, and day 1.
2. Docetaxel 75 mg/m² IV q 3 wks (n=288). Dexamethasone 8 mg bid on day -1, day 0, and day 1.

While median survival (8.3 months for pemetrexed, 7.9 months for docetaxel) and one-year survival (approximately 30%) were similar for both groups, pemetrexed was associated with significantly lower toxicity. Neutropenia, hair loss, and numbness in the arms and legs were all lower in the pemetrexed arm, as was the need for hospitalization for



Note. From “Pemetrexed Disodium: A Novel Antifolate Clinically Active Against Multiple Solid Tumors,” by A.R. Hanauske, V. Chen, P. Paoletti, & C. Niyikiza, 2001, *Oncologist*, 2001, 6, 363-73. Copyright 2001 by *Oncologist*. Reprinted with permission.

fever or other side effects (NCI, 2003b; Hanna et al., 2003, 2004 – **Tables 12 & 13**). Pemetrexed patients required less growth factor support (Hanna et al., 2003, 2004).

TABLE 12. Non-Hematological Toxicities (% of Patients) Pemetrexed vs. Docetaxel

	Pemetrexed (n=265) Grade 3/4	Docetaxel (n=276) Grade 3/4	p value
Alopecia	6.4	37.7	<.001
ALT	1.9	0	.028
Neurosensory	0	1.1	NS
Fatigue	5.3	5.4	NS
Nausea	2.6	1.8	NS
Vomiting	1.5	1.1	NS
Stomatitis	1.1	1.1	NS
Diarrhea	0.4	2.5	NS
Pulmonary Toxicity	0	1.4	NS
Rash	0.8	0.7	NS

Note. Data from "Randomized Phase III Trial of Pemetrexed vs. Docetaxel in Patients with Locally Advanced or Metastatic NSCLC Previously Treated with Chemotherapy," by N. Hanna et al., 2004, *Journal of Clinical Oncology*, 22, 1589-1597.

TABLE 13. Hematological Toxicities (Grade 3-4, % of Patients) Pemetrexed vs. Docetaxel

	Pemetrexed (n=265)	Docetaxel (n=276)	p value
Neutropenia	5.3	40.2	<.001
Febrile neutropenia	1.9	12.7	<.001
Infection with grade 3-4 neutropenia	0	3.3	.004
Anemia	4.2	4.3	1.00
Thrombocytopenia	2	<1	.116

Note. Data from "Randomized Phase III Trial of Pemetrexed vs. Docetaxel in Patients with Locally Advanced or Metastatic NSCLC Previously Treated with Chemotherapy," by N. Hanna et al., 2004, *Journal of Clinical Oncology*, 22, 1589-1597.

Researchers concluded that pemetrexed and docetaxel have similar efficacy in terms of response rates, progression-free survival, and overall survival. However, pemetrexed had a more favorable hematological toxicity profile when compared with docetaxel. It does have activity in second-line NSCLC

therapy. On the basis of this study, the FDA Oncologic Drugs Advisory Committee recommended accelerated approval of the drug at its July 2004 meeting. Accelerated approval was granted in August 2004.

Pemetrexed is in a phase III trial in second-line treatment of NSCLC to attempt to confirm its clinical benefit. This trial compares the current dose of 500 mg/m² to a 900 mg/m² dose of pemetrexed and has a planned completion in 2006. Two first-line trials of pemetrexed in combination with a platinum compound in NSCLC should also have begun by early 2005.

Pemetrexed Administration

Pemetrexed 500 mg/m² is given intravenously over 10 minutes every 21 days. It is prepared by diluting a 500 mg vial with 20 mL of normal saline for a final concentration of 25 mg/mL. The solution should be clear, but it may range in color from colorless to yellow to green-yellow. The appropriate dose is further diluted in 100 mL normal saline (Eli Lilly, 2004b).

Pemetrexed's toxicity profile is exacerbated in the presence of folate or vitamin B₁₂ deficiency. Supplementation with these vitamins is required to ease these effects. Prophylactic dexamethasone (Decadron®, Merck & Co., Inc. - corticosteroid) is also used to reduce the incidence and severity of cutaneous reactions. The recommended dose is 4 mg po bid the day before, the day of, and the day following administration of pemetrexed (Postmus & Green; Eli Lilly, 2004b - **Table 14**).

TABLE 14. B12 and Folic Acid Supplementation

B₁₂	Folic Acid
Patients must receive one IM injection of B ₁₂ during the week preceding the first dose of pemetrexed and every 3 cycles thereafter.	At least 5 daily doses (350-1000 micrograms) of folic acid must be taken during the 7 days preceding the first dose of pemetrexed.
Subsequent B ₁₂ injections may be given the same day as pemetrexed.	Dosing should continue daily while on therapy and for 21 days after the last dose of pemetrexed.

Note. From "Alimta® (pemetrexed) [Package insert]," by Eli Lilly, 2004, Indianapolis, IN: Author.

For pemetrexed, myelosuppression is usually the dose-limiting toxicity. Patients should not begin a new cycle unless the ANC is ≥ 1500 cells/mm³ and the platelet count is $\geq 100,000$ cells/mm³. Pemetrexed should not be given to patients with a creatinine clearance less than 45 mL/min. The drug is eliminated primarily unchanged by renal excretion. Therefore, it should be used with caution in patients with mild to moderate renal insufficiency (CrCL 45-79 mL/min) when given concurrently with non-steroidal anti-inflammatory drugs (NSAIDs). In patients with mild/moderate renal insufficiency, short-acting NSAIDs should be stopped two days before, the day of, and for two days following pemetrexed administration. In all patients, long-acting NSAIDs should be stopped five or more days before, the day of, and for two days following pemetrexed administration (Eli Lilly, 2004b).

New Biologics

The way clinicians look at treatment options for NSCLC is rapidly changing. For example, cytostatic therapies, which inhibit the growth and proliferation of new cells rather than killing existing cells, are becoming a major subject of study. Such agents may produce a synergistic effect when combined with cytotoxic therapies. Also, primary endpoints are changing; now, more important than overall response rate are survival and quality of life. Studies are likely to emphasize the safety and chronicity of a drug rather than its maximum tolerated dose. Innovative strategies for attacking NSCLC include anti-angiogenesis, induction of apoptosis, blocking of signal transduction pathways, neutralizing tumor growth factors, stimulating the immune system, and correcting genetic mutations (**Table 15**).

CASE STUDY – PEMETREXED

James is a 58-year-old African American man who makes his living as a blues guitarist. He has presented with a 2-month history of dyspnea on exertion and a 4-month history of nonproductive cough. He has a history of smoking 1 to 2 packs of cigarettes per day for the last 42 years. Chest X-ray reveals a right lower lobe mass, which is confirmed by CT scan and found to be 3 by 5 cm in diameter. A biopsy reveals poorly differentiated adenocarcinoma and a further staging workup reveals small bilateral adrenal masses. An appointment is made with a medical oncologist for discussion of treatment options for advanced NSCLC.

The patient is reluctant to proceed with any treatment as he is concerned about side effects. He is very adamant about being able to continue playing guitar. His physician discusses the various evidence-based treatment options with him and together they decide on a regimen of gemcitabine and carboplatin. He achieves a partial response after two cycles with resolution of his lung cancer-related symptoms. He completes a total of six cycles, which he tolerates reasonably well with the exception of some mild fatigue. Additionally, with his last cycle of treatment, he experiences neutropenia without fever for which he receives prophylactic antibiotics. After completion of the sixth cycle, he continues his musical career.

Seven months later, he presents with right-sided rib pain. A bone scan reveals diffuse bone metastases with multiple areas of increased uptake in his ribs. He is started on a pain management regimen and second-line treatment options are discussed with him including enrollment in a clinical trial. He elects to participate in a randomized clinical trial comparing docetaxel and pemetrexed. He is randomized to the pemetrexed arm with vitamin supplementation. He again achieves a partial response to treatment with excellent treatment tolerability.

TABLE 15. Novel Anticancer Therapeutic Strategies Under Clinical Development.

Process targeted	Factors	Mechanism of Action
Angiogenesis	Angiogenic factors Endogenous inhibitors	Inhibition of tumor vascularization
Apoptosis	<i>Bcl-2/Bax/Bcl-x</i> <i>p53</i> -mediated pathways	Apoptosis inducers TUNEL assay
Signal transduction pathways	<i>Ras</i> FTase	Specific blocking agents
Tumor growth factors	Expression of specific growth factors (<i>HER-2/neu</i> , EGFR, VEGF, etc.)	Neutralizing antibodies or agents; blocking agents
Altered immune function	Markers of immunocellular activation	Immune stimulation, dendritic cells, tumor-specific killer T cells
Gene mutation	Altered gene and its products	Gene replacement – <i>p53</i> , others

Novel Strategies: EGFR Targeting

The epidermal growth factor receptor (EGFR), which is involved in regulating the cellular signal transduction process, is expressed in 84% of squamous cell carcinomas, 65% of adenocarcinomas, and 68% of large cell carcinomas (Franklin et al, 2002). Interestingly, EGFR is not expressed in small-cell lung cancer. EGFR-TK (epidermal growth factor receptor–tyrosine kinase), an enzyme located inside the cell membrane, has receptors located along the cell surface. When ligands (epidermal growth factor or transforming growth factor- α) bind to the extracellular component of the receptor, the enzyme dimerizes (bonds), either homogeneously (with another EGFR receptor) or heterogeneously (with other members of the Erb receptor family) (Pallis et al., 2003; Wood, 2002). Upon dimerization, EGFR sends signals to the cell nucleus, regulating cell growth. EGFR is thought to promote tumor growth by increasing cellular proliferation and invasive capacity, inducing angiogenesis and metastasis, and inhibiting apoptosis. In normal cells, this activation process is tightly regulated. However, through mutations in receptors or overexpression of the ligands that bind to them, EGFR can be inappropriately turned on to cause these malignant processes (Wood, 2002 - **Figures 3a, 3b, 3c**).

EGFR inhibitors have become a recent focus of clinical research. These include small molecule tyrosine kinase inhibitors (EGFR-TKIs), which target EGFR within the cell, inhibiting cellular signaling after a ligand has bound to the extracellular receptor; and monoclonal antibodies, which bind to the external receptor or ligand, preventing ligand binding and subsequent receptor activation (Thomas, 2003b; Wood, 2002).

EGFR-TKIs - Gefitinib

Gefitinib (Iressa[®], ZD1839, AstraZeneca Pharmaceuticals LP, Wilmington, DE) is an oral TKI given daily. To date, more patients with NSCLC have been treated with gefitinib than with other EGFR inhibitors (Thomas, 2002). Two phase II trials, IDEAL (Iressa Dose Evaluation in Advanced Lung Cancer) 1 and IDEAL 2, showed response rates of 18.4% and 11.8% with a dose of 250 mg/day, and 19% and 8.8% with 500 mg/day, respectively (**Table 16**). The lower response rates for IDEAL 2 may be due to the status of the patients enrolled, as IDEAL 2 enrolled more heavily pretreated patients who were required to show NSCLC-related symptoms at the time of enrollment (Fukuoka et al., 2002; Kris et al., 2002; Thomas, 2002).

In IDEAL 1, disease-related symptoms were measured



FIGURE 3A. EGFR-TK. EGFR-TK exists as an inactive monomer; receptors on the outside of the cell are prepared to receive ligands.



FIGURE 3B. Dimerization and Activation of EGFR-TK. When EGFR-TK binds to a ligand on the cell surface, it dimerizes, either homogeneously or heterogeneously with another receptor of the Erb family. Upon dimerization, cellular signaling to the nucleus is activated.



FIGURE 3C. Dysregulation of EGFR-TK. EGFR-TK regulates cell growth through a variety of mechanisms. In normal cells, EGFR-TK signaling is strictly regulated. However, through receptor mutation or overproduction of ligands, EGFR-TK can activate a variety of malignant processes.

using the Functional Assessment of Chronic Illness Therapy–Lung (FACT-L) and the Lung Cancer Subscale. Symptom relief was rapid: median time to improvement was eight days. A correlation between tumor response and symptom improvement was also seen: 77.8% of patients with a partial response had symptom improvement, and 53.3% of patients with stable disease experienced symptom improvement. Patients with symptom improvement also had longer PFS and OS than those without (PFS: 4.2 vs. 2 mos; OS: median not reached vs. 6.7 mos). Improvement in quality of life was noted within one month. In IDEAL 2, symptom response occurred in 95% of patients who showed objective tumor response and in 71% of patients with stable disease. Eighty-six percent of patients with objective responses and 52% of patients with stable disease had improvements in quality of life. Longer survival was observed in all patients who experienced symptom response (8.1 mos vs. 3.7 mos for those with no symptom improvement) (Douillard et al., 2002; Natale et al., 2002). While the response rates were modest, they are comparable to those of other second-line therapies in advanced disease refractory to first-line treatment.

Gefitinib has also been evaluated in the first-line setting in combination with two different third-generation platinum-based chemotherapy regimens. However, neither trial showed an efficacy advantage over the chemotherapy regimens alone (INTACT 1 and 2 - Giaccone et al., 2002; Johnson et al., 2002). Gefitinib was approved by the FDA in May 2003 for the treatment of patients with advanced NSCLC who have failed both platinum-based chemotherapy and docetaxel (AstraZeneca, 2003). Further trials in advanced NSCLC will evaluate the potential role of gefitinib as first-line treatment in patients not considered candidates for chemotherapy. Results announced in late 2004 suggest that while gefitinib may benefit some subsets of patients, it does not prolong overall survival in NSCLC (AstraZeneca, 2004).

The most common toxicities with gefitinib are rash, diarrhea, and nausea and vomiting; these toxicities tend to be mild and reversible (Pallis et al., 2003). Rash has been cited as the most distinctive side effect of treatments targeting EGF and EGFR. The rash is most common on the face, head, and neck. It is considered sterile, and topical antibiotics are used to treat it, along with corticosteroids in mild cases. The rash associated with EGFR targeted-treatments is coming to be associated with efficacy; it appears that patients not experiencing rash may not respond, while those who do develop rash probably will (Perez-Soler, 2003). Standard anti-diarrheal therapies (i.e., loperamide) are applicable in grades 1-2 diarrhea. Therapy should be stopped in grades 3-4. In trials at 250 mg/day, about 48% of patients experienced diarrhea, but it was almost

TABLE 16. Clinical Trials of Gefitinib, Phase II Single Agent, Second-Line

	250 mg/day	500 mg/day	250 mg/day	500 mg/day
Response Rate (%)	18.4	19.0	11.8	8.8
Disease Control Rate (response + stable disease)(%)	54.4	51.4	43	36
Stable Disease (%)	36	32	31	27
Progression Free Survival (mos)	2.7	2.8	1.9	NR
Overall Survival (mos)	7.6	8.1	6.5	5.9

always grade I. Asymptomatic increases in liver transaminases have been observed, and liver function testing should be performed. Gefitinib should be stopped if elevations become severe. Interstitial lung disease (ILD) has been observed in a small proportion of patients, with a larger group of Japanese patients developing it than those of European descent. The overall incidence is about 1% in NSCLC patients treated with gefitinib. About 30% of

Note. Data from "Improvement in Disease-Related Symptoms and Quality of Life in Patients with Advanced Non-Small Cell Lung Cancer (NSCLC) Treated with ZD1839 ('Iressa') (IDEAL 1) [Abstract]," by J.-Y. Douillard et al., 2002, *Proceedings of the American Society of Clinical Oncology*, 20. Abstract No. 1195. Retrieved July 9, 2004, from http://www.asco.org/ac/1,1003,12-002640-00_19-0016-00_19-001195,00.asp; and "Improvement in Symptoms and Quality of Life for Advanced Non-Small-Cell Lung Cancer Patients Receiving ZD1839 ('Iressa') in IDEAL 2 [Abstract], by R.B. Natale et al., 2002, *Proceedings of the American Society of Clinical Oncology*, 20. Abstract No. 1167. Retrieved August 16, 2004, from http://www.asco.org/ac/1,1003,12-002640-00_18-0016-00_19-001167,00.asp.

affected patients died. ILD may present as interstitial pneumonia, pneumonitis, and alveolitis. Most patients experiencing ILD had received radiation therapy (31%) or prior chemotherapy (57%) (Hotta et al., 2004; Gustafson et al., 2004; Mohamed et al., 2004; AstraZeneca, 2003; Ervin & Toothaker, 2004).

CASE STUDY – GEFITINIB

Jane was a 54-year-old administrative assistant diagnosed with metastatic adenocarcinoma in 2000. First-line treatment with paclitaxel and carboplatin resulted in disease progression after four cycles. She also failed treatment with vinorelbine/gemcitabine and single-agent docetaxel. Jane then agreed to participate in the IDEAL 2 trial, in which she received gefitinib 250 mg/day. Within six weeks of therapy, she showed a partial tumor response and no longer required the use of continuous oxygen or a wheelchair, both of which she had previously needed. At the end of the treatment period, she continued to have improved quality of life and was able to return to work. The primary toxicity was rash on her face, which was treated with topical clindamycin; Jane also experienced grade 2 nausea, which was controlled with antiemetics. Jane died in February 2002 (Riddle et al., 2002).

EGFR-TKIs - Erlotinib

Erlotinib (Tarceva®, OSI 774, Genentech, Inc., San Francisco, CA), another oral EGFR-TKI, has also been investigated. Erlotinib inhibits tyrosine autophosphorylation and downstream intracellular signaling. It has multiple cellular effects. Erlotinib

- inhibits proliferation,
- inhibits angiogenesis,
- inhibits tumor cell repair after chemotherapy or radiation,
- inhibits motility and invasion, and
- promotes apoptosis (Hidalgo, 2003; Perez-Soler, 2004a & b; Okamoto et al., 2003).

In a phase II trial, it was tested at a 150 mg/day dose in 56 evaluable patients, many of whom were heavily pretreated. Twelve percent showed an objective response, including one patient with a complete response; an additional 26% maintained stable disease. Median survival was nine months, with one-year survival of 48%; the most common toxicity was a rash (Perez-Soler et al., 2001).

Results of phase III trials of erlotinib in combination with platinum-based chemotherapy (TALENT and TRIB-UTE), reported in 2004, showed no benefit of adding erlotinib to the regimens (Gatzemeier et al., 2004; Herbst et al., 2004). Both trials tested the combinations in patients with previously untreated NSCLC. These results paralleled those for gefitinib combined with chemotherapy, and researchers are exploring the implications of TKI efficacy in combination with chemotherapy regarding patient selection, sequence of administration, and more.

One important new development, however, has been the report of the first randomized, placebo controlled trial to demonstrate prolonged survival for stage IIIB/IV NSCLC patients. Erlotinib was tested in 731 patients in the second and third line: i.e., their previous chemotherapy had failed once or twice. The study was based in Canada, but included patients from Canada, Europe, North America, and Latin America (Shepherd et al., 2004).

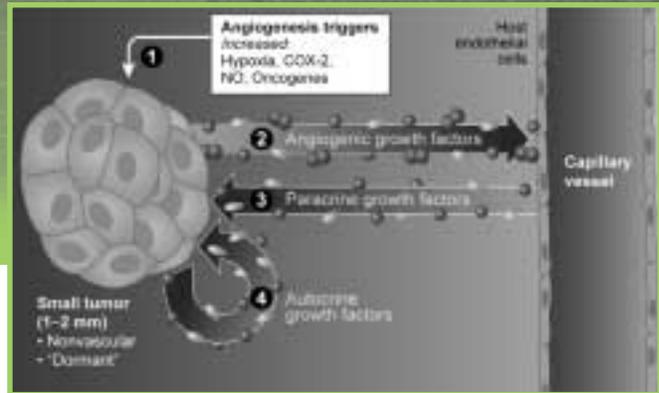
Patients were randomized 2:1 to receive erlotinib vs. placebo. The dosage was 150 mg per day, orally. Patient characteristics were well balanced. Fifty percent had received two prior regimens; 93% had received platinum, and 37% had prior taxanes. The overall response rate was about 9%, but patients who received erlotinib did show longer overall survival, longer progression-free survival, and improved quality of life (Shepherd et al., 2004).

TABLE 17. Results, NCIC CGT Trial Erlotinib vs. Placebo, Single Agent, Advanced NSCLC

	Erlotinib	Placebo	P value
Overall Survival	6.7 mos	4.7 mos	0.001
Progression-Free Survival	2.23 mos	1.84 mos	0.001

Note. Data from "A Randomized Placebo-Controlled Trial of Erlotinib in Patients with Advanced Non-Small Cell Lung Cancer (NSCLC) Following Failure of 1st Line or 2nd Line Chemotherapy. A National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) Trial [Abstract], by F.A. Shepherd, et al., *Proceedings of the American Society of Clinical Oncology*, 23. Abstract No. 7022. Retrieved August 16, 2004, from http://www.asco.org/ac/1,1003,12-002640-00_18-0026-00_19-00678,00.asp

Figure 4.
Angiogenesis
Signaling Cascade



Again, the most common side effects were rash and diarrhea. Only 5% of patients discontinued erlotinib for any toxicity compared to 2% of patients on placebo (Shepherd et al., 2004). Erlotinib was FDA approved in late 2004.

The side effects of EGFR inhibitors are typically not difficult to manage; for example, diarrhea can be treated with over-the-counter medications, such as loperamide. Skin rash, which may vary from mild skin dryness to eruptions on the face, neck, and/or trunk, usually occurs within the first three weeks of treatment and decreases in severity or resolves with continued therapy. The rash may be treated with topical or oral antibiotics, or clindamycin 1% gel if the rash progresses to grade 3 or higher (Riddle, Lee, & Purdom, 2002).

Research findings to date have prompted researchers to explore the possible predictors of efficacy for TKIs. Research on gefitinib has suggested correlations with female gender, non-smoking status, Asian ethnicity, adenocarcinoma (vs. other types of NSCLC), multiple pulmonary metastases, and HER family expression. Rash appears to be the most consistent correlate of efficacy in TKIs. Genetic mutations in the EGFR gene may provide more reliable markers of patients who may respond to TKIs. Over-expression of EGFR in NSCLC is not a predictor of response. Research is underway to identify the somatic mutations that can be used to predict sensitivity to the drugs (Perez-Soler, 2003; Lynch et al., 2004; Paez et al., 2004; Patel, 2004).

Monoclonal Antibodies Against EGFR

Cetuximab (IMC-C225, Erbitux™, ImClone Systems, New York, NY), a chimeric (human/murine) monoclonal antibody, has been more extensively evaluated in colorectal cancer and in cancer of the head and neck than in other cancers. Early phase I single-agent trials failed to show major responses in patients with NSCLC, although patients were not required to demonstrate EGFR expression; thus, expression or lack thereof may be important to consider in future trials. Cetuximab is associated with allergic and hypersensitivity reactions (as with other chimeric monoclonal antibodies) and with skin rashes (as with EGFR-TKIs), but not with diarrhea (Thomas, 2003b). The drug is also being evaluated in combination with docetaxel (second-line, phase II), paclitaxel/carboplatin (first-line, phase III), and gemcitabine/carboplatin (first-line, phase III) regimens, using an initial loading dose of 400 mg/m² of cetuximab and 250 mg/m² weekly thereafter. In the docetaxel trial, 4 of 20 patients (20%) had achieved a partial response after two

cycles of therapy, while six more patients (30%) maintained stable disease (Kim et al., 2002). If this high level of activity continues through the completion of the trial, a trial comparing docetaxel as a single agent with docetaxel plus cetuximab may be warranted (Thomas, 2002).

ABX-EGF (Abgenix, Fremont, CA), a fully human anti-EGFR antibody, has also shown biological activity at low doses in a phase I trial. Of 43 patients with a variety of tumors, two patients with NSCLC achieved stable disease. At doses exceeding 2.0 mg/kg, almost all patients developed rash; however, no infusion-related or hypersensitivity reactions have been noted. A phase II trial of paclitaxel and carboplatin versus paclitaxel, carboplatin, and ABX-EGF is ongoing (Thomas, 2002). Early reports of part I of the study demonstrated activity and tolerability of the combination. Efficacy results are pending (Crawford et al., 2004). Additional EGFR-TKIs and monoclonal antibodies being investigated in NSCLC include trastuzumab (Herceptin®, Genentech, South San Francisco, CA), which is currently approved for HER2/*neu* overexpressing breast cancer, the TKI PKI-166, and agents that inhibit more than one member of the epidermal growth factor family of receptors, such as GW2016 and CI-1033 (Thomas, 2002, 2003a).

Novel Strategies: Angiogenesis Inhibitors

Because of the need for tumor cells to be in close proximity to blood vessels to obtain oxygen and nutrients for growth, no tumor can grow to a size of more than 2.0 mm without angiogenesis (Folkman, 2001). In normal adults, angiogenesis is rare except in wound healing and menstruation; in tumor growth, it is essential. Thus, a current focus of research in NSCLC and in other cancers is the inhibition of angiogenesis.

The angiogenesis signaling cascade, depicted in **Figure 4**, involves secretion of vascular endothelial growth factor (VEGF) or other factors by the tumor. These growth factors then bind to receptors on the surface of endothelial cells, and the receptors in turn signal the endothelial cell nucleus to promote cell growth. Following endothelial cell activation, an activated cell secretes matrix metalloproteinases (MMPs) that digest the surrounding cell matrix, allowing the cell to migrate and divide to form new blood vessels.

Angiogenesis inhibitors can stop endothelial cell proliferation through one of three processes. First, the action of VEGF can be inhibited, so that endothelial cells never

receive the signal to become active. Second, endothelial cells can be stopped from secreting MMPs, so that they cannot digest the cellular matrix in order to move and divide. Finally, migration and division themselves can be prevented.

Bevacizumab (Avastin™, RhuMAB VEGF, Genentech BioOncology, South San Francisco, CA), an anti-VEGF monoclonal antibody that inhibits angiogenesis, has been tested as an addition to paclitaxel/carboplatin therapy in NSCLC. Patients received paclitaxel/carboplatin therapy alone or with low-dose (7.5 mg/kg every three weeks) or high-dose (15 mg/kg every three weeks) bevacizumab. Response rates and time to progression favored the high-dose arm; however, life-threatening hemoptysis was seen in 6 of 67 bevacizumab-treated patients. Four of these patients died (DeVore et al., 2000). It is important to note that these bleeding episodes were associated with large, centrally located tumors and squamous histology. Thus, future trials may exclude such patients for safety reasons. Because bevacizumab interferes with angiogenesis and thus with wound healing, patients also should not undergo surgery while the drug is being administered.

Because of bevacizumab's activity in the extracellular domain, it has also been proposed that its effects would compliment those of erlotinib. This concept has been tested in a small phase I/II study in patients with advanced NSCLC designed to establish safe dosages and explore efficacy and tolerability. The dose was set at 150 mg/day of erlotinib plus 15 mg/kg IV of bevacizumab every 21 days (N=40). Seven patients (17.5%) demonstrated a partial response, and 14 (35%) experienced stable disease. The overall survival was 9.3 months, and the average duration of progression-free survival was 4.6 months. The most commonly reported adverse events were rash, diarrhea (erlotinib), and proteinuria (bevacizumab) – never more than mild to moderate. There appeared to be no pharmacokinetic interaction between the two agents. Any synergistic interactions against the tumor were not evaluated in this study. Researchers did conclude that the combination of agents warrants further study (Sandler et al., 2004).

Another VEGF inhibitor in clinical trials is ZD6474 (AstraZeneca, Wilmington, DE), a tyrosine kinase inhibitor active against VEGFR. It is in phase II trials, in combination with docetaxel, in patients with advanced NSCLC refractory to platinum therapy. It is also being tested as a single agent or in combination with paclitaxel and carboplatin (Heymach et al., 2004).

BEVACIZUMAB CASE STUDY

Marie is a 67 year-old woman diagnosed with previously untreated, Stage III-IV metastatic non-small cell lung cancer. Marie was enrolled in a bevacizumab clinical trial. Requirements for enrollment included no metastasis to the central nervous system, no atherosclerotic vascular disease, sufficient renal, hepatic and hematologic function, and an ECOG status of I.

After informed consent, Marie was enrolled in a chemotherapy/bevacizumab trial, and began receiving bevacizumab with paclitaxel/carboplatin. She received paclitaxel/carboplatin with bevacizumab 15 mg/kg every three weeks.

Marie was able to complete her chemotherapy as an outpatient with no pre-medications. Side effects from the treatment were mild and well-tolerated. After her second bevacizumab infusion, Marie experienced hypertension, which was managed with an oral medication.

Other novel strategies

Other novel approaches being studied include apoptosis inducers, gene replacement therapy, immunotherapy via dendritic cells and tumor-specific killer T cells, and COX-2 inhibitors. It has been noted that VEGF levels are lower in cells that are missing the COX-2 gene, and a small study suggests that adding the COX-2 inhibitor celecoxib (Celebrex®, Pfizer, New York, NY) to standard chemotherapy in early-stage cancer (preoperative setting) increases the rate of complete response (Altorki et al., 2002). In other trials, celecoxib is being combined with gefitinib in patients with platinum refractory NSCLC (Gadgeel et al., 2004). Further trials are underway in a variety of cancers, but recent reports about cardiovascular problems with COX-2 inhibitors may limit continuing research.

CONCLUSIONS

Advanced NSCLC remains a discouraging disease with a poor prognosis for most patients. Recent advances in chemotherapy have improved the odds for a portion of NSCLC patients, and the new agent pemetrexed (approved in August 2004) may provide additional options for treatment with lower toxicity. Other research is exploring the development of targeted agents against EGFR and EGFR TKs in NSCLC therapy. Both gefitinib and erlotinib have been FDA approved for the treatment of NSCLC in the second line, but gefitinib's manufacturer is no longer promoting it in response to disappointing survival results from clinical trials reported in late 2004. While for the time being these agents benefit only a small proportion of patients affected by advanced NSCLC, research continues to identify which patients will respond and to isolate other agents or combinations of agents that have the potential to help even more.

References

- Abratt, R.P., Hacking, D.J., Goedhals, L., & Bezwoda, W.R. (1997). Weekly gemcitabine and monthly cisplatin for advanced non-small cell lung carcinoma. *Seminars in Oncology*, 24 (3 Suppl. 8), S8-S23.
- Abratt, R.P., Sandler, A., Crino, L., Steward, W.P., Shepherd, F.A., Green, M.R., et al. (1998). Combined cisplatin and gemcitabine for non-small cell lung cancer: Influence of scheduling on toxicity and drug delivery. *Seminars in Oncology*, 25 (4 Suppl. 9), 35-43.
- Altorki, N.K., Keresztes, R.S., Port, J.L., Flieder, D.B., Ferrara, C.A., Pasmantier, M.W., et al (2002) Celecoxib (Celebrex), a selective cox-2 inhibitor, enhances the responses to preoperative paclitaxel/carboplatin in early stage non-small cell lung cancer [Abstract]. *Proceedings of the American Society of Chemical Oncology*, 21. Retrieved December 22, 2004, from http://www.asco.org/ac/1,1003,_12-002643-00_18-10016-00_19-00101,00.asp.
- American Cancer Society. (2003a). *Cancer facts & figures 2003*. Atlanta, GA: American Cancer Society.
- American Cancer Society. (2003b). *How is lung cancer staged?* Retrieved June 2, 2003, from http://www.cancer.org/docroot/CRI/content/CRI_2_4_3X_How_is_lung_cancer_staged_26.asp?sitearea=
- AstraZeneca. (2003). Iressa® (gefitinib) [Package insert]. Wilmington, DE: AstraZeneca.
- AstraZeneca. (2004). [Press Release]. December 17, 2004.
- Aventis. (2004). Taxotere® (docetaxel) [Package insert]. Bridgewater, NJ: Aventis.
- Barr, F., Mirsky, H., Clinthorne, D., Bendel, S., & Smith, F. (1999). A phase III study of gemcitabine and vinorelbine salvage chemotherapy for taxane resistant non-small cell lung cancer (NSCLC) [Abstract]. *Proceedings of the American Society of Clinical Oncology*, 18. Retrieved April 14, 2003, from http://www.asco.org/ac/1,1003,_12-002324-00_18-001999-00_19-0016163-00_29-00A,00.asp.
- Belani, C.P. (1999). Docetaxel (Taxotere) in combination with platinum-based regimens in non-small cell lung cancer: Results and future developments. *Seminars in Oncology*, 26 (3 Suppl. 10), 15-18.
- Bonomi, P., Kim, K., Fairclough, D., Cella, D., Kugler, J., Rowinsky, E., et al. (2000). Comparison of survival and quality of life in advanced non-small-cell lung cancer patients treated with two dose levels of paclitaxel combined with cisplatin versus etoposide with cisplatin: Results of an Eastern Oncology Cooperative Group trial. *Journal of Clinical Oncology*, 18, 623-631.
- Carmichael, J., Allerheiligen, S., & Walling, J. (1996). A phase I study of gemcitabine and carboplatin in non-small cell lung cancer. *Seminars in Oncology*, 23 (5 Suppl. 10), 55-9.
- Chen, Y.M., Whang-Peng, J., Perng, R.P., Liu, T.W., Yang, K.Y., Lin, W.C., et al. (1999). A multi-center phase II study of gemcitabine (GEM) and vinorelbine (VNR) in patients with advanced stage IIIB-IV non-small cell lung cancer [Abstract]. *Proceedings of the American Society of Clinical Oncology*, 18. Retrieved April 14, 2003, from http://www.asco.org/ac/1,1003,_12-002324-00_18-001999-00_19-0016105-00_29-00A,00.asp.
- Ciardiello, F., De Vita, F., Orditura, M., & Tortora, G. (2004). The role of EGFR inhibitors in nonsmall cell lung cancer. *Current Opinion in Oncology*, 16, 130-135.
- Crawford, J., Detterbeck, F., Leopold, K.A., & Rivera, M.P. (2000). *Coordination of care for the management of non-small cell lung cancer*. Princeton, NJ: Bristol-Myers Squibb.
- Crawford, J., O'Rourke, M., Schiller, J.H., Spiridonitis, C.H., Yanovich, S., Ozer, H., et al. (1996). Randomized trial of vinorelbine compared with fluorouracil plus leucovorin in patients with stage IV non-small-cell lung cancer. *Journal of Clinical Oncology*, 14, 2774-2784.
- Crawford, J., Sandler, A. B., Hammond, L.A., Schiller, J., Belani, C., Kozloff, M., et al. (2004). ABX-EGF in combination with paclitaxel and carboplatin for advanced non-small cell lung cancer (NSCLC) [Abstract]. *Proceedings of the American Society of Clinical Oncology*, 23, 634. Abstract No. 7083.
- DeVore, R.F., Fehrenbacher, L., Herbst, R.S., Langer, C.J., Kelly, K., Gaudreault, E., et al. (2000). A randomized phase II trial comparing rhuMAb VEGF (recombinant humanized monoclonal antibody to vascular endothelial cell growth factor) plus carboplatin/paclitaxel (CP) to CP alone in patients with stage IIIB/IV NSCLC [Abstract]. *Proceedings of the American Society of Clinical Oncology*, 19, 485a. Abstract No. 1896.
- Douillard, J.-Y., Giaccone, G., Horai, T., Noda, K., Vansteenkiste, J.F., Takata, I., et al. (2002). Improvement in disease-related symptoms and quality of life in patients with advanced non-small cell lung cancer (NSCLC) treated with ZD1839 ('Iressa') (IDEAL 1) [Abstract]. *Proceedings of the American Society of Clinical Oncology*, 21. Retrieved July 9, 2004, from http://www.asco.org/ac/1,1003,_12-002640-00_19-0016-00_19-001195,00.asp. Abstract No. 1195.
- Earle, C.C., Tsai, J.S., Gelber, R.D., Weinstein, M.C., Neumann, P.J., & Weeks, J.C. (2001). Effectiveness of chemotherapy for advanced lung cancer in the elderly: instrumental variable and propensity analysis. *Journal of Clinical Oncology*, 19, 1064-70.
- Edelman, M.J. (2003). Gemcitabine and carboplatin regimens in advanced non-small cell lung cancer: Focus on randomized phase III trials. *Clinical Lung Cancer*, 4 (Suppl. 2), S40-S44.
- Eli Lilly. (2004a). GEMZAR® (gemcitabine HCl) [Package insert]. Indianapolis, IN: Author.
- Eli Lilly. (2004b). Alimta® (pemetrexed) [Package insert]. Indianapolis, IN: Author.
- Ervin, T.J., & Tothaker, S.R. (2004). Community practice experience with gefitinib (ZD1839) as treatment for patients with advanced non-small cell lung cancer (NSCLC) within an expanded access clinical program [Abstract]. *Proceedings of the American Society of Clinical Oncology*, 23, 704. Abstract No. 7367.
- Ettinger, D.S. (2002). Pemetrexed (Alimta®): A new antifolate for non-small-cell lung cancer. *Clinical Lung Cancer*, 3 (Suppl. 1), S22-S25.
- Fish-Stegall, A. (2000). *Multidisciplinary care in the management of non-small cell lung cancer* [Monograph]. Princeton, NJ: Bristol-Myers Squibb.
- Fisher, M.D., & D'Orazio, A. (2000). Phase II and III trials: comparison of four chemotherapy regimens in advanced non small-cell lung cancer (ECOG 1594). *Clinical Lung Cancer*, 2, 21-2.
- Folate antagonists. (2003). Retrieved June 16, 2003, from <http://www.cancerquest.org/index.cfm?page=449>.
- Folkman, J. (2001). Antiangiogenesis agents. In V.T. DeVita, Jr., S. Hellman, & S.A. Rosenberg (Eds.). *Cancer: Principles & practice of oncology* (6th ed., pp. 509-519). Philadelphia: Lippincott Williams & Wilkins.
- Fossella, F., DeVore, R., Kerr, R., Crawford, J., Natale, R., Dunphy, F., et al. (1999). Phase III trial of docetaxel 100 mg/m² or 75 mg/m² vs. vinorelbine/ifosfamide for non-small cell lung cancer (NSCLC) previously treated with platinum-based chemotherapy (PBC) [Abstract]. *Proceedings of the American Society of Clinical Oncology*, 18. Retrieved June 16, 2003, from http://www.asco.org/ac/1,1003,_12-002324-00_18-001999-00_19-0016025-00_29-00A,00.asp.
- Fossella, F., DeVore, R., Kerr, R., Crawford, J., Natale, R., Dunphy, F., et al. (2000). Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small cell lung cancer previously treated with platinum-containing chemotherapy regimens. *Journal of Clinical Oncology*, 18, 2354-2362.
- Fossella, F., Pereira, J., von Pawel, J., Pluzanska, A., Gorbounova, V., Kaukel, E., et al. (2003). 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. *Journal of Clinical Oncology*, 21, 3016-3024.
- Franklin, W.A., Veve, R., Hirsch, F.R., Helfrich, B.A., & Bunn, P.A., Jr. (2002). Epidermal growth factor receptor family in lung cancer and premalignancy. *Seminars in Oncology*, 29 (1 Suppl. 4), 3-14.

Fracchi, G., Lorusso, V., Panza, N., et al. (2000). Gemcitabine + vinorelbine (GV) yields better survival than vinorelbine (V) alone in elderly non-small cell lung cancer (NSCLC) patients. Final analysis of a Southern Italy Cooperative Group (SICOG) phase III trial [Abstract]. *Annals of Oncology*, 11 (Suppl. 4), 108.

Frei, E., III. (1997). Non-small cell lung cancer: Novel treatment strategies. *Chest*, 112 (Suppl. 4), 266S-268S.

Fukuoka, M., Yano, S., Giaccone, G., Tamura, T., Nakagawa, K., Douillard, J.-Y., et al. (2002). Final results from a phase II trial of ZD1839 ('Iressa') for patients with advanced non-small cell lung cancer (IDEAL 1) [Abstract]. *Proceedings of the American Society of Clinical Oncology*, 21. Retrieved July 9, 2004, from http://www.asco.org/ac/1,1003,12-002640-00_18-0016-00_19-001188,00.asp. Abstract No. 1188.

Gadgeel, S.M., Shehadeh, N.J., Ruckdeschel, J.C., Chaplen, R.A., Belzer, K., & Wozniak, A. (2004). Gefitinib and celecoxib in patients with platinum refractory non-small cell lung cancer (NSCLC) [Abstract]. *Proceedings of the American Society of Clinical Oncology*, 23, 636. Abstract No. 7094.

Gatzemeier, U., Pluzanska, A., Szczesna, A., Kaukel, E., Roubec, J., Brennscheidt, U., et al. (2004). Results of a phase III trial of erlotinib (OSI-774) combined with cisplatin and gemcitabine (GC) chemotherapy in advanced non-small cell lung cancer (NSCLC) [Abstract]. *Proceedings of the American Society of Clinical Oncology*, 23, 617. Abstract No. 7010.

Georgoulas, V., Papadakis, E., Alexopoulos, A., Stavrinidis, E., Bania, E., Rapti, A., et al. (1999). Docetaxel plus cisplatin versus docetaxel plus gemcitabine chemotherapy in advanced non-small cell lung cancer: A preliminary analysis of a multicenter randomized phase II trial [Abstract]. *Proceedings of the American Society of Clinical Oncology*, 18. Retrieved April 14, 2003, from http://www.asco.org/ac/1,1003,12-002324-00_18-001999-00_19-0016027-00_29-00A,00.asp.

Giaccone, G., Johnson, D.H., Manegold, C., Scagliotti, G.V., Rosell, R., Wolf, M., et al. (2002). A phase III clinical trial of ZD1839 ('Iressa') in combination with gemcitabine and cisplatin in chemotherapy-naïve patients with advanced non-small cell lung cancer (INTACT 1) [Abstract]. *Annals of Oncology*, 13 (Suppl. 5), 2-3. Abstract No. 40.

Ginsberg, R.J., Vokes, E.E., & Rosenzweig, K. (2001). Non-small cell lung cancer. In V.T. DeVita, Jr., S. Hellman, & S.A. Rosenberg (Eds.). *Cancer: Principles & practice of oncology* (pp. 925-982). Philadelphia: Lippincott Williams & Wilkins.

Gridelli, C., Perrone, F., Gallo, C., Cigolari, S., Rossi, A., Piantedosi, F., et al. (2003). Chemotherapy for elderly patients with advanced non-small-cell lung cancer: The Multicenter Italian Lung Cancer in the Elderly Study (MILES) phase III randomized trial. *Journal of the National Cancer Institute*, 95, 362-372.

Gustafson, N.F., Saltz, L., Cunningham, D., Lenz, H., Humphrey, R., & Adegbile, I.A. (2004). Safety profile of cetuximab in patients with metastatic colorectal cancer [Poster]. *Proceedings of the American Society of Clinical Oncology*, 23. Abstract No. 237. Retrieved June 30, 2004, from http://www.asco.org/ac/1,1003,12-002643-00_18-0027-00_19-00525,00.asp.

Haapioja, I.S. & Blendowski, C. (1999). Superior vena cava syndrome. *Seminars in Oncology Nursing*, 15, 183-189.

Haas, M.L. (2003). Controversies in detection and screening. In M. Haas (Ed.). *Contemporary issues in lung cancer* (pp. 24-29). Boston: Jones & Bartlett.

Hainsworth, J.D., Burris, H.A., III, Litchy, S., Morrissey, L.H., Barton, J.H., Bradof, J.E., et al. (2000). Weekly docetaxel in the treatment of elderly patients with advanced non-small cell lung carcinoma: A Minnie Pearl Cancer Research Network phase II trial. *Cancer*, 89, 328-333.

Hanna, N., Shepherd, F., Rosell, R., Pereira, J. R., De Marinis, F., Fossella, F., et al. (2003). Randomized phase III trial of pemetrexed vs. docetaxel in patients with locally advanced or metastatic NSCLC previously treated with chemotherapy [Abstract]. *Proceedings of the American Society of Clinical Oncology*, 22, 622. Abstract No. 2503.

Hanna, N., Shepherd, F.A., Fossella, F.V., Pereira, J.R., De Marinis, F., von Pawel, J., et al. (2004). Randomized phase III trial of pemetrexed versus docetaxel in patients with

non-small cell lung cancer previously treated with chemotherapy. *Journal of Clinical Oncology*, 22, 1589-1597.

Harper, P. (2003). Update on gemcitabine/carboplatin in patients with advanced non-small cell lung cancer. *Seminars in Oncology*, 30 (4 Suppl. 10), 2-12.

Harpham, W.S. (2001). Alternative therapies for curing cancer: What do patients want? What do patients need? *CA: A Cancer Journal for Clinicians*, 51, 131-141.

Herbst, R.S., Prager, D., Hermann, R., Miller, V., Fehrenbacher, L., Hoffman, P., et al. (2004). TRIBUTE: A phase III trial of erlotinib HCL (OSI-774) combined with carboplatin and paclitaxel (CP) chemotherapy in advanced non-small cell lung cancer (NSCLC) [Abstract]. *Proceedings of the American Society of Clinical Oncology*, 23, 617. Abstract No. 7011.

Heymach, J.V., Dong, R.P., Dimery, I., Wheeler, C., Fidias, P., Lu, C., Johnson, B., Herbst, R. (2004). ZD6474, a novel antiangiogenic agent in combination with docetaxel in patients with NSCLC: Results of the run-in phase of a two part, randomized phase II study. *Journal of Clinical Oncology*, 2004 ASCO Annual Meeting Proceedings (Post meeting edition). Vol 22, No 14S (July 15 Supplement), 3051.

Hidalgo, M. (2003). Erlotinib: preclinical investigations. *Oncology* (Huntington). 17 (11 Suppl. 12), 11-16.

Hirsh, V., Whittom, R., Ofiara, L., Desjardins, P., Ayoub, J., Charpentier, D., et al. (2003). Weekly paclitaxel and gemcitabine chemotherapy for metastatic non-small cell lung carcinoma (NSCLC): A dose-optimizing phase II trial. *Cancer*, 97, 2242-2247.

Hotta, K., Harita, S., Bessho, A., Yonei, T., Gemba, K., Aoe, K., et al. (2004). Interstitial lung disease (ILD) during gefitinib treatment in Japanese patients with non-small cell lung cancer (NSCLC): Okayama Lung Cancer Study Group [Abstract]. *Proceedings of the American Society of Clinical Oncology*, 23, 629. Abstract No. 7063.

Houlihan, N.G. (Ed.). (2004). *Lung cancer*. Pittsburgh, PA: Oncology Nursing Society.

ImClone Systems and Bristol-Myers Squibb. (2004). Erbitux™ (cetuximab). [Package Insert]. Branchburg and Princeton, NJ: Authors.

Jemal, A., Murray, T., Samuels, S., Ghafoor, A., Ward, E., & Thun, M. (2003). Cancer statistics, 2003. *CA: A Cancer Journal for Clinicians*, 53, 5-26.

Jemal, A., Tiwari, R.C., Murray, T., Ghafoor, A., Samuels, A., Ward, E., et al. (2004). Cancer statistics, 2004. *CA: A Cancer Journal for Clinicians*, 54, 8-29.

Johnson, D.H., Herbst, R., Giaccone, G., Schiller, J., Natale, R.B., Miller, V., et al. (2002). ZD1839 ('Iressa') in combination with paclitaxel and carboplatin in chemotherapy naïve patients with advanced non-small cell lung cancer (NSCLC): Results from a phase III clinical trial (INTACT 2) [Abstract]. *Annals of Oncology*, 13 (Suppl. 5), 127-128. Abstract No. 4680.

Kelly, K., Crowley, J., Bunn, P.A., Livingston, R.B., & Gandara, D.R. (1999). A randomized phase III trial of paclitaxel plus carboplatin (PC) versus vinorelbine plus cisplatin (VC) in untreated advanced non-small cell lung cancer (NSCLC): A Southwest Oncology Group (SWOG) trial [Abstract]. *Proceedings of the American Society of Clinical Oncology*, 18, 461a. Abstract No. 1777.

Kim, E.S., Mauer, A.M., Fossella, F.V., Jamison, T.A., Kies, M.S., Pisters, K.M., et al. (2002). A phase II study of Erbitux (CETUXIMAB), an epidermal growth factor receptor (EGFR) blocking antibody, in combination with docetaxel in chemotherapy refractory/resistant patients with advanced non-small cell lung cancer (NSCLC). *Proceedings of the American Society of Clinical Oncology*, 21. Retrieved June 17, 2003, from http://www.asco.org/ac/1,1003,12-002324-00_18-002002-00_19-001168-00_29-00A,00.asp.

Kris, M., Natale, R., Herbst, R., Lynch, T., Jr., Prager, D., Belani, C., et al. (2004). A phase II trial of ZD1839 ('Iressa') in advanced non-small cell lung cancer (NSCLC) patients who had failed platinum and docetaxel-based regimens (IDEAL 2) [Abstract]. *Proceedings of the American Society of Clinical Oncology*, 23. Retrieved July 9, 2004, from http://www.asco.org/ac/1,1003,12-002640-00_18-0016-00_19-001166,00.asp. Abstract No. 1166.

- Langer, C.J., Leighton, J.C., Comis, R.L., O'Dwyer, P.J., McAleer, C.A., Bonjo, C.A., et al. (1995). Paclitaxel and carboplatin in combination in the treatment of advanced non-small cell lung cancer: A phase II toxicity, response, and survival analysis. *Journal of Clinical Oncology*, 13, 1860-1870.
- Langer, C.J., Manola, J., Bernardo, P., Bonomi, P., Kugler, A., & Johnson, D. (2000). Advanced age alone does not compromise outcome in fit non-small cell lung cancer (NSCLC) patients (pts) receiving platinum (DDP)-based therapy (Tx): Implications of ECOG 5592 [Abstract]. *Proceedings of the American Society of Clinical Oncology*, 19, 489a. Abstract No. 1912.
- Langer, C.J., Vangel, M., Schiller, J., Harrington, D.P., Sandler, A., Belani, C.P., et al. (2003). Age-specific subanalysis of ECOG 1594: Fit elderly patients (70–80 yrs) with NSCLC do as well as younger pts (<70) [Abstract]. *Proceedings of the American Society of Clinical Oncology*, 22. Abstract No. 2571.
- Le Chevalier, T., Pujol, J.L., Douillard, J.Y., Alberola, V., Monnier, A., Riviere, A., et al. (1994). A three-arm trial of vinorelbine (Navelbine) plus cisplatin, vindesine plus cisplatin, and single-agent vinorelbine in the treatment of non-small cell lung cancer: An expanded analysis. *Seminars in Oncology*, 21 (5 Suppl. 10), 28-33; discussion, 33-4.
- Le Chevalier, T., for the IALT Investigators. (2004). Results of the randomized International Adjuvant Lung Cancer Trial (IALT): Cisplatin-based chemotherapy (CT) vs. not CT in 1867 patients (pts) with resected non-small cell lung cancer (NSCLC). *New England Journal of Medicine*, 350, 351-360.
- Lindsey, L.P., & Thielvold, D. (1999). Non-small cell lung cancer. In C. Miaskowski & P. Buchsel (Eds.). *Oncology nursing: Assessment and clinical care* (pp. 1331-1352). St. Louis, MO: Mosby.
- Lynch, T.J. (2004). Management of early-stage and locally advanced non-small cell lung cancer. American Society of Clinical Oncology 2004 Annual Meeting - Management of Lung Cancer CME, Medscape. Retrieved July 1, 2004, from http://www.medscape.com/viewprogram/3220_pnt.
- Maestu, I., Gomez-Aldaravi, L., Torregrosa, M.D., Camps, C., Llorca, C., Bosch, C., et al. (2003). Gemcitabine and low dose carboplatin in the treatment of elderly patients with advanced non-small cell lung cancer. *Lung Cancer*, 42, 345-354.
- Manegold, C., Gatzemeier, U., von Pawel, J., Pirker, R., Malayeri, R., Blatter, J., et al. (2000). Front-line treatment of advanced non-small-cell lung cancer with MTA (LY231514, pemetrexed disodium, Alimta®) and cisplatin: A multicenter phase II trial. *Annals of Oncology*, 11, 435-440.
- Miaskowski, C., & Viele, C. (1999). Cancer chemotherapy. In C. Miaskowski & P. Buchsel (Eds.). *Oncology nursing: Assessment and clinical care* (pp. 83-106). St. Louis, MO: Mosby.
- Miller, V. (1999). Docetaxel (Taxotere) in combination with vinorelbine in non-small cell lung cancer. *Seminars in Oncology*, 26 (3 Suppl. 10), 12-14.
- Mohamed, M.K., Ramalingam, S., Lin, Y., Gooding, W.E., Cronin, W., Eckardt, J.R., & Belani, C.P. (2004). Skin rash and good performance status (PS) predict improved survival with gefitinib for patients with advanced non-small cell lung cancer (NSCLC) [Abstract]. *Proceedings of the American Society of Clinical Oncology*, 23, 637. Abstract No. 7097.
- Mountain, C.F., Lukeman, J.M., Hammar, S.P., Chamberlain, D.W., Coulson, W.F., Page, D.L., et al. (1987). Lung cancer classification: The relationship of disease extent and cell type to survival in a clinical trials population. *Journal of Surgical Oncology*, 35(3), 147-156.
- Natale, R.B., Skarin, A.T., Maddox, A.-M., Hammond, L.A., Thomas, R., Gandara, D.R., et al. (2002). Improvement in symptoms and quality of life for advanced non-small-cell lung cancer patients receiving ZD1839 ('Iressa') in IDEAL 2 [Abstract]. *Proceedings of the American Society of Clinical Oncology*, 20. Abstract No. 1167. Retrieved August 16, 2004, from http://www.asco.org/ac/1,1003,12-002640-00_18-0016-00_19-001167,00.asp.
- National Cancer Institute. (2003a). Lung cancer (PDQ®): Screening. Retrieved June 2, 2003, from <http://cancer.gov/cancerinfo/pdq/screening/lung/healthprofessional/>.
- National Cancer Institute (2003b). Pemetrexed (Alimta®) is a less-toxic alternative for recurrent lung cancer. Retrieved August 15, 2003, from <http://www.nci.nih.gov/clinical-trials/results/pemetrexed-and-lung-cancer0603>.
- National Cancer Institute (NCI). (2004b). Treatment statement for health professionals: Small cell lung cancer. Retrieved August 5, 2004, from <http://www.meb.uni-bonn.de/cancer.gov/CDR0000062945.html>.
- National Comprehensive Cancer Network (NCCN). (2004). *Clinical practice guidelines in oncology™ – Non-small cell lung cancer*. Version 1.2004. Retrieved July 14, 2004, http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#site
- Ng, E.W., Sandler, A.B., Robinson, L., & Einhorn, L.H. (1999). A phase II study of carboplatin plus gemcitabine in advanced non-small-cell lung cancer (NSCLC): A Hoosier Oncology Group study. *Journal of Clinical Oncology*, 22, 550-3
- Okamoto, I., Kenyon, L.C., Emler, D.R., Mori, T., Sasaki, J., Hirosako, S., et al. (2003). Expression of constitutively activated EGFRvIII in non-small cell lung cancer. *Cancer Science*, 94, 50-6.
- Paez, J.G., Janne, P.A., Lee, J.C., Tracy, S., Greulich, H., Gabriel, S., et al. (2004). EGFR mutations in lung cancer: Correlation with clinical response to gefitinib therapy. *Science*, 304, 1497-1500.
- Pao, W., Zakowski, M., Cordon-Cardo, C., Ben-Porat, L., Kris, M.G., & Miller, V.A. (2004). Molecular characteristics of non-small cell lung cancer (NSCLC) patients sensitive to gefitinib. *Proceedings of the American Society of Clinical Oncology*, 23, 619. Abstract No. 7025.
- Pallis, A.G., Mavroudis, D., Androulakis, N., Souglakos, J., Kouroussis, C., Bozionelou, V., et al. (2003). ZD1839, a novel, oral epidermal growth factor receptor-tyrosine kinase inhibitor, as salvage treatment in patients with advanced non-small cell lung cancer. Experience from a single center participating in a compassionate use program. *Lung Cancer*, 40, 301-307.
- Patel, J.D., Pasche, B., & Argiris, A. (2004). Targeting non-small cell lung cancer with epidermal growth factor tyrosine kinase inhibitors: Where do we stand, where do we go? *Critical Reviews in Oncology and Hematology*, 50, 175-186.
- Paz-Ares, L., Bezares, S., Tabernero, J.M., Casellanos, D., & Cortes-Funes, H. Review of a promising new agent – Pemetrexed disodium. *Cancer*, 97 (8 Suppl.), 2056-2063.
- Perez-Soler, R. (2003). Can rash associated with HER1/EGFR inhibition be used as a marker of treatment outcome? *Oncology (Huntington)*, 17 (11 Suppl. 12), 12-28.
- Perez-Soler, R. (2004a). HER1/EGFR targeting: refining the strategy. *Oncologist*, 9, 58-67.
- Perez-Soler, R. (2004b). The role of erlotinib (Tarceva, OSI 774) in the treatment of non-small cell lung cancer. *Clinical Cancer Research*, 10 (10 Part 2), 4238s-4240s.
- Perez-Soler, R., Chachoua, A., Huberman, M., Karp, D., Rigas, J., Hammond, L., et al. (2001). A phase II trial of the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor OSI-774, following platinum-based chemotherapy, in patients (pts) with advanced, EGFR-expressing, non-small cell lung cancer (NSCLC) [Abstract]. *Proceedings of the American Society of Clinical Oncology*, 19, 310a. Abstract No. 1235.
- Postmus, P.E., & Green, M.R. (1999). Overview of MTA in the treatment of non-small cell lung cancer. *Seminars in Oncology*, 26 (1 Suppl. 4), 31-36.
- Ramanathan, R.K., & Belani, C.P. (1997). Chemotherapy for advanced non-small cell lung cancer: Past, present, and future. *Seminars in Oncology*, 24, 440-454.
- Riddle, J., Lee, P., & Purdom, M. (2002). The epidermal growth factor receptor as a novel target for cancer therapy: Case studies and clinical implications. *Seminars in Oncology Nursing*, 18(4 Suppl. 4), 11-19.

Sandler, A.B., Blumenschein, G.R., Henderson, T., Lee, J., Truong, M., Kim, E., et al. (2004). 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 [Abstract]. *Proceedings of the American Society of Clinical Oncology*, 23, 127. Abstract No. 2000.

Shepherd, F.A., Dancey, J., Ramlau, R., Mattson, K., Gralla, R., O'Rourke, M., et al. (2000). Prospective randomized trial of docetaxel versus best supportive care in patients with non-small cell lung cancer previously treated with platinum-based chemotherapy. *Journal of Clinical Oncology*, 18, 2095-2103.

Shepherd, F.A., Pereira, J., Ciuleanu, T.E., Tan, E.H., Hirsh, V., Thongprasert, S., et al. (2004). A randomized placebo-controlled trial of erlotinib in patients with advanced non-small cell lung cancer (NSCLC) following failure of 1st line or 2nd line chemotherapy. A National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) trial [Abstract]. *Proceedings of the American Society of Clinical Oncology*, 23. Abstract No. 7022. Retrieved August 16, 2004, from http://www.asco.org/ac/1,1003,12-002640-00_18-0026-00_19-00678,00.asp.

Stabile, L.P., Davis, A.L., Gubish, C.T., Hopkins, T.M., Luketich, J.D., Christie, N., et al. (2002). Human non-small cell lung tumors and cells derived from normal lung express both estrogen receptor alpha and beta and show biological responses to estrogen. *Cancer Research*, 62, 2141-2150.

Strauss, G., Herndon, J., Maddaus, M., et al. (2004). Randomized clinical trial of adjuvant chemotherapy with paclitaxel and carboplatin following resection in stage IB non-small cell lung cancer (NSCLC): Report of Cancer and Leukemia Group B (CALGB) Protocol 9633 [Abstract]. *Proceedings of the American Society of Clinical Oncology*, 23 (Suppl.), 17. Abstract No. 7019.

Thomas, M. (2002). Overview of clinical trials with epidermal growth factor receptor inhibitors in advanced non-small cell lung cancer. *Seminars in Oncology Nursing*, 18 (4 Suppl. 4), 20-27.

Thomas, M. (2003a). Advances in chemotherapy. In M. Haas (Ed.). *Contemporary issues in lung cancer: A nursing perspective* (pp. 49-82). Boston: Jones & Bartlett.

Thomas, M. (2003b). Overview of clinical trials with epidermal growth factor receptor inhibitors in advanced non-small cell lung cancer. Manuscript submitted for publication.

Tyson, L. (2004). Patient assessment. In Houlihan, N.G. (Ed.). (2004). *Lung cancer*. (pp. 35-45) Pittsburgh, PA: Oncology Nursing Society.

Volker, D.L., & Coward, D.D. (2003). End-of-life care. In M. Haas (Ed.). *Contemporary issues in lung cancer: A nursing perspective* (pp. 129-151). Boston: Jones & Bartlett.

Winton, T., Livingston, R., Johnson, D., et al. (2004). A prospective randomized trial of adjuvant vinorelbine (VIN) and cisplatin (CIS) in completely resected stage IB and II non-small cell lung cancer (NSCLC) Intergroup JBR.10 [Abstract]. *Proceedings of the American Society of Clinical Oncology*, 23 (Suppl.), 17. Abstract No. 7018.

Wood, L.S. (2002). Rationale for EGFR as a target for cancer therapy. *Seminars in Oncology Nursing*, 18 (4 Suppl. 4), 3-10.

Wozniak, A.J., Crowley, J.J., Balcerzak, S.P., Weiss, G.R., Spiridonidis, C.H., Baker, L.H., et al. (1998). Randomized phase III trial of cisplatin (CDDP) vs. CDDP plus navelbine (NVB) in the treatment of advanced non-small cell lung cancer (NSCLC): An update of a Southwest Oncology Group Study (SWOG-9308) [Abstract]. Retrieved June 13, 2003, from http://www.asco.org/ac/1,1003,12-002324-00_18-001998-00_19-0013881-00_29-00A,00.asp.

Zatloukal, P., Petruzella, L., Zemanova M., Kolek, V., Skrickova, J., Pesek, M., et al. (2003). Gemcitabine plus cisplatin vs. gemcitabine plus carboplatin in stage IIIb and IV non-small cell lung cancer: A phase III randomized trial. *Lung Cancer*, 41, 321-331.

Zinner, R., Obasaju, C.K., Fossella, F.V., Papdimitrakopoulou, V.A., Pisters, K.M.W., et al. (2003). Alimta plus carboplatin (AC) in patients (pts) with advanced non-small cell lung cancer (NSCLC): A phase II trial [Abstract]. *Proceedings of the American Society of Clinical Oncology*, 22, 642. Abstract No. 2580.

Glossary

adenocarcinoma: in NSCLC, a cancer that begins in the lining of the lungs. The majority of lung adenocarcinomas develop peripherally.

angiogenesis: the formation of new blood vessels, which feed a growing tumor.

angiogenesis inhibitors: therapeutic agents that curb tumor growth by inhibiting the formation of new blood vessels that would otherwise nourish the growing tumor.

apoptosis: programmed cell death.

epidermal growth factor receptor–tyrosine kinase (EGFR-TK): an enzyme located inside the cell membrane involved in the cellular signaling process that leads to cell growth.

folate antagonists: therapeutic agents that inhibit one or more steps in the folate pathway, blocking the formation of nucleotides and thus disrupting DNA replication in malignant cells.

large cell carcinoma: cancer that features relatively large cells with prominent nucleoli and morphologic differentiation. Large cell carcinoma typically develops peripherally and accesses the lymphatic system, increasing the likelihood of distant metastasis.

matrix metalloproteinases (MMPs): in angiogenesis, enzymes that digest the cellular matrix, allowing an activated endothelial cell to migrate and divide.

mediastinum: the mass of organs and tissues separating the left and right lungs, containing the heart, trachea, esophagus, thymus, and lymph nodes.

monoclonal antibodies: agents that bind to the receptors or ligands outside the cell, preventing the receptor from dimerizing and thus disrupting the cellular signaling process.

Pancoast's syndrome: a cluster of symptoms, including pain in the shoulder or upper arm, indicating that a lung tumor has invaded the intrathoracic nerves.

pneumocytes: cells that form the alveoli of the lungs.

protein kinase C (PKC): a family of signal transduction proteins involved in cellular signaling from the exterior of the cell to the nucleus.

squamous cell carcinoma: cancer in which the squamous cells of the epithelium undergo abnormal growth. Squamous cell carcinomas usually develop centrally and often remain within the thoracic cavity.

tyrosine kinase inhibitors (TKIs): agents that inhibit EGFR-TK inside the cell by preventing cellular signaling after the receptor has bound a ligand.

SVC (superior vena cava) syndrome: condition in which advanced disease (cancer in the right lung or mediastinal lymph nodes) has caused compression of the superior vena cava. SVC syndrome represents an oncologic emergency.

vascular endothelial growth factor (VEGF): ligand released by tumor cells that binds to surface receptors on endothelial cells to activate tumor angiogenesis.

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- 1. Which of the following statements about lung cancer is TRUE?**

 - There are over 300,000 new cases of lung cancer yearly.
 - There are more deaths annually from lung cancer than prostate, breast, and colorectal cancers combined.
 - Lung cancer deaths continue to increase in men, but deaths for women have declined.
 - The incidence and mortality rates are 1/3 higher for white Americans than for African Americans.
- 2. What percentage of all lung cancers is related to smoking?**

 - 95%
 - 90%
 - 85%
 - 80%
- 3. Non-small cell lung cancer includes the following subtypes, except:**

 - adenocarcinoma
 - squamous cell carcinoma
 - oat cell carcinoma
 - large cell carcinoma
- 4. Which of the following new chemotherapeutic approaches for lung cancer is a targeted antifolate?**

 - nab-paclitaxel
 - ixabepilone
 - pemetrexed
 - epothilone B
- 5. Patients receiving folate antagonists should:**

 - be monitored for signs of malnutrition
 - receive prophylactic antiemetic treatment
 - not be scheduled for surgery during their treatment
 - receive folic acid and vitamin B₁₂ supplementation
- 6. The most common side effects seen with oral EGFR tyrosine kinase inhibitors (TKIs) are:**

 - rash and diarrhea
 - nausea and vomiting
 - headache and blurred vision
 - nausea and constipation
- 7. The angiogenesis cascade can be stopped by:**

 - inhibiting the action of VEGF
 - inhibiting the secretion of MMPs by endothelial cells
 - preventing migration and division of endothelial cells
 - all of the above.
- 8. Which of these statements about elderly patients with NSCLC is true?**

 - Performance status is more important than chronological age in predicting treatment outcomes.
 - Older patients are well represented in clinical trials.
 - Survival rates for older patients are lower than those in younger patients.
 - Age is a more important prognostic factor than extent of disease.

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Key: 1 = Poor 2 = Fair 3 = Satisfactory 4 = Excellent

1. To what degree did you achieve the goal of this activity?

The goal of this program is to teach oncology nurses about available treatment options for advanced non-small cell lung cancer and ways to implement treatment advances to improve patient outcomes.

1 2 3 4

2. To what degree did you achieve the following objectives?

Discuss the efficacy of treatment options for advanced non-small cell lung cancer.

1 2 3 4

Discuss strategies to maximize quality of life for those with advanced non-small cell lung cancer.

1 2 3 4

Identify ways to use treatment efficacy data for advanced non-small cell lung cancer to improve patient outcomes in your clinical practice.

1 2 3 4

3. How would you rate the teaching effectiveness of the editor? Nancy G. Houlihan, RN, MA, AOCN®

1 2 3 4

Based on previous experience and knowledge, the level of information in this program was:

1 = Too basic 2 = Appropriate 3 = Too complex

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- ____ B. Importance of topic
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Will this print piece assist you in providing effective patient care?

- ____ A. Yes ____ B. No

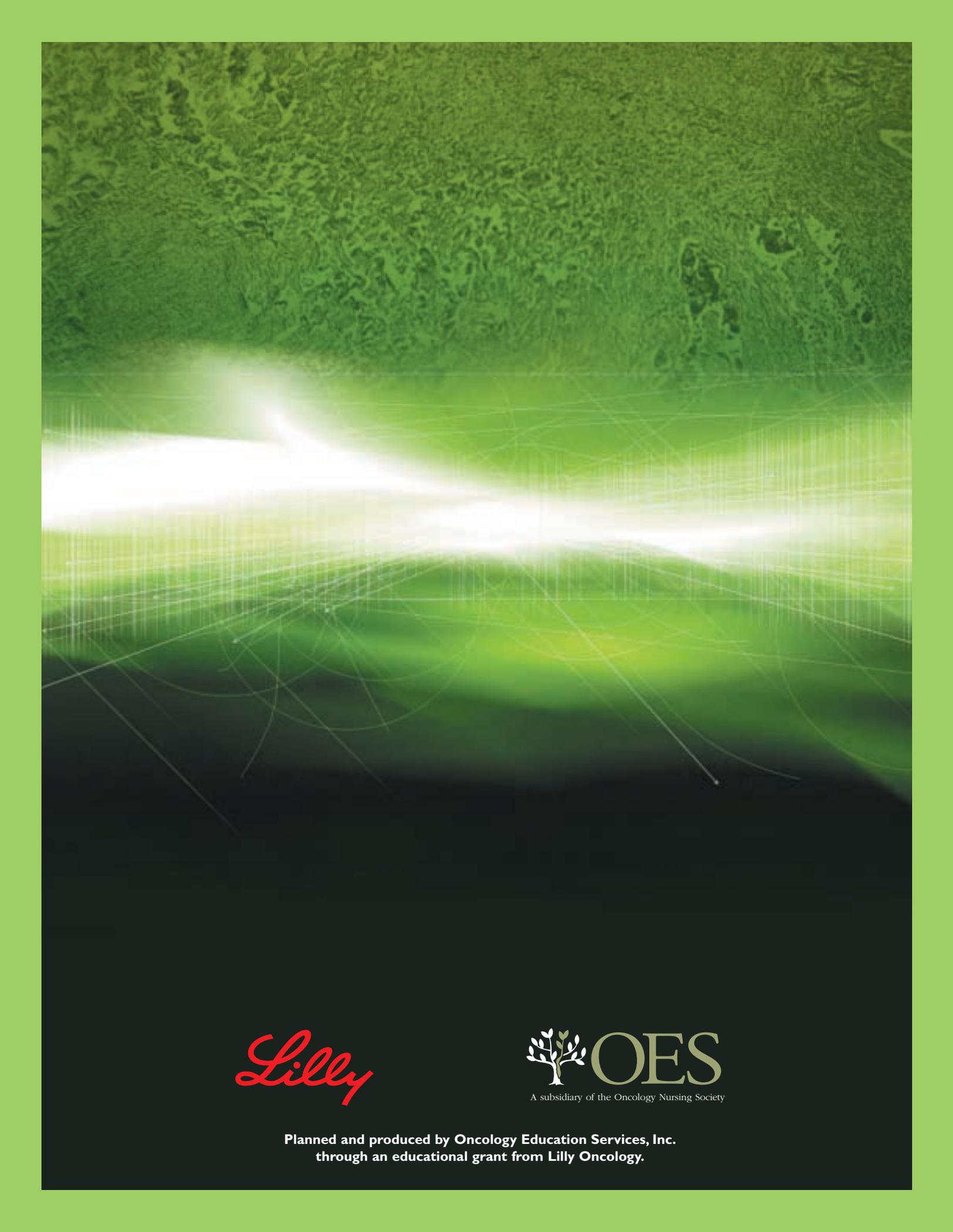
How will you modify your practice as a result of this monograph?

What topics would you like to see in the future?

Was this monograph free of commercial bias?

- ____ A. Yes ____ B. No

Comments and suggestions for improvements



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