IMPROVING THE CARE OF PATIENTS WITH NON-SMALL CELL LUNG CANCER: A Practical Guide for Performance Improvement

COMPLIMENTARY CME

This implementation guide is one of the educational activities available in Performance Improvement Strategies in Non-Small Cell Lung Cancer. This initiative offers a comprehensive series of activities designed to cover a broad range of topics on non-small cell lung cancer, with the ultimate goal of helping oncologists improve the care of patients with this condition. For additional information on this certified CME initiative or to view the other available activities, visit www.pi-iq.com/lungcancer.

Target Audience
The primary audience for this activity is medical oncologists and community oncologists.

Series Overview/Statement of Need
Lung cancer is a leading cause of cancer death, both in the United States and worldwide. A high proportion of patients with non-small cell lung cancer (NSCLC), which accounts for approximately 85% of lung cancer cases, present with extensive disease at the time of diagnosis. Five-year survival is typically low and varies widely with the stage of malignancy, from nearly half of patients with early-stage NSCLC to fewer than 5% of patients with metastatic disease. As a result, many clinical trials have been performed to help elucidate optimal treatment schema and prolong survival for patients with NSCLC; modest, positive advances have been made over the past several years.

Many topics of intense debate form the foundation of clinical practice gaps for the oncologists and other clinicians who manage the care of patients with NSCLC. These topics include the role of adjuvant therapy in patients with early-stage, resectable disease, as well as optimal treatment strategies and the role of maintenance therapy in patients with advanced disease. Furthermore, process barriers hampering the accurate determination of histologic subtype and tumor stage have important implications for treatment decisions and, in turn, may affect the consistent application of appropriate, evidence-based care in patients with NSCLC.

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PROGRAM DESCRIPTION

This performance improvement implementation guide is one of the educational activities available in Performance Improvement Strategies in Non-Small Cell Lung Cancer. This initiative offers a comprehensive series of activities designed to cover a broad range of topics on non-small cell lung cancer (NSCLC), with the ultimate goal of helping oncologists improve the care of patients with this condition.

The performance improvement track of this program guides physicians through a three-step process of assessing their current practice, implementing change to current practice, and evaluating the effects of the changes implemented. As part of the self-assessment process, healthcare professionals collect data retrospectively from 10 NSCLC patients in their practice and choose at least one of three benchmark areas to improve:

- Evaluation and staging
- Evidence-based surveillance and supportive care
- Evidence-based treatment

The suggestions offered for specific areas of care align with guideline and consensus statement recommendations and, where available, nationally recognized quality measures to encourage the delivery of evidence-based care.

THE PURPOSE OF THIS GUIDE

Although this guide can benefit all healthcare professionals who care for patients with NSCLC, it has primarily been designed to serve as a practical guide for those participating in the performance improvement track of this program. With this focus in mind, it offers targeted recommendations and practical tools that are specifically related to the measurable areas of care collected on the patient data forms, including diagnosis and staging, treatment, and follow-up.

This guide is not meant to be a comprehensive review of all possible options available for the treatment and long-term follow-up of patients with NSCLC; participants seeking this type of information should refer to clinical practice guidelines, such as those developed by the National Comprehensive Cancer Network (NCCN), the American Society of Clinical Oncology (ASCO), and the American College of Chest Physicians (ACCP). Instead, this guide will focus on key strategies outlined in guidelines and consensus statements, providing healthcare professionals with practical information and tools that can immediately be applied to practice. This information is integrated into a patient case, providing participants with the opportunity to envision how these tools can be used in their own practice.
INTRODUCTION

The National Cancer Policy Board (NCPB) was established in the 1990s to assess the quality of cancer care in the United States (US). They reviewed care across the entire continuum, from prevention to diagnosis, treatment, and palliation, and found that for many Americans with cancer, the reality of their care is far from the ideal. In fact, some patients did not receive care known to be effective for their condition. Among other findings, the NCPB highlighted the need to develop cancer care quality measures that could be used to increase accountability and improve clinical outcomes for patients.

Over the last decade, oncology organizations have responded to this call. ASCO initiated the National Initiative on Cancer Care Quality (NICCQ) in 2000 to evaluate the care of patients with breast and colorectal cancer, two of the most prevalent cancers in the US. ASCO also funded the development of the Quality Oncology Practice Initiative (QOPI), a comprehensive program designed by community oncologists to assess practice patterns across several different cancer types for use in individual oncology practices.

The current version of the QOPI measures includes several metrics specific to NSCLC (Table 1). These measures focus on treatment; however, quality measures can be used in clinical practice across the entire continuum, from diagnosis to surveillance. Although quality measures can be developed to evaluate the structure, process, or outcomes of care, the most relevant measures for gauging an individual practitioner’s performance are process measures. When directly linked to the desired outcome and derived from high-level evidence, such as randomized clinical trials and clinical practice guidelines, process measures serve as indicators for action.

This performance improvement implementation guide is based on quality metrics that have been developed in this fashion. It is designed to be a practical, action-oriented companion guide that will summarize the data behind the quality measures and provide helpful tips and tools that can be used to enhance adherence to evidence-based medicine in routine practice.

**Initial Office Visit for Newly Diagnosed Patient**

JP is a 70-year-old male smoker who was referred to you to discuss treatment options after surgery for early-stage NSCLC. He lives alone and retired from his job in sales about 6 years ago. At diagnosis, JP had no constitutional or organ-specific symptoms of lung cancer. A highly suspicious 5.2-cm mass in the periphery of the lower-left lobe was an incidental finding on a chest x-ray. Subsequent laboratory tests (complete blood count and serum chemistry panel) were within normal limits. A computed tomography (CT) scan of the chest confirmed the suspicious lesion but did not reveal enlarged mediastinal nodes or evidence of hepatic or adrenal gland involvement. After a negative positron emission tomography (PET) scan and mediastinoscopy, JP underwent a complete lobectomy approximately 5 weeks ago for clinical stage IB NSCLC (based on T2N0M0 classification). The pathology report indicates a squamous cell carcinoma. Surgical margins were clear, but cancer was found in one ipsilateral hilar lymph node.

**Pause and Reflect:** Were all appropriate staging tests completed? Did JP have clinical stage IB NSCLC? What is his pathologic stage?

### Table 1. NSCLC Quality Measures From the QOPI, Fall 2009

<table>
<thead>
<tr>
<th>MEASURE</th>
<th>DESIRABLE SCORE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjuvant chemotherapy recommended for patients with AJCC stage II or IIIA NSCLC</td>
<td>High score</td>
</tr>
<tr>
<td>Adjuvant chemotherapy received by patients with AJCC stage II or IIIA NSCLC</td>
<td>High score</td>
</tr>
<tr>
<td>Adjuvant cisplatin-based chemotherapy received within 60 days after curative resection by patients with AJCC stage II or IIIA NSCLC</td>
<td>High score</td>
</tr>
<tr>
<td>Adjuvant chemotherapy recommended for patients with AJCC stage I NSCLC</td>
<td>Low score</td>
</tr>
<tr>
<td>Adjuvant radiation recommended for patients with AJCC stage IB or II NSCLC</td>
<td>Low score</td>
</tr>
</tbody>
</table>

AJCC = American Joint Committee on Cancer.

*Score is based on the percentage of patients in the practice for whom the measure was met; for some measures, a high score indicates quality practice while for others, a low score indicates quality practice.

EVALUATION AND STAGING (BENCHMARK AREA 1)

DIAGNOSIS
When NSCLC is suspected, diagnostic tests are chosen to maximize the diagnostic yield and avoid unnecessary invasive procedures. An examination specimen can come from bronchial brushings, bronchial washings, fine-needle aspiration, core needle biopsy, endobronchial biopsy, or transbronchial biopsy. A diagnosis based on cytology findings is highly reliable, but sensitivity varies by tumor location. Often, a more invasive test is appropriate both for accuracy and, more recently, to yield sufficient tissue for histologic classification and evaluation of molecular markers. In cases where there is a solitary pulmonary nodule highly suspicious for malignancy, surgical resection without prior invasive testing is reasonable. For patients presenting with isolated extrathoracic metastasis, tissue diagnosis is recommended when feasible.

DETERMINING THE EXTENT OF THE DISEASE
After the diagnosis is confirmed, or for surgical candidates for whom the suspicion of NSCLC is high, it is critical to determine the extent of disease to identify the most appropriate treatment option and/or clinical trial. The presence of distant metastasis and the status of mediastinal lymph nodes are two critical determinants of subsequent treatment for NSCLC. The majority of cancers are initially detected on chest x-ray, but this modality is an insensitive measure of mediastinal lymph node status. Therefore, CT scan of the chest should be performed in all patients with lung cancer for whom further treatment is planned and who are amenable to further evaluation. The use of IV contrast is generally recommended to distinguish vascular structures from lymph nodes and to identify mediastinal invasion by central tumors. The scan should extend to include the liver and adrenal glands, common sites of metastatic disease.

If there is no evidence of distant metastasis on CT scan, fluorodeoxyglucose (FDG)-PET scanning is then recommended for further mediastinal and extrathoracic staging. If PET scan results are positive in the mediastinum, or if enlarged discrete mediastinal nodes were identified on chest CT (> 1 cm in shortest transverse axis), invasive evaluation is warranted before proceeding to definitive treatment of the primary tumor. Mediastinoscopy or endobronchial ultrasound biopsy should also be considered for patients if imaging results are not conclusive and/or the probability of involvement is high (based on tumor size and location). Because of the low prior probability of lymph node involvement in patients with peripheral T1 lesions, invasive evaluation of the mediastinum is not routinely conducted in patients with negative PET scan results and a peripheral T1 lesion (NCCN) or peripheral clinical stage I disease (ACCP). Chest MRI is not indicated for staging the mediastinum. Site-specific symptoms warrant further evaluation with appropriate imaging tests, but routine brain MRI and bone scans are not usually recommended for asymptomatic patients, with the following exceptions:

- The NCCN recommends brain MRI for all patients with stage II, III, or IV disease who are considered for aggressive combined-modality therapy to rule out metastasis
- The ACCP and ASCO recommend imaging for extrathoracic metastases (eg, head CT scan/MRI plus whole body PET or bone scan plus abdominal CT) for all patients with clinical stage III disease who are being considered for aggressive local therapy

JP appears to have undergone an appropriate staging work-up based on current clinical practice guidelines. According to the NCCN guidelines, mediastinoscopy was appropriate given the peripheral T2 lesion, and brain MRI was not warranted for clinical stage I disease.

TNM STAGING: MIGRATING TO THE 7TH EDITION
The TNM system describes the anatomical extent of disease based on the assessment of three components, which are then grouped to determine stage:

- T—the extent of the primary tumor
- N—the absence or presence and extent of regional lymph node metastasis
- M—the absence or presence of distant metastasis

For much of this decade, lung cancer staging has been based on the 6th edition of the AJCC Cancer Staging Manual. Beginning in 2010, clinicians are expected to migrate to the 7th edition staging criteria, which are considerably different. The new staging system was developed using data from approximately 100,000 lung cancer patients treated around the world, which is a much larger and more diverse group than that used to develop previous criteria. As a result, the new system creates more homogeneous and distinct stage grouping with respect to survival. Clinicians will have improved prognostic information with this new system and will be able to more accurately group patients for future clinical trials.

Tool 1, which can be found at the end of this guide, has been developed to increase familiarity with the new TNM system and corresponding disease stages. Perhaps the most clinically significant changes to be aware of with the revised staging system are:

- Upstaging of patients with T2bN0M0 from stage IB to IIA
- Downstaging of patients with T2aN1M0 from stage IIB to IIA
- Downstaging of patients with T4N0-1M0 from stage IIIB to IIA

Based on the revised staging criteria that were published in late 2009, JP would no longer be considered to have had clinical stage IB NSCLC. Instead, JP would now be classified as clinical T2bN0M0 (stage IIA) and pathologic T2bN1M0 (stage IIB), as described above.
**TABLE 2. Comparison of the 6th and 7th Editions of TNM Definitions for Lung Cancer**

<table>
<thead>
<tr>
<th>DESCRIPTOR</th>
<th>6TH EDITION</th>
<th>7TH EDITION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T - PRIMARY TUMOR</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in the sputum or bronchial washings but not visualized by imaging or bronchoscopy</td>
<td>No change</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
<td>No change</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
<td>No change</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (ie, not in the main bronchus)</td>
<td>Same description with creation of two subgroups: • T1a: tumor 2 cm or less in greatest dimension • T1b: tumor more than 2 cm but not more than 3 cm in greatest dimension</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor with any of the following features, size, or extent: • More than 3 cm in greatest dimension • Involves main bronchus, 2 cm or more distal to the carina • Invasive visceral pleura • Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung</td>
<td>Same description, except that tumor size criterion is refined to include tumors more than 3 cm but not more than 7 cm; also creates two subgroups: • T2a: tumor more than 3 cm but not more than 5 cm in greatest dimension • T2b: tumor more than 5 cm but not more than 7 cm in greatest dimension</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor of any size that directly invades any of the following: chest wall (including superior sulcus tumors), diaphragm, mediastinal pleura, parietal pericardium; or tumor in the main bronchus less than 2 cm distal to the carina, but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung</td>
<td>Tumor more than 7 cm or one that directly invades any of the following: chest wall (including superior sulcus tumors), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium; or tumor in the main bronchus less than 2 cm distal to the carina but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, esophagus, vertebral body, carina; separate tumor node(s) in the same lobe; or tumor with malignant pleural effusion[^1]</td>
<td>Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina; separate tumor node(s) in a different ipsilateral lobe to that of the primary</td>
</tr>
</tbody>
</table>

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[^1]: T1a also includes the uncommon superficial spreading tumor of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus

[^2]: Most effusions are due to tumor; however, when multiple microscopic examinations are negative for tumor, fluid is non-bloody and is not an exudate, and clinical judgment dictates that the effusion is not related to the tumor, the effusion should be excluded as a staging element

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EVIDENCE-BASED SUPPORTIVE CARE (BENCHMARK AREA 2)

Distress is an increasingly recognized issue for patients with cancer. The NCCN defines distress as “a multifactorial unpleasant experience of an emotional, psychological, social, or spiritual nature that interferes with the ability to cope with cancer, its physical symptoms, and its treatment.”16 As many as 40% of cancer patients experience distress, but fewer than 10% are referred for or receive psychosocial support.16 According to the NCCN, patients with an increased risk of experiencing distress include those with16:

- History of psychiatric disorder, substance abuse, depression, suicide attempt, physical or sexual abuse
- Cognitive impairment
- Communication barriers (eg, language, literacy, physical barriers)
- Severe comorbid illnesses
- Social issues (eg, family/caregiver conflicts, inadequate social support, living alone, financial problems, limited access to medical care, young/dependent children)
- Younger age or female gender
- Spiritual or religious concerns

JP attends the office visit alone. He appears somewhat stoic and states that he brought this illness on himself by smoking for the last 40 years. He asks whether he should try to quit smoking again now that he has lung cancer or whether it is too late to make a difference. He says he has tried to quit cold turkey in the past, but always ends up smoking again. He somberly states that it probably doesn’t matter anyway now that he has a terminal illness. He says that the surgeon told him he might be cured, but he can’t help feeling like his diagnosis is a death sentence.

Pause and Reflect: What tools could be used to more accurately gauge JP’s emotional state? What should you tell him about smoking cessation, and what can you offer him to increase the likelihood that he will quit smoking if he tries again?

SMOKING CESSATION

Smoking cessation should be encouraged for all patients with lung cancer.18,19 This recommendation may be particularly important for patients treated with curative-intent therapy, as smoking cessation at the time of lung cancer diagnosis may reduce the risk of metachronous tumors.18 In addition, patients who continue to smoke after lung cancer surgery have worse quality of life compared with never-smokers and former smokers.19 Older smokers (over 65 years of age) who quit can also reduce their risk of death from coronary heart disease and chronic obstructive pulmonary disease (COPD).20 Notably, Medicare covers tobacco dependence treatment, including prescription medications (through Medicare Part D), for these patients.20

Successful smoking cessation remains a challenge for many patients.20 Intensive programs offer the greatest potential for benefit and should include counseling and behavioral therapy, pharmacologic agents, and

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**TABLE 3. Comparison of 6th and 7th Editions of Stage Groupings of TNM Subsets for Lung Cancer**

<table>
<thead>
<tr>
<th>STAGE</th>
<th>6TH EDITION</th>
<th>7TH EDITION</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T</td>
<td>N</td>
</tr>
<tr>
<td>0</td>
<td>Tis</td>
<td>N0</td>
</tr>
<tr>
<td>IA</td>
<td>T1</td>
<td>N0</td>
</tr>
<tr>
<td>IB</td>
<td>T2</td>
<td>N0</td>
</tr>
<tr>
<td>IIA</td>
<td>T1</td>
<td>N1</td>
</tr>
<tr>
<td>IIIB</td>
<td>T2</td>
<td>N1</td>
</tr>
<tr>
<td>IIIA</td>
<td>T3</td>
<td>N0</td>
</tr>
<tr>
<td>IIIB</td>
<td>T4</td>
<td>N0-2</td>
</tr>
<tr>
<td>IV</td>
<td>Any T</td>
<td>N3</td>
</tr>
<tr>
<td></td>
<td>Any T</td>
<td>Any N</td>
</tr>
</tbody>
</table>

regular follow-up to increase abstinence rates. Individual, group, and telephone counseling are all effective; effectiveness increases with intensity and when used in combination with medication, such as bupropion SR (sustained-release), varenicline, and nicotine products such as gum, inhalers, lozenges, nasal spray, and patches. Careful consideration must be given to the patient’s history, medication preference, likely side effects, and contraindications when choosing a first-line pharmacologic therapy.20

Simple changes in clinical practice can increase physician awareness of each patient’s smoking status and help patients reach their abstinence goal, such as:

- Including tobacco use status in the vital signs that are collected at each office visit
- Using chart stickers or computer prompts to document status as current, former, or never-smoker
- Providing self-help brochures and lists of local resources, such as support groups and counseling programs; a list of quit-line phone numbers in each state and other resources are available from PACT (Professional Assisted Cessation Therapy) at www.endsmoking.org

**TABLE 4. Comparison of Clinical Practice Guideline Recommendations for Adjuvant Therapy in Completely Resected NSCLC**

<table>
<thead>
<tr>
<th>STAGE</th>
<th>ACCP 2007</th>
<th>ASCO 2007</th>
<th>NCCN 2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>Neither adjuvant chemotherapy nor RT are recommended</td>
<td>Neither adjuvant chemotherapy nor RT are recommended</td>
<td>Chemotherapy may be considered for patients with negative surgical margins and high-risk features; patients with positive surgical margins may undergo re-resection (± chemotherapy), chemoradiation (± chemotherapy), or RT</td>
</tr>
<tr>
<td>IB</td>
<td>Patients with good PS should receive platinum-based adjuvant chemotherapy; postoperative RT decreases local recurrence but does not affect survival and therefore is not recommended</td>
<td>Cisplatin-based chemotherapy is recommended; postoperative RT is not recommended</td>
<td>Chemotherapy can be considered when margins are negative; when margins are positive, re-resection with chemotherapy or chemoradiation and chemotherapy are recommended</td>
</tr>
<tr>
<td>IIA</td>
<td>Patients with incidental (occult) N2 disease found at time of resection and good PS should receive adjuvant platinum-based chemotherapy; adjuvant postoperative RT should be considered after chemotherapy to reduce local recurrence</td>
<td>Cisplatin-based chemotherapy is recommended for completely resected disease; postoperative RT is controversial and not recommended for routine use; RT recommendation may change pending results of ongoing trial</td>
<td>For T1-2, N1 disease, chemotherapy is recommended; chemoradiation + chemotherapy can be considered for adverse factors</td>
</tr>
<tr>
<td>IIB</td>
<td>Patients with incidental (occult) N2 disease found at time of resection and good PS should receive adjuvant platinum-based chemotherapy; adjuvant postoperative RT should be considered after chemotherapy to reduce local recurrence</td>
<td>Cisplatin-based chemotherapy is recommended for completely resected disease; postoperative RT is controversial and not recommended for routine use; RT recommendation may change pending results of ongoing trial</td>
<td>Chemotherapy (plus mediastinal RT) is recommended for patients with T1-2 and incidental (occult) N2 disease found at time of resection if margins are negative; chemoradiation plus chemotherapy is recommended if margins are positive</td>
</tr>
</tbody>
</table>

ACCP = American College of Chest Physicians; ASCO = American Society of Clinical Oncology; NCCN = National Comprehensive Cancer Network; PS = performance status; RT = radiation therapy.

Note that stages listed here are based on the 6th edition of the TNM classification system that was in use when the guidelines were developed.

High-risk disease includes poorly differentiated tumor, vascular invasion, wedge resection, and minimal margins.

Category 3 level of evidence, which indicates that there is some evidence to support the recommendation, but there was major disagreement among NCCN panel members.

Category 2b level of evidence, which indicates lower-level evidence and non-uniform agreement among panel members, but no major disagreement.

Adverse factors include inadequate mediastinal lymph node dissection, extracapsular spread, multiple positive hilar lymph nodes, and close margins.

Recall that JP is a 70-year-old male with stage IIB squamous cell NSCLC, according to the latest staging criteria. His history and physical exam are remarkable for moderate COPD, which is generally well-controlled with use of a daily long-acting bronchodilator inhaler, and stage I hypertension, which is controlled with diuretic therapy. His cardiac, renal, and liver functions are within normal limits. Recall also that JP has expressed some skepticism about his prognosis. He arrived at the appointment unsure that any additional therapy will be worth the risks.

**Pause and Reflect:** What is the potential benefit of chemotherapy for JP? How will you explain the risks and benefits to him? If recommending treatment, what regimen will you choose?

Adjuvant chemotherapy is now clearly established as a standard of care for stage II and stage IIIA NSCLC.
(Table 4), although none of the recommended regimens are currently indicated for use in early-stage disease. In Canada, referrals for adjuvant chemotherapy have increased substantially since presentation of the first positive adjuvant data in 2004, although older patients may not be referred at the same rate as younger patients. Research is needed in the US to determine referral patterns and usage trends, but the importance of adjuvant chemotherapy is reflected in the QOPI measures for NSCLC, all of which currently focus on its appropriate use (refer back to Table 1).

THE SURVIVAL BENEFIT OF CHEMOTHERAPY

Table 5 summarizes the multiple studies that have been completed to evaluate adjuvant platinum-based chemotherapy for NSCLC. Notably, all studies that included multiple stages of disease initially showed statistically significant improvements in overall survival (OS) at 5 years. The benefit associated with chemotherapy dissipated with time in the IALT study, but not in the ANITA or JBR.10 trials. One possible explanation for these differences is that both ANITA and JBR.10 combined cisplatin with the third-generation agent vinorelbine, while IALT allowed the use of several different cisplatin combinations, some of which included older, possibly less-active drugs. Another possible explanation recently proposed by the IALT investigators is that chemotherapy produces a differential effect on OS in the early versus late years of follow-up. Up to 5 years, there is a significant difference (P = 0.01) in OS in favor of chemotherapy, but after 5 years, it appears that having received chemotherapy is actually deleterious due to an excess of noncancer-related deaths (P = 0.04); the test for interaction between these two time periods was significant (P = 0.006). These results highlight the need for long-term patient follow-up and research into identifying promising new agents.

TABLE 5. Randomized Clinical Trials of Adjuvant Chemotherapy for NSCLC

<table>
<thead>
<tr>
<th>STUDY</th>
<th>POPULATION</th>
<th>REGIMEN</th>
<th>OS IMPROVEMENT WITH CHEMOTHERAPY*</th>
</tr>
</thead>
<tbody>
<tr>
<td>IALT</td>
<td>I-III</td>
<td>Cisplatin, given as either • 80 mg/m² on days 1, 22, 43, 64 • 100 mg/m² on days 1, 29, 57 • 100 mg/m² on days 1, 29, 57, 85 • 120 mg/m² on days 1, 29, 71 Plus either: • Vinodesine® 3 mg/m² weekly days 1-29, then Q2W after day 43 • Vinblastine® 4 mg/m² weekly days 1-29, then Q2W after day 43 • Vinorelbine 30 mg/m² weekly • Etoposide® 100 mg/m²/day days 1-3 with each dose of cisplatin</td>
<td>Absolute ↑ in OS at 5 years: 3.9%; HR for OS at 8 years: 0.91 (P = 0.10)</td>
</tr>
<tr>
<td>ANITA</td>
<td>IB-IIIA</td>
<td>Vinorelbine 30 mg/m² weekly x 16 plus Cisplatin 100 mg/m²/day 1 Q4W x 4 cycles versus observation</td>
<td>Absolute ↑ in OS at 5 years: 8.6%; Absolute ↑ in OS at 7 years: 8.4%</td>
</tr>
<tr>
<td>JBR.10</td>
<td>IB-II</td>
<td>Vinorelbine 25-30 mg/m² weekly x 16 plus Cisplatin 50 mg/m² days 1 and 8 Q4W x 4 cycles versus observation</td>
<td>Absolute ↑ in OS at 5 years: 11%; HR for OS at 9.3 yrs median follow-up: 0.78</td>
</tr>
<tr>
<td>CALGB 9633</td>
<td>IB (N = 304)</td>
<td>Paclitaxel 200 mg/m² plus Carboplatin AUC 6 mg/mL/minute Q3W x 4 cycles versus observation</td>
<td>HR for OS: 0.83 (P = 0.12)</td>
</tr>
</tbody>
</table>

ANITA = Adjuvant Navelbine International Trialist Association trial; CALGB = Cancer and Leukemia group B; HR = hazard ratio; IALT = International Adjuvant Lung Cancer Trial; OS = overall survival.

*All outcomes statistically significant unless otherwise indicated

- Vinodesine is not commercially available in the US.
- Drug is not currently indicated for use in NSCLC.


Improving the Care of Patients With Non-Small Cell Lung Cancer
ing factors that predict patient response to adjuvant chemotherapy.

The only trial of carboplatin-based therapy, CALGB 9633, was limited to patients with stage IB disease, and it failed to show a survival benefit with chemotherapy relative to observation.\textsuperscript{22} A subgroup analysis of CALGB 9633 suggested that there may be a survival benefit for patients with tumors 4.0 cm and greater (hazard ratio [HR]: 0.69; \( P = 0.043 \)), but not for those with smaller tumors (HR: 1.12, \( P = 0.32 \)).\textsuperscript{22} Updated data from JBR.10 suggest a similar trend: patients with tumors less than 4 cm had poorer survival when treated with chemotherapy (HR: 1.73, \( P = 0.06 \)), while those with tumors 4 cm or greater had a trend toward improved survival with chemotherapy relative to observation (HR: 0.66, \( P = 0.13 \); \( P = 0.02 \) for test of interaction between size and treatment).\textsuperscript{24} Importantly, with the new staging system, some patients with large tumors (between 5 cm and 7 cm) who were previously classified as having stage IB disease will now be classified as having stage II disease. Although clinical practice guidelines do not yet reflect the new International Association for the Study of Lung Cancer (IASLC) staging system, it seems reasonable to consider chemotherapy for these upstaged patients based on the currently available data.

Two meta-analyses that include the most recent adjuvant data provide further support of its benefit after surgery for NSCLC.\textsuperscript{20,21} The LACE pooled individual patient data from the five largest adjuvant studies conducted in the current era and found that cisplatin-based chemotherapy reduced the risk of death by 11\% (HR: 0.89, \( P = 0.005 \)) and produced a 5.4\% absolute survival benefit at 5 years.\textsuperscript{21} Again, benefit varied by stage, with the reduction in the risk of death significant for patients with stage II and stage III NSCLC, but not for those with stage IA or IB NSCLC. The benefit of chemotherapy was greatest in patients with good performance status (PS). A second study was conducted using a Bayesian statistical analysis, which facilitates sequential evaluations as new data emerge and determines the probability that a therapy produces a certain outcome.\textsuperscript{24} This meta-analysis included data from IALT, JBR.10, and ANITA and found that the probability of a 4\% absolute improvement in survival at 5 years due to chemotherapy increased from 64\% when IALT is considered alone to 82\% after inclusion of ANITA and JBR.10 results. Moreover, for stage II and III, this analysis supports a 6\% absolute survival benefit with 90\% probability and a 12\% benefit with 50\% probability.\textsuperscript{24}

Note that both of these meta-analyses considered trials in which cisplatin, rather than carboplatin, was evaluated. Currently, the only published randomized phase III trial that included carboplatin-based adjuvant chemotherapy is CALGB 9633, which was conducted in stage IB disease. It is currently unclear what effect the substitution of carboplatin for cisplatin might have in the adjuvant setting. Meta-analyses of studies conducted in advanced NSCLC support the superiority of cisplatin over carboplatin with respect to survival in one analysis and response rate in another.\textsuperscript{25,26} A third analysis provides additional indirect evidence of the superiority of cisplatin over carboplatin. In this meta-analysis, cisplatin-based therapy for advanced NSCLC significantly improved survival and response rates relative to non-platinum-based therapy, but carboplatin-based therapy did not.\textsuperscript{34} Cisplatin and carboplatin, however, have different safety profiles. Cisplatin is associated with greater rates and severity of nausea and vomiting, while carboplatin is associated with more thrombocytopenia.\textsuperscript{29,30} Until there are compelling efficacy data in the adjuvant setting, practice guidelines generally recommend cisplatin over carboplatin.\textsuperscript{25,26} More specifically, the NCCN recommends the adjuvant use of carboplatin only for patients with comorbidities or an inability to tolerate cisplatin.\textsuperscript{2}

### Treatment in Elderly Populations

Another consideration regarding the appropriateness of adjuvant chemotherapy for JP is his age. Approximately 50\% of patients diagnosed with NSCLC are 65 years of age or older, but elderly patients are frequently underrepresented in clinical trials, making it difficult to determine optimal treatment for these patients.\textsuperscript{32} The European Organization for Research and Treatment of Cancer (EORTC) and International Society for Geriatric Oncology (SIOG) have recently published guidelines for treating elderly patients with NSCLC, generally defined as patients 70 years of age and older.\textsuperscript{33} These organizations report that elderly patients appear to derive the same benefit from adjuvant chemotherapy as their younger counterparts, without increased toxicity. These conclusions are based on a pooled analysis of the trials included in LACE and a fully published subgroup analysis from JBR.10.\textsuperscript{30,37} LACE included 3,269 patients under 65 years of age, 901 patients 65 to 69 years of age, and 414 patients 70 and older. Although the elderly received significantly lower total doses of cisplatin and fewer total cycles of chemotherapy, survival was not compromised. The hazard ratios of death were 0.86, (95\% CI: 0.78-0.94), 1.01 (95\% CI: 0.85-1.21), and 0.90 (95\% CI: 0.70-1.16; test for trend: \( P = 0.29 \)) for the age groups, respectively.\textsuperscript{36} The JBR.10 analysis defined elderly as older than 65 years of age and found similar results. Elderly patients received less chemotherapy than the younger patients, yet the survival benefit was maintained relative to observation (HR: 0.61, \( P = 0.04 \)).\textsuperscript{37} Thus, treatment decisions should not be based solely on age but rather on estimated absolute benefit, life expectancy, treatment tolerance, cognition, comorbidities, and patient preference.\textsuperscript{35} Importantly, however, the risks and benefits for patients over the age of 75 do require additional study. Only 12 patients over the age of 75 participated in JBR.10, and only 61 were included in
LACE, making it difficult to determine safety and efficacy in this group at this time.

Taking all of this information into consideration, JP appears to be a candidate for adjuvant chemotherapy. Nonetheless, it remains difficult to quantify the potential risks and benefits for any individual patient, given the complex interplay of medical, psychological, and social issues that the patient is also experiencing. 22

CONVEYING THE BENEFITS OF TREATMENT

There are several relatively straightforward tools that can be used to help patients understand the potential benefits of treatment. Adjuvant! Online (www.adjuvantonline.com) contains an interactive tool that can be customized for patients who have undergone definitive surgery and pathologic staging for NSCLC. It is important to understand the assumptions behind the Adjuvant! algorithms, which in this case include an assumption that stages IB to IIA benefit equally from platinum-based adjuvant chemotherapy with a proportional risk reduction of 20%. As previously reviewed, this assumption is questionable at best, and patients with stage IB disease (as defined by the updated TNM definitions) are unlikely to benefit from adjuvant chemotherapy. Nonetheless, the tool may be useful in the current patient case because JP has pathologic stage IIB disease, and adjuvant chemotherapy has demonstrated a benefit in this population. Using JP’s data in this tool, we find that without chemotherapy, among a group of 100 patients with pathologic stage IIB disease similar to JP, approximately 27 will be alive in 5 years but 61 will have died from cancer. With chemotherapy, an additional 7 patients are alive in 5 years.

Data from clinical trials can also be used to estimate potential benefit. ASCO published a graphical representation of estimated survival risks and benefits from pivotal studies, by stage, in their most recent practice guideline. 24 Tool 3 in this guide is an adaptation of that figure, specific for stage II/III NSCLC. Another way to estimate benefit with clinical trial data is to calculate the number-needed-to-treat (NNT). The NNT estimates how many patients must be treated to attain one additional outcome of interest, in this case, survival. The NNT is the reciprocal of the absolute treatment benefit. Using data from JBR.10 as an example, we can calculate the NNT for adjuvant cisplatin/vinorelbine. The absolute survival benefit associated with this chemotherapy regimen at 5 years was 11%. The reciprocal of 11% (1.0/0.11) is 9, meaning that 9 patients need to be treated with chemotherapy for one additional patient to be alive at 5 years. There is no way to know whether JP will be that one patient, but these types of tools can help make complex clinical trial results more easily understood by patients and facilitate shared decision making, which can improve patients’ satisfaction with their care. 22

The NCCN estimated that, in the year 2000, more than 300,000 patients were living with lung cancer in the US. 8 Appropriate follow-up care for these patients includes consideration of two major issues: managing complications associated with curative-intent treatment and performing surveillance for recurrence and/or development of a new primary lesion. 18 Specialists must be involved in the first 3 to 6 months of follow-up, including the surgeon who will manage surgical complications and the oncologist who will evaluate chemotherapy complications. Ideally, the subsequent plan for surveillance would be coordinated through a multidisciplinary team. 18

The ACCP and NCCN recommendations for surveillance after curative-intent treatment for NSCLC include interval history, physical examinations, and imaging studies conducted every 4 to 6 months for the first 2 years, then annually. 8,18 The ACCP recommends either chest x-ray or CT, while the NCCN specifically recommends contrast-enhanced spiral CT scan during the first 2 years, followed by non-contrast-enhanced CT annually thereafter. Both organizations also recommend assessing smoking status at each office visit, with appropriate referral and follow-up for cessation when needed, and the NCCN guidelines include the following recommendations:

- Immunizations (eg, annual influenza vaccination; pneumococcal vaccination, with revaccination as appropriate)
- Counseling for wellness and health promotion (eg, maintenance of a healthy weight, adoption of physically active lifestyle, consumption of healthy diet, and limited alcohol intake)
- Additional health monitoring (eg, routine blood pressure, glucose, and cholesterol monitoring, bone density testing as appropriate, routine dental examinations, routine sun protection)

Tool 4 provides a checklist based on the NCCN guidelines that oncologists can use to ensure that patients are receiving appropriate long-term care.

EVIDENCE-BASED SURVEILLANCE
(BENCHMARK AREA 2)

JP decides to undergo systemic treatment, and, over the next few weeks, he completes three cycles of cisplatin/vinorelbine. The first cycle was generally well tolerated, but the second and third cycles were complicated by increasing peripheral neuropathy and fatigue. JP decides not to complete the fourth cycle, which is not uncommon among older patients in this setting. 25,27

Pause and Reflect: How soon do you need to see JP for follow-up? What constitutes appropriate long-term surveillance after curative-intent treatment for NSCLC?
EVIDENCE-BASED TREATMENT OF ADVANCED NSCLC
(BENCHMARK AREA 3)

Chemotherapy improves survival in advanced NSCLC, but appears to be underused in community settings, with significant variation reported based on race and geographic region within the US. Reasons for these discrepancies are not clear, but they suggest that the use of chemotherapy in advanced NSCLC is a reasonable metric for clinicians to assess their practice patterns relative to the evidence base.

FIRST-LINE THERAPIES
As shown in Table 6, professional organizations concur that a chemotherapy doublet should be considered for patients with advanced NSCLC and a good PS. Decisions are more complicated for elderly patients and those with poor PS (defined as Eastern Cooperative Oncology Group [ECOG] PS 2; see Tool 5); some of these patients may be able to tolerate doublet therapy, while others may be best treated with single-agent chemotherapy. The SIOG recommends single-agent docetaxel, gemcitabine, or vinorelbine for the first-line treatment of elderly patients with advanced NSCLC. Furthermore, they advise against the use of bevacizumab in elderly patients due to the potential for increased toxicity. Data are extremely limited for octogenarians; these patients may be good candidates for clinical trials of oral agents.

Taking a closer look at the evidence behind the guidelines reveals several important findings:
- Cisplatin is superior to carboplatin with respect to extending survival in this setting, yet no platinum-based regimen is recommended over another.
- Non-platinum-based doublets with demonstrated activity and reasonable tolerability can be used, particularly for patients with contraindications to platinum therapy.
- Histology is now an important consideration when choosing a chemotherapy regimen.
- The monoclonal antibodies bevacizumab and cetuximab may be used as a third drug in combination with chemotherapy for patients meeting criteria similar to those required in their respective pivotal trials; however, only bevacizumab is currently approved for this use by the US Food and Drug Administration (FDA).
- Therapy directed against specific molecular targets is emerging as a potential option for improving outcomes while maintaining a good quality of life for patients with advanced NSCLC.

Several analyses support the superiority of cisplatin over carboplatin in advanced disease, as reviewed earlier in this guide. However, the guidelines do not necessarily recommend cisplatin over carboplatin in the palliative setting, providing clinicians with a wealth of options for combination therapy. The choice between cisplatin and carboplatin should be based on individual patient factors and consideration of the side effect profile of each agent. ASCO states that cisplatin and carboplatin can be combined with any of the following third-generation cytotoxics to create a two-drug regimen for first-line therapy:
- Docetaxel
- Gemcitabine
- Irinotecan
- Paclitaxel
- Pemetrexed
- Vinorelbine

All of these agents are approved by the FDA for the first-line treatment of advanced NSCLC, with the exception of irinotecan; in addition, pemetrexed is indicated only for patients with non-squamous disease.

Non-platinum-based regimens with demonstrated activity can also be considered for first-line treatment, although ASCO recommends these regimens only for patients with contraindications to platinum therapy (eg, allergy, baseline hearing loss, renal insufficiency, intolerable nausea despite antiemetic prophylaxis, intolerance to corticosteroids used as antiemetics). Recent meta-analyses support the superiority of platinum-based chemotherapy and, more specifically, cisplatin-based chemotherapy over non-platinum-based chemotherapy in this setting. Because treatment is non-curative in this setting, however, the risk-to-benefit ratio for any given patient is clearly different than in the adjuvant setting, leading to a greater

Pause and Reflect: Is treatment appropriate for JP? If so, what are his treatment options?

JP does well for the first 4 years after completing chemotherapy. During his 5th year of follow-up, JP develops right-sided abdominal pain, with slight conjunctival icterus. A chest CT reveals enlarged nodes in the contralateral mediastinum, and additional work-up confirms metastatic disease in the liver. JP is now 74 years old. He has continued to have COPD exacerbations about once or twice per year and currently takes two medications for hypertension, including a diuretic and an angiotensin-converting enzyme (ACE) inhibitor. His liver function tests are three to four times the upper limits of normal, and a recent physical examination shows some age-related declines, with an estimated glomerular filtration rate of 30 mL/min. He states that he is still enjoying retirement and able to take care of things around his house on his own. He gets tired and naps some afternoons, but he feels like he is still in pretty good shape for his age. He is interested in further treatment, but only if he can avoid some of the side effects he experienced with his earlier regimen.

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range of treatment options that can be tailored based on safety profiles.

Histology is also emerging as an important consideration for the choice of cytotoxic agent. The results of a recent noninferiority trial comparing a combination of cisplatin/pemetrexed to cisplatin/gemcitabine for the first-line treatment of advanced NSCLC support the equivalence of the regimens overall. Results of preplanned subgroup analyses, however, demonstrated differential effects based on histology. OS was significantly longer with cisplatin/pemetrexed versus cisplatin/gemcitabine in patients with adenocarcinoma (12.6 vs. 10.9 months, respectively; $P = 0.03$) and large-cell carcinoma (10.4 months vs. 6.7 months, respectively; $P = 0.03$). Conversely, for patients with squamous cell histology, survival was significantly longer with cisplatin/gemcitabine (10.8 months vs. 9.4 months, respectively; $P = 0.05$). The authors postulated that this differential effect might be due to the increased baseline expression of thymidylate synthase (TS) gene and protein seen in squamous NSCLC relative to other histologies. Over expression of TS is associated with reduced sensitivity to pemetrexed in laboratory studies. Based on these data, the NCCN recommends the combination of cisplatin/pemetrexed for patients with PS0/1, previously untreated, non-squamous advanced NSCLC. In fact, pemetrexed is specifically indicated for first-line use only in conjunction with cisplatin for patients with advanced, non-squamous NSCLC.

Although three-drug cytotoxic regimens have no documented efficacy in this setting, there are now three-drug, monoclonal antibody-based regimens proven safe and effective in select patients. The ECOG evaluated the addition of bevacizumab to paclitaxel/carboplatin in the

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**TABLE 6. Comparison of Clinical Practice Guideline Recommendations for the First-Line Treatment of Advanced NSCLC**

<table>
<thead>
<tr>
<th>PATIENT CHARACTERISTIC</th>
<th>ACCP 2007</th>
<th>ASCO 2009</th>
<th>NCCN 2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good PS</td>
<td>Two-drug combination therapy</td>
<td>• Two-drug combination therapy; platinum-based regimens are preferred</td>
<td>• Two-drug combination therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Stop regimen at time of progression or after 4 cycles if no response</td>
<td>• Stop regimen at time of progression or after 4 cycles if no response</td>
</tr>
</tbody>
</table>
|                       |           | • After 6 cycles for all other patients | • After 6 cycles for all other patients | • Cetuximab may be added to cisplatin/vinorelbine for patients who meet criteria
d | • Cetuximab can be added to cisplatin/vinorelbine for patients who meet usage criteria
d
| PS2                   | Chemotherapy may improve response rates and palliate symptoms, but no specific regimen is recommended | • Single-agent chemotherapy | • Single-agent or platinum-based doublet regimen recommended |
|                       |           | • Data are insufficient to support or refute utility of two-drug regimens | • Data are insufficient to support or refute utility of two-drug regimens |
|                       |           | • Bevacizumab should be added to carboplatin/paclitaxel for appropriate patients | • Bevacizumab may be added to cisplatin/vinorelbine for patients who meet criteria
d |
| PS3/4                 | Not specifically addressed | Insufficient evidence to recommend specific agents or regimens based on age alone | Single-agent or platinum-based doublet regimen recommended |
| Elderly               | • Single-agent therapy for most patients 70 years and older, although some with good PS and no comorbidities may tolerate two-drug regimens | | |
|                       |           | • Benefit of chemotherapy is unclear in patients 80 years and older | |
| QOL                   | Measure QOL with FACT-L or EORTC QLQ-C30 because results are prognostic for survival | Not specifically addressed | Not specifically addressed |

ACCP = American College of Chest Physicians; ASCO = American Society of Clinical Oncology; EORTC QLQ-C30 = European Organisation for Research and Cancer Treatment Quality of Life Questionnaire; FACT-L = Functional Assessment of Cancer Therapy—lung questionnaire; NCCN = National Comprehensive Cancer Network; PS = Eastern Cooperative Oncology Group (ECOG) performance status; QOL = quality of life.

Contraindications for bevacizumab include squamous cell carcinoma, brain metastases, clinically significant hemoptysis, inadequate organ function, ECOG PS > 1, therapeutic anticoagulation, clinically significant cardiovascular disease, and medically uncontrolled hypertension. ASCO also cautions that elderly patients are at increased risk of toxicity.

Criteria for cetuximab use include NSCLC IIIB (pleural effusion)/IV, EGFR expression by immunohistochemistry (≥1% positive tumor cell), age 18 years, ECOG PS 0-2, no known brain metastases and no prior chemotherapy, or anti-EGFR therapy.

Cetuximab is not currently indicated for use in the treatment of advanced NSCLC.

Bevacizumab is indicated for use only in patients with non-squamous disease.

first-line setting in E4599 and demonstrated a statistically significant 2-month increase in median survival with this approach in a clinically selected subset of patients with advanced NSCLC. It is critical to note that enrollment for this trial was limited to patients with non-squamous NSCLC, no history of hemoptysis, and no untreated central nervous system (CNS) metastases. In earlier trials, patients with squamous histology or underlying hemoptysis experienced a high rate of life-threatening and fatal pulmonary hemorrhages related to bevacizumab, leading to their exclusion from E4599. Patients with CNS disease were excluded to minimize the potential for CNS hemorrhage. Note also that while chemotherapy was given every 3 weeks for 6 cycles, bevacizumab was continued every 3 weeks until progression or unacceptable toxicity, one of the first modern-day trials to suggest a benefit with a protracted or “maintenance” therapy approach in advanced NSCLC. Just over half (53%) of the patients initially randomized to the bevacizumab arm went on to receive bevacizumab monotherapy, and 50% of those received more than 5 cycles of bevacizumab monotherapy. Based on these data, bevacizumab is currently approved for the first-line treatment of advanced, non-squamous NSCLC in combination specifically with carboplatin/paclitaxel.

A second regimen comprising cetuximab with cisplatin/vinorelbine can be considered for patients with ECOG PS0-2 and epidermal growth factor receptor (EGFR)-positive NSCLC that has not previously been treated with anti-EGFR therapy, although this regimen is not currently approved for use by the FDA. Supportive data come from the randomized phase III FLEX study. As in E4599, the monoclonal antibody was continued as monotherapy after chemotherapy until disease progression or unacceptable toxicity. In contrast to earlier studies that evaluated oral EGFR tyrosine kinase inhibitors (TKIs) in combination with chemotherapy for advanced NSCLC, FLEX demonstrated a statistically significant 1.2-month increase in survival in the cetuximab-containing arm relative to cisplatin/vinorelbine alone. Patients of all histologies were eligible for the trial but were required to have EGFR-positive disease demonstrated on immunohistochemistry (IHC). Other potentially important biomarkers, such as KRAS status, EGFR mutation status, and EGFR gene copy number, were not considered for eligibility but were assessed for correlative studies. Until more information is known about potential predictive markers for cetuximab in NSCLC, it appears to be a reasonable treatment option for the initial treatment of appropriate patients with EGFR-positive NSCLC, particularly those with squamous histology who are not candidates for bevacizumab.

Finally, although the data currently have limited applicability in the US due in part to the unavailability of the EGFR TKI gefitinib, results of the IPASS study reveal that first-line treatment of patients in East Asia who are non-smokers or former light smokers with gefitinib is superior to treatment with carboplatin/paclitaxel with respect to progression-free survival (PFS). Patients were not selected for the trial based on EGFR tumor status, but EGFR gene mutations were shown to be a strong predictor of response. Among these patients, the risk of progression or death was reduced 52% relative to chemotherapy (P < 0.001), but among those whose tumors were EGFR mutation-negative, PFS was superior with chemotherapy (HR: 2.85, P < 0.001). OS, however, was similar between groups, suggesting that the order of drug administration may be less important than exposure to multiple lines of therapy over time. Whether these results can be applied to erlotinib in other populations remains to be determined. There is evidence from two open-label, single-arm studies that EGFR mutation status screening is both feasible and can be used to guide treatment decisions. In a study by Rosell and colleagues from the Spanish Lung Cancer Group, 350 of 2,105 screened patients had mutation-positive disease (17%). A total of 271 patients were subsequently treated with erlotinib (as first-, second-, or third-line treatment). The response rate was 71%, median PFS was 13 months, and median OS was 27 months. Further, a recently published report from the West Japan Oncology group, in which all of the patients enrolled in the study were EGFR mutation positive, compared first-line therapy with gefitinib to cisplatin/docetaxel. This study demonstrated that patients harboring the EGFR mutation treated with gefitinib had a significantly longer median PFS compared to patients treated with cisplatin/docetaxel (9.2 vs. 6.3 months; P < 0.0001). These results compare favorably to prior studies with chemotherapy administered to unselected populations, where response rates are typically 30%, PFS is approximately 5 months, and OS is approximately 12 months.

Currently, ASCO does not recommend the routine use of molecular markers to select systemic therapy in patients with advanced NSCLC. However, based on the results of IPASS, ASCO supports the first-line use of gefitinib, where available, over chemotherapy in patients whose tumors harbor EGFR mutation and suggests that these data justify attempts to test tumors for the presence of EGFR mutation.

SECOND-LINE AND MAINTENANCE THERAPIES

Prior to the results of trials such as E4599 and FLEX, there were clear recommendations to discontinue treatment after 4 to 6 cycles of chemotherapy and institute second-line therapy at the time of recurrence or failure to respond to first-line therapy. The benefits of docetaxel, pemetrexed, and erlotinib have all been demonstrated in this setting. These recommendations, however, are being confounded by the results of recent trials. As previously noted, both bevacizumab and cetuximab can be continued as monotherapy when used with first-line chemotherapy, and these therapies were not available when pivotal second-line studies were conducted. In addition, several other recent trials now suggest a role for maintenance therapy, defined as the initiation of a new agent immediately after completion of first-line chemotherapy (Table 2).
One of the first maintenance studies to be fully published evaluated the utility of pemetrexed maintenance after first-line, platinum-based chemotherapy (which could not include pemetrexed). Patients who had responded to or had stable disease after first-line chemotherapy were randomized to pemetrexed or placebo given every 21 days until progression. Median PFS, the primary endpoint, was significantly increased in the pemetrexed arm (4.3 months vs. 2.6 months, \( P < 0.0001 \)), as was OS (13.4 months vs. 10.6 months, \( P = 0.012 \)). As in other studies, the benefit was limited to patients with non-squamous histology. No treatment-related deaths were recorded, but rates of grade 3/4 fatigue and neutropenia were increased with pemetrexed (5% vs. 1%, \( P = 0.001 \); and 3% vs. 0%, \( P = 0.006 \), respectively). These results led to the approval of pemetrexed as a maintenance therapy in patients with advanced, non-squamous NSCLC who have not progressed after 4 cycles of cisplatin-based first-line chemotherapy. It is currently unclear, however, whether the survival benefits seen in this study are due to maintenance per se or to an increased access to an additional effective agent. While 98% of patients randomized to pemetrexed received it, only 67% of patients randomized to placebo eventually received second-line therapy, and even fewer of these patients received pemetrexed as second-line therapy.

A phase III study of docetaxel that was initially reported in 2006 provides interesting insight into the pemetrexed maintenance study. In the study by Fidias et al, nonprogressing patients were randomized after completing gemcitabine/cisplatin to receive docetaxel either immediately or at the time of progression. Although immediate docetaxel improved PFS relative to delayed docetaxel, with a trend toward improved OS, again, more than 30% of patients randomized to delayed therapy never received it. When patients who received immediate docetaxel were compared with those who actually received docetaxel at progression, there was no difference in survival, suggesting that access to second-line therapy is critical, whether it is given immediately or at progression. An important conclusion from these studies is that maintenance therapy appears to offer benefit to patients; however, for those who desire a break from treatment for personal reasons or due to toxicity, it is critical to monitor

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**TABLE 7. Clinical Trials of Maintenance Therapy in Advanced NSCLC**

<table>
<thead>
<tr>
<th>TRIAL</th>
<th>POPULATION</th>
<th>REGIMENTS</th>
<th>RESULTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATLAS</td>
<td>Stage IIIb (PE)/IV treated with platinum-based chemotherapy and BV and non-PD at randomization (N = 1,160)</td>
<td>Erlotinib 150 mg/day or placebo, given with continued BV until progression</td>
<td>↑ PFS with addition of erlotinib (HR: 0.722; ( P = 0.0012 )) OS data not yet mature</td>
</tr>
<tr>
<td>Early vs. late docetaxel</td>
<td>Stage IIIb (PE)/IV treated with GC and non-PD at randomization (N = 566)</td>
<td>Docetaxel 75 mg/m² Q3W x 6 immediately after completing GC or initiated at progression</td>
<td>↑ PFS with immediate docetaxel (5.7 vs. 2.7 months; ( P = 0.0001 )) Median OS, immediate vs. delayed (12.3 vs. 9.7 months; ( P = 0.085 ))</td>
</tr>
<tr>
<td>Pemetrexed</td>
<td>Stage IIIb/IV treated with platinum-based chemotherapy (not containing pemetrexed) and non-PD at randomization (N = 663)</td>
<td>Pemetrexed 500 mg/m² or placebo Q3W until progression</td>
<td>↑ PFS with pemetrexed (HR: 0.50; ( P &lt; 0.0001 )) ↑ OS, pemetrexed vs. placebo (HR: 0.79; ( P = 0.012 ))</td>
</tr>
<tr>
<td>SATURN</td>
<td>Stage IIIb/IV treated with platinum-based chemotherapy and non-PD at randomization (N = 889)</td>
<td>Erlotinib 150 mg/day or placebo continued until progression</td>
<td>↑ PFS with erlotinib (HR: 0.71; ( P &lt; 0.0001 )) Greatest effect in EGFR-mutated disease (HR: 0.10; ( P &lt; 0.0001 )) vs. WT (HR: 0.78; ( P = 0.0185 )) ↑ OS with erlotinib (HR: 0.81; ( P = 0.0088 ))</td>
</tr>
</tbody>
</table>

ATLAS = Assessment of Treatment With Lisinopril and Survival; BV = bevacizumab; EGFR = epidermal growth factor receptor; GC = gemcitabine/cisplatin; HR = hazard ratio; OS = overall survival; PD = progressive disease; PE = pleural effusion; PFS = progression-free survival; SATURN = Sequential Tarceva in Unresectable NSCLC; WT = wild type.

*Pemetrexed is the only agent referenced in this table that is currently approved for use as maintenance therapy after first-line treatment for advanced NSCLC.*

closely for progression so that the opportunity for administering additional active treatment is not lost. The risk of a delayed second-line treatment approach is that a substantial number of patients will be too ill to be safely treated upon progression, thus losing an important opportunity.22

Results of targeted therapy maintenance trials have also been recently reported and pose additional important questions to practicing oncologists.22 The randomized, placebo-controlled phase III SATURN study was presented at ASCO and updated at the 2009 World Conference on Lung Cancer.51,52 Patients with non-progressive disease were eligible for the trial independent of EGFR tumor status and randomized to daily erlotinib or placebo after completion of first-line chemotherapy. Both PFS and OS were significantly increased with maintenance erlotinib; the effect on PFS was greatest in patients with EGFR mutation-positive disease. Treatment with erlotinib was generally well tolerated. Approximately 60% of patients developed rash, and 20% experienced diarrhea, but there was no decline in quality of life.53,54 As in the chemotherapy trials, however, a substantial number of patients in the placebo arm (28%) failed to receive effective second-line therapy at progression, and only 21% received an EGFR TKI as second-line therapy, suggesting again that a maintenance therapy strategy clearly increases exposure to active agents, which may account for the survival benefits reported to date.

The ATLAS trial was also presented at ASCO in 2009 and evaluated the addition of erlotinib to bevacizumab maintenance following platinum-based chemotherapy. All patients received bevacizumab from the start of therapy until progression.26 Non-progressing patients, independent of tumor EGFR status, were randomized to erlotinib or placebo after completing chemotherapy. As in the SATURN study, the addition of erlotinib to the regimen significantly improved PFS. OS data have not yet been reported. The combination of bevacizumab plus erlotinib, however, produced many of the toxicities associated with each agent, resulting in a 44% rate of grade 3/4 adverse events (vs. 30% with bevacizumab plus placebo). Eight treatment-related deaths were reported in the combination arm (2.2%) versus four in the bevacizumab plus placebo arm (1.1%).24 Additional follow-up data from the ATLAS trial, including OS, are anxiously awaited.

Currently, ASCO does not recommend maintenance therapy after first-line treatment of NSCLC.2 It should also be noted, however, that the ASCO guidelines were developed prior to the complete publication of the pemetrexed maintenance study results as well as the release of results from the SATURN and ATLAS trials.24 ASCO intends to update its recommendations on maintenance therapy once these new data have been fully evaluated.22

CONCLUSION

The development of evidence-based quality measures has the potential to improve outcomes for patients with lung cancer, which is currently the leading cause of cancer mortality for men and women in the US.25 Quality measures used to improve performance should target processes of care that are linked to outcomes such as adequacy of staging, appropriate receipt of locoregional and systemic therapies, and routine surveillance, rather than outcomes such as survival rates. Currently published quality measures for NSCLC focus on the role of adjuvant chemotherapy in early-stage disease, but additional quality metrics can be developed for other clinical scenarios using the results of high-quality randomized clinical trials and reputable clinical practice guidelines. It is important to note that 100% adherence is not always the goal of a quality initiative, particularly for processes in which patient choice is paramount.26 There will always be patients whose unique clinical situations do not fit neatly into the algorithms contained in clinical practice guidelines, and in cases where clinical controversy exists, an appropriate quality measure should simply evaluate whether reasonable options were discussed. Nonetheless, it remains important for clinicians to evaluate the quality of care delivered at their individual practice sites as they strive to ensure that all patients receive the treatments that have been demonstrated effective for their disease.

It is clear that there are several options for JP to consider at this point, based on his age, histology, and PS. Because he has squamous cell NSCLC, neither pemetrexed nor bevacizumab are appropriate options for JP. In addition, the SIOG advises against bevacizumab for elderly patients such as JP. Based on the currently available evidence, single-agent chemotherapy may be most appropriate. Although maintenance therapy has not been evaluated specifically after single-agent chemotherapy, it would not be unreasonable to offer JP maintenance therapy if he completes chemotherapy without significant side effects and desires continued treatment. ASCO does not currently recommend testing archived tumor tissue for molecular markers to choose systemic therapy for advanced disease; however, increasing evidence suggests that testing for EGFR mutation is likely to become a standard of care in the near future once the data are fully considered in subsequent guideline iterations. Therefore, it is reasonable to consider EGFR mutation testing in JP’s case when weighing the potential risks and benefits of EGFR TKI therapy.

Tool 6 provides a treatment algorithm that can be applied in this case and others. Because JP was previously treated with vinorelbine and wishes to avoid the side effects he experienced in the past, reasonable options at this point include single-agent docetaxel with or without erlotinib maintenance and single-agent gemcitabine with or without erlotinib maintenance. If maintenance therapy is not used, JP should be followed particularly closely if he desires treatment upon progression so that it can be initiated before clinical deterioration precludes additional therapy.


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April 22, 2010 – 9 AM ET
July 22, 2010 – 9 AM ET

**FACULTY:**
Fred R. Hirsch, MD, PhD, and Robert M. Jotte, MD, PhD

Join two live, 30-minute Community of Practice Audioconferences with expert faculty and fellow specialists. Discuss strategies for overcoming process barriers in key benchmark areas of NSCLC care, including evaluation and staging, evidence-based surveillance and supportive care, and evidence-based treatment. Submit questions in advance or live on the phone for immediate faculty feedback in these interactive discussions. To register, call (toll-free) 866 858 7434 or e-mail concierge@med-iq.com.

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Choose a description on the left that best matches your patient's condition, then circle the corresponding descriptor on the right:

<table>
<thead>
<tr>
<th>EXTENT OF PRIMARY TUMOR (T)</th>
<th>DESCRIPTORS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinoma in situ</td>
<td>Tis</td>
</tr>
<tr>
<td>≤ 2 cm in greatest diameter</td>
<td>T1a</td>
</tr>
<tr>
<td>&gt; 2 cm and ≤ 3 cm in greatest diameter</td>
<td>T1b</td>
</tr>
<tr>
<td>&gt; 3 cm and ≤ 5 cm in greatest diameter</td>
<td>T2a</td>
</tr>
<tr>
<td>&gt; 5 cm and ≤ 7 cm in greatest diameter</td>
<td>T2b</td>
</tr>
<tr>
<td>&gt; 7 cm in greatest diameter</td>
<td>T3</td>
</tr>
<tr>
<td>Involves main bronchus, 2 cm or more distal to carina and is &gt; 3 cm and ≤ 5 cm</td>
<td>T2a</td>
</tr>
<tr>
<td>Involves main bronchus, 2 cm or more distal to carina and is &gt; 5 cm and ≤ 7 cm</td>
<td>T2b</td>
</tr>
<tr>
<td>Invades visceral pleura and is &gt; 3 cm and ≤ 5 cm</td>
<td>T2a</td>
</tr>
<tr>
<td>Invades visceral pleura and is &gt; 5 cm and ≤ 7 cm</td>
<td>T2b</td>
</tr>
<tr>
<td>Atelectasis present or obstructive pneumonitis that extends to hilar region but does not involve whole lung, and size is &gt; 3 cm and ≤ 5 cm</td>
<td>T2a</td>
</tr>
<tr>
<td>Atelectasis present or obstructive pneumonitis that extends to hilar region but does not involve whole lung, and size is &gt; 5 cm and ≤ 7 cm</td>
<td>T2b</td>
</tr>
<tr>
<td>Tumor directly invades chest wall (including superior sulcus tumors), diaphragm, phrenic nerve, mediastinal pleura, or parietal pericardium</td>
<td>T3</td>
</tr>
<tr>
<td>Tumor in the main bronchus &lt; 2 cm distal to the carina but without involvement of the carina (also includes superficial spreading tumor of any size if invasive component is limited to the bronchial wall)</td>
<td>T3</td>
</tr>
<tr>
<td>Atelectasis or obstructive pneumonitis of the entire lung</td>
<td>T3</td>
</tr>
<tr>
<td>Separate tumor nodule(s) in the same lobe as the primary</td>
<td>T3</td>
</tr>
<tr>
<td>Tumor of any size that invades mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, or carina</td>
<td>T4</td>
</tr>
<tr>
<td>Separate tumor nodule(s) in a different ipsilateral lobe to that of the primary</td>
<td>T4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NODAL STATUS (NO CHANGE FROM 6TH EDITION)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension</td>
</tr>
<tr>
<td>Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)</td>
</tr>
<tr>
<td>Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DISTANT METASTASIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>No distant metastasis</td>
</tr>
<tr>
<td>Separate tumor nodule(s) in a contralateral lobe</td>
</tr>
<tr>
<td>Tumor with pleural nodules or malignant pleural or pericardial effusion due to tumor</td>
</tr>
<tr>
<td>Distant metastasis present</td>
</tr>
</tbody>
</table>

TOOL 2. The Distress Thermometer and Problem List

Instructions: First, please circle the number (0-10) that best describes how much distress you have been experiencing in the past week including today.

Extreme distress

9
8
7
6
5
4
3
2
1
0
No distress

Yes No Practical Problems Yes No Physical Problems
- Child care
- Housing
- Insurance/financial
- Transportation
- Work/school

Yes No Family Problems
- Dealing with children
- Dealing with partner
- Ability to have children

Yes No Emotional Problems
- Depression
- Fears
- Nervousness
- Sadness
- Worry
- Loss of interest in usual activities

Yes No Spiritual/religious concerns
- Pain
- Nausea
- Nose dry/congested
- Sexual
- Skin dry/itchy
- Sleep
- Tingling in hands/feet

Other problems: __________________________________________

Second, please indicate if any of the following has been a problem for you in the past week including today. Be sure to check YES or NO for each.

- Appearance
- Bathing/dressing
- Breathing
- Changes in urination
- Constipation
- Diarrhea
- Eating
- Fatigue
- Feeling swollen
- Fevers
- Getting around
- Indigestion
- Memory/concentration
- Mouth sores
- Nose dry/congested
- Pain
- Sexual
- Skin dry/itchy
- Sleep


These Guidelines are a work in progress that will be refined as often as new significant data becomes available.

The NCCN Guidelines are a statement of consensus of its authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult any NCCN guideline is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient’s care or treatment. The National Comprehensive Cancer Network makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

These Guidelines are copyrighted by the National Comprehensive Cancer Network. All rights reserved. These Guidelines and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN.
**TOOL 3. Graphical Representation of Estimated Absolute Survival Benefit for 100 Patients With Stage II or III NSCLC Treated With Adjuvant Chemotherapy**

Graphical representation of estimated absolute risk and benefit for 100 patients with non–small-cell lung cancer treated with surgery and adjuvant chemotherapy, based on reported, stage-specific hazard ratio and death rate in the control arm of each clinical trial. Light blue corresponds to number of patients who have died at 5 years whether treated with chemotherapy or not; yellow is patients remaining alive at 5 years without chemotherapy treatment; darker blue is patients alive at 5 years because of chemotherapy treatment.

ANITA = Adjuvant Navelbine International Triallist Association trial; CALGB = Cancer and Leukemia Group B; IALT = International Adjuvant Lung Cancer Trial; JBR.10 = National Cancer Institute of Canada Clinical Trials Group JBR.10; LACE = Lung Adjuvant Cisplatin Evaluation.

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# TOOL 4. Planning Calendar for Surveillance After Curative-Intent Treatment for NSCLC

Date of diagnosis: _______________________________
Date of curative-intent surgery: _______________________________
Date of completion of adjuvant therapy: _______________________________

<table>
<thead>
<tr>
<th>FOLLOW-UP VISIT</th>
<th>FREQUENCY</th>
<th>DATES PERFORMED</th>
<th>RESULTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1st postoperative year</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hx, PE, contrast-enhanced spiral chest CT scan</td>
<td>Every 4 to 6 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking status assessment</td>
<td>Each visit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Influenza vaccine</td>
<td>Annually</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumococcal vaccine*</td>
<td>Once, with revaccination as appropriate</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>2nd postoperative year</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hx, PE, contrast-enhanced spiral chest CT scan</td>
<td>Every 4 to 6 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking status assessment</td>
<td>Each visit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Influenza vaccine</td>
<td>Annually</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subsequent years</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hx, PE, non-contrast-enhanced chest CT scan</td>
<td>Annually</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking status assessment</td>
<td>Each visit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Influenza vaccine</td>
<td>Annually</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CT = computed tomography; Hx = history; PE = physical examination.

*Pneumococcal vaccination is generally administered once to healthy individuals over the age of 65 years. Persons over the age of 65 should be administered a second dose of vaccine if they received the vaccine more than 5 years ago and were under the age of 65 at the time of primary vaccination. One revaccination is also recommended for persons at the highest risk of serious pneumococcal infection and those who are likely to have a rapid decline in pneumococcal antibody levels (such as patients with lung cancer), provided that 5 years have elapsed since the first vaccination.

### TOOL 5. ECOG Performance Status Scale

<table>
<thead>
<tr>
<th>DESCRIPTION</th>
<th>GRADE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fully active, able to carry on all pre-disease performance without restriction</td>
<td>0</td>
</tr>
<tr>
<td>Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work</td>
<td>1</td>
</tr>
<tr>
<td>Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours</td>
<td>2</td>
</tr>
<tr>
<td>Capable of only limited self-care, confined to bed or chair more than 50% of waking hours</td>
<td>3</td>
</tr>
<tr>
<td>Completely disabled, cannot carry on any self-care, totally confined to bed or chair</td>
<td>4</td>
</tr>
</tbody>
</table>

### CLINICAL ASSESSMENT

<table>
<thead>
<tr>
<th>DATE</th>
<th>PS GRADE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
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</tbody>
</table>

Figure 6. Algorithm for the First-Line Treatment of Advanced NSCLC

EGFR = epidermal growth factor receptor; IHC = immunohistochemistry; MAb = monoclonal antibody; PS = performance status.

Cetuximab is not currently indicated for this use but can be considered per NCCN and ASCO guidelines.

Contraindications for bevacizumab include squamous cell carcinoma, brain metastases, clinically significant hemoptysis, inadequate organ function, ECOG PS >1, therapeutic anticoagulation, clinically significant cardiovascular disease, and medically uncontrolled hypertension. ASCO also cautions that elderly patients are at increased risk of toxicity.

ASCO recommends that bevacizumab be used only with carboplatin/paclitaxel.

ASCO does not currently recommend maintenance therapy; however, this recommendation was made prior to the availability of results from recent clinical trials with pemetrexed and erlotinib and the subsequent FDA approval of pemetrexed in the maintenance setting.

SATURN enrolled patients with ECOG PS 0/1; however, because erlotinib is approved for use as second- and third-line therapy in PS2 patients, it is not unreasonable to consider it as an option for PS2 patients who desire maintenance therapy.

To earn CME credit, complete the following evaluation and the post-test, answering 70 percent of the post-test questions correctly. If completing the evaluation in print form, please use all capital letters and print your name, address, and other information requested below.

The purpose of this evaluation is to receive your feedback so we may improve future educational activities. All responses are confidential but may be evaluated in aggregate. Thank you.

**PARTICIPANT INFORMATION**

Date of Participation in Activity: ________________________________

First Name: ________________________________ Last Name: ________________________________

Degree/Profession: □ MD □ DO □ PharmD □ RPh □ PhD □ PA □ MBA □ RN □ NP □ LPN □ Other: ________________________________

Specialty: ________________________________

Address 1: ________________________________

Address 2: ________________________________

City/State/Zip: ________________________________

Phone: ________________________________ Fax: ________________________________ E-mail: ________________________________

Type of practice: □ Community/Private □ Academic □ Hospital □ HMO □ Other: ________________________________

Approximately how many patients do you see each week? __________ Of these patients, approximately what percentage have NSCLC? ____%

**ACTIVITY EVALUATION**

Rate the extent to which this CME activity met the following learning objectives:

<table>
<thead>
<tr>
<th>Learning Objective</th>
<th>Minimally</th>
<th>Partially</th>
<th>Fairly</th>
<th>Generally</th>
<th>Completely</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Describe the major differences between the 6th and 7th editions of the TNM staging systems used for NSCLC</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>2. Define the treatment recommendations from various national and international organizations and implement individualized treatment plans for patients with NSCLC based on these guidelines</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>3. Evaluate the role of tumor histology in patient outcomes and identify the most active pharmacologic agents against various subtypes of NSCLC</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>4. Identify patients who may benefit from NSCLC maintenance therapy and incorporate evidence-based treatment strategies into practice</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>5. Describe the key molecular targets that are currently under investigation in NSCLC and evaluate the clinical evidence for the pharmacologic agents directed against these targets</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>
Did this activity provide fair and balanced content free from commercial bias?  □ Yes □ No
(Commercial bias is defined as information presented that advocates a specific proprietary business product or service of a commercial interest.)

As a result of this learning experience, what will you do differently in the care of your patients?

__________________________________________________________________________

How will you implement these changes?

__________________________________________________________________________

Which of the following practice changes do you intend to implement as a result of participating in this learning experience?

A. I will routinely assess distress in all patients with NSCLC
B. I will consider the role of tumor histology when determining treatment options
C. I will adhere to the NCCN or ACCP recommendations for surveillance after initial treatment
D. I will use a new tool (eg, record flag, assessment form, planning calendar, etc.) in my practice
E. Other (please specify):
F. None

How confident are you in your ability to implement individualized treatment plans based on guideline recommendations for your patients with NSCLC?

A. Not at all confident  B. Somewhat confident  C. Moderately confident  D. Extremely confident

How confident are you in your ability to identify patients who may benefit from NSCLC maintenance therapy?

A. Not at all confident  B. Somewhat confident  C. Moderately confident  D. Extremely confident

Are there specific barriers to patient management that you feel better equipped to address as a result of this activity? If so, please list them.

__________________________________________________________________________

Are there specific barriers to patient management that this activity did not address? If so, please list them.

__________________________________________________________________________

__________________________________________________________________________

ATTESTATION AND SIGNATURE REQUIRED TO RECEIVE CREDIT:

Physicians:  I claim _______ (maximum 1.5) AMA PRA Category 1 Credits™

Signature: ____________________________ Date: ____________________________
1. SP is an NSCLC patient with a tumor that measures 5.5 cm at its greatest diameter. According to the 7th edition IASLC Cancer Staging Manual, which of the following would you assign as the appropriate tumor descriptor (T) for SP?
   A. T2
   B. T2a
   C. T2b
   D. T3

2. KR is an NSCLC patient with a tumor classified as T2b. Evaluation showed there were no positive lymph nodes (N0) and no distant metastases (M0). Based on these findings, how would you stage KR’s cancer?
   A. Stage IB
   B. Stage IIA
   C. Stage IIB
   D. Stage IIIA

3. Which of the following updates regarding clinically significant changes in the 7th edition staging system compared with the 6th edition is FALSE?
   A. Upstaging of stage IA to IB based on tumor size
   B. Upstaging of stage IB to IIA based on tumor size
   C. Downstaging of stage IIB to IIA based on tumor size
   D. Downstaging of stage IIIA to IIIIA based on N descriptor

4. According to practice guidelines, it is reasonable to obtain a brain MRI for all of the following patients to assess for distant metastases prior to initiating therapy EXCEPT:
   A. A patient experiencing nausea, vomiting, and headaches
   B. An asymptomatic patient with stage II disease being considered for aggressive single-modality therapy
   C. An asymptomatic patient with stage II disease being considered for aggressive combined-modality therapy
   D. Any patient with clinical stage III disease being considered for aggressive local therapy

5. According to clinical practice guidelines, carboplatin can be readily substituted for cisplatin in adjuvant chemotherapy regimens for NSCLC.
   A. True
   B. False

6. TA is an NSCLC patient who has just undergone curative-intent surgery. According to the ACCP, follow-up imaging tests for TA should be conducted as follows:
   A. Chest x-ray or CT every 3 months for 2 years, then annually
   B. Chest x-ray or CT every 6 months for 2 years, then annually
   C. Chest CT every 4 to 6 months for 1 year, then annually
   D. Chest x-ray every 4 to 6 months for 1 year, then annually

7. Which of the following patients is an appropriate candidate for bevacizumab as an adjunct to first-line chemotherapy for advanced NSCLC?
   A. A patient who is 76 years old
   B. A patient with adenocarcinoma
   C. A patient with documented brain metastases
   D. A patient on chronic anticoagulation for atrial fibrillation

8. The use of pemetrexed in all of the following clinical scenarios is appropriate EXCEPT:
   A. As part of first-line chemotherapy with cisplatin in a patient with advanced adenocarcinoma and good PS
   B. As a maintenance strategy following first-line treatment with cisplatin/gemcitabine in a patient with advanced large-cell carcinoma and good PS
   C. As first-line monotherapy for an elderly patient with advanced adenocarcinoma and PS2
   D. As second-line therapy for a patient with advanced large-cell carcinoma and good PS who progressed after initial treatment with cisplatin/vinorelbine

9. Which of the following statements regarding the use of maintenance erlotinib in advanced NSCLC as demonstrated by the SATURN trial is TRUE?
   A. Daily erlotinib significantly increased PFS, but not OS, relative to placebo
   B. The majority of patients in the placebo arm received erlotinib at progression as second-line therapy
   C. OS was significantly increased in the erlotinib arm, but quality of life was significantly reduced relative to placebo
   D. Both PFS and OS were significantly increased with erlotinib maintenance, and the effect on PFS was greatest for patients with EGFR mutations

10. Among patients harboring an EGFR mutation, first-line therapy with an EGFR TKI is associated with:
    A. No significant difference in PFS compared with platinum doublet
    B. An increase in PFS compared with platinum doublet
    C. An increase in OS compared with platinum doublet
    D. Lower response rate to therapy compared with platinum doublet

---

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