

# American Society of Clinical Oncology Clinical Practice Guideline Update on Chemotherapy for Stage IV Non–Small-Cell Lung Cancer

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## A B S T R A C T

The purpose of this article is to provide updated recommendations for the treatment of patients with stage IV non–small-cell lung cancer. A literature search identified relevant randomized trials published since 2002. The scope of the guideline was narrowed to chemotherapy and biologic therapy. An Update Committee reviewed the literature and made updated recommendations. One hundred sixty-two publications met the inclusion criteria. Recommendations were based on treatment strategies that improve overall survival. Treatments that improve only progression-free survival prompted scrutiny of toxicity and quality of life. For first-line therapy in patients with performance status of 0 or 1, a platinum-based two-drug combination of cytotoxic drugs is recommended. Nonplatinum cytotoxic doublets are acceptable for patients with contraindications to platinum therapy. For patients with performance status of 2, a single cytotoxic drug is sufficient. Stop first-line cytotoxic chemotherapy at disease progression or after four cycles in patients who are not responding to treatment. Stop two-drug cytotoxic chemotherapy at six cycles even in patients who are responding to therapy. The first-line use of gefitinib may be recommended for patients with known epidermal growth factor receptor (*EGFR*) mutation; for negative or unknown *EGFR* mutation status, cytotoxic chemotherapy is preferred. Bevacizumab is recommended with carboplatin-paclitaxel, except for patients with certain clinical characteristics. Cetuximab is recommended with cisplatin-vinorelbine for patients with *EGFR*-positive tumors by immunohistochemistry. Docetaxel, erlotinib, gefitinib, or pemetrexed is recommended as second-line therapy. Erlotinib is recommended as third-line therapy for patients who have not received prior erlotinib or gefitinib. Data are insufficient to recommend the routine third-line use of cytotoxic drugs. Data are insufficient to recommend routine use of molecular markers to select chemotherapy.

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## SPECIAL ANNOUNCEMENT

The US Food and Drug Administration (FDA) approved a new indication for pemetrexed for maintenance therapy in patients with advanced non–small-cell lung cancer (NSCLC) on July 2, 2009, when this guideline went to press. The data supporting this change have been recently presented and were outside the scope of the comprehensive data review for this guideline. The recommendation on maintenance therapy in this guideline will be updated pending consideration of recently published relevant data.

## INTRODUCTION

The American Society of Clinical Oncology (ASCO) first published a guideline on the treatment of unre-

sectable NSCLC in 1997. ASCO guidelines are updated periodically by a subset of the original Expert Panel and other experts, as necessary. ASCO produced the first unresectable NSCLC update in 2003. For the 2009 guideline update, an Update Committee met to review the literature published since the 2003 guideline publication.

As a result of the large volume of literature published in this field and the requirement to conduct a comprehensive systematic review of the literature,<sup>1</sup> the Update Committee limited the scope of this guideline to chemotherapy and biologic therapy for stage IV NSCLC (as defined by the International Association for the Study of Lung Cancer [IASLC] Lung Cancer Staging Project, for the seventh edition of the TNM Classification of Malignant Tumors).<sup>2</sup> The Update Committee added the topics of chemotherapy for the elderly and a discussion of

molecular analysis of tumor tissue. Therefore, this guideline does not update diagnostic evaluation, staging, radiotherapy, combining chemotherapy with radiotherapy, surgery, supportive care, surveillance and follow-up, smoking cessation, or chemoprevention.

ASCO's practice guidelines reflect expert consensus based on clinical evidence and literature available at the time they are written and are intended to assist physicians in clinical decision making and identify questions and settings for further research. Because of the rapid flow of scientific information in oncology, new evidence may have emerged since the time a guideline was submitted for publication. Guidelines are not continually updated and may not reflect the most recent evidence. Guidelines cannot account for individual variation among patients and cannot be considered inclusive of all proper methods of care or exclusive of other treatments. It is the responsibility of the treating physician or other health care provider, relying on independent experience and knowledge of the patient, to determine the best course of treatment for the patient. Accordingly, adherence to any guideline is voluntary, with the ultimate determination regarding its application to be made by the physician in light of each patient's individual circumstances. ASCO guidelines describe the use of procedures and therapies in clinical practice and cannot be assumed to apply to the use of these interventions in the context of clinical trials. ASCO assumes no responsibility for any injury or damage to persons or property arising out of or related to any use of ASCO's guidelines or for any errors or omissions.

## UPDATE METHODOLOGY

Experts in medical oncology, biostatistics, and translational research; a lung cancer survivor; and a family member representative constituted the 2009 Update Committee. Practitioners represented both academic and community practice. Update Committee members are listed in the Appendix.

### Literature Review and Analysis

**Literature search strategy.** This systematic review was initially developed by Cancer Care Ontario's Program in Evidence-Based Care. For the 2009 update, MEDLINE and EMBASE databases were searched from January 2002 through July 2008. Results were supplemented by a search of ASCO Annual Meeting Abstracts from 2007 and 2008 and of the IASLC Annual Meeting from 2007 and additional suggestions from Update Committee members. Search terms included the following: "non-small-cell lung cancer," "advanced non-small-cell lung cancer," "bronchioloalveolar carcinoma," "antineoplastic protocols," "drug therapy combinations," "drug therapy," "receptor protein-tyrosine kinase," "receptor, epidermal growth factor," "mutation or genes, ras," "serum tumor markers," other specific molecular markers, and "performance status." Additional terms included generic and brand names of chemotherapeutic and biologic agents. Searches were limited to randomized controlled trials (RCTs), practice guidelines, systematic reviews, and meta-analyses. For chemotherapy, searches were limited to phase III RCTs; for biologic agents, searches included phase II and III randomized trials. In this article, however, the term chemotherapy refers to any anticancer drug, regardless of its mechanism of action (ie, cytotoxic and biologic agents included) unless otherwise specified. For molecular analysis, the search protocol permitted retrospective and subgroup analyses from

clinical trials, as well as cohort studies. For chemotherapy and biologic agent trials, cohort studies were excluded. Other study designs excluded for all topics were phase I or case-control trials. Publications that were fully published English-language reports involving human subjects in peer-reviewed journals were eligible.

**Inclusion and exclusion criteria.** Articles were selected for inclusion if they met the following criteria: participants were not candidates for surgery or definitive radiotherapy with curative intent, and participants were randomly assigned to a treatment arm or a control arm (control arm could consist of placebo, best supportive care, the same treatment at an alternate dose or a different schedule of administration or for a different duration, a different treatment, or the same treatment combined with a different treatment). Outcome measures reported included at least one of the following for chemotherapy and biologic therapies: overall survival (OS), progression-free survival (PFS), objective response rate (ORR), toxicity, and quality of life (QOL)/symptom relief. For molecular analysis studies, outcome measures included one of the following: objective response, OS, or PFS. The primary outcome of interest was OS, and recommendations were primarily based on statistically significant improvements in OS documented in prospective RCTs. The Update Committee acknowledges the trend of phase III clinical trials for stage IV NSCLC where the primary end point is PFS. Treatments that improve only PFS prompted greater scrutiny for toxicity, adverse effects, and QOL.

An a priori decision was made to exclude papers on individual molecular markers (molecular analysis) after completion of the systematic review if there were less than five retrospective studies and no prospective studies of the particular marker. To allow the Update Committee to consider more recent phase III data not yet published in the literature, a separate search was conducted of all phase III abstracts presented at the 2007 and 2008 annual meetings of ASCO and the 2007 meeting of the IASLC. Whenever data from an abstract had any impact on a guideline recommendation, the Update Committee recognized these data as inferior to data published in the literature and were careful to specify the source of the data in the language of the recommendation and in the discussion section for each recommendation.

**Data extraction.** Relevant articles were selected and reviewed by two reviewers sequentially, and the reference lists from those sources were searched for additional trials. Evidence was selected and reviewed by one member of the Program in Evidence-Based Care, and this systematic review was updated and completed by one ASCO staff member. Each article meeting the inclusion criteria underwent data extraction for patient characteristics, study design and quality, intervention, and outcomes, including adverse events. Evidence summary tables were developed based on data extracted from studies meeting the criteria for inclusion.

**Study quality and limitations of the literature.** There were limited numbers of trials enrolling patients with poor performance status (PS; PS  $\geq$  2 based on the Eastern Cooperative Group [ECOG]/Zubrod scale or PS < 70% on the Karnofsky scale) or elderly patients. In addition, there is currently a lack of phase III data on patients who have been treated with third-line therapy and beyond.

### Future Update Options

ASCO guidelines are normally updated every 3 years. The Update Committee recognizes that major new evidence could emerge before that time that may warrant reconsideration of a

recommendation(s) in this guideline. ASCO has several options for updating guidelines before the 3-year point. An annual search of the literature is conducted for any new evidence (within the parameters of the guideline) that is directly pertinent to the recommendations. If data emerge from that or other sources, members of the Update Committee will review it. New data may or may not change the recommendation. ASCO will provide a review of the update and publish it online and/or in print.<sup>1</sup>

### Consensus Development Based on Evidence

The entire Update Committee met once; additional work on the guideline was completed through a steering group. The purposes of the Update Committee meeting were to draft guideline recommendations and distribute writing assignments. During review of the results of the literature search, members of the Update Committee were allowed to nominate studies recently published but not identified in the literature search or presented as an abstract(s) but not identified in the search of abstracts from ASCO 2007, ASCO 2008, or IASLC 2007 meetings for consideration by the rest of the Update Committee. Members of the Update Committee participated in the preparation of the draft guideline document, which was then disseminated for review by the entire Update Committee. The guideline was submitted to the *Journal of Clinical Oncology* for peer review. The content of the guidelines and the manuscript were reviewed and approved by the Clinical Practice Guidelines Committee and by the ASCO Board of Directors before publication.

### Guideline and Conflicts of Interest

The Update Committee was assembled in accordance with ASCO's Conflict of Interest Management Procedures for Clinical Practice Guidelines (summarized at [http://www.asco.org/ASCO/Downloads/Cancer%20Policy%20and%20Clinical%20Affairs/Clinical%20Affairs%20\(derivative%20products\)/Summary%20CS%20Edits\\_062508\\_clean%20\\_2\\_.pdf](http://www.asco.org/ASCO/Downloads/Cancer%20Policy%20and%20Clinical%20Affairs/Clinical%20Affairs%20(derivative%20products)/Summary%20CS%20Edits_062508_clean%20_2_.pdf)). Members of the Update Committee completed ASCO's disclosure form, which requires disclosure of financial and other interests that are relevant to the subject matter of the guideline, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as the result of promulgation of the guideline. Categories for disclosure include employment relationships, consulting arrangements, stock ownership, honoraria, research funding, and expert testimony. In accordance with the Procedures, the majority of the members of the Update Committee did not disclose any of these relationships. Disclosure information for each member of the Update Committee is published adjunct to this guideline.

## RESULTS

### Literature Search

Searches identified 14,684 articles. After reviewing abstracts, 13,931 were excluded as a result of not meeting the inclusion criteria or being duplicates. Seven hundred fifty-three full-text publications were reviewed for the interventions, populations, and outcomes identified earlier. A further 591 were excluded. The most common reasons for exclusion were as follows: narrative reviews, study plans or descriptions, consensus statements, earlier stage NSCLC, nonrandomized study designs, or molecular analysis studies of a biomarker for which

there were fewer than five retrospective studies and no prospective studies of the marker. Data were extracted from 190 papers that met the inclusion criteria. Of these 190 papers, 94 reported on chemotherapy, 23 reported on biologic therapy, and 73 reported on molecular analysis. In addition, data were extracted from publications, abstracts, and presentations added after the completion of the systematic review.

### Previous Guidelines and Consensus Statements

The American College of Chest Physicians, the National Comprehensive Cancer Network, and Cancer Care Ontario have produced guidelines, and the European Society for Medical Oncology and Gridelli et al<sup>3</sup> have produced consensus statements that make recommendations regarding stage IV NSCLC. The Committee has evaluated the guidelines and consensus statements and found them to be consistent with the ASCO guidelines.<sup>3-7</sup>

## GUIDELINE RECOMMENDATIONS

The recommendations are listed in Table 1. Recommendations are organized as follows. Those on first-line chemotherapy begin with "A," those on second-line chemotherapy being with "B," those on third-line chemotherapy being with "C," and those on molecular analysis begin with "D."

### First-Line Chemotherapy

**1. Clinical question.** Which patients with stage IV (as defined by the International Association for the Study of Lung Cancer Lung Cancer Staging Project<sup>2</sup>) NSCLC should be treated with chemotherapy? (Note: In this document, the term "chemotherapy" refers to any anticancer drug, regardless of its mechanism of action [ie, cytotoxic and biologic drugs included] unless otherwise specified.)

**2003 recommendations.** Chemotherapy is appropriate for selected patients with stage IV NSCLC. In stage IV disease, chemotherapy prolongs survival and is most appropriate for individuals with good PS (ECOG/Zubrod PS of 0 or 1 and possibly 2). In patients with stage IV disease, if chemotherapy is to be administered, it should be initiated while the patient still has a good PS.

**2009 recommendation A1.** Evidence supports the use of chemotherapy in patients with stage IV NSCLC with ECOG/Zubrod PS of 0, 1, and possibly 2.

**Literature update and discussion.** Only 2% of patients diagnosed with clinical stage IV NSCLC are alive at 5 years. Although prognosis remains poor for these patients, there is no doubt that chemotherapy improves OS compared with supportive care only.<sup>8,9</sup> Most studies performed in patients with advanced disease included patients with stage IV disease but also a variable number of patients with stage IIIB disease (mainly those with malignant pleural effusions).

A recent update of a meta-analysis of 16 randomized trials comparing chemotherapy with supportive care only for patients with advanced NSCLC included 2,714 patients and documented a 23% reduction in the risk of death (hazard ratio [HR] = 0.77; 95% CI, 0.71 to 0.83;  $P \leq .0001$ ) and an absolute improvement in survival of 9% at 12 months with chemotherapy (from 20% to 29%).<sup>10</sup> In this meta-analysis, in 13 trials reporting PS, patients with PS of 2 or greater also received benefit from chemotherapy, although the level of benefit was smaller than for patients with PS of 0 to 1

**Table 1.** Summary of Recommendations

Recommendation No.	Recommendation
<b>A. First-line chemotherapy</b>	
Recommendation A1	Evidence supports the use of chemotherapy* in patients with stage IV† NSCLC with ECOG/Zubrod performance status of 0, 1, and possibly 2.
Recommendation A2	In patients with performance status of 0 or 1, evidence supports using a combination of two cytotoxic drugs for first-line therapy. Platinum combinations are preferred over nonplatinum combinations because they are superior in response rate, and marginally superior in overall survival. Nonplatinum therapy combinations are reasonable in patients who have contraindications to platinum therapy. Recommendations A8 and A9 address whether to add bevacizumab or cetuximab to first-line cytotoxic therapy.
Recommendation A3	Available data support the use of single-agent chemotherapy in patients with a performance status of 2. Data are insufficient to make a recommendation for or against using a combination of two cytotoxic drugs in patients with performance status of 2.
Recommendation A4	The evidence does not support the selection of a specific first-line chemotherapy drug or combination based on age alone.
Recommendation A5	The choice of either cisplatin or carboplatin is acceptable. Drugs that may be combined with platinum include the third-generation cytotoxic drugs docetaxel, gemcitabine, irinotecan, paclitaxel, pemetrexed, and vinorelbine. The evidence suggests that cisplatin combinations have a higher response rate than carboplatin and may improve survival when combined with third-generation agents. Carboplatin is less likely to cause nausea, nephrotoxicity, and neurotoxicity than cisplatin but more likely to cause thrombocytopenia.
Recommendation A6	In patients with stage IV NSCLC, first-line cytotoxic chemotherapy should be stopped at disease progression or after four cycles in patients whose disease is not responding to treatment. Two-drug cytotoxic combinations should be administered for no more than six cycles. For patients who have stable disease or who respond to first-line therapy, evidence does not support the continuation of cytotoxic chemotherapy until disease progression or the initiation of a different chemotherapy prior to disease progression.
Recommendation A7	In unselected patients, erlotinib or gefitinib should not be used in combination with cytotoxic chemotherapy as first-line therapy. In unselected patients, evidence is insufficient to recommend single-agent erlotinib or gefitinib as first-line therapy. The first-line use of gefitinib may be recommended for patients with activating <i>EGFR</i> mutations. If <i>EGFR</i> mutation status is negative or unknown, then cytotoxic chemotherapy is preferred. (see Recommendation A2)
Recommendation A8	Based on the results of one large phase III randomized controlled trial, the Update Committee recommends the addition of bevacizumab, 15 mg/kg every 3 weeks, to carboplatin/paclitaxel, except for patients with squamous cell carcinoma histologic type, brain metastases, clinically significant hemoptysis, inadequate organ function, ECOG performance status > 1, therapeutic anticoagulation, clinically significant cardiovascular disease, or medically uncontrolled hypertension. Bevacizumab may be continued, as tolerated, until disease progression.
Recommendation A9	On the basis of the results of one large phase III randomized controlled trial, clinicians may consider the addition of cetuximab to cisplatin/vinorelbine in first-line therapy in patients with an EGFR-positive tumor as measured by immunohistochemistry. Cetuximab may be continued, as tolerated, until disease progression.
<b>B. Second-line chemotherapy</b>	
Recommendation B1	Docetaxel, erlotinib, gefitinib, or pemetrexed is acceptable as second-line therapy for patients with advanced NSCLC with adequate performance status when the disease has progressed during or after first-line, platinum-based therapy.
Recommendation B2	The evidence does not support the selection of a specific second-line chemotherapy drug or combination based on age alone.
<b>C. Third-line chemotherapy</b>	
Recommendation C1	When disease progresses on or after second-line chemotherapy, treatment with erlotinib may be recommended as third-line therapy for patients with performance status of 0 to 3 who have not received prior erlotinib or gefitinib.
Recommendation C2	The data are not sufficient to make a recommendation for or against using a cytotoxic drug as third-line therapy. These patients should consider experimental treatment, clinical trials, and best supportive care.
<b>D. Molecular analysis</b>	
Recommendation D1	Evidence is insufficient to recommend the routine use of molecular markers to select systemic treatment in patients with metastatic NSCLC.
Recommendation D2	In order to obtain tissue for more accurate histologic classification or for investigational purposes, the Update Committee supports reasonable efforts to obtain more tissue than what is contained in a routine cytology specimen.

Abbreviations: NSCLC, non-small-cell lung cancer; ECOG, Eastern Cooperative Oncology Group.

\*In this document, the term "chemotherapy" refers to any anticancer drug, regardless of its mechanism of action (ie, cytotoxic and biologic drugs included), unless otherwise specified.

†As defined by the International Association for the Study of Lung Cancer Lung Cancer Staging Project, for the 7th Edition of the TNM Classification of Malignant Tumors.<sup>2</sup>

(absolute effect at 12 months: 8% for PS 0 to 1; 6% for PS  $\geq$  2; trend  $P = .76$ ). (Note: This meta-analysis was published after the systematic review was completed.)

The Update Committee recognizes PS as the most important prognostic factor for patients with stage IV NSCLC. Patients with PS of 0 to 1 live longer than patients with PS of 2, regardless of therapy. Poor PS may also predict less benefit from chemotherapy. Patients with poor or borderline PS are more susceptible to the toxic adverse effects of chemotherapy. These patients are also difficult to classify because poor PS may be related to medical comorbidities and/or

the physiologic effects of cancer. Furthermore, the scales of PS are open to subjective interpretation (Table 2). As a result, patients described with a PS of 2 who are enrolled onto a clinical trial may be different from patients assigned this PS in treatment outside a clinical trial such that clinical trial data looking at patients with PS of 2 may not be generalizable to patients in routine practice. Therefore, the guideline recommendations for patients with PS of 2 rely heavily on the clinician's informed interpretation of each individual patient's PS. There are no data to support treatment of patients with PS of 3 or 4 with cytotoxic chemotherapy.

**Table 2.** Scales of Performance Status

ECOG Scale*	Zubrod Scale†	ECOG/Zubrod Score	Karnofsky‡		
			Status		Scale
Fully active, able to carry on all pre-disease performance without restriction	Normal activity	0	100%	Normal; no complaints; no evidence of disease	Able to carry on normal activity and to work. No special care is needed (80%-100%)
Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework or office work)	Symptoms, but nearly fully ambulatory	1	90%	Able to carry on normal activity; minor signs or symptoms of disease	
			80%	Normal activity with effort; some signs or symptoms of disease	
Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about > 50% of waking hours	Some bed time, but needs to be in bed less than 50% of normal daytime	2	70%	Cares for self. Unable to carry on normal activity or to do active work	Unable to work. Able to live at home, care for most personal needs. A varying amount of assistance is needed (50%-70%)
			60%	Requires occasional assistance, but is able to care for most of his/her needs	
Capable of only limited self-care, confined to a bed or chair > 50% of waking hours	Needs to be in bed > 50% of normal daytime.	3	50%	Requires considerable assistance and frequent medical care	Unable to care for self. Requires equivalent of institutional or hospital care. Disease may be progressing rapidly (0%-40%)
			40%	Disabled; requires special care and assistance	
Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair	Unable to get out of bed.	4	30%	Severely disabled; hospitalization is indicated although death not imminent	
			20%	Very sick; hospitalization necessary; active supportive treatment necessary	
			10%	Moribund; fatal processes progressing rapidly	
Dead		5	0%	Dead	

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

\*Data from Oken et al.<sup>11</sup>

†Data from Orr and Aisner.<sup>12</sup>

‡Data from Schag et al.<sup>13</sup>

Besides stage of disease and poor PS, male sex is the only other unfavorable clinical prognostic factor commonly used to stratify patients being enrolled onto randomized trials of chemotherapy for metastatic NSCLC. Weight loss greater than 5% of baseline, elevated serum lactate dehydrogenase, and more than one metastatic site of disease have also been validated in prospective trials as poor prognostic factors.<sup>14</sup> With the discovery of higher response rates to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) among patients with stage IV NSCLC who never smoked cigarettes, there is increasing interest in never smokers as a subgroup. Never smoking, or former light smoking (< 15 pack-years), has recently been identified as a significant favorable prognostic factor in patients with stage IV NSCLC.<sup>15</sup> Although all of these factors are prognostic, none except PS 2 is predictive of benefit from traditional cytotoxic chemotherapy, and therefore, these factors should not be used to exclude patients from chemotherapy.

**2. Clinical questions.** What is the most effective first-line chemotherapy for the treatment of patients with stage IV NSCLC? What are

the benefits, with respect to OS, PFS, toxicity, and QOL/symptom relief, in the treatment of stage IV NSCLC with chemotherapy?

**2003 recommendations.** First-line chemotherapy administered to patients with advanced NSCLC should be a two-drug combination regimen. Non-platinum-containing chemotherapy regimens may be used as alternatives to platinum-based regimens in the first line.

**2009 recommendation A2.** In patients with PS of 0 or 1, evidence supports using a combination of two cytotoxic drugs for first-line therapy. Platinum combinations are preferred over nonplatinum combinations because they are superior in response rate and marginally superior in OS. Nonplatinum combinations are reasonable in patients who have contraindications to platinum therapy. Recommendations A8 and A9 address whether to add bevacizumab or cetuximab to first-line cytotoxic therapy.

**Literature update and discussion.** By definition, first-line chemotherapy is for patients who have never received chemotherapy for their disease. However, since the 2003 guideline update, more patients are receiving chemotherapy to treat earlier stages of NSCLC.<sup>16</sup> For

patients with recurrent NSCLC who received adjuvant or neoadjuvant chemotherapy or chemotherapy combined with radiation earlier in their clinical course, evidence is not sufficient to make a recommendation regarding selection of first-line chemotherapy for advanced disease. It is the consensus opinion of the Update Committee that clinicians may consider alternative chemotherapy for patients who have recurrent disease within a year of completing prior chemotherapy.

The best first-line chemotherapy for patients with good PS and no prior chemotherapy exposure is a combination of two cytotoxic drugs (Table 3). Combining cytotoxic drugs with additive or synergistic effects usually improves radiologic response rate but also increases toxic adverse effects. As a result, testing whether combinations of cytotoxic drugs improve OS compared with single agents has been the subject of numerous clinical trials.

Most trials and a meta-analysis comparing two drugs versus one were able to demonstrate improvement in radiologic response rate for patients receiving two drugs,<sup>23,35-38</sup> and one trial and the meta-analysis found statistically significant improvements in OS.<sup>35,38</sup> None of the individual trials or the meta-analysis testing combinations of three cytotoxic drugs versus two were able to demonstrate a survival benefit with the use of three drugs, but they all demonstrated increases in toxic adverse effects.<sup>35,39-41</sup> These data corroborate the 2003 recommendation that a combination of two cytotoxic drugs is better than a single cytotoxic drug and also better than a combination of three cytotoxic drugs.

The recommendation in favor of platinum-based combination chemotherapy is based on individual trial publications and four literature-based meta-analyses,<sup>42-45</sup> which reported a significant advantage in response to platinum-based therapy compared with nonplatinum-based regimens. It was also based on evidence from the four meta-analyses and one individual study that showed a significant survival advantage to platinum-based therapy.<sup>38</sup>

All four meta-analyses found a statistically significantly greater radiologic response rate for participants receiving platinum-based regimens compared with patients receiving nonplatinum-based regi-

mens, as did seven other trials not included in these analyses.<sup>23,36-40,46</sup> Odds ratios (ORs) of response rate findings from the meta-analyses ranged from 1.62 (95% CI, 1.46 to 1.8;  $P < .0001$ )<sup>42</sup> to 2.32 (95% CI, 1.68 to 3.2),<sup>43</sup> both in favor of platinum-based regimens.

All four meta-analyses and a trial not included in those analyses<sup>38</sup> found statistically significant increases in survival for participants receiving platinum-based regimens compared with patients receiving nonplatinum-based regimens. The meta-analyses reported outcomes in disparate ways; examples include a survival improvement of 13% (HR = 0.87; 95% CI, 0.8 to 0.94;  $P < .001$ )<sup>43</sup> and a decrease in OR of death by 12% (OR = 0.88; 95% CI, 0.78 to 0.99;  $P = .044$ ).<sup>44</sup>

The meta-analyses also found toxicity to be greater with platinum-based doublets than with nonplatinum-based regimens. In addition, 12 individual trials showed statistically significantly higher hematologic toxicities in platinum treatment arms,<sup>19,23,36-38,40,41,46-50</sup> and seven trials showed significantly higher nonhematologic toxicities in platinum arms.<sup>23,36,39-41,46,47</sup> Five studies found no differences or higher nonhematologic adverse effects in the nonplatinum arms (both significant and nonsignificant).<sup>38,48,50-52</sup> Problems specific to platinum include nephrotoxicity (OR of nephrotoxicity = 3.09; 95% CI, 1.88 to 5.06;  $P < .0001$ )<sup>42</sup> and GI problems (OR of GI toxicity = 2.88; 95% CI, 2.24 to 3.71;  $P < .0001$ ).<sup>44</sup>

The Update Committee recognizes that some patients have contraindications to platinum-based therapy, which include allergy to cisplatin or carboplatin, baseline hearing loss, renal insufficiency, intolerable nausea despite optimal emesis prophylaxis (see ASCO guideline on antiemetics<sup>53</sup>), and intolerance of corticosteroids needed for emesis prophylaxis, or a patient may refuse to take a platinum drug. For these patients, nonplatinum combinations are acceptable alternatives.

Some clinical trials have looked at alternative schedules of administration. Evidence on schedule of administration is limited to studies of paclitaxel/carboplatin regimens.<sup>54,55</sup> Evidence demonstrates that there is no difference in weekly versus every-3-week administration of paclitaxel/carboplatin. In both studies identified in this update, differences in median survival were not significant.

**Table 3.** Range of Efficacy Outcomes (worst to best) From Both Arms of All Prospective Randomized Clinical Trials Comparing Similar Treatments Identified by the Systematic Review of the Literature (2003-2008), Tabulated by Treatment Regimen and Subgroup

Treatment	Range of Worst to Best Outcomes				
	Overall Survival (months)	Progression-Free Survival (months)	1-Year Survival Rate (%)	2-Year Survival Rate (%)	Overall Response Rate (%)
First-line chemotherapy, all patients: two cytotoxic drugs v two cytotoxic drugs	6 <sup>17</sup> -14 <sup>18</sup>	3.9 <sup>19</sup> -6.0 <sup>17</sup>	20 <sup>20</sup> -60 <sup>18</sup>	7 <sup>21</sup> -31 <sup>18</sup>	15 <sup>22</sup> -46 <sup>17</sup>
First-line chemotherapy, patients with PS 2: one or two cytotoxic drugs v one or two drugs (including EGFR TKIs)	2.4 <sup>23</sup> -9.7 <sup>24</sup>	1.9 <sup>24</sup> -5.0 <sup>25</sup>	14 <sup>23</sup> -31 <sup>25</sup>	11-13 <sup>25</sup>	4 <sup>24</sup> -37 <sup>25</sup>
First-line chemotherapy, elderly patients: one or two cytotoxic drugs v one or two cytotoxic drugs	4.3 <sup>26</sup> -5.8 <sup>23</sup>	Not reported	33 <sup>27</sup> -59 <sup>26</sup>	7 <sup>27</sup> -24 <sup>28</sup>	10 <sup>26</sup> -36 <sup>23</sup>
Second-line chemotherapy, all patients: one drug (including gefitinib or erlotinib) v one drug (including EGFR TKIs)	6.7 <sup>29,30</sup> -8.3 <sup>31</sup>	2.2 <sup>30</sup> -2.9 <sup>31</sup>	29 <sup>32</sup> -34 <sup>33</sup>	Not reported	4 <sup>29</sup> -12 <sup>32</sup>
Second-line chemotherapy, elderly patients: one drug (including gefitinib or erlotinib) v one drug (including EGFR TKIs)	7.1-9.5 <sup>34</sup>	Not reported	20-23 <sup>34</sup>	Not reported	5-6 <sup>34</sup>

NOTE. Although the systematic review included literature published since January 2002, this table does not include literature published in 2002 because these trials included older protocols, do not reflect more current regimens, and do not truly reflect current survival times.

Abbreviations: PS, performance status; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.

In one study with 444 participants, the response rate was greater in the every-3-week arm ( $P = .037$ ).<sup>54</sup> Adverse events varied by administration schedule, but a clear pattern did not emerge. Hematologic toxicities were greater in the every-3-week schedules. For nonhematologic toxicities, one study reported that toxicities were greater with weekly administration,<sup>54</sup> and the other study reported mixed results.<sup>55</sup> For example, neuropathy was significantly less in the weekly arm of one study,<sup>55</sup> whereas in the other, it was less in the every-3-week arm, as was arthralgia.<sup>54</sup>

Some clinical trials have demonstrated that, when combined with cisplatin, some cytotoxic drugs lead to better outcomes than others. For example, when investigators compared docetaxel/cisplatin with vinorelbine/cisplatin in a study with 1,218 participants, OS was statistically significantly higher with the docetaxel/cisplatin doublet (median OS, 11.3 months [95% CI, 10.1 to 12.4 months]  $\nu$  10.1 months [95% CI, 9.2 to 11.3 months], respectively;  $P = .044$ ; HR = 1.183; 97.2% CI, 0.989 to 1.416).<sup>56</sup> In another study, which had 1,725 participants, although there was no difference in OS between pemetrexed/cisplatin versus gemcitabine/cisplatin across the entire study population, there were differences between subgroups based on a preplanned analysis based on tumor histology.<sup>57</sup> OS was statistically superior for cisplatin/pemetrexed versus cisplatin/gemcitabine in patients with adenocarcinoma ( $n = 847$ ; 12.6  $\nu$  10.9 months, respectively; HR = 0.84; 95% CI, 0.71 to 0.99;  $P = .03$ ) and large-cell carcinoma histology ( $n = 153$ ; 10.4  $\nu$  6.7 months, respectively; HR = 0.67; 95% CI, 0.48 to 0.96;  $P = .03$ ). For patients with squamous cell histology, however, there was a significant improvement in survival with cisplatin/gemcitabine versus cisplatin/pemetrexed ( $n = 473$ ; 10.8  $\nu$  9.4 months, respectively; HR = 1.23; 95% CI, 1.00 to 1.51;  $P = .05$ ).<sup>57</sup> These results prompted the FDA to approve pemetrexed for first-line use only for patients with nonsquamous NSCLC.

The observations that docetaxel/cisplatin is superior to vinorelbine/cisplatin in a general population with NSCLC, that pemetrexed/cisplatin is superior to gemcitabine/cisplatin for patients with nonsquamous NSCLC, and that gemcitabine/cisplatin is superior to pemetrexed/cisplatin for patients with squamous NSCLC are based on individual clinical trials or retrospective (although preplanned) subgroup analysis. These clinical trial results may assist the clinician in choosing one chemotherapy over another if their clinical decision has been narrowed down to the two choices studied in the clinical trial. However, the data are not sufficient to narrow down the selection of a platinum-based doublet to only two choices based on efficacy alone, and the clinician must often choose one chemotherapy regimen over another based on other factors, including drug schedule and adverse effects.

**3. Clinical question.** What is the best chemotherapy for treatment of patients with PS 2 with stage IV NSCLC?

**2003 recommendation.** For elderly patients or patients with an ECOG/Zubrod PS of 2, available data support the use of single-agent chemotherapy.

**2009 recommendation A3.** Available data support the use of single-agent chemotherapy in patients with a PS of 2. Data are insufficient to make a recommendation for or against using a combination of two cytotoxic drugs for patients with a PS of 2.

**Literature update and discussion.** This recommendation remains unchanged from the 2003 guideline update. In reviewing the literature published since 2003, it remains unclear whether administering combination chemotherapy, as opposed to single-agent

chemotherapy, improves survival for patients with PS of 2. Single-agent chemotherapy has less toxicity than combination chemotherapy and is therefore safer to deliver to patients with PS of 2. Use of single-agent vinorelbine, docetaxel, or paclitaxel has led to improved survival in phase III comparisons versus best supportive care in patients with PS of 0 to 2.<sup>58-60</sup> As a result of concerns about toxicity and drug tolerance, patients with stage IV NSCLC and PS of 2 have been routinely excluded from prospective trials of novel combination chemotherapy.<sup>61,62</sup> These data provide the foundation for recommending single-agent chemotherapy for patients with PS of 2.

With regard to combination chemotherapy for patients with PS of 2, the systematic review identified two new phase III trials with planned subgroup analyses by PS,<sup>23,63</sup> one new phase III trial designed exclusively for patients with PS of 2, and a new phase II trial comparing traditional cytotoxic chemotherapy with erlotinib in patients with PS of 2.<sup>24,25</sup> One study of 561 participants, with a planned subgroup analysis, compared paclitaxel monotherapy with paclitaxel/carboplatin and found a survival improvement with the doublet exclusively in patients with PS of 2. Although the patients with PS of 0 to 1 enrolled onto this trial lived longer in general, only the patients with PS of 2 had significantly better OS with combination chemotherapy compared with the single agent (HR = 0.60; 95% CI, 0.40 to 0.91;  $P = .016$ ).<sup>23</sup> Radiologic response rate was significantly better with the doublet for all patients (including those with PS of 2). Although this trial did not distinguish patients whose poor PS was a result of comorbid illness versus the physiologic effects of cancer, these data suggest that more aggressive chemotherapy may be especially helpful for patients who are physically debilitated by cancer. On the basis of the results of this study, a recent prospective trial looking exclusively at patients with PS of 2 used the combination carboplatin/paclitaxel as its control arm. This study did not report any worrisome safety signals but failed to demonstrate improved survival in the experimental arm, in which patients with PS of 2 were treated with carboplatin and paclitaxel poliglumex.<sup>25</sup>

In contrast, another study compared single-agent docetaxel with docetaxel/gemcitabine for patients either older than age 65 years or with PS of 2 (35% of a 345-person study population) and found that the chemotherapy doublet did not increase survival. For patients with PS of 0 to 1, patients receiving doublet chemotherapy had a median survival time of 7.2 months compared with 8 months for patients receiving single-agent chemotherapy, a difference that was not statistically significant ( $P = .5$ ). For patients with PS of 2, the survival difference was also not statistically significant (3.8 months with doublet  $\nu$  2.9 months with singlet;  $P = .62$ ). Time to progression (TTP) and ORR were significantly better with the doublet for participants overall.<sup>63</sup> In a randomized phase II study, with 103 participants, comparing a chemotherapy doublet with erlotinib as first-line treatment for people with PS of 2, doublet chemotherapy conferred a statistically significant survival advantage versus erlotinib alone (median survival, 6.6 months for erlotinib  $\nu$  9.7 months for carboplatin and paclitaxel; HR = 1.73; 95% CI, 1.09 to 2.73;  $P = .018$ ). PFS and ORR were not significantly different. There was not a clear pattern that toxicities overall were worse in one arm.<sup>24</sup>

In summary, as a result of heterogeneity among patients classified as having PS of 2, subjectivity within the scoring system, and lack of consistent data in favor of an optimal chemotherapy regimen, the Update Committee was unable to recommend a combination of two cytotoxic drugs for patients with PS of 2 and recognizes that some

patients classified as having PS of 2 may be unfit even for single-agent chemotherapy.

**4. Clinical question.** What is the best chemotherapy for treatment of elderly patients with stage IV NSCLC?

**2003 recommendation.** For elderly patients or patients with an ECOG/Zubrod PS of 2, available data support the use of single-agent chemotherapy.

**2009 recommendation A4.** The evidence does not support the selection of a specific first-line chemotherapy drug or combination based on age alone.

**Literature update and discussion.** The median age of patients with lung cancer is approximately 70 years, and two thirds of lung cancer patients in the United States are 65 years of age or older.<sup>64,65</sup> Patients who are elderly tend to have more comorbid medical illnesses, have more baseline organ dysfunction, and take more concomitant medications. In general, they are more susceptible to the toxic adverse effects of chemotherapy, most notably neutropenia. However, age is not a significant prognostic factor for patients with stage IV NSCLC and has never been shown to predict benefit from chemotherapy (Table 3). Also, the definition of older age is a matter of debate. Chronologic age does not take into account physiologic age, and few clinical trials use the necessary geriatric assessments needed to account for this. As a result, patients who are older have been understudied on clinical trials and are at risk of being undertreated in routine practice.

In clinical practice, physiologic instead of chronologic age should be considered. In other words, PS is more important than age in selecting chemotherapy. At present, however, chronologic age has served as a frame of reference for clinical trials, and a cutoff of 70 years of age has been most popular. With regard to the literature update, the search found four new RCTs and four planned subgroup analyses that addressed the question of optimal first-line treatment for people older than 65 or 70 years.

In a retrospective analysis of a phase III RCT with 237 participants, patients  $\geq 70$  years old experienced significantly longer TTP, compared with patients less than 70 years old who received the same chemotherapy treatment (4.8 v 3 months, respectively;  $P = .049$ ). Survival was not significantly different.<sup>27</sup> In a planned subgroup analysis of a phase III RCT where participants were stratified by three different doublets and, for the analysis, were further stratified by age (cutoff of 65 years), results in survival did not differ greatly by age.<sup>28</sup> In a planned subgroup analysis of another phase III RCT, survival results in subgroups by age were not significantly different.<sup>23</sup> A retrospective subgroup meta-analysis found no significant difference in survival with a cutoff of 70 years of age. In addition, age was not a significant factor in a multivariate analysis of clinical prognostic factors.<sup>66</sup> Other studies enrolled only patients older than 65 or 70 years and compared regimens; one study showed an HR of 0.606 (95% CI, 0.45 to 0.816;  $P < .001$ ) in PFS for treatment with docetaxel versus vinorelbine for people  $\geq 70$  years old in favor of docetaxel, and response was significantly greater with docetaxel. The study did not report significant differences in OS; this study had 180 participants.<sup>26</sup> A second trial showed no significant difference by age in survival between a doublet (docetaxel/gemcitabine) and a single agent (docetaxel).<sup>63</sup>

Four of these studies reported toxicities. Two studies compared single-agent docetaxel with other treatments. One of the studies, which compared docetaxel with vinorelbine, found that older people had significantly more hematologic and nonhematologic toxicities with docetaxel.<sup>26</sup> The second study found significantly less hemato-

logic toxicities with docetaxel alone versus a docetaxel-containing doublet for patients older than age 65 (or with PS of 2).<sup>63</sup> One analysis found more grade 3 or 4 mucositis in patients  $\geq 70$  years old.<sup>66</sup> Two studies showed no difference in health-related QOL (HRQOL) on the basis of age,<sup>27,67</sup> whereas one found better HRQOL with docetaxel for elderly participants.<sup>26</sup>

In summary, clinical trial data since the 2003 update reinforce the recommendation that age alone should not be used to select chemotherapy for patients with stage IV NSCLC. Older patients may experience more toxicity from cytotoxic chemotherapy than younger patients but may garner an equal amount of benefit.

**5. Clinical question.** Is cisplatin more effective than carboplatin in the first-line treatment of stage IV NSCLC?

**2003 recommendation.** This was not specifically addressed in the 2003 recommendation.

**2009 recommendation A5.** The choice of either cisplatin or carboplatin is acceptable. Drugs that may be combined with platinum include the third-generation cytotoxic drugs docetaxel, gemcitabine, irinotecan, paclitaxel, pemetrexed, and vinorelbine. The evidence suggests that cisplatin combinations have a higher response rate than carboplatin and may improve survival when combined with third-generation agents. Carboplatin is less likely to cause nausea, nephrotoxicity, and neurotoxicity than cisplatin but is more likely to cause thrombocytopenia.

**Literature update and discussion.** This recommendation is based on a lack of consistent superiority of either agent in terms of OS, toxicity, or QOL across the literature. The literature search identified three meta-analyses and 10 individual RCTs that compared cisplatin with carboplatin in combination with a variety of other cytotoxic drugs.

Two literature-based meta-analyses<sup>68,69</sup> and one individual patient data (IPD) meta-analysis<sup>70</sup> found significantly better response rates with cisplatin versus carboplatin. The IPD meta-analysis found response rates of 30% for cisplatin versus 24% for carboplatin; the OR for nonresponse with cisplatin was 1.37 (95% CI, 1.16 to 1.61;  $P < .001$ ).<sup>70</sup>

Two literature-based meta-analyses<sup>68,69</sup> and the IPD meta-analysis<sup>70</sup> found no significant differences in survival between cisplatin and carboplatin. One individual trial, with 618 participants, found that cisplatin/paclitaxel improved survival compared with carboplatin/paclitaxel (9.8 months [95% CI, 8.2 to 11 months] v 8.2 months [95% CI, 7.4 to 9.6 months], respectively;  $P = .019$ ; HR = 1.22; 90% CI, 1.06 to 1.40).<sup>71</sup> A smaller study (153 participants) combining platinum with mitomycin/vinblastine found the opposite to be true, with a survival benefit in favor of carboplatin (7.2 months for cisplatin v 10.0 months for carboplatin;  $P = .019$ ),<sup>72</sup> and one trial (422 participants) that combined carboplatin with gemcitabine versus cisplatin/mitomycin/ifosfamide also found carboplatin to be superior (10 v 7.6 months, respectively; HR = 0.76; 95% CI, 0.61 to 0.93;  $P = .008$ ).<sup>73</sup> One trial with three arms that combined docetaxel with either cisplatin or carboplatin, each compared with cisplatin/vinorelbine, found that cisplatin/docetaxel was superior to cisplatin/vinorelbine in terms of survival but that carboplatin/docetaxel was not.<sup>56</sup> Other individual trials found no difference in survival.<sup>18,74,75</sup>

In the meta-analyses, cisplatin was superior to carboplatin in terms of survival in certain subgroups. The Hotta et al<sup>68</sup> meta-analysis looked exclusively at clinical trials combining either cisplatin or carboplatin with newer chemotherapy agents (docetaxel, gemcitabine,

and paclitaxel) and omitted the trials that used older drugs (etoposide, vindesine, mitomycin, and vinblastine). When cisplatin was combined with newer agents, there was a statistically significant survival benefit over carboplatin (HR = 1.11; 95% CI, 1.01 to 1.22;  $P = .039$ ).<sup>68</sup> Similarly, the IPD meta-analysis by Ardizzoni et al<sup>70</sup> found that cisplatin was superior to carboplatin in survival in clinical trials using docetaxel, gemcitabine, and paclitaxel (HR = 1.11; 95% CI, 1.01 to 1.21). Ardizzoni et al<sup>70</sup> also documented the superiority of cisplatin over carboplatin for patients with nonsquamous histology (HR = 1.12; 95% CI, 1.01 to 1.23). The authors admit that both of these favorable subgroup analyses were not necessarily a result of important drug interactions or histology as a predictive factor, but may simply be a result of the exclusion of a single clinical trial in patients with squamous histology that combined cisplatin or carboplatin with mitomycin/vindesine, which was, notably, the only trial with a survival result in favor of carboplatin.

Carboplatin is less likely than cisplatin to cause nausea<sup>56,68-75</sup> but increases myelosuppression.<sup>68-70,73,75,76</sup> There are several individual trials that demonstrated that carboplatin was more likely than cisplatin to cause thrombocytopenia.<sup>68-70,75</sup> Data on neurotoxicity are confounded by a preponderance of trials that combine carboplatin with taxanes, which are among the most neurotoxic drugs.<sup>74</sup> There is no question that, as individual drugs, cisplatin is more likely to cause ototoxicity and peripheral neuropathy than carboplatin. The risk of some of these toxicities may preclude one platinum drug or the other, or even both. For example, some relative contraindications to cisplatin include baseline hearing loss; renal insufficiency; or comorbid illness, such as congestive heart failure or urinary problems, which limit intravenous saline hydration, or diabetes, which limits use of corticosteroids for emesis prophylaxis. Relative contraindications to carboplatin include baseline thrombocytopenia or bleeding risk.

QOL may be a consideration when making a choice between cisplatin and carboplatin. Of the eight studies that reported HRQOL measures, five showed a benefit in HRQOL with use of carboplatin,<sup>22,56,72,73,76</sup> one showed a benefit with cisplatin,<sup>71</sup> and two reported mixed outcomes.<sup>74,77</sup>

In summary, there is evidence from meta-analyses that cisplatin is superior to carboplatin in terms of ORR and may be superior in terms of survival when combined with docetaxel, gemcitabine, or paclitaxel or when used to treat nonsquamous NSCLC. For otherwise fit patients with severe cancer-related symptoms, such as cough, shortness of breath, or pain, the potential increased response rate offered by cisplatin over carboplatin results in a better chance at tumor shrinkage.

However, overzealous use of cisplatin is ill-advised in patients with baseline renal impairment, hearing loss, peripheral neuropathy, or other clinical characteristic (such as PS  $\geq 2$  or advanced age) that would make the patient especially vulnerable to the toxicities of cisplatin.<sup>78</sup> Few would argue that carboplatin is logistically easier to administer than cisplatin.

The concern for vomiting has become less with improved antiemetics and the use of a lower dose of cisplatin (75 to 80 mg/m<sup>2</sup> every 3 weeks instead of the historical 100 mg/m<sup>2</sup> or more). No clinical trial has documented a dose-response effect within this range, but the risk of nausea is lower with lower doses of cisplatin.<sup>79</sup> However, for patients with stage IV NSCLC in whom the goal is disease control, avoiding toxicity becomes more important, especially when there may be only a small difference in survival when using a less toxic regimen.

**6. Clinical question.** What is the optimal duration of first-line chemotherapy for stage IV NSCLC?

**2003 recommendation.** In patients with stage IV NSCLC, first-line chemotherapy should be stopped at four cycles in patients who are not responding to treatment. The panel consensus is that first-line chemotherapy should be administered for no more than six cycles in patients with stage IV NSCLC.

**2009 recommendation A6.** In patients with stage IV NSCLC, first-line cytotoxic chemotherapy should be stopped at disease progression or after four cycles in patients whose disease is not responding to treatment. Two-drug cytotoxic combinations should be administered for no more than six cycles. For patients who have stable disease or who respond to first-line therapy, evidence does not support the continuation of cytotoxic chemotherapy until disease progression or the initiation of a different chemotherapy before disease progression.

**Literature update and discussion.** This recommendation is based on four RCTs published since the previous guideline addressing the optimal duration of first-line doublet chemotherapy.<sup>80-83</sup> None of the trials showed a significant survival advantage with additional/longer durations beyond four cycles. Two of the trials found statistically significantly better PFS/TTP with additional chemotherapy.<sup>80,81</sup> One study showed an advantage in TTP from four cycles of cisplatin/gemcitabine followed by gemcitabine (until progressive disease or patient or doctor request) versus being followed by best supportive care (TTP: 3.6 months [95% CI, 2.8 to 4.1 months]  $\nu$  2.0 months [95% CI, 1.6 to 2.6 months], respectively;  $P < .001$ ); the study began with 352 participants receiving induction chemotherapy.<sup>80</sup> Another study of 452 participants showed an advantage in TTP of six cycles versus four cycles of carboplatin/paclitaxel for Korean patients with either stable disease or response after two cycles (6.2 months [95% CI, 5.7 to 6.7 months]  $\nu$  4.6 months [95% CI, 4.4 to 4.8 months], respectively;  $P = .001$ ).<sup>81</sup> Of the three trials that reported HRQOL measures, one found advantage in HRQOL for six versus three cycles on one measure, and one found advantage for four versus six cycles on another single measure.<sup>81,83</sup>

All trials reported toxicities. One found peripheral neuropathy greater in the arm with continuous chemotherapy.<sup>82</sup> A second found greater thrombocytopenia with six cycles ( $\nu$  three cycles).<sup>83</sup> Otherwise, the studies did not report significant differences in toxicity between shorter versus longer durations.

Immediate sequential or alternating use of non–cross-resistant drugs for the treatment of patients with NSCLC has not historically proven to be superior to optimal first-line combination chemotherapy.<sup>84</sup> With the advent of drugs that improve survival for patients with progressive cancer after first-line chemotherapy (ie, second-line drugs), there is renewed interest in whether initiation of a non–cross-resistant drug immediately after completion of first-line therapy may improve survival. One theoretical advantage is that more patients will receive the second-line drug if it is started earlier in the clinical course, before a complication from the cancer has a chance to render the patient unfit for second-line chemotherapy. Disadvantages include a decreased ability to assess radiologic response if the patient has already responded to the first-line drugs and cumulative toxicity without the benefit of a drug holiday. Although this is, in essence, a sequential approach, the immediate initiation of second-line chemotherapy before disease progression is often referred to as maintenance or consolidation chemotherapy.

A recently published trial by Fidias et al<sup>85</sup> randomly assigned 309 patients with stage IV NSCLC and no evidence of disease progression after four cycles of carboplatin/gemcitabine to receive immediate docetaxel 75 mg/m<sup>2</sup> every 21 days for up to six cycles or to receive docetaxel on disease progression. Median PFS for docetaxel given immediately was significantly greater than for delayed docetaxel (5.7 v 2.7 months, respectively;  $P = .0001$ ). The lack of placebo control or blinding may have biased this end point. Median OS for immediate docetaxel was greater than for delayed docetaxel, but the difference was not statistically significant (12.3 v 9.7 months, respectively;  $P = .0853$ ).<sup>85</sup> Of note, only 63% of the patients allocated to receive docetaxel at disease progression ever received the drug, versus 95% of patients allocated to immediate docetaxel. The most common reasons were debility as a result of progressive cancer or patient decision. Those patients in the delayed arm who were well enough to receive docetaxel at disease progression had the same OS as the immediate docetaxel group. Grade 3 and 4 toxicities were higher with immediate docetaxel compared with delayed administration, although not significantly so.<sup>85</sup>

A trial presented as an abstract at the 44th Annual Meeting of ASCO in 2008 assessed the efficacy of initiating pemetrexed immediately, versus placebo, in 663 patients with no evidence of disease progression after four cycles of platinum-based therapy containing docetaxel, gemcitabine, or paclitaxel.<sup>86</sup> Of note, only 11% of the patients on the placebo arm went on to receive pemetrexed at any time in their clinical course. In a preliminary report, there was no statistically significant difference in OS (13 months with pemetrexed [95% CI, 11.4 to 14.42 months] v 10.2 months with placebo [95% CI, 8.57 to 13.17 months]; HR = 0.798; 95% CI, 0.63 to 1.01;  $P = .06$ ). Similar to the trial by Fidias et al,<sup>85</sup> there was a statistically significant difference in PFS with immediate pemetrexed versus placebo (4.04 v 1.97 months, respectively; HR = 0.599; 95% CI, 0.49 to 0.73;  $P < .00001$ ). Grade 3 and 4 neutropenia (2.7% with pemetrexed v 0% with placebo;  $P = .011$ ) and fatigue (4.3% with pemetrexed v 0.5% with placebo;  $P = .004$ ) were significantly higher with the additional chemotherapy.<sup>86</sup> The Update Committee anticipates the results of two studies looking at erlotinib as a maintenance therapy and will consider them when published.

In summary, until more mature data are presented showing a survival benefit, these data suggest that PFS, but not OS, may be improved either by continuing an effective chemotherapy beyond four cycles or by immediate initiation of alternative chemotherapy. The improvement in PFS is tempered by an increase in adverse effects from additional cytotoxic chemotherapy.

**7. Clinical question.** What are the benefits, with respect to OS, PFS, toxicity, and QOL/symptom relief, in the treatment of stage IV NSCLC with targeted therapies?

**2003 recommendation.** Initial treatment with an investigational agent or regimen is appropriate for selected patients with stage IV NSCLC, provided that patients are crossed over to an active treatment regimen if they have not responded after two cycles of therapy.

**2009 recommendation A7.** In unselected patients with stage IV NSCLC, erlotinib or gefitinib should not be used in combination with cytotoxic chemotherapy as first-line therapy. In unselected patients, evidence is insufficient to recommend single-agent erlotinib or gefitinib as first-line therapy. The first-line use of gefitinib may be recommended for patients with activating *EGFR* mutations. If *EGFR*

mutation status is negative or unknown, then cytotoxic chemotherapy is preferred (see recommendation A2).

**Literature update and discussion.** Two randomized trials found no advantage in efficacy outcomes to adding erlotinib to first-line chemotherapy. The Tarceva Responses in Conjunction with Paclitaxel and Carboplatin (TRIBUTE) study, which included 1,079 patients, found no advantage in survival, TTP, or response from adding erlotinib to paclitaxel/carboplatin (survival HR = 0.995; 95% CI, 0.86 to 1.16;  $P = .95$ ).<sup>87</sup> In the Tarceva Lung Cancer Investigation (TALENT) study (1,172 patients), there was no advantage in the same efficacy outcomes when adding erlotinib to gemcitabine/cisplatin (survival HR = 1.06; 95% CI, 0.90 to 1.23;  $P = .49$ ).<sup>88</sup> There were no significant differences between arms in either study in hematologic toxicities. In one study, there was more rash and diarrhea in the erlotinib-containing arm.<sup>88</sup> Two large trials investigated the use of gefitinib in combination with chemotherapy for participants in the first-line setting. Neither found a significant difference in survival ( $P = .456$  and  $P = .6385$ ) or other efficacy outcomes when gefitinib was added to platinum-based doublets (both were three-arm studies with two different doses of gefitinib v chemotherapy alone).<sup>89,90</sup> In both trials, toxicities were significantly lower in the placebo arms when compared with the gefitinib arms (diarrhea,  $P < .0001$  [gefitinib 500 mg]; skin,  $P < .001$  [both doses]<sup>89</sup>; diarrhea,  $P < .0001$  [500 mg],  $P = .0011$  [250 mg]; and skin,  $P < .0001$  [both doses]<sup>90</sup>).

There is not sufficient evidence to support the use of erlotinib as a single agent in the first-line setting in patients who have not been selected based on clinical or molecular characteristics. A randomized phase II study compared a chemotherapy doublet of carboplatin/paclitaxel with erlotinib as first-line treatment for people with PS of 2. Doublet chemotherapy conferred a significant survival advantage versus erlotinib alone (HR = 1.73; 95% CI, 1.09 to 2.73;  $P = .018$ ), although PFS and ORR were not significantly different.<sup>24</sup> This study indicated that erlotinib is not to be preferred to chemotherapy in patients with poor PS.

In the Iressa Pan Asia Study (IPASS; outside the date parameters of the systematic review, originally presented as an abstract), investigators compared gefitinib with carboplatin/paclitaxel as first-line treatment in populations specific to East Asia; all of the 1,217 patients had adenocarcinoma and were light or never smokers. The primary end point of the study was PFS, and the finding was statistically significant prolongation with gefitinib versus carboplatin/paclitaxel (HR = 0.74; 95% CI, 0.65 to 0.85;  $P < .001$ ; median PFS, 5.7 v 5.8 months, respectively). Overall response rate was increased with gefitinib (ORR = 1.59; 95% CI, 1.25 to 2.01;  $P = .001$ ). Preliminary findings in OS were not significantly different (HR = 0.91; 95% CI, 0.76 to 1.10,  $P$  not reported; median OS, 18.6 with gefitinib v 17.3 months with carboplatin/paclitaxel), with follow-up ongoing. Hematologic adverse effects, alopecia, neuropathy, and nausea were higher with chemotherapy, whereas diarrhea and skin toxicities were greater with gefitinib. A significantly higher proportion of patients in the gefitinib arm had an improvement in QOL as measured by a trial-specific outcome index and Functional Assessment of Cancer Therapy–Lung instrument. The results of analysis of PFS by *EGFR* mutation status (see the section on molecular markers later in this article) found that patients with mutations experienced a better outcome with gefitinib and patients whose tumors lacked mutations benefited more from chemotherapy.<sup>91</sup> The findings of this study strongly suggest that

the use of clinical characteristics may identify patients who have similar benefits with gefitinib and with platinum-based chemotherapy. The IPASS study also suggests that for patients with tumors with *EGFR* mutations, gefitinib is superior to carboplatin and paclitaxel in terms of PFS. Activating mutations in *EGFR* consist mainly of deletions in exon 19 or a point mutation in exon 21 leading to substitution of arginine for leucine at position 858 (L858R).

The Update Committee awaits OS results from this trial. Meanwhile, as a result of the PFS benefit, improvement in QOL, and favorable toxicity profile, gefitinib may be preferred to chemotherapy in first-line treatment compared with cytotoxic chemotherapy for patients whose tumors are found to contain *EGFR* mutation. In addition, the presence of *EGFR* mutation also indicates that erlotinib or gefitinib is the preferred drug for second-line chemotherapy for patients who did not receive these drugs during first-line therapy (see recommendation B1).

Randomized studies of first-line erlotinib for patients with tumors with *EGFR* mutation are ongoing. More data are needed to determine whether first-line use of gefitinib or erlotinib for patients with *EGFR* mutation improves OS. These early data justify attempts to test NSCLC for the presence of *EGFR* mutation; however, the *EGFR* mutation status of most patients' tumors is negative or unknown, and current evidence is insufficient to recommend the routine use of molecular markers to select systemic treatment in patients with metastatic NSCLC (see recommendation D1). In cases where the *EGFR* mutation status is negative or unknown, cytotoxic chemotherapy is preferred (see recommendation A2).

**2009 recommendation A8.** On the basis of the results of one large phase III RCT, the Update Committee recommends the addition of bevacizumab, 15 mg/kg every 3 weeks, to carboplatin/paclitaxel, except for patients with squamous cell carcinoma histologic type, brain metastases, clinically significant hemoptysis, inadequate organ function, ECOG PS more than 1, therapeutic anticoagulation, clinically significant cardiovascular disease, or medically uncontrolled hypertension (based on exclusion criteria for Sandler et al<sup>61</sup> registration trial). Bevacizumab may be continued, as tolerated, until disease progression.

**Literature update and discussion.** This recommendation is based on one randomized phase II and one phase III clinical trial comparing bevacizumab added to chemotherapy with chemotherapy alone. The registration trial, which added bevacizumab to paclitaxel/carboplatin (*v* paclitaxel/carboplatin alone) and had 850 participants, showed a significant decrease in the HR for death and improvement in OS (median OS, 10.3 months with paclitaxel/carboplatin alone *v* 12.3 months with bevacizumab plus paclitaxel/carboplatin; HR for death = 0.79; 95% CI, 0.67 to 0.92; *P* = .003). Response and PFS (4.5 months with paclitaxel/carboplatin alone *v* 6.2 months with bevacizumab plus paclitaxel/carboplatin; decreased HR for progressive disease, HR = 0.66, *P* < .001) were significantly higher with the addition of bevacizumab.<sup>61</sup>

Hematologic toxicities were reported in both studies and were greater in the bevacizumab plus chemotherapy arms. The phase II RCT had six cases of major bleeding; four were fatal.<sup>92</sup> The toxicities in the phase II trial led to a narrowing of eligibility criteria in the phase III trial (exclusion criteria were histologic evidence of predominantly squamous cell carcinoma, brain metastases, clinically significant hemoptysis, inadequate organ function, ECOG PS > 1, history of hemorrhagic diathesis or coagulopathy, therapeutic anticoagulation,

therapeutic antiplatelet therapy including aspirin > 325 mg/d, nonsteroidal anti-inflammatory agents or other agents known to inhibit platelet function, clinically significant cardiovascular disease, and medically uncontrolled hypertension). In the phase III trial, grade 4 and 5 hematologic toxicities were significantly greater in the bevacizumab arm, as were nonhematologic toxicities. There were significantly more bleeding events in the bevacizumab arm versus the chemotherapy-alone arm, including five pulmonary hemorrhages (4.4% *v* 0.7%, respectively; *P* < .001). There were 15 treatment-related deaths in the bevacizumab arm compared with two such deaths in the chemotherapy-alone arm (the authors noted that most deaths occurred in the first two treatment cycles).<sup>61</sup> The dose used in this trial was 15 mg/kg. The studies did not report HRQOL.

Published phase III data, originally presented at the 2007 ASCO and ESMO meetings, from the Avastin in Lung Cancer trial compared two doses of bevacizumab (7.5 and 15 mg/kg every 3 weeks) plus chemotherapy (cisplatin/gemcitabine) with a control arm of chemotherapy plus placebo in 1,043 patients, with a primary end point of PFS, using similar exclusion criteria as the registration trial.<sup>93,94</sup> (Note: The publication was outside the date parameters of the systematic review.) These results confirmed a marginal, albeit significant, improvement of PFS in both bevacizumab arms (placebo-containing arm *v* bevacizumab-containing arm 7.5 mg/kg: 6.1 *v* 6.7 months, respectively; HR = 0.75; 95% CI, 0.62 to 0.91; *P* = .003; placebo-containing arm *v* bevacizumab-containing arm 15 mg/kg: 6.1 *v* 6.5 months, respectively; HR = 0.82; 95% CI, 0.68 to 0.98; *P* = .03). However, there was no difference in interim results of survival data between the placebo arm and either bevacizumab arm; for OS, a secondary end point, follow-up was not of a sufficient duration when the researchers produced the full publication. In addition, the rates of grade 3 or greater pulmonary hemorrhages and fatal pulmonary hemorrhages were not significantly different between bevacizumab doses. This study also reported a longer median survival than anticipated in the control arm. The results of this large randomized study suggest that there may be differences in outcomes depending on which chemotherapy regimen is used together with bevacizumab and also suggest that a lower dose of bevacizumab may be as effective as a high dose.

Because the addition of bevacizumab to gemcitabine and cisplatin did not improve OS and because of the lack of phase III data combining bevacizumab with other cytotoxic regimens, data were not sufficient for the Update Committee to recommend adding bevacizumab to cytotoxic chemotherapy regimens other than carboplatin and paclitaxel. The improvements in PFS and ORR, although clinically significant, are tempered by an increase in toxicity from bevacizumab. For bevacizumab, there is special concern for toxicity in elderly populations. A subgroup analysis of patients at least 70 years old enrolled onto a trial of carboplatin/paclitaxel with or without bevacizumab revealed more grade 3 to 5 toxicities with the use of bevacizumab (87% *v* 61%, respectively; *P* < .001), including higher rates of neutropenia and bleeding, and seven treatment-related deaths in the bevacizumab arm compared with two in the control arm. Perhaps related to this added toxicity, there was no obvious improvement in OS in the elderly subgroup.<sup>95</sup> (Note: The publication was outside the date parameters of the systematic review.) The optimal duration of bevacizumab beyond chemotherapy is yet to be determined.

**2009 recommendation A9.** On the basis of the results of one large phase III RCT, clinicians may consider the addition of cetuximab to

cisplatin/vinorelbine in first-line therapy in patients with an EGFR-positive tumor as measured by immunohistochemistry (IHC). Cetuximab may be continued, as tolerated, until disease progression.

**Literature update and discussion.** In a phase III study, which was first reported as an abstract and subsequently published after the systematic review,<sup>96</sup> including 1,125 patients who received cisplatin/vinorelbine with or without the addition of cetuximab 400 mg/m<sup>2</sup> initial dose followed by weekly doses of 250 mg/m<sup>2</sup>, OS was significantly greater in the cetuximab arm versus the cisplatin/vinorelbine-only arm (median OS, 11.3 v 10.1 months, respectively; HR = 0.871; 95% CI, 0.762 to 0.996; *P* = .0441), although PFS was not (4.8 v 4.8 months, respectively; HR = 0.943; 95% CI, 0.825 to 1.077; *P* = not significant).<sup>97</sup> In addition, the response rate was greater in the cetuximab plus chemotherapy arm versus the chemotherapy-alone arm (36% v 29%, respectively; *P* = .012). In a post hoc analysis, time to treatment failure was improved with cetuximab (HR = 0.860; 95% CI, 0.761 to 0.971; *P* = .015). Febrile neutropenia (grade 3: cetuximab arm = 16%, control arm = 11%; grade 4: cetuximab arm = 6%, control arm = 4%; *P* = .0086 for grades 3 and 4), grade 3 acne/rash (*P* = .0001), grade 3 or 4 infusion-related reactions (*P* = .017), and grade 3 or 4 diarrhea (*P* = .047) were significantly greater in the cetuximab arm. Eligibility required that all patients have their tumor tested for EGFR expression by IHC and that at least one tumor cell stained positive. The protocol used the DakoCytomation pharmDx kit (Dako, Glostrup, Denmark) and found at least one positive tumor cell in the majority (85%) of patients tested.<sup>96</sup>

Before this study, investigators published two phase II RCTs on cetuximab.<sup>98,99</sup> These trials both compared a chemotherapy doublet with a triplet including cetuximab (one was also cisplatin/vinorelbine). Neither trial showed significant differences between the doublet and cetuximab-containing triplet in efficacy outcomes. There were nonsignificant trends favoring cetuximab for OS, PFS, and ORR, prompting the larger, phase III studies. In one trial, 14.1% of people in the cetuximab arm had grade 3 or 4 rash versus none in the doublet arm.<sup>98</sup> Both studies reported toxicities. One showed greater hematologic toxicities in the cetuximab arm<sup>99</sup>; the other had mixed results (eg, neutropenia 4.5% with cetuximab v 1.5% in control arm; and thrombocytopenia 57.8% with cetuximab v 44.6% in control arm).<sup>98</sup> One study showed greater nonhematologic toxicities in the cetuximab arm,<sup>98</sup> and the other study showed greater toxicities in the control arm<sup>99</sup>; however, neither study reported significant differences for these toxicities.

In a phase III trial with 676 participants, published as an abstract, cetuximab combined with carboplatin/paclitaxel or docetaxel did not improve the primary end point of PFS as determined by the Independent Radiologic Review Committee (4.24 months with carboplatin/taxane v 4.4 months with carboplatin/taxane/cetuximab; HR = 0.902; 95% CI, 0.76 to 1.07; *P* = .24).<sup>100</sup> The final assessment for median PFS was 3.8 with carboplatin/taxane versus 4.4 months with carboplatin/taxane/cetuximab (HR = 0.79, *P* = .0036); OS was not statistically significantly different (9.7 v 8.4 months; HR = 0.89; 95% CI, 0.75 to 1.05; *P* = .17).<sup>100,101</sup>

The results of these studies suggest that cetuximab may add benefit in terms of survival when combined with cisplatin/vinorelbine. Again, as for bevacizumab, these results may not be directly translated to all chemotherapy regimens.

The duration of cetuximab is recommended to continue until intolerance or progression of the disease, based on the design of the

studies. However, the optimal duration of treatment with cetuximab beyond chemotherapy is not known.

## Second-Line Chemotherapy

**1. Clinical questions.** Is there an optimal second-line treatment for stage IV NSCLC? Is there evidence to support the use of combination biologic therapy as second-line therapy? Is there an optimal schedule of administration in second-line treatment for stage IV NSCLC?

**2003 recommendation.** Docetaxel is recommended as second-line therapy for patients with locally advanced or metastatic NSCLC with adequate PS who have experienced progression on first-line, platinum-based therapy. Gefitinib is recommended for the treatment of patients with locally advanced or metastatic NSCLC after failure of both platinum-based and docetaxel chemotherapies.

**2009 recommendation B1.** Docetaxel, erlotinib, gefitinib, and pemetrexed are acceptable as second-line therapy for patients with advanced NSCLC with adequate PS when the disease has progressed during or after first-line, platinum-based therapy.

**Literature update and discussion.** These recommendations are based on nine new phase III RCTs, two new phase II RCTs, a new IPD meta-analysis, a new systematic review, and two new retrospective subgroup analyses of phase III trials on second-line chemotherapy (see Table 3 for range of outcomes). The recommendation for docetaxel is based on evidence presented in the 2003 guideline. A systematic review published since that guideline included 19 phase II and III studies (total number of participants was not available). It found a significant survival benefit to docetaxel versus best supportive care.<sup>102,103</sup>

One phase III trial, with 571 participants, found pemetrexed to be noninferior in efficacy to docetaxel.<sup>31</sup> OS was 8.3 months for pemetrexed and 7.9 months for docetaxel (HR = 0.99; 95% CI, 0.82 to 1.2; *P* = not significant); the test for noninferiority was 0.226. PFS for both arms was 2.9 months, and 29.7% of patients in both arms were alive at 1 year. All significant grade 3 or 4 hematologic and nonhematologic toxicities were higher with docetaxel, except ALT levels. Grade 3 and 4 neutropenia occurred in 5.3% of patients receiving pemetrexed versus 40.2% of patients receiving docetaxel (*P* < .001). This trial used a 500 mg/m<sup>2</sup> dose of pemetrexed.<sup>31</sup> The systematic review concluded that pemetrexed showed similar OS and PFS to docetaxel with less toxicity, based on these results.<sup>102</sup> An analysis of the efficacy of pemetrexed based on histology was conducted similar to the one performed in the first-line trial, albeit retrospectively and with fewer patients.<sup>104</sup> (Note: The publication was outside the date parameters of the systematic review.) In this subgroup analysis, regarding OS, pemetrexed was similar to docetaxel for adenocarcinoma (*n* = 302; HR = 0.92; 95% CI, 0.69 to 1.22), superior for large-cell carcinoma (*n* = 47; HR = 0.27; 95% CI, 0.11 to 0.63), and inferior to docetaxel for the treatment of squamous NSCLC (*n* = 172; HR = 1.56; 95% CI, 1.08 to 2.26). As a result, the FDA has approved pemetrexed for second-line use only in patients with nonsquamous NSCLC. A second RCT compared two doses of pemetrexed and found a better, but not statistically significant, response with 500 versus 900 mg/m<sup>2</sup> and no survival, PFS, or toxicity differences.<sup>29</sup>

There is evidence from one phase III trial (BR21) comparing erlotinib to placebo in 731 patients after failure of prior chemotherapy to support its use as second-line therapy. The trial found a significant improvement in OS with erlotinib (HR = 0.70; 95% CI, 0.58 to 0.85; *P* < .001) and a difference in median survival versus

placebo (6.7 v 4.7 months, respectively). The response rate was greater with erlotinib versus placebo (8.9% v < 1%, respectively;  $P < .001$ ). An improvement in survival was observed in all subgroups examined (eg, sex, smoking status, histology, race, and so on), except when participants were grouped by PS.<sup>30</sup> There was significantly increased rash and diarrhea in the erlotinib arm (both  $P < .001$ ).<sup>30</sup> A follow-up study found that an increased grade of rash in this trial correlated with significantly longer OS and PFS and higher response rate with erlotinib.<sup>105</sup>

Since the 2003 guideline, a phase III trial (Iressa Survival Evaluation in Lung Cancer [ISEL] trial) of gefitinib as second- or third-line treatment was published that found no significant improvement from gefitinib versus best supportive care/placebo in OS.<sup>106</sup> This trial, with 1,692 patients, showed an advantage in median time to treatment failure (HR = 0.820; 95% CI, 0.73 to 0.95;  $P = .0006$ ) and ORR (OR = 7.28; 95% CI, 3.1 to 16.9;  $P < .0001$ ). After the announcement of results from this trial, the FDA mandated changes in the availability of gefitinib because it had granted approval before and contingent on the completion of this trial (<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm163112.htm>). Initial approval had been based on two phase II trials discussed in the 2003 guideline.

However, there are emerging data indicating that gefitinib may be noninferior to docetaxel for second-line treatment. In a small randomized phase II trial with 141 patients who had progressive disease during or after nontaxane chemotherapy, median survival time was 7.5 months for gefitinib versus 7.1 months for docetaxel. PFS and response rates were also not significantly different. Grade 3 and 4 toxicities were nearly three times greater in the docetaxel arm.<sup>107</sup> A recent phase III publication (Iressa NSCLC Trial Evaluating Response and Survival Against Taxotere [INTEREST]) of 1,466 patients showed the noninferiority of gefitinib compared with docetaxel in terms of OS. (Note: The publication was outside the date parameters of the systematic review.) Median OS was 7.6 months with gefitinib versus 8.0 months with docetaxel (HR = 1.02; 96% CI, 0.905 to 1.15). Grade 3 and 4 adverse events were lower with gefitinib than docetaxel (9% v 41%, respectively). The rates of serious adverse events overall were 4% versus 18% for gefitinib and docetaxel, respectively.<sup>33</sup> As of press time (September 2009), gefitinib was not available to patients in the United States who were not receiving this drug and experiencing benefit as of June 2005.

If a patient's tumor is discovered to have an activating *EGFR* mutation and the patient has not yet received either erlotinib or gefitinib, then erlotinib or gefitinib is the preferred drug for second-line chemotherapy. This is an extrapolation of the results of the IPASS study in which patients with tumors with *EGFR* mutation had improved PFS with gefitinib compared with cytotoxic chemotherapy (carboplatin and paclitaxel) as first-line therapy (see recommendation A7),<sup>91</sup> as well as phase II data that patients with *EGFR* mutation have higher radiologic response rates to erlotinib or gefitinib (see section on molecular markers later in this article).<sup>108-110</sup> More data are needed to determine whether second-line use of erlotinib or gefitinib in patients with *EGFR* mutation improves OS compared with cytotoxic chemotherapy. For example, there was no difference in OS in the small subgroup of *EGFR* mutation-positive patients randomly assigned between gefitinib and docetaxel in the INTEREST study.<sup>33</sup>

**Combination biologic therapy.** At the time of this guideline's completion, there were not any published phase II or III trials with positive results for OS using erlotinib in combination with bevacizumab.

In a randomized phase II trial of 120 patients, bevacizumab was tested in combination with chemotherapy or with erlotinib when one platinum-containing regimen failed for patients (three-arm study: bevacizumab/chemotherapy v bevacizumab/erlotinib v chemotherapy/placebo).<sup>111</sup> Docetaxel or pemetrexed was the chemotherapy control arm (at investigator discretion). Adjusted HR for risk of progressive disease was 0.66 for bevacizumab and chemotherapy versus chemotherapy/placebo (95% CI, 0.38 to 1.16) and 0.72 for bevacizumab and erlotinib versus chemotherapy/placebo (95% CI, 0.42 to 1.23). Five of 120 patients experienced grade 3 to 5 hemorrhage. There were three deaths caused by pulmonary hemorrhage in the two bevacizumab-containing arms of this study.<sup>111</sup>

The results of a recently completed phase III RCT presented as an abstract compared bevacizumab and erlotinib with erlotinib alone after standard first-line chemotherapy failed for 636 patients.<sup>112</sup> There was a doubling of the ORR (12.6% with bevacizumab/erlotinib, 6.2% with erlotinib alone;  $P = .006$ ) and the PFS (3.4 months with bevacizumab/erlotinib, 1.7 months with erlotinib alone;  $P < .0001$ ). The median OS was 9.3 months for bevacizumab/erlotinib versus 9.2 months for erlotinib alone ( $P = .75$ ; HR = 0.97; 95% CI, 0.80 to 1.18), making this a negative study for OS.<sup>112</sup> The Committee awaits publication of further trial results on the bevacizumab/erlotinib combination in second-line therapy.

**Schedule of administration of second-line therapy.** Trials have investigated the schedule of administration of docetaxel. Three RCTs compared the administration of weekly docetaxel to every-3-week administration.<sup>113-115</sup> None of the trials showed an advantage to treatment with weekly administration of docetaxel versus every-3-week administration in terms of survival (5.4 months for weekly v 6.6 months for every-3-week,  $P = .076$ <sup>113</sup>; 25 weeks for weekly v 29 weeks for every-3-week<sup>114</sup>; 9.2 months for weekly v 6.3 months for every-3-week,  $P = .07$ <sup>115</sup>). There was also no statistically significant difference in PFS (reported by two of the three studies) or response.<sup>113,115</sup> Note that the total dose of the three weekly administrations was greater than the dose in the every-3-week administration; the latter dose was 75 mg/mg<sup>2</sup> in each trial.

All three trials reported toxicities. Hematologic toxicities were generally significantly greater in the every-3-week schedule. One study reported significant differences in nonhematologic toxicities, with mixed results; a majority of the toxicities showed an advantage to the every-3-week schedule (grade 3 or 4 mucositis, dyspnea, and diarrhea of any grade were significantly greater in weekly administration).<sup>113</sup> Almost all hematologic toxicities were significantly greater with every-3-week administration in the three trials. Two studies reported HRQOL,<sup>114,115</sup> and one found differences; the weekly schedule showed greater benefit by the measures reported (except diarrhea).<sup>114</sup> These results suggest that weekly administration of docetaxel may be preferred as a result of a milder toxicity profile compared with the every-3-week schedule, but efficacy is not improved.

There were no data available on the duration of second-line therapy. The phase III clinical trials of docetaxel,<sup>103,116</sup> erlotinib,<sup>30</sup> gefitinib,<sup>33,91,106</sup> and pemetrexed<sup>31</sup> allowed patients on study to continue chemotherapy, as tolerated, until disease progression. For example, in the phase III trial comparing docetaxel and pemetrexed in patients with previously treated stage IV NSCLC, the median number of cycles of chemotherapy administered was four in each group, with a range of one to 20 for pemetrexed and one to 14 for docetaxel.<sup>31</sup>

**2. Clinical question.** What is the optimal second-line treatment for elderly patients with stage IV NSCLC?

**2003 recommendation.** This was not specifically addressed in a 2003 recommendation.

**2009 recommendation B2.** The evidence does not support the selection of a specific second-line chemotherapy drug or combination based on age alone.

**Literature update and discussion.** The search identified a new retrospective subset analysis of an RCT on second-line chemotherapy for older people, a topic new to the guideline.<sup>34</sup> (See Table 3 for range of outcomes.) The analysis compared outcomes from docetaxel versus pemetrexed by age. There were 571 patients on the registration trial for pemetrexed from which this analysis was drawn. Patients  $\geq$  age 70 years received similar benefit from both agents. The difference in survival between patients  $\geq$  age 70 compared with patients younger than age 70 taking docetaxel was not significant (median OS: 7.7 v 8.0 months, respectively;  $P =$  not significant). Patients  $\geq$  age 70 had longer, survival and TTP with pemetrexed compared with patients younger than age 70 (median OS: 9.5 v 7.8 months, respectively), but the difference was not statistically significant. Toxicity did not differ significantly by age. The analysis did not report QOL measures.<sup>34</sup>

### Third-Line Chemotherapy and Beyond

**3. Clinical question.** Is there a role for third-line therapy in the treatment of stage IV NSCLC?

**2003 recommendation.** This was not specifically addressed in a 2003 recommendation.

**2009 recommendation C1.** When disease progresses on or after second-line chemotherapy, treatment with erlotinib may be recommended as third-line therapy for patients with PS of 0 to 3 who have not received prior erlotinib or gefitinib.

**Literature update and discussion.** In the BR21 trial, patients were allowed to have received two previous regimens of chemotherapy and patients had a PS of 0 to 3.<sup>30</sup> Patients taking erlotinib as second- or third-line therapy experienced a survival benefit (see results in earlier section on second-line chemotherapy). In a univariate subgroup analysis, survival did not differ by number of prior regimens (one prior regimen: HR = 0.8; 95% CI, 0.6 to 1.1;  $P = .03$ ; two or three prior regimens: HR = 0.8; 95% CI, 0.6 to 1.1;  $P = .02$ ). In a multivariate analysis of survival, the difference was not significant. The response rate was not influenced by number of prior regimens (one prior, 8.9%; two or three prior regimens, 8.9%). Neither survival nor response rate differed by response to prior therapy. Therefore, erlotinib seems to be as beneficial as third-line therapy as for second-line therapy.<sup>30</sup>

There is a paucity of trials that enrolled patients who have had more than one previous treatment with cytotoxics or biologic agents. A recent search of the National Cancer Institute's Physician Data Query clinical trial site found that only five of 162 trials listed could be offered to a patient who had already completed two lines of therapy. Trial designers should consider offering inclusion to patients with good PS, regardless of number of prior regimens, especially in large phase III RCTs on third-line treatment with targeted agents. As was seen in BR21, whether the EGFR TKI treatment given was second- or third-line therapy, the magnitude of the benefit was the same.

**2009 recommendation C2.** The data are not sufficient to make a recommendation for or against using a cytotoxic drug as third-line therapy. These patients should consider clinical trials, experimental treatment, or best supportive care.

**Literature update and discussion.** A retrospective analysis of the outcome of 700 patients who had received two or more prior chemo-

therapy regimens, including a platinum and docetaxel regimen, for recurrent NSCLC<sup>117</sup> was the only result of the literature search for this clinical question. Response rates decreased with each subsequent regimen (first-line, 20.9%; second-line, 16.3%; third-line, 2.3%; fourth-line, 0%), as did disease control rates (first-line, 62.8%; second-line, 74.4%; third-line, 30.2%; fourth-line, 21.4%). Survival also declined (first-line, 15.7 months; second-line, 9.8 months; third-line, 5.4 months; fourth-line, 5.9 months). Median OS from the start of the last treatment was 4 months.<sup>117</sup> Patients receiving third- and fourth-line cytotoxic therapy have infrequent responses, the responses are of short duration, and the toxicities are considerable. For these patients, supportive care only is a reasonable option, in addition to experimental treatments and clinical trials.

### Use of Molecular Markers to Select Therapy

**1. Clinical question.** For the purposes of prescribing chemotherapy, what is the relevance of molecular analysis of tissue?

**2003 recommendation.** NSCLC histology is not an important prognostic factor in patients with advanced, unresectable disease. The use of newer, putative prognostic factors such as *RAS* mutations or *p53* mutations is investigational and should not be used in clinical decision making.

**2009 recommendation D1.** Evidence is insufficient to recommend the routine use of molecular markers to select systemic treatment in patients with metastatic NSCLC.

**Literature update and discussion.** Recommendation A7 supports the first-line use of gefitinib over carboplatin and paclitaxel in patients whose NSCLC harbors *EGFR* mutation based on a clinically significant improvement in PFS, favorable toxicity profile, and improved QOL. These data justify attempts to test patients with NSCLC for the presence of *EGFR* mutation. However, no study to date has demonstrated an improvement in OS when chemotherapy is selected on the basis of a molecular marker.

Numerous molecular markers are being tested for their prognostic and/or predictive value in the management of patients with stage IV NSCLC. Prognostic markers provide information on the risk of death as a result of NSCLC, independent of therapy. Predictive markers provide information on the potential benefit of a specific therapy. Some markers also provide both prognostic and predictive information at the same time. Molecular tests may be performed on tumor tissue or surrogates such as peripheral blood. For this guideline update, members of the Update Committee identified molecular tests they believed might have clinical relevance, and these suggestions informed some of the terms used in the literature search, including *EGFR*, *RAS*, *ERCC1*, *RRM1*, and *VEGF*, and serum tumor markers. Emerging data suggest that some of these markers may become clinically informative in the near future (see the following sections). However, current evidence is insufficient to recommend the routine use of molecular markers to select systemic treatment in patients with NSCLC.

**EGFR.** EGFR (human epidermal growth factor [HER] 1/ErbB1) is a receptor tyrosine kinase of the ErbB family, which consists of the following four closely related members: HER1/ErbB1, HER2/*neu*/ErbB2, HER3/ErbB3, and HER4/ErbB4. On ligand binding and receptor activation (phosphorylation), EGFR signals key downstream cellular processes that regulate cell proliferation and apoptosis. Aberrant EGFR signaling can lead to uncontrolled tumor growth. Such unrestrained signaling can occur via too much EGFR

(eg, from amplification of the gene at the DNA level)<sup>118</sup> or too active EGFR (eg, from mutation of the kinase domain of the receptor).<sup>119-121</sup> Activating mutations consist mainly of deletions in exon 19 or point mutations in exon 21; the latter lead to substitutions of arginine for leucine at position 858 (L858R). Drugs that target EGFR include selective small-molecule TKIs (ie, gefitinib and erlotinib) and receptor-specific antibodies (eg, cetuximab).

Multiple studies have attempted to elucidate whether EGFR status can be used to predict response to EGFR TKIs. EGFR status is assessed in tumors using the following three major methods: at the protein level by IHC; at the DNA copy number level, such as by fluorescent in situ hybridization (FISH); and at the DNA sequence level by mutational analysis. All tests can be performed on paraffin-embedded tumor sections, but mutational analysis requires extraction of DNA. The percentage of NSCLC tumors positive for each assay varies greatly; in North American populations, for example, approximately 60% of tumors are IHC positive, approximately 30% to 45% are FISH positive, and approximately 10% are mutation positive. Notably, *EGFR*-mutant samples frequently display *EGFR* amplification. Fewer studies have examined the use of EGFR status as a biomarker predictive of response to EGFR-directed antibodies. In the First-Line Erbitux in Lung Cancer (FLEX) study (chemotherapy plus cetuximab v placebo), eligibility required that tumors contain at least one EGFR-positive cell as determined by IHC, a low threshold that allowed 85% of patients (1,442 of 1,688 patients) screened to be eligible.<sup>96</sup>

The systematic review found 37 reports on studies involving EGFR status and, primarily, use of EGFR TKIs.<sup>109,122-157</sup> Twenty-four studies were retrospective, including five analyses of the major clinical trials involving gefitinib and erlotinib.<sup>124,126,128,131,141</sup> It is important to note that in these five analyses, tumor specimen collection was not mandated, and the percentage of patients' tumors examined for biomarkers was low. For example, only approximately 20% of patients were assessed for *EGFR* mutations. The authors of seven papers described them as prospective, including six phase II trials. Most of the reports involved gefitinib; five used erlotinib. Five studies involved chemotherapy either with or without an EGFR TKI.<sup>124,137,138,149,155</sup>

Thirty-one of the studies reported OS. Twenty reported on OS by mutation status, and 14 of those studies showed a significant benefit for patients with tumors that were *EGFR* mutation positive (measured by any of three methods). Of five studies that reported on survival by EGFR IHC results, four reported a significant survival benefit when the tumors stained positive.<sup>128,129,141,150</sup> Six studies reported *EGFR* gene copy number status as assessed by FISH, four of which showed a survival benefit for people with FISH-positive/amplified tumors.<sup>128,129,141,150</sup>

Twenty-eight of the studies reported PFS (or TTP). Twenty-one reported PFS by mutation status, 16 of which reported significant benefit to patients with mutation-positive tumors. Two studies reported PFS/TTP on IHC testing; one showed a statistically significantly longer TTP for IHC-positive tumors.<sup>129,150</sup> Six studies reported on FISH, with two showing significant PFS benefit for patients with FISH-positive tumors.<sup>127,150</sup>

An IPD meta-analysis included 506 participants from mainland China who received gefitinib, 57 of whom tumors had complete treatment data.<sup>110</sup> All studies were after 2003. Survival did not differ by mutation status, but response was significantly greater among patients with mutated *EGFR* tumors (OR = 5.78; 95% CI, 1.95 to 17.13;

$P = .002$ ). The study concluded that adenocarcinoma histology and a history of never smoking are independent predictors for *EGFR* mutations and that response to gefitinib favors patients with *EGFR*-mutant tumors.

A systematic review of studies that selected patients for treatment with an EGFR TKI based on the presence of *EGFR* mutations in their tumor included five trials (phase II and prospective), all conducted in Japan, with a total of 101 participants.<sup>108</sup> OS was not reached by the time of the review, with the exception of one nonrandomized study, in which it was 15.4 months.<sup>151</sup> The collective overall ORR was 80.8%. Two percent of participants developed interstitial lung disease, and three percent had grade 3 or 4 skin toxicities. The systematic review did not report the statistical significance of adverse events. The study concluded that gefitinib is beneficial to people with *EGFR*-mutant tumors (preselected) in terms of response. People whose tumors had L858R and/or exon 19 mutations had similar response benefits.

Recently, results were reported from the phase III, randomized, open-label, first-line study of gefitinib versus carboplatin/paclitaxel in never or light East Asian smokers with advanced NSCLC (ie, IPASS).<sup>91</sup> The results of analysis of PFS by *EGFR* mutation status found that patients with mutations experienced longer PFS with gefitinib and patients without mutations had longer PFS with chemotherapy (*EGFR* mutation positive: HR = 0.48; 95% CI, 0.36 to 0.64;  $P < .001$  [favors gefitinib]; *EGFR* mutation negative: HR = 2.85; 95% CI, 2.05 to 3.98;  $P < .001$  [favors chemotherapy]).<sup>79</sup> These data, as highlighted in recommendation A7, justify attempts to test NSCLC for the presence of *EGFR* mutation. However, based on lack of tumor tissue, the *EGFR* mutation status of most patients' tumors is negative or unknown. For these patients, cytotoxic chemotherapy is preferred (see recommendation A2). Recommendation D2 addresses the issue of whether additional biopsies are justified if *EGFR* mutation status cannot be determined from available tumor tissue.

A phase II trial treated 229 patients with previously untreated metastatic NSCLC with the anti-EGFR antibody cetuximab with carboplatin plus paclitaxel. *EGFR* FISH was assessable in 76 patients with available tumor tissue and classified as positive (four or more gene copies per cell in  $\geq 40\%$  of the cells or gene amplification) in 59%. Response rates and PFS were higher in patients with FISH-positive tissue compared with patients with FISH-negative tissue, and patients with FISH-positive tissue had a median survival time of 15 months compared with 7 months for patients who were FISH negative ( $P = .046$ ).<sup>109</sup> (Note: The publication was outside the date parameters of the systematic review.) These results have not yet been validated in a prospective study.

**KRAS.** *KRAS* is one of three *RAS* family genes (*KRAS*, *HRAS*, and *NRAS*) that encode a family of membrane-bound 21-kDa guanosine triphosphate (GTP)-binding proteins that regulate cell growth, differentiation, and apoptosis. These signaling proteins act downstream of EGFR. *RAS* proteins acquire transforming potential when an amino acid at position 12, 13, or 61 is replaced as a result of a point mutation in the gene.<sup>158</sup> These mutations lead to forms of *RAS* that have impaired GTPase activity, leading to constitutive activation of *RAS* signaling. *RAS* mutations are found in approximately one third of all human malignancies.<sup>158</sup> *KRAS* accounts for 90% of *RAS* mutations in lung adenocarcinomas, and approximately 97% of *KRAS* mutations in NSCLC involve codons 12 or 13.<sup>159</sup> *KRAS* mutations are uncommon in squamous cell carcinomas.<sup>160,161</sup> Multiple studies have

attempted to elucidate whether *KRAS* mutations can be used as a biomarker predictive of lack of response to EGFR TKIs.

The literature search identified seven papers on trials involving *KRAS*.<sup>124,125,128,129,137,162,163</sup> Two were retrospective analyses of RCTs, two were retrospective tissue analyses, one was a prospective analysis of patients in an expanded access program, one was a pooled analysis, and one was a correlative study of a prospective phase II single-arm trial with people  $\geq 70$  years of age. All papers reported mutation rates for *KRAS*. They studied responses to a variety of chemotherapeutic agents and both EGFR TKIs (often the same paper assessed *EGFR* status).

Six of the seven analyses reported response, three reported median survival, and four reported PFS/TTP. For patients whose tumors had *KRAS* mutations, none of the analyses reported a benefit in response, survival, or PFS from either erlotinib or gefitinib. Response to EGFR TKIs in patients whose tumors harbor a *KRAS* mutation is close to zero.

**ERCC1 and RRM1.** Several molecules impact the metabolism and efficacy of chemotherapeutic agents. One is ribonucleotide reductase subunit 1 (RRM1), which is important for nucleotide metabolism and is the dominant molecular determinant of gemcitabine efficacy. Another is excision repair cross-complementing group 1 (ERCC1), a component of the nucleotide excision repair complex that is important for platinum-induced DNA adduct repair. Both of these markers can be measured at the mRNA level and at the protein level by IHC using protein-specific antibodies. Of note, the definition of low, versus high, levels of ERCC1 and RRM1 varies from one study to another in the literature.

The literature search identified seven publications that included analysis of predictive values of ERCC1 (and reported those independently from predictive values of RRM1). All seven reports used tissue from phase II or III clinical trials; four were retrospective, two were prospective, and one was correlative. Two analyses found that low ERCC1 was a significant predictor of improved survival with cisplatin-based doublets.<sup>164,165</sup> Two others found nonsignificant trends of survival benefit from cisplatin-based doublets for patients with tumors with low ERCC1 compared with for patients with tumors with high ERCC1 and unselected tumors.<sup>166,167</sup> An eighth paper, which analyzed ERCC1 polymorphisms, showed significant correlations between certain polymorphisms and response.<sup>168</sup>

Three publications analyzed RRM1 independently from ERCC1; two were retrospective, and one was correlative.<sup>164,167,169</sup> All three analyses found that low RRM1 levels were predictive of increased survival benefit of cisplatin/gemcitabine doublets versus either gemcitabine monotherapy or other combinations. Tests finding high RRM1 were predictive of a greater risk of progressive disease, whereas for patients with low RRM1 expression, the risk decreased (both significantly).

Three studies analyzed the two markers together; one was retrospective, one was correlative, and one was a prospective phase II trial.<sup>164,167,170</sup> Two of the studies found that patients whose tumors expressed both low levels of ERCC1 and RRM1 had better survival with cisplatin/gemcitabine than patients with tumors with high levels of both or one high and one low.<sup>164,167</sup> One of those studies also found this correlation for TTP.<sup>167</sup> The third study did not find that OS differed by treatment regimen for patients with different levels.<sup>170</sup> The cutoff value of expression levels was different in each study (ranges, 1.4 to 7.5 for RRM1 and 1.7 to 8.7 for ERCC1).

**VEGF.** Angiogenesis, the growth of new vessels from preexisting vessels, is a fundamental step in tumor growth and progression. Vascular endothelial growth factor (VEGF) is a key angiogenic factor implicated in tumor blood vessel formation and permeability. Overexpression of VEGF has been observed in a variety of cancers and has been associated with worse relapse-free survival and OS. The antiangiogenic agent bevacizumab, a monoclonal antibody directed against VEGF, has shown clinical benefit in multiple cancers, including NSCLC. VEGF levels are commonly measured in serum or plasma by enzyme-linked immunosorbent assays.

The literature search identified five studies analyzing VEGF in serum; four were prospective, in which participants received chemotherapy (ie, none received bevacizumab).<sup>171-174</sup> All four reported response, whereas only two reported survival. The single study reporting significant figures found that patients with low levels of VEGF had almost twice the survival time of patients with high ( $> 500$  pg/mL) levels ( $P < .03$ ).<sup>171</sup> A fifth VEGF study was a prospective corollary study of bevacizumab plus chemotherapy from the ECOG 4599 trial. It found that baseline plasma levels of VEGF predicted PFS. In addition, patients with higher baseline levels had significantly better responses to bevacizumab plus chemotherapy than to chemotherapy alone. Low levels of VEGF were not predictive of response or survival.<sup>175</sup>

**2009 recommendation D2.** To obtain tissue for more accurate histologic classification or for investigational purposes, the Update Committee supports reasonable efforts to obtain more tissue than what is contained in a routine cytology specimen.

**Literature update and discussion.** Traditionally, chemotherapeutic regimens have been chosen for patients with stage IV NSCLC irrespective of tumor histology or molecular subtype. Furthermore, the diagnosis of stage IV NSCLC is commonly made with a cytologic specimen prepared from a fine-needle aspirate, which often provides a scant amount of cells that may be insufficient for histologic classification or additional molecular tests. Such an approach was adequate when treatment options were limited; however, emerging data suggest that this paradigm is changing. Some agents seem to be more effective or less toxic with certain histologic subtypes (see discussions after first-line recommendations A5, A7, and A8). Moreover, recent studies have demonstrated that the efficacy of treatments could potentially be improved further by selecting drugs based on molecular markers. Collectively, these trends have provoked an attempt to prioritize treatments based on the likelihood of the most benefit and least toxicity.

The Update Committee also recognizes the importance of ongoing and anticipated clinical trials of novel drugs or combinations of drugs that demand histologic or molecular classification for enrollment. Molecular tests promise to redefine NSCLC into subgroups of patients in which different optimal treatment pathways will emerge. Some studies, such as those testing new drugs for patients with acquired resistance to erlotinib or gefitinib, have been informed by molecular changes acquired during TKI therapy observed in patients who have been subjected to serial biopsies during their clinical course.

Thus, especially in routine care of patients, the Update Committee supports reasonable efforts to obtain more tissue than what is contained in a cytology specimen. The Update Committee recognizes that the ability to distinguish squamous from nonsquamous NSCLC or to have additional tissue available for molecular testing, such as *EGFR* mutation, may be valuable but not vital to patient management. For example, the ability to rule out squamous histology in a patient

with NSCLC would allow an oncologist to consider drugs that lower the patient's risk of death by 20% to 30%, which improves median survival time by approximately 2 months. When considering a more invasive or additional biopsy, such as a core biopsy, the treating oncologist must balance the potential for improved efficacy based on drug selection against the risk of delaying treatment and/or the risk of the biopsy procedure itself on an individual patient basis.

### FUTURE DIRECTIONS OF RESEARCH

The survival of patients with stage IV NSCLC remains poor, and all eligible patients should be encouraged to participate in clinical research trials at any time during the course of their disease. More research on strategies to improve communication between clinicians and patients with stage IV NSCLC may improve shared decision making and increase participation in research.

The data available for review by the Update Committee prompted special consideration of patients who are elderly and/or have poor PS. Future studies focusing on these subgroups are needed. In future studies, the elderly should be defined by physiologic age using geriatric assessments. Patients with PS  $\geq 2$  related to NSCLC should be distinguished from patients impaired by comorbid medical illness.

Recent clinical trials have identified other tumor or patient characteristics that can have prognostic and/or predictive importance, including histology (squamous *v* nonsquamous),<sup>38</sup> molecular subgroups (*EGFR* mutation, *EGFR* amplification, *EGFR* expression, or *KRAS* mutation),<sup>91,124,128,129,141,150</sup> number of prior therapies (no, one, or  $\geq$  two prior therapies),<sup>30,31</sup> time on prior therapy,<sup>31</sup> smoking status (including never smokers [ $< 100$  cigarettes over lifetime], former light smokers [ $< 15$  pack-years], and heavy smokers [ $\geq 15$  pack-years]),<sup>15,30,87</sup> and Asian ethnicity.<sup>30,91</sup> Future clinical trials should build on these discoveries, enrich for patients most likely to benefit, and stratify by prognostic factors, including PS, sex, smoking status, prior therapy, and molecular characteristics, whenever there is a potential for imbalance in enrollment. Techniques for molecular testing of tumor tissue should be optimized and standardized before being tested in prospective clinical trials. Ideally, new technologies should be refined so that they may be more readily adopted into the community practice setting.

To date, incremental progress in the treatment of patients with stage IV NSCLC has come from the discovery of new drugs, or combinations of drugs, applied to relatively heterogeneous patient populations. Altering the sequence or schedule of administration of these drugs in unselected patient populations has not yielded an improvement in OS.<sup>54,85,86</sup> When the benefit of a new therapy is small, its impact may be diluted by subsequent therapy. As a result, the impact of a new drug or drug sequence may only be evident in terms of PFS, and not OS.<sup>85,86,94</sup>

The recommendations in this guideline were based primarily on statistically significant improvements in OS documented in prospective RCTs. As a result, potentially important issues in the selection of treatment, including toxicity and QOL, were discounted by the Update Committee during the review process. Treatments that improve only PFS require greater scrutiny for toxicity, adverse effects, QOL, and cost effectiveness. For example, in the case of *EGFR* TKIs for

patients with *EGFR* mutation, the Committee considered a PFS benefit combined with favorable toxicity profile and improved QOL and concluded that the treatment strategy was beneficial to patients and clinicians, even in the absence of demonstrated OS benefit. Hopefully, as our knowledge of the biology of NSCLC increases in parallel with the discovery of new drugs, the link between predictive patient characteristics and drug selection will increase, allowing future therapies to have greater impact and future clinical trials to focus on improving OS.

### PATIENT-PHYSICIAN COMMUNICATION

The purpose of this section is to help physicians communicate with their patients regarding the benefits, risks, and prognosis of chemotherapy for stage IV NSCLC to foster shared decision making. Methods of improving communication on this topic will be suggested. Of note, the literature cited in this section was not identified by the systematic review, but through separate literature searches and Update Committee members' suggestions, and communication methods have not been validated in prospective clinical trials. Therefore, unlike the guideline recommendations, this section represents consensus opinion that is not based on the evidence in the systematic review but is based on literature on questionnaires, surveys, interviews, observations and analysis of office consultations, and other qualitative research.

Effective communication can be a challenge for some clinicians. Insufficient time and training, system-level barriers, and/or patient factors, such as misconceptions about the disease and treatment, can constitute barriers.<sup>176</sup> Patients with NSCLC often have complex medical, psychological, and social issues that their physicians must take into account before discussing therapy. Many patients have pain, impaired breathing, cough, fatigue, or adverse effects from prior treatments. Patients with lung cancer may have underlying debility as a result of smoking-related or other illnesses, and many may have depression or psychological distress as a result of their diagnosis of lung cancer, a disease with a decidedly bad prognosis. Patients with lung cancer may have experienced loss of sense of self, fears of pain and death, and/or feelings of alienation.<sup>177</sup> Furthermore, lung cancer carries a unique social stigma because of its association with cigarette smoking, a stigma that increases stress and impairs communication with family, friends, and caregivers. Some patients are angry because they never smoked but have the social stigma thrust on them. Smoking cessation, which should be encouraged for patients with stage IV NSCLC to improve outcome, may result in increased stress in patients who are addicted to nicotine.

Studies of communication in lung cancer have identified some particular issues. Physicians may use blaming words regarding patients' smoking histories and the subsequent inability of oncologists to treat the lung cancer effectively. A study of recorded office visit interviews found that oncologists missed opportunities to express empathy about lung cancer prognosis 90% of the time.<sup>178</sup> In the largest prospective trials of communication, doctors only ever discussed prognosis with their patients with advanced cancer in 38% of cases<sup>179</sup> and only had a conversation about imminent death in 37% of cases.<sup>180</sup> Many patients with cancer feel abandoned by their oncologists at the end of life. This is stressful for patients, families, and the oncologist.<sup>181</sup> In addition, lack of having a conversation about death

from the disease is strongly associated with higher end-of-life care costs.<sup>182</sup> However, delay or avoidance of a direct discussion of prognosis may be preferred by certain patients,<sup>183</sup> making empathic exchanges about prognosis difficult unless one specifically asks what the patient wants to know.<sup>184,185</sup>

Physicians should be especially sensitive when communicating with patients of different cultural or ethnic backgrounds. In a study of recorded lung cancer consultations between clinicians of various races and patients with lung cancer of different races (than the clinicians'), these consultations were characterized by less information provided by the clinicians and less participation from the patients than in visits between patients and clinicians of the same race.<sup>186</sup> Another study looked at how much patients with lung cancer trust their doctors and found that white patients reported higher trust after a consultation, whereas African American patients were less likely to increase trust in the oncologist. African American patients found the oncology clinicians' communication to be "less supportive, less informative and less partnering" than white patients did.<sup>187</sup>

The Institute of Medicine has identified patient-centered care as a key part of achieving improved quality of care.<sup>188</sup> One way to involve the patient in shared decision making is to offer a session dedicated solely to the discussion of treatment options. In such a session, we suggest that clinicians consider that patients prefer realistic information. (Note: This is based on a study conducted in Australia that may or may not be generalizable to English speakers in North America and Britain).<sup>189</sup> Clinicians should recognize patients' learning styles and knowledge of their situations. A patient's limited understanding of his or her situation may impair his or her ability to make an autonomous decision.<sup>190</sup> At the beginning of the interview, clinicians should determine the patient's level of understanding by asking open-ended questions such as, "Tell me what you know about your lung cancer?" in addition to asking, "How much do you want to know?"<sup>191</sup> An article on lung cancer by Morse et al<sup>178</sup> suggests making empathetic statements early in the discussion and throughout the discussion with the patient, for example, "Sounds like what you are telling me is . . ." or "It sounds like you were really frightened when you got that news about the cancer." These statements have not been found to make the visit longer and may enable patients with lung cancer to better listen when clinicians present medical information.<sup>178,192</sup> Minimizing blame of the patient for his or her illness; showing sensitivity to race/ethnicity, culture, and socioeconomic status; and considering a patient's level of medical literacy can improve communication. Although effective communication can be challenging, intensive training has been shown to help physicians to communicate more effectively with people with cancer.<sup>178,187</sup>

It is important to ask the patient how he or she would like to hear information regarding the risks and benefits of treatment and the prognosis. Some patients prefer general terms, versus specific use of numbers, or visual aids (charts or graphs). In the approximately 20% of patients who do not want to discuss prognostic information, the physician must try to determine why in empathic ways to accommodate the patients' wishes and needs.<sup>191</sup>

The presence of a caregiver during appointments can help elicit more information from the oncologist, as seen in a study of consultations on lung cancer or pulmonary nodules.<sup>186</sup> Oncologists have reported that the presence of a caregiver can facilitate shared decision making.<sup>176</sup> Physicians can encourage the participation of companions through partnership building and supportive communication, as re-

ported in analysis of recorded lung cancer consultations.<sup>193</sup> With increased promulgation of information about cancer on the internet and in mass media, both patients and companions/caregivers are bringing more information and questions for their doctor to consider.<sup>194-196</sup> Physicians must be receptive and supportive of a patient's or caregiver's attempt to learn more. Unreliable information should be identified as such, and reasonable suggestions should be listened to attentively. This is the essence of shared decision making.

### **Communicating Benefit**

Nearly all of the recommendations in this guideline are based on clinical trials that demonstrate improvements in OS using chemotherapy, with improvement (or lack of detriment) in QOL. To communicate the level of benefit to patients who are not interested in statistics, it is reasonable to use qualitative statements, such as, "Chances are you will live longer if you take this chemotherapy versus another, or no chemotherapy." If a patient requests a discussion of benefit involving statistics, the oncologist should be prepared to offer statistics and explain their meaning. Case series show that patients with stage IV NSCLC treated with supportive care only have a median survival time of 3 months, a 1-year survival rate of less than 10%, and a 2-year survival rate of less than 2%.<sup>197</sup> The most promising statistics for first-line chemotherapy show median survival times of 10 to 12 months, a 1-year survival rate of 40% to 50%, and a 2-year survival rate of 15% to 25%.<sup>56,57,61</sup> A recent meta-analysis of clinical trials comparing first-line chemotherapy with supportive care only demonstrated a 23% reduction in the risk of death (HR = 0.77; 95% CI, 0.71 to 0.83;  $P < .0001$ ; see also the discussion in recommendation A1).<sup>10</sup> (Note: The meta-analysis included studies with participants with stage IIIB tumors and a small number of earlier stage tumors. In addition, all trials included had completed accrual before 2002.) This translated into an absolute improvement of 9% at 12 months, increasing the 1-year survival rate from 20% to 29%. On the basis of these statistics, an example of a reasonable quantitative statement regarding first-line chemotherapy is the following: "Chemotherapy will improve your chance of being alive in 1 year from 10% to 20% up to 30% to 50%."

It is important to be completely honest with people, if they desire. An alternative way to present the data would be to say, based on the meta-analysis, the following: "Without any chemotherapy, the average person will live approximately 4 and a half months. With chemotherapy, most will live longer and some will live a shorter time. More recent chemotherapy trials have shown that people live about 3 months longer than if they did not get chemotherapy. Even with chemotherapy, the chance of being alive at 1 year is approximately 30% to 50%; the chance of dying within this year is 50% to 70%."<sup>180</sup>

Although most clinical trials report the median survival time of the control arm and the experimental arm, it is the consensus of the Update Committee that quoting comparative median survival times to a patient can be misleading. For example, a patient who is considering whether to take bevacizumab with carboplatin/paclitaxel may learn that bevacizumab improves median survival by 2 months (from 10.3 to 12.3 months).<sup>61</sup> A common misconception of an individual patient is that taking bevacizumab will allow him or her to live 2 months longer. On the contrary, some patients experience treatment-related death related to bevacizumab, whereas other patients may live

**Table 4.** Regimens and Prices for Treatment of Stage IV NSCLC (for a patient with BSA 1.96 [weight = 81.5 kg, height = 169 cm] from July 1, 2009 reimbursement data for Medicare Plan B\*)

Treatment Setting	Drug	Initial Dose	HCPCS Code Dosage (mg)	Medicare Payment Limit for Parenterals (\$)	Reimbursement for 1 Purchase for 1 Treatment for Parenterals or Price of 1 Month of Treatment for Oral Medication (\$)	Regimen	Price for Two Cycles (\$)
First-line	Bevacizumab†	15 mg/kg (recommended only in combination with carboplatin/paclitaxel)‡	10	57	7,020\$	Every 3 weeks	14,040
First-line	Carboplatin†	700 mg, every 3 weeks‡	50	5	73	Every 3 weeks	146
First-line	Cetuximab†	400 mg/m <sup>2</sup> initial dose followed by 250 mg/m <sup>2</sup> (recommended only in combination with cisplatin/vinorelbine)‡	10	50	3,894\$ (note: initial dose only)	Weekly	18,981
First-line	Cisplatin†	75 mg/m <sup>2</sup> , every 3 weeks	50	12	34\$	Every 3 weeks	68
First- and second-line	Docetaxel†	75 mg/m <sup>2</sup> , every 3 weeks	20	345	2,530\$	Every 3 weeks	5,060
Second-line	Erlotinib¶	150 mg per day‡	—	—	4,557	Daily	9,114
First- and second-line	Gefitinib¶	250 mg per day‡	—	—	2,127	Daily	4,255
First-line	Gemcitabine†	1,250 mg/m <sup>2</sup> ‡	200	141	1,729\$	Days 1 and 8, every 3 weeks	6,914
First-line	Irinotecan†	60 mg/m <sup>2</sup>	20	15	88\$	Days 1, 8, and 15, every 4 weeks	527
First-line	Paclitaxel†	200 mg/m <sup>2</sup>	30	8	101\$	Every 3 weeks	201
First- and second-line	Pemetrexed†	500 mg/m <sup>2</sup> (note: monotherapy in second-line setting)‡	10	49	4,841\$	Every 3 weeks	9,682
First-line	Vinorelbine†	25 mg/m <sup>2</sup>	10	13	64\$	Days 1 and 8, every 3 weeks	257

NOTE. Drug prices were estimated from a third-party payer perspective, based on reimbursement rates from the Centers for Medicare and Medicaid Services that are widely accepted by providers, computed at the manufacturer's average sales price. Other treatment-related direct and indirect costs were not considered, such as infusions, anti-nausea drugs, and diagnostic laboratory tests or imaging such as computed tomography scans. Actual treatment costs and reimbursement will vary considerably across regions, payers, institutions, and practices, as well as over time, and the reader should consult current local cost information specific to his or her practice setting. Trade names and manufacturers of drugs are as follows: bevacizumab (Avastin; Genentech, South San Francisco, CA), cetuximab (Erbix; Bristol-Myers Squibb, Princeton, NJ; ImClone Systems, New York, NY), erlotinib (Tarceva; Genentech/Roche, South San Francisco, CA), gefitinib (Iressa; AstraZeneca, Wilmington, DE), pemetrexed (Alimta; Eli Lilly, Indianapolis, IN), and gemcitabine (Gemzar; Eli Lilly).

Abbreviations: NSCLC, non-small-cell lung cancer; BSA, body-surface area; HCPCS, Healthcare Common Procedure Coding System.

\*Except with regard to the oral agents erlotinib and gefitinib.

†Cost for injectable drugs was based on Medicare Part B payment allowance limits effective July 1, 2009 (with no administration fees or other adjustments; Medicare Part B Drug Average Sales Price, [http://www.cms.hhs.gov/McrPartBDrugAvgSalesPrice/01a1\\_2009aspfiles.asp](http://www.cms.hhs.gov/McrPartBDrugAvgSalesPrice/01a1_2009aspfiles.asp)).

‡These doses are specifically enumerated in guideline; the other doses were based on doses used in major clinical trials.

§Calculations assumed an 81.5-kg and 169.25-cm adult (McDowell MA, Fryar CD, Ogden CL, et al: Anthropometric reference data for children and adults: United States, 2003-2006. National Health Statistics Reports. Hyattsville, MD, National Center for Health Statistics, 2008). Males ≥ 20 years old = mean weight, 88.3 kg; mean height, 176.3 cm; females ≥ 20 years old = mean weight, 74.7 kg; mean height, 162.2 cm. Mosteller formula was to calculate BSA.

||Notable hydration costs associated.

¶Oral agent costs represent ambulatory care prescriptions. Calculations were as follows: assumed a 30-day prescription (without dispensing fee), 2-month cost estimate is twice this amount (Medscape: Erlotinib oral. <http://www.medscape.com/druginfo/pricebrandimage?cid=med&drugid=92157&drugname=Erlotinib+Oral&monotype=pricebrandimage>; Medscape: Gefitinib oral. <http://www.medscape.com/druginfo/pricebrandimage?cid=med&drugid=75201&drugname=Gefitinib+Oral&monotype=pricebrandimage>).

many months longer as a result of the beneficial effects of the drug. Patients who request statistics must be reminded that these numbers are based on the experience of thousands of patients, with median survival time representing the experience of the majority of patients. Physicians can explain what median survival time means—that is, half of the patients live longer, and half die sooner. However, there are patients who live much longer or much shorter than the median survival time. Patients alerted to extremes of possibility may take comfort in the uncertainty and also sensibly brace themselves for the worst case scenario. Using tools, such as the ASCO Discussion Guides (available at [www.asco.org/guidelines/nscl](http://www.asco.org/guidelines/nscl)), on this topic may help in the discussion. There is evidence from a randomized trial that a similar

tool used in the adjuvant therapy of breast cancer was well received, helped people understand their prognosis (even if bad), did not lead to additional stress, and allowed people to make better chemotherapy decisions, especially to avoid chemotherapy when the benefit was low.<sup>198</sup>

It is critically important that doctors state at least one pessimistic aspect (eg, “The chance of dying is . . .”); if not, patients with advanced cancer may overestimate their prognosis substantially just based on the clinicians’ optimistic statements.<sup>199</sup> If a physician is asked “Can you cure me?” an honest answer is, “No, I can’t, but we have good chances of prolonging your life and keeping you comfortable, and we will always be here to help you and your family.”

## Communicating Risk

Risk of adverse effects and/or complications should be presented from most common to least common, with serious adverse effects, including the risk of death, highlighted. Providing percentage figures can help patients put these risks into perspective. Clinicians should be able to quote relevant statistics. Work in risk assessment for breast cancer has led others to recommend that health care providers present women with the risks and benefits in both absolute and relative terms.<sup>198,200</sup> It is important to remember that results obtained in healthy, motivated patients with PS of 0 to 1 cannot be generalized to patients who are elderly, have comorbid illnesses and/or poor PS, or lack social support. In addition, although this guideline recommends single-agent chemotherapy for patients with PS of 2, it also notes heterogeneity within that classification. Special care should be taken to inform patients of potential permanent effects (such as neuropathy) and to point out the personal circumstances that may increase the risk of adverse events. Each patient and caregiver has individual experiences, beliefs, and risk and benefit perceptions that the clinician should address. In oncology, recognition of patients' pre-existing beliefs, concern about mortality, adverse effects, experiences of stigma, and mental health status are all important.<sup>176</sup> Although this guideline does not recommend making treatment decisions based on a person's chronologic age, this does not discount the possibility of considering physiologic age in avoiding certain therapies with a high likelihood of toxic adverse effects. In the end, the patient should be presented with a personalized description of his or her individual risks and benefits.<sup>201</sup>

The trade-offs that patients with lung cancer are willing to accept for treatments such as chemotherapy vary widely. In patients interviewed after treatment with chemotherapy, three fourths of patients would not make the same choice again, did not remember being offered best supportive care, and may not have heard or understood descriptions of the risks and benefits of chemotherapy.<sup>202</sup> Physician presumptions about which trade-offs patients are willing to accept may not always be accurate or may not align with patient-reported attitudes.<sup>203</sup> Some patients are willing to undertake treatment even when the benefits may be small and are willing to experience toxicity for those small benefits.<sup>204</sup> Patients with lung cancer may overestimate the survival benefits of potentially toxic treatment,<sup>190,205</sup> and patients who overestimate survival do not live any longer but may experience more bad deaths, for instance, dying in the intensive care unit, with intubation, and experiencing toxicities.<sup>205,206</sup> Therefore, it is advisable for the clinician to assess the patient's preferences and the accuracy of his or her perception of the risks and benefits involved in chemotherapy or biologic therapy for stage IV NSCLC.<sup>190</sup> Enhancing clinician-patient communication in this way can assist in successful shared decision making.

## HEALTH DISPARITIES

Because ASCO clinical practice guidelines represent expert recommendations on the best practices in disease management to provide the highest level of cancer care, it is important to note that many patients have limited access to medical care. Racial and ethnic disparities in health care contribute significantly to this problem in the United States. Patients from minority racial/ethnic groups with cancer suffer disproportionately from comorbidities, experience more substantial obstacles to receiving care, are more likely to be

uninsured, and are at greater risk of receiving care of poor quality than other Americans. Many other patients lack access to care because of their geographic location and distance from appropriate treatment facilities.

Racial and ethnic disparities are notable in lung cancer. For example, African American men have an 87% mortality rate versus 69% for white men (2001 to 2005 Surveillance, Epidemiology, and End Results [SEER] 17 data).<sup>207</sup> From 2000 to 2006, the incidence rates were 77 per 100,000 for white men (54% stage IV) and 104 per 100,000 for African American men (58% stage IV; 2000 to 2006 SEER 17 data).<sup>208</sup> Forty-two percent of American Indian or Alaska Native people diagnosed with lung cancer are less than 65 years of age compared with only 30% of non-Hispanic whites.<sup>209</sup> Lung cancer health care disparities can result from patients' risk behaviors (smoking, smoke inhalation,<sup>210</sup> or number of cigarettes smoked daily), socioeconomic status (including education level),<sup>211</sup> access to health services, and comorbid illnesses.<sup>210,212</sup> Ethnic and racial minorities experience poorer outcomes compared with whites in all stages of lung cancer. The economic costs of the agents discussed in this guideline vary, and although a cost-effectiveness analysis is beyond the scope of this guideline and did not impact the recommendations, Table 4 lists estimated costs for reference based on data from the Centers for Medicare and Medicaid Services (Rockville, MD).

Health disparities frequently are the result of ineffectual communication between health care providers and patients.<sup>217</sup> This ineffective communication between provider and patient results in less health care information being shared, noncollaborative health decision making, fewer referrals and less access to specialists, fewer diagnostic and staging procedures, and less treatment options being discussed and offered. Ineffective communication may result in patients receiving poorer quality care. See Patient-Physician Communication for further discussion.

One of the critical responsibilities of an oncologist is to communicate effectively and to offer the best available cancer care. A population-based regression analysis demonstrated that the use of recommended therapy for all stages of NSCLC was less likely if one was single, older, or African American.<sup>218</sup> This study also showed that only 36% of African Americans with stage IV NSCLC received first-line chemotherapy. In a retrospective cohort study of SEER data on referral patterns of patients with advanced lung cancer, 36% of the patients studied were never seen by an oncologist and were never offered chemotherapy.<sup>212</sup> A similar analysis reported that black patients had surgery for early-stage lung cancer less often than whites.<sup>219</sup> African Americans were more likely not to have surgery offered and were more likely to decline surgery compared with whites in the study. In each study, not all of the patients were told of all the choices available to them.

When patients receive uniform clinical care, differences in outcomes between racial groups are minimized. A retrospective cohort analysis of five consecutive Cancer and Leukemia Group B lung cancer clinical trials of systemic treatment found that patients who entered had the same 1-year survival rate and median survival time regardless of race.<sup>211</sup> Patients on clinical trials are more likely to receive uniform care. Patient differences in PS, weight loss, marital status, employment, and type of medical insurance resulted in greater impact on survival than race alone, and patients with similar clinical profiles can be expected to receive the same

benefit from treatment. As the treatment of lung cancer is becoming more customized and individualized, it remains important that racial and ethnic minorities and patients of diverse socioeconomic status be encouraged to participate in clinical trials.

Awareness of these disparities in access to care should be considered in the context of this clinical practice guideline, and health care providers should strive to deliver the highest level of cancer care to all patients.

## DEDICATION

This guideline is dedicated to the memories of Karen Parles and Anita Johnston who, while living with NSCLC, educated, influenced, and inspired countless clinicians, researchers, advocates, and others with and affected by NSCLC. Their work and their memories will continue to do so.

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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### Appendix

**Table A1.** Update Committee Panel Members

Member	Institution
Christopher G. Azzoli, MD, Co-Chair	Memorial Sloan-Kettering Cancer Center
Giuseppe Giaccone, MD, Co-Chair	National Cancer Institute
John R. Strawn, MD, patient representative	Houston, TX
Reily Smith, patient representative	Bakersfield, CA
Timothy Aliff, MD	Northwest Oncology & Hematology Associates
Sherman Baker Jr, MD	Virginia Commonwealth University, Massey Cancer Center
Julie Brahmer, MD	Sidney Kimmel Cancer Comprehensive Center, Johns Hopkins University
David H. Johnson, MD, Co-Chair 2003 update and current panelist	Vanderbilt-Ingram Cancer Center
Janessa L. Laskin, MD	British Columbia Cancer Agency
Gregory Masters, MD	Helen F. Graham Cancer Center
Daniel Milton, MD	Hematology/Oncology of Indiana, PC
Luke Nordquist, MD	Nebraska Cancer Specialists, PC
William Pao, MD, PhD	Vanderbilt-Ingram Cancer Center
David G. Pfister, MD, Co-Chair 2003 update and current panelist	Memorial Sloan-Kettering Cancer Center
Steven Piantadosi, MD, PhD	Samuel Oschin Comprehensive Cancer Institute
Joan H. Schiller, MD	University of Texas, Southwestern Medical Center
Thomas J. Smith, MD	Virginia Commonwealth University, Massey Cancer Center
David Trent, MD, PhD	Virginia Cancer Center