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ASCO SPECIAL ARTICLE

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

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Editor's Note: This guideline represents an abridged version of the complete guideline update and contains the updated recommendations and a brief discussion of the relevant literature. The complete guideline, with a comprehensive discussion of the literature and additional tables, is available at www.asco.org/guidelines/nsclc.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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The Acknowledgment and Appendix are included in the full-text version of this article; they are available online at www.jco.org. They are not included in the PDF version (via Adobe® Reader®).

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ABSTRACT

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 approved a new indication for pemetrexed for maintenance therapy for 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) originally published clinical practice guidelines concerning unresectable NSCLC in 1997 and updated them in 2003. ASCO guidelines are reviewed on an ongoing basis, and guidelines are selected for updates when new peer-reviewed studies are reported that might change the guideline's recommendations. Since 2003, a large number of publications relevant to this guideline were reported in the literature, and ASCO decided to update the guideline. Because of the volume of literature, the scope of this guideline was limited to chemotherapy and biologic therapy for stage IV NSCLC and review of molecular markers. The recommendations were made based on literature published from January 2002 to May 2009 and primarily based on statistically significant improvements in overall survival (OS) documented in prospective, randomized controlled trials (RCTs). Treatment strategies demonstrated to improve only progression-free survival

(PFS) prompted greater scrutiny regarding issues such as toxicity and quality of life. Table 1 provides a summary of the updated recommendations.

GUIDELINE QUESTIONS

First-Line Chemotherapy

1. Which patients with stage IV (as defined by the International Association for the Study of Lung Cancer Lung Cancer Staging Project[1]) 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.)
2. 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 quality of life/symptom relief, in the treatment of stage IV NSCLC with chemotherapy?
3. What is the best chemotherapy for treatment of patients with performance status (PS) 2 with stage IV NSCLC?
4. What is the best chemotherapy for treatment of elderly patients with stage IV NSCLC?

Table 1. Summary of Recommendations

Recommendation No.	Recommendation
A. First-line chemotherapy	
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 *EGFR* mutations. If *EGFR* 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. Second-line chemotherapy	
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.
C. Third-line chemotherapy	
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.
D. Molecular analysis	
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.[1]

5. Is cisplatin more effective than carboplatin in the first-line treatment of stage IV NSCLC?
6. What is the optimal duration of first-line chemotherapy for stage IV NSCLC?
7. What are the benefits, with respect to OS, PFS, toxicity, and quality of life/symptom relief, in the treatment of stage IV NSCLC with targeted therapies?

Second-Line Chemotherapy

1. 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?
2. What is the optimal second-line treatment for elderly patients with stage IV NSCLC?

Third-Line Chemotherapy

1. Is there a role for third-line therapy in the treatment of stage IV NSCLC?

Molecular Analysis

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

UPDATE METHODOLOGY

Literature Review

For the 2009 update, MEDLINE, EMBASE, and the Cochrane databases were searched from 2002 to July 2008 for studies meeting the inclusion criteria of the guideline update protocol. In brief, treatment studies were eligible for inclusion if they randomly assigned patients with stage IV NSCLC to one type of chemotherapy versus another, chemotherapy versus best supportive care (BSC), or chemotherapy versus placebo and reported efficacy outcomes (OS, PFS, or objective response), toxicity, or health-related quality of life (HRQOL)/symptom relief. For cytotoxic chemotherapy, searches were limited to phase III RCTs; for biologic agents, searches included phase II and III randomized trials. For molecular analysis, the search included phase II and III trials, cohort studies, and retrospective and subgroup analyses from clinical trials. This systematic review was initially conducted by Cancer Care Ontario's Program in Evidence-Based Care and completed by ASCO. For a full discussion of the literature review update methodology and process, refer to the online version of this guideline, available at www.asco.org/guidelines/nsclc.

Panel Composition and Consensus Development Based on Evidence

The ASCO Clinical Practice Guidelines Committee convened an Update Committee consisting of experts in medical oncology, in both academic and community practice, and in statistics; and two patient representatives. All members of the Committee participated in the preparation of the draft guideline document, which was then disseminated for review by the entire 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.

RESULTS

Summary of Literature Review

Since the last update, the systematic review identified 190 papers that related to at least one of the clinical questions published for the first time or that published updated results. Not all guideline questions had new data available. Of the 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. The recommendations were based on 52 RCTs and 29 meta-analyses (MAs), plus retrospective tissue analyses that were included only for molecular analysis. Studies that met the eligibility criteria, which were included in the full guideline update, are listed in Table 2.

Limitations of the Literature

There were limited numbers of trials enrolling patients with poor PS (PS $\geq$ 2 based on the Eastern Cooperative Oncology Group [ECOG]/Zubrod scale or $<$ 70% on the Karnofsky PS 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. The recommendations in this guideline were based on statistically significant improvements in outcomes documented in prospective RCTs, primarily in OS. As a result, potentially important issues in the selection of treatment, including toxicity, quality of life, and cost effectiveness, were discounted by the Update Committee during the review process. For some clinical questions, only improvement in PFS was observed. Treatments that improved only PFS prompted greater scrutiny for toxicity, adverse events (AEs), and quality of life.

STAGE IV NSCLC GUIDELINE UPDATE RECOMMENDATIONS

Recommendations on first-line chemotherapy begin with A, those on second-line chemotherapy begin with B, those on third-line chemotherapy begin with C, and those on molecular analysis begin with D.

First-Line Chemotherapy

1. Clinical question. Which patients with stage IV NSCLC should be treated with chemotherapy?

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. The conclusions of this recommendation are consistent with those of the 2003 guideline update. Since the publication of the previous guideline update, there has been an update in an MA of trials comparing chemotherapy with supportive care only in

Table 2. Studies Meeting Eligibility Criteria Included in Guideline

Question	Intervention	New Studies
First-line chemotherapy for patients with stage IV NSCLC		
A1. Which patients with stage IV NSCLC should be treated with chemotherapy?	Chemotherapy *v* BSC	1 RCT,[3] 1 MA[2]
A2. What is the most effective first-line chemotherapy for the treatment of patients with stage IV NSCLC?	Platinum *v* nonplatinum chemotherapy; 2 cytotoxic drugs *v* 1 cytotoxic drug or *v* 3 cytotoxic drugs; weekly *v* every-3-week administration of paclitaxel/carboplatin	17 RCTs,[4-7,9-19,25,134] 5 MAs,[8,20-23] 2 preplanned subgroup analyses[26,27]
A3. What is the best chemotherapy for treatment of patients with PS 2?	1 or 2 cytotoxic drugs *v* 1 or 2 drugs (including EGFR TKIs)	2 RCTs,[29,30] 2 subset analyses of RCTs[5,28]
A4. What is the best chemotherapy for treatment for the elderly?	1 or 2 cytotoxic drugs *v* 1 or 2 cytotoxic drugs; same treatment for patients younger than and older than age cut-off	3 RCTs,[28,32,33] 2 subgroup analyses,[5,34] 1 retrospective analysis,[35] 1 pooled analysis[36]
A5. Is cisplatin more effective than carboplatin?	Cisplatin *v* carboplatin	9 RCTs,[24,40-47] 3 MAs[37-39]
A6. What is the optimal duration of first-line treatment for stage IV NSCLC?	Different Nos. of cycles compared; maintenance chemotherapy; immediate *v* delayed alternative chemotherapy	6 RCTs[48-53]
A7. What are the benefits, with respect to overall survival, progression-free survival, toxicity, and quality of life/symptom relief, in treatment with targeted therapies?		
Recommendation A7	Chemotherapy *v* chemotherapy plus EGFR TKI; chemotherapy *v* EGFR TKI	6 RCTs[30,54-58]
Recommendation A8	Bevacizumab plus chemotherapy doublet *v* chemotherapy doublet	3 RCTs,[31,59-61] 1 subgroup analysis of RCT[63]
Recommendation A9	Cetuximab plus chemotherapy doublet *v* chemotherapy doublet	4 RCTs[64-67]
Second-line chemotherapy for patients with stage IV NSCLC		
B1. 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?	Pemetrexed *v* docetaxel; EGFR TKI *v* placebo/BSC; gefitinib *v* docetaxel; bevacizumab/erlotinib *v* erlotinib or *v* chemotherapy or *v* bevacizumab/chemotherapy; weekly docetaxel *v* every-3-week docetaxel	11 RCTS,[62,71-76,80-83] 2 subgroup analyses,[77,78] 1 SR,[70] 1 IPDMA[69]
B2. What is the best second-line treatment for the elderly?	Docetaxel *v* pemetrexed by age	1 retrospective subset of RCT[135]
Third-line chemotherapy for patients with stage IV NSCLC		
C. Is there a role for third-line therapy?		
Recommendation C1	Erlotinib *v* placebo	1 RCT[74]
Recommendation C2	Third- or fourth-line chemotherapy	1 retrospective analysis[84]
Molecular analysis		
D1. For the purposes of prescribing chemotherapy, what is the relevance of molecular analysis of stage IV NSCLC tissue?		
EGFR	Gefitinib, erlotinib, chemotherapy	37 analyses (including 5 clinical trials),[68,85-120] 1 SR,[79] 1 IPDMA[69]
KRAS	Gefitinib, erlotinib, chemotherapy	7 analyses[87,88,91,92,100,121]
ERCC1/RRM1	Chemotherapy: cisplatin, gemcitabine, others	7 analyses[122-128]
VEGF	Chemotherapy, bevacizumab	5 analyses[129-133]

Abbreviations: NSCLC, non–small-cell lung cancer; RCT, randomized controlled trial; MA, meta-analysis; PS, performance status; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; BSC, best supportive care; SR, systematic review; IPDMA, independent patient data meta-analysis.

patients with NSCLC.[2] This MA compared the efficacy of chemotherapy with BSC and showed a benefit to chemotherapy in reduction of risk of death (hazard ratio = 0.77; 95% CI, 0.71 to 0.83; $P \leq .0001$) and an increase in 1-year survival. The MA included 16 trials with a total of 2,714 patients; 12 trials used platinum-based regimens, and 13 reported PS. The MA found that patients with a PS of 2 also received a benefit, although it was less than the benefit seen in patients with a PS of 0 to 1.

The most common grade 3 or 4 AEs of an RCT with 725 participants comparing chemotherapy plus BSC versus BSC alone published since the last update[3] were hematologic AEs, nausea, and vomiting. Rare but serious AEs included neurologic and renal toxicities.

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

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 a 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. Since the publication of the previous guideline, four trials[4-7] and an MA[8] comparing two drugs versus one drug demonstrated improvement in radiologic response rate for patients receiving two drugs, and one trial[7] and the MA[8] found statistically significant improvements in OS. The range of number of participants in the individual trials was 289[4] to 561 patients.[5] None of the individual trials, or the MA, testing combinations of three cytotoxic drugs versus two drugs demonstrated a survival benefit with the use of three cytotoxic drugs, but they all demonstrated increases in toxic AEs with three cytotoxic drugs.[8-11] These data corroborate the previous recommendation on the benefit of a combination of two cytotoxic drugs and also show that a combination of two cytotoxic drugs is better than a combination of three cytotoxic drugs.

Since the 2003 guideline, 15 RCTs[4-7,9-19] and four literature-based MAs[20-23] were published comparing platinum- with non–platinum-containing regimens. The number of participants in the MAs ranged from 2,351[20] to 7,633 patients,[21] and the number of participants in the individual RCTs ranged from 281[17] to 1,725 patients.[21] Seven trials[4-7,9,10,15] and the four MAs[20-23] reported a significant advantage in response to platinum-based therapy compared with non–platinum-based regimens, and the four MAs[20-23] and one individual study[7] showed a significant survival advantage with platinum-based therapy.

The toxicities reported were higher with platinum agents. AEs specific to platinum include nephrotoxicity and GI problems. Twelve individual trials[4-7,10-14,16,17,136] showed statistically significantly higher hematologic toxicities in platinum treatment arms, and seven trials[4,5,9-11,13,15] showed significantly higher nonhematologic toxicities in platinum arms. Contraindications to platinum-based therapy include allergy to cisplatin or carboplatin, baseline hearing loss, renal insufficiency, intolerable nausea despite optimal emesis prophylaxis (see ASCO guideline on antiemetics[156]), intolerance to corticosteroids needed for emesis prophylaxis, and patient refusal to take a platinum drug. For these patients, nonplatinum combinations are acceptable alternatives.

This section of the guideline reviewed data on alternative schedules of administration. The evidence was limited to two studies of paclitaxel/carboplatin regimens[24,25] and demonstrated no difference in weekly versus every-3-week administration of paclitaxel/carboplatin. Hematologic toxicities were greater in the every-3-week schedules.

Some cisplatin-based combinations lead to better outcomes than others. Observations that docetaxel/cisplatin was superior to vinorelbine/cisplatin in a general NSCLC population, that pemetrexed/cisplatin was superior to gemcitabine/cisplatin for patients with nonsquamous NSCLC, and that gemcitabine/cisplatin was superior to pemetrexed/cisplatin for patients with squamous NSCLC were based on individual clinical trials or retrospective (although preplanned) subgroup analyses.[26,27] 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 AEs.

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. This recommendation remains unchanged from the 2003 guideline update. Since that update, new evidence examining single agents versus two-drug combinations for patients with a PS of 2 included two phase III trials with planned subgroup analyses by PS,[5,28] one phase III trial designed exclusively for patients with PS 2,[29] and a phase II trial comparing traditional cytotoxic chemotherapy with erlotinib in patients with PS 2.[30] This recommendation is also based, in part, on evidence of exclusion of participants with PS 2 from at least one new study.[31] Four analyses reported survival results,[5,28-30] and three reported PFS or time to progression (TTP)[5,28,29]; all reported response rates. Participant sizes ranged from 103[30] to 561 patients.[5]

One RCT and a subset analysis found no survival benefit between comparators for patients with PS 2 (a doublet *v* a doublet[29] and a singlet *v* a doublet[28]), whereas the other subset analysis and other RCT found that patients with PS 2 had a survival benefit from a doublet versus a single agent.[5,30] The only analysis reporting on AEs stratified by PS found no difference between singlet and doublet therapy.[5]

Because of heterogeneity among patients classified as PS 2, subjectivity of scoring PS, 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 2, and the Committee recognizes that some patients classified as PS 2 may not be able to tolerate even single-agent chemotherapy.

4. Clinical question. What is the best chemotherapy for treatment of the elderly 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. Since the publication of the previous guideline update, updated evidence included three new RCTs,[28,32,33] two new subgroup analyses,[5,34] one retrospective analysis,[35] and one pooled analysis[36] that addressed this question. These studies examined optimal first-line treatment for patients older than 65 or 70 years (definitions of elderly varied between studies). The size of the elderly populations in the trials and three analyses (not the MA) ranged from 67[35] to 401 patients.[34]

The results of the three analyses[5,34,35] and the pooled analysis[36] found no differences in survival between patients defined as elderly and those described as younger. In addition, two trials compared two regimens, with all participants older than 65 or 70 years.[28,32] The evidence as a whole did not demonstrate the superiority of one regimen over another for patients who were elderly in terms of survival. Four of the studies reported toxicities, with two finding higher toxicities with a doublet versus a singlet.[28,32]

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. This recommendation is based on a lack of consistent superiority of either agent in terms of OS, toxicity, or quality of life across the literature. The literature search identified three MAs[37-39] and nine individual RCTs[24,40-47] that compared cisplatin with carboplatin in combination with a variety of other cytotoxic drugs. The participant size of the individual RCTs ranged from 153[43] to 1,218 patients.[26] Two literature-based MAs[38,39] and one individual patient data MA (IPDMA)[37] found significantly better response rates with cisplatin versus carboplatin. The three MAs and three individual trials found no significant differences in survival between cisplatin and carboplatin.[42,46,47] In the MAs, cisplatin was superior to carboplatin in terms of survival in certain subgroups, including nonsquamous NSCLC, and when combined with third-generation agents.

Carboplatin is more likely to increase myelosuppression and to cause thrombocytopenia and is less likely to cause nausea than cisplatin. There were several individual trials that have demonstrated that carboplatin is more likely than cisplatin to cause thrombocytopenia.[20,37,39,47] Data on neurotoxicity are confounded by a preponderance of trials that combine carboplatin with taxanes, which are among the most neurotoxic drugs.[46] Cisplatin is more likely to cause ototoxicity and peripheral neuropathy than carboplatin. The risk of some of these toxicities may preclude cisplatin or carboplatin or both. For example, some relative contraindications to cisplatin include baseline hearing loss, renal insufficiency, comorbid illnesses such as congestive heart failure or urinary problems that limit intravenous saline hydration, and diabetes, which limits use of corticosteroids for emesis prophylaxis. Relative contraindications to carboplatin include baseline thrombocytopenia and bleeding risk.

In summary, cisplatin may have better results in efficacy outcomes than carboplatin; carboplatin may have less toxicity. Clinicians must take individual patient factors into consideration when recommending cisplatin or carboplatin to their patients.

6. Clinical question. What is the optimal duration of first-line treatment 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 prior to disease progression.

Literature update. This recommendation is based on four RCTs[48-51] published since the last update. In addition, there were two RCTs on the issue of continuation or initiation of different chemotherapy (published in abstract form only).[52,53] The range of numbers of participants in the four published RCTs on duration was 230[50] to 452 patients.[49] 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 or TTP with additional chemotherapy.[48,49] Of the three trials that reported HRQOL measures,[49-51] one found an advantage in HRQOL for six versus three cycles on one measure,[49] and one found advantage for four versus six cycles on another single measure.[51] Peripheral neuropathy[50] and thrombocytopenia were greater with prolonged chemotherapy[51]; however, the studies did not report other 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.[137] With the advent of second-line drugs that improve survival for patients after first-line chemotherapy, there is renewed interest in whether initiation of a non–cross-resistant drug immediately after completion of first-line therapy may improve survival. Neither of the two RCTs found a statistically significant improvement in survival with this strategy; in both, there was a statistically significant difference in PFS in favor of immediate administration; however, the full guideline notes possible biases in these studies.[52,53] The Update Committee anticipates the results of two studies looking at erlotinib as a maintenance therapy.

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, however, is tempered by an increase in AEs from additional cytotoxic chemotherapy.

7. Clinical question. What are the benefits, with respect to OS, PFS, toxicity, and quality of life/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. Since the last update, there were six RCTs on these topics.[30,54-58] Four trials examined using erlotinib or gefitinib in combination with cytotoxic chemotherapy doublets in the first-line setting.[54-57] Sample size ranged from 1,037[56] to 1,172 patients.[57] All four trials reported all efficacy outcomes and found no advantage in survival, PFS, or response with the addition of an EGFR tyrosine kinase inhibitor (TKI) to chemotherapy. In three of the four trials, there were more AEs in the arm with the EGFR TKI (primarily skin toxicities and diarrhea).[54,56,57]

The sole publication on erlotinib as first-line monotherapy was a small phase II trial comparing it with carboplatin/paclitaxel for patients with PS 2.[30] Doublet chemotherapy conferred a significant survival advantage versus erlotinib alone, although PFS and overall response rate were not significantly different. Participants were not selected on the basis of *EGFR* mutation status.

In the phase III Iressa Pan Asia Study (IPASS), investigators compared gefitinib with carboplatin/paclitaxel as first-line treatment in populations specific to East Asia, all of whom had adenocarcinoma and were light or never smokers.[58] The primary end point was PFS, which was statistically significantly longer with gefitinib; OS, as secondary end point, was not. Hematologic AEs, alopecia, neuropathy, and nausea were greater with chemotherapy, whereas diarrhea and skin toxicities were greater with gefitinib. The results of analysis of PFS by *EGFR* mutation status found that patients with mutations experienced a better outcome with gefitinib and patients without mutations benefited more from chemotherapy. The *EGFR* mutation status of most patients' tumors is negative or unknown, in which case 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 of more than 1, therapeutic anticoagulation, clinically significant cardiovascular disease, or medically uncontrolled hypertension (based on exclusion criteria for Sandler et al[31] registration trial). Bevacizumab may be continued, as tolerated, until disease progression.

Literature update. There were three RCTs (two phase III) published on the antiangiogenesis agent bevacizumab.[31,59-61] The number of participants ranged from 99[59] to 1,043.[61] Two of the studies reported OS and PFS,[31,59] and one reported PFS only.[61] The phase III trial that added bevacizumab to carboplatin/paclitaxel and reported OS found statistically significant increases for OS, as well as for PFS and response.[31] The second phase III trial, of bevacizumab with cisplatin/gemcitabine, confirmed the PFS benefits, but the analysis of survival results was not yet available when the investigators published the trial's results.[61]

The primary AEs with bevacizumab included grade 4 and 5 hematologic events, as well as nonhematologic toxicities. Serious bleeding was initially seen in the phase II trial with certain tumors, leading to a narrowing of eligibility criteria in phase III to patients with non–squamous cell carcinoma, as well as excluding patients with any of the criteria outlined in recommendation A8. Toxic deaths have occurred in all trials, including a trial of bevacizumab as second-line therapy with and without chemotherapy or erlotinib.[62] Because the addition of bevacizumab to gemcitabine and cisplatin did not improve OS and because of the lack of phase III data on 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. Improvements in PFS and overall response rate, while clinically significant, are tempered by an increase in toxicity from bevacizumab. For bevacizumab, there is special concern for toxicity in the elderly population, based on a subgroup analysis of the major phase III trial, which showed increased toxicity and no obvious improvement in OS in the elderly subgroup.[63] The optimal duration of bevacizumab beyond chemotherapy has yet to be determined.

2009 recommendation A9. Based on 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. Four RCTs compared cetuximab plus chemotherapy with chemotherapy alone.[64-67] In the phase III FLEX (First-Line Erbitux in Lung Cancer) study, which included 1,125 participants, patients who received cisplatin/vinorelbine with the addition of cetuximab had a median OS that was 1.2 months greater than in the cisplatin/vinorelbine arm ($P = .0441$), although PFS was the same in both arms.[67] In another phase III abstract, PFS was statistically significantly greater with the addition of cetuximab to chemotherapy, but survival was not.[66] Positive EGFR protein expression assessed by IHC was an eligibility criterion of the FLEX trial.[67] A correlative study of a phase II trial not eligible for the systematic review found that patients with *EGFR* amplification as measured by fluorescent in situ hybridization experienced better PFS and median OS time.[68] These results have not yet been validated in a prospective study.

Febrile neutropenia, acne/rash, diarrhea, and infusion-related reactions were AEs seen with cetuximab combined with chemotherapy. The results of these studies suggest that cetuximab may add benefit in terms of survival when combined with cisplatin/vinorelbine. As in the case of bevacizumab, there are insufficient data to recommend the addition of cetuximab to other chemotherapy regimens. The duration of cetuximab is recommended to continue until intolerance or progression of 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, or pemetrexed is 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. These recommendations include both cytotoxic chemotherapy and targeted therapies. They are based on nine

new phase III RCTs, two new phase II RCTs, a new IPDMA,[69] a new systematic review,[70] and two subgroup analyses of phase III trials on second-line chemotherapy that showed overall benefit for docetaxel, erlotinib, gefitinib, or pemetrexed. Five new phase III RCTs,[71-75] one phase II RCT,[76] two retrospective analyses of clinical trials,[77,78] one systematic review,[79] and one IPDMA[69] were on chemotherapy; one phase II RCT[62] and one phase III RCT[80] were on combination biologic therapy; and three phase III trials were on schedules of administration.[81-83] Seven of the RCTs compared new treatment (with or without standard treatment) with standard treatment or compared new targeted agents with placebo.[62,72-76,80] Pemetrexed was compared with docetaxel,[72] erlotinib was compared with placebo,[74] and gefitinib was compared with BSC/placebo[75] and also with docetaxel.[73,76] Study size ranged from 120 to 1,692 patients.[62,75] The recommendation for docetaxel is supported by data cited in the 2003 update and a newer systematic review. Of the eight new second-line RCTs on treatment, with primary efficacy end points, one showed a statistically significant benefit in OS,[74] and four of them showed noninferiority.[71-73,76] Three trials were negative; two trials used combinations including bevacizumab plus erlotinib, and the other trial compared gefitinib versus placebo.[62,75,80]

Four studies compared different dosages or schedules of administration of docetaxel.[71,81-83] The three trials comparing schedules of administration found that there was no survival advantage to weekly administration (compared with every-3-week administration)[81-83]; hematologic toxicities were generally significantly greater in the every-3-week schedule.

In some of the studies that compared docetaxel with newer agents, AEs of docetaxel included neutropenia, febrile neutropenia, use of granulocyte colony-stimulating factor, diarrhea, and alopecia. The most common AEs of erlotinib were rash and diarrhea. In addition, a low incidence of interstitial lung disease was seen.[55] Common AEs of pemetrexed were neutropenia, febrile neutropenia, and use of granulocyte colony-stimulating factor, but these were seen less often than with docetaxel. Common AEs of gefitinib were rash and diarrhea; in addition, a low incidence of interstitial lung disease was observed.

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. Since the previous guideline, a new retrospective subset analysis of an RCT on second-line chemotherapy for patients with stage IV NSCLC older than age 70 years was published that compared outcomes from docetaxel and pemetrexed by age.[135] Five hundred seventy-one participants took part in the registration trial for pemetrexed from which this analysis is drawn. People ≥ age 70 received similar benefit from both agents. The difference in survival between patients ≥ age 70 versus younger than age 70 taking docetaxel was not significant (median OS, 7.7 *v* 8.0 months, respectively; P = not significant). People ≥ age 70 had longer OS (not statistically significant) and TTP with pemetrexed than patients younger than age 70 (median OS, 9.5 *v* 7.8 months, respectively; P = not significant). Toxicity did not differ significantly by age.

Third-Line Chemotherapy

1. 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 0 to 3 who have not received prior erlotinib or gefitinib.

Literature update. This recommendation is based on one RCT, the erlotinib versus placebo trial, which was the basis for recommending erlotinib as a second-line therapy option (see recommendation B1).[74] This trial included participants who had received one or two prior regimens. Erlotinib seems to be as beneficial as third-line therapy as for second-line therapy. In a multivariate analysis of survival, the difference between prior numbers of regimens was not significant. In general, there is a paucity of clinical trial data on participants who have had two prior regimens of chemotherapy.

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 BSC.

Literature update. There are currently no phase III data supporting the routine use of cytotoxic chemotherapy in the third-line setting. Therefore, this recommendation refers to a retrospective analysis of the outcome of 700 patients who had received two or more prior chemotherapy regimens, including at least one platinum and docetaxel regimen, for recurrent NSCLC.[84] The study found that survival and response rates decreased with each subsequent regimen. 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.

Molecular Analysis

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. This is a topic new to this guideline update. The guideline reviewed molecular markers for which there were more than five peer-reviewed publications. The systematic review found ≥ five publications on the following markers: *EGFR*, *KRAS*, ERRC1/RRM1, and VEGF.

EGFR. 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 three major methods: at the protein level by IHC; at the DNA copy number level, such as by fluorescent in situ hybridization; 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 literature included 37 reports on studies involving EGFR status and, primarily, use of EGFR TKIs (mostly gefitinib).[68,85-120] In addition, the review included a systematic review[79] and an IPDMA.[69] The number of tumors analyzed per study ranged from 20[98] to 731.[104] Twenty-four studies were retrospective, including five analyses of the major clinical trials involving gefitinib and erlotinib. In these five analyses,[87,89,91,94,104] tumor specimen collection was not mandated, and the percentage of patients' tumors examined for biomarkers was low. There were three meta-analyses or pooled analyses[69,79,92]; five clinical trials,[88,90,105,114] including one phase III RCT[58]; and four retrospective analyses of clinical trials.[68,91,104,113]

Thirty-one studies reported OS. Twenty of 31 studies reported on OS by mutation status, and 14 of 31 studies showed a significant benefit for patients with tumors that were *EGFR* mutation positive (measured by any of three methods). Twenty-eight of 31 studies reported PFS (or TTP); 21 of 31 studies reported PFS by mutation status, 16 of which reported significant benefit for patients with mutation-positive tumors (measured by any of three methods).

Recommendation A7 supports the first-line use of gefitinib over carboplatin and paclitaxel in patients whose NSCLC tumors harbor *EGFR* mutation based on a clinically significant improvement in PFS, favorable toxicity profile, and improved quality of life. These data justify attempts to test NSCLC tumors 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.

KRAS. *KRAS* accounts for 90% of *RAS* mutations in lung adenocarcinomas, and approximately 97% of *KRAS* mutations in NSCLC involve codons 12 or 13; mutations are uncommon in squamous cell carcinomas.[138,139] 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 publications on trials involving *KRAS*.[87,88,91,92,100,121,157] Numbers of tumors analyzed ranged from 41[88] to 274.[87] Two studies were retrospective analyses of RCTs,[87,91] two were retrospective tissue analyses,[100] one was a prospective analysis of patients in an expanded access program,[121] one was a pooled analysis,[92] and one was a correlative study of a prospective phase II single-arm trial with people $\geq$ 70 years of age.[88] All studies reported *KRAS* mutation rates. The analyses studied responses to a variety of chemotherapeutic agents and both EGFR TKIs. 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 rate to EGFR TKIs in patients whose tumors harbor a *KRAS* mutation is close to zero. Prospective phase III data are currently lacking.

ERCC1/RRM1. Several molecules impact the metabolism and efficacy of chemotherapeutic agents, including ribonucleotide reductase subunit 1 (RRM1), which is important for nucleotide metabolism and is the dominant molecular determinant of gemcitabine efficacy, and excision repair cross-complementing (or cross-complementation) group 1 (ERRC1), a component of the nucleotide excision repair complex that is important for platinum-induced DNA adduct repair. The guideline reviewed seven publications on these markers,[122-128] including four retrospective analyses of clinical trials, two prospective analyses from RCTs, and one correlative study. Samples sizes ranged from 53[127] to 346.[123] The chemotherapy in the studies included cisplatin, carboplatin, paclitaxel, docetaxel, gemcitabine, vinorelbine, and ifosfamide. The studies suggest that low levels of these markers may be predictive of benefit from chemotherapy; however, there are currently insufficient prospective phase III data to recommend use of these markers.

VEGF. 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. Bevacizumab, a monoclonal antibody directed against VEGF, has shown clinical benefit in 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 studies (not all of RCTs), and all participants in these four trials received chemotherapy (ie, none received bevacizumab).[129-133] All four studies reported response, whereas only two reported OS. The study sizes ranged from 21[130] to 160[129] patients. The single study that reported significant figures found that patients with low levels of VEGF had almost twice the survival time of patients with high ($>$ 500 pg/mL) levels.[130] A fifth VEGF study was a small, prospective corollary study of the ECOG 4599 trial.[129] 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, and low levels of VEGF were not predictive of response or survival.

2009 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.

Literature update. 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 the discussions in the full guideline after first-line recommendations A2, 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 patients with NSCLC into subgroups of patients in whom 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 EGFR 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 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 may lower the patient's risk of death by 20% to 30%, which may improve 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.

For a full discussion of methods and studies identified, including those in Table 2, refer to the online version of this guideline, available at www.asco.org/guidelines/nsclc; also available are guideline-based clinical tools and resources.

FUTURE RESEARCH DIRECTIONS

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 ≥ 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),[27] molecular subgroups (*EGFR* mutation, *EGFR* amplification, EGFR expression, or *KRAS* mutation),[58,87,91,92,104,113] number of prior therapies (no, one, or $\geq$ two prior therapies),[72,74] time on prior therapy,[72] smoking status (including never smokers [$<$ 100 cigarettes over lifetime],[55,74,140] former light smokers [$<$ 15 pack-years], and heavy smokers [$\geq$ 15 pack-years]),[55,74,140] and Asian ethnicity.[58,74] 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.

PATIENT-PHYSICIAN COMMUNICATION

This section represents consensus opinion that was not based on the evidence in the systematic review, unlike the guideline recommendations, but was based on literature that used questionnaires, surveys, interviews, observations and analyses of office consultations, and other qualitative research methods.

Patients with NSCLC often have complex medical, psychological, and social issues that their physicians must take into account before discussing therapy. For example, patients with lung cancer may experience depression as a result of diagnosis with this disease with a bad prognosis, loss of sense of self, fears of pain and death, and/or feelings of alienation. Lung cancer carries a unique social stigma because of its association with cigarette smoking. Some patients are angry because they never smoked but have the social stigma thrust on them. Insufficient time and training, system-level barriers, and/or patient factors, such as misconceptions about the disease and treatment, can constitute barriers to effective communication by clinicians.

Research on communication between clinicians and patients with NSCLC has found missed opportunities for expressing empathy,[141] observed clinicians using blaming words, observed a lack of discussion on prognosis (20% of patients may not want discussion of prognostic information),[142] and found a lack of information exchange and trust between patients and clinicians of different racial/ethnic backgrounds.[143,144]

Although effective communication can be challenging, intensive training has been shown to help physicians to communicate more effectively with patients with cancer.[141,144] A way to involve the patient in shared decision making is to offer a session dedicated solely to the discussion of treatment options; the clinician should present the patient with a personalized description of his or her individual risks and benefits. Another factor to support shared decision making concerning stage IV NSCLC treatment is the presence of a caregiver at appointments, which can help elicit more information from the oncologist, among other benefits.[143,145,146] In the session on treatment options, a balanced presentation of benefits and risks is important. The trade-offs that patients with lung cancer are willing to accept for treatments such as chemotherapy vary widely.[147-149] Physician presumptions about which trade-offs patients with NSCLC are willing to accept may not always be accurate or may not align with patient-reported attitudes.[147] Patients with lung cancer may overestimate the survival benefits of potentially toxic treatment.[150,151] 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.[150] The full guideline also has an in-depth discussion of presenting benefits and risks of NSCLC treatment and suggests language for clinicians to consider using in consultations.

HEALTH DISPARITIES

This section of the guideline was based on an environmental scan of the literature. Racial and ethnic disparities are notable in lung cancer. Ethnic and racial minorities experience poorer outcomes compared with whites in all stages of lung cancer. Lung cancer health care disparities can result from patients' risk behaviors (smoking, smoke inhalation, and number of cigarettes smoked daily), socioeconomic status (including education level), access to health services, and comorbid illnesses.[152-154] Health disparities frequently are the result of ineffectual communication between health care providers and patients.[155] When patients receive uniform clinical care, differences in outcomes between racial groups are minimized.[152] Awareness of these disparities in access to care should be considered in the context of the stage IV NSCLC clinical practice guideline update, and health care providers should strive to deliver the highest level of cancer care to all patients.

Table 3. 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^2 initial dose followed by 250 mg/m^2 (recommended only in combination with cisplatin/vinorelbine)‡	10	50	3,894§ (note: initial dose only)	Weekly	18,981
First-line	Cisplatin†	75 mg/m^2, every 3 weeks	50	12	34§	Every 3 weeks	68‖
First- and second-line	Docetaxel†	75 mg/m^2, 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^2‡	200	141	1,729§	Days 1 and 8, every 3 weeks	6,914
First-line	Irinotecan†	60 mg/m^2	20	15	88§	Days 1, 8, and 15, every 4 weeks	527
First-line	Paclitaxel†	200 mg/m^2	30	8	101§	Every 3 weeks	201
First- and second-line	Pemetrexed†	500 mg/m^2 (note: monotherapy in second-line setting)‡	10	49	4,841§	Every 3 weeks	9,682
First-line	Vinorelbine†	25 mg/m^2	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, antinausea 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 (Erbitux; 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).

‡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).

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 3 provides estimated costs for reference based on data from the Centers for Medicare and Medicaid Services (Rockville, MD).

ASCO GUIDELINES

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

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GUIDELINE AND CONFLICTS OF INTEREST

The Update Committee was assembled in accordance with ASCO's Conflict of Interest Management Procedures for Clinical Practice Guidelines. Members of the panel 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 Committee did not disclose any of these relationships. Disclosure information for each member of the Committee is published adjunct to this guideline.

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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