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ASCO SPECIAL ARTICLE

2011 Focused Update of 2009 American Society of Clinical Oncology Clinical Practice Guideline Update on Chemotherapy for Stage IV Non–Small-Cell Lung Cancer

Christopher G. Azzoli, Sarah Temin, Timothy Aliff, Sherman Baker Jr, Julie Brahmer, David H. Johnson, Janessa L. Laskin, Gregory Masters, Daniel Milton, Luke Nordquist, William Pao, David G. Pfister, Steven Piantadosi, Joan H. Schiller, Reily Smith, Thomas J. Smith, John R. Strawn, David Trent, and Giuseppe Giaccone

Christopher G. Azzoli and David G. Pfister, Memorial Sloan-Kettering Cancer Center, New York, NY; Sarah Temin, American Society of Clinical Oncology, Alexandria; Sherman Baker Jr and Thomas J. Smith, Virginia Commonwealth University, Massey Cancer Center; David Trent, Virginia Cancer Center, Richmond, VA; Timothy Aliff, Northwest Oncology and Hematology Associates, Coral Springs, FL; Julie Brahmer, Sidney Kimmel Cancer Comprehensive Center, Johns Hopkins University, Baltimore; Giuseppe Giaccone, National Cancer Institute, Bethesda, MD; David H. Johnson and Joan H. Schiller, University of Texas, Southwestern Medical Center, Dallas; John R. Strawn, patient representative, Houston, TX; Janessa L. Laskin, British Columbia Cancer Agency, Vancouver, British Columbia, Canada; Gregory Masters, Helen F. Graham Cancer Center, Newark, DE; Daniel Milton, Hematology/Oncology of Indiana, Indianapolis, IN; Luke Nordquist, Nebraska Cancer Specialists, Omaha, NE; William Pao, Vanderbilt-Ingram Cancer Center, Nashville, TN; Steven Piantadosi, Samuel Oschin Comprehensive Cancer Center Institute, Los Angeles; and Reily Smith, patient representative, Bakersfield, CA.

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Corresponding author: American Society of Clinical Oncology, 2318 Mill Rd, Suite 800, Alexandria, VA 22314; e-mail: guidelines@asco.org.

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ABSTRACT

Purpose
An American Society of Clinical Oncology (ASCO) focused update updates a single recommendation (or subset of recommendations) in advance of a regularly scheduled guideline update. This document updates one recommendation of the ASCO Guideline Update on Chemotherapy for Stage IV Non–Small-Cell Lung Cancer (NSCLC) regarding switch maintenance chemotherapy.

Clinical Context
Recent results from phase III clinical trials have demonstrated that in patients with stage IV NSCLC who have received four cycles of first-line chemotherapy and whose disease has not progressed, an immediate switch to alternative, single-agent chemotherapy can extend progression-free survival and, in some cases, overall survival. Because of limitations in the data, delayed treatment with a second-line agent after disease progression is also acceptable.

Recent Data
Seven randomized controlled trials of carboxyaminoimidazole, docetaxel, erlotinib, gefitinib, gemcitabine, and pemetrexed have evaluated outcomes in patients who received an immediate, non–cross resistant alternative therapy (switch maintenance) after first-line therapy.

Recommendation
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 stable but not responding to treatment. Two-drug cytotoxic combinations should be administered for no more than six cycles. For those with stable disease or response after four cycles, immediate treatment with an alternative, single-agent chemotherapy such as pemetrexed in patients with nonsquamous histology, docetaxel in unselected patients, or erlotinib in unselected patients may be considered. Limitations of this data are such that a break from cytotoxic chemotherapy after a fixed course is also acceptable, with initiation of second-line chemotherapy at disease progression.

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EDITOR'S NOTE

This is the complete American Society of Clinical Oncology (ASCO) Clinical Practice Guideline Focused Update and provides an updated recommendation with a comprehensive discussion of the relevant literature for this individual recommendation. The full guideline[1] to which this revision applies is available at http://www.asco.org/guidelines/nsclc.

In addition, the recommendations for the use of epidermal growth factor receptor (*EGFR*) mutation testing for patients with stage IV non–small-cell lung cancer (NSCLC) who are candidates for EGFR tyrosine kinase therapy have been updated since the publication of the full guideline.[1] The new guidance is now reflected in a provisional clinical opinion on *EGFR* testing in NSCLC.[2]

INTRODUCTION

The ASCO Clinical Practice Guideline Update on Chemotherapy for Stage IV NSCLC was most recently published in November 2009.[1] ASCO guidelines are updated at regular intervals; however, there may be new evidence that potentially changes a recommendation and becomes available between

scheduled updates. ASCO produced this 2011 focused update in response to new peer-reviewed publications of phase III randomized clinical trials (RCTs) on maintenance chemotherapy published since the literature search date cutoff for the November 2009 update. The 2009 stage IV NSCLC update (available at http://www.asco.org/guidelines/nsclc) states that new evidence may be published that would potentially warrant reconsideration of a recommendation in the guideline before the regularly scheduled update.

Focused updates of clinical practice guidelines are approved by the ASCO Board of Directors Executive Committee, and this one reflects new evidence regarding the recommendation on maintenance therapy in the previous version of this guideline.[1] This focused update summarizes an updated literature search and reviews and analyzes new data regarding this recommendation since the systematic review for the previous update.

Switch maintenance therapy is alternative therapy administered to patients who have undergone first-line therapy for a specified number of cycles (usually four to six) and have either experienced response or achieved stable disease. Continuation maintenance therapy is continuation of one or more drugs used during first-line therapy beyond four to six cycles. Second-line therapy is initiation of alternative therapy in patients whose disease has progressed during or after first-line chemotherapy. Table 1 provides a summary of the 2009 and 2011 recommendations. This 2011 focused update addresses switch maintenance therapy only. This focused update does not address the continuation of the same regimen of chemotherapy beyond the standard number of cycles recommended in the previous guideline, nor does it address the continuation of drugs contained in an initial regimen and continued beyond chemotherapy included in the control arm. This focus follows from the bulk of the evidence.

THE BOTTOM LINE

FOCUSED UPDATE

2011 Focused Update of 2009 ASCO Clinical Practice Guideline Update on Chemotherapy for Stage IV Non–Small-Cell Lung Cancer

Intervention

- Switch maintenance (alternative therapy administered to patients who have undergone first-line therapy for specified number of cycles [usually four to six] and experienced response or achieved stable disease).

Target audience

- Medical oncologists.

Recommendation

- 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 stable but not responding to treatment. Two-drug cytotoxic combinations should be administered for no more than six cycles. For patients with stable disease or response after four cycles, immediate treatment with an alternative, single-agent chemotherapy such as pemetrexed in patients with nonsquamous histology, docetaxel in unselected patients, or erlotinib in unselected patients may be considered. Limitations of these data are such that a break from cytotoxic chemotherapy after a fixed course is also acceptable, with initiation of second-line chemotherapy at disease progression.

Methods

- This represents an update of a single recommendation from the ASCO 2009 Stage IV Chemotherapy Guideline Update. Systematic review and analysis of medical literature was performed by update committee of expert panel.

The 2009 guideline update, data supplements, and clinical tools can be found at http://www.asco.org/guidelines/NSCLC.

GUIDELINE QUESTIONS

Because this focused update addresses solely one clinical question, the guideline questions for the full guideline are available in the Data Supplement.

METHODS

For the 2011 focused update, the NSCLC update committee (Appendix Table A1, online only) reviewed and analyzed data from new peer-reviewed publications of phase III RCTs on maintenance chemotherapy published since the search date cutoff for the November 2009 guideline update. The update committee addressed the maintenance aspect of the clinical question, "What is the optimal duration of first-line chemotherapy for stage IV NSCLC?" from the previous guideline. To be included in this 2011 focused update, a trial had to compare outcomes for patients receiving new maintenance/consolidation/sequential chemotherapy before disease progression versus those receiving a regular course of chemotherapy/placebo/observation/best supportive care after first-line therapy. This type of maintenance therapy is also known as switch maintenance or consolidation therapy.

The evidence base for this 2011 focused update comprises of peer-reviewed publications of five RCTs[3-7] and two RCTs presented in abstract form.[8-10] Because of the literature search parameters, some studies discussed in the 2009 update were considered for the 2011 focused update.

Guideline Policy

This focused update of an ASCO clinical practice guideline is intended for physicians. The practice guideline and this focused update are not intended to substitute for the independent professional judgment of the treating physician. Practice guidelines do not account for individual variation among patients and may not reflect the most recent evidence. This focused update does not recommend any particular product or course of medical treatment. Use of the practice guideline and this focused update is voluntary. The full practice guideline and additional information are available at http://www.asco.org/guidelines/nsclc.

Conflicts of Interest

The update committee was assembled in accordance with the ASCO conflict of interest management procedures for clinical practice guidelines. Members of the update committee completed the ASCO disclosure form, which requires disclosure of financial and other interests 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

Table 1. Summary of Recommendations

Recommendation	Summary
A. First-line chemotherapy	
A1	Evidence supports use of chemotherapy in patients with stage IV* NSCLC with ECOG/Zubrod performance status of 0, 1, possibly 2
A2	In patients with performance status of 0 or 1, evidence supports using 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 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
A3	Available data support use of single-agent chemotherapy in patients with performance status of 2; data are insufficient to make recommendation for or against using combination of two cytotoxic drugs in patients with performance status of 2
A4	Evidence does not support selection of specific first-line chemotherapy drug or combination based on age alone
A5	Choice of either cisplatin or carboplatin is acceptable; drugs that may be combined with platinum include third-generation cytotoxic drugs docetaxel, gemcitabine, irinotecan, paclitaxel, pemetrexed, and vinorelbine; evidence suggests cisplatin combinations result in higher response rates 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
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 **stable but** not responding to treatment; two-drug cytotoxic combinations should be administered for no more than six cycles; **for patients with stable disease or response after four cycles, immediate treatment with alternative, single-agent chemotherapy such as pemetrexed in patients with nonsquamous histology, docetaxel in unselected patients, or erlotinib in unselected patients may be considered; limitations of this data are such that break from cytotoxic chemotherapy after fixed course is also acceptable, with initiation of second-line chemotherapy at disease progression**
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; first-line use of gefitinib may be recommended for patients with activating *EGFR* mutations; if *EGFR* mutation status is negative or unknown, cytotoxic chemotherapy is preferred (see A2)
A8	On basis of results of one large phase III RCT, update committee recommends 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
A9	On basis of results of one large phase III RCT, clinicians may consider addition of cetuximab to cisplatin/vinorelbine in first-line therapy in patients with EGFR-positive tumor as measured by immunohistochemistry; cetuximab may be continued as tolerated until disease progression
B. Second-line chemotherapy	
B1	Docetaxel, erlotinib, gefitinib, or pemetrexed is acceptable as second-line therapy for patients with advanced NSCLC with adequate performance status when disease has progressed during or after first-line platinum-based therapy
B2	Evidence does not support selection of specific second-line chemotherapy drug or combination based on age alone
C. Third-line chemotherapy	
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
C2	Data are not sufficient to make recommendation for or against using cytotoxic drug as third-line therapy; these patients should consider experimental treatment, clinical trials, and best supportive care
D. Molecular analysis	
D1	Evidence is insufficient to recommend routine use of molecular markers† to select systemic treatment in patients with metastatic NSCLC
D2	To obtain tissue for more accurate histologic classification or investigational purposes, update committee supports reasonable efforts to obtain more tissue than that contained in routine cytology specimen

NOTE. Bold font indicates 2011 focused update changes.

Abbreviations: ASCO, American Society of Clinical Oncology; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; NSCLC, non–small-cell lung cancer; OS, overall survival; RCT, randomized clinical trial; TKI, tyrosine kinase inhibitor.

*As defined by the International Association for the Study of Lung Cancer Staging Project, for the 7th edition of the TNM Classification of Malignant tumors.[10a]

†In April 2011, ASCO issued a Provisional Clinical Opinion regarding EGFR testing; it will be incorporated into future updates of NSCLC guideline: On the basis of the results of five phase III RCTs, patients with NSCLC who are being considered for first-line therapy with an EGFR TKI (patients who have not previously received chemotherapy or an EGFR TKI) should have their tumor tested for *EGFR* mutations to determine whether an EGFR TKI or chemotherapy is appropriate first-line therapy (http://www.asco.org/pco/egfr).

employment relationships, consulting arrangements, stock ownership, honoraria, research funding, and expert testimony. In accordance with these procedures, the majority of the members of the update committee did not disclose any such relationships. Further description of the methodology may be found at the end of this document.

GUIDELINE RECOMMENDATION

Clinical Question: What Is the Optimal Duration of First-Line Chemotherapy for Stage IV NSCLC?

2009 update recommendation. 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 initiation of a different chemotherapy before disease progression.

2011 focused update recommendation. 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 **stable but** not responding to treatment. Two-drug cytotoxic combinations should be administered for no more than six cycles. For patients with stable disease **or response after four cycles, immediate treatment**

with an alternative, single-agent chemotherapy such as pemetrexed in patients with nonsquamous histology, docetaxel in unselected patients, or erlotinib in unselected patients may be considered. Limitations of this data are such that a break from cytotoxic chemotherapy after a fixed course is also acceptable, with initiation of second-line chemotherapy at disease progression. (Changes from the previous recommendation are indicated in bold text).

Literature Review and Analysis

Randomized trials have studied the effects of extended duration first-line chemotherapy in three basic ways: first, delivering a fixed number of additional cycles of two-drug chemotherapy; second, continuing the nonplatinum drug beyond four cycles until disease progression; and third, initiation of alternative chemotherapy immediately after four cycles and before disease progression. This 2011 focused update reviews new evidence on the third strategy, for which important new data have been published. The 2009 update discussed two relevant trials on maintenance therapy. The discussion of one, a published docetaxel trial, will be briefly repeated. Preliminary results on the second trial were previously available in abstract form (from the ASCO 2008 and 2009 Annual Meetings), and final results are discussed here.

Trials using docetaxel, pemetrexed (for those with nonsquamous cell carcinoma), erlotinib, gefitinib, and gemcitabine have shown increased progression-free survival (PFS) with maintenance therapy. In the study of pemetrexed and in one of two studies of erlotinib, overall survival (OS) was statistically significantly increased with switch maintenance therapy. Evidence tables summarizing outcomes from and selected characteristics of these trials are provided in the Data Supplement.

The docetaxel trial showed that the median PFS for docetaxel administered to those without progressive disease after first-line treatment (immediate) was greater than that for those who received docetaxel at disease progression (delayed; 5.7 *v* 2.7 months; $P < .001$). Although the difference in OS was not statistically significant, there was a trend toward improved survival with immediate docetaxel (12.3 *v* 9.7 months; $P = .0853$). The 2009 update noted that the PFS results may have been biased by a lack of placebo control or blinding. It also noted that 63% of those in the delayed arm versus 95% in the immediate arm received docetaxel.[3]

The results of the pemetrexed trial were the basis of the US Food and Drug Administration (FDA) approval of pemetrexed maintenance therapy. Final peer-reviewed results were published after the 2009 update.[4] This trial randomly assigned 663 participants to pemetrexed and best supportive care versus placebo and best supportive care after they had received four cycles of platinum-based chemotherapy containing docetaxel, gemcitabine, or paclitaxel with no evidence of disease progression. The primary end point of this trial was PFS; OS was a secondary end point. There were statistically and clinically significant benefits observed in both PFS and OS in the pemetrexed arm. In the final results, median PFS for the maintenance arm versus placebo was 4.3 months (95% CI, 4.1 to 4.7) versus 2.6 months (95% CI, 1.7 to 2.8; hazard ratio [HR], 0.502 [95% CI, 0.42 to 0.61]; $P < .001$.) Median survival was 13.4 months for maintenance (95% CI, 11.9 to 15.9) versus 10.6 months for placebo (95% CI, 8.7 to 12; HR, 0.79 [95% CI, 0.65 to 0.95]; $P = .012$). However, similar to the results of the clinical trial testing first-line pemetrexed/cisplatin,[11] the benefit of consolidation pemetrexed was only apparent in patients with nonsquamous histology (74% of total patients). In the nonsquamous subgroup, consolidation pemetrexed improved PFS (HR, 0.447 [95% CI, 0.36 to 0.6055]; $P < .001$) and OS (HR, 0.70 [95% CI, 0.56 to 0.88]; $P = .002$). The response rate was also improved: 3.4% versus 0.5% ($P = .042$), as assessed by independent review. Grade 3 to 4 neutropenia (3% *v* 0%) and fatigue (5% *v* 1%) were significantly higher with pemetrexed. Of note, only 18% of patients in the placebo arm went on to receive pemetrexed at any time in their clinical course. Twenty-nine percent of patients in the placebo arm received subsequent docetaxel, compared with 22% in the pemetrexed arm. Nearly one third of patients in the placebo arm did not receive any poststudy therapy, despite the success of their first-line chemotherapy. As such, the clinical benefits from consolidation pemetrexed seen in this study may have been related to inadequate treatment in the control arm. Mandatory crossover to pemetrexed in the control arm at the time of disease progression would have helped counter this criticism to some extent. On the other hand, patients in the control arm may have become ineligible for additional therapy because of symptoms of disease progression.

Another study that found an OS benefit with maintenance therapy was published in 2010; earlier results led to FDA approval for a maintenance indication for erlotinib. This study observed 1,949 patients with stage IIIB-IV NSCLC receiving two-drug, platinum-based therapy and identified 889 with stable disease or response after four cycles, who were then randomly assigned to immediate erlotinib versus placebo. The primary end points were PFS in all participants, regardless of molecular marker status (ie, regardless of *EGFR* mutation or EGFR protein expression by immunohistochemistry [IHC]), as well as PFS in the subgroup of participants with IHC-positive EGFR expression. OS was a secondary end point. This study demonstrated improvement in overall PFS; however, the difference was only 1.2 weeks (median PFS, 12.3 *v* 11.1 weeks; HR, 0.71 [95% CI, 0.62 to 0.82]; $P < .001$). PFS for those with IHC-positive *EGFR* tumors was also 12.3 weeks versus 11.1 weeks ($P < .001$). Patients with *EGFR* mutations benefited most from erlotinib (HR, 0.10; $P < .001$). The difference in OS was 1 month (intent to treat: median OS, 12 *v* 11 months; HR, 0.81 [95% CI, 0.7 to 0.95] $P = .0088$). The response rate to erlotinib was 11.9% compared with 5.4% with placebo. No subgroups were identified by sex, ethnicity, histology, or smoking status that did not have improvement in PFS. There were no unexpected toxicities, with 60% of patients receiving erlotinib reporting rash (9% grade 3 to 4) and 20% diarrhea (2% grade 3 to 4). Similar to the pemetrexed study, only 72% of patients in the placebo arm received any second-line therapy, and only 21% received any EGFR tyrosine kinase inhibitors (TKIs).[5]

Another trial of switch maintenance therapy involving erlotinib, presented as an abstract and not yet published in a peer-reviewed journal, tested whether the addition of erlotinib to bevacizumab maintenance improves PFS after first-line chemotherapy plus bevacizumab.[9,10] This study was powered to detect a difference in PFS only. In this study, 1,160 patients were enrolled and treated with platinum-based chemotherapy plus bevacizumab for up to four cycles. Of the 1,160 enrolled, 768 patients demonstrated response or stable disease after four cycles and were randomly assigned to bevacizumab plus erlotinib versus bevacizumab plus placebo. Median PFS was 4.8 months for the erlotinib arm versus 3.7 months for placebo (HR, 0.72 [95% CI, 0.59 to 0.88]; $P = .0012$).[9] There were no unexpected toxicities. There was no significant difference in OS (HR, 0.90 [95% CI, 0.74 to 1.09]; $P = .2686$).[10] An equal percentage of patients (40%) in both

arms received subsequent therapy with an EGFR TKI. The update committee chose not to specify erlotinib plus bevacizumab as an acceptable switch maintenance regimen because of lack of data showing OS benefit of either maintenance bevacizumab alone or switch maintenance erlotinib plus bevacizumab.

An earlier trial (included in systematic review for 2009 update) did not find a benefit with maintenance therapy with carboxyaminoimidazole. This trial was closed because of slow accrual and did not find a benefit with carboxyaminoimidazole versus placebo after 3 to 6 months of chemotherapy treatment. The primary end point was OS; time to progression was a secondary end point. OS was 11.4 months versus 10.5 months, and time to progression was 2.8 months versus 2.4 months; neither difference was statistically significant. Fatigue (7.8% *v* 3.3%), ataxia (11.1% *v* 3.3%), and neurosensory events (8.9% *v* 0%) were greater in the maintenance arm. There were three grade 5 events in each arm. Sixty-four percent of participants in the maintenance arm received poststudy therapy versus 67% in the placebo arm.[6]

Another trial used an EGFR TKI as maintenance therapy after platinum-based chemotherapy. This study randomly assigned 604 participants to gefitinib after a platinum doublet or to continued chemotherapy (up to six cycles). The primary end point was OS; PFS was a secondary end point. There was no statistically significant difference in OS between the maintenance gefitinib and chemotherapy arms (median OS, 13.7 *v* 12.9 months; HR, 0.86 [95% CI, 0.72 to 1.03]; $P = .11$). The difference in PFS was statistically but not clinically significant (4.6 *v* 4.3 months; HR, 0.68 [95% CI, 0.57 to 0.80]; $P < .001$). Grade 3 to 4 anemia, leucopenia, thrombocytopenia, neutropenia, and fatigue were greater in the chemotherapy arm, and grade 3 to 4 AST/ALT elevation was higher in the gefitinib arm. The proportion of those receiving poststudy therapy was higher in the gefitinib arm (88.5% *v* 73%). Specifically, more participants in the gefitinib arm received poststudy EGFR TKI therapy (75.2%) versus those in the chemotherapy arm (54.5%).[7]

A recent announcement of trial results on maintenance therapy was presented at the 2010 ASCO Annual Meeting.[8] Four hundred sixty-four participants who did not have progressive disease after receiving four cycles of cisplatin/gemcitabine were randomly assigned to either maintenance therapy (gemcitabine or erlotinib) or observation. The prespecified second-line therapy for those with progressive disease after these interventions was pemetrexed. The primary end point was PFS. PFS was greater with either maintenance therapy versus observation (gemcitabine: 3.8 *v* 1.9 months; HR, 0.55 [95% CI, 0.43 to 0.7]; $P < .001$; erlotinib: 2.9 *v* 1.9 months; HR, 0.82 [95% CI, 0.73 to 0.93]; $P = .002$). HRs of preliminary results of OS were not significant (gemcitabine: HR, 0.86 [95% CI, 0.66 to 1.12]; erlotinib: HR, 0.91 [95% CI, 0.80 to 1.04]). Grade 3 to 4 adverse events were greater in the maintenance arms than observation. The largest difference was neutropenia (21% gemcitabine *v* 0.6% erlotinib *v* 0.6% observation). There were two drug-related deaths in the gemcitabine arm. The proportions of those receiving postdiscontinuation therapy were 60% for gemcitabine; 63%, erlotinib, and 76%, observation.

According to ASCO guidelines regarding duration of first-line chemotherapy, patients with radiologic response after four cycles of cytotoxic drug therapy may be considered for additional cycles of first-line chemotherapy (ie, cycles five and six).[1] In keeping with this recommendation, the data on switch maintenance chemotherapy suggest that switching to a cytotoxic drug after four cycles of platinum-based chemotherapy seems to be more beneficial to patients with radiologic response. Fidias et al[3] recently reported that switch maintenance docetaxel seemed to be more beneficial in those who had prior responses (PFS: prior response HR, 0.47; stable disease HR, 0.81; OS: prior response HR, 0.61; stable disease HR, 1.02).[12] Similarly, in the study by Perol et al,[8] the benefit of switch maintenance gemcitabine seemed to be greater in those who had a response than those with stable disease (PFS: prior response HR, 0.44 [95% CI, 0.31 to 0.63]; stable disease HR, 0.68 [95% CI, 0.48 to 0.97]).

In contrast, when patients were switched to erlotinib for maintenance therapy, this trend toward greater benefit in responders was less apparent or nonexistent. Perol et al[8] reported that the benefit of switch maintenance erlotinib was similar between responders and those with stable disease (PFS: disease response HR, 0.80 [95% CI, 0.68 to 0.95]; stable disease HR, 0.85 [95% CI, 0.71 to 1.01]). In the trial by Cappuzzo et al,[5] patients with radiologic response to first-line cytotoxic chemotherapy experienced no apparent benefit from maintenance erlotinib, whereas those with stable disease experienced greater benefit than the overall study population (OS: disease response HR, 0.94 [95% CI, 0.74 to 1.20]; $P = .618$; stable disease HR, 0.72 [95% CI, 0.59 to 0.89]; $P = .0019$).

It has long been known that patients with NSCLC that is sensitive to initial cytotoxic therapy are more likely to benefit from additional cytotoxic drug therapy. This observation has affected the design of randomized trials of second-line cytotoxic chemotherapy, which have stratified or actively balanced enrollment based on response to prior cytotoxic chemotherapy.[13,14] On the other hand, sensitivity to initial cytotoxic therapy does not predict sensitivity to erlotinib, presumably because of its unique mechanism of action.[15] Subgroup analyses based on radiologic response to first-line chemotherapy are not reported in the switch maintenance studies of pemetrexed or gefitinib.[4,7] Overall, these data on trends in benefit from switch maintenance chemotherapy based on radiologic response to first-line chemotherapy are in keeping with existing ASCO guidelines regarding duration of therapy. Because they are subgroup analyses, they were not considered important enough by the update committee to be reflected in the updated guideline recommendation.

There are no data to delineate first-line versus second-line versus switch maintenance gefitinib or erlotinib in *EGFR* mutation–positive patients. Similarly, there are no data to delineate the relative efficacy of other drugs compared with erlotinib when used as second- or third-line or switch maintenance therapy in unselected patients.

In summary, six studies have demonstrated that immediate initiation of alternative, prolonged non–cross-resistant chemotherapy improves PFS, with acceptable toxicity.[3-5,7-10] Of note, the Perol et al[8] study also tested continuation of gemcitabine, which was used during initial chemotherapy, and the ATLAS (A Study Comparing Bevacizumab Therapy With or Without Eriotinib for First-Line Treatment of Non-Small Cell Lung Cancer) trial tested continuation of bevacizumab, which was used in first-line therapy.[9,10] Two of these studies showed improvement in OS (for consolidation pemetrexed and consolidation erlotinib), but there is concern that not enough patients in the placebo arm received any second-line chemotherapy, considering all patients had achieved disease control before random assignment.[4,5] Specific reasons for lack of second-line treatment were not reported; presumably the symptoms of disease progression rendered some patients unfit for second-line treatment.

As more drugs for the treatment of stage IV NSCLC are discovered, patients are living longer. However, median survival time in the

control arm of clinical trials of first-line chemotherapy has increased from 8 to 13 months over the past decade, using the same first-line therapy.[16,17] This trend is clearly not related to the discovery of any one drug but rather to multiple drugs now in common use as second- and third-line therapy and potentially to patient selection for clinical trials. Because patients with stage IV NSCLC have longer OS in clinical trials, the impact of any one drug, or the timing of its use, on that survival becomes more difficult to detect as patients receive sequential therapies. This complexity will increase the importance of PFS as an end point in future clinical trials of novel drugs in patients with stage IV NSCLC.

Any improvement in PFS is tempered by increases in adverse effects. As such, the change in the recommendation regarding switch maintenance generally applies to those patients whose fitness is sufficient to tolerate increased adverse effects. Furthermore, the recommendation for pemetrexed as an option for switch maintenance does not apply to those who have received pemetrexed as part of their initial treatment, because these patients were not included in the Ciuleanu et al[4] trial. Similarly, data are not sufficient to comment on the best approach for switch maintenance therapy in patients who receive bevacizumab or cetuximab with first-line chemotherapy, because these patients were not included in any trial showing OS benefit. In addition, there are no data to inform the best treatment for a patient who is still responding after four cycles of first-line, platinum-based combination chemotherapy and tolerating treatment well. In these patients, the traditional approach has been to continue the active chemotherapy, as tolerated, and data showing that delivery of cycles five and six significantly improves PFS without increasing toxicity support this approach.[18] Conspicuously, recommendation A6 makes a careful distinction between two-drug and one-drug continuation maintenance.[1] The guideline recommends that two-drug cytotoxic combinations should be administered for no more than six cycles, but it does not recommend specifically for or against one-drug continuation maintenance thereafter for lack of compelling data. Notably, the clinical trial data used to establish guidelines for duration of first-line chemotherapy involve drugs such as mitomycin, taxanes, vinca alkaloids, and platinum drugs, all of which cause cumulative toxicity, including peripheral neuropathy, fatigue, bone marrow toxicity, and potential for developing platinum hypersensitivity. The discovery of new drugs without cumulative toxicity, along with biomarkers linked to the efficacy of those drugs, will complicate and perhaps diminish the importance of the question of optimal duration of therapy. The question of duration of therapy may become an issue of cost rather than cumulative toxicity.

The panel looks forward to further peer-reviewed publication of studies showing OS benefit with the maintenance approach. Of interest is analysis of the reasons why some patients in the placebo arms of these trials, whose treatment had resulted in control of their disease after four cycles of chemotherapy, did not receive any second-line therapy. Until the time of further OS benefit shown in studies in which there was sufficient second-line therapy offered to participants in the control arm, and given the limitations of current data, the panel accepts as viable the traditional approach of allowing patients a break from cytotoxic chemotherapy after a fixed course of first-line therapy, with initiation of second-line chemotherapy at disease progression. Important randomized trials of continuation maintenance therapy with pemetrexed and bevacizumab are ongoing. Currently, therefore, whether to offer continuation maintenance, switch maintenance, or a chemotherapy holiday to a patient who is still responding after four cycles of first-line chemotherapy is a decision with no absolute right or wrong answer and must be shared with each patient individually. The decision must take into account subjective clinical factors such as magnitude of clinical benefit, virulence of disease, toxicity, tolerance, molecular markers, and patient preferences, none of which have been settled by the randomized studies published to date.

LITERATURE SEARCH AND UPDATE DEVELOPMENT METHOD

A computerized literature search of Medline was performed for English-language literature published between January 2008 and June 2010 to address recommendation A6 in the 2009 update.[1] Searches of ASCO 2009 and 2010 Annual Meeting abstracts and International Association for the Study of Lung Cancer meeting abstracts from 2008, 2009, and 2010 were also performed. Searches were limited to phase III RCTs, meta-analyses, or systematic reviews. Search terms and inclusion and exclusion criteria were the same as those used for the 2009 guideline. Search terms included "lung neoplasms," "non–small-cell lung cancer," "antineoplastic protocols," and specific names of chemotherapeutic agents. Publications that were fully published English-language reports involving humans in peer-reviewed journals were eligible.

Abstracts were considered but given less weight because of their interim nature. Four hundred twenty-seven abstracts of published articles were retrieved from Medline and reviewed by one reviewer. Seven articles were selected for full-text review and data extraction. Titles of 545 abstracts from ASCO 2009 and 2010 Annual Meetings were reviewed. In addition, titles and abstracts from International Association of the Study of Lung Cancer 2008, 2009, and 2010 meetings were searched for the word "maintenance" and reviewed. One abstract from the ASCO 2009 Annual Meeting and two abstracts from the ASCO 2010 Annual Meeting (one provided additional data from study in 2009 abstract) met the inclusion criteria. Ultimately, eight reports of seven RCTs were included. Details of the search strategy and a quality of reporting of meta-analyses document with numbers of articles included and excluded are provided in the Data Supplement.

Consensus Development Based on Evidence

The 2009 update committee cochairs and ASCO staff drafted this 2011 focused update and circulated it to the entire update committee for approval. The ASCO Clinical Practice Guideline Committee leadership reviewed and approved the final document. The focused update was submitted to *Journal of Clinical Oncology* for peer review. The content of the 2011 focused update was also reviewed and approved by the ASCO Board of Directors Executive Committee before publication. Only recommendation A6[1] is changed by this update. The original clinical questions corresponding to all recommendations are provided in the Data Supplement.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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