Guideline Summary

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

By Christopher G. Azzoli, MD, Giuseppe Giaccone, MD, and Sarah Temin, MSPH

Memorial Sloan-Kettering Cancer Center, New York, NY; National Cancer Institute, Bethesda, MD; and American Society of Clinical Oncology, Alexandria, VA

Context

To update its recommendations on the use of chemotherapy for advanced stage non–small-cell lung cancer (NSCLC), ASCO convened an Update Committee of its Treatment of Unresectable NSCLC Guideline Expert Panel. ASCO first published a guideline on this topic in 1997¹ and updated it in 2003.² The current version covers treatment with chemotherapy and biologic agents and molecular markers for stage IV NSCLC and reviews literature published from 2002 through May 2009.³

Changes From Previous Guideline Version

This version of the guideline differs from the previous update version in 2003 in a variety of ways:

1. The scope of this guideline update covers chemotherapy, biologic therapy, and molecular markers for stage IV NSCLC because of the volume of new literature in these areas. Because there have been relatively few prospective randomized clinical trials (RCTs) on other issues covered in the 2003 guideline (eg, diagnosis, staging, and radiation therapy), they are not covered.
2. This version adds dedicated sections on the roles of age and performance status (PS) in treatment decisions in both the first- and second-line settings. In addition, there are new sections on third-line therapy and molecular markers.
3. Since the last guideline, there have been several regulatory actions regarding new agents. The US Food and Drug Administration (FDA) approved bevacizumab, erlotinib, and pemetrexed in certain indications. The guideline reviews evidence on these agents and on cetuximab (as of publication, it has not yet been approved for the NSCLC indication). Although the 2003 version of the ASCO guideline originally recommended gefitinib as a second-line treatment option, the FDA and the Canadian Agency for Drugs and Technologies in Health have restricted access to gefitinib.^{4,5} In 2009, the European Medicines Agency recommended approval for gefitinib in all lines of therapy for patients with NSCLC, which harbors an activating mutation in the tyrosine kinase domain of the gene *EGFR*.⁶

Recommendations

The recommendations in this guideline were developed primarily on the basis of statistically significant improvements in over-

all survival (OS) documented in prospective RCTs. Treatment strategies demonstrated to improve only progression-free survival (PFS) prompted greater scrutiny regarding issues such as toxicity and quality of life. The recommendations are designated as follows: First-line therapy recommendations begin with A, second-line recommendations with B, third-line recommendations with C, and molecular analysis recommendations with D.

First-Line Chemotherapy

In this summary, the term chemotherapy refers to any anticancer drug, regardless of its mechanism of action (ie, cytotoxic and biologic drugs are included).

Recommendation A1. Evidence supports the use of chemotherapy in patients with stage IV non–small-cell lung cancer with Eastern Cooperative Oncology Group (ECOG)/Zubrod PS 0, 1, and possibly 2. (Note: Stage IV as defined by the International Association for the Study of Lung Cancer Lung Cancer Staging Project, for the seventh edition of the TNM Classification of Malignant Tumors.)

Recommendation A2. In patients with PS 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 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 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 in patients with a PS of 2.

Comment. PS is the most important prognostic factor for patients with stage IV NSCLC; patients with a PS of 0 to 1 live longer than patients with a PS of 2, regardless of therapy. Use of single-agent vinorelbine, docetaxel, or paclitaxel has led to improved survival in phase III comparisons versus best supportive care in patients with a PS of 0 to 2. Because of concerns about toxicity and drug tolerance, patients with stage IV NSCLC and a PS of 2 are routinely excluded from prospective trials of novel

combination chemotherapy. Because of heterogeneity among patients classified as having a PS of 2, subjectivity within the scoring system, and lack of consistent data in favor of an optimal chemotherapy regimen, the Update Committee was unable to recommend a combination of two cytotoxic drugs for patients with a PS of 2 and recognizes that some patients classified as having a PS of 2 may be not be able to tolerate even single-agent chemotherapy.

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

Comment. 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. The guideline emphasizes that physiologic age and PS are more important in treatment selection.

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.

Comment. Cisplatin is slightly more effective than carboplatin but also has more adverse effects. Therefore, either is acceptable, depending on the individual.

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

Comment. With the advent of drugs that improve survival for patients with progressive cancer after first-line chemotherapy (ie, second-line drugs), there is renewed interest in whether initiation of a non-cross-resistant drug immediately after completion of first-line therapy may improve survival. There have been some preliminary results on such a strategy, but until more mature data are presented showing a survival benefit, these results suggest that PFS, but not OS, may be improved either by continuing an effective chemotherapy beyond four cycles or by immediately initiating alternative chemotherapy. The improvement in PFS is tempered by an increase in adverse effects from additional cytotoxic chemotherapy. Special announcement: The FDA approved a new indication for pemetrexed for maintenance therapy in patients with advanced NSCLC on July 2, 2009, when this guideline went to press. The data supporting this change were recently presented and were outside the scope of the comprehensive data review for this guideline. The rec-

ommendation on maintenance therapy in this guideline will be updated pending consideration of recently published relevant data.

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).

Comment. There is no current evidence that adding an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor to cytotoxic chemotherapy as first-line treatment is beneficial. In addition, there is no current evidence that erlotinib monotherapy is beneficial in the first-line setting in unselected patients. There is evidence that first-line gefitinib monotherapy improves PFS and has less adverse events compared with carboplatin and paclitaxel in patients of Asian ethnicity who are former or light smokers or have never smoked. In a recent trial, patients with tumors with *EGFR* mutations receiving gefitinib experienced longer PFS, and those whose tumors lacked *EGFR* mutations had longer PFS with chemotherapy. The *EGFR* mutation status of most patients' tumors, however, is negative or unknown. Current evidence is insufficient to recommend the routine use of molecular markers to select systemic treatment for patients with metastatic NSCLC (Recommendation D1). In cases in which the *EGFR* mutation status is negative or unknown, cytotoxic chemotherapy is preferred.

Recommendation A8. Based on 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 greater than 1, therapeutic anticoagulation, clinically significant cardiovascular disease, or medically uncontrolled hypertension.⁷ Bevacizumab may be continued, as tolerated, until disease progression.

Comment. Because of bleeding events and deaths observed in earlier clinical trials using bevacizumab for NSCLC, use of this drug was restricted in phase III testing, which informed the list of exclusion criteria in the recommendation. A recent trial suggested that there may be differences in outcomes depending on which chemotherapy regimen is combined with bevacizumab and also suggested that a lower dose of bevacizumab may be as effective as a high dose; however, OS benefit has not yet been shown from combining bevacizumab with other cytotoxic chemotherapy regimens. The duration recommendation is based on the design of RCTs of bevacizumab. The optimal duration of bevacizumab beyond chemotherapy has not yet been determined.

Recommendation A9. On the basis of the results of one large phase III RCT, clinicians may consider the addition of cetuximab to cisplatin/vinorelbine in first-line therapy in patients with an *EGFR*-positive tumor as measured by immuno-

histochemistry. Cetuximab may be continued, as tolerated, until disease progression.

Comment. Eligibility for this phase III RCT required that all patients have their tumor tested for EGFR expression by immunohistochemistry and that at least one tumor cell stained positive. This trial showed a benefit in OS and response rate with the addition of cetuximab to this chemotherapy doublet. The OS benefit may not directly translate to all chemotherapy regimens. The duration recommendation is based on the design of RCTs on cetuximab. However, the optimal duration of treatment with cetuximab beyond chemotherapy is not known.

Second-Line Chemotherapy

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.

Comment. In addition to considering optimal regimen, the guideline evaluated data on schedules of administration for second-line therapy, which were available only for docetaxel. These data do not show any differences in efficacy of docetaxel based on schedule. A weekly schedule appears less toxic than a schedule of every 3 weeks, especially for hematologic toxicities.

The data on combination biologic therapy as second-line therapy are limited to the combination of bevacizumab and erlotinib. At publication time, there were no published RCTs with positive results for OS using this combination. There are no data available on the optimal duration of second-line therapy. Phase III clinical trials of docetaxel, erlotinib, gefitinib, and pemetrexed allowed patients to continue chemotherapy, as tolerated, until disease progression.

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

Comment. There is a paucity of research on people considered elderly who are receiving second-line therapy. The available evidence shows that benefits and toxicity do not differ by age.

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

Comment. This recommendation is based on the registration trial for erlotinib (Recommendation B1). This trial included participants who had received one or two prior regimens, and an analysis of survival showed no significant difference between prior numbers of regimens.

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.

Comment. Only a retrospective analysis was available on this issue. It found 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.

Molecular Analysis

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

Comment. Recommendation A7 supports the first-line use of gefitinib for patients whose NSCLC harbors *EGFR* mutation on the basis of a clinically significant improvement in PFS, favorable toxicity profile, and improved quality of life. These data justify attempts to test NSCLC for the presence of *EGFR* mutation. The guideline reviewed publications on molecular tests that might have clinical relevance, including EGFR, *KRAS*, excision repair cross-complementing group 1, ribonucleotide reductase subunit 1, vascular endothelial growth factor, and serum tumor markers. Emerging data suggest that some of these markers may become clinically informative in the near future. However, no study to date has demonstrated an improvement in OS when chemotherapy is selected on the basis of a molecular marker, and therefore, current evidence is insufficient to recommend the routine use of molecular markers to select systemic treatment in patients with NSCLC.

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

Comment. Given the probability that some markers and use of histology may be recommended in future updates of the guideline, a core biopsy or surgical biopsy is reasonable to obtain a sufficient quantity of tissue for more accurate histologic classification or for investigational purposes.

Patient-Physician Communication

The guideline reviewed research on communication between clinicians and patients with NSCLC that demonstrated missed opportunities for expressing empathy, observed clinicians using “blaming” words, observed a lack of discussion on prognosis (however, 20% of patients may not want discussion of prognostic information), and found a lack of information exchange and trust between patients and clinicians of different racial/ethnic backgrounds. In addition, the guideline cites research that patients with lung cancer may overestimate the survival benefits of potentially toxic treatment. The guideline notes that intensive training for clinicians can help, as can the presence of a caregiver at appointments, and suggests language clinicians may use in consultations (see Suggested Clinician-Patient Language).

Health Disparities

An environmental scan of literature on lung cancer and health disparities was conducted. 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, socioeconomic status (including education level), access to health services, and comorbid illnesses.

Suggested Clinician-Patient Language

Examples of suggested language for clinician-patient communication regarding stage IV non-small-cell lung cancer treatment:

- “Tell me what you know about your lung cancer.”
- “How much do you want to know?”
- “It sounds like you were really frightened when you got the news about the cancer.”
- Qualitative statements: “Chances are you will live longer if you use this chemotherapy versus another agent or no chemotherapy.”
- Quantitative statements: “Chemotherapy will improve your chance of being alive in 1 year from 10% to 20% up to 30% to 50%.”
- “Without any chemotherapy, the average person will live about 4.5 months. With chemotherapy, most people will live longer, and some will live a shorter time. More recent chemotherapy trials have shown that people live about 3 months longer than if they did not get chemotherapy. Even with chemotherapy, the chance of being alive at 1 year is approximately 30% to 50%; the chance of dying within this year is 50% to 70%.”
- A patient asks, “Can you cure me?” The answer could be: “No, I cannot, but we have good chances of prolonging your life and keeping you comfortable, and we will always be here to help you and your family.”

Health disparities can be the result of ineffectual communication between health care providers and patients. When patients receive uniform clinical care, differences in outcomes between racial groups are minimized. Awareness of these disparities in access to care should be considered in the context of the stage IV NSCLC clinical practice guideline update.

Future Research Directions

The guideline states that research is needed with participants who are elderly (age ≥ 65 or ≥ 70 years) and who have an ECOG PS of 2 or greater (researchers should distinguish between those with a PS of ≥ 2 as a result of NSCLC and those impaired by comorbidities). Research is needed that enriches trial participant populations with people with tumors with recently discovered prognostic markers and clinical characteristics (eg, histology, molecular characteristics, number of prior therapies and when they were administered, known smoking status) and that stratifies participants by these prognostic factors.

Treatments that improve only PFS prompted greater scrutiny for toxicity, adverse effects, and quality of life. There is a need to establish more data on biologic factors of NSCLC in parallel with drug discovery. Finally, more research on strategies to improve patient-clinician communication in stage IV

NSCLC is needed, and the guideline stresses the importance of encouraging patients to participate in clinical research trials.

Methodology

The ASCO Update Committee reviewed searches of MEDLINE, EMBASE, and the Cochrane Collaboration Library and conducted a systematic review of the literature published from January 2002 through July 2008. Panel members and reviewers subsequently suggested literature meeting the inclusion criteria of the systematic review but published after the data parameters of the systematic review, and literature published by May 2009 was then included. The Update Committee will continue to periodically monitor the published literature and update the guideline as necessary.

Additional Resources

Journal of Clinical Oncology published an abridged version of this guideline on November 23, 2009. The full-text guideline, along with the abridged version, is available at <http://www.asco.org/guidelines/nsclc>, along with a slide set and other clinical tools and resources. Patient information is available there as well as at <http://www.cancer.net>.

Authors

“The American Society of Clinical Oncology Clinical Practice Guideline Update on Chemotherapy for Stage IV Non-Small-Cell Lung Cancer” was developed and written by Christopher G. Azzoli, MD, Sherman Baker Jr, MD, Sarah Temin, MSPH, William Pao, MD, PhD, Timothy Aliff, MD, Julie Brahmer, MD, David H. Johnson, MD, Janessa L. Laskin, MD, Gregory Masters, MD, Daniel Milton, MD, Luke Nordquist, MD, David G. Pfister, MD, Steven Piantadosi, MD, PhD, Joan H. Schiller, MD, Reily Smith, Thomas J. Smith, MD, John R. Strawn, MD, David Trent, MD, PhD, and Giuseppe Giaccone, MD.

Accepted for publication on November 6, 2009.

Authors' Disclosures of Potential Conflicts of Interest

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a “U” are those for which no compensation was received; those relationships marked with a “C” were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: None **Consultant or Advisory Role:** None **Stock Ownership:** None **Honoraria:** None **Research Funding:** Christopher G. Azzoli, Allos Therapeutics, Genentech, BioOncology, sanofi-aventis **Expert Testimony:** None **Other Remuneration:** None

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

DOI: 10.1200/JOP.091065

References

1. American Society of Clinical Oncology: Clinical practice guidelines for the treatment of unresectable non-small-cell lung cancer: Adopted on May 16, 1997, by the American Society of Clinical Oncology. J Clin Oncol 15:2996-3018, 1997
2. Pfister DG, Johnson DH, Azzoli CG, et al: American Society of Clinical Oncology treatment of unresectable non-small-cell lung cancer guideline: Update 2003. J Clin Oncol 22:330-353, 2004
3. Azzoli CG, Baker S Jr, Temin S, et al: American Society of Clinical Oncology Clinical Practice Guideline Update on Chemotherapy for Stage IV Non-Small-Cell Lung Cancer. J Clin Oncol doi:10.1200/JCO.2009.23.5622
4. US Food and Drug Administration: FDA alert for health care professionals: Gefitinib (marked as Iressa). <http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm126182.pdf>
5. Canadian Agency for Drugs and Technologies in Health: Gefitinib. <http://www.cadth.ca/index.php/en/cdr/search/?&status=all&keywords=gefitinib>
6. European Medicines Agency: Iressa: Gefitinib—EPAR summary for the public. <http://www.emea.europa.eu/humandocs/PDFs/EPAR/iressa/H-1016-en1.pdf>
7. Sandler A, Gray R, Perry MC, et al: Paclitaxel-carboplatin alone or with bevacizumab for non-small cell lung cancer. N Engl J Med 355:2542-2550, 2006

The Editors and Staff wish to sincerely thank the following authors (L-Z) who wrote articles for *Journal of Oncology Practice* in 2009.

Beth LaVasseur
 Susanne Lazanov
 Lynne Lederman
 Kevin J. Leonard
 Thomas Leyden
 Jim Z. Li
 Len Lichtenfeld
 Howard J. Lim
 Jay Lin
 Deborah P. Lubeck
 Jorge M. Luna
 Gary H. Lyman
 Jean M. Lynn
 Catherine A. Lyons
 Gail Macartney
 Kelsey Mace
 Rosalind Malhotra
 Mary Malloy
 Jennifer E. Marcello
 Alfred C. Marcus
 Thomas Marsland
 C. Jane Martin
 Barbara McAneny
 Mary S. McCabe

Julie McKellar
 Barbara Melosky
 Neal Meropol
 M. Dror Michaelson
 Karen Miller
 Jon D. Miller
 Lesley-Ann Miller
 Robert Miller
 Deborah Milliken
 Michael A. Morse
 Roscoe F. Morton
 Robert J. Motzer
 Therese M. Mulvey
 Matthew P. Mumber
 Arash Naeim
 Marcus Neubauer
 Michael N. Neuss
 Lee Newcomer
 Lisa Newman
 Vikki Newton
 Ian N. Olver
 Susan O'Reilly
 David J. Pasta
 Meenal Patwardhan

Timothy M. Pawlik
 W. Charles Penley
 Shannon M. Phillips
 Susan Poirier
 Patricia Reid Ponte
 David G. Poplack
 Janine Prime
 Harry Raftopoulos
 Edward Reed
 Maria Alma Rodriguez
 Krista L. Rowe
 Thomas Ruane
 Ayman Saad
 Sheila Santacroce
 Bela Sastry
 Eric C. Schneider
 Lowell E. Schnipper
 Stacey Schulman
 Lisa Schwartz
 Lawrence N. Shulman
 Charles L. Shapiro
 Robert D. Siegel
 Joseph V. Simone
 Caroline Speers

Stephen Stemkowski
 Christopher Stokoe
 Courtney D. Storm
 Karen Syrjala
 Sarah Temin
 Savannah Thompson-Hoffman
 Paul W. Thurman
 Elaine L. Towle
 Julia Tomkins
 Maureen Trudeau
 Hema Viswanathan
 Padraig Warde
 Jane L. Wheeler
 Kimberly B. Whitlock
 Marian Wiseman
 Margaret Wolfe
 Chantal Worzala
 Daniel Yagoda
 Guiping Yang
 S. Yousuf Zafar

American Society of Clinical Oncology