Guideline Summaries

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

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## Introduction

The full American Society of Clinical Oncology (ASCO) Clinical Practice Guideline Update on Chemotherapy for Stage IV Non–Small-Cell Lung Cancer (NSCLC) was most recently published in November 2009 in *Journal of Clinical Oncology* (*JCO*).[1] The 2009 publication stated that new evidence may be published that would potentially warrant reconsideration of a recommendation in the guideline before the regularly scheduled update. Because of the rapid pace of research in lung cancer, there have been several phase III randomized clinical trials (RCTs) published on maintenance chemotherapy since the literature search cutoff date for that update. Concurrently, ASCO developed a new mechanism for providing evidence-based guidance: the focused update. Therefore, ASCO produced the 2011 Focused Update[2] based on these RCTs, addressing a single clinical question from the 2009 Guideline Update: What is the optimal duration of first-line chemotherapy for stage IV NSCLC?

## Maintenance Chemotherapy in NSCLC

In addressing this clinical question, this 2011 Focused Update addresses only switch maintenance therapy. 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 a 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.

## Scope of Update and Literature Review

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 the chemotherapy included in the control arm. This update focuses on switch maintenance because the RCTs addressed this issue.

### Changes From Prior Recommendation

*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 the 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 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.**

Changes from the previous recommendation are indicated in bold text.

The *JCO* publication of the focused update[2] summarizes an updated literature search. It reviews and analyzes new data from seven phase III RCTs regarding this recommendation (Recommendation A6) since the systematic review for the previous update. Trials using docetaxel, pemetrexed

(for those with nonsquamous cell carcinoma), erlotinib, gefitinib, and gemcitabine have shown increased progression-free survival with maintenance therapy, with acceptable toxicity. In the study of pemetrexed and in one of two studies of erlotinib, overall survival was statistically significantly increased with switch maintenance therapy. The focused update notes that any improvement in progression-free survival is tempered by increases in adverse effects. Therefore, 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 received pemetrexed as part of their initial treatment.

According to ASCO guidelines regarding duration of first-line chemotherapy, patients with a radiologic response after four cycles of cytotoxic drug therapy may be considered for additional cycles of first-line chemotherapy (ie, cycles five and six). 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. In contrast, when patients are switched to erlotinib for maintenance therapy, this trend toward greater benefit in responders is less apparent or nonexistent.

For clinicians, 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; it 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.

## Recommendations

Table 1 provides a summary of the 2009 and 2011 recommendations. The *JCO* publication, data supplements, and an updated slide set, patient guide, and other resources are available at http://www.asco.org/guidelines/NSCLC.

## Authors

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## THE BOTTOM LINE

### ASCO GUIDELINE FOCUSED UPDATE

### 2011 FOCUSED UPDATE OF 2009 AMERICAN SOCIETY OF CLINICAL ONCOLOGY 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 a specified number of cycles [usually four to six] and have either experienced a 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.
- Note: this represents an update of a single recommendation from the 2009 ASCO Guideline Update

***Methods***

- Systematic review and analysis of medical literature by an Expert Panel Update Committee

***Additional Information***

**The 2009 Guideline Update, a data supplement of evidence tables, and clinical tools can be found at http://www.asco.org/guidelines/NSCLC.**

**Table 1.** Summary of Recommendations

| Recommendation No. | Recommendation |
|---|---|
| First-line chemotherapy | |
| A1 | Evidence supports the use of chemotherapy in patients with stage IV NSCLC with ECOG/Zubrod performance status of 0, 1, and possibly 2. |
| 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 a 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 the use of single-agent chemotherapy in patients with 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. |
| A4 | The evidence does not support the selection of a specific first-line chemotherapy drug or combination based on age alone. |
| 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. |
| 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 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.** |
| 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, then cytotoxic chemotherapy is preferred (see Recommendation A2). |
| 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. |
| 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 EGFR-positive tumor as measured by immunohistochemistry. Cetuximab may be continued, as tolerated, until disease progression. |
| 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 | The evidence does not support the selection of a specific second-line chemotherapy drug or combination based on age alone. |
| Third-line chemotherapy | |
| C1 | When disease progresses during 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 | 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. |
| Molecular analysis | |
| D1 | Evidence is insufficient to recommend routine use of molecular markers* to select systemic treatment in patients with metastatic NSCLC. |
| D2 | In order to obtain tissue for more accurate histologic classification or for investigational purposes, Update Committee supports reasonable efforts to obtain more tissue than what is contained in a routine cytology specimen. |

NOTE. Bold font indicates changes in 2011 Focused Update.[1]
Abbreviations: ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; NSCLC, non–small-cell lung cancer; TKI, tyrosine kinase inhibitor.
* In April 2011, the American Society of Clinical Oncology issued 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 randomized controlled trials, patients with NSCLC who are being considered for first-line therapy with EGFR TKI (patients who have not previously received chemotherapy or EGFR TKI) should have their tumor tested for *EGFR* mutations to determine whether EGFR TKI or chemotherapy is the appropriate first-line therapy (http://www.asco.org/pco/egfr).

Only Recommendation A6 is changed by this update. To view the original clinical questions corresponding to all recommendations, please refer to Data Supplement 3.

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***Authors' Disclosures of Potential Conflicts of Interest***

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## References

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**2.** Azzoli CG, Temin S, Aliff T, et al: 2011 focused update of American Society of Clinical Oncology Clinical Practice Guideline Update on chemotherapy for stage IV non–small-cell lung cancer. J Clin Oncol 29:3825-3831, 2011