Guideline 7-10 Version 3

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Systemic Treatment for Patients with Advanced Non-Small Cell Lung Cancer

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Report Date: November 14, 2016

This is a rapidly developing field and we are aware that new trials have been published since the search date of the literature review. The results of these trials will be incorporated as soon as feasible.

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PUBLICATIONS RELATED TO THIS REPORT
Since the posting of this guideline on Cancer Care Ontario’s website, an updated systematic review has been published in Clinical Lung Cancer:

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Systemic Treatment for Patients with Advanced Non-Small Cell Lung Cancer

Section 1: Recommendations

This section is a quick reference guide and provides the guideline recommendations only. For key evidence associated with each recommendation, see Section 2.

GUIDELINE OBJECTIVE
The guideline objective is to determine the most effective systemic treatment options in terms of overall survival, quality of life, and response in the management of advanced non-small cell lung cancer (NSCLC).

TARGET POPULATION
This guideline targets adult and elderly patients with advanced NSCLC who are candidates for systemic therapy. Advanced disease is defined as stage IV and stage IIIB not amenable to curative treatment approaches.

INTENDED USERS
The intended users of this guideline are oncologists involved in the systemic treatment of patients with NSCLC.

BACKGROUND INFORMATION
This guideline is based on content from the American Society of Clinical Oncology (ASCO) and is reprinted with permission [1] with any modifications indicated in italics. Explanations for any modifications to ASCO’s recommendations can be found in Section 2.

PEBC KEY RECOMMENDATIONS (extracted from ASCO recommendations [with Program in Evidence-Based Care (PEBC) modifications in italics]; see PEBC RECOMMENDATIONS with CLINICAL QUESTIONS following these KEY RECOMMENDATIONS)

Key Points
See PEBC Recommendations with Clinical Questions and Key Evidence in Section 2 for full details.

- There is no cure for patients with stage IIIB/IV NSCLC.
- Decisions on chemotherapy should not be made on the basis of age alone.

First-Line Treatment for Patients:
- Without an epidermal growth factor receptor (EGFR)-sensitizing mutation or ALK gene rearrangement, and Eastern Cooperative Oncology Group performance status (PS) 0 to 1 (or appropriate PS 2), a variety of combination cytotoxic chemotherapies are recommended. Platinum-based doublets are preferred, along with early concurrent palliative care and symptom management. Based on tumour histology (ie, squamous vs. non-squamous), there are some variations.
- Adding bevacizumab to carboplatin plus paclitaxel is recommended if there are no contraindications. An alternative treatment strategy for patients who are eligible for

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carboplatin, paclitaxel, and bevacizumab would include cisplatin or carboplatin plus pemetrexed and maintenance pemetrexed.

- With PS 2: combination or single-agent chemotherapy or palliative care alone may be used.
- With sensitizing EGFR mutations: afatinib, erlotinib, or gefitinib is recommended.
- With ALK gene rearrangements: crizotinib is recommended.
- With ROS1 rearrangement: crizotinib is recommended.
- With large-cell neuroendocrine carcinoma: platinum plus etoposide or the same treatment as other patients with non-squamous carcinoma may be administered.
- First-line cytotoxic chemotherapy should be stopped at disease progression or after four cycles in patients with nonresponsive stable disease.
- With stable disease or response after four to six cycles of a platinum-based chemotherapy: pemetrexed (in patients with non-squamous cell carcinoma [NSCC]) or EGFR tyrosine kinase inhibitors (TKIs) are options for maintenance therapy.

November 29, 2016 - We are aware of the results of these new trials (refs) that were published after our systematic review search date. The results from these trials will be incorporated as soon as feasible.

Second-Line Treatment for Patients:
- With NSCC: nivolumab (in all patients with NSCLC) or pembrolizumab (in patients with programmed cell death ligand 1 [PD-L1]-positive tumours) is preferred over docetaxel, erlotinib, gefitinib, or pemetrexed.
- With squamous cell carcinoma (SCC): nivolumab (in all patients with NSCLC) or pembrolizumab (in patients with PD-L1-positive tumours) is preferred over docetaxel, erlotinib, or gefitinib.
- With sensitizing EGFR mutations who did not respond to a first-line EGFR TKI: combination cytotoxic chemotherapy as listed in under first-line treatment or a third-generation EGFR TKI such as osimertinib in patients shown to have a T790M mutation is recommended for those with NSCC.
- With sensitizing EGFR mutations who received a first-line EGFR TKI and experienced disease progression after an initial response: may be switched to chemotherapy or a third-generation EGFR TKI such as osimertinib in patients shown to have a T790M mutation as second-line therapy.
- With ALK rearrangement and progression after first-line crizotinib: chemotherapy or ceritinib may be offered.

Third-Line Treatment for Patients:
- Who have not received erlotinib or gefitinib and have PS 0 to 3: erlotinib may be recommended.
- With NSCC and progression on nivolumab or pembrolizumab: docetaxel, erlotinib, gefitinib, or pemetrexed may be recommended.
- With SCC and progression on nivolumab or pembrolizumab: docetaxel, erlotinib, or gefitinib may be recommended.
**PEBC RECOMMENDATIONS with CLINICAL QUESTIONS** (extracted from ASCO recommendations [with PEBC modifications in italics])

**Clinical Question A1**
Which patients with stage IIIB/IV NSCLC should be treated with chemotherapy?

<table>
<thead>
<tr>
<th>Recommendation A1.a</th>
</tr>
</thead>
<tbody>
<tr>
<td>For patients with PS of 0 or 1, a combination of two cytotoxic drugs is recommended. Platinum combinations are recommended over nonplatinum therapy; however, nonplatinum therapy combinations are recommended for patients who have contraindications to platinum therapy. Chemotherapy may also be used to treat selected patients with PS 2 who desire aggressive treatment after a thorough discussion of the risks and benefits of such treatment.</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Recommendation A1.b</th>
</tr>
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<tbody>
<tr>
<td>Because there is no cure for patients with stage IIIB/IV NSCLC, early concomitant palliative care assistance has improved the survival and well-being of patients and is therefore recommended.</td>
</tr>
</tbody>
</table>

**Clinical Question A2**
What is the most effective first-line therapy for patients with stage IIIB/IV NSCLC with NSCC, negative or unknown EGFR-sensitizing mutation and ALK gene rearrangement status, and PS 0 to 1 or possibly PS 2?

<table>
<thead>
<tr>
<th>Recommendation A2</th>
</tr>
</thead>
<tbody>
<tr>
<td>For patients who have the characteristics described in Clinical Question A2 and who have non-squamous histology, the following options are acceptable:</td>
</tr>
<tr>
<td>● Cisplatin-based combinations</td>
</tr>
<tr>
<td>● Cisplatin plus docetaxel</td>
</tr>
<tr>
<td>● Cisplatin plus paclitaxel</td>
</tr>
<tr>
<td>● Cisplatin plus pemetrexed</td>
</tr>
<tr>
<td>● Cisplatin plus vinorelbine</td>
</tr>
<tr>
<td>● Cisplatin plus gemcitabine</td>
</tr>
<tr>
<td>● Carboplatin-based combinations</td>
</tr>
<tr>
<td>● Carboplatin plus albumin-bound (nab)-paclitaxel</td>
</tr>
<tr>
<td>● Carboplatin plus paclitaxel</td>
</tr>
<tr>
<td>● Carboplatin plus pemetrexed</td>
</tr>
<tr>
<td>● Carboplatin plus docetaxel</td>
</tr>
<tr>
<td>● Carboplatin plus gemcitabine</td>
</tr>
<tr>
<td>● Nonplatinum doublets</td>
</tr>
</tbody>
</table>

**Clinical Question A2.a**
What is the most effective first-line therapy for patients with stage IIIB/IV NSCLC with negative or unknown EGFR/ALK status, NSCC, and no contraindications to bevacizumab?

| Recommendation A2.a.1 |
For patients receiving carboplatin plus paclitaxel, the addition of bevacizumab 15 mg/kg once every three weeks is recommended, except for patients with SCC histologic type, clinically significant hemoptysis, a known bleeding disorder, inadequate organ function, Eastern Cooperative Oncology Group PS > 1, clinically significant cardiovascular disease, or medically uncontrolled hypertension. Caution should be exercised in patients with brain metastases. Bevacizumab may be continued, as tolerated, until disease progression. An alternative treatment strategy for patients who are eligible for carboplatin, paclitaxel, and bevacizumab would include cisplatin or carboplatin plus pemetrexed and maintenance pemetrexed.

**Recommendation A2.a.2**

There is insufficient evidence (for or against) to recommend pemetrexed in combination with bevacizumab plus carboplatin for patients who do not have contraindications to bevacizumab.

**Clinical Question A2.b**

What is the most effective first-line therapy for patients with stage IIIIB/IV NSCLC with PS 2, NSCC, and negative or unknown EGFR-sensitizing mutation and ALK gene rearrangement status?

**Recommendation A2.b**

In the context of shared decision making, combination therapy, single-agent chemotherapy, or palliative therapy alone may be used for patients in this population with PS 2.

**Clinical Question A3**

What is the most effective first-line therapy for patients with stage IIIIB/IV NSCLC with SCC, negative or unknown EGFR-sensitizing mutation and ALK gene rearrangement status, and PS 0 to 1 or possibly PS 2?

**Recommendation A3**

Patients with the characteristics listed in Clinical Question A3 and with SCC histology should be offered the following options:

- Cisplatin-based combinations
  - Cisplatin plus docetaxel
  - Cisplatin plus gemcitabine
  - Cisplatin plus paclitaxel
  - Cisplatin plus vinorelbine
- Carboplatin-based combinations
  - Carboplatin plus gemcitabine
  - Carboplatin plus paclitaxel
  - Carboplatin plus nab-paclitaxel
  - Carboplatin plus docetaxel
- Nonplatinum doublets

**Clinical Question A3.a**

What is the most effective first-line therapy for patients with stage IIIIB/IV NSCLC with negative or unknown EGFR/ALK status, SCC, and PS 2?

**Recommendation A3.a**
In the context of shared decision making, combination chemotherapy, single-agent chemotherapy, or palliative therapy alone may be used for patients with the characteristics described in Clinical Question A3.a.

**Clinical Question A4**
What is the most effective first-line therapy for patients with stage IIIB/IV NSCLC with an *EGFR*-sensitizing mutation and PS 0 to 1 or possibly PS 2?

**Recommendation A4**
If patients have stage IIIB/IV NSCLC and a sensitizing *EGFR* mutation, first-line afatinib, erlotinib, or gefitinib is recommended.

**Clinical Question A5**
What is the most effective first-line therapy for patients with stage IIIB/IV NSCLC with *ALK* gene rearrangement and PS 0 to 1 or possibly PS 2?

**Recommendation A5**
If patients have stage IIIB/IV NSCLC and *ALK* rearrangements, first-line crizotinib is recommended.

**Clinical Question A6**
What is the most effective first-line therapy for patients with stage IIIB/IV NSCLC with *ROS1* rearrangement, no *ALK* gene rearrangement, negative or unknown *EGFR*-sensitizing mutation status, and PS 0 to 1 or possibly PS 2?

**Recommendation A6**
If patients have stage IIIB/IV NSCLC with *ROS1* rearrangement, single-agent crizotinib is recommended, because it has shown some results indicating improved response rate and duration of response.

**Clinical Question A7**
What is the most effective first-line therapy for patients with stage IIIB/IV NSCLC with negative or unknown *EGFR/ALK* status and large-cell neuroendocrine carcinoma?

**Recommendation A7**
Patients with large-cell neuroendocrine carcinoma may receive the same treatment as other patients with NSCC or treatment with etoposide in platinum combinations.

**Clinical Question A8**
What is the best chemotherapy for treatment of elderly patients with stage IIIB/IV NSCLC?

**Recommendation A8**
Decisions on the selection of chemotherapy should not be made or altered based on age alone.

**Clinical Question A9**
What is the optimal treatment for patients with stable disease or response after four cycles of cytotoxic chemotherapy?
Recommendation A9

This clinical question was covered by the recent PEBC 7-22 guideline [2]. The recommendations from this guideline are as follows:

Maintenance therapy is recommended as an option for therapy as described below:

- Maintenance therapy with pemetrexed should be considered an option for patients with non-squamous NSCLC. Maintenance therapy with pemetrexed is not recommended for patients with squamous NSCLC.
- Maintenance therapy with EGFR TKIs may be considered an option. No recommendation can be made with respect to the choice of gefitinib or erlotinib. Any decision should be made in conjunction with discussion with the patient.
- There is insufficient evidence to recommend docetaxel or gemcitabine as maintenance chemotherapies.
- In patients who elect to have a break following first-line therapy, second-line therapy should be considered at the time of progression.

Qualifying statements

- These recommendations apply both to patients who previously received pemetrexed or non-pemetrexed-containing platinum-doublet chemotherapy.
- Trials have evaluated both erlotinib and gefitinib, but no trials directly compared these two agents as maintenance therapy. However, the strongest data would support the use of erlotinib in this setting, although the overall survival advantage was modest for both agents.
- The recommendation for EGFR TKIs applies to both EGFR mutation-positive and wild-type patients.
- Since the cut-off date of the review of the literature, a notification has been released by Health Canada based on the results of the IUNO trial [3,4]. While the results are not available in the public domain, Health Canada has recommended that EGFR TKI maintenance therapy should not be used in patients with EGFR wild-type advanced NSCLC [3].
- In patients receiving maintenance bevacizumab, it is unclear whether the addition of maintenance pemetrexed improves overall survival.

Clinical Question B1
What is the most effective second-line therapy for patients with stage IIIB/IV NSCLC with negative or unknown EGFR/ALK status and NSCC?

Recommendation B1
For patients with advanced NSCLC, NSCC, negative or unknown EGFR/ALK status, and adequate PS, when disease has progressed during or after first-line platinum-based therapy, **nivolumab (in all patients with NSCLC) or pembrolizumab (in patients with PD-L1-positive tumours) is preferred**, if either is available, over docetaxel, erlotinib, gefitinib, or pemetrexed as second-line therapy.

Clinical Question B2
What is the most effective second-line therapy for patients with stage IIIB/IV NSCLC with negative or unknown EGFR/ALK status and SCC?

Recommendation B2
For patients with advanced NSCLC, SCC, negative or unknown EGFR/ALK status, and adequate PS, when disease has progressed during or after first-line platinum-based therapy, nivolumab (in all patients with NSCLC) or pembrolizumab (in patients with PD-L1-positive tumours) is preferred, if either is available, over docetaxel, erlotinib, or gefitinib as second-line therapy.

Clinical Question B3.a
What is the most effective second-line therapy for patients with stage IIIB/IV NSCLC with a sensitizing EGFR mutation who received a first-line EGFR TKI and experienced disease progression?

Recommendation B3.a
For patients with a sensitizing EGFR mutation who did not respond to a first-line EGFR TKI, combination cytotoxic chemotherapy (Recommendation A2) or a third-generation EGFR TKI such as osimertinib in patients shown to have a T790M mutation is recommended, following the first-line recommendations for patients with NSCC.

Clinical Question B3.b
What is the most effective second-line therapy for patients with stage IIIB/IV NSCLC with a sensitizing EGFR mutation who received a first-line EGFR TKI and experienced disease progression after an initial response?

Recommendation B3.b
Patients who received an EGFR TKI in the first-line setting, had an initial response, and subsequently experienced disease progression may be switched to chemotherapy or a third-generation EGFR TKI such as osimertinib in patients shown to have a T790M mutation as second-line therapy. There is insufficient evidence to recommend the use of other EGFR TKIs, such as afatinib, in previously treated patients, as available data do not demonstrate any improvement in overall survival.

Clinical Question B4
What is the most effective second-line therapy for patients with stage IIIB/IV NSCLC with ALK rearrangement with progression after first-line crizotinib?

Recommendation B4
Patients whose tumours have ALK rearrangements and who received crizotinib in the first-line setting may be offered the option of chemotherapy (after first-line recommendations for patients with NSCC [see Recommendation A2]) or ceritinib in the second-line setting.

Clinical Question B5
What is the optimal second-line treatment for elderly patients with stage IIIB/IV NSCLC?

Recommendation B5
The evidence does not support the selection of a specific second-line chemotherapy drug or combination based on age alone. As stated in Recommendation A8, age alone is not a contraindication to chemotherapy for NSCLC.

Clinical Question C
Is there a role for third-line therapy or beyond in the treatment of stage IIIB/IV NSCLC?
<table>
<thead>
<tr>
<th>Recommendation C1</th>
</tr>
</thead>
<tbody>
<tr>
<td>When disease progresses during or after second-line chemotherapy, treatment with erlotinib may be recommended as third-line therapy for patients with a PS of 0 to 3 who have not received prior erlotinib or gefitinib.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommendation C2a</th>
</tr>
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<tbody>
<tr>
<td>Docetaxel, erlotinib, gefitinib, or pemetrexed may be used in patients with stage IIIB/IV NSCLC with negative or unknown EGFR/ALK status and NSCC after progression on nivolumab or pembrolizumab, although data are limited.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommendation C2b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel, erlotinib, or gefitinib may be used in patients with stage IIIB/IV NSCLC with negative or unknown EGFR/ALK status and SCC after progression on nivolumab or pembrolizumab, although data are limited.</td>
</tr>
</tbody>
</table>