WRHA/CCMB Oncology Pharmacotherapeutic (P & T) Subcommittee
Systemic Therapy Summary
Review/Update

STS Title: Second-Line Treatment of Metastatic Non-Small Cell Lung Cancer with Pemetrexed
Protocol Code: LUNG - Pemetrexed
Effective: June 2010
Annual Review: February 2014

The above-named CancerCare Manitoba Practice Guideline was under review for the following reason(s) – Please check all applicable:

☐ New evidence exists which affects the recommendation statement(s) and/or clinical content of the guideline
☐ New information exists which necessitates change in other content
☐ The guideline is no longer applicable and is to be retired from use
☑ The guideline is due for review as per P&T Subcommittee protocol
☐ Other

The DSG Chair and/or designated DSG member(s) have reviewed the content of the STS. Any modifications to the document subsequent to DSG review have been discussed by the P&T Subcommittee STS Working Group.

Review of this CCMB Systemic Therapy Summary is now complete. The updated version is approved for re-distribution and clinical application according to policies and procedures as CCMB, WRHA Community Oncology sites, and Community Cancer Programs Network sites. The next scheduled date of review is:

Approved by:

[Signature]
DSG Chair/Designate
Dr. C. A. Harding

[Signature]
Dr. Ralph PW Wong, BSc, MD, FRCPC
Chair, WRHA/CCMB
Pharmacotherapeutic Subcommittee

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Dr. Piotr Czaykowski, BSc, MD, MSc, FRCPC
Lead and Steering Committee Chair,
CCMB Clinical Practice Guidelines Initiative

Date
Feb 26/13

Date
May 31/13

Date
6 June 2013

cc. WRHA/CCMB Oncology P&T Subcommittee
Systemic Therapy Summaries Working Group
Associated Program Directors/Department Heads
Practice Guideline: Systemic Therapy Summary

Second-Line Treatment of Metastatic Non-Small Cell Lung Cancer with Pemetrexed

(LUNG - Pemetrexed)

Effective: June 2010
Required Update: February 2014
Annual Review: February 2013

CCMB Electronic Posting Date:
ACKNOWLEDGEMENT AND SPONSORSHIP DISCLAIMERS
Introduction

This document has been prepared by the Winnipeg Regional Health Authority/CancerCare Manitoba (WRHA/CCMB) Oncology Pharmacotherapeutic (P&T) Subcommittee’s Systemic Therapy Summaries Working Group, as a means of disseminating drug information and formulary decisions made by the Subcommittee. The CCMB Provincial Pharmacy Program, Provincial Oncology Drug Program (PODP), and Clinical Practice Guidelines Initiative (CPGI) have contributed to the development of this summary.

Systemic Therapy Summaries (STS) are being developed for drugs/or indications where clinical benefit has been accepted by the P&T Subcommittee, based on scientific data. All STS documents are approved by the P&T Subcommittee Chair and the CPGI Lead/Advisory Panel Chair.

The content of this STS was in large part adapted from the Formulary Addition Request submitted to the P&T Subcommittee by the CCMB Gastro-Intestinal (GI) Disease Site Group, May, 2010. This document will be reviewed, and updated as necessary, once in every twelve-month period; unless emerging evidence from scientific research dictates otherwise.

Purpose

This document is intended as a guide to facilitate the safe and effective clinical use of pemetrexed in the second-line treatment of metastatic non-small cell lung cancer.

For this purpose, it may be used by qualified and licensed healthcare practitioners involved with the care of oncology patients, which may include (but is not limited to): physicians, nurses, and pharmacists at CancerCare Manitoba, Community Cancer Programs Network (CCPN) sites, and WRHA Community Oncology Program sites.

Disclaimer

Use of this document should not preclude the practitioner’s independent clinical judgment, nor should it replace consultation with the oncologist.

It is the responsibility of the practitioner to develop an individualized treatment plan for each patient under his/her care, and ideally this should take place within the context of a multidisciplinary team. The unique needs and preferences of the patient and the family should always be reflected in the plan of care.

This document is not a comprehensive drug monograph. Practitioners must refer to other sources for complete drug information.
Second-Line Treatment of Metastatic Non-Small Cell Lung Cancer with Pemetrexed

Protocol Code: LUNG - Pemetrexed
Developed by: Thoracic Disease Site Group
Date of Presentation to P&T Subcommittee: June 2010

Treatment Recommendation

The CCMB Thoracic Disease Site Group recommends pemetrexed as the preferred agent for second-line treatment of metastatic non-small cell lung cancer of non-squamous histology, in patients who meet the inclusion criteria (see below).

Treatment Intent

- Non-curative
- Prolongation of overall survival and progression-free survival
- Improved quality of life

Rationale

Lung cancer is the most common cause of cancer related death worldwide in both men and women. Three quarters of lung cancers are histologically categorized as non-small cell lung cancers (NSCLC). Surgery and adjuvant chemotherapy with curative intent have become the worldwide standard in the treatment of early stage lung cancer. Unfortunately, the majority of patients with lung cancer present with advanced, incurable stages. Also, many patients previously treated with surgery relapse. Currently, chemotherapy is the standard of care in patients with advanced NSCLC and good performance status. Docetaxel has been the accepted standard for second-line treatment. Pemetrexed also has demonstrated activity in second line therapy, and appears to be well tolerated.
Clinical Benefit (Level 1b Evidence see Appendix I)

Pemetrexed is a multitargeted antifolate that appeared to be active and well tolerated in second line therapy in patients with NSCLC. A large phase III trial was undertaken to compare single agent docetaxel versus single agent pemetrexed in NSCLC that had failed previous first line therapy. Four hundred and seventy one patients were randomized to either docetaxel 75 mg/m2 or pemetrexed 500 mg/m2 each given on a 21 day cycle. The primary objective of the study was to compare overall survival between the two groups in an intent-to-treat manner. The trial was statistically powered to detect non-inferiority for survival times. Secondary endpoints included comparisons of toxicity profiles and quality of life measures. The results of the study showed no statistically significant objective response rate difference between the two drugs (pemetrexed: 9.1%; docetaxel: 8.9%). On the intent-to-treat analysis, the median survival time for pemetrexed was 8.3 months and 7.9 months for the docetaxel group (HR 0.99; 95% CI, 0.82 to 1.2; non-inferiority P = 0.226). The one year overall survival rate was 29.7% for both arms. There was no difference in the quality of life analysis between the two treatment groups. However, pemetrexed was associated with significantly less grade 3 or 4 neutropenia, febrile neutropenia, hair loss, infections, the use of G-CSF support, hospitalizations due to neutropenic related events, or hospitalizations due to other drug related adverse events. It was therefore felt that pemetrexed was better tolerated than docetaxel. Later subset analysis from this trial (and future first line trials with pemetrexed) have shown that pemetrexed is more active in non-squamous histology and less active in squamous histology as compared to other standard second generation chemotherapeutic agents in the treatment of NSCLC.

Patient Population and Selection Criteria

Inclusion criteria (June 2010)

For second line treatment of metastatic NSCLC with disease progression after first line therapy, in patients who meet the following criteria:

- Advanced NSCLC restricted to non-squamous histology,* and
- Prior treatment and failure with first-line chemotherapy, and
- Eastern Cooperative Oncology Group (ECOG) performance status of 0-2 (see Appendix II), and
- Adequate bone marrow function (ANC greater than or equal to 1.5 x 10^9/L, platelets greater than 100 x 10^9/L), renal function, and liver function

* Pemetrexed may be used to treat NSCLC with squamous cell histology, in cases where treatment with docetaxel is contraindicated.
CCMB Formulary Status

1. **Formulary definition**: Restricted

2. **Adjudication process**:

   Request form to use: Non-Formulary Request Form (J: \Forms\Pharmacy)

   Approval required by: DSG Chair or delegate; adjudication is required every 4 cycles following repeat imaging. Continued treatment after 8 cycles will need Non-Formulary approval from P&T Subcommittee Chair or delegate.

### Mandatory Vitamin Supplementation – All Patients

<table>
<thead>
<tr>
<th>Vitamin</th>
<th>Dose</th>
<th>Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Folic acid</td>
<td>1 mg daily</td>
<td>Orally, starting 7-14 days prior to the first cycle, continuing until 21 days after the last pemetrexed dose</td>
</tr>
<tr>
<td>Vitamin B12</td>
<td>1000 mcg every 9 weeks</td>
<td>IM, starting 7-14 days prior to the first cycle, continuing until 21 days after the last pemetrexed dose</td>
</tr>
</tbody>
</table>

### Treatment Regimen – LUNG – Pemetrexed

1 cycle = 21 days (until disease progression)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Administration Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pemetrexed</td>
<td>500 mg/m² every 21 days</td>
<td>IV in 100 mL NS over 10 minutes</td>
</tr>
</tbody>
</table>

### Premedications and Supportive Care

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Administration Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metoclopramide</td>
<td>20 mg</td>
<td>Orally, 30 minutes before chemotherapy</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>4 mg twice daily for 3 days</td>
<td>Orally, beginning the day before chemotherapy</td>
</tr>
</tbody>
</table>
Clinical Monitoring and Follow-Up Recommendations

Hematology and Chemistry Laboratory Tests
Baseline and before each treatment: CBC with differential, platelets, sodium, potassium, chloride, calcium, magnesium, phosphorus, albumin, urea, serum creatinine, AST, ALT, alkaline phosphatase, LDH, GGT, bilirubin
Day 14: CBC with differential and platelets

Assessment of Treatment Response
Following 4 cycles of therapy, repeat imaging will be obtained in order to document disease stability or response. If patients respond or are stable, treatment may be continued for another 4 cycles.

Common or Clinically Important Adverse Events
(Refer to individual drug monographs for full details of adverse events)

| Blood/ bone marrow/ febrile neutropenia | Myelosuppression is normally the dose limiting toxicity. Dose reductions are based on nadir ANC, platelet count, and non-hematologic toxicity seen in the previous cycle (see Dose Modifications).
Anemia is reported in 19% of patients, with 4% severe. Thrombocytopenia is reported at 8%, with 2% severe. Neutropenia is reported at 11% with 5% severe. The incidence of severe febrile neutropenia is 2%.
The incidence and severity of bone marrow suppression can be reduced with vitamin supplementation. Folic acid and Vitamin B12 must be started at least a week prior to the first dose of pemetrexed (see Premedications). |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Constitutional symptoms</td>
<td>Fatigue has been reported in 34% of patients, with 5% severe.</td>
</tr>
<tr>
<td>Dermatology/skin</td>
<td>Rash/desquamation is reported in patients who were not pre-treated with a corticosteroid. Standard therapy to reduce the incidence and severity of skin reactions includes oral dexamethasone 4 mg twice daily given the day before, the day of, and the day after pemetrexed administration (see Premedications).</td>
</tr>
</tbody>
</table>

continued on the next page
Common or Clinically Important Adverse Events - cont’d

| Gastrointestinal | Emetogenic potential: low (10-30%)<sup>6,8</sup>
|                  | In clinical trials, nausea was seen in 31% of patients (3% severe), and vomiting in 16% of patients (2% severe). Diarrhea was reported in 13% of patients (0.4% severe).
|                  | In rare cases, gastrointestinal toxicity may lead to severe dehydration. Gastrointestinal toxicities should be managed aggressively (see Dose Modifications).
|                  | The incidence and severity of diarrhea and mucositis can be reduced with vitamin supplementation. Folic acid and Vitamin B12 must be started at least a week prior to the first dose of pemetrexed (see Premedications).
| Metabolic/laboratory | Increases in liver enzymes have been reported (ALT elevation 8%, severe 2%; AST elevation 7%, severe 1%), as well as changes in renal function (decreased creatinine clearance 2%, severe less than 1%; increased serum creatinine 2%, 0% severe).

Precautions

| Interaction with NSAIDs | Non-steroidal anti-inflammatory drugs (NSAIDs) can increase pemetrexed levels by reducing its renal clearance (see Drug Interactions).
| Renal insufficiency    | Dose reductions are required in patients with poor renal function (see Dose Modifications). Renal events, including acute renal failure have been reported with pemetrexed.
| Respiratory toxicity   | Interstitial pneumonitis with respiratory insufficiency, (sometimes fatal) has been reported in clinical trials. Pemetrexed therapy should be interrupted in
## Dose Modifications*

**Pemetrexed dose adjustment guidelines**

<table>
<thead>
<tr>
<th>Renal failure</th>
<th>Creatinine Clearance</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greater than or equal to 45 mL/min</td>
<td></td>
<td>100%</td>
</tr>
<tr>
<td>Less than 45 mL/min</td>
<td></td>
<td>Delay</td>
</tr>
</tbody>
</table>

Cockcroft-Gault GFR = N* x (140-age) x IBW (kg) x SCR in umol/L

Ideal Body Weight (IBW)

Male = 50 kg + [(Ht in cm – 152 cm) x 0.91]  
Female = 45.5 kg + [(Ht in cm – 152 cm) x 0.91]  
see Reference 9

<table>
<thead>
<tr>
<th>Hematological toxicity</th>
<th>Nadir ANC less than 0.5 x 10^9/L and Nadir platelets greater than or equal to 50 x 10^9/L</th>
<th>75% of previous dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nadir platelets less than 50 x 10^9/L, regardless of nadir ANC</td>
<td>75% of previous dose</td>
</tr>
<tr>
<td></td>
<td>Nadir platelets less than 50 x 10^9/L with bleeding, regardless of nadir ANC</td>
<td>50% of previous dose</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Non-Hematological toxicity</th>
<th>If patients develop non-hematologic toxicities greater than or equal to Grade 3 (see Appendix III), pemetrexed should be withheld until resolution to less than or equal to the patient's pre-therapy value. Treatment should be resumed as follows:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucositis Grade 3 or 4</td>
<td>50% of previous dose</td>
</tr>
<tr>
<td>Diarrhea Grade 3 or 4 or any grade requiring hospitalization</td>
<td>75% of previous dose</td>
</tr>
</tbody>
</table>
Drug Interactions\textsuperscript{5,6}

Pemetrexed is primarily excreted unchanged through the kidneys as a result of glomerular filtration and tubular secretion.

Concomitant administration of nephrotoxic drugs (e.g. aminoglycosides, radiographic media, sulphonamides) could result in delayed clearance of pemetrexed and should be avoided.

Concomitant administration of substances that are also tubularly secreted (e.g. probenecid) could potentially result in delayed clearance of pemetrexed and should be avoided.

Interactions with NSAIDs

NSAIDs can increase pemetrexed levels by reducing its renal clearance.

- Ibuprofen (up to 400 mg four times daily), and other NSAIDs with short half-lives (e.g. diclofenac, indomethacin, ketorolac) should be held for at least two days before, the day of, and for at least two days after pemetrexed administration, in patients with mild to moderate renal insufficiency (i.e. CrCl 45-79 mL/min). Patients with normal renal function (i.e. CrCl greater than or equal to 80 mL/min) do not require dose adjustments.

- NSAIDs with long half-lives (e.g. meloxicam, peroxicam) should be held for at least five days before, the day of, and for at least two days after pemetrexed in all patients.

- ASA at doses up to 325 mg four times daily can be continued without concerns.

- If concomitant administration of an NSAID is necessary, patients should be monitored closely for toxicity, especially myelosuppression, renal and gastrointestinal toxicity.
References


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We gratefully acknowledge the support of CancerCare Manitoba, and the CancerCare Manitoba Foundation. The Provincial Oncology Clinical Practice Guidelines Initiative
## Appendix I

### Levels of Evidence

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia</td>
<td>Evidence obtained from meta-analysis of randomised controlled trials</td>
</tr>
<tr>
<td>Ib</td>
<td>Evidence obtained from at least one randomised controlled trial</td>
</tr>
<tr>
<td>IIA</td>
<td>Evidence obtained from at least one well-designed controlled study without randomisation</td>
</tr>
<tr>
<td>IIB</td>
<td>Evidence obtained from at least one other type of well-designed, quasi-experimental study</td>
</tr>
<tr>
<td>III</td>
<td>Evidence obtained from well-designed, non-experimental descriptive studies, such as comparative studies, correlation studies and case studies</td>
</tr>
<tr>
<td>IV</td>
<td>Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities</td>
</tr>
</tbody>
</table>

### Appendix II

#### ECOG Performance Status Scale

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all pre-disease activities without restriction (Karnofsky 90-100)</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physical strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light housework or office work (Karnofsky 70-80)</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about greater than or equal to 50% of waking hours (Karnofsky 50-60)</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self-care, confined to bed or chair greater than or equal to 50% of waking hours (Karnofsky 30-40)</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled, cannot carry on any self-care, totally confined to bed or chair (Karnofsky 10-20)</td>
</tr>
</tbody>
</table>

## Appendix III

### Common Terminology Criteria for Adverse Events (CTCAE) version 4.0

**Publish Date: 18 May 2009**

<table>
<thead>
<tr>
<th>Grades</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade 1</strong></td>
<td>Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.</td>
</tr>
<tr>
<td><strong>Grade 2</strong></td>
<td>Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.</td>
</tr>
<tr>
<td><strong>Grade 3</strong></td>
<td>Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.</td>
</tr>
<tr>
<td><strong>Grade 4</strong></td>
<td>Life-threatening consequences; urgent intervention indicated.</td>
</tr>
<tr>
<td><strong>Grade 5</strong></td>
<td>Death related to AE.</td>
</tr>
</tbody>
</table>

A semi-colon indicates ‘or’ within the description of the grade.  
A single dash (-) indicates a grade is not available.  
Not all grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for grade selection.

**Grade 5:** Grade 5 (Death) is not appropriate for some AEs and therefore is not an option.

### Activities of Daily Living (ADL):

* Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
* Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.
