PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Pemetrexed (Alimta) for Non-Squamous Non-Small Cell Lung Cancer

November 19, 2013

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1 GUIDANCE IN BRIEF

1.1 Background

The purpose of this review is to evaluate the safety and efficacy pemetrexed (Alimta) on patient outcomes compared to standard therapies or placebo in the continuation of maintenance treatment for patients with locally advanced or metastatic non-squamous, non-small cell lung cancer who received pemetrexed and cisplatin as first-line treatment.

Pemetrexed is a multi-targeted anti-folate drug. It has a Health Canada approval for use as a maintenance treatment in patients with locally advanced or metastatic non-squamous non-small cell lung cancer, who have good performance status patients and are without disease progression immediately following four cycles of first-line platinum doublet chemotherapy.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The pCODR systematic review included one double-blind randomized controlled trial (RCT), PARAMOUNT (Paz-Ares 2012 and 2013) which compared pemetrexed plus best supportive care to placebo plus best care for the maintenance treatment of patients with advanced (locally advanced or metastatic) non squamous, non-small cell lung cancer (NSNSCLC). All patients had received 4 cycles of the induction therapy of pemetrexed plus cisplatin and achieved complete response (CR)/partial response (PR) or stable disease (SD).

The PARMOUNT study randomized 539 patients in a 2:1 ratio to pemetrexed plus BSC (n=359, 500 mg/m^2 IV) or placebo plus BSC (n=180). The majority of patients had ECOG PS 0 or 1. Baseline patient characteristics appeared to be comparable between the two groups. The maintenance treatment continued until disease progression.

Efficacy

The primary outcome was investigator assessed progression free survival (PFS). Median PFS at the March 5, 2012 cut-off was 4.1 vs. 2.8 months in the pemetrexed compared to placebo arm, respectively (HR: 0.62, 95% CI, 0.49 to 0.79). Median final overall survival (March 5, 2012 cut-off) was 13.9 vs. 11.0 months (HR: 0.78, 95% CI, 0.64 to 0.96, P = 0.0199) in the pemetrexed group and placebo group, respectively. The risks of death or risks of disease progression were similar in all predefined subgroups patients and showed a statistically significant reduction with pemetrexed compared with placebo.

Quality of life was measured using the EuroQol 5-dimensional scale (EQ-5D) at baseline, on day 1 of every cycle of induction and maintenance therapy, and at the 30-day post discontinuation visit. Overall results at end of treatment (cut-off date June 30, 2010) indicated a similar decline in patients' health related quality of life (HRQoL) in both the pemetrexed and placebo groups.

Harms

Serious adverse events occurred in 25% patients in pemetrexed group and 14% in placebo group. More patients in the pemetrexed group reported non-fatal serious adverse events including anemia (2.5%), fatigue (0.8%) and febrile neutropenia (1.7%) at the cut-off date March 5, 2013. Only one patient (0.6%) in placebo arm reported serious fatigue. No patients in the placebo arm reported serious anemia or febrile neutropenia.

Overall, more adverse events (AE) occurred in the pemetrexed group than placebo group (82% vs. 67%, respectively) at cut-off March, 2012. Common possible drug related AE's include fatigue (22% vs. 12%), anemia (18.1% vs. 5%), and neutropenia (11% vs. 0.6%) in the pemetrexed vs. placebo arms, respectively.[1]

As of the June 30, 2010 cut-off, of all randomised patients, 10 deaths were reported in both arms of which 5 were attributed to progressive disease (4 vs. 1 in the pemetrexed and placebo arm, respectively). Of the remaining 5 deaths, 2 were possibly related to study drug (1 AE of pneumonia in the pemetrexed arm and 1 AE of sudden death in the placebo arm; there were 3 additional deaths within 30 days of last study dose administered (1 in the pemetrexed arm and 2 in the placebo arm).

Withdrawals due to adverse events (WDAE) occurred in 18% and 7% patients in the pemetrexed and placebo groups respectively (cut-off: March 5, 2012).

1.2.2 Additional Evidence

pCODR received input on pemetrexed for non-squamous non-small cell lung cancer from the following patient advocacy groups who collaborated and provided one joint input, Canadian Cancer Survivor Network (CCSN) and Lung Cancer Canada (LCC). Provincial Advisory group input was obtained from eight of the nine provinces participating in pCODR.

No supplemental questions were identified for this review.

1.2.3 Interpretation and Guidance

Burden of Illness and Need

Lung cancer remains the leading cause of cancer-related deaths globally.[2] It is estimated that in 2013 there will be 25,500 new cases and 20,200 deaths associated with lung cancer in Canada.[3] Adenocarcinomas are the most common non-squamous cell carcinoma, and occur more frequently in women than men.

Maintenance therapy following induction with four cycles of a platinum-based doublet has been shown to improve progression-free survival.[4,5] However, the benefit of maintenance erlotinib and pemetrexed appears to be restricted to those with a good performance status following induction chemotherapy, and a best response of stable disease. While questions remain about the overall benefit of this strategy,[6] both drugs have been approved as maintenance therapy by Health Canada and other regulators.

Effectiveness

PARAMOUNT, demonstrates a PFS and OS advantage for maintenance pemetrexed in those patients with advanced non-squamous non-small cell lung cancer (NS-NSCLC). This benefit was seen in patients with a performance status of ECOG 0 or 1 who achieved stable disease or better with 4 cycles of induction cisplatin/pemetrexed and was associated with no apparent major negative impact on quality of life.

There were no statistically significant differences in quality of life outcomes between the two groups, assessed using the EQ-5D index and a visual analog scale.

Although the majority of patients in both arms of the study went on to receive further systemic therapy, it is not possible to determine to what extent post-study treatment affected overall survival.

Safety

The reported adverse events were typical for pemetrexed, and were associated with a withdrawal rate on maintenance pemetrexed of 18% versus 7% on placebo.

1.3 Conclusions

The Clinical Guidance Panel concluded that there is a net overall benefit to maintenance pemetrexed in treatment of patients with advanced or metastatic NS-NSCLC who have a good performance status and achieve at least stable disease with induction cisplatin/pemetrexed. This is based on the results of one double-blind randomized controlled trial (RCT), PARAMOUNT, which demonstrated a PFS and OS advantage and no apparent major negative impact on quality of life (QOL) with the use of maintenance pemetrexed in patients with advanced non-squamous non-small cell lung cancer (NS-NSCLC).

The Clinical Guidance Panel also considered that from a clinical perspective:

- There are a number of key factors that determine patient suitability for continuation maintenance treatment, including performance status and disease response post induction cisplatin/pemetrexed.
- It is unknown how this strategy (pemetrexed maintenance) compares with the strategy of close monitoring during the maintenance phase and use of pemetrexed as a second-line therapy at the time of disease progression.
- There is no evidence to support the use of pemetrexed in poor performance status patients (ECOG 2 or greater) following induction chemotherapy.
- The utility of this specific treatment program is dependent on whether first-line pemetrexed in combination with cisplatin is available given that pemetrexed is not funded currently for first-line treatment in many Canadian jurisdictions.

2 CLINICAL GUIDANCE

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding pemetrexed (Alimta) for advanced non-small cell lung cancer. The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the pCODR website, www.pcodr.ca.

This Clinical Guidance is based on: a systematic review of the literature pemetrexed (Alimta) for advanced non-small cell lung cancer conducted by the Lung Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues are fully reported in Sections 6 and 7. Background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on pemetrexed and a summary of submitted Provincial Advisory Group Input on pemetrexed are provided in Sections 3, 4 and 5 respectively.

2.1 Context for the Clinical Guidance

2.1.1 Introduction

Health Canada recently approved pemetrexed monotherapy for the maintenance treatment of locally advanced or metastatic nonsquamous non-small cell lung cancer, in good performance status patients without disease progression immediately following four cycles of first-line platinum doublet chemotherapy. Health Canada has previously approved the use of pemetrexed in patients with Malignant Pleural Mesothelioma (2004) and in patients with nonsquamous-NSCLC (NS-NSCLC) with stage IIIB/IV advanced and metastatic disease in the second-line (2007), first-line (2008), and maintenance settings (2010). Importantly, the 2010 indication, also termed switch maintenance, is for pemetrexed maintenance monotherapy following platinum doublet induction treatment with an approved agent other than pemetrexed. Therefore, pemetrexed currently has four indications approved by Health Canada including treatment for Malignant Pleural Mesothelioma, first-line (combined with cisplatin) second-line, and maintenance therapy (including switch and continuation maintenance) for advanced or metastatic NS-NSCLC.[7]

Pemetrexed is a multi-targeted anti-folate drug that inhibits at least three different enzymes in the folate pathway: thymidylate synthase, dihydrofolate reductase and glycinamide ribonucleotide formyl transferase. These enzymes are involved in ribonucleic acid (both DNA & RNA) synthesis: inhibition of these enzymes is particularly toxic in rapidly dividing cells, in particular, tumour cells. The recommended dose of pemetrexed in the continuous maintenance phase is 500 mg/m^2 administered every 21 days and continues until disease progression. Supplementation of folic acid and vitamin B12 was administered. Current standard maintenance therapies following first line pemetrexed/cisplatin induction therapy is the best supportive care although erlotinib plus BSC has sometimes been used in some Canadian jurisdiction.

2.1.2 Objectives and Scope of pCODR Review

The objective of this review is to evaluate the effect of pemetrexed (Alimta) plus best supportive care on patient outcomes compared to erlotinib or placebo plus best supportive care in the continuation maintenance treatment of patients with locally advanced or metastatic non-squamous, non-small cell lung cancer following first-line treatment of pemetrexed and cisplatin.

2.1.3 Highlights of Evidence in the Systematic Review

One multi-national, multicentre phase III, double-blind randomized controlled trial (RCT)[1,8-10] (PARAMOUNT) was included in this review. The study compared pemetrexed (Alimta) plus best supportive care versus placebo plus best care for the maintenance treatment of patients with advanced (locally advanced or metastatic) non squamous, non-small cell lung cancer (NSNSCLC) following 4 cycles of the induction therapy of pemetrexed plus cisplatin and achieved complete response (CR) / partial response (PR) or stable disease (SD). Five hundred and thirty nine patients were randomized in the maintenance phase a 2:1 ratio into pemetrexed plus BSC (n=359) and placebo plus BSC (n=180). Patients received pemetrexed (500 mg/m^2) administered IV or placebo. All patients received in addition best supportive care (BSC). The maintenance treatment continued until disease progression. Patients were of median age 61 to 62 years and ECOG PS 0 or 1. 58% were male. Majority were White (95%). Baseline patient characteristics appeared to be comparable between the two groups.

Key efficacy and safety findings from the PARAMOUNT study,[1,8-10] are summarized in Table 1. Efficacy analyses were based on intent-to-treat population. Safety analyses considered patients who had received at least one dose of treatment.

As a secondary outcome in the study, the final OS was analysed on the cut-off March 5, 2012. Median final overall survival was 13.9 months in the pemetrexed group and 11.0 months in the placebo group, which indicated a gain in overall survival of 2.9 months for the pemetrexed group. The hazard ratio for overall survival (pemetrexed versus placebo) was 0.78 (95%CI, 0.64 to 0.96, P = 0.0199) indicating a 22% reduction in the risk of death in the pemetrexed group. Progression free survival (PFS) was the primary end-point in the study. The hazard ratio for PFS (pemetrexed versus placebo) was 0.62 (95%CI, 0.49 to 0.79) and p<0.0001 indicating a 38% reduction of risk of disease progression in the pemetrexed group compared to the placebo group. The risks of death or risks of disease progression were similar in all predefined subgroups patients (such as baseline cancer stage: IIIB vs IV; response to induction response: complete response plus partial response vs. stable disease and ECOG performance: 0 vs. 1) and showed a statistically significant reduction with pemetrexed compared with placebo. Overall results at end of treatment (cut-off date June 30, 2010) indicated a similar decline in patients' health related quality of life (HRQoL) in both the pemetrexed and placebo groups. Overall, more adverse events occurred in pemetrexed group than placebo group (82% vs. 67%) at cut-off March, 2012). Common adverse events occurring in patients treated with pemetrexed include fatigue (PEM vs. PBO, 31% vs. 14%), anemia (PEM vs. PBO, 25% vs. 6%), and neutropenia (PEM, 12% vs. 0.6%). Among them, common possible drug related are fatigue (PEM vs. PBO, 22% vs. 12%), anemia (PEM vs. PBO, 18.1% vs. 5%), and neutropenia (PEM, 11% vs. 0.6%).[1] SAEs occurred in 25% patients in pemetrexed group and 14% in placebo group. More patients in the pemetrexed group reported the non-fatal serious adverse events including anemia (2.5%), fatigue (0.8%) and febrile neutropenia (1.7%) at the cut-off date March. 5, 2013. Only one patient (0.6%) in placebo arm reported serious fatigue. No patients in the placebo arm reported serious anemia or febrile neutropenia.

Withdrawals due to adverse events (WDAE) occurred in 18% and 7% patients in the pemetrexed and placebo groups respectively (cut-off: March 5, 2012).

At the cut-off date Mar. 5, 2012, 64 % patients from pemetrexed and 72 % from placebo arm received post-discontinuation subsequent systematic anticancer treatment. The two most common used anticancer agents for PDC were erlotinib (39.6% for pemetrexed; 43.3% for placebo as of March 5, 2012 cut-off) and docetaxel (32.3% for pemetrexed; 43.3% for placebo as of March 5, 2012 cut-off). Other common agents included gemcitabine (10.0% for pemetrexed; 8.3% for placebo as of March 5, 2012 cut-off) and vinorelbine (7.8% for pemetrexed; 6.1% for placebo as of March 5, 2012 cut-off).[1,10]

Table 1: Summary of Key Outcomes[1,8-10]		
	PEM+ BSC N=359	PBO + BSC N=180
OS: Cut-off date: March 5, 2012		
Final OS†, median (95% CI) months (from randomization)	13.9 (12.8 - 16.0)	11.0 (10.0 -12.5)
Final OS median Tx difference (PEM – PBO) (mos)	2.9 (95%CI: NR, P = 0.0195)	
Final OS-HR from randomization (95% CI)	0.78 (0.64-0.96) P =0.0199	
PFS: Cut-off date: June 30, 2010		
PFS†, median (95% CI) months	4.1(3.2 - 4.6)	2.8 (2.6 - 3.1)
PFS HR (95%CI)	0.62 (0.49-0.79) P<0.0001 PEM vs. pbo	
QOL Change from baseline[9]		
EQ-5D index score during Mtx phase at cycle 6	-0.02 P = 0.05	0.04
VAS at cycle 6	1.55 (p = 0.044, PEM vs. pbo)	5.99
Harms		
Overall SAE	90 (25.1)	26 (14.4)
Overall AEs	294 (81.9)	121 (67.2)
WDAE	65 (18)	12(7)
AE= adverse event; CI = confidence interval; CR=complete response; EQ-5D= EuroQol 5-dimensional questionnaire; HR=hazard ratio; mos = months; Mtx=maintenance therapy; NR=not reported; NS: not statistically significant; OS = overall survival; PEM = pemetrexed; Pbo = Placebo; PR=partial response; QOL=quality of life; SAE = serious adverse event; SD=stable disease; Tx= therapy; VAS = visual analog scale; WDAE = withdrawal due to adverse event		

† Kaplan-Meier method

2.1.4 Comparison with Other Literature

The pCODR Clinical Guidance Panel and the pCODR Methods Team did not identify other relevant literature providing supporting information for this review.

2.1.5 Summary of Supplemental Questions

No supplemental questions were identified for this review.

2.1.6 Other Considerations

See Section 4 and Section 5 for a complete summary of patient advocacy group input and Provincial Advisory Group (PAG) Input, respectively.

Patient Advocacy Group Input

From a patient perspective, modest improvements in response of a couple of months are generally considered to be important gains due to the relatively short survival of patients with advanced NS-NSCLC. The patient advocacy groups reported that the combination of cisplatin and pemetrexed represents an improvement for patients with NS-NSCLC because this regimen involves one chemo-clinic visit every 21 days in comparison to two chemo-clinic visits every 21 days for cisplatin and gemcitabine. Treatment regimens that result in fewer visits to the doctor or clinic would allow patients more time to spend with families and loved ones. Although there were some

adverse effects reported by those who took pemetrexed, most were deemed acceptable because the drug halted disease progression and respondents experienced a reduction in side effects from the treatment.

PAG Input

Input on the pemetrexed (Alimta) review was obtained from three of the nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. From a PAG perspective, the current patient population eligible to receive pemetrexed in the first line setting is small however a funding recommendation in the 1st line and maintenance setting is it likely to increase the patient population. Implementation is also likely to increase chemotherapy chair time but PAG recognised that as a drug that has an established treatment protocol; therefore, patients are likely to be able to receive pemetrexed in outreach settings closer to home.

Possible barriers to implementation were noted around drug pricing. PAG noted that the 100mg vial is more expensive than the 500mg vial and this is likely to be an issue in treatment centers with low patient volumes where minimizing drug wastage will require that jurisdictions purchase the more expensive 100mg vial. PAG also noted that based on the treatment regimen used in the pivotal study (cisplatin + pemetrexed) it may be difficult in assessing use of pemetrexed in selected patients that are not able to receive cisplatin as the combination therapy.

2.2 Interpretation and Guidance

Burden of Illness and need

Lung cancer remains the leading cause of cancer-related deaths globally.[2] It is estimated that in 2013 there will be 25,500 new cases and 20,200 deaths associated with lung cancer in Canada.[3] The majority will have non-small cell lung cancer (NSCLC) and are initially diagnosed with advanced disease that currently is considered incurable. The two main histological subtypes of NSCLC are squamous cell carcinoma and adenocarcinoma. Squamous cell carcinomas account for 30-40% of all NSCLC, and are more common in men than women.[12] Adenocarcinomas are the most common non-squamous cell carcinoma, and occur more frequently in women than men.

Platinum-based doublets are the mainstay of first-line treatment in good performance status patients, with a number of accepted regimens combining cisplatin or carboplatin with vinca alkaloids (i.e. vinorelbine), taxanes (i.e. paclitaxel, docetaxel), and antimetabolites (i.e. gemcitabine, pemetrexed). Maintenance therapy following induction with four cycles of a platinum-based doublet has been shown to improve progression-free survival.[4,5] However, the benefit of maintenance erlotinib and pemetrexed appears to be restricted to those with a good performance status following induction chemotherapy, and a best response of stable disease. While questions remain about the overall survival benefit of this strategy,[6] both drugs have been improved as maintenance therapy by Health Canada and other regulators.

Effectiveness

The randomized placebo-controlled phase III trial, PARAMOUNT, demonstrates a progression-free (PFS) and overall survival (OS) advantage for maintenance pemetrexed in those patients with advanced non-squamous non-small cell lung cancer (NS-NSCLC). This benefit was seen in patients with a performance status of ECOG 0 or 1 who achieved stable disease or better with 4 cycles of induction cisplatin/pemetrexed and was associated with no apparent major negative impact on quality of life (QOL).

PFS with maintenance pemetrexed was reported as 4.1 months as compared to 2.8 months with placebo. This difference was statistically significant, with a hazard ratio (HR) of 0.62 and 95%

confidence interval (CI) 0.49-0.79. Maintenance pemetrexed was also associated with an improvement in OS, 13.9 months, as compared to placebo, 11.0 months (HR 0.78, 95% CI 0.64-0.96).

The reported adverse events were typical for pemetrexed, and were associated with a withdrawal rate on maintenance pemetrexed of 18% versus 7% on placebo. There were no statistically significant differences in QOL outcomes between the two groups, assessed using the EQ-5D index and a visual analog scale.

A caveat regarding the OS results is that salvage therapy following disease progression was not trial mandated. Although the majority of patients in both arms of the study went on to receive further systemic therapy, it is not possible to determine to what extent post-study treatment affected OS. Pemetrexed was not used consistently as second-line therapy in those in the placebo arm at the time of disease progression, and it is notable that some of the salvage regimens that were prescribed were not evidence-based.

The PARAMOUNT trial results are of sufficient benefit to support use of maintenance pemetrexed following induction cisplatin/pemetrexed in individuals with advanced or metastatic NS-NSCLC with a good performance status who achieve a best response to induction of at least stable disease. It is not appropriate based on the lack of evidence to extend eligibility to those with a poor performance status (ECOG 2 or greater) following induction chemotherapy. The utility of this specific treatment program is dependent on whether first-line pemetrexed in combination with cisplatin is available given that pemetrexed is not funded currently for first-line treatment in many Canadian jurisdictions.

2.3 Conclusions

The Clinical Guidance Panel concluded that there is a net overall benefit to maintenance pemetrexed in treatment of patients with advanced or metastatic NS-NSCLC who have a good performance status and achieve at least stable disease with induction cisplatin/pemetrexed. This is based on the results of one double-blind randomized controlled trial (RCT), PARAMOUNT, which demonstrated a PFS and OS advantage and no apparent major negative impact on quality of life (QOL) with the use of maintenance pemetrexed in patients with advanced non-squamous non-small cell lung cancer (NS-NSCLC).

The Clinical Guidance Panel also considered that from a clinical perspective:

- There are a number of key factors that determine patient suitability for continuation maintenance treatment, including performance status and disease response post induction cisplatin/pemetrexed.
- It is unknown how this strategy (pemetrexed maintenance) compares with the strategy of close monitoring during the maintenance phase and use of pemetrexed as a second-line therapy at the time of disease progression.
- There is no evidence to support the use of pemetrexed in poor performance status patients (ECOG 2 or greater) following induction chemotherapy.
- The utility of this specific treatment program is dependent on whether first-line pemetrexed in combination with cisplatin is available given that pemetrexed is not funded currently for first-line treatment in many Canadian jurisdictions.

3 BACKGROUND CLINICAL INFORMATION

Please note that this section was completed by the pCODR Lung Clinical Guidance Panel and is not based on a systematic review of the literature.

3.1 Description of the Condition

Non-small cell lung cancer (NSCLC) remains the leading cause of cancer-related deaths globally.[2] It is estimated that in 2013 there will be 25,500 new cases and 20,200 deaths associated with lung cancer in Canada.[3] The majority will have NSCLC and present with advanced disease that is incurable.

3.2 Accepted Clinical Practice

Systemic therapy for advanced stage NSCLC improves survival and quality of life outcomes compared to supportive care alone.[13] However, with respect to chemotherapy, this benefit is seen primarily in fit individuals, i.e. those with a good performance status and no significant comorbid conditions.

Platinum-based doublets are the mainstay of first-line treatment, with a number of accepted regimens combining cisplatin or carboplatin with vinca alkaloids (i.e. vinorelbine), taxanes (i.e paclitaxel, docetaxel), and antimetabolites (i.e. gemcitabine, pemetrexed). The median duration of response is approximately 4 months, with second- and third-line options for single-agent chemotherapy (e.g., docetaxel or pemetrexed) or an oral epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (e.g., erlotinib).[14]

In selected cases, it is appropriate to consider earlier treatment with an oral targeted agent.[15,16] Tests that are positive for sensitizing EGFR and anaplastic lymphoma kinase (ALK) mutations predict for benefit from EGFR tyrosine kinase inhibitors (e.g., gefitinib) or ALK inhibitors (e.g., crizotinib). At the time of disease progression, chemotherapy may still be an option.

Maintenance therapy following induction with four cycles of a platinum-based doublet has been shown to improve progression-free survival.[4,5] However, the benefit of maintenance erlotinib and pemetrexed appears to be restricted to those with a good performance status following induction chemotherapy, and a best response of stable disease. While questions remain about the overall benefit of the strategy,[6] both drugs have been approved as maintenance therapy by Health Canada and other regulators.

In the H3E-MC-JMEN trial of maintenance pemetrexed versus placebo, induction chemotherapy included a variety of platinum-based doublets, but not a platinum plus pemetrexed combination.[4]

3.3 Evidence-Based Considerations for a Funding Population

Addressing the question of continuing with pemetrexed as maintenance therapy after it has been used as part of the induction chemotherapy regimen, the PARAMOUNT trial compared pemetrexed to placebo.[8] Median progression-free survival was 4.1 months (95% CI 3·2–4·6) for pemetrexed and 2·8 months (95% CI 2·6–3·1) for placebo. As expected, treatment-related adverse events were more common in the group who received pemetrexed. Grade 3-4 laboratory adverse events occurred in 9% of those treated with pemetrexed versus 1% who received placebo. Grade 3-5 non-laboratory adverse events occurred in 9% and 4% of patients, respectively. One patient in each group died with a possible treatment-related cause.

The pemetrexed group required more active support, such as transfusions (13.4% vs 5.0%), prescription of growth factors (5.3% vs 0%), antimicrobials (25.3% vs 16.7%), and hospital stays (8.4% vs 3.3%).[9] However, the adverse events and need for additional intervention did not seem to have a negative impact on quality of life.[9]

Of further interest is the latest report of an overall survival benefit.[1] Median overall survival was 13.9 months for pemetrexed and 11.0 months for placebo, with a hazard ratio of 0.78 (95% CI 0.64-0.96). This advantage was seen regardless of whether the best response to induction cisplatin and pemetrexed was stable disease or complete/partial response.

3.4 Other Patient Populations in Whom the Drug May Be Used

Pemetrexed has an established role in treatment of malignant mesothelioma, and has been tested in a variety of other cancers. However, there are no randomized trial data of its use as a maintenance therapy in other malignancies.

4 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

Two patient advocacy groups provided a joint submission on pemetrexed (Alimta) for advanced non-squamous non-small cell lung cancer ("NS-NSCLC") and their input is summarized below:

- Canadian Cancer Survivor Network ("CCSN")
- Lung Cancer Canada ("LCC")

The CCSN and LCC conducted an online survey to gather information about patient and caregiver experiences with NS-NSCLC. The survey was publicized on CCSN's website and in their e-letters, on Twitter and on CCSN and LCC Facebook pages. A total of 3 respondents with metastatic disease participated in the survey.

From a patient perspective, modest improvements in response of a couple of months are generally considered to be important gains due to the relatively short survival of patients with advanced NS-NSCLC. The patient advocacy groups reported that the combination of cisplatin and pemetrexed represents an improvement for patients with NS-NSCLC because this regimen involves one chemo-clinic visit every 21 days in comparison to two chemo-clinic visits every 21 days for cisplatin and gemcitabine. Treatment regimens that result in fewer visits to the doctor or clinic would allow patients more time to spend with families and loved ones. Although there were some adverse effects reported by those who took pemetrexed, most were deemed acceptable because the drug halted disease progression and respondents experienced a reduction in side effects from the treatment.

Please see below for a summary of specific input received from the patient advocacy groups. Be advised that cited responses are not corrected for spelling or grammar.

4.2 Condition and Current Therapy Information

4.2.1 Experiences patients have with NS-NSCLC

The patient advocacy groups noted that the majority of patients with advanced non-squamous non-small cell lung cancer ("NS-NSCLC") either present with or subsequently develop metastatic disease. These patients have significant symptom burdens including cough, shortness of breath, pain, fatigue and other constitutional symptoms. These symptoms from lung cancer result in a substantial reduction in daily function. The majority of patients with advanced disease are unable to work and many experience a decline in their ability to function within their household and families.

When asked what symptoms or problems they experienced with advanced lung cancer that affected their day-to-day living and quality of life, survey respondents replied:

> Fatigue: 100%
> Living with uncertainly: 100%
> Anxiety, panic attacks or depression: 67%
> Not sleeping at night – restless: 67%
> Shortness of breath: 33%
> Pain: 33%
>
> Survey respondents then rated their top five symptoms that are the most important to control: fatigue, shortness of breath, pain, living with uncertainty, anxiety, panic attacks or depression and weight loss/lack of appetite.

Based on the responses received, all respondents suffered from fatigue; nearly two-thirds suffered pain and shortness of breath. As well, two-thirds are living with uncertainly, anxiety, panic attacks and depression.

Patients with advanced NS-NSCLC have a limited life expectancy, with a median survival of 10-12 months. From a patient perspective, treatment to control the lung cancer is the best way to control symptoms and preserve quality of life, and as such, respondents are eager to access new therapies that might promote healing and halt disease progression.

4.2.2 Patients' Experiences with Current Therapy for NS-NSCLC

The most frequently administered first-line chemotherapy for patients with advanced NS-NSCLC in Canada currently is cisplatin plus gemcitabine. This involves two treatment visits every 21 days. Common side effects experienced by patients include nausea, vomiting, fatigue, neutropenia, thrombocytopenia and infections including febrile neutropenia. Many patients require supportive treatments including transfusions of blood or platelets. Approximately one in three patients experience a substantial reduction in their cancer with treatment and the expected median survival is around 10-12 months.

Based on the survey conducted, 100% of respondents confirmed that they were being treated with chemotherapy. All respondents noted that they found chemotherapy to be somewhat effective. One respondent noted that, "*My first line treatment was Carboplatin/Germcitabine (4 cycles). Now using Altima as second line treatment*."

Respondents reported the following adverse effects from current therapies as follows:

Fatigue, feeling tired and run down: 100%
Diarrhea: 67%
Nausea: 67%
Pain: 67%
Feeling sick: 67%
Neutropenia or Neutropenic sepsis: 33%
Headaches: 33%

One respondent added depression and anxiety to the list of adverse effects. All respondents stated that all the adverse side effects listed above were difficult to deal with.

In addition to the above, respondents also indicated that their needs in their current therapies that are not being met. These include:

"*There is too much pain and I keep getting worse.*"

"*I would like to feel better and also stop disease progression.*"

Respondents also commented on the ability to access therapies. According to the survey, 67% of respondents did not have issues accessing treatment, while 33% did not. Reasons given for access issues included travel costs associated with getting treatment (34%); and supplies or issues with administration (33%).

One respondent included the following comment: "*I moved from Victoria, British Columbia to Montreal, Quebec for first line treatment. I am now on Alimta and still in Montreal. I would like to move back home, but I am worried about access to Alimta at the BC Cancer Agency (6 cycles maximum, need a 'compassionate care' designation to continue). Here in Montreal, I'm told they will treat me with Alimta as long as it keeps working.*"

4.2.3 Impact of NS-NSCLC and Current Therapy on Caregivers

Patient advocacy groups input noted that they did not receive any completed surveys from caregivers. Notwithstanding, CCSN and LCC indicated that caregivers of those with any metastatic cancer find that their lives are changed drastically when their loved ones are diagnosed.

Generally-speaking, caregivers are worried about prognosis and the financial burden of managing the disease. As one caregiver of a metastatic cancer patient put it, "*My number one concern is the stress of worrying about the prognosis. As a wife or partner you experience all the same concerns as the person experiencing the disease except for the actual pain but live all the other feelings that come with the disease.*"

4.3 Information about the Drug Being Reviewed

4.3.1 Patient Expectations for and Experiences To Date with Pemetrexed

Based on the survey conducted by CCSN and LCC, one of the three respondents stated they had no experience with pemetrexed. The respondent indicated that the expectations for a new drug were to be better able to control symptoms; reduce side effects from current medications or treatments; and halt disease progression. Specifically, the respondent stated: "*Fewer side effects so I could feel better and not feel so sick all the time and also something that would stop my cancer from getting worse.*"

The patient advocacy groups also noted that given the relatively short survival of patients with advanced / metastatic NSCLC, modest improvements in response of a couple of months are generally considered to be important gains. An improvement of two to three months would represent a relative improvement in survival of 25%. Additionally, more active treatment would be expected to increase the proportion of patients achieving control of their disease and therefore improvement in symptoms from their disease. Given the symptom burden of patients with advanced NSCLC, improvement in symptoms would be meaningful. Lastly treatment regimens that result in fewer visits to the doctor or clinic would allow patients more time to spend with families and loved ones.

The remaining two respondents confirmed that they had experience with using pemetrexed. The respondents found that:

- 50% were better able to control symptoms
  100% experienced a reduction in side effects from current medications or treatments
- 50% found pemetrexed easier to use
- 100% found that pemetrexed halted disease progression

A respondent replied that "*I am using Alimta now and am having success with it, in terms of controlling/shrinking my tumours. I also have minimal side effects*."

According to the survey, when asked if the respondents were better able to control side effects than on their previous therapy, 100% of the respondents found that they were better able to control nausea, while 50% of the respondents found that they were better able to control diarrhea, fatigue, weight loss or lack of appetite, neutropenia, pain, headaches, low blood cell levels and feeling sick.

One respondent noted that pemetrexed was easier to use because "*infusion time is shorter (15 minutes).*"

However, respondents also reported that adverse effects while taking pemetrexed. These included: fatigue (100%), diarrhea, nausea and feeling sick (50%).

The respondents reported the following:

> "*Fatigue is mild*."

> "*[Alimta] can cause constipation. I'm now taking a stool softener.*"

According to respondents, most side effects were acceptable, except for fatigue (50%) and feeling sick (50%).

Although there were some adverse effects reported by those who took pemetrexed, most were deemed acceptable because they felt the drug halted disease progression and respondents experienced a reduction in side effects from current medications and treatments.

In addition to the above, when asked about the respondents' expectations for long-term health and well-being as a result of taking pemetrexed, respondents noted the following:

> "*I hope I will feel better and that my cancer won't keep getting worse*."

> "*Hoping for disease regression or at least stability*."

Overall, the CCSN and LCC believe that the combination of cisplatin and pemetrexed represents an improvement for patients with NS-NSCLC. This regimen involves one visit every 21 days in comparison to two visits every 21 days for cisplatin and gemcitabine. This saves patients time and money.

The patient advocacy groups also consider that cisplatin and pemetrexed is more effective treatment resulting in longer survival for patients, and that the side effect profile is generally more favourable than cisplatin and gemcitabine. The CCSN and LCC noted fewer patients experienced febrile neutropenia or the need for blood and platelet transfusions.

Accordingly, both the CCSN and LCC believe that Canadian NS-NSCLC patients should have access to pemetrexed in both the first-line and maintenance settings to provide access to the most effective treatment for their disease.

4.4 Additional Information

No information was provided in this section by CCSN and LCC.

5 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The following issues were identified by the Provincial Advisory Group (PAG) as factors that could affect the feasibility of implementing a funding recommendation for pemetrexed (Alimta) for the treatment of non-small cell lung cancer (NSCLC). The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website (www.pcodr.ca).

Overall Summary

Input on the pemetrexed (Alimta) review was obtained from eight of the nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. From a PAG perspective, the current patient population eligible to receive pemetrexed in the first line setting is small however a funding recommendation in the 1st line and maintenance setting is it likely to increase the patient population. Implementation is also likely to increase chemotherapy chair time but PAG recognised that as a drug that has an established treatment protocol; therefore, patients are likely to be able to receive pemetrexed in outreach settings closer to home.

Possible barriers to implementation were noted around drug pricing. PAG noted that the 100mg vial is more expensive than the 500mg vial and this is likely to be an issue in treatment centers with low patient volumes where minimizing drug wastage will require that jurisdictions purchase the more expensive 100mg vial. PAG also noted that based on the treatment regimen used in the pivotal study (cisplatin + pemetrexed) it may be difficult in assessing use of pemetrexed in selected patients that are not able to receive cisplatin as the combination therapy.

Please see below for more detailed PAG input on individual parameters.

5.2 Factors Related to Comparators

PAG members indicated that pemetrexed + cisplatin or carboplatin doublet therapy is currently used in some provinces in the first line setting for the treatment of patients with NSCLC. Currently, patients receiving pemetrexed as part of a treatment regiment in the first line setting are not able to get pemetrexed maintenance and must choose between non-pemetrexed containing options. In light of this, PAG indicated that data that may support the use of pemetrexed in the maintenance setting following induction with a pemetrexed containing regimen may present a new therapeutic option for patients with non-squamous NSCLC.

PAG noted that a submission comparing pemetrexed first line + maintenance to the current standard of care first line + pemetrexed maintenance would be essential for those jurisdictions that do not fund pemetrexed first line.

5.3 Factors Related to Patient Population

PAG noted that currently the patient population eligible to receive pemetrexed in the first line setting is small. This is because in those jurisdictions which fund 1st line treatment, physicians must choose the setting in which to use pemetrexed for patients with non squamous NSCLC (1st line, 2nd line or maintenance). If a funding recommendation is made to fund pemetrexed in the 1st line and maintenance setting, PAG noted that is it likely to increase the eligible patient population.

If pemetrexed is implemented, PAG noted that a large number of patients receiving pemetrexed in the first line setting would likely go onto maintenance therapy although some patients may prefer to not

continue with a chemotherapy regimen in the maintenance setting. As such, it is not clear how widely pemetrexed would be used in the maintenance setting.

Some jurisdictions noted that there may be the potential for indication creep with pemetrexed into other cancers as pemetrexed has several off-label uses, such as bladder, ovarian and thymic malignancies.

5.4 Factors Related to Accessibility

PAG recognized that pemetrexed will need to be administered intravenously and as a result would require that patients travel to hospitals or chemotherapy clinics for treatment and likewise increase chemotherapy chair time. PAG did however note that as pemetrexed is not a new drug and has an established treatment protocol; patients may be able to receive treatment in outreach settings closer to home, limiting the impact of travelling on patients.

PAG recognised that pemetrexed treatment is normally initiated with prior folate and B12 therapy. In view of this, in patients with rapidly increasing symptoms and who require immediate treatment, initiating immediate treatment with pemetrexed may be an issue.

5.5 Factors Related to Dosing

Potential barriers to implementation involved the pricing of pemetrexed. PAG noted that the 100mg vial is more expensive that the 500mg vial. This presents as a barrier to implementation as efforts to avoid drug wastage will require that jurisdictions buy the more expensive vial. PAG indicated this to be likely in treatment centers with low patient volumes where drug wastage may be an issue. PAG also noted that in the pivotal trial being presented as part of the submission for pemetrexed, only cisplatin was used as the combination drug with pemetrexed. This could be a potential barrier, when assessing use of pemetrexed in selected patients that are not able to receive cisplatin as the combination therapy.

5.6 Factors Related to Implementation Costs

As an enabler to implementation, PAG recognised that most lung cancer is currently being diagnosed as squamous or non-squamous histology and as a result determining pemetrexed eligibility will not require additional resources. PAG did however indicate that in some instances poor pathology samples and the inability to re-sample may prevent the confirmed diagnosis of patients.

5.7 Other Factors

No other factors that could affect the feasibility of implementing a funding recommendation were identified.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the effect of pemetrexed (Alimta) plus best supportive care on patient outcomes compared to erlotinib or placebo plus best supportive care in the maintenance treatment of patients with locally advanced or metastatic non-squamous, non-small cell lung cancer following first-line treatment of pemetrexed and cisplatin (see Table 1 in Section 6.2.1 for outcomes of interest and comparators).

Note: No supplemental question relevant to the pCODR review and to the Provincial Advisory Group was suggested.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the Clinical Guidance Panel and the pCODR Methods Team. Studies were chosen for inclusion in the review based on the criteria in the table 2 below. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold.

Table 2: Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators	Outcomes
Published or unpublished DB RCTs	Patients with locally advanced or metastatic NS-NSCLC in maintenance treatment following first-line treatment of pemetrexed and cisplatin Subgroups: • Histologic type (adenocarcinoma vs. large cell carcinoma) • ECOG PS (0–1 vs. ≥2) • CR/PR vs. stable disease • Smoker vs. non-smokers • Gender (male vs. female) • Age (< 65 yrs vs. ≥65 yrs)	Pemetrexed at recommended dose 500 mg/m^2 (I.V) on day 1 of each 21-day cycle plus BSC[†]	**Active** Erlotinib plus BSC **Non-active** • Placebo plus BSC[†]	• **OS** • **PFS** • **QOL** • Time to progression • Time to deterioration of symptoms • Time to salvage treatment • Response rate (CR, PR) • SAEs • AEs (including **fatigue,** cytopenias, hospitalizations, anemia, chest pain) • WDAEs

AE=adverse events; BSC=best supportive care; CR=complete response; DB=double blind; ECOG PS=Eastern Cooperative Oncology Group Performance Status Scale; NS-NSCLC=Non-Squamous Non-small Cell Lung Cancer; PFS = Progression-free survival; OS=overall survival; PR=partial response; QOL=quality of life; RCT=randomized controlled trial; SAE=serious adverse events; WDAE=withdrawals due to adverse events

† Best supportive care included analgesics, antiemetic drugs, anti-infective drugs, colony-stimulating factors, erythropoiesis-stimulating agents, transfusions, palliative radiation to extrathoracic structures, and nutritional support and treatment-related admissions to hospital, etc.

6.2.2 Literature Search Methods

The literature search was performed by the pCODR Methods Team using the search strategy provided in Appendix A.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-) with in-process records & daily updates via Ovid; Embase (1974-) via Ovid; The Cochrane Central Register of Controlled Trials (2013, Issue 6) via Wiley; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Alimta, pemetrexed and non-small-cell lung cancer.

Methodological filters were applied to limit retrieval to randomized controlled trials and controlled clinical trials. Where possible, retrieval was limited to the human population. The search was also limited to English language documents, but not limited by publication year. The search is considered up to date as of October 3, 2013.

Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies (Food and Drug Administration and European Medicines Agency), clinical trial registries (U.S. National Institutes of Health – clinicaltrials.gov and Ontario Institute for Cancer Research – Ontario Cancer Trials) and relevant conference abstracts. Searches of conference abstracts of the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) were limited to the last five years. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the Clinical Guidance Panel. In addition, the manufacturer of the drug was contacted for additional information as required by the pCODR Review Team.

6.2.3 Study Selection

One member of the pCODR Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. Two members of the pCODR Methods Team independently made the final selection of studies to be included in the review and differences were resolved through discussion.

Included and excluded studies (with reasons for exclusion) are identified in section 6.3.1.

6.2.4 Quality Assessment

Assessment of study bias was performed by one member of the pCODR Methods Team with input provided by the Clinical Guidance Panel and other members of the pCODR Review Team. SIGN-50 Checklists were applied as a minimum standard. Additional limitations and sources of bias were identified by the pCODR Review Team.

6.2.5 Data Analysis

No additional data analyses were conducted as part of the pCODR review.

6.2.6 Writing of the Review Report

This report was written by the Methods Team, the Clinical Guidance Panel and the pCODR Secretariat:

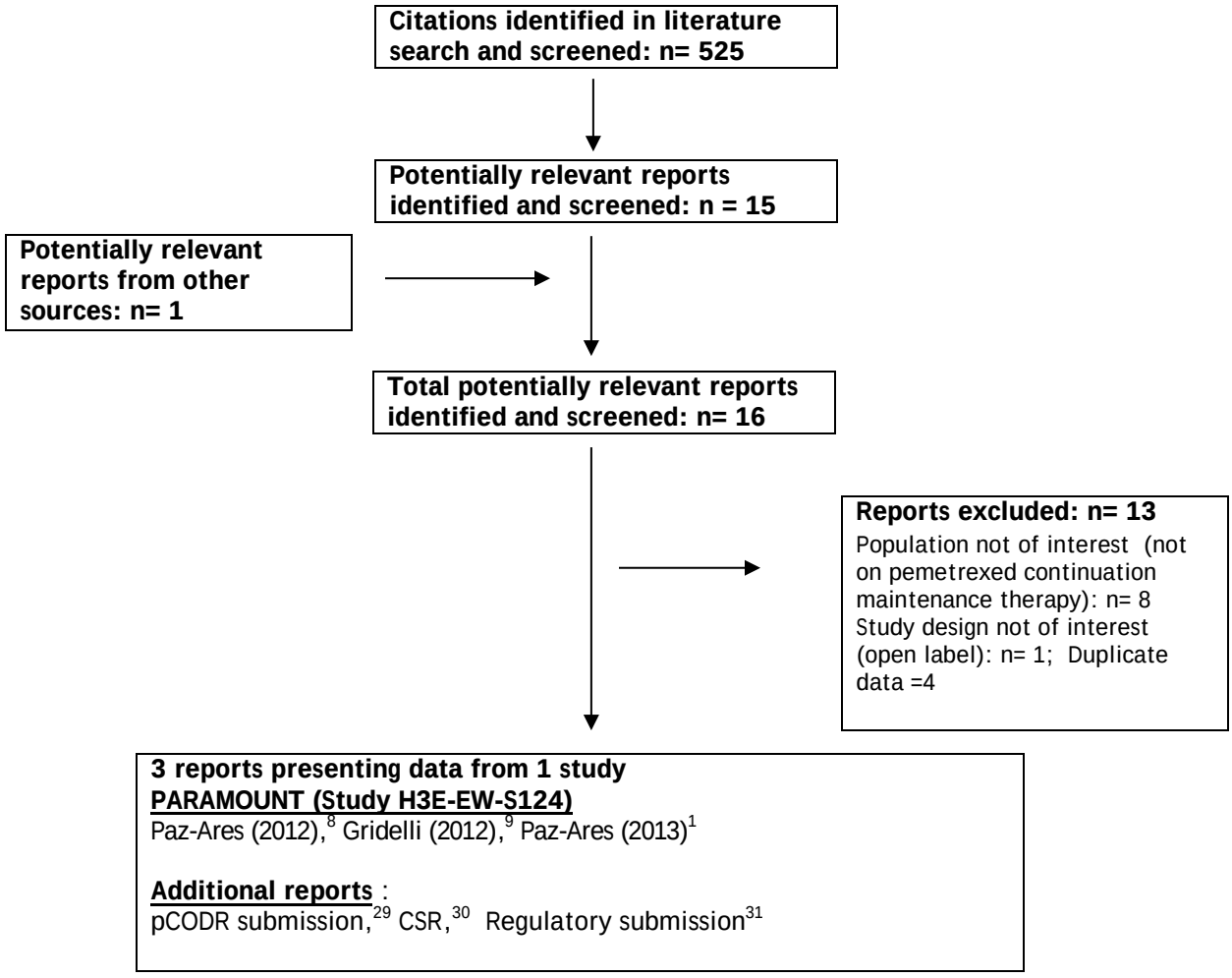
- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions on the net overall clinical benefit of the drug.
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups and by the Provincial Advisory Group (PAG).

6.3 Results

6.3.1 Literature Search Results

Of the 16 potentially relevant reports identified, 3 reports based on one DB RCT (PARAMOUNT) were included in the pCODR systematic review[1,8,9] and 13 reports were excluded.[4,17-28] Studies were excluded because they were not following a first line of pemetrexed plus cisplatin combination therapy, but switch maintenance therapy,[4,18-20,24-27] and one was an open label study,[28] and four abstracts reported the duplicate data of other included studies.[17,21-23]

QUOROM Flow Diagram for Inclusion and Exclusion of studies



6.3.2 Summary of Included Studies

One clinical trial presented in three reports[1,8,9] met the inclusion criteria for this systematic review. The PARAMOUNT (study H3E-EW-S124) was a multinational, multicentre, phase 3, double blind, placebo controlled study of the efficacy and safety of pemetrexed plus best supportive care in patients with locally advanced or metastatic non squamous, non-small cell lung cancer (NSNSCLC) following four cycles of the induction therapy of pemetrexed plus cisplatin and achieved complete response (CR) / partial response (PR) or stable disease (SD). A summary of the trials is presented in Table 3.

The data presented in this review were extracted primarily from the published reports[1,8,9] and additional submission material[29,30] and regulatory submission documents for PARAMOUNT.[31] All outcomes except the final overall survival (OS) were extracted based on the pre-specified trial cut-off date June 30, 2010. The final OS was analyzed on the pre-specified cut-off date on Mar. 5, 2012. Additional data, such as overall AEs, serious AEs at both cut-off data June 30, 2010 and Mar. 5, 2012 are presented. Detail post-discontinuation drug use were provided by submitter at the request of pCODR.[10]

6.3.2.1 Detailed Trial Characteristics

Table 3: Summary of Trial Characteristics of the Included Studies*

Trial Design	Inclusion Criteria	Intervention and Comparator	Outcomes
Paramount (Study H3E-EW-S124)[1,8,9] 19 November 2008 – April 23 June 2010 Phase 3 MC, MN, DB (n = 1022 enrolled total n=939 enrolled in induction phase) **n=539 randomized in MT phase (ITT population)** n = 500 treated (at least one dose of MT) Funded by manufacturer, Eli Lilly and Company	**Inclusion criteria at Randomization (maintenance phase):** ● locally advanced or metastatic NSNSCLC (stage IIIb or Stage IV) ● After completion of 4 cycles of PEM plus CIS IT ● ECOG PS of 0 or 1 ● Documented radiographic evidence of a tumor response of CR, PR, or SD. ● Tumor assessment must have occurred between cycle 4 (day 1) of IT and the date of randomization ● Patients must have started MT no earlier than 21 days and no later than 42 days from Day 1 of the fourth cycle of IT. **(Diagnosis and Main Criteria for Inclusion at induction phase (not randomized):** ● Adult (≥18 years of age) with a NSNSCLC ● Stage IIIB or Stage IV prior to IT that was not amenable to curative therapy ● ECOG PS of 0 or 1 ● No prior systemic chemotherapy for lung cancer. ● Patients with prior radiation therapy were eligible for this study if they met the following guidelines: - Previous radiation therapy was allowed to <25% of the bone marrow but should have been limited and must not have included whole pelvis radiation. - Patients must have recovered from the toxic effects of the treatment prior to study enrollment. - Prior thoracic radiotherapy must have been completed 30 days before study enrollment. ● At least 1 unidimensionally measurable lesion meeting RECIST version 1.0 criteria ● Estimated life expectancy of at least 12 weeks ● Adequate bone marrow reserve, hepatic function, and renal function)	Pemetrexed (500 mg/m^2, IV on day 1 every 21 days) plus BSC vs. placebo plus BSC*	***Primary*** Progression-free survival (investigator assessed) ***Secondary*** • Overall survival Progression-free survival (independent assessesment) • QOL (EQ-5D) • Response rate (CR, PR) (RECIST 1.0) • SAEs • AEs • WDAEs

AE=adverse events; BSC= base supportive care; CR = complete response; DB = double blind; ECOG-PS = Eastern Cooperation Oncology Group performance status; EQ-5D = EuroQol 5-dimensional scale; IT=induction therapy; MC = multicentre; MN = multinational; MT = maintenance treatment; NR = not reported; NSNSCLC = non squamous non-small cell lung cancer; QOL=quality of life; PEM = pemetrexed; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SAE= serious adverse events; SD = stable disease; WDAE = withdrew due to adverse events.
[a] *Best supportive care included analgesics, antiemetic drugs, anti-infective drugs, colony-stimulating factors, erythropoiesis-stimulating agents, transfusions, palliative radiation to extrathoracic structures, and nutritional support) and treatment-related admissions to hospital, etc.*

Data source from references[1,7-11,30]

a) Trials

PARAMOUNT (Study H3E-EW-S124)

PARAMOUNT study was a two-phase clinical trial including induction phase and continuation maintenance phase. Induction phase was a non-randomized phase. The inclusion criteria for induction phase to receive the induction therapy of pemetrexed and cisplatin was presented in Table 3. Briefly, if they met all of the following criteria : Adult patients with a NSNSCLC; Stage IIIB or Stage IV prior to induction therapy that was not amenable to curative therapy; ECOG PS of 0 or 1; Patients had no prior systemic chemotherapy for lung cancer; Patients with prior radiation therapy were eligible for this study if they met the following guideline: Previous radiation therapy was allowed to <25% of the bone marrow but should have been limited and must not have included whole pelvis radiation; Patients must have recovered from the toxic effects of the treatment prior to study enrollment; Prior thoracic radiotherapy must have been completed 30 days before study enrollment; At least 1 unidimensionally measurable lesion meeting Response Evaluation Criteria in Solid Tumours (RECIST version 1.0) criteria; Estimated life expectancy of at least 12 weeks and adequate bone marrow reserve, hepatic function, and renal function.

The PARAMOUNT Study[1,8,9] maintenance phase was a phase 3, multicentre, multinational, double blind placebo controlled study examining the safety and efficacy of pemetrexed (Alimta) continuation maintenance plus best supportive care (BSC) compared with placebo plus BSC in patients with locally advanced or metastatic non squamous non-small cell lung cancer (NSNSCLC) following 4 cycles of first line induction combination treatment of pemetrexed and cisplatin.

The inclusion criteria at randomization includes: 1) after completion of 4 cycles of induction chemotherapy; 2) had Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; 3) documented radiographic evidence of a tumor response of complete response, partial response or stable disease; 4) Tumor assessment must have occurred between cycle 4 (Day 1) of induction therapy and the date of randomization. 5) Patients must have started maintenance therapy no earlier than 21 days and no later than 42 days from day 1 of the fourth cycle of induction therapy.

Nine hundred and thirty nine patients had been enrolled in the induction phase from 83 study centers in 16 countries (Australia, Belgium, Canada, Finland, France, Germany, Greece, India, Italy, The Netherlands, Poland, Portugal, Romania, Spain, Turkey, and the United Kingdom) between Nov 19, 2008 and April 23, 2010. Five hundred and thirty nine patients were randomized in the maintenance phase into pemetrexed plus BSC (n=359) and placebo plus BSC (n=180) (ratio 2:1, block of three). A total of 500 patients had received at least one dose of pemetrexed (N= 333, in pemetrexed, and N=167 in placebo). Randomization was stratified for the following 3 prognostic factors: 1). ECOG PS just prior to randomization (0 versus 1); 2) Tumor response to induction chemotherapy (CR/PR versus SD) and 3) disease stage prior to administration of induction therapy (IIIB versus IV).[30] Maintenance therapy continued until the patient met one of the prespecified reasons for discontinuation: investigator, patient, or sponsor decision; patient required treatment with another therapeutic agent; patient had evidence of disease progression; patient became pregnant or failed to use adequate birth control; patient was noncompliant with study procedures; patient had 2 dose reductions and experienced an adverse event (AE) requiring a third dose reduction; and patient could not receive study treatment within 42 days of the beginning of the previous cycle.[30]

The primary outcome was PFS. PFS was measured from the date of randomization to the first date of objective progression disease (PD) or of death from any cause. Patients not known to have died or progressed at the data cut-off date were censored at the last objective progression-free assessment date. Though an independent review of PFS was conducted, investigator assessment of radiological data was considered primary analysis for PFS. The Secondary outcomes included OS, QOL and tumor response rate. OS was measured from the date of randomization to the date of death from any cause. Patients who had not died at the cut-off date were censored at the last contact date. Patients rated their present health condition using the standardised EuroQol 5-

dimensional scale (EQ-5D) at baseline, on day 1 of every cycle of induction and maintenance therapy, and at the 30-day post-discontinuation visit. EQ-5D data were converted into a weighted health-state index score using UK-based weights since most of the patients were enrolled at sites in Europe.[32]. A visual analogue scale (VAS) that allowed patients to rate their present health condition was also reported. Objective tumor responses to maintenance therapy were measured by both investigator and independent reviewer and recorded using the RECIST guidelines version 1.0.

b) Populations

The patient characteristics are comparable between pemetrexed treatment arm and placebo arm.[1,8,9] (See table 4). Median age was 61 to 62 years. 34% to 38% were 65 years old or older. The female and male were 44% and 56%, respectively, in the pemetrexed group. The majority of the patients were Caucasian and ever smokers, had a diagnosis of adenocarcinoma. 99% patients had an ECOG performance status of ≤1.

Table 4: Baseline Patient Characteristics[1,8,9]

	Pemetrexed n=359	Placebo N=180
Male, n (%)	201 (56)	112 (62)
Age, median years (range)	61 (32-79)	62 (35-83)
Age groups, n (%)		
<65 years	238 (66)	112 (62)
≥65 years	121 (34)	68 (38)
Ethnic origin, n (%)		
Asian	16 (4)	8 (4)
African	4 (1)	1 (<1)
White	339 (94)	171 (95)
ECOG PS performance status, n (%)		
0	115 (32)	55 (31)
1	243 (68)	123 (68)
2–3*	1 (<1)	2 (1)
Smoking status, n (%)		
Ever smoker	275 (77)	144 (80)
Never smoked	82 (23)	34 (19)
Unknown	2 (<1)	2 (1)
Disease stage before maintenance therapy†, n (%)		
Stage IIIB	31 (9)	19 (11)
Stage IV	328 (91)	161 (89)
Histologic subtype, n (%)		
Bronchoalveolar	6 (2)	2 (1)
Adenocarcinoma	304 (85)	158 (88)
Large-cell carcinoma	24 (7)	12 (7)
Other or indeterminate¶	25 (7)	8 (4)
Time from start of induction therapy to randomisation (mos)		
Median (range, mos)	2.96 (2.14–4.14)	2.96 (2.53–3.71)
Best tumour response to induction therapy		
Complete or partial response	166 (46)	76 (42)
Stable disease	186 (52)	94 (52)
Progressive disease*	1 (<1)	3 (2)
Unknown*	6 (2)	7 (4)

ECOG = Eastern Cooperative Oncology Group; NS NSCLC = non squamous non-small cell lung cancer; mos= months; MTX=maintenance therapy; NSCLC=non-small-cell lung cancer; PS = performance status.

*Randomised patients with an ECOG PS of 2 or 3, or a best response to induction therapy of progressive disease or unknown were considered protocol violations.
†Lung Cancer Staging Guidelines, Version 5.22
¶Represents patients with a primary diagnosis of NSCLC whose disease did not clearly qualify as adenocarcinoma or large-cell carcinoma and includes NSCLC not otherwise specified, poorly differentiated, and adenocarcinoma, mucinous.

c) Interventions/comparators

During the induction phase, patients were treated with intravenous pemetrexed (500 mg/m²) and intravenous cisplatin (75 mg/m²) on day 1 of a 21-day cycle for four cycles. This phase was followed by a maintenance phase in which eligible patients were randomly assigned to receive intravenous pemetrexed (500 mg/m²) plus best supportive care or placebo (intravenous 0·9% sodium chloride) plus best supportive care, both on day 1 of a 21-day cycle. Maintenance treatment began 7 days or less from the date of randomisation and 21–42 days from day 1 of the fourth cycle of induction therapy. Maintenance therapy was continued until disease progression, unacceptable adverse events, or decision of the patient or physician. Patients were followed up until death or study closure.

BSC was defined as treatment without a specific antineoplastic regimen, given with the intent to maximize QOL, as determined by the treating physician. It included analgesics, antiemetic drugs, anti-infective drugs, colony-stimulating factors, erythropoiesis-stimulating agents, transfusions, palliative radiation to extrathoracic structures, and nutritional support and treatment-related admissions to hospital, etc. BSC specifically excluded anticancer surgery, immunotherapy, radiation to intrathoracic structures, anticancer hormonal therapy, and systemic chemotherapy in which the goal was to either eradicate or slow disease progression. During both periods of the study, treatment (both pemetrexed and placebo) was fully supplemented with folic acid, vitamin B12, and prophylactic dexamethasone as per the pemetrexed label.[9] As of the most recent study cut-off date (March 5, 2012), the mean number of maintenance cycles was 7.9 (range, one to 44) for pemetrexed and 5.0 (range, one to 38) for placebo.

d) Patient Disposition

The trial started with the induction phase on 19 November 2008. 939 patients were enrolled into induction phase. 539 eligible patients were randomized into maintenance phase after finishing the induction phase (359 and 180 in Pemetrexed and placebo, respectively). The last patient completed entire study, study ongoing and data cut-off for the trial was 30 June 2010. Table 5 below outlines these populations and provides information on the disposition. 62% in Pemetrexed and 76% in placebo discontinued based on prespecified criteria for discontinuation. 38% in Pemetrexed and 24% in placebo were receiving ongoing maintenance treatment on the cut-off date for the trials. 58% patients from pemetrexed and 64% from placebo arm at the end of the trial (cut-off date June, 30, 2010) received post-discontinuation subsequent systematic anticancer treatment (Table 5) post-discontinuation chemotherapy (PDC) was given at the discretion of the investigator. A similar proportion of patients in both groups received post-discontinuation therapy. 217 patients had not received post-discontinuation therapy at the time of this analysis; 179 (82%) of these patients were still receiving maintenance treatment at this time. At the cut-off date Mar. 5, 2012, 64 % patients from pemetrexed and 72 % from placebo arm received post-discontinuation subsequent systematic anticancer treatment. The two most common used anticancer agents for PDC were erlotinib (39.6% for pemetrexed; 43.3% for placebo as of March 5, 2012 cut-off) and docetaxel (32.3% for pemetrexed; 43.3% for placebo as of March 5, 2012 cut-off). Other common agents included gemcitabine (10.0% for pemetrexed; 8.3% for placebo as of March 5, 2012 cut-off) and vinorelabine (7.8% for pemetrexed; 6.1% for placebo as of March 5, 2012 cut-off).[1,10] At the end of cut-off date June 30, 2010, 25% in pemetrexed arm and 34% in placebo arm received one regimen. 6% in pemetrexed arm and 8% in placebo arm received more than one regimen PDC. At the end of cut-off date Mar. 5, 2012, 41 % in both pemetrexed arm and placebo arm received one regimen. 22% in pemetrexed arm and 28% in placebo arm received more than one regimen PDC.[10] The reason for those patients who did not receive the PDC

includes no other systemic treatment options available; Physician perception that subject would not tolerate additional systemic treatment due to subject's poor performance status or unresolved toxicity or not benefit from additional systemic treatment; Subject refused additional systemic treatment; subject died prior to initiation of additional planned systemic treatment and unknown reason.(see Table 6)

Table 5: Patient Disposition[1,8,9]

	Cut-off date: June 30, 2010		Cut-off date: Mar. 5, 2012	
	PEM + BSC	PBO + BSC	PEM + BSC	PBO + BSC
Patient enrolled	1022			
Patient enrolled into induction phase	939			
Patient enrolled into maintenance phase	359	180	359	180
Efficacy population (ITT)	359	180	359	180
Harms population (ITT)	359	180	359	180
Patients treated (total 500)	333	167	333	167
Ongoing tx on cutoff date, n (%)*	136 (37.9)	43 (23.9)	9 (3)	2(1)
Discontinued, n (%)	223 (62.1)	137 (76.1)	350(97)	178(99)
Adverse events	33 (9.2)	7 (3.9)	65(18)	12 (7)
Progressive disease	162 (45.1)	117 (65.0)	249(69)	152(84)
Total Death	7 (1.95)	3 (1.7)	256 (71)	141 (78)
Death due to NSNSCLC	4 (1.1)	1 (0.6)	3 (0.8)	1 (0.6)
Death due to study drug	1 (0.3)	1 (0.6)	1 (0.3)	2 (1)
Death due to AEs	2 (0.6)	1 (0.6)	4(1)	1(0.6)
Patients decision	16 (4.5)	6 (3.3)	21(6)	8(4)
Investigators decision	3 (0.8)	4 (2.2)	3(0.8)	2(1)
Other (protocol entry criteria not met, lost to follow-up)	2 (0.6)	0 (0)	4(1)	0(0)

BSC = best supportive care; ITT = intention –to-treat; MTX=maintenance treatment; NSNSCLC = non squamous non-small cell lung cancer; PEM=pemetrexed; pbo=placebo; tx = treatment

Data source from figure 1 in reference[8] and figure 1 in reference 1
% in cut-off June 30, 2010[33] was calculated by Methods Team

The median time from induction to randomization was 2.96 months in both arms.

Table 6: Summary of patient that did not received post-discontinuation Chemotherapy (PDC)

Patients that did not receive PDC	Cut-off date June 30, 2010		Cut-off date March 5, 2012	
	PEM plus BSC (N=359) n (%)	PBO Plus BSC (N=180) n (%)	PEM plus BSC (N=359) n (%)	PBO Plus BSC (N=180) n (%)
Patients that did not receive PDC	243 (67.7)	102 (56.7)	128 (35.7)	51 (28.3)
Reasons why did not receive PDC				
No other systemic treatment options available	3 (0.8)	3 (1.7)	13 (3.6)	5 (2.8)

Table 6: Summary of patient that did not received post-discontinuation Chemotherapy (PDC)				
Patients that did not receive PDC	Cut-off date June 30, 2010		Cut-off date March 5, 2012	
	PEM plus BSC (N=359) n (%)	PBO Plus BSC (N=180) n (%)	PEM plus BSC (N=359) n (%)	PBO Plus BSC (N=180) n (%)
Physician perception that subject would not tolerate additional systemic treatment due to subject's poor performance status	10 (2.8)	7 (3.9)	18 (5.0)	13 (7.2)
Physician perception that subject would not tolerate additional systemic treatment due to unresolved toxicity	0	0	2 (0.6)	0
Physician perception that subject would not tolerate additional systemic treatment due to other reasons	4 (1.1)	0	6 (1.7)	1 (0.6)
Physician perception that subject would not benefit from additional systemic treatment	3 (0.8)	2 (1.1)	7 (1.9)	3 (1.7)
Subject refused additional systemic treatment	5 (1.4)	3 (1.7)	14 (3.9)	7 (3.9)
Subject died prior to initiation of additional planned systemic treatment	12 (3.3)	6 (3.3)	20 (5.6)	12 (6.7)
Still on study treatment	136 (37.9)	43 (23.9)	9 (2.5)	2 (1.1)
No record present for reason not done	70 (19.5)	38 (21.1)	39 (10.9)	8 (4.4)
PDC= post-discontinuation chemotherapy				

Data source: data received from manufacturer on Aug. 9, 2013[10]

e) Limitations/Sources of Bias

The PAROMOUNT study was a double blind RCT conducted in multiple-nation, multiple-center. Allocation concealment, Intention to treat analysis were well described. Randomization was stratified by ECOG PS (0 vs. 1); baseline cancer stages (stage IIIB vs. stage IV) and induction phase response (CR/PR vs. SD). However, some key limitations are described below:

- Population: The patients included in this study were limited to P S 0 and 1. Performance status is a well-established prognostic factor in advanced NSCLC. Consequently, the beneficial effects of pemetrexed may have been overestimated among a study population with better survival probabilities than typically seen in practice. Therefore, whether the findings in this study could be generalizable to all NSNSCLC population included PS greater than one is unclear.
- Intervention and comparator: no active comparator: such as PEM continuation maintenance vs. non –PEM anti-tumor switch continuation following PEM plus cisplatin induction therapy.
- Outcomes: Confounding factor: Final OS could be cofounded by post-discontinuation chemotherapy. At the cut-off date March 5, 2012, 64% patients in pemetrexed arm and 72% in placebo arm received post-discontinuation chemotherapy. Most patients received erlotinib or docetaxel, therefore, after June 30, 2010, there is an uncertainty as to the effect on OS of pemetrexed vs. placebo. Quality of life (QOL) was not analysed with ITT population. 46.2% (163 of 359 patients completed the required QOL questionnaire at each of their visits) for the pemetrexed arm and 44.1% (79 of 180 patients completed the required QOL questionnaire at each of their visits) for the placebo arm. According to clinical guidance panel, the QOL of patients receiving chemotherapy usually gets worse; therefore, the findings of QOL could be

biased in favor of pemetrexed arm due to a high percentage of non-compliance in completing questionnaire. In addition, the response rate analysis was based on the evaluable patients population in which the patients died was not included. Therefore, the response effect could be potentially overestimated.

- When PFS is used as a primary endpoint in pivotal studies and OS as a secondary endpoint, the issues are as follows: 1). PFS has not been validated as surrogate endpoint for OS either in first line treatment or as maintenance therapy of advanced NSCLC. No detailed meta-analysis is available on surrogacy of PFS for OS with first line platinum based combination in the literature;[34] 2) PFS data are follow up schedule dependent[34] PFS data was based on the cut-off date was June 30, 2010.[8] however, the final overall survival was based on the cut-off date was March 5, 2012.[1] 3) When PFS is used as an endpoint, it neglects the impact of therapy on subsequent effective therapies after progression. Prolonged side effect of maintenance therapy may prohibit the use of subsequent standard second line therapy. Nevertheless, pCODR CPG indicated that there is debate among clinicians whether PFS is considered as a validated surrogate outcome for OS.
- Difference across study sites was not reported. The participants of the study PARAMOUNT were from Europe. The findings from this study might have a potential generalizable issue to Canadian practice.
- The RCT was funded by the manufacturer. The manufacturer in collaboration with the trial investigators designed the study, collected data and interpreted the results.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

The key results are presented in Table 7 and Table 8 below according to the hierarchy of outcomes established in the systematic review protocol (section 6.2.1).

Table 7 : Summary of Key results

	PEM + BSC N=359	PBO + BSC N=180
OS: Cutoff date March 5, 2012		
Final OS†, median (95% CI) months (from randomization)	13.9 (12.8 - 16.0)	11.0 (10.0 -12.5)
Final OS median Tx difference (PEM – placebo) (mos)	2.9 (95%CI: NR, P = 0.0195)	
Final OS-HR from randomization (95% CI)	0.78 (0.64-0.96) P =0.0199	
Survival rate (%) (95%CI]		
1 - year	58 (53 - 63) P = 0.0062 (PEM vs. Pbo)	45 (38 - 53)
2 - year	32 (27 - 37) P = 0.0103 (PEM vs. Plb)	21 (15 - 28)
OS HR subgroup		
OS HR sub: CR+PR (n=234) (unadjusted)	0.81 (0.59 - 1.11) P = 0.194	
OS HR sub: SD (n=285) (unadjusted)	0.76 (0.57 - 1.01) P = 0.0575	
PFS: Cut-off date: June 30, 2010 (Primary endpoint)		
PFS†, median (95% CI) months (assessed by investigator)	4.1(3.2 - 4.6)	2.8 (2.6 - 3.1)
PFS HR (95%CI) (assessed by investigator)	0.62 (0.49-0.79) P<0.0001 PEM vs. pbo	
QOL Change from baseline[9] (cutoff date: June 30, 2010)		
EQ-5D index score during Mtx phase at cycle 6	-0.02	0.04

Table 7 : Summary of Key results		
	PEM + BSC N=359	PBO + BSC N=180
	P = 0.05	
VAS at cycle 5	0.69 (P = 0.01 PEM vs. pbo)	6.15
VAS at cycle 6	1.55 (p = 0.044, PEM vs. pbo)	5.99
Response rate: cut-off date: June 30, 2010		
Overall response rate‡, n (% [95% CI])	9 (3 [1.3 -5.3])	1 (0.6 [0.02 - 3.5])
Complete response	0	0
Partial response (during MTX)	9 (3 [1.3-5.3])	1 (0.6 [0.02 - 3.5])

AE= adverse event; CI = confidence interval; CR=complete response; EQ-5D= EuroQol 5-dimensional questionnaire; HR=hazard ratio; mos = months; NR=not reported; NS: not statistically significant; OS = overall survival; PEM = pemetrexed; PBO = Placebo; PR=partial response; QOL=quality of life; SAE = serious adverse event; SD=stable disease; VAS = visual analog scale; WDAE = withdrawal due to adverse event

† Kaplan-Meier method

‡ Response rates were calculated based on the number of evaluable patients

Data source: references[8-11,30]

Table 8 : Summary of key adverse events				
	Cut-off date: June 30, 2010		Cut-off date: Mar. 5, 2012	
All-cause mortality, n(%)	7 (2)	3(1.7)	256 (71)	141 (78)
Overall SAEs (≥1 SAE) n(%)	68 (18.9)	22 (12.2)	90 (25.1)	26 (14.4)
AEs (pts with ≥1 AE), n(%)	246 (68.5)	103 (57.2)	294 (81.9)	121 (67.2)
Fatigue	79 (22.0)	22 (12.2)	111 (30.9)	26 (14.4)
Anemia	61 (17.0)	10 (5.6)	90 (25.1)	11 (6.1)
Neutropenia	32 (8.9)	1 (0.6)	43 (12.0)	1 (0.6)
Leukopenia	14 (3.9)	0	19 (5.3)	0
Thrombocytopenia	12 (3.3)	1 (0.6)	20 (5.6)	0
Hospitalizations (≥ 1)	69 (19.2)	32 (17.8)	89 (24.8)	36 (20.0)
Pain (other than Pulmonary Pain)	80 (22.3)	39 (21.7)	104 (29.0)	45 (25.0)
Pulmonary Pain	16 (4.5)	8 (4.4)	24 (6.7)	11 (6.1)
WDAEs, n(%)	33(9.2)	7(3.7)	65(18)	12(7)

AE= adverse event; CI = confidence interval; CR=complete response; EQ-5D= EuroQol 5-dimensional questionnaire; HR=hazard ratio; mos = months; NR=not reported; NS: not statistically significant; OS = overall survival; PEM = pemetrexed; PIb = Placebo; PR=partial response; QOL=quality of life; SAE = serious adverse event; SD=stable disease; VAS = visual analog scale; WDAE = withdrawal due to adverse event

† Kaplan-Meier method

‡ Response rates were calculated based on the number of evaluable patients

Efficacy Outcomes

Overall survival

Overall survival (OS) time was defined as the time from the date of randomization to the date of death from any cause. For patients not known to have died as of the data cut-off date, OS was censored at the last contact date (last contact for patients in post-discontinuation period or last known alive date in mortality status).[30] A prespecified interim analysis of overall survival after 123 deaths (77 of 359 patients in the pemetrexed group; 46 of 180 in the placebo group), with censoring rates of 79% (282 of 359 patients) in the pemetrexed group and 74% (134 of 180) in the placebo group. At the cut-off date of June 30, 2010, the results of the preliminary (interim) survival analysis were immature and did not meet the predefined level of statistical significance (p>0·0001). The final analysis of OS was performed in March 2012 (but it was pre-specified and scheduled in the fourth quarter of 2012) and based on a nominal alpha level of 0.0498)

After 397 deaths (pemetrexed, 71%; placebo, 78%) and a median follow-up of 24.3 months for alive patients (95% CI, 23.2 to 25.1 months), pemetrexed therapy resulted in a statistically significant 22% reduction in the risk of death. (HR, 0.78; 95% CI, 0.64 to 0.96; P=0.0195; the overall survival (OS) median were 13.9 months [12.8 to 16.0] and 11.0 [10.0 to 12.5] in pemetrexed and placebo arm respectively. The treatment difference was 2.9 mos, (P =0.0195) (Table 9).[1]

Patients with complete or partial response to the induction therapy (n = 234) achieved a numerical higher OS (HR, 0.81; 95% CI, 0.59 to 1.11) compared patients with stable disease (n = 285) OS (HR, 0.76; 95% CI, 0.57 to 1.01). Patients with ECOG performance score 1 (prior to randomization) had a numerical higher OS (HR, 0.82) compared patients with ECOG score 0 (0.70). Patients with stage III B prior to administration of induction therapy and patient with stage IV achieved a similar OS (0.82 and 0.79 respectively). Overall survival on pemetrexed was consistently improved for all prespecified patient subgroup analyses (Table 10).

Table 9 : Summary of Overall survival[1,8,9]

	PEM + BSC N = 359	PBO + BSC N = 180
OS†, median (95% CI) months (from randomization)		
Cut-off of June 30, 2010		
Interim analysis:	NE*	NE*
Cut-off of Mar. 5, 2012		
Overall survival†, median (95% CI) months (from randomization)	13.9 (12.8-16.0)	11.0 (10.0-12.5)
OS Tx median difference (PEM – PBO) (mos)	2.9 (P=0.0195)	
Unadjusted OS-HR from randomization[1]	0.78 (0.64 - 0.96) P =0.0199	
Survival rate (%) [95%CI][1,8]		
cut-off date: June 30, 2010		
Interim analysis Survival with high censoring rates	78.6% (NS. PEM vs. PBO)	74.4%
Cut-off date: March 5, 2012		
1 - year	58 (53 – 63)	45 (38 – 53)
2 - year	32 (27 – 37)	21 (15 – 28)
Overall survival†, median [95% CI] months (from induction)	16.9 (15.8 - 19.0)	14.0 (12.9 - 15.5)
Unadjusted OS-HR from induction	0.78 (0.64 - 0.96) P = 0.0191	

BSC = best supportive care; CI = confidence interval; NE= not estimable; NR=not reported; OS = overall survival; PBO=placebo; PEM=pemetrexed; TX = therapy

† A nominal 2-sided alpha level of 0.0498 was used for the analysis of OS

* The results of the preliminary (interim) survival analysis did not meet the predefined level of statistical significance (p>0.0001).

Table 10 : Overall survival hazard ratios (pemetrexed over placebo) in subgroups according to baseline characteristics		
Subgroups	n	Hazard Ratio* (PEM + BSA vs. pbo + BSA
Cut-off date: June 30, 2010	539	NR
Cut-off date: March 5, 2012		
All randomly assigned patients	539	0.78
Stage*		
IV	490	0.79
IIIB	49	0.82
Induction Response*		
CR/PR	234	0.81 (0.59 – 1.11)
SD	285	0.76 (0.57 – 1.01)
Pre–random assignment ECOG PS*		
1	363	0.82
0	173	0.70
Smoking history		
Nonsmoker	117	0.75
Smoker	418	0.83
Sex		
Male	313	0.82
Female	226	0.73
Age, years		
< 70	447	0.75
≥ 70	92	0.89
< 65	350	0.82
≥ 65	189	0.71
Diagnosis		
Other histologic diagnosis	32	0.81
Large-cell carcinoma	36	0.44
Adenocarcinoma	471	0.80

CR/PR= complete tumor response/partial tumor response; ECOG PS, Eastern Cooperative Oncology Group performance status; PEM=pemetrexed; PBO=placebo; SD=stable disease.
*Prespecified and randomization stratified subgroups.

Data source: ref 1, fig. 3.

Progression-free survival

Progression-free survival (PFS) was evaluated at the prespecified cut-off date (June 30, 2010) as primary endpoint of the study. Statistically significant increase in investigator-assessed PFS was reported for patients treated with pemetrexed (unadjusted HR 0.62, 95% CI 0.49 to 0.79; log-rank p<0.0001). The median PFS was 4.1 months (95% CI 3.2 to 4.6) for pemetrexed (175 of 359, 49% censored) and 2.8 months (95% CI 2.6 to 3.1) for placebo (62 of 180, 34% censored). The PFS assessed by radiologists was reportedly similar to that assessed by investigator. (Table 11) An updated PFS was evaluated on Mar. 5, 2012. A statistically significant increase in investigator-assessed progression-free survival (PFS) was reported for patients treated with pemetrexed (unadjusted HR 0·60, 95% CI 0.50 to 0.73; log-rank p<0.001). The median PFS was 4.4 months (95% CI 4.1to 5.7) for pemetrexed and 2.8 months (95% CI 2.6 to 3.0) for placebo. The PFS assessed by radiologists was reportedly similar to that assessed by investigator. The unadjusted HR of 0.60 (95% CI, 0.50 to 0.73; P 0.001) was similar to the HR originally reported: 0.62 (95% CI, 0.49 to 0.79; P0.001).(Table 11)

The effect of maintenance treatment with pemetrexed was consistent across all prespecified subgroup analyses based on baseline characteristics (Table 12) and similar to that observed in the primary unadjusted analysis of PFS. A subgroup analysis of investigator PFS data for all randomised patients with an induction response of complete or partial response yielded an statistically significant unadjusted HR of 0.48 (95% CI, 0.34 to 0.67) and a median PFS of 4.1 months (95% CI, 3.1 to 6.0) for the pemetrexed group (n=166) versus 2.6 months (1.6 to 2.9) for

the placebo group (n=76). However, patients with an induction response of stable disease had an unadjusted HR of 0.74 (95% CI, 0.53 to 1.04), median PFS of 4.1 months (95% CI 3.0 to 4.6) for the pemetrexed group (n=186) while that for patients in the placebo group (n=94) was 3.0 months (2.8 to 4.1). Patient diagnosed with adenocarcinoma had a statistically significant unadjusted HR of 0.62 (95% CI, 0.49 to 0.80), but, unadjusted PFS HR is not statistically significant in patients with large cell carcinoma (HR of 0.62, 95% CI, 0.49 to 0.80).

Table 11 : Summary of PFS[1,8,9]

	Cut-off date: June 30, 2010		Cut-off date: March 5, 2012	
	PEM + BSC N=359	PBO + BSC N=180	PEM + BSC N=359	PBO + BSC N=180
PFS†, median [95% CI] months (assessed by investigator)	4.1[3.2-4.6]	2.8 [2.6-3.1]	4.4[4.1- 5.7]	2.8 [2.6-3.0]
PFS HR (95%CI) (assessed by investigator)	0.62 (0.49-0.79) P<0.0001 PEM vs. PBO		0.60 (0.50-0.73) P<0.001 PEM vs. PBO	
PFS†, median [95% CI] months (assessed by radiologists)	3.9 [3.0-4.2]	2.6 [2.2-2.9]	NR	NR
PFS HR (95%CI) (assessed by radiologists)	0.64 (0.51-0.81) P<0.00025 PEM vs. PBO		NR	

CI = confidence interval; HR = Hazard ratio; NR = not reported; PBO = placebo; PEM = pemetrexed; PFS = progression-free survival

† Kaplan-Meier method

Table 12 Progression-free survival HRs in pre-specified subgroups according to baseline characteristics as assessed by investigator

Cut-off date: June 30, 2010	N	PFS HR (95% CI) (PEM vs. PBO)
All	539	0.62 (0.49 - 0.79)
Baseline stage		
IIIB	50	0.55 (0.24 – 1.26)
IV	489	0.62 (0.49 – 0.80)
Induction response		
CR/PR	242	0.48 (0.34 – 0.67)
SD	280	0.74 (0.53 – 1.04)
Pre-randomization ECOG PS		
0	170	0.53 (0.35 – 0.79)
1	366	0.67 (0.50 – 0.90)
Smoking status		
Non-smoker	116	0.41 (0.24 – 0.71)
Smoker	419	0.70 (0.53 – 0.90)
Sex		
Male	313	0.74 (0.55 – 1.00)
Female	226	0.49 (0.34 – 0.72)
Age (years)		
<65	350	0.70 (0.53 – 0.94)
≥65	189	0.51 (0.34 – 0.75)
Histology		
Adenocarcinoma	471	0.62 (0.49 – 0.80)
Large cell carcinoma	36	0.39 (0.14 – 1.07)
Other	32	0.64 (0.22 – 1.89)
Cut-off date: Mar. 5, 2010	NR	

HR=hazard ratio; CR = complete response; ECOG PS=Eastern Cooperative Oncology Group performance status; PBO=placebo; PEM=pemetrexed; PFS = progression-free survival; PR = partial response; SD = stable disease.

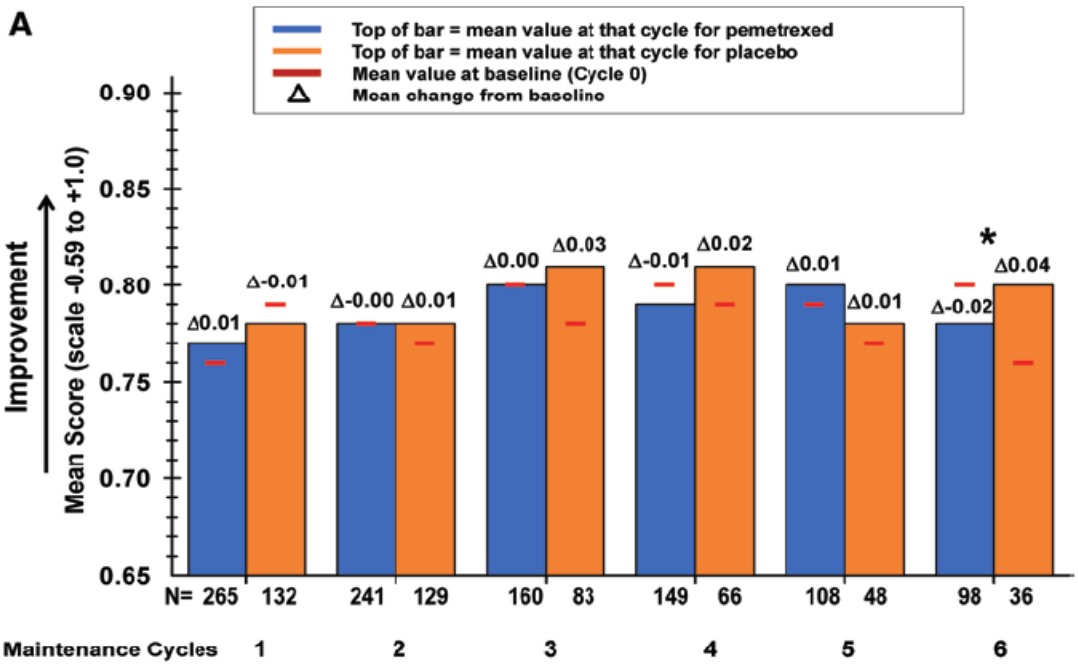
Data source: reference[8]

Quality of life

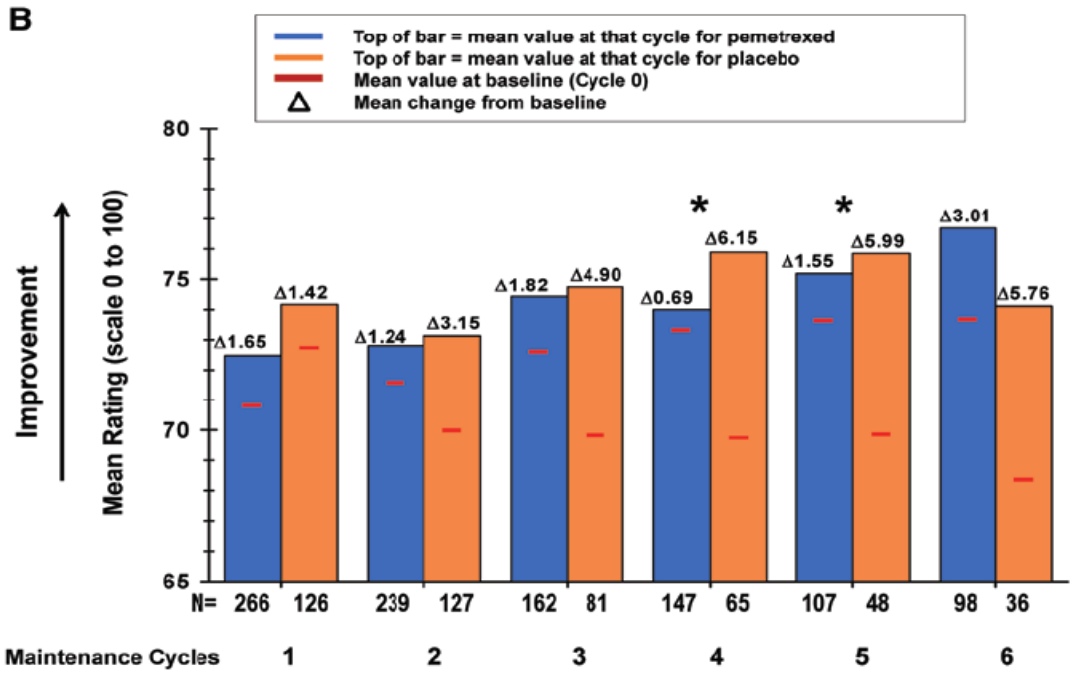
Quality of life (QOL) was evaluated with EQ-5D. The compliance of participating the QOL survey during the maintenance treatment was 46.2% (163 of 359 patients completed the EQ-5D questionnaire at each of their visits) for the pemetrexed arm and 44.1% (79 of 180 patients) for the placebo arm. For the post-discontinuation visit, 43.9% of patients in the pemetrexed and 44.3% of patients in the placebo arm completed the EQ-5D questionnaire. The most commonly reported reason for not completing the EQ-5D was failure by the investigative site to administer the questionnaire.[9] In the comparison of treatment differences using a paired t test, statistically significant differences were observed between the pemetrexed and placebo arms in mean changes from baseline on the index score at cycle 6 (pemetrexed: −0.02, placebo: 0.04, p = 0.050; see Fig. 2A) and the VAS rating at cycle 4 (pemetrexed: 0.69, placebo: 6.15, p = 0.010) and cycle 5 (pemetrexed: 1.55, placebo: 5.99, p = 0.044; Fig. 2B). However, the changes from baseline were not clinically relevant according to the minimally important differences (MIDs) for lung cancer (0.08 for the U.K. population-based index score and 7 for the VAS score) determined by Pickard and colleagues.[35] The MID is defined as the smallest change in a patient-reported outcome measure that is perceived by patients as beneficial or that would result in a change in treatment.[35] No statistically significant differences were observed between treatment arms after cycle 6.At the discontinuation visit, the index score decreased from baseline for patients in both treatment arms. The index score of the pemetrexed arm was 0.77 at baseline and 0.66 at discontinuation (p<0.001) and 0.79 at baseline and 0.70 at discontinuation (p=0.022) for placebo.[9]

The VAS scores indicated an increasing trend toward "best-imaginable health state" with some significant increases from baseline at various time points. However, at discontinuation, patients receiving pemetrexed reported a significant decrease in health state compared to baseline. Patients receiving placebo experienced a similar decrease at discontinuation.[9]

Overall, the EQ-5D index scores and VAS scores suggested that patients treated with pemetrexed did not experience worse health states over the course of maintenance therapy compared to patients treated with placebo (see Figure 1).[9]



*p ≤0.05, comparing the difference in mean changes from baseline between treatment arms
Note: At each cycle, patients with both baseline & post-baseline data are included. Thus, the denominators and mean baseline values shown represent only those patients with both baseline & post-baseline data at that cycle, which varies across cycles.



*p ≤0.05, comparing the difference in mean changes from baseline between treatment arms
Note: At each cycle, patients with both baseline & post-baseline data are included. Thus, the denominators and mean baseline values shown represent only those patients with both baseline & post-baseline data at that cycle, which varies across cycles.

Figure 1: A, EQ-5D U.K. population-based index score during maintenance: all randomized patients. B, EQ-5D VAS rating during maintenance: all randomized patients. EQ-5D= EuroQol 5-dimensional questionnaire; VAS= visual analog scale.

Source: reference[9]

Time to progression, time to deterioration of symptoms, and time to salvage treatment

There was no information reported for time to progression, time to deterioration of symptoms, and time to salvage treatment.

Response rate to the maintenance treatment

Tumor responses (complete response [CR], partial response [PR]) to maintenance therapy were measured and recorded using the Response Evaluation Criteria In Solid Tumors (RECIST) guidelines version 1.0. A greater proportion of patients receiving pemetrexed achieved disease control (complete or partial response, or stable disease lasting ≥6 weeks) than did those receiving placebo when assessed by the independent reviewer (Table 13). The response analysis was based on the evaluable patients population in which the patients died was not included. Therefore, the response effect could be potentially overestimated.

Table 13 : Summary of response rate[8]

Cut-off date: June 30, 2010	PEM + BSC N=359	PBO + BSC N=180
Overall response*, n (% [95% CI])	9 (3 [1.3 - 5.3])	1 (0.6 [0.02 - 3.5])
Complete response	0	0
Partial response	9 (3 [1.3 - 5.3])	1 (0.6 [0.02 - 3.5])
Stable	219 (69 [63.6 -74·1]) P = 0.039	92 (59 [50.8 – 66.8])
Disease control rate† % (95% CI)	72(66.5 -76.7) P =0.0009 (PEM vs. PBO)	60 (51.5 – 67.4)

BSC = best supportive care; CI = confidence interval; CR = complete response; NR = not reported; PEM = pemetrexed; Pbo = placebo; PR = partial response

* Response rates were calculated based on the number of evaluable patients,

† Disease control rate includes complete response, partial response or stable disease lasting a minimum of 6 weeks

Harms Outcomes

All-cause mortality

During maintenance therapy, as of the cut-off date of June 30, 2010, of all randomized patients (N = 539), ten on-study deaths occurred.(Table 5) Of these, 5 were attributed to progressive disease (PD, 4 in the pemetrexed arm and 1 in the placebo arm). Of the remaining 5 deaths, 2 were possibly related to study drug (1 AE of pneumonia in the pemetrexed arm and 1 AE of sudden death in the placebo arm; there were 3 additional deaths within 30 days of last study dose administered (1 in the pemetrexed arm and 2 in the placebo arm). The cause of death for the majority of the patients listed as disease progression.[30] At the cut-off March, 5, 2012, 256 and 141 deaths had occurred in pemetrexed and placebo group respectively.[1] (Table 5)

Serious adverse events

The main SAEs regardless of causality during the maintenance treatment of the patients are presented in Table 14. The most frequently reported serious adverse events were anaemia, febrile neutropenia and pneumonia. At cut-off date June 30, 2010, in the pemetrexed group, 2.5% patients experienced serious anemia; 1.7% patients had serious febrile neutropenia and 1.4% had pneumonia. At the cut-off data March 5, 2012, serious anemia, serious febrile neutropenia and serious pneumonia occurred in 3.1%, 1.7 and 1.4% of patients in pemetrexed group respectively. 0.6% patients in the placebo arm suffered from serious pneumonia in both cut-off dates. No patients in the placebo group reported anemia or febrile neutropenia.

Table 14 Summary of Selected Serious Adverse Events (Maintenance Treatment) All Randomized Patients Regardless of Causality				
	Cut-off date June 30, 2010		Cut-off date March 5, 2012	
Preferred Term	**PEM plus BSC (N=359) n (%)**	**PBO Plus BSC (N=180)n (%)**	**PEM plus BSC (N=359)n (%)**	**PBO Plus BSC (N=180)n (%)**
Patients with at ≥ 1 SAE	68 (18.9)	22 (12.2)	90 (25.1)	26 (14.4)
Anemia	9 (2.5)	0	11 (3.1)	0
Febrile Neutropenia	6 (1.7)	0	6 (1.7)	0

BSC = best supportive care; N = total number of patients; n = number of patients in each category; PBO=placebo; PEM=pemetrexed; SAE = serious adverse event.

Data source: Received from manufacturer on Aug. 9, 2013[10]

Adverse events

A brief overview of AEs in the maintenance treatment is reported in Table 17. The safety reporting period includes the study therapy and within 30 days of discontinuation from study therapy. A significantly higher percentage of patients in the pemetrexed arm experienced adverse event compared with placebo except constipation and neuropathy sensory, which occurred more often in placebo than pemetrexed arm (Table 15).

Table 15: Summary of Selected Adverse Events (at least 5% by preferred term during maintenance treatment) All Randomized Patients Regardless of Causality				
	Cut-off date June 30, 2010		Cut-off date March 5, 2012	
Preferred Term	**PEM plus BSC (N=359) n (%)**	**PBO Plus BSC (N=180) n (%)**	**PEM plus BSC (N=359) n (%)**	**PBO Plus BSC (N=180) n (%)**
Patients with at ≥ 1 AE	246 (68.5)	103 (57.2)	294 (81.9)	121 (67.2)
Key AEs				
Fatigue	79 (22.0)	22 (12.2)	111 (30.9)	26 (14.4)
Anemia	61 (17.0)	10 (5.6)	90 (25.1)	11 (6.1)
Neutropenia	32 (8.9)	1 (0.6)	43 (12.0)	1 (0.6)
AE = adverse event; BSC = best supportive care; N = total number of patients; n = number of patients in each category; PBO=placebo; PEM=pemetrexed; SAE = serious adverse event.				

Data source: data received from manufacturer on Aug. 9, 2013[10]

Withdrawal due to adverse events

At cut-off date June 30, 2010: Withdrawal due to adverse (WDAE) events occurred in 33 (9.2%) patients in the pemetrexed group and seven (3.9%) patients in the placebo group. (Table 4).[8] Overall, 17 patients discontinued maintenance treatment due to SAEs, regardless of causality. There were no relevant differences between study arms in terms of discontinuations due to SAEs or deaths regardless of causality or possibly related to study drug.[30]

At cut-off date March 5, 2012: Withdrawal due to adverse events occurred in 65 (18%) patients in the pemetrexed group and 12 (7%) patients in the placebo group.[1](Table 4)

6.4 Ongoing Trials

No ongoing trials were identified.

7 SUPPLEMENTAL QUESTIONS

No supplemental questions were identified in this review.

8 ABOUT THIS DOCUMENT

This Final Clinical Guidance Report was prepared by the pCODR Lung Clinical Guidance Panel and supported by the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on pemetrexed (Alimta) for non-squamous non-small cell lung cancer. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant pCODR Economic Guidance Report. Details of the pCODR review process can be found on the pCODR website (www.pcodr.ca).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the *pCODR Disclosure of Information Guidelines*. There was no non-disclosable information in the Clinical Guidance Report provided to pERC for their deliberations.

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report. Note that no revisions were made in between posting of the Initial and Final Clinical Guidance Reports.

The Lung Clinical Guidance Panel is comprised of three oncologists. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the pCODR website (www.pcodr.ca). Final selection of the Clinical Guidance Panels was made by the pERC Chair in consultation with the pCODR Executive Director. The Panel and the pCODR Methods Team are editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

APPENDIX A: LITERATURE SEARCH STRATEGY

See section 6.2.2 for more details on literature search methods.

1. Literature search via OVID platform

Database(s): **Embase** 1974 to present**, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)** 1946 to present

#	Searches	Results
1	(pemetrexed* or Alimta* or Rolazar* or Tifolar* or 04Q9AIZ7NO or LY 231514 or LY231514 or LY 231,514 or 137281-23-3 or 150399-23-8).ti,ab,ot,sh,hw,rn,nm.	7390
2	Carcinoma, Non-Small-Cell Lung/ or NSCLC.ti,ab.	89841
3	(exp Adenocarcinoma/ or Carcinoma, Large Cell/ or exp Carcinoma, Squamous Cell/) and (lung* or pulmonary or bronch* or pulmon* or lobular* or peribronch*).ti,ab.	65277
4	((non-small cell or nonsmall cell or macrocell* or large cell or squamous or bronchoalveolar or bronchiolo alveolar or adenocarcinoma*) and (adenocarcinoma* or neoplasm* or cancer* or carcinoma* or tumor* or tumour*) and (lung* or pulmonary or bronch* or pulmon* or lobular* or peribronch*)).ti,ab.	136613
5	1 and (2 or 3 or 4)	4050
6	5 use pmez	950
7	*pemetrexed/ or (pemetrexed* or Alimta* or Rolazar* or Tifolar* or 04Q9AIZ7NO or LY 231514 or LY231514 or LY 231,514).ti,ab.	4276
8	*Lung non small cell cancer/ or NSCLC.ti,ab.	59254
9	(*Adenocarcinoma/ or *Large cell carcinoma/ or *Squamous cell carcinoma/ or adenocarcinoma*.ti,ab.) and (lung* or pulmonary).ti,ab.	63426
10	7 and (8 or 9 or 4)	2284
11	10 use oemezd	1424

12	6 or 11	2374
13	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw.	379963
14	(Randomized Controlled Trial or Controlled Clinical Trial).pt.	451013
15	Randomized Controlled Trial/	715103
16	Randomized Controlled Trials as Topic/	123404
17	"Randomized Controlled Trial (topic)"/	32491
18	Controlled Clinical Trial/	484342
19	Controlled Clinical Trials as Topic/	6823
20	"Controlled Clinical Trial (topic)"/	1828
21	Randomization/	140844
22	Random Allocation/	140844
23	Double-Blind Method/	243003
24	Double Blind Procedure/	117674
25	Double-Blind Studies/	200690
26	Single-Blind Method/	35950
27	Single Blind Procedure/	17533
28	Single-Blind Studies/	35950
29	Placebos/	265227
30	Placebo/	232645
31	Control Groups/	46741

32	Control Group/	46741
33	(random* or sham or placebo*).ti,ab,hw.	2130063
34	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw.	379963
35	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw.	753
36	(control* adj3 (study or studies or trial*)).ti,ab.	663829
37	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw.	58765
38	allocated.ti,ab,hw.	81068
39	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw.	45911
40	or/14-39	2682419
41	12 and 40	841
42	remove duplicates from 41	545
43	limit 42 to english language	514

2. Literature search via PubMed

Search	Query	Items found
#3	Search #1 AND #2 AND publisher[sb]	21
#2	Search (non-small cell[tiab] OR nonsmall cell lung[tiab] OR non-squamous[tiab] OR nonsquamous[tiab] OR bronchoalveolar[tiab] OR bronchiolo alveolar[tiab]) AND (neoplasm*[tiab] OR cancer*[tiab] OR carcinoma*[tiab] OR tumor*[tiab] OR tumour*[tiab]) AND (lung*[tiab] OR pulmonary[tiab])	48563
#1	Search pemetrexed [Supplementary Concept] OR 04Q9AIZ7NO[rn] OR LY 231514[tiab] OR LY231514[tiab] OR LY 231,514[tiab] OR pemetrexed[tiab] OR Alimta*[tiab] OR Rolazar*[tiab] OR Tifolar*[tiab]	1601

3. Cochrane Central Register of Controlled Trials (Central)

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There are 48 results from 704315 records for your search on 'pemetrexed* OR Alimta* OR Rolazar* OR Tifolar* OR LY 231514 OR LY231514 OR LY 231,514 in title abstract keywords AND non small or large cell or squamous in title abstract keywords AND monotherapy or second or maintenance or supportive care in title abstract keywords in Trials'

4. Grey Literature search via:

Clinical trial registries:

U.S. NIH ClinicalTrials.gov
http://www.clinicaltrials.gov/

Canadian Partnership Against Cancer Corporation. Canadian Cancer Trials
http://www.canadiancancertrials.ca/

Search terms: Alimta or pemetrexed

Select international agencies including:

Food and Drug Administration (FDA):
http://www.fda.gov/

European Medicines Agency (EMA):
http://www.ema.europa.eu/

Search terms: Alimta or pemetrexed

Conference abstracts:

American Society of Clinical Oncology (ASCO)
http://www.asco.org/

European Society for Medical Oncology (ESMO)
http://www.esmo.org/

Search terms: Alimta or pemetrexed / last 5 years

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