NHS
National Institute for Health and Clinical Excellence

Single Technology Appraisal

Pemetrexed for maintenance treatment following induction therapy with pemetrexed and cisplatin for non-squamous non-small-cell lung cancer

Evaluation Report

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Pemetrexed for maintenance treatment following induction therapy with pemetrexed and cisplatin for non-squamous non-small-cell lung cancer

Contents:

Any information supplied to NICE which has been marked as confidential has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Premeeting briefing

Pemetrexed for maintenance treatment following induction therapy with pemetrexed and cisplatin for non-squamous non-small-cell lung cancer

This premeeting briefing is a summary of:

- the evidence and views submitted by the manufacturer, the consultees and their nominated clinical specialists and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal. Please note that this document is a summary of the information available before the manufacturer has checked the ERG report for factual inaccuracies.

Key issues for consideration

Clinical effectiveness

- Does the Committee consider the results of the PARAMOUNT trial to be generalisable to patients in England and Wales? The ERG note the following:
  - trial participants were younger and of better performance status (PS) than people with non-small-cell lung cancer (NSCLC) in UK clinical practice
  - the majority of the trial population (91%) consisted of people with stage IV disease
  - within the trial, maintenance treatment was given until disease progression or unacceptable toxicity, with some patients receiving more than 6 cycles. It is unclear whether this will reflect clinical practice in England and Wales.

Cost effectiveness

- The approach adopted within the manufacturer's submission to model overall survival (OS) is based on using a single parametric function designed to generate OS projection estimates for both trial arms simultaneously. The ERG comments that this is not the most appropriate method and proposes an alternative approach. What is the Committee's view on the most appropriate method of modelling OS?
- The ERG does not agree with the manufacturer's selection of time point for projecting survival beyond Kaplan-Meier survival estimates, suggesting an alternative method is more appropriate. What is the Committee's view on the most appropriate method?
- Does the Committee agree with basic adjustments proposed by the ERG identified in table 10 of this report? In particular, the adjustments made for:
  - pemetrexed drug cost
  - mid-cycle correction
  - differences in further chemotherapy rates
  - co-medication costs
  - adjusted utility model

End of life criteria

- Does pemetrexed meet the criteria to be considered as an end-of-life treatment?
- The manufacturer estimates that the cumulative population eligible for pemetrexed is 5531 (4034 NSCLC and 1497 malignant pleural mesothelioma). The ERG presents a scenario in which 7871 patients may be eligible to receive pemetrexed across its licensed indications. A third scenario calculated by the NICE technical team the number of patients in England and Wales for whom pemetrexed is licensed could be above 8200. What is the Committee's view on whether pemetrexed is licensed or otherwise indicated for a small patient population?

1 Background: clinical need and practice

1.1 In England and Wales 36,051 people were diagnosed with lung cancer in 2010. Around 70 to 80% of lung cancers are non-small-cell lung cancers (NSCLC) equivalent to around 26,550 cases per year. In 2011 the histological diagnosis rate for patients with lung cancer in England and Wales was 76.9%.The majority of people with NSCLC are diagnosed in the later stages with 21% presenting in stage IIIB and 48% presenting in stage IV.

- In stage IIIB lung cancer, the cancer has spread to either of the following; the lymph nodes on either side of the chest, another important part of the body, such as the oesophagus, trachea, heart or into a main blood vessel
- In stage IV lung cancer, the cancer has spread to a remote part of the body, such as the bones, liver or brain.

Lung cancer incidence and mortality rates are strongly associated with smoking and socio-economic deprivation. Lung cancer has one of the lowest survival rates of any type of cancer. For people presenting with NSCLC stage IIIB the 5-year survival rate is around 7 to 9%, for people presenting with NSCLC stage IV the 5-year survival rate varies from 2 to 13%.

1.2 First-line treatment options for people with NSCLC depend on the stage of the disease and the performance status of the patient. The NICE clinical guideline (CG121) covering the diagnosis and treatment of people with lung cancer recommends that "Chemotherapy should be offered to patients with stage III or IV NSCLC and good performance status (WHO 0, 1 or a Karnofsky score of 80–100), to improve survival, disease control and quality of life".

1.3 The manufacturer defines maintenance treatment as active treatment given to patients who do not experience disease progression following first-line induction chemotherapy. The aim of maintenance treatment with pemetrexed is to prolong the period of remission after first-line chemotherapy and possibly increase eligibility for second-line chemotherapy. Based on market research data, the manufacturer reports that currently in the NHS only 6% of non-squamous NSCLC patients who receive first-line treatment go on to receive maintenance treatment.

1.4 Pemetrexed was previously licensed for the treatment of locally advanced, metastatic non-squamous NSCLC in the first-line and second-line settings and for maintenance treatment in patients without disease progression following first-line therapy with non-pemetrexed containing regimens (that is, “switch maintenance”). In October 2011 the European Medicines Agency (EMA) approved an extension to the existing marketing authorisation. Pemetrexed is now also licensed for treatment of locally advanced or metastatic, non-squamous NSCLC which has not progressed following four cycles of pemetrexed/cisplatin first-line (that is, “continuation maintenance”). The current appraisal will investigate the clinical and cost-effectiveness of pemetrexed continuation maintenance in this population.

There are two treatments currently licensed for maintenance treatment in the UK; pemetrexed and erlotinib. A summary of NICE guidance on these technologies is provided in table 1 below.

Table 1. NICE guidance on maintenance treatment options in the NHS

Guidance	Year	Title	Recommendations
TA190	2010	Pemetrexed for the maintenance treatment of NSCLC	Pemetrexed is recommended as an option for the maintenance treatment of people with locally advanced or metastatic non-small-cell lung cancer other than predominantly squamous cell histology if disease has not progressed immediately following platinum-based chemotherapy in combination with gemcitabine, paclitaxel or docetaxel. People who have received pemetrexed in combination with cisplatin as first-line chemotherapy cannot receive pemetrexed maintenance treatment.
TA227	2011	Erlotinib monotherapy for maintenance treatment of NSCLC	Erlotinib monotherapy is not recommended for maintenance treatment in people with locally advanced or metastatic non-small-cell lung cancer who have stable disease after platinum-based first-line chemotherapy.

2 The technology

2.1 Pemetrexed (Alimta, Lilly UK) is a multi-targeted anti-cancer antifolate agent that disrupts crucial folate-dependent metabolic processes essential for cell replication. Pemetrexed has a marketing authorisation as monotherapy for the maintenance treatment of locally advanced or metastatic non-small-cell lung cancer other than predominantly squamous cell histology in patients whose disease has not progressed immediately following platinum-based chemotherapy.

2.2 The summary of product characteristics reports that the most common adverse reactions of pemetrexed are bone marrow suppression manifested as anaemia, neutropenia, leucopenia, thrombocytopenia; and gastrointestinal toxicities, manifested as anorexia, nausea, vomiting, diarrhoea, constipation, pharyngitis,

mucositis, and stomatitis. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3 The recommended dose of pemetrexed is 500mg/m^2 of body surface area; it is administered as an intravenous infusion over 10 minutes on the first day of each 21 day cycle. The list price for pemetrexed is £160.00 for 100 mg vial and £800.00 for 500 mg vial (excluding VAT; 'British national formulary [BNF] edition 64). Based on an average body surface area of 1.79m^2 the drug cost for each treatment cycle, including wastage is £1440. As patients are treated until disease progression or toxicity, the number of cycles varies; in the clinical trial (PARAMOUNT) the mean number of cycles given was 7.86 (average total treatment cost of approximately £11,300). Costs may vary in different settings because of negotiated procurement discounts.

3 Remit and decision problem

3.1 The remit from the Department of Health for this appraisal was: to appraise the clinical and cost effectiveness of pemetrexed, within its licensed indication, for maintenance treatment of non-squamous non-small-cell lung cancer for people whose disease has not progressed following induction therapy with pemetrexed and cisplatin.

Decision problem

	Final scope issued by NICE	Decision problem addressed in the submission
Population	People with advanced or metastatic (stage IIIB and IV) NSCLC, other than predominately squamous histology, whose disease has not progressed following induction treatment with pemetrexed and cisplatin	People with advanced or metastatic (stage IIIB and IV) NSCLC, other than predominately squamous histology, with good performance status (PS 0-1), who experience complete or partial response or stable disease after first-line treatment with pemetrexed/cisplatin.
Intervention	Pemetrexed	Pemetrexed plus BSC
Comparators	Best supportive care (includes bisphosphonates and palliative radiotherapy)	Placebo (watch and wait) plus BSC. In the PARAMOUNT study, BSC was defined as treatment without a specific antineoplastic regimen given with the intent to maximise quality of life. Specifically excluded were: anticancer surgery, immunotherapy, radiation to intrathoracic structures, anticancer hormonal therapy, and systemic CTX in which the goal was to either eradicate or slow the progression of the study disease. Therapies considered acceptable included, but not limited to, palliative radiation to extrathoracic structures, antibiotics, analgesics, antiemetics, thoracentesis, pleurodesis, blood transfusions, and/or nutritional support (enteral or parenteral)
Outcomes	• Overall survival • Progression-free survival • Response rates • Adverse effects of treatment (according to grade) • Health-related quality of life	Primary outcome measure • Progression-free survival Secondary outcome measures • Overall survival • Response rate • Health-related quality of life • Toxicity •
Economic evaluation	The reference case	The reference case

3.2 Manufacturer and ERG comments on the decision problem

Population

3.3 The manufacturer highlighted that as per NICE clinical guideline CG121, only patients with advanced disease and good performance status (WHO 0, 1 or Karnofsky score of 80-100) should be offered chemotherapy. The inclusion criteria for the PARAMOUNT trial also specified that only patients with good performance status (PS 0-1) were to be included. Accordingly, the manufacturer notes that their submission presents the clinical and economic case for patients with PS 0-1 only.

3.4 The ERG considered that limiting the population within the submission to patients with a PS 0-1 to be appropriate. The ERG highlighted that in clinical practice in England and Wales, only patients with a PS of 0 or 1 are eligible for chemotherapy treatment. The ERG also noted that a substantial proportion of people with NSCLC in England and Wales have a PS of 2.

Comparators

3.5 The ERG considered that the comparator defined by the manufacturer matches BSC as defined in NICE's scope.

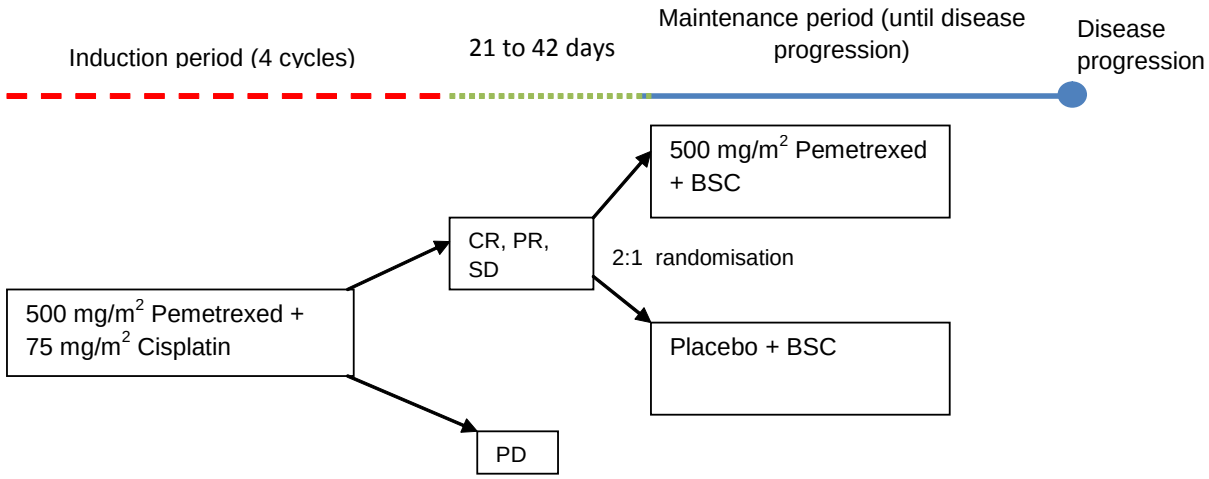
Outcomes

3.6 The ERG noted that data are reported in the manufacturers submission for all of the five outcomes specified in the scope.

4 Clinical-effectiveness evidence

4.1 The review of clinical effectiveness is based on a single trial: the PARAMOUNT trial. This was an international, multicentre (83 sites across 16 countries including the UK), double-blind, phase III, randomised trial comparing maintenance therapy with pemetrexed plus BSC versus placebo plus BSC in patients with Stage IIIB or Stage IV non-squamous NSCLC whose disease had not progressed during 4 cycles of pemetrexed/cisplatin induction. The study design for PARAMOUNT is presented in figure 1.

Figure 1. PARAMOUNT trial design (manufacturer's submission page 48)[1]



4.2 The PARAMOUNT study randomised a total of 539 patients to either pemetrexed plus BSC (n=359) or placebo plus BSC (n=180). Patients in the pemetrexed arm received pemetrexed 500 mg/m^2 on day 1 of the 21-day cycle, administered as an infusion, plus BSC. Patients in the placebo arm received normal saline (0.9% sodium chloride) on day 1 of the 21-day cycle, administered as an infusion, plus BSC. Maintenance therapy (pemetrexed or placebo) was continued until disease progression, unacceptable adverse events,

[1] CR – complete response, PR – partial response, PD – progressive disease

or decision of the patient or physician. Patients were followed up until death or study closure. Both arms received concomitant medication with folic acid, vitamin B_{12} and dexamethasone.

4.3 The median number of cycles of maintenance treatment was identical (4.0 cycles) in both arms of the trial, however the mean number of cycles in the pemetrexed plus BSC group was 7.86 compared to 4.99 in the placebo plus BSC group (table 13, page 62 of the MS). In the trial, 27.6% of patients in the pemetrexed plus BSC arm and 11.7% of patients in the placebo plus BSC arm received at least 10 cycles. The ERG commented that the mean number of cycles in the trial may be greater than in clinical practice in England and Wales.

4.4 The demographic characteristics of the patients in the trial at baseline are provided in table 10 (p54) of the manufacturer's submission. The median age was 61 years. The majority (91%) had stage IV disease; all patients randomised to the maintenance phase were of good performance status (PS 0–1). Approximately 22% had never smoked. The ERG commented that the characteristics were well-balanced across the 2 arms of the trial. Clinical opinion to the ERG suggested that PARAMOUNT included a higher proportion of patients considered to be of PS 0, a substantially higher proportion of participants with stage IV disease and lower proportions of ever smokers.

4.5 The planned primary analysis for progression free survival (PFS) was performed in July 2010 based on a data cut from June 2010. The final analysis for overall survival (OS) was based on the March 12 2012 data cut. PFS data are presented in table 2. At both analysis time-points a PFS gain for pemetrexed plus BSC compared with placebo plus BSC is reported; a median of 1.28 months in June 2010 and 1.68 months in March 2012. OS data are reported in table 3. At the final data cut-off in March 2012, a median OS benefit of 2.85 months is reported for pemetrexed plus BSC compared with placebo plus BSC.

Table 2. PARAMOUNT progression-free survival at key analysis time points (ERG report, p28)

Data cut-off	Treatment	Number of events (%)	Median PFS (months) (95% CI)	Hazard ratio (HR) (95% CI)
June 30, 2010	Pemetrexed + BSC	184 (51.3)	4.11 (3.15 to 4.57)	0.62 (0.49 to 0.79)
	Placebo + BSC	118 (65.6)	2.83 (2.60 to 3.12)	
March 5, 2012	Pemetrexed + BSC	Not reported	4.4 (4.11 to 5.65)	0.60 (0.50 to 0.73)
	Placebo+ BSC	Not reported	2.76 (2.6 to 3.02)	

Table 3. PARAMOUNT overall survival at key analysis time points (ERG report, p28)

Data cut-off	Treatment	Number of deaths n(%)	Median OS (months) (95% CI)	Hazard ratio (HR) (95% CI)
June 30, 2010	Pemetrexed + BSC	Not reported	Not reported	Not reported
	Placebo +BSC	Not reported	Not reported	
May 16, 2011	Pemetrexed + BSC	188 (52.4)	Not reported	0.78 (0.61 to 0.98)
	Placebo+ BSC	111 (61.7)	Not reported	
March 5, 2012	Pemetrexed + BSC	256 (71.3)	13.86 (12.75 to 16.03)	0.78 (0.64 to 0.96)
	Placebo + BSC	141 (78.3)	11.01 (9.95 to 12.52)	

4.6 Subgroup analyses were performed for both OS and PFS on age, smoking status, response to induction therapy, pre-randomisation PS, gender and histology. The manufacturer reported that all

results were consistent with the results of the whole population (see figure 6, pg 65 of the MS).

4.7 Grade 3 or 4 adverse events were reported by 11.7% in the pemetrexed plus BSC group and 4.4% in the placebo plus BSC group (table 4).The frequency of grade 3 and 4 adverse events occurring in 5% or more of people in the trial are described in table 5. Fatigue, anaemia and neutropenia were all reported at a significantly greater frequency by participants in the pemetrexed plus BSC arm compared with a placebo plus BSC (table 5). The ERG considered that adverse events underlying the hospitalisations reported in the PARAMOUNT trial reflect those generally experienced in lung cancer trials. Further discussion of adverse events can be found in the ERG report on pages 31-34.

Table 4. Selected adverse event data in the PARAMOUNT trial (manufacturer's submission, p74-75)

Adverse Event (AE)	Pemetrexed+BSC N=359 N(%)	Placebo+BSC N=180 N(%)	p-value
Grade 3 or 4 non laboratory AEs	42 (11.7)	8 (4.4)	<0.001
Treatment discontinued due to AE	43 (12)	8 (4.4)	0.005
Hospitalisations for treatment-related AE	39 (10.9)	6 (3.3)	0.003
Patients receiving transfusions	66 (18.4)	11 (6.1)	<0.001

Table 5. Grade 3 and 4 adverse events occurring in ≥5% of trial participants in the maintenance phase of the PARAMOUNT trial (manufacturer's submission, p75)

Adverse Event (Grade 3 or 4)	Pemetrexed + BSC N=359 N(%)	Placebo + BSC N=180 N(%)	p-value
Fatigue	19 (5.3)	2 (1.1)	0.017
Anaemia	24 (6.7)	1 (0.6)	<0.001
Neutropenia	22 (6.1)	0 (0.0)	<0.001

4.8 Health-related quality of life data were collected during the PARAMOUNT trial using the EQ-5D questionnaire. Patients rated their current health condition at baseline, on day 1 of each cycle of induction and maintenance therapy, and at the 30-day post-discontinuation visit. The results are presented in table 6 and indicate no statistically significant difference in quality of life between the 2 arms of the trial.

Table 6. EQ-5D index scores from PARAMOUNT (manufacturer's submission, p69)

Measurement time points	**UK EQ-5D index scores (standard deviation or 95% confidence interval)**	
	Pemetrexed/BSC	**Placebo/BSC**
Prior to first-line treatment * N=805; single-arm open-label phase. (2010 data lock reported in CSR)	0.71 (SD 0.258)	
Maintenance baseline, i.e. prior to randomisation for maintenance treatment * N=325 pemetrexed; N=165 placebo (2012 data lock: DOF)	0.77 (SD 0.210)	0.77 (SD 0.190)
Maintenance phase ** i.e. includes EQ-5D data from maintenance baseline, all maintenance cycles and the 30-day post-discontinuation visit	0.7841* (0.7608-0.8074)*	0.8020* (0.7660-0.8381)*
30-days post-maintenance treatment discontinuation * N=131 pem/BSC; N=77 placebo/BSC (2012 data lock: DOF)	0.68 (SD 0.300) (p<0.001 vs baseline)	0.68 (SD 0.287) (p=0.001 vs baseline)

* Analysed with paired t-test and MMRM ** Analysed in STATA

4.9 The ERG concluded (ERG report, p35) that the data presented by the manufacturer clearly demonstrate a statistically significant difference in favour of pemetrexed plus BSC over placebo plus BSC care for both OS and PFS in a population of people of good PS who have stage IIIB/IV non-squamous NSCLC.

5 Comments from other consultees

5.1 Professional groups pointed out that pemetrexed maintenance therapy will still not be appropriate for all people with NSCLC due to a number of factors. Firstly, people with squamous histology derive no benefit from pemetrexed treatment. Secondly, poor performance status may exclude some people from treatment. Thirdly, only a proportion of patients starting induction therapy will complete the planned course, thus reducing the proportion that may receive maintenance therapy. Finally, it was highlighted that some patients may prefer to have a break from treatment and regular hospital appointments following initial therapy.

5.2 In a submission from a patient group it was stated that improvements in quality of life and small extensions in duration of life are of considerable significance to the individual and their family. Symptom relief is also important; symptoms such as breathlessness are very difficult to manage clinically. Therapies with anti-tumour activity often provide the best option for symptom relief. However, few active options currently exist. Anecdotal patient experience suggests that this maintenance therapy appears to be well tolerated.

6 Cost-effectiveness evidence

6.1 A guide to the location of key economic information within the manufacturer's submission and the ERG report is provided in table 7.

Table 7. Location of key economic information with the manufacturer's submission and ERG report (adapted from ERG report, p36)

	Manufacturer's submission		ERG report
Key information	**Page**	**Tables/figures**	**Page**
Details of the systematic review of the economic literature	87-92		36-37
De novo analysis	92-98	Tables 22, Figure 12	38-40
Clinical evidence used in economic evaluation	99-112	Tables 23-27, Figure 13	40-43
Measurement and valuation of health effects	113-120	Tables 28-29	42
Resource identification, measurement and valuation	121-131	Tables 30-48	43-46
Sensitivity analysis	132-138	Table 49	46-49
Results – base case analysis*	139-155	Tables 50-60	49
Subgroup analysis*	156-157		48
Interpretation of economic evidence*	158-159		
Assessment of factors relevant to the NHS and other parties*	160-168	Tables 61-72	
*also the addendum provided by the manufacturer at clarification stage.			

6.2 The manufacturer's literature search identified 2 existing cost effectiveness models which were developed for technology appraisal (TA) 190 and TA227. The manufacturer stated that neither of these 2 models was suitable for the purposes of this appraisal (page 91 of the manufacturer's submission). Therefore the manufacturer built a de novo economic model, a state-transition Markov model compromising 3 health states; pre-progression, post-progression and dead. The base-case analysis uses PARAMOUNT trial population data (March 2012 data cut) and assumes that the trial population is representative of the non-squamous stage IIIB or IV NCSLC population in England and Wales whose disease has not progressed following platinum-based chemotherapy, and who are PS 0 or 1.

6.3 Survival estimates (OS and PFS) were obtained from extrapolating the data; the censoring rates were 28.7% for pemetrexed plus BSC and 21.7% for placebo plus BSC, for OS, further detail in the MS, page 100. Six alternative parametric distributions were explored by the manufacturer before concluding that the gamma distribution was the most appropriate distribution for OS and PFS. Table 50 (pg 140) in the MS reports that the model gave an incremental mean OS benefit of 4.21 months (median 3.09 months) and an incremental mean PFS benefit of 3.25 months (median 1.67 months) for pemetrexed plus BSC compared with placebo plus BSC.

6.4 The manufacturer stated that it was not possible to use the EQ-5D data from PARAMOUNT to distinguish between patient experience in the pre- and post-progression states, as the trial data did not provide suitable values, and therefore a mixed regression analysis was carried out by the manufacturer to obtain utility values for the health states. The values for 4 pre-progression states (ranging between 0.4099 and 0.7758) and 4 post-progression states (ranging between 0.3369 and 0.7028) are given in table 26 (pg109) of the MS.

6.5 Drug costs in the manufacturer's model were calculated using UK list prices applied to the minimum number of vials required (based on the mean body surface area for UK lung cancer patients weighted by gender). The base-case model included drug wastage for part-used vials with NHS Reference Costs used to estimate the delivery costs. The drug and administration costs used in the manufacturer's model are presented in table 8.

6.6 The manufacturer excluded the costs of concomitant medications that are required to be administered with pemetrexed, that is,

vitamin B12, folic acid and dexamethasone as they assumed that the cost of these drugs is included within the NHS Reference Cost for chemotherapy delivery (MS, p127).

6.7 The cost of treating grade 3 and 4 adverse events was calculated by the manufacturer using the costs used in a previous appraisal (TA190) and inflating these to 2011 values. The costs were weighted according to the adverse event rates for each arm of the PARAMOUNT trial. Costs for BSC and terminal care were also adapted from TA190 and updated to 2011 values (MS, p130-131).The costs of second-line chemotherapy were included for patients in the post-progression health state. In the manufacturer's base case, 4.82 cycles of docetaxel and 6.27 cycles of erlotinib were assumed for consistency with similar approaches in previous appraisals. The cost of docetaxel was calculated as £1231 per cycle, the cost of erlotinib was £1104 per cycle.

Table 8. Drug and administration costs used in the manufacturer's model (adapted from ERG report, p44)

Costs	Calculation	Value	Source
Pemetrexed			
Body Surface Area (BSA)	58% male: mean BSA 1.89m^2 42% female: mean BSA 165m^2	1.79m^2	PARAMOUNT Sacco et al. 2010
Drug cost	SPC dose: 500mg/m^2 Vials: 1 x 500mg + 4 x 100mg Cost: 1 x £800 + 4 x £160	£1440	BNF 2012
Administration cost	SB12Z - Deliver simple parental CTX at first attendance (day case and regular day/night)	£208	NHS Reference Cost (NHS Trusts & PCTs) 2010/2011

6.8 The base-case incremental cost-effectiveness ratio (ICER) results generated by the manufacturer's model are presented in table 9. Following receipt of the clarification letter, the manufacturer identified an error in their economic model and submitted a revised model and updated cost effectiveness results (as an addendum).

Only the results reported in the manufacturer's addendum are reported here. For an additional £12,153, pemetrexed plus BSC gave a quality-adjusted life year (QALY) gain of 0.2554, representing an ICER of £47,576 per QALY gained compared with placebo plus BSC.

Table 9. Manufacturer's base-case results

	Pemetrexed + BSC	Placebo + BSC	Increment results
Therapy costs	£13,125	£0	£13,125
Adverse events costs	£64	£4	£59
Follow-up care costs	£10,177	£11,170	-£993
Terminal care	£2,699	£2,738	-£39
Total costs	**£26,064**	**£13,912**	**£12,153**
Life Years Gained	1.7047	1.3537	0.3511
QALY	1.1743	0.9188	0.2554
ICER			**£47,576**

6.9 The manufacturer carried out 59 deterministic sensitivity analyses. The ICERs for these analyses ranged from £31,760 to £58,091 per QALY gained. Full details of the analyses are provided in table 59 of the addendum to the initial manufacturer's submission. The manufacturer's probabilistic sensitivity analysis gave a mean ICER of £48,218 per QALY gained and showed that, at a threshold of £50,000 per QALY gained, pemetrexed plus BSC would be considered cost-effective in 54% of simulations compared with placebo plus BSC. The manufacturer stated that the key drivers of cost effectiveness are the efficacy of pemetrexed, the use of alternative parametric distributions and the use of utility values from TA190. No subgroup analyses were carried out.

ERG comments on the cost-effectiveness evidence

6.10 Regarding model design, the ERG noted that the core of the model, tracing the progression of the two cohorts of patients from initiation to death appeared to be largely sound.

6.11 Regarding parameters within the model, the ERG found 8 parameters, mainly relating to costs, which it suggested could be estimated more accurately. The details of these are reported on pages 50-53 of the ERG report). Table 10 is reproduced from page 54 of the ERG report. As identified in table 10, changes to the mid-cycle correction and the difference in further chemotherapy rates had the greatest impact.

Table 10. ERG exploratory analyses - effect of cost, resource use and utility amendments made by the ERG (ERG report, p54)

	Incremental cost	Incremental QALYs	ICER (£/QALY)	Change in ICER
Base-case analysis	**£12,153**	**0.2554**	**£47,576**	**-**
Pemetrexed drug cost	£12,479	0.2554	£48,854	+ £1,278
No mid-cycle correction	£12,906	0.2554	£50,524	+ £2,948
No difference in further CTX rates	£13,112	0.2554	£51,332	+ £3,756
Docetaxel drug cost*	£12,186	0.2554	£47,707	+ £131
Co-medication costs	£12,179	0.2554	£48,785	+ £ 1,209
PFS monitoring costs	£12,266	0.2554	£47,707	+ £ 131
Terminal care costs	£12,138	0.2554	£47,518	- £58
Adjusted utility model	£12,153	0.2468	£49,235	+ £1,659
All ERG cost, resource & utility changes	**£14,339**	**0.2468**	**£58,092**	**+ £10,516**

*Using least expensive BNF prices (eMIT prices give incremental cost of £12,293, ICER of £48,126

6.12 The ERG noted that the manufacturer had developed adjusted statistical models for projecting OS and PFS beyond the trial data in which the influence of baseline covariates of patient characteristics in the PARAMOUNT trial was accounted for. The ERG stated that the covariates exhibited statistically significant parameter values indicating significantly superior model fit

compared with the unadjusted models. However, the manufacturer used the unadjusted models in the base case, giving the reason that it is unnecessary to take these factors into account since the randomised allocation of patients should ensure that all relevant variables are fully balanced within the trial data set. The ERG stated that this would be appropriate when calculating results directly from trial data, but may not be valid in relation to a parametric model fitted to those data (page 54 ERG report). The effects of using an adjusted model are shown in table 11. The ERG concluded that if the manufacturer's preferred gamma functions are used for projecting PFS and OS beyond the observed data, then it is inappropriate to base the base-case analysis on the unadjusted models.

Table 11. Effect of covariate adjusted survival models on cost effectiveness of pemetrexed maintenance therapy (ERG report, p55)

	Incremental cost	Incremental QALYs	ICER (£/QALY)	Change in ICER
Base-case analysis	**£12,153**	**0.2554**	**£47,576**	**-**
PFS adjusted model	£12,155	0.2553	£44,609	+ £33
OS adjusted model	£12,135	0.2450	£49,534	+ £1,958
Both adjusted models	**£12,137**	**0.2449**	**£49,567**	**+ £1,991**

6.13 The ERG raised concerns regarding the choice of time point at which projective modelling takes over from observed trial data. The manufacturer's model used the time point where 20% of patients remained at risk in the trial, which occurred at cycle 31 in the placebo arm and cycle 37 in the pemetrexed arm. The manufacturer explained that this avoids any potential bias that may occur if the Kaplan-Meier curves are cut at a specific number of cycles for both arms. This method was also chosen by the manufacturer on the basis that it had been adopted by the ERG during the NICE Technology Appraisal 227 of erlotinib for

maintenance treatment of non-small-cell lung cancer. However the ERG explained that in TA227 maturity referred to the results from the Kaplan-Meier analysis of the data, that is, the proportion of the original cohort that is estimated to be event free at a particular time point, regardless of the absolute number of individuals not yet censored. In contrast to the manufacturer's method, the ERG conducted an exploratory analysis using a common survival rate between both arms to determine the point at which projection should take over from trial data. This was carried out at survival thresholds of 15%, 20% and 25%. In all cases, the ICER was less favourable to pemetrexed. Using a survival threshold of 20%, the ERG estimated that the ICER would increase by £7360, to £54,936 per QALY gained (page 56 of the ERG report).

6.14 The ERG questioned why the manufacturer's model resulted in a survival advantage for pemetrexed following progression (27% of the undiscounted gain for pemetrexed occurred in the post progression phase). The ERG analysed the post progression survival data from PARAMOUNT and found that the prognosis for patients in the post progression phase was the same. To understand the effect on the ICER of taking out the post progression gain for pemetrexed, the ERG removed the excess QALY gain and made a pro-rata adjustment to post-progression follow up, with the result that the base case ICER increased to £55,000 per QALY gained (pages 56-57 of the ERG report).

6.15 The ERG further explored the manufacturer's approach to survival modelling by re-analysing the overall survival data from the trial. In doing so the ERG concluded that there is a mismatch between the manufacturer's fitted gamma model and the observed OS trial data. This is most pronounced for the placebo plus BSC group (which is based on the smaller sample size). In this group, the trend is

towards steadily increasing underestimation of survival, whereas in the pemetrexed plus BSC group the trend is towards steadily increasing overestimation of OS. The ERG concluded that the consequence of the manufacturer's approach to projecting OS is that differences in expected OS are biased towards pemetrexed plus BSC. The ERG found that this is the main source of the gain in post progression survival (see section 6.14). To investigate whether a closer fit to the data could be found the ERG used long term projective exponential models to the Kaplan Meier data. These were found to have a close correspondence with the Kaplan-Meier data in both arms of the trial. Substituting the long term overall survival trends in place of the gamma function (without any other changes to the manufacturer's base case) had a significant impact on the ICER, increasing by £14,859 to £62,435 per QALY gained. (See page 61 of the ERG report for more details.)

6.16 Using combinations of these amendments to the manufacturer's model, the ERG produced 3 alternative exploratory analyses as follows:

Scenario 1 – manufacturer's base-case (no changes)

ERG Scenario 2 - assumes all structures and analyses in the manufacturer's model are appropriate, and only formula errors and parameter values need amending.

ERG Scenario 3 - assumes that the survival modelling using gamma functions is appropriate; adequately reflecting the trial data, provided casemix adjustments are applied and projections are applied consistently between the arms of the evaluation.

ERG Scenario 4 -rejects the use of a single OS gamma function based on the proportional hazards assumption which generates

additional PPS gain for pemetrexed, and prefers the ERG approach to modelling long-term survival.

The results of the ERG exploratory analyses are re-presented below in table 12.

Table 12. Results from the ERG exploratory analyses (ERG report, p65)

Adjustment	Placebo + BSC				Pemetrexed + BSC				Incremental				
	Therapy cost	Other costs	Survival (months)*	QALYs	Therapy cost	Other costs	Survival (months)*	QALYs	Survival (months)*	Cost	QALYs	ICER (£/QALY)	ICER change
Scenario 1 Base case	**£0**	**£13,912**	**16.82**	**0.9188**	**£13,125**	**£12,939**	**21.46**	**1.1743**	**4.65**	**£12,153**	**0.2554**	**£47,576**	**-**
Scenario 2 Basic alterations only	**£0**	**£13,340**	**16.82**	**0.9103**	**£14,251**	**£13,427**	**21.46**	**1.1571**	**4.65**	**£14,339**	**0.2468**	**£58,092**	**+£10,516**
Scenario 3 Basic alterations + casemix adjusted survival models	**£0**	**£13,307**	**16.39**	**0.8890**	**£14,251**	**£13,332**	**20.24**	**1.0964**	**3.85**	**£14,276**	**0.2075**	**£68,810**	**+£21,234**
Scenario 4 Basic alterations + casemix adjusted PFS model + ERG OS model	**£0**	**£13,403**	**17.52**	**0.9488**	**£14,251**	**£13,394**	**20.89**	**1.1354**	**3.38**	**£14,242**	**0.1866**	**£76,344**	**+£28,768**

*survival is undiscounted, all other figures are discounted

Summary of exploratory analyses conducted by the ERG

6.17 All 3 of the ERG scenarios indicate an amended ICER greater than £50,000 per QALY gained and substantially greater than the manufacturer's base-case of £47,576. As identified in table 12 adjustments to overall survival have the greatest impact on the ICER calculations.

End-of-life considerations

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	The National Lung Cancer Audit (2011) reports the median overall survival in England and Wales is 181 days (around 6 months) and year 1 survival rates of 32%. The manufacturer notes that the 1 and 2 year survival rates reported in the PARAMOUNT trial are 58% and 32% respectively.
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	Extrapolating the trial survival data over a lifetime horizon (to a point when 99.9% of patients have died) to account for censoring, the manufacturer reports a modelled mean overall survival of 4.2 months. Using the ERG's preferred approach to modelling survival indicates a most likely gain in mean overall survival of 3.38 months.
The treatment is licensed or otherwise indicated for small patient populations	The manufacturer estimates (manufacturer's submission, p81-83) that the cumulative population of patients eligible for pemetrexed treatment across all NSCLC indications and mesothelioma is 5531. Of these, 4034 are eligible for pemetrexed as per the licence indications for NSCLC: • First line: ALIMTA in combination with cisplatin is indicated for the first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) other than predominantly squamous

	cell histology • Maintenance (switch and continuation): ALIMTA is indicated as monotherapy for the maintenance treatment of locally advanced or metastatic NSCLC other than predominantly squamous cell histology in patients whose disease has not progressed immediately following platinum-based chemotherapy • Second line: ALIMTA is indicated as monotherapy for the second-line treatment of patients with locally advanced or metastatic NSCLC other than predominantly squamous cell histology The manufacturer has included only those patients whose performance status is PS0-1. The manufacturer's calculation is based on those who are eligible for pemetrexed in the first-line setting; the manufacturer states that it is not necessary to count patient numbers for each individual setting of NSCLC as this would amount to counting the same patients twice. A breakdown of the manufacturer's calculation is given in appendix C below. The ERG presents an alternative scenario (p67, ERG report) in which they consider numbers of people treated at each stage of the patient pathway. In this scenario the population increases to 7871. The ERG note that all scenarios are likely to overestimate the uptake of chemotherapy treatment in the population. Two additional pieces of exploratory analyses have been undertaken by the NICE technical team, and are presented in appendix C of this paper. The first exploratory analysis ('Manufacturer's submission – latest figures') uses the manufacturer's assumptions but uses updated figures from the most recent National Lung Cancer Audit (NLCA) Report. This increases the estimated eligible population to 6060. In the second piece of exploratory analysis undertaken by the NICE technical team ('NICE exploratory analysis') an alternative source of data and assumptions are presented:

	• the incidence of lung cancer (including mesothelioma) in England and Wales is taken from cancer registrations, rather than data published in the National Lung Cancer Audit. • the proportion of lung cancers that are NSCLC is estimated to be 78% as per NICE guideline (CG121, p4). Using the assumptions above the number of patients eligible for pemetrexed can be estimated as being around 8200. This may be an underestimate, as the estimated figure presented only includes patients with PS 0-1. In clinical practice a proportion of patients with PS2 may also received first-line chemotherapy (the licensed indication does not specify a PS of 0-1). In both of these exploratory analyses, the population does not take account of people who may receive pemetrexed for their NSCLC more than once in their treatment pathway.

7 Equalities issues

7.1 No specific equality issues were raised during the scoping stage of this appraisal or in any of the submissions.

8 Innovation

8.1 The manufacturer puts forward a case for pemetrexed continuation maintenance treatment as an innovative treatment (manufacturer's submission p36-37). The manufacturer proposes the treatment is innovative because:

- it offers patients a survival benefit of 2.85 months and a progression free survival benefit of 1.68 months (this extended survival is in addition to the survival benefit experienced by patients from pemetrexed/cisplatin in the first-line setting)

- it has a favourable and manageable tolerability profile, which means that the increased survival is not at the cost of patients' quality of life.

- because pemetrexed is a single-agent treatment requiring a 10 minute infusion it has the potential benefit of moving the care of patients from hospitals and into the community, which is more convenient for patients and their carers.

- pemetrexed continuation therapy makes it possible for clinicians to prescribe pemetrexed/cisplatin as a first-line treatment (within TA190 people who have received pemetrexed in combination with cisplatin as first-line chemotherapy cannot receive pemetrexed maintenance treatment).

8.2 The ERG's opinion was that there is limited scope for the technology to be considered as innovative. The ERG noted that pemetrexed is already recommended for use in the NHS by NICE as a maintenance treatment for people with locally advanced or metastatic NSCLC other than predominantly squamous histology who were previously treated with platinum-based treatment other than pemetrexed.

9 Authors

Mark Minchin

Technical Lead

Joanne Holden

Technical Adviser

with input from the Lead Team (Darren Ashcroft, John Dervan and Murray Smith).

Appendix A: Supporting evidence

Related NICE guidance

Published

- Lung cancer: The diagnosis and treatment of lung cancer (update of NICE clinical guideline 24). NICE clinical guideline 121 (2011). Available from: www.nice.org.uk/guidance/CG121
- Erlotinib monotherapy for the maintenance treatment of non-small-cell lung cancer. NICE technology appraisal guidance 227 (2011). Available from: www.nice.org.uk/guidance/TA227
- Gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer. NICE technology appraisal guidance 192 (2010). Available from: www.nice.org.uk/guidance/TA192
- Pemetrexed for the maintenance treatment of non-small-cell lung cancer. NICE technology appraisal guidance 190 (2010). Available from: www.nice.org.uk/guidance/TA190
- Pemetrexed for the first-line treatment of non-small-cell lung cancer. NICE technology appraisal guidance 181 (2009). Available from: www.nice.org.uk/guidance/TA181
- Erlotinib for the treatment of non-small-cell lung cancer. NICE technology appraisal guidance 162 (2008), Available from: www.nice.org.uk/guidance/TA162
- Bevacizumab for the treatment of non-small-cell lung cancer (terminated appraisal). NICE technology appraisal 148 (2008). Available from: http://guidance.nice.org.uk/TA148

Under development

NICE is developing the following guidance (details available from www.nice.org.uk):

NICE technology appraisal guidance:

- Erlotinib and gefitinib for the treatment of non-small-cell lung cancer following prior chemotherapy (Review of TA162 and TA175).
  Expected publication - June 2014
- Crizotinib for the treatment of previously treated non-small-cell lung cancer associated with an anaplastic lymphoma kinase fusion gene.
  Expected publication - June 2013

NICE diagnostics guidance:

- Epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation testing in adults with locally advanced or metastatic non-small-cell lung cancer
  Expected publication - August 2013

NICE pathways:

- There is a NICE pathway on lung cancer, which is available from http://pathways.nice.org.uk/pathways/lung-cancer

Appendix B: Clinical efficacy section of the European public assessment report

The European public assessment report for pemetrexed was first published on 9th October 2009 and is available from:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000564/human_med_000638.jsp&mid=WC0b01ac058001d124

Appendix C: Estimates of the licensed population for pemetrexed in mesothelioma and NSCLC first-line treatment

	Manufacturer's submission (MS, p82-83)		Manufacturer's submission - latest figures		NICE Exploratory analysis	
	Numbers	Reference	Numbers	Reference	Numbers	Reference
Patients with lung cancer in England and Wales	32,347	1	33,463	4	36,051	5
Patients with confirmed diagnosis of NSCLC	19,163	1	20,081	4	28,120	2
Patients with confirmed NSCLC PS0-1 and stage IIIB/IV	5,932	1	6,698	4	9,379	Calculated (6698/20081)
Patients with confirmed NSCLC, PS 0-1 and a non-squamous histology	**4,034**	2	**4,555**	2	**6,378**	2
Patients with mesothelioma	1,815	1	1,825	4	2,211	6
Advanced MPM	**1,497**	3	**1,505**	Calculated (1497/1815)	**1,824**	Calculated (1497/1815)
Patients eligible for pemetrexed treatment	**5,531**		**6,060**		**8,202**	

References for data sources

1 - National Lung Cancer Audit Report 2011

2 - NICE Clinical Guideline 121: The diagnosis and treatment of lung cancer (2011, p4)

3 - Manufacturer's submission

4 - National Lung Cancer Audit Report 2012

5 - Office of National Statistics Cancer Registrations in England (2010) and Welsh Cancer incidence (2010)

6 - Office of National Statistics Cancer Registrations in England (2010) - (ICD C45)

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal

Crizotinib for the treatment of previously treated non-small-cell lung cancer associated with an anaplastic lymphoma kinase fusion gene

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of crizotinib within its licensed indication for the treatment of previously treated non-small-cell lung cancer associated with an anaplastic lymphoma kinase fusion gene.

Background

In England and Wales 34,949 people were diagnosed with lung cancer in 2008, with 30,254 deaths registered in 2008. Lung cancer falls into two main histological categories: around 85% – 90% are non-small-cell lung cancers (NSCLC) and the remainder are small-cell lung cancers. Approximately 30% of people with NSCLC present with local potentially resectable disease and about 50% of these will be suitable for surgery. About 30% of people present with locally and regionally advanced disease (Stage IIIb) and 40% with advanced disease (Stage IV in which the cancer has spread to other parts of the body). The prognosis for people with NSCLC is poor, with a one-year survival rate of 28% and a five-year survival rate of 8%.

It is estimated that approximately 3% to 5% of people with NSCLC have chromosomal alterations described as anaplastic lymphoma kinase (ALK) fusion genes. These are fusions between the tyrosine kinase portion of the ALK gene and other genes and are believed to be involved in tumour cell growth and survival. It is thought that people with NSCLC with an ALK fusion gene mutation do not harbour epidermal growth factor receptor (EGFR) mutations. ALK fusion genes may be associated with resistance to EGFR tyrosine kinase inhibitors such as erlotinib and gefitinib.

While one-third of people with NSCLC have disease which is suitable for potentially curative surgical resection, for the majority of people with NSCLC , cure is not possible and the aims of therapy are to prolong survival and improve quality of life. NICE clinical guideline 121 (CG121) recommends a combination of docetaxel, gemcitabine, paclitaxel or vinorelbine plus carboplatin or cisplatin as first line treatment options for patients with stage III or IV NSCLC and a good performance status. People who are unable to tolerate a platinum combination may be offered single-agent chemotherapy. NICE technology appraisal guidance 192 and 258 recommend gefitinib (TA192) and erlotinib (TA258) as options for the first-line treatment of people with locally advanced or metastatic NSCLC if they test positive for the EGFR-tyrosine kinase mutation. NICE technology appraisal guidance 181 and 190 recommend pemetrexed as an option for the first-line treatment (TA181) and

maintenance treatment (TA190) of advanced and metastatic non-squamous NSCLC. Recommended second line treatment options include erlotinib (TA162), and docetaxel monotherapy (CG121). Pemetrexed is not recommended for treatment of locally advanced or metastatic NSCLC after prior chemotherapy (TA124).

The technology

Crizotinib (Xalkori, Pfizer) is an orally administered inhibitor of ALK fusion protein. Crizotinib does not currently have a UK marketing authorisation for the treatment of NSCLC. It is being studied as monotherapy in clinical trials compared with pemetrexed or docetaxel in adults with previously treated advanced or metastatic NSCLC that is positive for ALK fusion genes.

Intervention(s)	Crizotinib
Population(s)	People with previously treated locally advanced or metastatic non-small-cell lung cancer that is positive for anaplastic lymphoma kinase fusion (ALK) genes.
Comparators	• Docetaxel • Erlotinib • Best supportive care
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rate • adverse effects of treatment • health-related quality of life
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. This appraisal should consider the implications of

	additional testing.
Related NICE recommendations	Related Technology Appraisals: Technology Appraisal No. 175, July 2009, 'Gefitinib for the second-line treatment of locally advanced or metastatic non-small-cell lung cancer (terminated appraisal)'. Currently being reviewed. Technology Appraisal No. 162, November 2008, 'Erlotinib for the treatment of non-small-cell lung cancer'. Review date: Currently being reviewed. Technology Appraisal No. 124, August 2007, 'Pemetrexed for the treatment of non-small-cell lung cancer'. Guidance on static list. Technology appraisal in preparation, 'Erlotinib and gefitinib for the second-line treatment of non-small-cell lung cancer (review of TA162 and TA175). Earliest anticipated date of publication: June 2014. Related Guidelines: Clinical Guideline No.121. April 2011, 'The diagnosis and treatment of lung cancer' (update of Clinical Guideline 24). Review date TBC.

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Crizotinib for the treatment of previously treated non-small-cell lung cancer associated with an anaplastic lymphoma kinase fusion gene

Matrix of consultees and commentators

Consultees	**Commentators (no right to submit or appeal)**
Manufacturers/sponsors • Pfizer (crizotinib) Patient/carer groups • Afiya Trust • Black Health Agency • British Lung Foundation • Cancer Black Care • Cancer Equality • Counsel and Care • Equalities National Council • Helen Rollason Heal Cancer Charity • Macmillan Cancer Support • Maggie's Centres • Marie Curie Cancer Care • Muslim Council of Britain • Muslim Health Network • Roy Castle Lung Cancer Foundation • South Asian Health Foundation • Specialised Healthcare Alliance • Tenovus • United Kingdom Lung Cancer Coalition Professional groups • Association of Cancer Physicians • Association of Respiratory Nurse Specialists • British Association for Services to the Elderly • British Geriatrics Society • British Institute of Radiology • British Psychosocial Oncology Society • British Thoracic Society • Cancer Networks Pharmacists Forum	General • Allied Health Professionals Federation • Board of Community Health Councils in Wales • British National Formulary • Care Quality Commission • Commissioning Support Appraisals Service • Department of Health, Social Services and Public Safety for Northern Ireland • Healthcare Improvement Scotland • Medicines and Healthcare Products Regulatory Agency • National Association for Primary Care • National Pharmacy Association • NHS Alliance • NHS Commercial Medicines Unit • NHS Confederation • Public Health Wales NHS Trust • Scottish Medicines Consortium Comparator manufacturers • Actavis UK (docetaxel) • Hospira UK (docetaxel) • Medac UK (docetaxel) • Roche Products (erlotinib) • Sandoz (docetaxel) • Sanofi Aventis (docetaxel) • Teva UK (docetaxel) Relevant research groups • British Thoracic Oncology Group • Cochrane Lung Cancer Group • Institute of Cancer Research • MRC Clinical Trials Unit

Consultees	**Commentators (no right to submit or appeal)**
• Cancer Research UK • National Lung Cancer Forum for Nurses • Primary Care Respiratory Society UK • Royal College of General Practitioners • Royal College of Nursing • Royal College of Pathologists • Royal College of Physicians • Royal College of Radiologists • Royal Pharmaceutical Society • Royal Society of Medicine • Society and College of Radiographers • United Kingdom Clinical Pharmacy Association • United Kingdom Oncology Nursing Society <u>Others</u> • Department of Health • Greater Manchester PCT Cluster • Southampton, Hampshire, Isle of Wight and Portsmouth PCT Cluster • Welsh Assembly Government	• National Cancer Research Institute • National Cancer Research Network • National Institute for Health Research • Research Institute for the Care of Older People <u>Evidence Review Group</u> • NHS Centre for Reviews and Dissemination and Centre for Health Economics, York • National Institute for Health Research Health Technology Assessment Programme <u>Associated Guideline Groups</u> • National Collaborating Centre for Cancer <u>Associated Public Health Groups</u> • None

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people who share a protected characteristic and those who do share it. Please let us know if we have missed any important organisations from the lists in the matrix, and which organisations we should include that have a particular focus on relevant equality issues.

Definitions:

Consultees

Organisations that accept an invitation to participate in the appraisal; the manufacturer(s) or sponsor(s) of the technology; national professional organisations; national patient organisations; the Department of Health and the Welsh Assembly Government and relevant NHS organisations in England.

The manufacturer/sponsor of the technology is invited to make an evidence submission, respond to consultations, nominate clinical specialists and has the right to appeal against the Final Appraisal Determination (FAD).

All non-manufacturer/sponsor consultees are invited to submit a statement[1], respond to consultations, nominate clinical specialists or patient experts and have the right to appeal against the Final Appraisal Determination (FAD).

Commentators

Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement, are able to respond to consultations and they receive the FAD for information only, without right of appeal. These organisations are: manufacturers of comparator technologies; NHS Quality Improvement Scotland; the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines); other related research groups where appropriate (for example, the Medical Research Council [MRC], National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Alliance and NHS Commercial Medicines Unit, and the British National Formulary.

All non-manufacturers/sponsors commentators are invited to nominate clinical specialists or patient experts.

Evidence Review Group (ERG)

An independent academic group commissioned by the National Institute for Health Research (NIHR) Health Technology Assessment Programme (HTAProgramme) to assist the Appraisal Committee in reviewing the manufacturer/sponsor evidence submission to the Institute.

[1] Non manufacturer consultees are invited to submit statements relevant to the group they are representing.

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single technology appraisal (STA)

Pemetrexed in continuation maintenance treatment of non-squamous NSCLC

15th October 2012

Table of Contents

List of tables and figures

.

Instructions for manufacturers and sponsors

This is the specification for submission of evidence to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal (STA) process. It shows manufacturers and sponsors what information NICE requires and the format in which it should be presented. NICE acknowledges that for medical devices manufacturers particular sections might not be as relevant as they are for pharmaceuticals manufacturers. When possible the specification will refer to requirements for medical devices, but if it hasn't done so, manufacturers or sponsors of medical devices should respond to the best of their ability in the context of the question being addressed.

Use of the specification and completion of appendices 1 to 13 (sections 9.1 to 9.13) are mandatory (when applicable), and the format should be followed whenever possible. Reasons for not following this format must be clearly stated. Sections that are not considered relevant should be marked 'N/A' and a reason given for this response. The specification should be completed with reference to the NICE document 'Guide to the methods of technology appraisal' (www.nice.org.uk), particularly with regard to the 'reference case'. Users should see NICE's 'Guide to the single technology appraisal (STA) process' (www.nice.org.uk) for further details on some of the procedural topics referred to only briefly here.

If a submission is based on preliminary regulatory recommendations, the manufacturer or sponsor must advise NICE immediately of any variation between the preliminary and final approval.

A submission should be as brief and informative as possible. It is expected that the main body of the submission will not usually exceed **100 pages excluding the pages covered by the template**. The submission should be sent to NICE electronically in Word or a compatible format, and not as a PDF file.

The submission must be a stand-alone document. Additional appendices may only be used for supplementary explanatory information that exceeds the level of detail requested, but that is considered to be relevant to the submission. Appendices are not normally presented to the Appraisal Committee. Any additional appendices should be clearly referenced in the body of the submission and should not be used for core information that has been requested in the specification. For example, it is not acceptable to attach a key study as an appendix and to complete the clinical-effectiveness section with 'see appendix X'. Clinical trial reports and protocols should not be submitted, but must be made available on request.

Trials should be identified by the first author or trial ID, rather than by relying on numerical referencing alone (for example, 'Trial 123/Jones et al.[126]' rather than 'One trial[126]').

For information on submitting cost-effectiveness analysis models, disclosure of information and equality and diversity, users should see ‘Related procedures for evidence submission’, appendix 10.

If a patient access scheme is to be included in the submission, please refer to the patient access scheme submission template available on request. Please submit both documents and ensure consistency between them.

Abbreviations used in this submission

AIC	Akaike Information Criterion
ANC	Absolute Neutrophil count
ASCO	American Society of Clinical Oncology
AUC	Area under the curve
AWMSG	All Wales Medicines Strategy Group
BIC	Bayesian Information Criterion
BSA	Body surface area
BSC	Best supportive care
BTOG	British Thoracic Oncology Group
CDF	Cancer Drugs Fund
CHMP	Committee for Medicinal Products for Human use
Cis	Cisplatin
CSR	Clinical Study report
CR	Complete response (RECIST criteria)
CR/PR/SD	Complete Response/Partial Response/Stable Disease
CT	Clinical Trial
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease control rate
DHFR	Dihydrofolate reductase
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
eMIT	Electronic Market Information Tool
EPAR	European Public Assessment Report
EQ-5D	EuroQol 5-dimension: Standardised instrument used as a measure of health outcomes
ESMO	European Society for Medical Oncology
GARFT	Glycinamide ribonucleotide formyltransferase
HR	Hazard ratio
HRG	Healthcare Resource Group
HRQL	Health related Quality of Life
IASLC	International Association for the Study of Lung Cancer
ICER	Incremental cost-effectiveness ratio
IPD	Individual-patient level data
ITT	Intention-to-treat
JMDB	Pivotal study for pemetrexed/cisplatin in the first-line NSCLC setting
JMEI	Pivotal study for pemetrexed in the second-line setting
JMEN	Pivotal study for pemetrexed in maintenance treatment following first-line treatment with non-pemetrexed regimens
KM	Kaplan-Meier
LUCADA	See NLCA
LYG/LYS	Life years gained/Life years saved

LCSS	Lung Cancer Symptom Scale
MMRM	Mixed-Effect Model Repeated Measure Model
MPM	Malignant Pleural Mesothelioma
NCI CTCAE	National Cancer Institute, Common Terminology Criteria for Adverse Events
NICE	National Institute for Health and Clinical Excellence
NLCA	Lung Cancer Audit Data (also known as LUCADA)
NS NSCLC	Non-squamous non-small cell lung cancer
NSCLC NOS	Non-small cell lung cancer not otherwise specified
NSCLC	Non-small cell lung cancer
OPCS	Office of Population, Censuses and Surveys (NHS data coding system for classification of interventions and procedures)
OS	Overall survival
PARAMOUNT	Pivotal trial for pemetrexed maintenance treatment following pemetrexed/cisplatin first-line treatment
PD	Progressive disease (RECIST criteria)
PDT	Post-discontinuation treatment (e.g. second-line chemotherapy)
Pem	Pemetrexed
Pem/cis	Pemetrexed in combination with cisplatin (or pemetrexed/cisplatin)
PFS	Progression free survival
PH	Proportional hazard
PR	Partial response (RECIST criteria)
PS	Performance status
QALY	Quality adjusted life year
QoL	Quality of Life
RECIST	Response Evaluation Criteria in Solid Tumours
RCT	Randomised Controlled Trial
SD	Stable disease (RECIST criteria)
SOC	Standard of care
SMC	Scottish Medicines Consortium
SPC	Summary of product characteristics
TA	Technology appraisal
TS	Thymidylate synthase
TTO	Time trade off
TWS	Time to worsening of symptoms
VAS	Visual analogue scale
WCC	White cell count

Executive summary

Please provide an executive summary that summarises the key sections of the submission. All statements should be directly relevant to the decision problem, be evidence-based when possible and clearly reference the relevant section of the submission. The summary should cover the following items.

Executive summary

Lung cancer

Improving survival in lung cancer patients is a key government priority as shown by its inclusion in the NHS Outcomes Framework 2011/2012. Lung cancer is the leading cause of cancer-related death in England and Wales (Cancer Research UK 2010), with about a third of patients dying within one year after diagnosis. Survival in lung cancer patients is the worst among the 'big four' cancers (lung, breast, bowel and prostate).

Survival rates for lung cancer in both men and women have improved over the last two decades (Cancer Research UK). One-year survival in men increased from 15% in the 1970s to 29% in 2005-2009. 5-year and 10-year survival rates increased too though at a slower pace. These rates possibly do not reflect the technological advances that occurred later in the mid to late-2000s, i.e., availability of pharmacological treatment options like pemetrexed, and the biological agents erlotinib and gefitinib for use in the first-line setting which have since transformed the standard of care for patients with NSCLC in the UK.

Treatment of lung cancer

NSCLC is asymptomatic in the early stages of the disease. Since lung cancer is largely asymptomatic in the early stages, patients usually present at an advanced stage, by which time their cancer is likely to be inoperable. For those with non-resectable cancer, the treatment options are chemotherapy and radiotherapy. First-line chemotherapy treatment is given following diagnosis with the aim of reducing tumour size (response), improving progression-free and overall survival whilst maintaining health-related quality of life (HRQL). Maintenance chemotherapy treatment aims to prolong the response achieved in the first-line treatment setting in patients whose disease has not progressed, i.e. to extend the duration of disease control thereby maintaining HRQL, improving progression-free survival and overall survival with minimal side-effects. Second-line treatment aims to relieve symptoms due to disease progression.

Maintenance treatment in the NHS

The administration of an active maintenance treatment immediately following first-line therapy improves overall survival in NSCLC by allowing more patients to benefit from additional treatment while tumour and symptom burden is low, patient tolerance is high and before the inevitable deterioration in performance status and disease progression occurs. Market research data show that currently in the NHS only 6% of non-squamous NSCLC patients who receive first-line treatment go on to receive maintenance treatment. Although these figures appear low, they reflect the fact that active maintenance treatment for NSCLC is a relatively new concept with the first active treatment (pemetrexed for switch maintenance) being licensed for use in the NHS as recently as 2009, and has yet to become embedded within clinical practice in the NHS.

Pemetrexed in maintenance treatment of non-squamous NSCLC

Pemetrexed was previously licensed for the treatment of locally advanced, metastatic (stage IIIB/IV) non-squamous NSCLC in the first-line and second-line settings and for maintenance treatment in patients without disease progression following first-line therapy with non-pemetrexed containing regimens (i.e., "switch maintenance"). The recent (24th October 2011) amendment to the licence allows the use of pemetrexed in advanced, metastatic (stage IIIB/IV) non-squamous NSCLC in patients who have not progressed after four cycles of pemetrexed/cisplatin first-line treatment.

There are two licensed maintenance treatment options available in the NHS, pemetrexed and erlotinib. Pemetrexed has been recommended by NICE for switch maintenance treatment of non-squamous NSCLC (TA 190). Erlotinib is not recommended by NICE for maintenance treatment of NSCLC.

Pemetrexed continuation maintenance

Pemetrexed is now licensed for treatment of patients with locally advanced or metastatic, non-squamous NSCLC who have not progressed following four cycles of pemetrexed/cisplatin first-line. The current submission presents the clinical and cost-effectiveness case for pemetrexed continuation maintenance in this population.

The PARAMOUNT study

Since pemetrexed/cisplatin is the standard of care for first-line non-squamous NSCLC in the NHS, there was a clinical demand to determine whether patients receiving pemetrexed/cisplatin first-line would benefit from further treatment with pemetrexed monotherapy in the maintenance setting. The PARAMOUNT study was designed to address this question. Key results from this study are as follows:

- Pemetrexed-treated patients experienced a significantly higher PFS benefit of 1.28 months over placebo/BSC (median overall PFS at final data lock of 4.44 months compared to 2.76 months) and a 40% reduction in risk of disease progression (HR for pemetrexed/BSC vs placebo/BSC: 0.60).

- Pemetrexed-treated patients experienced significant OS benefit of 2.85 months (median overall survival of 13.86 months vs 11.01 months for pemetrexed/BSC vs placebo/BSC, log-rank p=0.0195) and a 22% reduction in the risk of death compared to placebo-treated patients (HR for pemetrexed/BSC vs placebo/BSC: 0.78). This OS benefit was in addition to that experienced by patients treated with pemetrexed/cisplatin in the first-line treatment setting.

- 1-year and 2-year survival rates for pemetrexed treated patients were 58% and 32% respectively, compared to 45% and 21% for placebo treated patients.

- EQ-5D data were collected in PARAMOUNT with compliance rates of over 80% in the maintenance phase. No statistically significant differences in changes from baseline in EQ-5D index scores were seen between pemetrexed/BSC and placebo/BSC.

- The analysis of performance status showed that patients were able to maintain their performance status and there were no between group differences in changes in performance status from baseline. These data show that patients can tolerate long-term pemetrexed continuation maintenance without significant detrimental impact on QoL.

- Pemetrexed was well-tolerated in PARAMOUNT, with an adverse events profile consistent with the known safety profile of pemetrexed given as single-agent switch maintenance treatment in the JMEN study and second-line treatment in the JMEI study. The grade 3/4 toxicities that were significantly different between pemetrexed and placebo were neutropenia (5.8% vs 0%, p=0.0002), anaemia (6.4% vs 0.6% p=0.001) and fatigue (4.7% vs 1.1%, p=0.044).

Patient perspective on pemetrexed continuation maintenance

The implications of the PARAMOUNT study for patients suffering from this terminal disease are as follows:

- Pemetrexed continuation maintenance makes it possible for clinicians to give patients the most effective treatment (pemetrexed/cisplatin) upfront, so that patients are able get the most benefit in terms of increased survival and symptom palliation (Scagliotti et al 2008). Patients can continue pemetrexed monotherapy enabling them to maintain benefit of first-line treatment and avoid cisplatin-associated toxicities like nausea, vomiting, ototoxicity and neurotoxicity as well as hospital stays for cisplatin-required hydration.

- Pemetrexed continuation maintenance improves the outlook for patients suffering from non-squamous NSCLC by providing them with an opportunity for increased survival while maintaining their performance status and without significant detrimental impact on their quality of life. Since patients are fit enough to receive treatment, this could potentially improve their chances of receiving further chemotherapy in the second-line setting.

- Pemetrexed as a single-agent treatment requires a ten-minute infusion once every three weeks and can be administered in chemotherapy units or in the community/at home. This has the added benefit of potentially moving care of these patients from the hospital into the community, which is more convenient for patients and carers.

Pemetrexed continuation maintenance fulfils all the criteria of the NICE 'End of Life' supplementary advice

Pemetrexed continuation maintenance fulfils all three criteria specified in NICE's 'Supplementary Advice for Appraising Life Extending, End of Life Treatments' and therefore the supplementary advice should be applied to this appraisal.

- Criterion 1: The cumulative population of patients eligible for pemetrexed treatment across all NSCLC indications and mesothelioma is **5,531** (4,034 NSCLC pts; 1,497 MPM pts), which is less than the population size implicitly set at < 7,000.

- Criterion 2: The overall survival benefit for patients treated with pemetrexed/BSC from the PARAMOUNT trial was 2.85 months. Due to the high censoring for OS data, an extrapolation of the trial survival data over a lifetime horizon was undertaken. This provided a modelled mean overall survival of 4.2 months in the basecase analysis (range from the parametric distributions explored: 3.4 to 4.7 months).

- Criterion 3: The median overall survival in England and Wales is lower than 24 months

Cost-effectiveness analysis

The economic analysis compared the cost-effectiveness of pemetrexed/BSC with that of placebo ("watch and wait")/BSC as continuation maintenance in patients with locally advanced, metastatic NSCLC (stage IIIB/IV) who have not progressed following four cycles of first-line pemetrexed/cisplatin. A cost-effectiveness analysis has been conducted from the perspective of the NHS in England and Wales with a lifetime horizon. The analysis is based on a Markov model populated with individual patient data (IPD) from the PARAMOUNT study.

The survival models developed from the IPD are extrapolated and incorporated into an Excel-based state-transition Markov model.

The economic evaluation gives a deterministic ICER of £49,258 and a probabilistic ICER of £51,249. A wide range of one-way sensitivity analyses have been conducted which demonstrates consistent results across a range of alternative plausible data inputs. The Cost Effectiveness Acceptability Curves (CEAC) shows that at a £50,000 WTP threshold pemetrexed/BSC is cost-effective in 44% of simulations. At a WTP threshold of £55,000 pemetrexed/BSC is cost-effective in 56% of simulations

Conclusion

Pemetrexed continuation maintenance offers patients who currently have no treatment options immediately following first-line treatment with pemetrexed/cisplatin, but who are appropriate candidates for active chemotherapy, a cost-effective treatment under conventional thresholds when the end of life criteria are applied.

Table 1 Base-case cost-effectiveness results

	Pemetrexed	Placebo	Incremental results
Therapy costs*	£13,125	£0	£13,125
Adverse event costs	£56	£2	£54
Follow up care costs	£5,802	£6,360	-£558
Terminal care costs	£2,699	£2,738	-£39
Total costs	**£21,682**	**£9,099**	**£12,582**
LYG	1.7047	1.3537	0.3511
QALYs	1.1743	0.9188	0.2554
ICER			**£49,258**

Note: * Therapy costs includes drug acquisition, delivery and additional monitoring costs (See table 5, Section 7.7.5 for further details of cost categories);; LYG, life years gained; QALY(s), quality-adjusted life year(s); ICER, incremental cost-effectiveness ratio

- When appropriate, please present the results for the intervention and comparator(s) incrementally to indicate when options are dominated or when there is extended dominance.

Not applicable

- Subgroup analyses considered and clinical- and cost-effectiveness results.

None

Section A – Decision problem

1 Description of technology under assessment

1.1 Give the brand name, approved name and, when appropriate, therapeutic class. For devices, provide details of any different versions of the same device.

Brand Name	Alimta ®
Approved Name	Pemetrexed disodium
Therapeutic Class	Antineoplastic, folate antagonist: folic acid analogue

1.2 What is the principal mechanism of action of the technology?

Mechanism of action

Pemetrexed is a multi-targeted anti-cancer antifolate agent that disrupts crucial folate-dependent metabolic processes essential for cell replication. In vitro studies have shown that pemetrexed behaves as a multi-targeted antifolate by inhibiting thymidylate synthase (TS), dihydrofolate reductase (DHFR), and glycinamide ribonucleotide formyltransferase (GARFT), which are key folate-dependent enzymes for the de novo biosynthesis of thymidine and purine nucleotides.

Efficacy in 'other than predominantly squamous' (i.e., non-squamous) vs squamous histology

Clinical evidence from the studies JMEI (Peterson et al 2007, Scagliotti et al 2009), NS01 (Ohe et al 2008), JMDB (Scagliotti et al 2008) and JMEN (Ciuleanu et al 2009) shows that pemetrexed has greater efficacy in patients with NSCLC of other than predominantly squamous (i.e., non-squamous) histology compared to squamous histology.

Early preclinical data on pemetrexed had shown a correlation between over-expression of TS with reduced sensitivity to pemetrexed in antifolate-resistant cell lines (Sigmond et al. 2003; Giovannetti et al. 2005). Subsequently, Ceppi et al (2006) showed that TS expression was higher in Non-small cell lung cancer (NSCLC) specimens from patients with squamous cell carcinoma, as compared to adenocarcinoma. These results suggested that the reduced clinical efficacy of pemetrexed in patients with predominantly squamous cell carcinoma may be attributed to higher TS expression in these tumours.

1.3 Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, give the date on which authorisation was received. If not, state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

The indication relevant to this submission is the maintenance treatment of NSCLC, as described in the summary of product characteristics (SPC) for pemetrexed:

Pemetrexed is indicated as monotherapy for the maintenance treatment of locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology in patients whose disease has not progressed immediately following ***platinum-based chemotherapy.***

Pemetrexed was previously licensed for maintenance treatment following first-line treatment with non-pemetrexed containing regimens. Marketing authorisation for the use of pemetrexed monotherapy as maintenance treatment following first-line *pemetrexed/cisplatin* was received on 24th October 2011 after which the text of the maintenance indication was revised to reflect the licence extension. NICE has previously issued positive guidance on the use of pemetrexed as maintenance treatment following first-line regimens not including pemetrexed (TA190).

In line with the licence, this submission presents the clinical and cost-effectiveness case for pemetrexed in locally advanced or metastatic (stage IIIB/IV), non-squamous NSCLC in patients whose disease has not progressed immediately following first-line chemotherapy with *pemetrexed/cisplatin* and are of good performance status (PS 0-1).

Note: *Maintenance* treatment is anti-cancer treatment given to patients who do not experience disease progression following first-line treatment. The terms '*continuation maintenance*' and '*switch maintenance'* are used in relation to maintenance treatment in this submission as explained below:

Continuation maintenance: The agent used for maintenance treatment is the same as one of the agents used for first-line treatment, e.g. pemetrexed following pemetrexed/cisplatin first-line.

Switch maintenance: The agent used for maintenance treatment is different from the agent(s) used for first-line treatment, e.g. pemetrexed following gemcitabine/cisplatin or any other regimen not including pemetrexed first-line.

The current submission is for '*continuation maintenance'* with pemetrexed.

1.4 Describe the main issues discussed by the regulatory organisation (preferably by referring to the [draft] assessment report [for example, the EPAR]). If appropriate, state any special conditions attached to the marketing authorisation (for example, exceptional circumstances/conditions to the marketing authorisation).

The EU regulatory submission for pemetrexed maintenance was based on the progression free survival (PFS) data from the pivotal PARAMOUNT study (Paz-Ares et al, 2012) and the European Public Assessment Report (EPAR) was published towards the end of 2011. Subsequently, the overall survival (OS) results for this study were disclosed (Paz-Ares et al. June 2012) and have also been submitted to the regulator. The updated EPAR with the OS data is expected to be available in November 2012.

The section on benefit-risk balance in the current EPAR states:

"The benefit-risk balance of pemetrexed as maintenance treatment after a first line platinum-pemetrexed combination is considered as positive, as the demonstrated statistically significant gain in PFS outweighs the added toxicity of pemetrexed given as maintenance treatment after induction chemotherapy with a platinum-pemetrexed combination."

In the discussion on the benefit-risk balance, the EPAR document refers to the PARAMOUNT trial, which is the pivotal trial for pemetrexed in continuation maintenance treatment of

NSCLC. It also refers to previous studies on pemetrexed in first-line and switch maintenance treatment of NSCLC - study JMDB (Scagliotti et al 2008) and study JMEN (Ciuleanu et al 2009). The EPAR states:

"The PARAMOUNT study added a new piece of information on the use of pemetrexed as maintenance treatment of NSCLC other than predominantly squamous cell histology after first line induction treatment with platinum chemotherapy that included pemetrexed. Two questions resulting from the pemetrexed maintenance treatment had been: 1) whether the OS benefit observed in trial JMEN was only due to the delayed administration of otherwise efficacious pemetrexed and 2) whether pemetrexed maintenance is beneficial (even) after pemetrexed induction. PARAMOUNT showed that patients derive additional benefit from continuing pemetrexed as maintenance treatment after induction chemotherapy which includes pemetrexed."

"Based on PARAMOUNT and earlier studies in both maintenance (JMEN) and first-line (JMDB) treatment, there is little uncertainty in the knowledge of favourable and unfavourable effects in the use of pemetrexed as maintenance treatment after a first line platinum-pemetrexed combination to change the benefit-risk balance."

1.5 What are the (anticipated) indication(s) in the UK? For devices, provide the (anticipated) CE marking, including the indication for use.

Pemetrexed is licensed in the UK for the treatment of malignant pleural mesothelioma and first-line, maintenance and second-line treatment of non-squamous NSCLC. The details of the licensed indications are presented below.

Malignant pleural mesothelioma:

Pemetrexed in combination with cisplatin is indicated for the treatment of chemotherapy naive patients with unresectable malignant pleural mesothelioma.

Non-small cell lung cancer:

First-line treatment:

Pemetrexed in combination with cisplatin is indicated for the first-line treatment of patients with locally advanced or metastatic NSCLC other than predominantly squamous cell histology.

Maintenance treatment: (indication relevant to this submission)

Pemetrexed is indicated as monotherapy for the maintenance treatment of locally advanced or metastatic NSCLC other than predominantly squamous cell histology in patients whose disease has not progressed immediately following platinum-based chemotherapy.

Second-line treatment:

Pemetrexed is indicated as monotherapy for the second-line treatment of patients with locally advanced or metastatic NSCLC other than predominantly squamous cell histology.

1.6 Please provide details of all completed and ongoing studies from which additional evidence is likely to be available in the next 12 months for the indication being appraised.

There are two ongoing Lilly-sponsored phase 3 studies on pemetrexed as maintenance treatment from which results are expected during the next 12 months, as shown in Table 2.

Table 2 Completed and ongoing studies on pemetrexed in continuation maintenance treatment of NSCLC for which results are anticipated during the next 12 months

NCT No. / Trial acronym	Objective	Study design	Date of completion
NCT00948675 / H3E-US-S130	To compare progression free survival (PFS) without grade 4 toxicity on pemetrexed +carboplatin[1] followed by pemetrexed maintenance versus paclitaxel+ carboplatin + bevacizumab followed by bevacizumab maintenance in patients with stage IIIB or IV NSCLC.	Randomised, open-label, phase 3 study	June 2013 (as per clinical trials.gov)
NCT00762034 / H3E-MC-JMHD	To compare overall survival on first-line treatment with pemetrexed[1] + carboplatin + bevacizumab, followed by maintenance pemetrexed[2]+bevacizumab versus paclitaxel + carboplatin + bevacizumab followed by maintenance bevacizumab, in patients with stage IIIB or IV non-squamous NSCLC.	Randomised, open-label, phase 3 study	Results presented at the IASLC September 2012. Publication expected end 2012

[1]: Pemetrexed is only licensed for use in combination with cisplatin in first-line NSCLC. [2] Pemetrexed is only licensed for use as monotherapy in maintenance NSCLC.
IASLC: International Association for the Study of Lung Cancer

1.7 If the technology has not been launched, please supply the anticipated date of availability in the UK.

Pemetrexed is already licensed and marketed in the UK for all the indications listed in 1.5 above. (Also see 1.3 above).

1.8 Does the technology have regulatory approval outside the UK? If so, please provide details.

Pemetrexed is approved for maintenance treatment of NSCLC following platinum-based chemotherapy within the EU, Switzerland, the US and Australia. Regulatory submissions based on PARAMOUNT data have been filed in US and Canada, approval is currently pending.

1.9 Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?

Pemetrexed in continuation maintenance treatment of non-squamous locally advanced or metastatic NSCLC following first-line chemotherapy has not yet been submitted for assessment to the Scottish Medicines Consortium (SMC). A submission to the SMC in the specified timeframe (within 12 weeks of the product being available for use) was not feasible since overall survival (OS) results from the pivotal study for this indication (PARAMOUNT, Paz-Ares et al 2012) were not available at that time. OS being a key secondary endpoint, these results were necessary for a comprehensive assessment of pemetrexed for continuation maintenance. In the absence of a submission, the SMC issued negative advice for pemetrexed in continuation maintenance (SMC No. 770/12) in February 2012.

Pemetrexed in continuation maintenance treatment of non-squamous locally advanced or metastatic NSCLC following first-line chemotherapy has not been submitted for assessment to the All Wales Medicines Strategy Group (AWMSG), since a submission to NICE later during the year was anticipated. In the absence of a submission, the AWMSG issued negative advice for pemetrexed in continuation maintenance in February 2012.

1.10 For pharmaceuticals, please complete the table below. If the unit cost of the pharmaceutical is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Table 3 Unit costs of technology being appraised

Pharmaceutical formulation	Powder for concentrate for solution for infusion
Acquisition cost (excluding VAT)	The list price for pemetrexed (MIMS March 2012) is as follows: 100 mg vial : £160.00 500 mg vial: £800.00
Method of administration	Intravenous infusion
Doses	In patients treated for non-squamous NSCLC after prior (first-line) chemotherapy, the recommended dose of pemetrexed is 500mg/m^2 of body surface area (BSA) administered as an intravenous infusion over 10 minutes on the first day of each 21-day cycle.
Dosing frequency	Pemetrexed is administered on the first day of each 21-day cycle
Average length of a course of treatment	Patients in the pivotal PARAMOUNT study (Paz-Ares et al 2012) received a mean of 7.86 cycles of and a median of 4 cycles of pemetrexed in the maintenance phase. In the PARAMOUNT trial, patients continued to receive treatment until disease progression, toxicity or patient or physician decision. In actual clinical practice, patients are treated to progression or until toxicity precludes further chemotherapy.
Average cost of a course of treatment	Drug cost for each treatment cycle is £1440 based on an average BSA of 1.79m^2. Since patients are treated until disease progression or toxicity, the duration of a course of treatment and consequently its cost is variable.
Anticipated average interval between courses of treatments	Patients will not receive more than one course of maintenance treatment
Anticipated number of repeat courses of treatments	Patients will not receive more than one course of maintenance treatment
Dose adjustments	Dose adjustments at the start of each subsequent cycle should be based on nadir haematologic counts or maximum non-haematologic toxicity from the preceding cycle of therapy. *Please see the summary of product characteristics (SPC) for pemetrexed, Section 4.2, for details of dosage adjustment due to haematologic, non-haematologic or neurotoxicity due to pemetrexed*.

1.11 For devices, please provide the list price and average selling price. If the unit cost of the device is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Not applicable

1.12 Are there additional tests or investigations needed for selection, or particular administration requirements for this technology?

- No additional histological diagnostic tests or radiological scans are required for selection of patients prior to pemetrexed maintenance treatment.
- There are no additional administration requirements for pemetrexed.

Since the licence for pemetrexed in continuation maintenance restricts the use of pemetrexed to patients who have not progressed following first-line treatment with pemetrexed/cisplatin, the histological subtype would already have been identified prior to first-line treatment and no additional histological diagnostic tests would be required before pemetrexed maintenance treatment.

Since only those patients who have not progressed following first-line chemotherapy are eligible for maintenance treatment, a CT scan / X-ray is necessary to assess response to first-line treatment prior to initiating maintenance treatment. According to the BTOG National survey on follow-up of advanced NSCLC patients after first-line chemotherapy (Beckett et al 2012), in routine clinical practice, patients usually have a CT-scan/ X-ray after the second and fourth cycles of first-line chemotherapy. Patients eligible for pemetrexed continuation maintenance could be identified based on this assessment itself and therefore no additional X-ray/CT scan is required before starting pemetrexed maintenance treatment.

Pemetrexed as a single-agent treatment requires a ten-minute infusion once every three weeks and can be administered by clinical staff trained in administration of oncolytics in chemotherapy units or in the community/ at home. There are no additional requirements for pemetrexed administration.

1.13 Is there a need for monitoring of patients over and above usual clinical practice for this technology?

According to the summary of product characteristics (SPC), patients receiving pemetrexed should be monitored before each dose with a complete blood count, including a differential white cell count (WCC) and platelet count. Prior to each chemotherapy administration, blood chemistry tests should be collected to evaluate renal and hepatic function. Before the start of any cycle of chemotherapy, patients are required to have the following: absolute neutrophil count (ANC) should be ≥ 1,500 cells/mm^3 and platelets should be ≥ 100,000 cells/mm^3.

There is no data on the frequency of monitoring during maintenance treatment in current NHS clinical practice. According to data from the BTOG survey on follow-up after first-line chemotherapy, patients with NSCLC typically see a consultant four to six weeks after completing first-line treatment (Beckett et al 2012). At this visit 14% of patients routinely receive a CT scan. X-rays are more commonly used with 46% of patients receiving them.

Further follow up visits routinely take place at six- to 12-week intervals. Only 3% of patients receive CT scans at every visit whilst 58% receive x-rays at every visit. CT scans are mainly used only when symptoms worsen (Beckett et al, 2012).

In PARAMOUNT, the mean duration of treatment was 5 cycles of placebo/BSC and 7.9 cycles of pemetrexed/BSC, i.e. approximately 15 weeks for placebo/BSC and 24 weeks for pemetrexed/BSC. If we assume that, after the first follow up visit between four to six weeks, follow up visits routinely occur every nine weeks, we anticipate that over the 24-week mean duration of pemetrexed maintenance treatment, patients on pemetrexed maintenance treatment will require one additional consultant visit and additional CT scans and x-rays. However, not all patients are expected to undergo chest X-rays and CT scans, as data from the BTOG survey reported above shows.

1.14 What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

Pemetrexed is administered as a 10 minute IV infusion. Concomitant vitamin supplementation and corticosteroid prophylaxis is required, as specified in Section 4.2 of the pemetrexed SPC.

Concomitant Medication Regimen

Vitamin Supplementation

Folic acid – Daily oral folic acid or a multivitamin containing folic acid (350-1,000mcg). At least five doses of folic acid must be taken in the seven days preceding the first dose of pemetrexed. Dosing must continue during the full course of therapy and for 21 days after the last dose of pemetrexed.

Vitamin B_{12} – Intramuscular injection of vitamin B_{12} (1000mcg) in the week preceding the first dose of pemetrexed and once every three cycles thereafter. Subsequent vitamin B_{12} injections may be given on the same day as pemetrexed.

Corticosteroids

A corticosteroid should be given the day prior to, on the day of, and the day after pemetrexed administration.

2 Context

2.1 Please provide a brief overview of the disease or condition for which the technology is being used. Include details of the underlying course of the disease.

Lung cancer incidence and mortality

Lung cancer is the leading cause of cancer-related death in England and Wales (Cancer Research UK, 2010). It is also the second most common cancer in England and Wales with 35,406 new cases reported in 2009 (Cancer Research UK, 2009). About 90% of lung cancers are due to smoking.

Lung cancer consists of two main histological categories. The majority (78%) are non-small cell type (NSCLC) with the rest being small cell lung cancer (NICE CG121). NSCLC may be further classified into histological subtypes of squamous (32%), adenocarcinoma (26%), NSCLC not otherwise specified (NOS, 35%) and large cell carcinoma (4%) (NICE CG121). The histological diagnosis rate for patients with lung cancer in England and Wales is 76% (National Lung cancer Audit report (NLCA), 2011).

The prognosis for patients with lung cancer depends on the disease stage at diagnosis, i.e, the size and degree of spread of the tumour. Since lung cancer is largely asymptomatic in the early stages, patients usually present at an advanced stage. NLCA data shows that 65% of patients with histologically confirmed NSCLC have advanced metastatic (stage IIIB or stage IV tumours) cancer at the time of presentation (NLCA information sheet 2011). Late presentation in turn translates into lower survival rates. One-year survival rates of 32% (NLCA information sheet 2011) and a 5-year survival rate of 9% (Office of National Statistics, 2010) have been reported.

Treatment of NSCLC

Treatment options for NSCLC depend on the stage of the disease at presentation. For stage IIIB or IV NSCLC, options include radiotherapy or chemotherapy alone or a combination of the two. Chemotherapy may be recommended for patients with non-resectable stage III or IV disease, provided they are of good performance status (PS 0-1). Approximately 53% of NSCLC patients with advanced disease (stage IIIB/IV) and good performance status (PS 0-1) receive chemotherapy for NSCLC in England and Wales (NLCA information sheet 2011). Patients with EGFR positive mutation status are given erlotinib or gefitinib in the first-line setting.

Pemetrexed/cisplatin is established as the chemotherapy regimen of choice for the first-line treatment of patients with non-squamous, EGFR mutation negative NSCLC. Patients without disease progression after first-line pemetrexed/cisplatin usually receive no further active treatment but instead undergo “watch and wait” plus BSC until disease progression, upon which second-line treatment may be initiated.

Maintenance treatment of NSCLC

Maintenance treatment of NSCLC is a relatively new concept which aims to maintain the clinical benefit achieved after first-line chemotherapy, postpone disease progression and ultimately prolong overall survival along with palliation of disease symptoms. Maintenance treatment of NSCLC is not yet well-established in the NHS given that licensed and recommended treatment have only been available since 2010.

Pemetrexed switch maintenance

Pemetrexed is the first and only active treatment option to be licensed and recommended by NICE (TA190) for switch maintenance treatment of locally advanced or metastatic non-squamous NSCLC. Even after a positive NICE recommendation, the uptake of pemetrexed switch maintenance has been low, since the use of pemetrexed /cisplatin in the first-line setting precluded the use of maintenance pemetrexed (prior to October 2011). This meant that a large number of patients were treated with pemetrexed/cisplatin first-line and consequently were not eligible for pemetrexed maintenance treatment. The only option open to these patients was to undergo "watch and wait" plus BSC. No treatment option other than pemetrexed is licensed **and** NICE-recommended for maintenance treatment of non-squamous NSCLC in the NHS.

Continuation maintenance with pemetrexed

Subsequent to the licence amendment allowing the use of pemetrexed as continuation maintenance in patients without disease progression after first-line pemetrexed/cisplatin (in October 2011), patients who previously could not avail of pemetrexed maintenance treatment, will now become eligible for this. **The evidence base for pemetrexed continuation maintenance consists of the phase 3, double-blind, randomised, placebo-controlled registration study PARAMOUNT (Paz-Ares et al, ASCO presentation 2012), the first study to demonstrate an OS benefit in the continuation maintenance setting**. Results from the PARAMOUNT trial have shown that pemetrexed continuation maintenance offered increased overall and progression free survival and was well-tolerated which meant that patients were able to continue pemetrexed monotherapy without any significant impact on their quality of life.

The increased number of patients eligible for pemetrexed maintenance and positive results from the PARAMOUNT study are likely to contribute towards an increased acceptance of maintenance treatment of NSCLC within the NHS.

Benefits of pemetrexed continuation maintenance from the viewpoint of patients and clinicians

Pemetrexed continuation maintenance makes it possible for clinicians to give patients the most effective treatment (pemetrexed/cisplatin) upfront, so that patients are able get the most benefit in terms of increased survival and symptom palliation (Scagliotti et al 2008). Patients can continue pemetrexed monotherapy enabling them to maintain benefit of first-line treatment and avoid cisplatin-associated toxicities like nausea, vomiting, ototoxicity and neurotoxicity as well as hospital stays for cisplatin-required hydration.

Pemetrexed continuation maintenance improves the outlook for patients suffering from non-squamous NSCLC by providing them with an opportunity for increased survival while maintaining their performance status and without significant detrimental impact on their quality of life. As a result, patients may remain fit enough to receive treatment even after disease progression.

Pemetrexed as a single-agent treatment requires a ten-minute infusion once every three weeks and can be administered in chemotherapy units or in the community/ at home. This has the added benefit of potentially moving care of these patients from the hospital into the community, which is more convenient for patients and carers.

Pemetrexed continuation maintenance could potentially improve one and five year survival rates, which are a key government priority.

2.2 Please provide the number of patients covered by this particular therapeutic indication in the marketing authorisation and also including all the therapeutic indications for the technology, or for which the technology is otherwise indicated, in England and Wales and provide the source of the data.

Pemetrexed is licensed for maintenance treatment of non-squamous NSCLC. NICE TA190 addressed pemetrexed switch maintenance while the current submission is for pemetrexed continuation maintenance treatment.

The eligible population for this appraisal consists of non-squamous, locally advanced or metastatic (stage IIIB/IV) NSCLC patients with good performance status (PS 0-1), whose disease has not progressed following four cycles of first-line chemotherapy with pemetrexed/cisplatin.

Table 4 shows that approximately **535** patients in England and Wales are eligible for continuation maintenance treatment with pemetrexed, assuming that every patient who is eligible for pemetrexed continuation maintenance, would go on to receive it. Market research data shows that uptake of maintenance treatment in the NHS so far has been low, with only 6% of first-line non-squamous patients receiving maintenance treatment in the NHS (Market research data, Q2 2012). One reason for the low uptake is that patients receiving pemetrexed/cisplatin in the first-line setting could not go on to receive pemetrexed maintenance treatment prior to October 2011. Uptake of pemetrexed maintenance treatment is anticipated to rise now that it can be given following pemetrexed/cisplatin in the first-line setting.

See Section on End of Life Supplementary Criteria for details of the number of patients covered in the marketing authorisation for all the therapeutic indications.

Table 4 Patients eligible for continuation maintenance with pemetrexed in England and Wales, according to the licensed indication in the SPC

Description	% patients	Number	References
Patients with Lung cancer		32,347 (reported)	NLCA audit report 2011
Patients with confirmed NSCLC		19,163 (reported)	NLCA audit report 2011
Patients with stage IIIB/IV NSCLC and PS 0-1		5,932 (reported)	NLCA audit report 2011
Non-squamous NSCLC patients with stage IIIB/IV NSCLC and PS 0-1	68% (reported)	4,034 (calculated)	NICE Lung Cancer Clinical Guideline 121, 2011
Non-squamous NSCLC patients with stage IIIB/IV and PS 0-1 receiving chemotherapy	52.8% (reported)	2130 (calculated)	NLCA audit report 2011
Patients receiving pem/cis first-line	43% (reported)	916 (calculated)	Market research data, Q2 2012
Patients eligible for pemetrexed continuation maintenance (i.e., pts without disease progression following 1st line treatment)	58.4% (calculated as proportion of patients eligible to enter the maintenance phase in PARAMOUNT)	535 (calculated)	PARAMOUNT study, Paz-Ares et al Lancet Oncology 2012

2.3 Please provide information about the life expectancy of people with the disease in England and Wales and provide the source of the data.

According to the lung cancer audit data for the 2010 analysed population (N=32,344), the median OS and interquartile range by network for patients was 181 (54 - 318) days (NLCA information sheet 2011), which is approximately 6 (1.8 - 10.5) months. 1-year survival in men increased from 15% in the 1970s to 29% in 2005-2009. 5-year and 10-year survival rates increased too though at a slower pace.

2.4 Please give details of any relevant NICE guidance or protocols for the condition for which the technology is being used. Specify whether any specific subgroups were addressed.

The NICE guideline on lung cancer (CG121) and the clinical practice guideline of the European Society for Medical Oncology (ESMO) (Peters et al 2012) on metastatic lung cancer are relevant to clinical practice in the UK. In addition to these guidelines, NICE has also issued Technology Appraisal guidance on pemetrexed (TA190) and erlotinib (TA 227) for switch maintenance of NSCLC. Pemetrexed and erlotinib are the only two agents licensed for maintenance treatment of NSCLC in the UK. However, pemetrexed remains the only NICE recommended maintenance (i.e. switch maintenance).

Key aspects of these guidelines /guidance are presented below.

NICE guideline on diagnosis and treatment of lung cancer CG121 (April 2011)

The NICE guideline (CG121) covers the diagnosis and treatment of patients with lung cancer. At the time this guideline was published, there were a number of technology appraisals for pemetrexed, gefitinib and erlotinib, with mandatory funding directives in place. As a result, it was not considered necessary to update the NSCLC chemotherapy section within the guideline, instead, existing recommendations from the older (CG24, 2005) guideline pertaining mainly to first-line treatment, were retained. The recommendations currently in CG121 were drafted before pemetrexed became standard of care for first-line treatment of NSCLC and well in advance of the licensing and positive NICE guidance for pemetrexed in switch maintenance treatment of NSCLC. The recommendations are as follows:

1.4.40. Chemotherapy should be offered to patients with stage III or IV NSCLC and good performance status (WHO 0, 1 or a Karnofsky score of 80–100), to improve survival, disease control and quality of life.

1.4.41. Chemotherapy for advanced NSCLC should be a combination of a single third-generation drug (docetaxel, gemcitabine, paclitaxel or vinorelbine) plus a platinum drug. Either carboplatin or cisplatin may be administered, taking account of their toxicities, efficacy and convenience.

1.4.42. Patients who are unable to tolerate a platinum combination may be offered single-agent chemotherapy with a third-generation drug.

CG121 does not contain any recommendations on maintenance treatment and instead refers to the NICE guidance on pemetrexed (TA190), and erlotinib (TA227, in progress at the time) under the heading 'Related guidance'.

European Society for Medical Oncology (ESMO) guideline on metastatic NSCLC

The European Society for Medical Oncology (ESMO) clinical practice guideline (Peters et al 2012) on metastatic NSCLC includes a recommendation on pemetrexed continuation maintenance treatment which is as follows:

"Randomised trials investigating continuation maintenance have consistently shown an improvement of the PFS but not the OS. Recently, a large phase III randomised trial of continuation maintenance with pemetrexed versus placebo after four induction cycles of cisplatin plus pemetrexed chemotherapy demonstrated a PFS and OS improvement. Continuing pemetrexed following the completion of first-line cisplatin plus pemetrexed chemotherapy is therefore recommended in patients with a non-squamous histology."

NICE guidance on pemetrexed (switch maintenance) and erlotinib pertaining to maintenance treatment of NSCLC

Pemetrexed for maintenance treatment of non-small cell lung cancer (TA190, June 2010)

At the time TA190 was issued, pemetrexed was licensed for use in patients who had not progressed following first-line treatment with non-pemetrexed regimens. Accordingly, TA190 only covers the relevant patient population. Based on the results of the PARAMOUNT clinical study, the licensed indication for pemetrexed has since been revised to allow treatment in patients who have received first-line platinum-based chemotherapy in general (including pemetrexed/cisplatin).

The guidance states:

People who have received pemetrexed in combination with cisplatin as first-line chemotherapy cannot receive pemetrexed maintenance treatment.

1.1 Pemetrexed is recommended as an option for the maintenance treatment of people with locally advanced or metastatic non-small-cell lung cancer other than predominantly squamous cell histology if disease has not progressed immediately following platinum-based chemotherapy in combination with gemcitabine, paclitaxel, or docetaxel.

Erlotinib monotherapy for maintenance treatment of NSCLC (TA 227, June 2011)

The guidance states:

1.1 Erlotinib monotherapy is not recommended for maintenance treatment in people with locally advanced or metastatic non-small-cell lung cancer who have stable disease after platinum-based first-line chemotherapy.

1.2 People currently receiving erlotinib monotherapy for maintenance treatment of locally advanced or metastatic non-small-cell lung cancer who have stable disease after platinum-based first-line chemotherapy should have the option to continue treatment until they and their clinician consider it appropriate to stop.

2.5 Please present the clinical pathway of care that depicts the context of the proposed use of the technology. Explain how the new technology may change the existing pathway. If a relevant NICE clinical guideline has been published, the response to this question should be consistent with the guideline and any differences should be explained.

Figure 1 shows the care pathway for NSCLC in England and Wales for patients diagnosed with advanced, non-squamous, EGFR mutation negative NSCLC. The relevant NICE guideline / guidance is indicated at each stage in the treatment pathway.

Pemetrexed/cisplatin is established as the chemotherapy regimen of choice for the first-line treatment of patients with non-squamous, EGFR mutation negative NSCLC, with a market share of 43% (Market research data, Q2 2012) of all stage IIIB/IV NSCLC patients. Another available option is gemcitabine in combination with cisplatin or carboplatin (2% and 12% market share respectively, Q2 2012, Market research data).

Treatment options following first-line therapy

The majority of patients who do not progress following first-line (induction) chemotherapy are not immediately given further active treatment. Induction treatment is routinely followed by a period of 'watch and wait' during which patients undergo clinical assessment and receive best supportive care (BSC), as necessary. On disease progression, patients are usually offered second-line chemotherapy with docetaxel or erlotinib, depending on performance status and eligibility.

Active treatment with pemetrexed is an alternative to the 'watch and wait' phase of the treatment pathway, for patients who have not progressed after four cycles of first-line treatment. The aim of maintenance treatment is to extend the benefit of successful first-line therapy while maintaining patients' quality of life. Administration of a well-tolerated maintenance regimen immediately following first-line therapy allows patients to benefit from additional treatment while tumour and symptom burden is low, patient tolerance is high and before the inevitable deterioration in performance status and disease progression occurs.

Pemetrexed as switch maintenance

As stated earlier, pemetrexed was the first and only licensed and NICE-recommended option for switch maintenance treatment following first-line treatment with platinum-based chemotherapy other than pemetrexed (TA190).

Pemetrexed as continuation maintenance

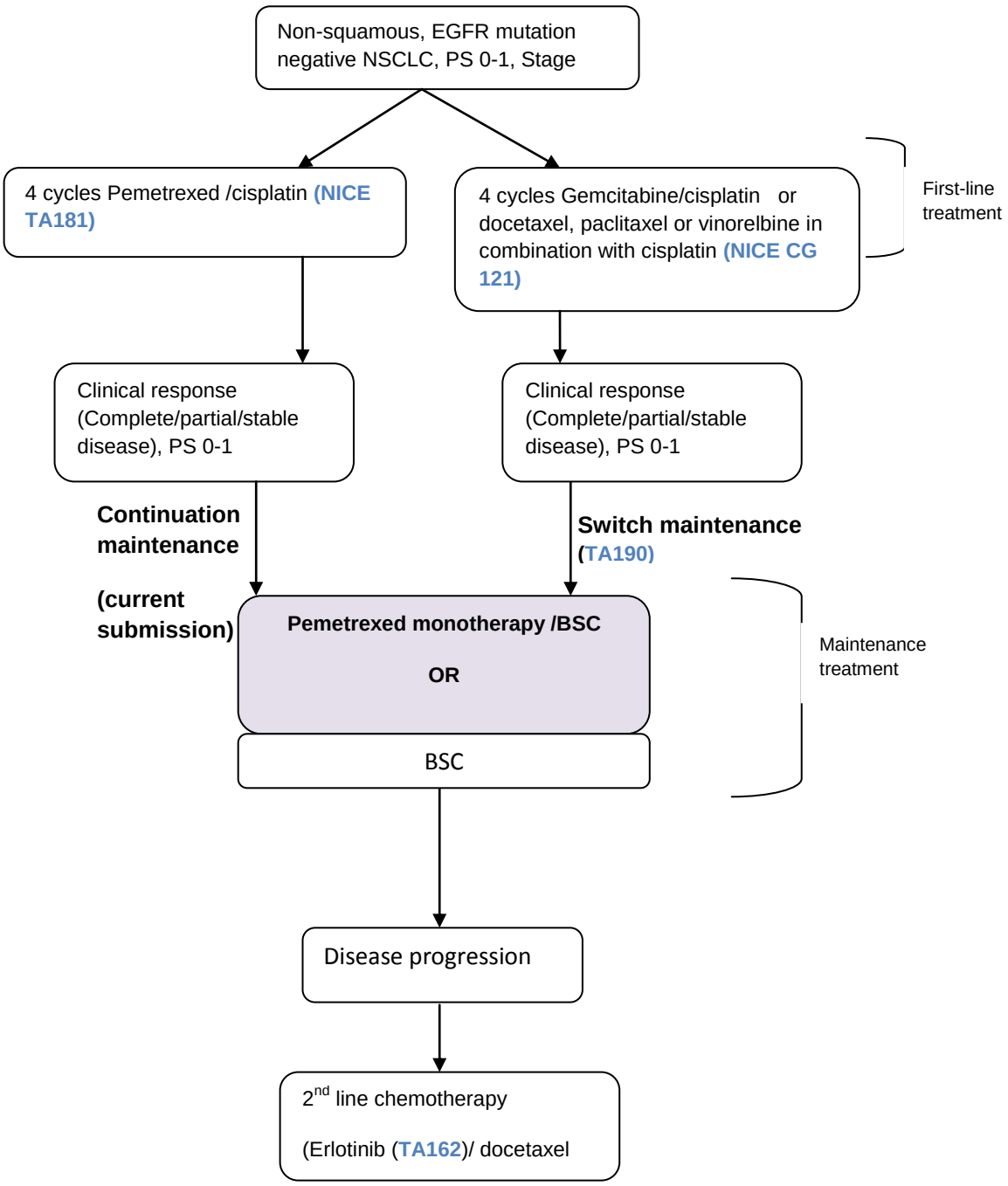
Pemetrexed/cisplatin is the standard of care in first-line treatment of patients with non-squamous.. Prior to 24th October 2011, these patients would not have been eligible for pemetrexed maintenance treatment since pemetrexed was only licensed for switch maintenance. The only alternative for these patients would have been best supportive care (BSC). The recent licence extension for pemetrexed as a maintenance treatment following first-line therapy with pemetrexed/cisplatin (i.e., continuation maintenance) allows patients whose disease has not progressed following pemetrexed/cisplatin first-line therapy to continue on pemetrexed monotherapy in the maintenance phase.

Pemetrexed is now the only active treatment option licensed for use in the maintenance setting that can be given to patients regardless of the regimen (i.e., pemetrexed/non-pemetrexed containing) they receive as first-line treatment. Pemetrexed continuation maintenance offers patients increased survival while maintaining their performance status and without significant detrimental impact on their quality of life. Since patients are fit enough to receive treatment, this could potentially improve their chances of receiving further chemotherapy in the second-line setting.

Pemetrexed as a single-agent treatment requires a ten-minute infusion once every three weeks and can be administered in chemotherapy units or in the community/ at home. This has the added benefit of potentially moving care of these patients from the hospital into the community, which is more convenient for patients and carers.

Pemetrexed continuation maintenance makes it possible for clinicians to give patients the most effective treatment (pemetrexed/cisplatin) upfront, so that patients are able get the most benefit in terms of increased survival and symptom palliation (Scagliotti et al 2008). Patients can continue pemetrexed monotherapy enabling them to maintain benefit of first-line treatment and avoid cisplatin-associated toxicities like nausea, vomiting, ototoxicity and neurotoxicity as well as hospital stays for cisplatin-required hydration.

Figure 1 Treatment pathway for advanced EGFR mutation negative, non-squamous NSCLC in NHS England and Wales



2.6 Please describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

Absence of guidelines on radiological investigations for follow-up of advanced NSCLC patients in the UK NHS: There are no formal clinical guidelines on the radiological investigations to be conducted on patients before, during and following active chemotherapy for NSCLC. In the absence of guidelines, there does not appear to be any consensus on what radiological tests should be conducted on patients with active maintenance treatment. Evidence for this comes from a survey of UK oncologists (N=106) by the BTOG on the follow-up of patients with advanced NSCLC following first-line chemotherapy, which showed considerable variation in radiological tests performed before, during and post-treatment (Beckett et al, 2012).

In the absence of guidelines or recommendations and in light of variations in clinical practice, the frequency of radiological scans for pemetrexed continuation maintenance treatment incorporated in the cost-effectiveness analysis for this submission is based on clinical practice followed by the majority of respondents to the BTOG survey described previously.

2.7 Please identify the main comparator(s) and justify their selection.

Since most patients who do not progress following first-line treatment in routine clinical practice undergo “watch and wait” plus BSC in the maintenance phase rather than active treatment, “watch and wait” plus BSC (i.e. placebo plus BSC) is the only comparator to maintenance treatment with pemetrexed monotherapy in patients who have not progressed following four cycles of first-line treatment with pemetrexed/cisplatin.

Rationale

Options for maintenance treatment

Of the pharmacological treatment options available for maintenance treatment of NSCLC, only erlotinib and pemetrexed are licensed for use in the UK. Market research data (Q2 2012) shows that currently, uptake for maintenance treatment in the NHS is low, with only 6% of non-squamous NSCLC patients receiving first-line therapy going on to receive maintenance treatment. Given that 916 patients with non-squamous NSCLC currently receive first-line chemotherapy (see Table 5), only 55 would go on to receive maintenance treatment. Of these, 66% (36 patients) receive pemetrexed as maintenance therapy. Of these 32% (12 patients) receive continuation maintenance and the remaining (24 patients) switch maintenance (Market research data, Q2 2012). As explained in Section 2.2, the low patient numbers in the maintenance phase reflect the high uptake of pemetrexed/cisplatin in the first-line setting, which precluded the use of pemetrexed in the maintenance setting. Subsequent to the amendment to the label allowing the use of pemetrexed as continuation maintenance and in the light of the positive results from the PARAMOUNT trial, uptake of pemetrexed maintenance treatment in the NHS is likely to increase as the number of patients eligible for such treatment increases.

Pemetrexed continuation maintenance

Pemetrexed is the only NICE-approved option for **switch maintenance** treatment of NSCLC. Pemetrexed/cisplatin is currently the standard of care for first-line treatment of non-squamous NSCLC in the UK. The recent licence extension for pemetrexed permits its use as **continuation maintenance** in patients who have not progressed i.e. have complete/partial response (CR/PR) or stable disease (SD) immediately following treatment with first-line pemetrexed/cisplatin.

Erlotinib

Erlotinib is indicated as monotherapy for maintenance treatment in patients with locally advanced or metastatic NSCLC with ***stable disease*** after four cycles of standard platinum-based first-line chemotherapy. Erlotinib is not licensed for maintenance treatment for patients with CR/PR following first-line chemotherapy and is not recommended by NICE for maintenance treatment (TA227). As a result, it is not established in NHS clinical practice and is available only through the Cancer Drugs fund.

2.8 Please list therapies that may be prescribed to manage adverse reactions associated with the technology being appraised.

To reduce the incidence and severity of skin reactions, a prophylactic corticosteroid should be given the day prior to, on the day of, and the day after pemetrexed administration. The corticosteroid should be equivalent to 4mg of dexamethasone administered orally twice a day. To reduce toxicity, patients treated with pemetrexed must also receive vitamin supplementation in the form of oral folic acid or a multivitamin containing folic acid (350 to 1,000 micrograms) on a daily basis, starting a week before the first dose of pemetrexed, continuing during treatment until 21 days after the last dose. An intramuscular injection of vitamin B_{12} (1,000 micrograms) must also be administered in the week preceding the first dose of pemetrexed and once every three cycles thereafter.

Please refer to the pemetrexed SPC for detailed information

2.9 Please identify the main resource use to the NHS associated with the technology being appraised. Describe the location of care, staff usage, administration costs, monitoring and tests. Provide details of data sources used to inform resource estimates and values.

Pemetrexed has been licensed and NICE approved for use as switch maintenance in the NHS and its use as continuation maintenance would require similar resource use and costs. Patients may be treated in any unit or centre capable of delivering chemotherapy (i.e, hospital, community or home setting).

Pemetrexed is administered as a 10-minute infusion and may be administered in the community/home setting, which allows patients to be treated closer to home and could potentially free up capacity in chemotherapy units.

2.10 Does the technology require additional infrastructure to be put in place?

The use of pemetrexed as continuation maintenance is not expected to require additional infrastructure. As mentioned under 2.9 above, pemetrexed has been licensed and NICE approved for use as switch maintenance in the NHS and its use as continuation maintenance is expected to allow selected non-squamous NSCLC patients who have not progressed following first-line treatment with pemetrexed/cisplatin to continue on pemetrexed monotherapy.

3 Equality

3.1 Identification of equality issues

3.1.1 Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;

- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology

- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Not applicable

Please provide us with any evidence that would enable the Committee to identify and consider such impacts.

Not applicable

3.1.2 How has the analysis addressed these issues

Not applicable

4 Innovation

4.1.1 Discuss whether and how you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits, and whether and how the technology is a 'step-change' in the management of the condition.

Context

Advances in the pharmacological treatment of lung cancer, along with the identification of histological sub-types of NSCLC, molecular markers and improvements in diagnostic technologies have all contributed to an increase in survival rates for patients with lung cancer. Despite improved survival rates, median overall survival in patients with lung cancer remains poor at 6 months (NLCA information sheet 2011). Lung cancer has by far the worst one-year survival rate of the 'big four' cancers (lung, breast, bowel and prostate, (Explaining variations in Lung cancer in England, 2011)) with only 32% patients alive one year after diagnosis (NLCA information sheet 2011). The UK has the worst one and five year survival rate for lung cancer compared to other similar countries, like Australia, Canada, Norway, Sweden, and Denmark, in part due to lower uptake of chemotherapy. Improving one and five year survival is a key priority for the Government, as shown by the inclusion of these outcomes in the NHS Outcomes Framework 2011/2012.

Pemetrexed continuation maintenance

Pemetrexed continuation maintenance treatment of NSCLC could potentially increase survival and improve the outlook for patients through active treatment of this terminal disease. Pemetrexed is the first and only licensed and NICE recommended treatment option in the maintenance phase for locally advanced or metastatic, non-squamous NSCLC in the NHS. Pemetrexed was previously licensed and recommended by NICE for switch maintenance and is now also licensed for use as continuation maintenance treatment. The pivotal study establishing the efficacy of pemetrexed continuation maintenance is the phase 3 double-blind randomised PARAMOUNT trial (Paz-Ares et al 2012), the first study to demonstrate an OS benefit in the continuation maintenance setting. PARAMOUNT was also the first study on pemetrexed in maintenance NSCLC from which EQ-5D data were available for a high proportion of patients in the trial over the maintenance phase. Pemetrexed is an innovative treatment option for continuation maintenance treatment of advanced, non-squamous NSCLC because:

- it offers patients a survival benefit of 2.85 months and a progression free survival benefit of 1.68 months. This extended survival is in addition to the survival benefit experienced by patients from pemetrexed/cisplatin treatment in the first-line setting.

- Pemetrexed has a favourable and manageable tolerability profile, which means that the increased survival is not at the cost of patients' quality of life. Evidence for this comes from EQ-5D data from the PARAMOUNT study, which showed no significant differences between treatment arms. This is further supported by data showing that the patients maintained their performance status throughout maintenance treatment.

- Pemetrexed as a single-agent treatment requires a ten-minute infusion once every three weeks and can be administered in chemotherapy units or in the community/ at home. This has the added benefit of potentially moving care of these patients from the hospital into the community, which is more convenient for patients and carers.

- Pemetrexed continuation maintenance makes it possible for clinicians to give patients the most effective treatment (pemetrexed/cisplatin) upfront, so that patients are able get the most benefit in terms of increased survival and symptom palliation (Scagliotti et al 2008). Patients can continue pemetrexed monotherapy enabling them to maintain benefit of first-line treatment and avoid cisplatin-associated toxicities like nausea, vomiting, ototoxicity and neurotoxicity as well as hospital stays for cisplatin-required hydration.

- There are only two licensed treatments (pemetrexed and erlotinib), and only one NICE-recommended option (pemetrexed in 'switch maintenance') for maintenance treatment of NSCLC in England and Wales. For continuation maintenance treatment of patients with non-squamous, EGFR mutation negative NSCLC, pemetrexed is the only treatment option available.

In the context of low median and one-year overall survival rates in patients with NSCLC and limited active treatment options in the maintenance phase, pemetrexed continuation maintenance is a valuable and innovative treatment which could potentially help improve one year and five year survival rates in non-squamous NSCLC patients, a key government priority.

Data from the PARAMOUNT study show that more than 50% of patients treated with pemetrexed continuation maintenance were alive one year after diagnosis and almost 33% were alive two years from diagnosis. Data on EQ-5D, together with ECOG performance status and the adverse event profile from PARAMOUNT suggest that the increased survival is not accompanied by deterioration in QoL, with patients maintaining their QoL while continuing to tolerate long-term treatment with pemetrexed. The availability and effectiveness of pemetrexed continuation maintenance also allows clinicians the opportunity to delay use of other treatment options for use in subsequent lines of therapy.

Pemetrexed continuation maintenance also fulfils all three criteria under the NICE 'Supplementary advice for appraisal of life extending, end of life treatments'. The cumulative patient population eligible to receive pemetrexed across all NSCLC indications and mesothelioma in England and Wales is 5,531, which is below the cut-off of 7,000 patients. Pemetrexed offers a median survival benefit of 2.85 months (from the PARAMOUNT study). Due to high censoring of the OS data at the completion of the trial, an extrapolation of the OS using six different parametric distributions yielded median survival estimates of between 3.4 and 4.7 months. Additionally, life expectancy in NSCLC patients is short, with median overall survival of about 6 months. Since all three criteria are fulfilled, this supplementary advice should be applied to pemetrexed continuation maintenance.

4.1.2 Discuss whether and how you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation.

All health-related benefits have been included in the QALY calculation.

4.1.3 Please identify the data you have used to make these judgements, to enable the Appraisal Committee to take account of these benefits.

Not applicable

5 Statement of the decision problem

Table 5 Statement of the decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Population	People with advanced or metastatic (stage IIIB and IV) NSCLC, other than predominantly squamous histology, whose disease has responded to induction treatment with pemetrexed and cisplatin	People with advanced or metastatic (stage IIIB and IV) NSCLC, other than predominately squamous histology, with good performance status (PS 0-1), who experience complete or partial response or stable disease after first-line treatment with pemetrexed/cisplatin.	The population in the submission is as per the licensed population for pemetrexed continuation maintenance. As per the NICE clinical guideline CG121, only patients with advanced disease and good performance status (WHO 0, 1 or Karnofsky score of 80-100) should be offered chemotherapy. The inclusion criteria for the PARAMOUNT trial specified that only patients with good performance status (PS 0-1) were to be included. Accordingly, this submission presents the clinical and economic case for patients with PS 0-1 only.
Intervention	Pemetrexed as maintenance treatment of non squamous non small cell lung cancer in patients whose disease has not progressed immediately following platinum-based chemotherapy, specifically pemetrexed and cisplatin	Pemetrexed as maintenance treatment of non squamous non small cell lung cancer in patients whose disease has not progressed immediately following platinum-based chemotherapy with pemetrexed and cisplatin.	
Comparator(s)	Best supportive care (BSC, includes bisphosphonates and palliative radiotherapy): defined as "treatment without a specific antineoplastic regime given with the intent to maximise quality of life. It would exclude any treatment which aims to eradicate or slow the progression of the disease."	The comparator for pemetrexed in this submission is placebo (watch and wait) plus BSC. In the PARAMOUNT study, BSC was defined as treatment without a specific antineoplastic regimen given with the intent to maximise quality of life. 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 the progression of the study disease. Those therapies considered acceptable included, but were not limited to, palliative radiation to extrathoracic structures, antibiotics, analgesics, antiemetics, thoracentesis, pleurodesis, blood transfusions, and/or nutritional support (enteral or parenteral).	

Outcomes	• Progression free survival • Overall survival • Response rate • Health-related quality of life • Adverse events (according to grade)	The primary outcome measure was progression free survival. Secondary outcomes included overall survival, response rate, health-related quality of life and toxicity.
Economic analysis	Cost-effectiveness will be in cost/QALY. Time horizon Costs from an NHS and PSS perspective	Cost-effectiveness has been expressed in terms of cost/QALY and LYG. The analysis will have a lifetime time horizon, i.e., when 99.9% patients are modelled to have died, which for the basecase equates to 15.99 years for patients in the pemetrexed arm, based on a gamma distribution for the parametric extrapolation, placebo arm. The cost-effectiveness analysis has been conducted from an NHS and PSS perspective
Subgroups to be considered	No subgroups were specified	No subgroups were considered
Special considerations, including issues related to equity or equality	None	_

Section B – Clinical and cost effectiveness

6 Clinical evidence

6.1 Identification of studies

6.1.1 Describe the strategies used to retrieve relevant clinical data, both from the published literature and from unpublished data that may be held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 10.2, Appendix 2.

A comprehensive literature search was performed on 25th July 2012 to identify studies of pemetrexed maintenance in patients with advanced NSCLC. The literature search was conducted in EMBASE, Medline and other relevant databases (see Appendix 2 for details of literature search methodology). Additionally, the website of the American Society of Clinical Oncology (ASCO) was also searched electronically for relevant abstracts. A total of 45 published articles were identified in the literature search of which 42 remained after removal of duplicates. A further 37 were subsequently excluded since they did not fit the search criteria, yielding a final count of 5.

After the literature search was conducted, a search of internal Lilly databases yielded a further 4 abstracts pertaining to the PARAMOUNT study (Gridelli et al 2011; Scagliotti et al 2011; Pujol et al 2012; Reck et al 2012), which amounted to a total of 9 abstracts relevant to the PARAMOUNT study. Figure 2 shows the QUOROM flow diagram for the literature search. The results of the literature search are presented in the responses to 6.2.1 and 6.2.2.

6.2 Study selection

6.2.1 Describe the inclusion and exclusion selection criteria, language restrictions and the study selection process. A justification should be provided to ensure that the rationale is transparent. A suggested format is provided below.

The inclusion and exclusion criteria for the literature search are shown in Table 6.

Table 6 Eligibility criteria used in search strategy

	Clinical effectiveness
Inclusion criteria	Population: Trials conducted in adult patients with advanced (stage IIIB/IV) NSCLC Interventions: Pemetrexed as monotherapy given as maintenance treatment after first-line pemetrexed/cisplatin Outcomes: Trials with primary outcome measures of either Progression free survival (PFS) and overall survival (OS) Study design: Phase 3 randomised, controlled studies Language restrictions: English
Exclusion criteria	Population: Trials in paediatric patients, early stage NSCLC. Interventions: Pemetrexed given in combination as maintenance treatment, Pemetrexed in combination with carboplatin as induction treatment Outcomes: Trials with primary outcome measure other than either OS or PFS Study design: Non-randomised trials, phase I/II trials; review articles, notes or correspondence, editorials.

6.2.2 A flow diagram of the numbers of studies included and excluded at each stage should be provided using a validated statement for reporting systematic reviews and meta-analyses such as the QUOROM statement flow diagram (www.consort-statement.org/?o=1065). The total number of studies in the statement should equal the total number of studies listed in section 6.2.4.

Results of the literature search

The QUOROM statement flow diagram for the literature search is shown in Figure 1 below. The literature search identified the following 9 publications pertaining to the pivotal PARAMOUNT study comparing pemetrexed/cisplatin plus BSC with placebo plus BSC in patients with advanced, non-squamous, NSCLC:

1. Paz-Ares L, de Marinis F, Dediu M, Thomas M, Pujol J-L, Bidoli P. Maintenance therapy with pemetrexed plus best supportive care versus placebo plus best supportive care after induction therapy with pemetrexed plus cisplatin for advanced non-squamous non-small-cell lung cancer (PARAMOUNT): a double-blind, phase 3, randomised controlled trial. *Lancet Oncol*. 2012;3(3):247-55.

2. Paz-Ares L, De Marinis F, Dediu M, Thomas M, Pujol J-L, Bidoli P, et al. PARAMOUNT: Final overall survival (OS) results of the phase III study of maintenance pemetrexed (pem) plus best supportive care (BSC) versus placebo (plb) plus BSC immediately following induction treatment with pem plus cisplatin (cis) for advanced non-squamous (NS) non-small cell lung cancer (NSCLC). J Clin Oncol 30, 2012 (suppl; abstr LBA7507).

3. Gridelli C., Thomas M., Prabhash K., El Kouri C., Blackhall F., Melemed S., Zimmermann A., Chouaki N., Visseren-Grul C., Paz-Ares L.G.. Pemetrexed (PEM) maintenance therapy in elderly patients (pts) with good performance status (PS) - Analysis of paramount phase III study of PEM versus placebo in advanced non-squamous non-small cell lung cancer (NSCLC). *European Journal of Cancer*. Conference: 2011 European Multidisciplinary Cancer Congress Stockholm Sweden. September 2011, 47(pp S613).

4. Paz-Ares L, De Marinis F, Dediu M, Thomas M, Pujol J-L, Bidoli P, et al. PARAMOUNT: Phase III study of maintenance pemetrexed (pem) plus best supportive care (BSC) versus placebo plus BSC immediately following induction treatment with pem plus cisplatin for advanced non-squamous non-small cell lung cancer (NSCLC). *J Clin Oncol* 29: 2011 (suppl; abstr CRA7510).

5. Paz-Ares L, Altug S, Vaury A, Jaime J, Russo F, Visseren-Grul C, Treatment rationale and study design for a phase III, double-blind, placebo-controlled study of maintenance pemetrexed plus best supportive care versus best supportive care immediately following induction treatment with pemetrexed plus cisplatin for advanced non-squamous non-small cell lung cancer. *BMC Cancer* 2010, 10:85.

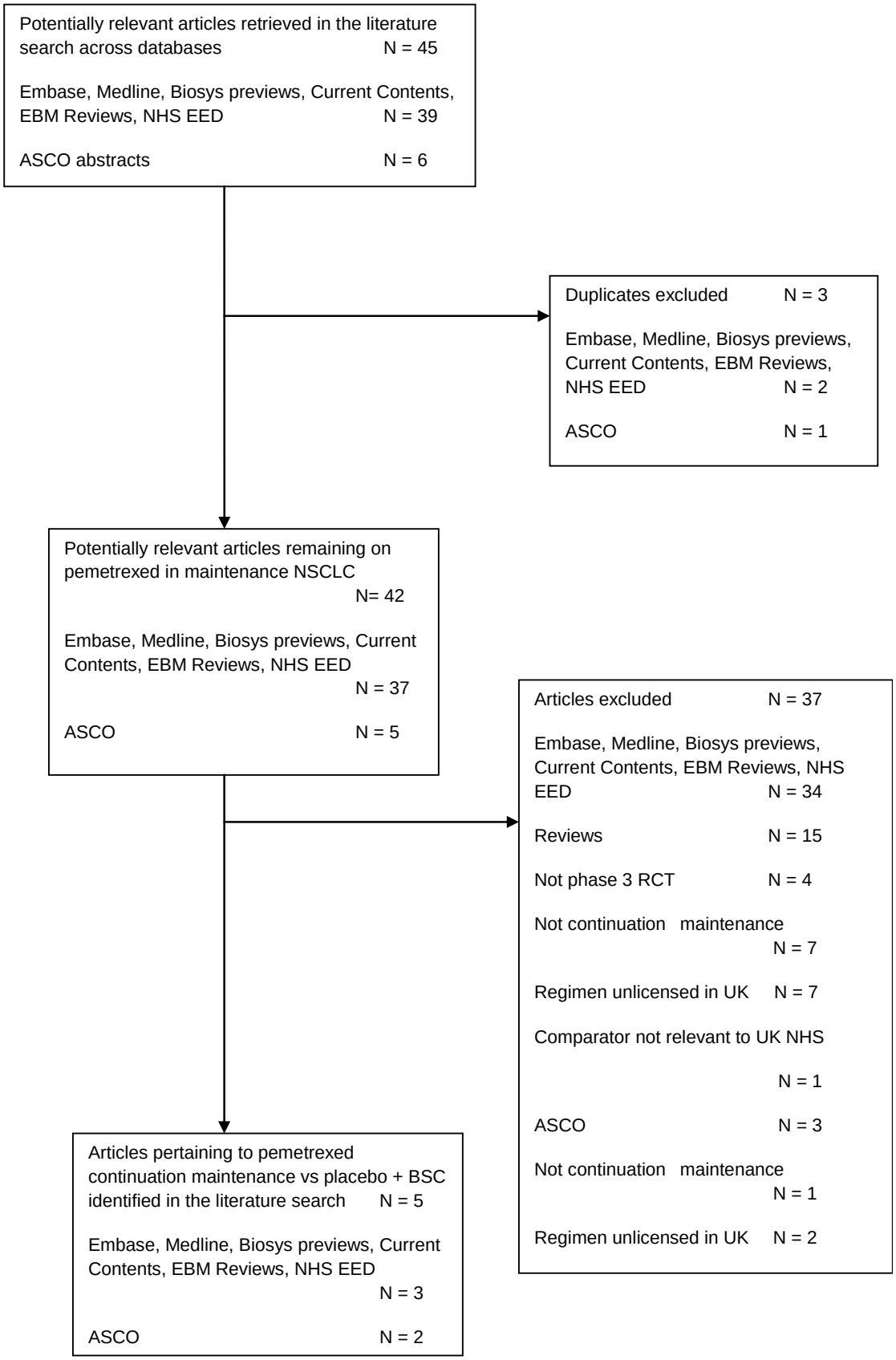
6. Gridelli C, de Marinis F, Pujol J-L, Reck M, Ramlau R, Parente B, et al. Safety, resource use, and quality of Life (QoL) results from PARAMOUNT: A phase III study of maintenance pemetrexed plus best supportive care (BSC) versus placebo plus BSC immediately following induction treatment with pemetrexed-cisplatin for advanced non-squamous non-small cell lung cancer (NSCLC). J Thorac Oncol 2011;6 (6 (suppl 2)):S323-4.

7. Scagliotti G., Gridelli C., De Marinis F., Thomas M., Dedui M., Pujol J-P.,et al. First-line chemotherapy with pemetrexed plus cisplatin in advanced non-squamous non-small cell lung cancer (NSCLC): a comparison of two phase III trials. Journal of thoracic Oncology, 6(2): 2011, P3.007.

8. Pujol J. L., Visseren-Grul C., Paz-Ares L., Dediu M., Thomas M., Bidoli P.,et al. Updated safety and quality of life (QOL) results of a phase III study (PARAMOUNT): maintenance (mtc) pemetrexed (pem) + best supportive care (BSC) versus placebo (pbo) + BSC immediately following induction treatment with pem + cisplatin (cp) for advanced non-squamous non-small cell lung cancer (NS-NSCLC). Presented at the annual meeting of European Society for Medical Oncology (ESMO), Vienna, September 28th - October 2nd 2012.

9. Reck M., Paz-Ares L., de Marinis F., Molinier O., Sahoo TP., Laack E., et al. PARAMOUNT: Descriptive subgroup analyses of final overall survival (OS) for the phase III study of maintenance pemetrexed (pem) versus placebo (plb) following induction treatment with pem plus cisplatin (cis) for advanced non-squamous (NS) non-small cell lung cancer (NSCLC). Presented at the annual meeting of European Society for Medical Oncology (ESMO), Vienna, September 28th- October 2nd 2012.

Figure 2 QUOROM flow diagram for literature search



6.2.3 When data from a single RCT have been drawn from more than one source (for example, a poster and a published report) and/or when trials are linked (for example, an open-label extension to an RCT), this should be made clear.

All publications identified in the literature search were relevant to the PARAMOUNT study. Table 7 provides a brief description of these publications.

Table 7 Publications pertaining to the PARAMOUNT study

Trial No. (acronym)	Citation	Description	Intervention	Comparator	Population
PARAMOUNT, NCT00789373	Paz-Ares L, de Marinis F, Dediu M, Thomas M, Pujol J-L, Bidoli P. Maintenance therapy with pemetrexed/BSC care versus placebo/BSC after induction therapy with pemetrexed/ cisplatin for advanced non-squamous non-small-cell lung cancer (PARAMOUNT): a double-blind, phase 3, randomised controlled trial. *Lancet Oncol*. 2012;3(3):247-55.	Primary study reference	Pemetrexed/cisplatin + best supportive care (BSC)	Placebo + BSC	Patients with stage IIIB-IV, locally advanced or metastatic, NSCLC of not predominantly squamous (i.e., non-squamous) histology with complete or partial response or stable disease after 4 cycles of induction therapy with pemetrexed/cisplatin.
Additional publications related to the PARAMOUNT study					
1	Paz-Ares L, De Marinis F, Dediu M, Thomas M, Pujol J-L, Bidoli P, et al. PARAMOUNT: Final overall survival (OS) results of the phase III study of maintenance pemetrexed (pem) plus best supportive care (BSC) versus placebo (plb) plus BSC immediately following induction treatment with pem plus cisplatin (cis) for advanced non-squamous (NS) non-small cell lung cancer (NSCLC). *J Clin Oncol* 30, 2012 (suppl; abstr LBA7507).			First presentation of final overall survival results from PARAMOUNT	
2	Gridelli C., Thomas M., Prabhash K., El Kouri C., Blackhall F., Melemed S., Zimmermann A., Chouaki N., Visseren-Grul C., Paz-Ares L.G.. Pemetrexed (PEM) maintenance therapy in elderly patients (pts) with good performance status (PS) - Analysis of paramount phase III study of PEM versus placebo in advanced non-squamous non-small cell lung cancer (NSCLC). *European Journal of Cancer*. Conference: 2011 European Multidisciplinary Cancer Congress Stockholm Sweden. September 2011, 47(pp S613).			Sub-group analysis in elderly patients	

3	Paz-Ares L, De Marinis F, Dediu M, Thomas M, Pujol J-L, Bidoli P, et al. PARAMOUNT: Phase III study of maintenance pemetrexed (pem) plus best supportive care (BSC) versus placebo plus BSC immediately following induction treatment with pem plus cisplatin for advanced non-squamous non-small cell lung cancer (NSCLC). *J Clin Oncol* 29: 2011 (suppl; abstr CRA7510)	PFS results from the PARAMOUNT study
4	Paz-Ares L, Altug S, Vaury A, Jaime J, Russo F, Visseren-Grul C, Treatment rationale and study design for a phase III, double-blind, placebo-controlled study of maintenance pemetrexed plus best supportive care versus best supportive care immediately following induction treatment with pemetrexed plus cisplatin for advanced non-squamous non-small cell lung cancer. *BMC Cancer* 2010, 10:85.	Design and rationale for PARAMOUNT
5	Gridelli C, de Marinis F, Pujol J-L, Reck M, Ramlau R, Parente B, Pieters T, Middleton G, Winfree K, Melemed S, Zimmermann A, John W, Beyrer J, Chouaki N, Visseren-Grul C, Paz-Ares LG. Safety, resource use, and quality of Life (QoL) results from PARAMOUNT: A phase III study of maintenance pemetrexed plus best supportive care (BSC) versus placebo plus BSC immediately following induction treatment with pemetrexed-cisplatin for advanced non-squamous non-small cell lung cancer (NSCLC). J Thorac Oncol 2011;6(6 (suppl 2)):S323-4.	Safety, resource use and QoL from PARAMOUNT PFS data lock
6	Scagliotti G., Gridelli C., De Marinis F., Thomas M., Dedui M., Pujol J-P.,et al. First-line chemotherapy with pemetrexed plus cisplatin in advanced non-squamous non-small cell lung cancer (NSCLC): a comparison of two phase III trials. Journal of thoracic Oncology, 6(2): 2011, P3.007	Compares results of first-line treatment in PARAMOUNT with those of JMDB study (Scagliotti et al, 2008).
7	Pujol J. L., Visseren-Grul C., Paz-Ares L., Dediu M., Thomas M., Bidoli P.,et al. Updated safety and quality of life (QOL) results of a phase III study (PARAMOUNT): maintenance (mtc) pemetrexed (pem) + best supportive care (BSC) versus placebo (pbo) + BSC immediately following induction treatment with pem + cisplatin (cp) for advanced non-squamous non-small cell lung cancer (NS-NSCLC). Presented at the annual meeting of European Society for Medical Oncology (ESMO), Vienna, September 28th - October 2nd 2012.	Safety and QOL data from PARAMOUNT.
8	Reck M., Paz-Ares L., de Marinis F., Molinier O., Sahoo TP., Laack E., et al. PARAMOUNT: Descriptive subgroup analyses of final overall survival (OS) for the phase III study of maintenance pemetrexed (pem) versus placebo (plb) following induction treatment with pem plus cisplatin (cis) for advanced non-squamous (NS) non-small cell lung cancer (NSCLC). Presented at the annual meeting of European Society for Medical Oncology (ESMO), Vienna, September 28th- October 2nd 2012.	Subgroup analysis from final OS data

Complete list of relevant RCTs

6.2.4 Provide details of all RCTs that compare the intervention with other therapies (including placebo) in the relevant patient group. The list must be complete and will be validated by independent searches conducted by the Evidence Review Group. This should be presented in tabular form. A suggested format is presented below.

The PARAMOUNT study compares pemetrexed with the specified comparator in the designated population, i.e., patients with non-squamous, advanced NSCLC, as stated in the decision problem.

6.2.5 Please highlight which of the RCTs identified above compares the intervention directly with the appropriate comparator(s) with reference to the decision problem. If there are none, please state this.

The PARAMOUNT study compares pemetrexed/best supportive care (BSC) to placebo/ BSC, which is the comparator specified in the decision problem.

6.2.6 When studies identified above have been excluded from further discussion, a justification should be provided to ensure that the rationale for doing so is transparent. For example, when studies have been identified but there is no access to the level of trial data required, this should be indicated.

All publications retrieved in the literature search pertained to the PARAMOUNT study which forms the evidence base for this submission.

List of relevant non-RCTs

6.2.7 Please provide details of any non-RCTs (for example experimental and observational data) that are considered relevant to the decision problem and a justification for their inclusion. Full details should be provided in section 5.8 and key details should be presented in a table; the following is a suggested format.

No non-RCT data have been presented in this submission.

6.3 Summary of methodology of relevant RCTs

Background to the PARAMOUNT trial

Pemetrexed in first-line and second-line NSCLC

Pemetrexed was initially licensed for the second-line treatment of NSCLC based on the results of the phase III study JMEI (Hanna et al 2004) which compared pemetrexed with docetaxel. JMEI demonstrated that pemetrexed resulted in clinically similar efficacy outcomes with significantly fewer side effects compared to docetaxel in the overall NSCLC population. Subsequently, a retrospective analysis of this trial showed a statistically significant treatment-by-histology interaction, suggesting that pemetrexed produced better survival in non-squamous NSCLC, compared with docetaxel (Scagliotti et al 2009).

The phase 3 study JMDB (Scagliotti et al, 2008) established the efficacy of pemetrexed/cisplatin versus gemcitabine/cisplatin as first-line treatment of locally advanced and metastatic NSCLC. Study JMDB showed that in the non-squamous population,

pemetrexed/cisplatin resulted in significantly better OS compared with gemcitabine/cisplatin. As a consequence of this finding, the label for pemetrexed was amended, restricting its use to 'not predominantly squamous' (i.e., non-squamous) patients only.

Pemetrexed as 'switch' maintenance in NSCLC

The first maintenance trial of pemetrexed, JMEN (Ciuleanu et al 2009), was a phase 3, multicentre, randomised, double-blind, placebo-controlled study enrolling 663 patients (441 pemetrexed, 222 placebo) with advanced NSCLC. The study showed that maintenance pemetrexed therapy offered superior PFS and OS compared with placebo in patients whose disease had not progressed following four cycles of platinum-based therapy not including pemetrexed (i.e., '*switch maintenance'*). Prospective analyses revealed a statistically significant treatment-by-histology interaction for both PFS and OS (Ciuleanu et al 2009). Based on the results of this study, pemetrexed was approved in the EU as a '*switch maintenance*' therapy. The licensed indication only permitted induction regimens that were included in the JMEN study, i.e., docetaxel, gemcitabine and paclitaxel in combination with carboplatin or cisplatin.

In recent years, pemetrexed/cisplatin has become established as the standard of care for first-line non-squamous NSCLC in the NHS in England and Wales. The efficacy of pemetrexed maintenance following pemetrexed/cisplatin, however, remained a clinically relevant question for both clinicians and patients alike. This led to PARAMOUNT, the first study conducted to assess the efficacy of administering pemetrexed continuation maintenance after pemetrexed/cisplatin first-line treatment.

The primary objective of PARAMOUNT was to evaluate the progression free survival (PFS) of patients treated with maintenance pemetrexed/BSC compared with patients treated with placebo/BSC for patients who had not progressed following four cycles of induction treatment with pemetrexed/cisplatin. Secondary endpoints included assessing overall survival (OS), objective response rate (RR), patient-reported outcomes using the EuroQol 5-dimensional scale (EQ-5D), and safety. The study was fully powered for both the primary analysis of PFS and the secondary endpoint of OS. Results from the PARAMOUNT study demonstrated that continuation maintenance with pemetrexed is a well-tolerated treatment option that both delays disease progression and improves survival for patients with advanced non-squamous NSCLC.

This section of the submission presents clinical data from the PARAMOUNT study, the pivotal trial for pemetrexed in 'continuation maintenance'.

6.3.1 As a minimum, the summary should include information on the RCT(s) under the subheadings listed in this section. Items 2 to 14 of the CONSORT checklist should be provided, as well as a CONSORT flow diagram of patient numbers (www.consort-statement.org). It is expected that all key aspects of methodology will be in the public domain; if a manufacturer or sponsor wishes to submit aspects of the methodology in confidence, prior agreement must be requested from NICE. When there is more than one RCT, the information should be tabulated.

6.3.2 Describe the RCT(s) design (for example, duration, degree and method of blinding, and randomisation) and interventions. Include details of length of follow-up and timing of assessments. The following tables provide a suggested format for when there is more than one RCT.

The methodology of PARAMOUNT is described below and summarised in Table 8.

Pemetrexed as 'continuation' maintenance in non-squamous NSCLC – the PARAMOUNT study (S124)

Study objective and design

PARAMOUNT (S124, Paz-Ares et al 2012) was a double-blind, randomised, placebo-controlled, phase 3 multicentre study, initiated specifically to examine pemetrexed maintenance following pemetrexed /cisplatin first-line therapy; i.e., as '*continuation* maintenance'. The study design included pemetrexed/cisplatin as a mandatory first-line regimen (see Figure 3).

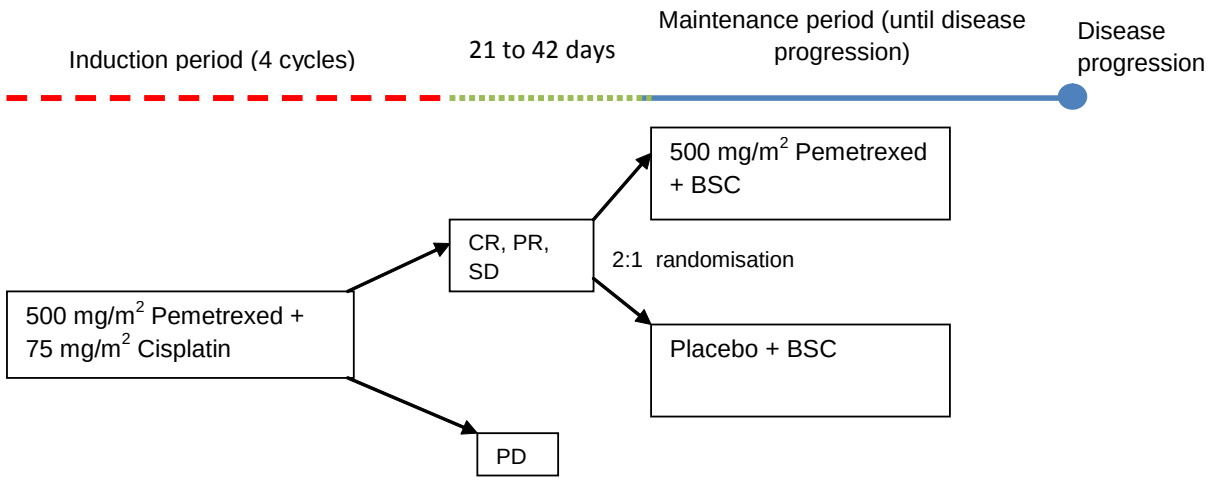
The primary objective of this study was to compare maintenance therapy with pemetrexed/ BSC versus placebo/BSC, in terms of objective PFS time in patients with Stage IIIB or Stage IV non-squamous NSCLC whose disease had not progressed during 4 cycles of pemetrexed/cisplatin induction. **PFS was measured from the time that patients were randomised to the maintenance treatment up to disease progression**, although data from the induction phase was also collected and analysed. **This submission describes the maintenance phase of the study only.**

The study consisted of 2 treatment periods – induction and maintenance periods.

Induction treatment period: Four cycles of unblinded induction treatment in which all patients received pemetrexed/cisplatin.

Maintenance treatment period: Subsequent to induction, patients with a documented complete or partial response (CR, PR), or stable disease (SD) and good performance status (PS 0-1) were randomised to maintenance treatment with pemetrexed or placebo, starting immediately (or not later than 3 weeks) after induction and continuing until disease progression.

Figure 3 Study design for the PARAMOUNT trial



PD: Progressive disease; BSC: Best supportive care;

Trial sites: The study was conducted in 83 sites across 16 countries including the UK (Australia, Belgium, Canada, Finland, France, Germany, Greece, India, Italy, Netherlands, Poland, Portugal, Romania, Spain, Turkey and the UK)

Interventions

All patients had received pemetrexed/cisplatin in the induction phase. In the maintenance phase patients received either pemetrexed/BSC or placebo/BSC.

Intervention: Pemetrexed 500 mg/m^2 administered IV on day 1 of a 21 day cycle, plus BSC.

Placebo comparator: Normal saline (0.9% sodium chloride) administered IV on day 1 every 21 days, plus BSC.

Best supportive care

Patients received BSC as judged by their physician. Best supportive care (BSC) was defined as treatment without a specific antineoplastic regimen given with the intent to maximize quality of life. 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 the progression of the study disease. Those therapies considered acceptable included, but were not limited to, palliative radiation to extrathoracic structures, antibiotics, analgesics, antiemetics, thoracentesis, pleurodesis, blood transfusions, and/or nutritional support (enteral or parenteral). If it was unclear whether a therapy should be regarded as BSC, the Lilly physician was to be consulted.

Concomitant medications

All patients were required to take folic acid and vitamin B_{12} supplementation, and dexamethasone prophylaxis during the induction phase, as outlined below. All patients randomised to the maintenance phase were required to continue vitamin supplementation and dexamethasone prophylaxis to maintain the double-blind design of the study.

Folic acid: Administered as 350µg-1000µg daily dose, starting 1-2 weeks before the first dose of study treatment and continuing throughout treatment until 3 weeks after the last dose of study treatment.

Vitamin B_{12}: 1000µg intramuscular injection, administered in the week before the first dose of study therapy, and approximately every 3 cycles thereafter.

Dexamethasone: 4 mg, orally twice per day. Should be taken on the day before, the day of, and the day after each dose of study therapy.

Randomisation sequence generation

After induction treatment, eligible patients were randomised with the help of an interactive voice response system (IVRS) in a 2:1 ratio with a block size of three, to receive maintenance treatment with pemetrexed/BSC or with placebo/BSC. Randomisation was stratified by ECOG performance status (0 vs 1) tumour response to first-line treatment (complete or partial response vs stable disease) and disease stage before administration of induction therapy (IIIB vs IV).

Allocation concealment and Blinding

To protect the blinding of patients and investigators, the following measures were taken:

- Patients received the same supplementation regimens.

- The IV bag containing pemetrexed or placebo was indistinguishable for both treatment arms. Investigators provided patient information to an unmasked third party, e.g. a pharmacist, who in turn obtained the patient's treatment assignment from the IVRS. The blinded study drug for infusion was also prepared by the unblinded pharmacist or designee at each site.

- Routine laboratory assessments were scheduled immediately before the start of each cycle to minimise observation of haematological nadirs associated with treatment.

- Treatment group code and other variables that could link patients to study arm were blinded in the database until primary data lock (30th June 2010). To preserve the integrity of the final OS results, investigators and patients on study remained blinded to treatment assignments.

Table 8 Summary of methodology of PARAMOUNT

Trial no. (acronym)	S124 (the PARAMOUNT study)
Location	83 sites located in Australia, Belgium, Canada, Finland, France, Germany, Greece, India, Italy, Netherlands, Poland, Portugal, Romania, Spain, Turkey and the UK.
Design	Phase 3, multicentre, randomised, double-blind placebo-controlled study
Duration of study	All enrolled patients received four 21-day cycles of induction chemotherapy with pemetrexed/cisplatin. Subsequently, eligible patients were randomised to maintenance treatment consisting of 21-day cycles of treatment with pemetrexed/ BSC or placebo/ BSC, administered until disease progression or toxicity or death due to any cause. Patients in both the pemetrexed and placebo arms received a median of 4 cycles of treatment in the maintenance phase. The mean number of cycles in the maintenance phase was 7.86 in the pemetrexed arm and 4.99 in the placebo arm (CSR addendum, Table S124.4.8, page 23).
Method of randomisation	Randomisation was carried out in a 2:1 ratio with the help of an interactive voice response system (IVRS) and stratified by performance status, tumour response to induction treatment and disease stage prior to randomisation.
Method of blinding (care provider, patient and outcome assessor)	Both pemetrexed and placebo IV bags appeared identical. An unblinded pharmacist / designee obtained patient's treatment allocation from the IVRS and prepared the blinded study drug for infusion. Lab investigations took place immediately before each cycle to minimise unblinding due to lab toxicities. Variables linking patients to study arm remained blinded in the database until primary data lock. Both arms received identical supplementation regimens.
Intervention(s) and comparator(s)	Intervention (N= 359): Pemetrexed 500 mg/m^2 administered IV on day 1 every 21 days, plus BSC. Placebo comparator (N=180): Normal saline (0.9% sodium chloride) administered IV on day 1 every 21 days, plus BSC.
Primary outcomes (including scoring methods and timings of assessments)	**Primary outcome**: **Objective Progression free survival (PFS)** as defined from date of randomisation to maintenance phase to the first date of objectively determined disease progression or death from any cause. Tumour imaging was done by CT scans, MRI or chest X-rays and tumour response was assessed by the RECIST guidelines. Scans at cycle 4 of induction phase were mandatory to determine eligibility for and serve as baseline for the maintenance phase, subsequently, once randomised to maintenance treatment, patients were followed every other cycle (6 ±1 weeks) until progression. Confirmation of response was required ≤ 4 weeks from the first evidence of response.
Secondary outcomes (including scoring methods and timings of assessments)	**Secondary outcome measures**: **Overall survival (OS)**: defined as the time from the date of randomisation to the date of death from any cause. **Objective tumour response rate:** defined as percentage of patients with complete or partial response; assessed every other cycle in the maintenance phase. Confirmation required ≤ 4 weeks from the first evidence of response. Thereafter, a responding patient was followed every other cycle (6 weeks ± 1 week). **EQ-5D:** Patients rated their current health condition at baseline, on day 1 of each cycle of induction and maintenance therapy, and at the 30-day post-discontinuation visit. **Toxicity:** assessed before every cycle using the National Cancer Institute (NCI) CTCAE (Common Terminology Criteria for Adverse Events) scale, version 3.0.
Duration of follow-up	Median patient follow-up (measured from time of randomisation), was 12.5 months (11.1 – 13.7) for all patients and 24.3 months (23.2 – 25.1) for all alive patients (Paz-Ares et al, ASCO ppt 2012).

Participants

6.3.3 Provide details of the eligibility criteria (inclusion and exclusion) for the trial. The following table provides a suggested format for the eligibility criteria for when there is more than one RCT. Highlight any differences between the trials.

Inclusion /exclusion criteria

Key inclusion criteria for the **induction phase** are presented in Table 9. Inclusion criteria for the **maintenance phase** are as stated below.

Inclusion criteria for the maintenance phase

Patients were eligible for the maintenance phase of the study if they had

- ECOG performance status of 0 or 1 and
- completed four cycles of induction therapy with pemetrexed/cisplatin with documented radiographic evidence of a partial (PR) or complete tumour response (CR) or stable disease (SD). The 'best observed induction response' was used, i.e, if the patient had CR/PR or SD during cycles 2 or 3 but had a subsequent 'unknown' response at cycle 4, the patient was considered to have had stable disease and was eligible for randomisation. This is consistent with actual clinical practice.

Inclusion criteria for the induction phase

Table 9 Key eligibility criteria for the induction phase in PARAMOUNT

Inclusion criteria	Exclusion criteria
Patients were to be included in the study if they met any of the following criteria: • cytological or histological diagnosis of advanced non-squamous NSCLC (squamous cell and/or mixed small cell histology is not permitted). • Stage IIIB or stage IV prior to induction therapy • Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. • no previous systemic chemotherapy for lung cancer • at least one measurable lesion meeting the RECIST (Response Evaluation Criteria In Solid Tumours) criteria 1.0 • ≥18 years • adequate organ function;	Patients were to be excluded from the study if they met any of the following criteria: • concurrent administration of other antitumour therapy • prior systemic anticancer therapy for lung cancer (including adjuvant early-stage treatment for NSCLC). • serious systemic disorder • serious cardiac condition, or prior malignancy other than NSCLC, carcinoma in situ of the cervix, or non-melanoma skin cancer, unless that prior malignancy was diagnosed and definitively treated at least 5 years previously with no subsequent evidence of recurrence; • CNS metastases (unless the patient has completed successful local therapy for CNS metastases and has been off corticosteroids for at least 4 weeks before starting study therapy). • clinically significant third-space fluid collections.

6.3.4 Describe the patient characteristics at baseline. Highlight any differences between study groups. The following table provides a suggested format for the presentation of baseline patient characteristics for when there is more than one RCT.

Table 10 shows that the two study arms were balanced with respect to baseline demographic characteristics and randomisation factors. The majority of patients in both arms were male, Caucasian, less than 65 years of age, had Stage IV disease, an ECOG PS of 1, and reported a history of smoking. The characteristics of this study are generally reflective of the overall population of patients with advanced non-squamous NSCLC enrolled on clinical trials. As shown in Table 11, all patients enrolled in the study had non-squamous histology, with the majority of patients having adenocarcinoma.

Patients in PARAMOUNT were broadly representative of patients eligible to receive pemetrexed in routine clinical practice in the NHS.

Although patients in the PARAMOUNT study were younger than the typical NSCLC patient in routine clinical practice (median age 62 years vs 72 years in the lung cancer audit (NLCA 2010), this is expected since patients enrolled in clinical trials will usually be younger than those seen in routine clinical practice. In PARAMOUNT, all patients randomised to the maintenance phase were of good performance status (PS 0-1) while in the audit, only 45% patients were of good performance status. In practice, only patients with good performance status would be eligible for pemetrexed maintenance treatment. The distribution of male and female patients in PARAMOUNT was similar to that observed in the NLCA data (58% males vs 56% males).

Table 10 Demographic characteristics and randomisation factors for patients prior to randomisation in PARAMOUNT (Source: Table S124.7.1 PARAMOUNT CSR addendum, page 30; 19th March 2012 data lock)

Variable	Pemetrexed plus BSC N=359	Placebo plus BSC N=180	Total N=539
Baseline Characteristics			
Gender n (%)			
Male	201 (56.0)	112 (62.2)	313 (58.1)
Female	158 (44.0)	68 (37.8)	226 (41.9)
Age at randomisation (years)			
Mean age	60.34	62.17	60.95
Median age	60.95	62.35	61.39
(range)	(31.9-78.7)	(34.9-83.3)	(31.9-83.3)
Age group n (%)			
Age <65 years	238 (66.3)	112 (62.2)	350 (64.9)
Age ≥65 years	121 (33.7)	68 (37.8)	189 (35.1)
Origin n (%)			
Caucasian	339 (94.4)	171 (95.0)	510 (94.6)
Asian	16 (4.5)	8 (4.4)	24 (4.5)
Black	4 (1.1)	1 (0.6)	5 (0.9)
Smoking status n (%)			
Ever smoker	274 (76.3)	144 (80.0)	418 (77.6)
Never smoker	83 (23.1)	34 (18.9)	117 (21.7)
Unknown	2 (0.6)	2 (1.1)	4 (0.7)
Baseline Randomisation Factors			
ECOG PS n (%)			
0	113 (31.5)	60 (33.3)	173 (32.1)
1	245 (68.2)	118 (65.6)	363 (67.3)
2[a]	0 (0.0)	1 (0.6)	1 (0.2)
3[a]	1 (0.3)	1 (0.6)	2 (0.4)
Disease stage prior to induction n (%)[b]			
Stage IIIB	31 (8.6)	18 (10.0)	49 (9.1)
Stage IV	328 (91.4)	162 (90.0)	490 (90.9)
Time from start of induction therapy to randomisation[c] mean (range) 2.96 (2.14 – 4.14)		2.96 (2.53 – 3.71)	
Best tumour response to induction therapy n (%)			
Complete/Partial response	159 (44.3)	75 (41.7)	234 (43.4)
Stable Disease	190 (52.9)	95 (52.8)	285 (52.9)
Progressive disease [a]	1 (0.3)	2 (1.1)	3 (0.6)
Not done	0 (0.0)	0 (0.0)	0 (0.0)
Unknown [a]	9 (2.5)	8 (4.4)	17 (3.2)

N = total number of patients randomised to maintenance study treatment; n = number of patients in category.

[a] 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.

[b] Lung Cancer Staging Guidelines Version 5 (Source: Fleming et al. 1997; Mountain 1997). [c]Source; Paz-Ares et al 2012

Table 11 Histological classification of patients in PARAMOUNT (Source: Table S124.11.4 page 85 of main PARAMOUNT CSR)

Histologic classification	Pemetrexed N= 359	Placebo N=180	Total N=539
Adenocarcinoma	310 (86.4%)	161 (89.4%)	471 (87.4%)
Large-cell carcinoma	24 (6.7%)	12 (6.7%)	36 (6.7%)
Other[a] / indeterminate	25 (7.0%)	7 (3.9%)	32 (5.9%)
Total	**359 (100%)**	**180 (100%)**	**539 (100%)**

[a]Patients with primary diagnosis of NSCLC whose diagnosis did not clearly qualify as adenocarcinoma or large-cell carcinoma

Outcomes

6.3.5 Provide details of the outcomes investigated and the measures used to assess those outcomes. Indicate which outcomes were specified in the trial protocol as primary or secondary, and whether they are relevant with reference to the decision problem. This should include therapeutic outcomes, as well as patient-related outcomes such as assessment of health-related quality of life (HRQL), and any arrangements to measure compliance. Data provided should be from pre-specified outcomes rather than post-hoc analyses. When appropriate, also provide evidence of reliability or validity, and current status of the measure (such as use within UK clinical practice). The following table provides a suggested format for presenting primary and secondary outcomes when there is more than one RCT.

The primary outcome of the study was to compare **Progression Free Survival (PFS)** of patients treated with pemetrexed continuation maintenance/BSC with placebo/BSC. Secondary outcomes included **overall survival (OS)**, **tumour response rate**, **patient-reported outcomes (EQ-5D)** and **toxicities**.

Primary outcome measure:

Progression Free Survival (PFS)

- PFS was defined as time from the date of **randomisation to maintenance phase** to the first date of objectively determined progressive disease (PD) or death from any cause.

- The primary analysis of PFS was based on investigator assessed PFS.

Validation of investigator assessed PFS

- Investigator assessed PFS was validated by independent radiologists masked to treatment assignment.

Secondary outcome measures:

Overall survival (OS)

- OS was defined as the time from the date of randomisation to the maintenance phase to the date of death from any cause.

Tumour Response rate (RR)

- Tumour RR was calculated per study arm **as the proportion of randomised patients having a confirmed tumour response to maintenance therapy of PR or CR.**

- Tumour measurements were carried out by CT scan, MRI or chest X-ray which were conducted at baseline and repeated at every other cycle. Tumour measurements were conducted at baseline and repeated at every other cycle. All patients were to have a tumour assessment at cycle 4 of the induction phase to determine eligibility for maintenance phase.

- Tumour response was assessed by the RECIST 1.0 guidelines (Therasse et al 2000).

- The last radiological assessment performed before randomisation was considered as baseline.

- Tumour responses of complete or partial response (CR/PR) in the maintenance phase were confirmed ≤ 4 weeks from the first evidence of response. Thereafter, a responding patient was followed every other cycle (6 weeks ± 1 week).

- 'Best observed response' was determined from the sequence of responses assessed as described below:

    1. For CR, two objective status determinations before progression were required.
    2. For PR, two determinations before progression, but not qualifying for a CR, were required.
    3. Best response of SD was defined as disease that did not meet the criteria for CR, PR or PD and had been evaluated at least once, at least 6 weeks after the start of study treatment.

Patient-reported outcomes:

- Patients were given an EQ-5D questionnaire to assess their overall health status.

- Patients rated their current health condition at baseline, on day 1 of each cycle of induction and maintenance therapy, and at the 30-day post-discontinuation visit.

- All enrolled patients who provided baseline and at least 1 subsequent measurement for EQ-5D were included in the analysis of patient-reported outcomes.

- The EQ-5D results were summarised for all randomised patients at baseline, at each cycle of treatment during the maintenance phase and at the 30-day discontinuation visit by randomised treatment arms.

Toxicity

- Patients were assessed for adverse events before every cycle using the National Cancer Institute (NCI) CTCAE (Common Terminology Criteria for Adverse Events) scale, version 3.0. (NCI 2003).

Statistical analysis and definition of study groups

6.3.6 State the primary hypothesis or hypotheses under consideration and the statistical analysis used for testing hypotheses. Also provide details of the power of the study and a description of sample size calculation, including rationale and assumptions. Provide details of how the analysis took account of patients who withdrew (for example, a description of the intention-to-treat analysis undertaken, including censoring methods; whether a per-protocol analysis was undertaken). The following table provides a suggested format for presenting the statistical analyses in the trials when there is more than one RCT.

Primary/secondary efficacy and safety analyses were conducted on the ITT population consisting of all patients who were randomised to the maintenance phase of the study. In addition, safety was also evaluated for the induction phase on all patients who were enrolled in the study (treated with at least 1 dose of pemetrexed or cisplatin during the induction phase).

The primary objective of PARAMOUNT was to compare maintenance therapy with pemetrexed versus placebo in terms of PFS, with OS as a secondary objective. The study was fully powered for the analysis of OS. The Kaplan-Meier method was used to estimate parameters in the ITT population for PFS and OS by assigned treatment group. Hazard Ratios were estimated using the Cox proportional hazards model with assigned treatment as the only covariate, reported with 2-tailed 95% confidence intervals (CIs).

The primary statistical analysis of PFS was unadjusted log-rank test using a nominal two-sided alpha level of 0.05. The same analysis approach was used for the preliminary and final analyses of OS.

In addition, log-rank tests stratified by the following 3 randomisation factors were run for PFS and OS to assess the robustness of the unadjusted/non-stratified analyses: ECOG performance status prior to randomisation (0 vs 1); tumour response to induction therapy (CR/PR vs SD), disease stage prior to randomisation (stage IIIB vs IV).

Cofactor-adjusted Cox models were run for PFS and OS with the following potentially prognostic cofactors: treatment arm (pemetrexed versus placebo); ECOG PS just prior to randomization (0 vs 1); tumour response to induction chemotherapy (CR/PR vs SD); disease stage prior to administration of induction therapy (IIIB vs IV); sex (female vs male); changes from baseline in EQ-5D were analysed using a paired t-test and a mixed-effects model (MMRM).

Tumour response (CR + PR) rate and disease control (DCR=CR + PR + SD) rate were reported. Tumour response rate to induction therapy was calculated as the proportion of patients who achieved a CR or PR (confirmed or not). Disease control rates (DCRs) to maintenance therapy were calculated as the proportion of randomised patients in each treatment arm who achieved a confirmed CR, PR, or SD. Tumour response and DCRs were reported with 95% CI and were compared between randomisation arms using the Fisher exact test.

Changes from baseline in EQ-5D were analysed using a paired t-test and a mixed-effects model (MMRM).

Sample size, power calculation

As per the final protocol (see Appendix 10 for a detailed description of protocol amendments), a total number of 900 patients treated in induction were estimated in order to provide 558 patients randomised to maintenance treatment. The calculation assumed a PFS HR of 0.65 and 238 events for PFS, and an OS HR of 0.70 and 390 events for OS. This analysis was fully powered for both PFS (90%) and OS (93%).

Type I (alpha) error was controlled for the analyses of both PFS and OS so as to maintain an overall two-sided alpha level of 0.05. A gate keeping and alpha spending scheme approach was introduced to control the overall alpha error in testing both PFS and OS. Assuming a statistically significant result for the primary analysis of PFS, this approach maintained full statistical power to assess OS at the time of survival maturity, without an adjustment in sample size.

All time-to-event endpoints were measured from the date of randomisation, after completion of induction chemotherapy, unless noted otherwise.

Data management, patient withdrawals

For each patient who was not known to have died or to have had objective PD as of the data-inclusion cut-off date for the analysis, PFS was censored at the date of the patient's last tumour assessment prior to that cut-off date. For patients not known to have died as of the data cut-off date, OS was censored at the last contact date.

When scoring the quality of life scales for an individual questionnaire (EQ-5D), scores were imputed if at least 50% of the items within the scale were completed, based on the mean of the completed items.

6.3.7 Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were pre-planned or post-hoc.

Log-rank tests of PFS and OS stratified by subgroup were pre-specified in the statistical analysis plan to determine if the relative treatment effect of pemetrexed varied with stage of disease, performance status prior to randomisation, smoking status, age, gender and histology.

- Age: <70 vs ≥70 years; <65 vs ≥65 years
- Smoking status: Non-smokers vs smokers
- Response to induction treatment: CR/PR vs SD
- Pre-randomisation ECOG performance status: PS 0 vs 1
- Histology: Adenocarcinoma vs Large cell carcinoma vs other histology

ECOG performance status, response to first-line treatment, and disease stage before induction were also stratification factors for randomisation.

Participant flow

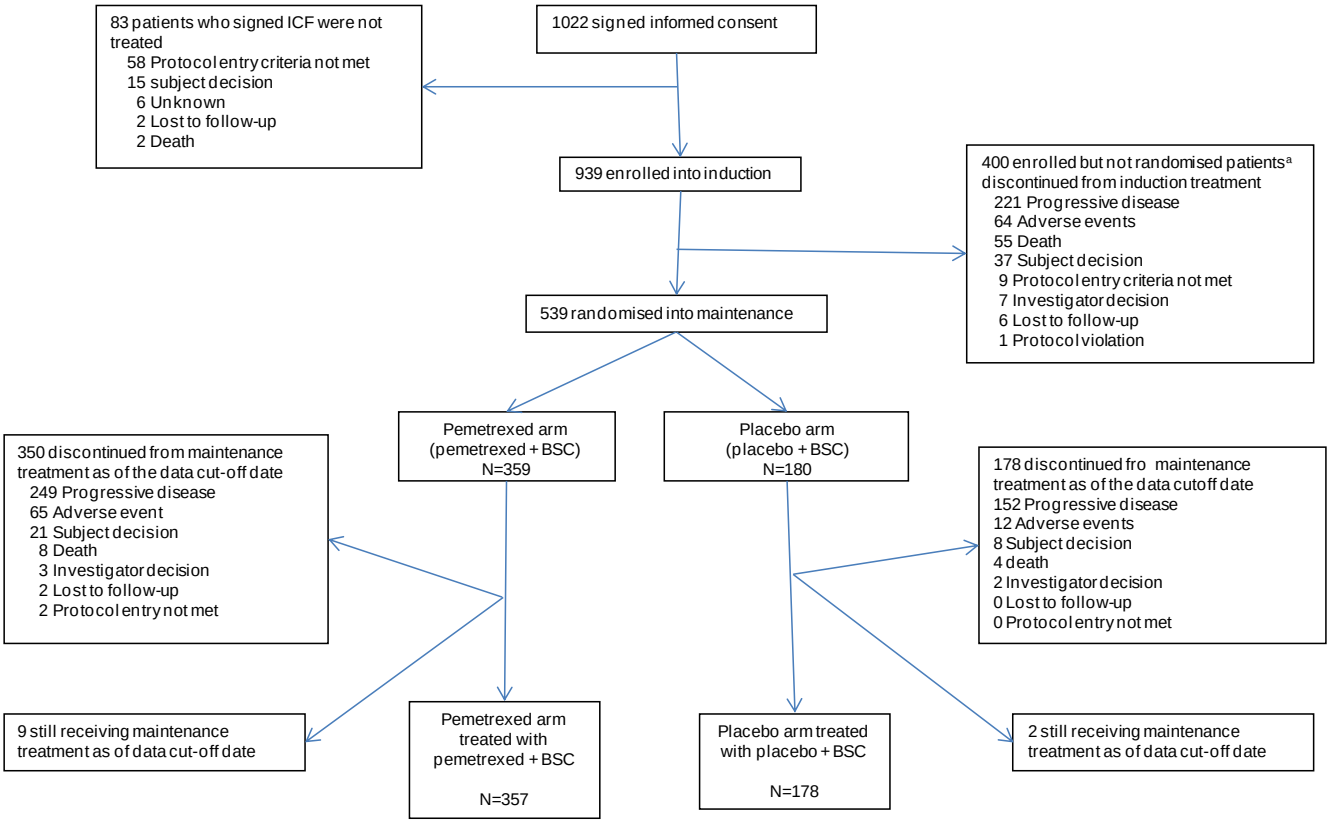
6.3.8 Provide details of the numbers of patients who were eligible to enter the RCT(s), randomised, and allocated to each treatment. Provide details of, and the rationale for, patients who crossed over treatment groups and/or were lost

to follow-up or withdrew from the RCT. This information should be presented as a CONSORT flow chart.

Figure 4 depicts patient disposition for the PARAMOUNT trial.

Of the 939 patients who received induction therapy, 539 patients were randomly assigned to maintenance treatment with either pemetrexed/BSC (n=359) or placebo/BSC (n=180). Of the 359 patients randomised to the pemetrexed arm, 357 received at least 1 cycle of treatment. Of the 180 patients randomised to placebo arm, 178 received at least 1 cycle of treatment. Four patients (two patients in each treatment arm) were randomised but discontinued in their last visit of induction (cycle 4) before receiving maintenance treatment.

Figure 4 Patient disposition in the PARAMOUNT study (source CSR Addendum page 8)



[a]: 1 patient was not randomised but received maintenance treatment. This patient discontinued due to progression after 2 cycles of maintenance treatment; ICF: Informed consent form; N = Number of randomised patients; BSC: best supportive care. Data lock date: 19th March 2012

6.4 Critical appraisal of relevant RCTs

6.4.1 The validity of the results of an individual study will depend on the robustness of its overall design and execution, and its relevance to the decision problem. Each study that meets the criteria for inclusion should therefore be critically appraised. Whenever possible, the criteria for assessing published studies should be used to assess the validity of unpublished and part-published studies. The critical appraisal will be validated by the ERG. The following are

the minimum criteria for assessment of risk of bias in RCTs, but the list is not exhaustive.

6.4.2 Please provide as an appendix a complete quality assessment for each RCT. See section 10.3, appendix 3 for a suggested format.

See Appendix 3 for a critical appraisal of the PARAMOUNT study.

6.4.3 If there is more than one RCT, tabulate a summary of the responses applied to each of the critical appraisal criteria. A suggested format for the quality assessment results is shown below.

The evidence base for this submission includes only one RCT, the PARAMOUNT study.

6.5 Results of the relevant RCTs

6.5.1 Provide the results for all relevant outcome measure(s) pertinent to the decision problem. Data from intention-to-treat analyses should be presented whenever possible and a definition of the included patients provided. If patients have been excluded from the analysis, the rationale for this should be given. If there is more than one RCT, tabulate the responses.

6.5.2 The information may be presented graphically to supplement text and tabulated data. If appropriate, please present graphs such as Kaplan–Meier plots.

6.5.3 For each outcome for each included RCT, the following information should be provided.

- The unit of measurement.
- The size of the effect; for dichotomous outcomes, the results ideally should be expressed as both relative risks (or odds ratios) and risk (or rate) differences. For time-to-event analysis, the hazard ratio is an equivalent statistic. Both absolute and relative data should be presented.
- A 95% confidence interval.
- Number of participants in each group included in each analysis and whether the analysis was by 'intention to treat'. State the results in absolute numbers when feasible.
- When interim RCT data are quoted, this should be clearly stated, along with the point at which data were taken and the time remaining until completion of that RCT. Analytical adjustments should be described to cater for the interim nature of the data.
- Other relevant data that may assist in interpretation of the results may be included, such as adherence to medication and/or study protocol.
- Discuss and justify definitions of any clinically important differences.
- Report any other analyses performed, including subgroup analysis and adjusted analyses, indicating those pre-specified and those exploratory.

Results

The first patient was enrolled on 19th November 2008 and the last patient was enrolled on 23rd April 2010. The final reporting database for the final analysis of overall survival (OS) was locked on 19th March 2012. The database included data from all 939 patients who signed informed consent and entered the study, of which 539 (57.4%) were randomised to receive maintenance treatment with pemetrexed/BSC (N=359) or placebo/BSC (N=180). Table 12 shows the data lock dates for the key endpoints from PARAMOUNT reported in this submission.

The first data lock (30 July 2010) was the database lock for the primary endpoint of PFS, safety and all secondary endpoints. The second data lock (Feb 2011) was for the four- month safety update needed for submission to the US FDA. The final lock (19th March 2012) was for the final analysis of OS. Post-discontinuation therapy (PDT) and study drug exposure, PFS, adverse events and QoL data were also updated.

Table 12 Timing of data locks for clinical data from PARAMOUNT presented in this submission

Primary / secondary endpoint	Data lock date
• Primary PFS analysis (investigator assessed and independently reviewed) • Tumour response • Health related quality of life	30 July 2010
• 4-month safety update	8th March 2011
• Final OS analysis • PDT and study drug exposure • Updated PFS analysis • Updated safety • Updated QoL	19th March 2012

Primary and secondary efficacy analyses were conducted in the ITT population, defined as all patients who were randomised to the maintenance phase (to be analysed by treatment arm as randomised).

All patients enrolled in the study (treated with at least 1 dose of pemetrexed/cisplatin during the induction phase) were evaluated for safety. All toxicities potentially related to study treatment were summarised separately for induction and maintenance phases of study treatment.

Number of cycles of maintenance treatment (data lock 19th March 2012)

Table 13 shows the extent of exposure to pemetrexed maintenance treatment in the PARAMOUNT study. All patients received 4 cycles of *induction* therapy with pemetrexed/cisplatin prior to being randomised to maintenance treatment. The median number of cycles of *maintenance* treatment was identical (4.0 cycles) in both pemetrexed and placebo arms, although the mean number of maintenance treatment cycles was higher in the pemetrexed arm (7.86 cycles) vs placebo (4.99 cycles). A greater proportion of patients in the pemetrexed arm completed at least 6 cycles of maintenance treatment compared with the placebo arm (47.1% vs 30.0%).

Table 13 Number of cycles of pemetrexed maintenance treatment administered (source: PARAMOUNT CSR addendum, Table S124.4.8; data lock 19th March 2012)

No. of cycles per pt	Pemetrexed plus BSC (N=359)	Placebo plus BSC (N=180)
No. of pts with ≥1 cycle	357	178
Mean (SD)	7.86 (8.28)	4.99 (5.16)
Median	4.0	4.0
Minimum	1.0	1.0
Maximum	44	38
Total no. of cycles received	2807	888
No of pts (%) completing at least 6 cycles	169 (47.1)	54 (30.0)
No of pts (%) completing at least 10 cycles	99 (27.6)	21(11.7)
Median follow-up (months, 95% CI)		
All patients	12.5 (11.1 – 13.7)	
Alive patients	24.3 (23.2 – 25.1)	

Progression-free survival - primary PFS analysis (data lock 30th July 2010)

The results of the primary PFS analysis are presented in Table 14 and described below. Figure 5 presents Kaplan-Meier curves for PFS.

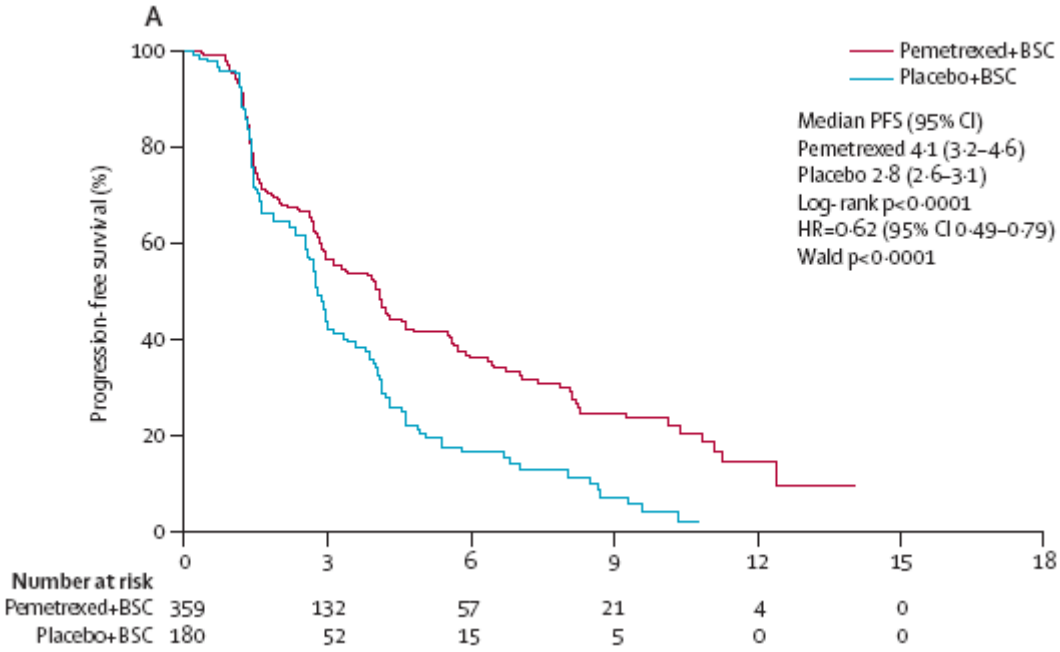
Investigator-assessed PFS

- PARAMOUNT met its primary objective, demonstrating a significant improvement in investigator-assessed PFS for patients treated with pemetrexed/BSC versus placebo/BSC. The investigator-assessed HR for PFS was 0.62 (95% CI: 0.49 to 0.79). For patients receiving pemetrexed, this represents a statistically significant 38% reduction in the risk of disease progression (log-rank p=0.00006).

- A statistically significant, clinically meaningful increase in PFS was reported in patients treated with pemetrexed/BSC. The median PFS from randomisation was 4.11 months (95% CI: 3.15 to 4.57) for pemetrexed and 2.83 months (95% CI: 2.60 to 3.12) for placebo, (log rank p=0.00006). Figure 5 shows the Kaplan-Meier curves for PFS in pemetrexed treated patients compared to placebo.

- These results show that pemetrexed maintenance treatment offers additional progression free survival after pemetrexed/cisplatin induction therapy, i.e. pemetrexed continuation maintenance is a beneficial treatment strategy.

Figure 5 Kaplan-Meier graph of investigator-assessed objective PFS - all randomised patients (source: Paz-Ares et al. Lancet Oncology 2012)



Independent review of PFS

- The results of the central review of PFS conducted by independent radiologists were consistent with that of the investigator assessed PFS (HR = 0.64; 95% CI: 0.51-0.81; Wald's p=0.00025).

PFS across subgroups

- Analyses of the PFS within pre-specified subgroups of age, smoking status, response to induction treatment, PS, and histology showed that the relative treatment effect of pemetrexed was internally consistent across subgroups (see Figure 6) and similar to that observed in the primary unadjusted analysis of investigator-assessed PFS for all randomised patients.

Table 14 Summary of investigator assessed PFS (Source: Table S124.11.10 main PARAMOUNT CSR page 96; data lock 30th July 2010 and March 19th 2012)

	Pemetrexed plus BSC N=359	Placebo plus BSC N=180
PFS July 30th 2010 data lock		
Number (%) of events	184 (51.3)	118 (65.6)
Number (%) censored	175 (48.7)	62 (34.4)
Median PFS - months (95% CI)	4.11 (3.15 - 4.57)	2.83 (2.60 - 3.12)
Log-rank p-value	0.00006	
Hazard ratio (95% CI)[a]	0.62 (0.49 - 0.79)	
Wald's p-value	0.00007	
PFS March 19th 2012 data lock		
Median PFS months (95% CI)	4.4 (4.11 – 5.65)	2.76 (2.60 – 3.02)
Log rank p-value	<0.00001	
Hazard ratio (95% CI)	0.60 (0.50 – 0.73)	
Wald's p-value	<0.00001	

[a]: Unadjusted HR and p-values from Cox model with treatment as the only cofactor. HR<1 favours pemetrexed study arm, HR>1 favours comparator.

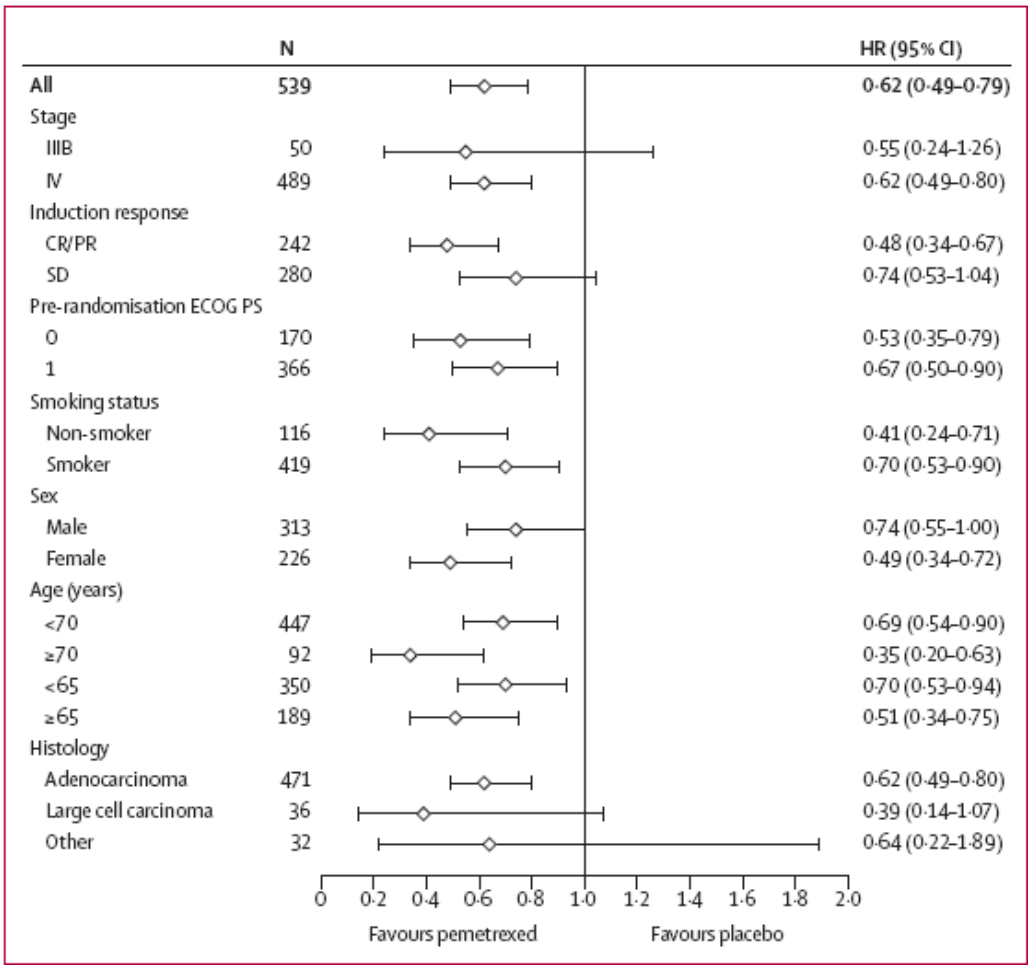
PFS at final OS data lock (March 19th 2012)

- In addition to the primary PFS analysis, an updated analysis of PFS was also conducted at the time of final OS data lock (19th March 2012). The unadjusted treatment HR was 0.60 (95% CI: 0.50 to 0.73), which is a 40% reduction in the risk of disease progression.

- The median PFS in the pemetrexed arm was 4.44 months (95% CI: 4.11 - 5.65) compared to 2.76 months (95% CI 2.60 - 3.02) in the placebo arm, a PFS benefit of 1.68 months.

- These results are consistent with those reported in the primary PFS analysis. Unadjusted log rank test: $p < 0.00001$, unadjusted Wald (for HR): $p<0.00001$.

Figure 6 Investigator assessed PFS hazard ratios (pemetrexed over placebo) in subgroups according to baseline characteristics - all randomised patients (source: Paz-Ares et al Lancet Oncology 2012)



Tumour response rate (data lock 30th July 2010)

Response to maintenance therapy was analysed relative to the sum of lesion measurements at randomisation to the maintenance phase. Tumour RR was calculated per study arm as the proportion of randomised patients having a confirmed tumour response to maintenance therapy of PR or CR.

Independently assessed tumour response rates in the maintenance phase are presented in Table 15.

- Results for the tumour response based on investigator assessment showed an overall response rate (CR+PR) of 4.2% in the pemetrexed arm and 1.1% in the placebo arm. (p=0.067).

- The tumour response to maintenance therapy represents a further tumour reduction in patients who already had a baseline response of CR, PR or SD to induction chemotherapy, so a high response in the maintenance setting would not be expected. This is consistent with clinical goals of maintenance treatment, i.e., the focus is on maintaining the clinical benefit achieved with first-line treatment.

Disease control rate (DCR)

- The independently assessed disease control rate (CR+PR+SD) was 71.8% for patients receiving pemetrexed and 59.6% for patients receiving placebo (p =0.009). Independently reviewed DCR is considered to be more reliable than investigator assessed DCR and is preferred by regulators for registration studies.

- The results show that pemetrexed continuation maintenance helps maintain the tumour response obtained after pemetrexed/cisplatin first-line treatment.

Table 15 Independently assessed tumour response rate in all randomised patients (Source Main PARAMOUNT CSR Table S124.11.16, page 110; data lock 30th July 2010)

Best tumour response[a]	Pemetrexed/BSC N= 316[d]	Placebo/BSC N=156[d]	p-value[b]
Complete response (CR) % patients, 95% CI	0%	0%	NE
Partial response (PR)	2.8% (1.31 - 5.34)	0.6% (0.02-3.52)	0.176
Overall response (CR + PR)	2.8% (1.31 - 5.34)	0.6% (0.02-3.52)	0.176
Stable disease	69.0% (63.57- 74.05)	59.0% (50.83- 6.78)	0.039
Disease control rate (CR+PR+SD)	**71.8% (66.53 - 76.73)**	**59.6% (51.47- 67.39)**	**0.009**
Progressive disease	27.8% (22.98 - 33.14)	39.1% (31.40-47.23)	0.015
Unknown[c]	0.3% (0.01 - 1.75)	1.3% (0.16 - 4.55)	NE

[a]RECIST critieria; [b]p-value from Fisher exact text. [d]The independent review only included patients for whom a baseline scan and at least one other scan during maintenance treatment was available. Not all patients had completed only cycle of treatment before the cut-off date for the independent review.

At this data cut-off, 179 patients were still in the maintenance treatment phase. The best overall response is not known for all patients; NE: Not estimable

N= number of patients randomised; n=number of patients in category; CR: complete response; PR: partial response; SD: stable disease.

Final Overall survival (OS) (data lock 19th March 2012)

Table 16 presents final overall survival results from PARAMOUNT

- PARAMOUNT demonstrated a clinically meaningful, statistically significant benefit in OS that favoured pemetrexed continuation maintenance. The hazard ratio was 0.78 (95% CI 0.64 to 0.96) for patients receiving maintenance pemetrexed vs placebo, which represents a 22% reduction in the risk of death in patients treated with pemetrexed

- The median OS, measured from the date of randomisation was 13.86 months (95% CI 12.75 to 16.03) for the pemetrexed arm and 11.01 months (95% CI 9.95 to 12.52) for the placebo arm (log-rank p=0.0195), an OS benefit of 2.85 months.

- 1 year survival for patients on continuation maintenance with pemetrexed was 58% vs 45% for those on placebo. 2-year survival was 32% in patients on pemetrexed versus 21% for those on placebo.

- Results of the cofactor-adjusted analyses of the study-treatment effect (including pre-specified cofactors of performance status, response to induction, disease stage, gender, and histology) were similar and consistent with the results of the main unadjusted analysis. The results of this pre-specified analysis indicate that no specific subgroup was driving the results of the OS and PFS analysis and demonstrates the consistent benefit of continuing pemetrexed as maintenance therapy.

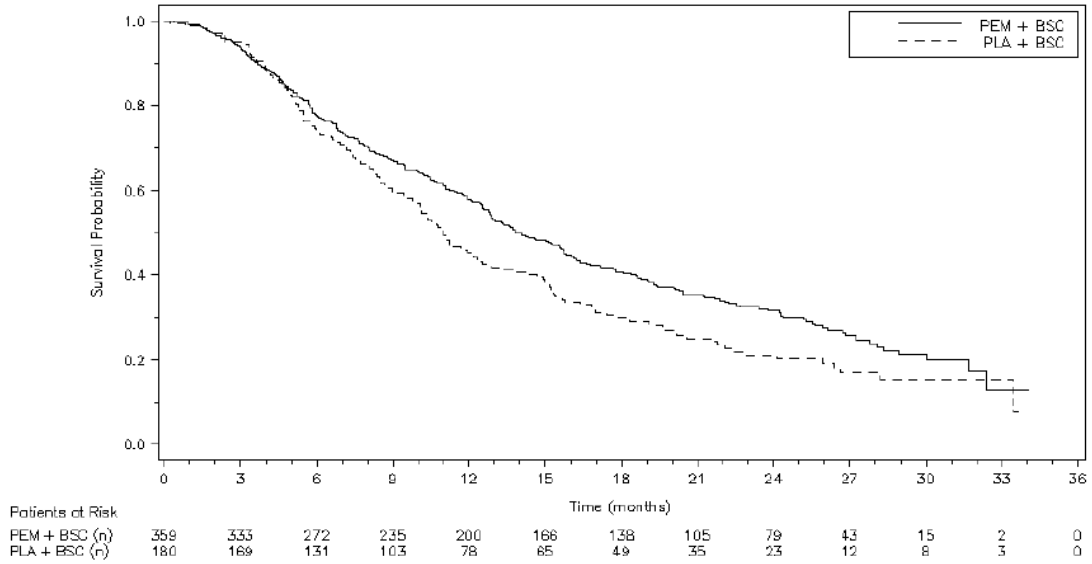
Table 16 Summary of final overall survival in the PARAMOUNT study - all randomised patients (Source: Table S124.4.3 PARAMOUNT CSR addendum, page 13; data lock 19th March 2012)

	Pemetrexed plus BSC N=359	Placebo plus BSC N=180
Events, N (%)	256 (71.3)	141 (78.3)
Events censored, N (%)	103 (28.7)	39 (21.7)
Median OS, months (95% CI)	13.86 (12.75 - 16.03)	11.01 (9.95 - 12.52)
Patients surviving at least		
1 year (%) (95% CI)	58 (53 - 63)	45 (38 - 53)
2 year (%) (95% CI)	32 (27 - 37)	21 (15 - 28)
Log rank p-value, unadjusted[a]	0.0195	
HR (95% CI)[b]	0.78 (0.64 - 0.96)	
Wald's p-value	0.0199	

[a]: the predefined alpha for the final analysis of OS is 0.0498 for the log-rank test (SAP version 3)

[b]: Unadjusted HR and p-values from Cox model with treatment as the only cofactor. An HR <1.0 favours the pemetrexed study arm; HR>1.0 favours the placebo.

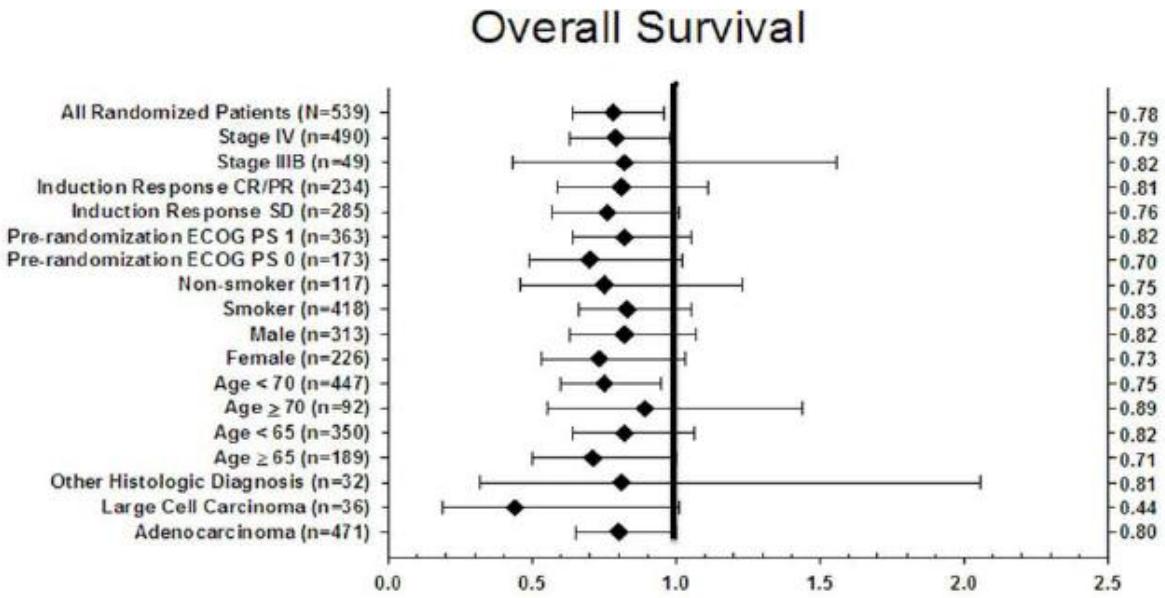
Figure 7 Kaplan-Meier curve for final analysis of Overall Survival by treatment arm - all randomised patients (source - CSR addendum, page 14)



Final OS across subgroups

- Analyses of the overall survival in patients on pemetrexed continuation maintenance within pre-specified subgroups of age, smoking status, response to induction treatment, PS, and histology showed that the relative treatment effect of pemetrexed was internally consistent across subgroups and similar to that observed in all randomised patients (see Figure 8). All subgroups appeared to benefit equally from pemetrexed continuation maintenance and the overall benefit was not driven by any specific subgroup.

Figure 8 Final overall survival across pre-specified subgroups in PARAMOUNT



EQ-5D (March 19th 2012 data lock)

HRQL data were collected during the PARAMOUNT trial to assess patient-reported overall health status during the study. Patients in the trial were asked to rate their present health condition using the EQ-5D instrument. The EQ-5D index data were valued using UK population-based index scores using the preference-based approach described by Dolan (1997). This is in line with the NICE reference case that requires HRQL data reported directly by patients, preferably using the EQ-5D instrument for adult patients.

EQ-5D questionnaire completion rates were high in the PARAMOUNT trial, which is rare for HRQL measures in the terminal disease setting. Compliance was defined as the number of completed EQ-5D assessments divided by the number of visits attended, i.e. expected EQ-5D assessments by patients still on study at that time Overall, compliance in the PARAMOUNT trial was 83.6% for the pemetrexed arm and 81.9% in the placebo.

The EQ-5D questionnaire was administered and completed at the following time points during the PARAMOUNT trial:

- Prior to the first cycle of first-line chemotherapy[1]

[1] For the analysis of EQ-5D data in the PARAMOUNT trial 'baseline' data refers to this pre-randomisation, pre- first-line therapy visit.

- On day 1 of each cycle of first-line treatment, prior to treatment administration
- On day 1 of each cycle of maintenance therapy, prior to treatment administration
- At the 30-day post-discontinuation follow-up visit, i.e. 30 days following maintenance treatment discontinuation. Discontinuation was due to either disease progression or other reasons.

A total of 325 patients in the pemetrexed/BSC arm and 165 patients in the placebo/BSC arm had data at baseline and least one subsequent measurement for during maintenance treatment and were included in the analysis.

The EQ-5D index data from PARAMOUNT were analysed to compare treatment differences. This was done in two ways:

1. A paired t-test and mixed effects repeated measures model (MMRM) were used to analyse changes from baseline.
2. An analysis in STATA was used to estimate mean observed index scores. This was done by clustering individual patient data across all visits during the maintenance phase i.e. including maintenance baseline, all maintenance cycles and the 30-day post-discontinuation visit.

The results of both sets of analyses showed that there were no statistically significant differences observed between the pemetrexed and placebo arms in mean changes from baseline on the index score during any cycle of maintenance treatment or at the 30-day discontinuation visit. During the maintenance period, no significant treatment-by-time interactions and no overall treatment differences were observed in the MMRM analyses of the EQ-5D index score. These EQ-5D index data are summarised in Table 17.

Table 17 UK EQ-5D index scores from PARAMOUNT (CSR; Lilly data on file; STATA analysis)

Measurement time points	**UK EQ-5D index scores (SD or 95% CI)**	
	Pemetrexed/BSC	**Placebo/BSC**
Prior to first-line treatment *	0.71	
N=805; single-arm open-label phase.	(SD 0.258)	
(2010 data lock reported in CSR)		
Maintenance baseline, i.e. prior to randomisation for maintenance treatment *	0.77	0.77
N=325 pemetrexed; N=165 placebo	(SD 0.210)	(SD 0.190)
(2012 data lock: DOF)		
Maintenance phase **		
i.e. includes EQ-5D data from maintenance baseline, all maintenance cycles and the 30-day post-discontinuation visit	0.7841* (0.7608-0.8074)*	0.8020* (0.7660-0.8381)*
30-days post-maintenance treatment discontinuation *	0.68 (SD 0.300)	0.68 (SD 0.287)
N=131 pem/BSC; N=77 placebo/BSC	(p<0.001 vs baseline)	(p=0.001 vs baseline)
(2012 data lock: DOF)		

* *Analysed with paired t-test and MMRM* **Analysed in STATA*

Overall, the EQ-5D index scores suggest that patients treated with pemetrexed did not experience worse HRQL over the course of maintenance therapy compared to patients treated with placebo and that patients can tolerate long-term maintenance pemetrexed without significant worsening of HRQL.

The majority of worsening in HRQL as captured by the EQ-5D was observed at post-discontinuation visit. At this visit the change from baseline in the index score was -0.13 on the pemetrexed arm and -0.12 on the placebo arm. Although this treatment difference for the change from baseline index score was not statistically significant (p = 0.792). At this visit patients had discontinued maintenance therapy most commonly due to disease progression so this worsening in HRQL is not unexpected.

The analysis of performance status changes from baseline showed no differences between the maintenance pemetrexed placebo arms (p=0.3673) (Gridelli et al 2012). The majority of patients were able to maintain performance status (77.8% on pemetrexed, 77.3% on placebo) and a similar number showed an improvement (7.5% o pemetrexed, 10.2% on placebo) or a worsening in performance status (14.7% on pemetrexed, 12.6% on placebo).

At baseline, 31.5% of patients had a performance status of 0 and 67.9% of the patients had a performance status of 1, 42 patients improved (25 on pemetrexed and 17 on placebo) (Gridelli et al 2012). The low proportion of patients with improvement from performance status 1 to 0 was expected, as performance status improvement from 1 to 0 is clinically difficult (i.e., from symptomatic to asymptomatic).

Summary of clinical efficacy results for pemetrexed continuation maintenance from the PARAMOUNT study

- The evidence for pemetrexed continuation maintenance comes from the PARAMOUNT study, a double-blind, randomised, placebo-controlled, phase 3 multicentre study, initiated specifically to assess the efficacy of pemetrexed maintenance in patients who had not progressed following four cycles of pemetrexed /cisplatin first-line therapy.

- Pemetrexed continuation maintenance offers patients a **1.68 month PFS benefit** (median PFS in pemetrexed/BSC vs placebo/BSC 4.44 months vs 2.76 months) and a **40% reduction in the risk of disease progression** (HR 0.60; 95% CI: 0.50 to 0.73).

- Pemetrexed continuation maintenance offers patients a **2.85 month survival benefit** (median OS in pemetrexed/BSC vs placebo/BSC 13.86 vs 11.01 months) and a **22% reduction in the risk of death** in patients treated with pemetrexed (HR 0.78; 95% CI 0.64 to 0.96).

- 1 year and 2 year survival rates for patients on pemetrexed continuation maintenance were **58% and 32% respectively** vs 45% and 21% for patients on placebo.

- The relative treatment effect of pemetrexed in terms of PFS and OS was internally consistent across subgroups.

- Pemetrexed continuation maintenance helps maintain the tumour response obtained after pemetrexed/cisplatin first-line treatment, as shown by a disease control rate of 71.8% in patients treated with pemetrexed vs 59.6% for patients receiving placebo (p =0.009).

- EQ-5D compliance rates in PARAMOUNT were above 80% in both arms which is rare in the terminal disease setting. The results show that patients may tolerate long-term maintenance pemetrexed without significant worsening of QoL.

- The results from the MMRM and STATA analyses showed that there were no statistically significant differences observed between the pemetrexed and placebo arms in mean changes from baseline on the index score during any cycle of maintenance treatment or at the 30-day discontinuation visit.

- The majority of patients on pemetrexed continuation maintenance maintained their ECOG performance status (77.8% on pemetrexed vs 77.3% on placebo) during the study. The PS changes from baseline were not significantly different between arms (p= 0.3673).

6.6 Meta-analysis

When more than one study is available and the methodology is comparable, a meta-analysis should be undertaken. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.3.9 to 5.3.12.

6.6.1 The following steps should be used as a minimum when presenting a meta-analysis.

- Perform a statistical assessment of heterogeneity. If the visual presentation and/or the statistical test indicate that the RCT results are heterogeneous, try to provide an explanation for the heterogeneity.
- Statistically combine (pool) the results for both relative risk reduction and absolute risk reduction using both the fixed effects and random effects models (giving four combinations in all).
- Provide an adequate description of the methods of statistical combination and justify their choice.
- Undertake sensitivity analysis when appropriate.
- Tabulate and/or graphically display the individual and combined results (such as through the use of forest plots).

6.6.2 If a meta-analysis is not considered appropriate, a rationale should be given and a qualitative overview provided. The overview should summarise the overall results of the individual studies with reference to their critical appraisal.

6.6.3 If any of the relevant RCTs listed in response to section 5.2.4 (Complete list of relevant RCTs) are excluded from the meta-analysis, the reasons for doing so should be explained. The impact that each exclusion has on the overall meta-analysis should be explored.

6.7 Indirect and mixed treatment comparisons

Data from head–to–head RCTs should be presented in the reference-case analysis, if available. If data from head–to–head RCTs are not available, indirect treatment comparison methods should be used. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.3.13 to 5.3.22.

6.7.1 Describe the strategies used to retrieve relevant clinical data on the comparators and common references both from the published literature and from unpublished data. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 10.4, appendix 4.

6.7.2 Please follow the instructions specified in sections 6.1 to 6.5 for the identification, selection and methodology of the trials, quality assessment and the presentation of results. Provide in section 10.5, appendix 5, a complete quality assessment for each comparator RCT identified.

6.7.3 Provide a summary of the trials used to conduct the indirect comparison. A suggested format is presented below. Network diagrams may be an additional valuable form of presentation.

6.7.4 For the selected trials, provide a summary of the data used in the analysis.

6.7.5 Please provide a clear description of the indirect/mixed treatment comparison methodology. Supply any programming language in a separate appendix.

6.7.6 Please present the results of the analysis.

6.7.7 Please provide the statistical assessment of heterogeneity undertaken. The degree of, and the reasons for, heterogeneity should be explored as fully as possible.

6.7.8 If there is doubt about the relevance of a particular trial, please present separate sensitivity analyses in which these trials are excluded.

6.7.9 Please discuss any heterogeneity between results of pairwise comparisons and inconsistencies between the direct and indirect evidence on the technologies.

6.8 Non-RCT evidence

Non-RCT, both experimental and observational, evidence will be required, not just for those situations in which RCTs are unavailable, but also to supplement information from RCTs when they are available. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 3.2.8 to 3.2.10.

6.8.1 If non-RCT evidence is considered (see section 6.2.7), please repeat the instructions specified in sections 6.1 to 6.5 for the identification, selection and methodology of the trials, and the presentation of results. For the quality assessments of non-RCTs, use an appropriate and validated quality assessment instrument. Key aspects of quality to be considered can be found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 10.6 and 10.7, appendices 6 and 7.

No non-RCT evidence has been presented in this submission.

6.9 Adverse events

This section should provide information on the adverse events experienced with the technology in relation to the decision problem. Evidence from comparative RCTs and regulatory summaries is preferred; however, findings from non-comparative trials may sometimes be relevant. For example, post-marketing surveillance data may demonstrate that the technology shows a relative lack of adverse events commonly associated with the comparator, or the occurrence of adverse events is not significantly associated with other treatments.

6.9.1 If any of the main trials are designed primarily to assess safety outcomes (for example, they are powered to detect significant differences between treatments with respect to the incidence of an adverse event), please repeat the instructions specified in sections 6.1 to 6.5 for the identification, selection, methodology and quality of the trials, and the presentation of results. Examples for search strategies for specific adverse effects and/or generic adverse-effect terms and key aspects of quality criteria for adverse-effects data can found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 10.8 and 10.9, appendices 8 and 9.

The PARAMOUNT study included toxicity as a secondary endpoint only. There are no trials on pemetrexed in maintenance NSCLC with safety as a primary outcome measure.

6.9.2 Please provide details of all important adverse events for each intervention group. For each group, give the number with the adverse event, the number in the group and the percentage with the event. Then present the relative risk and risk difference and associated 95% confidence intervals for each adverse event. A suggested format is shown below.

All safety variables were evaluated at the time of the primary analysis for PFS (data lock 30th July 2010) and again during the safety update (data lock 8th March 2011) and at data lock for final OS (19th March 2012). All data reported in this section is from the final 19th March 2012 data lock.

As mentioned earlier, all patients enrolled in the study (treated with at least 1 dose of pemetrexed/cisplatin during the induction phase) were evaluated for safety. All toxicities related to study treatment were summarised separately for induction and maintenance phases of study treatment. Only safety results for the **maintenance** phase are reported in this submission.

Table 18 shows the frequency of grade 3/4 adverse events occurring in ≥5% patients on either treatment arm in PARAMOUNT.

- Grade 3/4 non- laboratory adverse events were reported by 11.7% (42/359) patients in the pemetrexed arm and 4.4% (8/180) patients in the placebo arm, while grade 3/4 laboratory adverse events were reported by 13.1% of patients (47/359) in the pemetrexed arm and 0.6% (1/180) in the placebo arm ($p<0.001$). The grade 3/4 toxicities that were significantly different between pemetrexed/BSC and placebo/BSC

were anaemia (6.7% vs 0.6% p<0.001), neutropenia (6.1% vs 0.0%, p<0.001), and fatigue (5.3% vs 1.1%, p=0.017).

- More patients discontinued treatment due to treatment-related adverse events in the pemetrexed arm (12.0% [43/359] vs 4.4% [8/180], p=0.005).

- In patients who received >6 cycles of maintenance treatment, the overall incidence of grade 3/4/5 laboratory (11.1% vs 16.5%, p =0.147) and non-laboratory adverse events (12.4% vs 11.3%, p=0.867) was not significantly different from that reported in patients receiving ≤6 cycles of maintenance pemetrexed. The incidence of neutropenia was significantly higher in patients receiving >6 cycles (9.8% (13/133) vs 4.0% (9/226), p=0.039). The incidence of all other adverse events was not significantly different between the groups.

Table 18 Grade 3/4 adverse events[a] occurring in ≥5% of patients in either arm in the maintenance phase of the PARAMOUNT trial (source: Lilly data on file, data lock 19th March 2012).

	Pemetrexed (N=359)	Placebo (N=180)	
	Grade 3/4	Grade 3/4	p value
Fatigue	19 (5.3)	2 (1.1)	0.017
Anaemia	24 (6.7)	1 (0.6)	<0.001
Neutropenia	22 (6.1)	0 (0.0)	<0.001

[a]: toxicities were reported using the CTCAE version 3.0 (NCT 2006).

- More patients were hospitalised due to treatment-related adverse events in the pemetrexed arm than in the placebo arm (10.9% [39/359] vs 3.3% [6/180], p=0.003).

- Overall, more patients on pemetrexed received transfusions than on placebo (18.4% [66/359] vs 6.1% [11/180], p<0.001). Most patients received packed red blood cell transfusions (16.2% [58/359] vs 5.6% [10/180], p<0.001).

6.9.3 Give a brief overview of the safety of the technology in relation to the decision problem.

- Previous randomised phase III studies (Studies JMEI and JMEN) have demonstrated that single-agent pemetrexed is well tolerated as a treatment for advanced NSCLC.

- The incidence of toxicities in PARAMOUNT was similar to the established safety profile of single-agent pemetrexed in the maintenance (study JMEN) and second-line (study JMEI) settings.

- No new safety signals emerged from the PARAMOUNT study in comparison to previous trials involving pemetrexed monotherapy (JMEN and JMEI).

6.10 Interpretation of clinical evidence

6.10.1 Please provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and harms from the technology.

Pemetrexed has proven efficacy in the treatment of locally advanced or metastatic, non-squamous NSCLC in the first-line, second-line and switch maintenance settings. With pemetrexed becoming standard of care for first-line non-squamous NSCLC, there was a clinical demand to determine whether patients receiving pemetrexed/cisplatin first-line would benefit from further treatment with pemetrexed in the maintenance setting.

The PARAMOUNT trial was a robust, well-designed, double-blind, phase 3, randomised, controlled trial, the first study specifically designed to assess the efficacy of pemetrexed maintenance treatment following successful pemetrexed/cisplatin induction therapy. PARAMOUNT was also the first study to demonstrate an OS benefit in the continuation maintenance setting and is the only study on pemetrexed maintenance where EQ-5D data were collected with compliance rates >80% throughout the maintenance phase which is rare in these stages of the disease. The PFS and OS benefits described below are from the maintenance phase and are in addition to the benefit for pemetrexed seen in the first-line setting.

The significant improvement offered by pemetrexed continuation maintenance treatment in terms of PFS and OS in PARAMOUNT without detrimental effect on health related quality of life, together with the favourable tolerability profile show that maintenance pemetrexed after induction with pemetrexed/cisplatin is a valuable treatment option for patients with advanced non-squamous NSCLC.

Results from the PARAMOUNT study

Patients treated with pemetrexed/BSC are 38% less likely to experience disease progression compared to placebo-treated patients. They also experience a significantly longer survival of about 1.68 months without disease progression compared to patients on placebo ('watch and wait')/BSC.

- Pemetrexed/BSC offered significantly higher PFS of 4.11 months compared to 2.83 months for placebo/BSC (p=0.00006) with a HR of 0.62, representing a 38% reduction in the risk of disease progression in pemetrexed compared to placebo.

- This means that pemetrexed continuation maintenance helps patients remain symptom free for longer than placebo or prevents their cancer from getting worse.

Patients treated with pemetrexed/BSC are 22% less likely to die than patients on placebo. They also experience a significantly higher survival benefit of 2.85 months over compared to placebo ('watch and wait)/BSC

- Pemetrexed/BSC offered significantly higher survival benefit of 2.85 months compared to placebo/BSC (the median overall survival for pemetrexed/BSC vs placebo/BSC was 13.86 months vs 11.01 months). The HR for overall survival was 0.78, which represents a 22% lower risk of death compared to placebo/BSC.

- This means that patients treated with pemetrexed continuation maintenance live almost 3-4 months longer than patients on placebo (see economic section for survival estimates based on uncensored data).

Patients treated with pemetrexed/BSC have higher 1-year survival rates compared to placebo ('watch and wait')/BSC

- 1 year survival for patients on pemetrexed/BSC was 58% vs 45% for those on placebo/BSC as measured from randomisation. Data from the National lung cancer audit show that 1 year survival rates for patients with lung cancer in England and Wales are only 32%.

- This means that more than half of patients treated with pemetrexed were still alive at 1 year after diagnosis and almost a third were alive at 2 years from diagnosis. Pemetrexed continuation maintenance could increase survival in non-squamous NSCLC patients thereby contributing to an improvement in 1-year and 5-year survival rates, a key priority for the government.

The efficacy of pemetrexed/BSC is consistent across subgroups

- Patients on pemetrexed/BSC benefitted equally from treatment, regardless of age, gender, histological subtype (adenocarcinoma or large cell), response to induction chemotherapy, disease stage, performance status at randomisation or smoking status.

Pemetrexed/BSC helps maintain the beneficial effect of first-line chemotherapy with pemetrexed/cisplatin

- The independently reviewed disease control rate (CR+PR+SD) was 71.8% for patients receiving pemetrexed and 59.6% for patients receiving placebo (p =0.009).

- This means that 71.8% patients on pemetrexed did not experience worsening of their cancer or remained symptom free in the maintenance phase.

Pemetrexed/BSC had no adverse impact on patients' quality of life on EQ-5D/ ECOG performance status

- The increase in PFS and OS was not at the expense of the patients' quality of life. Patients treated with pemetrexed/BSC did not experience worse health states over the course of maintenance therapy compared to patients treated with placebo/BSC.

The adverse event profile of pemetrexed/BSC was similar to previous pemetrexed monotherapy studies

- Adverse events reported on pemetrexed in the PARAMOUNT were consistent with the known safety profile of pemetrexed given as single-agent switch maintenance treatment in the JMEN study and second-line treatment in the JMEI study. Results indicated that pemetrexed is well-tolerated as a continuation maintenance treatment.

- The most commonly reported drug-related treatment-emergent adverse events reported in ≥5% patients were anaemia, fatigue, nausea and neutropenia.

- The grade 3/4 toxicities that were significantly different between pemetrexed and placebo were neutropenia (5.8% vs 0%, p=0.0002), anaemia (6.4% vs 0.6% p=0.001) and fatigue (4.7% vs 1.1%, p=0.044).

This means that patients on pemetrexed continuation maintenance benefit from increased survival without significant detrimental impact on their quality of life.

Continuation maintenance treatment with pemetrexed/BSC maintains the clinical benefit achieved after first-line chemotherapy with pemetrexed/cisplatin, postpones disease progression, ultimately prolonging overall survival. Pemetrexed is well-tolerated as a maintenance treatment and its adverse event profile has no significant detrimental impact on these patients' quality of life.

Pemetrexed is the only treatment option licensed for continuation maintenance and the only one licensed and NICE approved for switch maintenance of advanced non-squamous NSCLC. The availability of pemetrexed continuation maintenance allows patients to get the most effective treatment option (pemetrexed/cisplatin) in the first-line setting and then continue to benefit from pemetrexed monotherapy without the adverse effects of cisplatin and related hydration requirement.

Pemetrexed continuation maintenance is therefore a valuable and innovative treatment option which could potentially increase one and five-year survival rates in non-squamous NSCLC patients, thus helping achieve a key government priority and improving the outlook for patients with this terminal disease.

6.10.2 Please provide a summary of the strengths and limitations of the clinical-evidence base of the intervention

6.10.3 Please provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice.

Strengths and relevance of the evidence base

PARAMOUNT is the second phase 3 trial to demonstrate the efficacy of pemetrexed maintenance treatment, and is the first study investigating pemetrexed as continuation maintenance. Results from the PARAMOUNT and JMEN (Ciuleanu et al 2010) studies together establish pemetrexed as an effective option in both switch and continuation maintenance NSCLC settings.

Prior to PARAMOUNT, no therapies had been studied as maintenance treatment after induction with a pemetrexed/cisplatin regimen. First-line doublet therapy containing pemetrexed was not included in the pemetrexed 'switch' maintenance study (JMEN; Ciuleanu et al 2009). Therefore, describing the efficacy and safety of pemetrexed maintenance therapy following initial treatment of pemetrexed/cisplatin and pemetrexed maintenance specifically is a clinically relevant question and of great importance to both patients and physicians. The PARAMOUNT trial has addressed this question.

Study design

The evidence base for the submission, the PARAMOUNT trial, was a robust, well-designed, double-blind, phase 3, randomised, controlled trial enrolling 939 patients of which 539 were randomised to maintenance treatment. Patients received four cycles of first-line treatment with pemetrexed/cisplatin, which is routine clinical practice in the NHS in England and Wales.

Interventions

The study compared pemetrexed/BSC to placebo/BSC (i.e., “watch and wait” or no active treatment) which is the current standard of care in the NHS after first-line therapy. Adequate measures were taken to ensure against accidental unblinding. All patients received first-line treatment with pemetrexed/cisplatin which is currently the standard of care for first-line treatment of NSCLC in the NHS. In PARAMOUNT, patients were treated to disease progression or unacceptable toxicity. In routine clinical practice too, a majority of responding patients are likely to be treated to disease progression or toxicity.

End-points

The primary end-point in PARAMOUNT was PFS. The study was also fully powered to assess OS, which was an important secondary endpoint. Both OS and PFS are routinely used endpoints in trials of cancer drugs. The investigator assessed PFS in PARAMOUNT was validated by independent review of tumour scans, as were response and disease control rates.

Patients

Patients in PARAMOUNT were broadly representative of the patients in the NHS in England and Wales who are expected to receive pemetrexed maintenance treatment in actual clinical practice.

PARAMOUNT only included patients with NSCLC of a non-squamous histology, based on the significant treatment-by-histology interaction observed in three phase 3 RCTs - JMEN, JMEI, and JMDB and as per the licensed indication for pemetrexed. This is consistent with the patient population eligible to receive pemetrexed maintenance treatment in England and Wales.

Although patients in the PARAMOUNT study were younger than the typical NSCLC patient in routine clinical practice (median age 62 years vs 72 years in the lung cancer audit (NLCA 2010), this is expected since patients enrolled in clinical trials are usually younger than those seen in routine clinical practice. The NLCA audit data also show that the proportion of patients receiving active treatment for lung cancer in England and Wales decreases with age, with 75% patients below 65 years likely to receive active treatment compared to only 56% of patients aged between 65-80 years. This shows that the trial population reflects the actual patient population receiving active treatment in the NHS. Besides, data from the PARAMOUNT trial showed that the relative treatment effect of pemetrexed was consistent across all subgroups (see Figures 6 and 8) including age.

In PARAMOUNT, all patients randomised to the maintenance phase were of good performance status (PS 0-1). This reflects the licence for pemetrexed, according to which only patients with good performance status (PS 0-1) are eligible for pemetrexed maintenance treatment. In actual clinical practice, only patients with good performance status would be eligible for pemetrexed maintenance treatment. The NICE guideline on lung cancer (CG121) also recommends that chemotherapy should be recommended to patients on with stage III or IV NSCLC and good performance status (WHO 0, 1) to improve survival, disease control and quality of life.

The distribution of male and female patients in PARAMOUNT was similar to that observed in the NLCA data (58% males vs 56% males).

Post-discontinuation treatment

The most commonly used post-discontinuation treatments were erlotinib and docetaxel, which are both routinely used in the NHS. Use of pemetrexed as second-line treatment, which is not used in clinical practice in the NHS England and Wales, was negligible. The use of post-discontinuation treatments was balanced across both arms and was not expected to have any impact on the OS results.

6.10.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice; for example, how the technology was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select patients for whom treatment would be suitable based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the SPC?

As described in 6.10.3 above, the study design, interventions, endpoints and patients in PARAMOUNT were similar to those in current clinical practice in the NHS.

Criteria for selection of patients

Pemetrexed continuation maintenance is suitable for patients with advanced non-squamous NSCLC who have not progressed after 4 cycles of induction treatment with pemetrexed/cisplatin and a good performance status (ECOG PS 0-1). No additional criteria are required for the selection of patients over and above histological testing and X-rays / CT-scans already carried out in routine clinical practice.

The doses used within the PARAMOUNT study are as specified in the pemetrexed SPC.

End of life

Pemetrexed continuation maintenance fulfils all three criteria specified in NICE's 'Supplementary Advice for Appraising Life Extending, End of Life Treatments' and therefore the supplementary advice should be applied to this appraisal.

Criterion 1. <u>The treatment is licensed or otherwise indicated, for small patient populations.</u>

- **The cumulative patient population (all settings of NSCLC and mesothelioma) that pemetrexed is licensed for is 5,531.**

Justification

Pemetrexed is licensed for the following indications:

1. **Non-small cell lung cancer (non-squamous)**

- *First line* treatment for patients with advanced or metastatic non-squamous NSCLC
- *Maintenance* treatment for patients with advanced or metastatic non-squamous NSCLC (switch and continuation maintenance).
- *Second line* treatment patients with advanced or metastatic non-squamous NSCLC

2. **Malignant pleural mesothelioma (MPM)**

- Chemotherapy naive patients with unresectable malignant pleural mesothelioma

Estimated number of patients eligible for pemetrexed treatment in non-squamous NSCLC indication:

Patients eligible for pemetrexed treatment in any NSCLC setting (i.e., first-line, maintenance or second-line) **must meet all the criteria listed below**, according to the SPC:

- Advanced or metastatic (ie, Stage IIIB/IV) NSCLC
- Non-squamous histological sub-type
- Patients must be fit enough to receive chemotherapy treatment, i.e., must be of good performance status (PS 0 or 1)

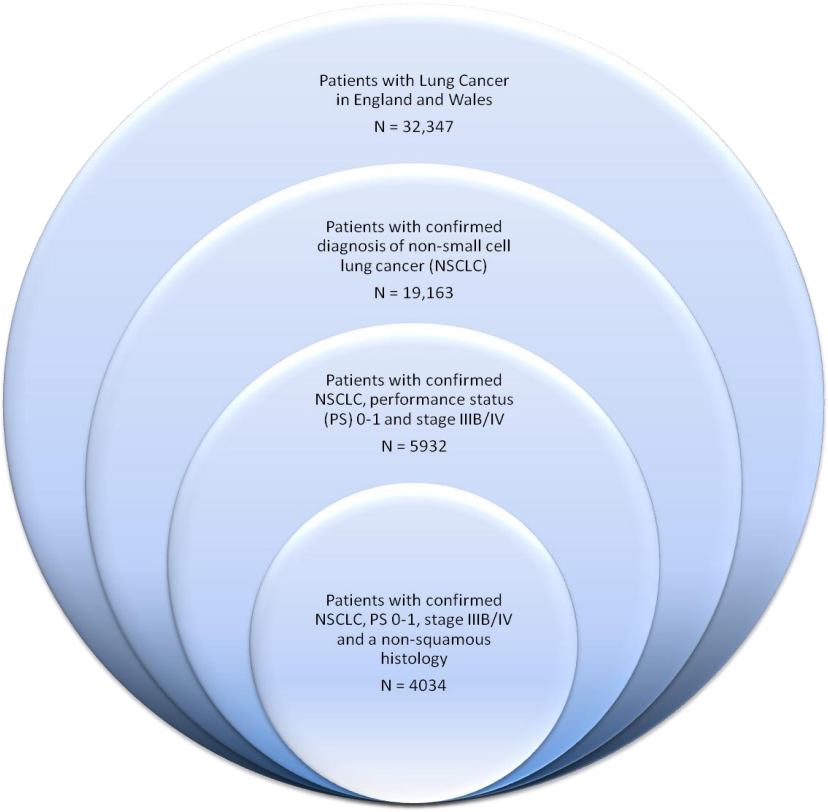
Figure 9 shows patients eligible for pemetrexed treatment in any NSCLC setting in England and Wales. The calculation of these patient numbers is reported in Table 4 in Section 2.2 of this submission.

As shown in the figure, there are 4,034 patients in England and Wales who fulfil the above-mentioned criteria for pemetrexed treatment. It follows that any patient receiving pemetrexed in any NSCLC setting would have to be part of this pool of 4,034 patients diagnosed with non-squamous, stage IIIB/IV NSCLC and of good performance status (PS 0-1), as shown in Figure 9.

In general, according to clinical practice, receiving pemetrexed in an earlier NSCLC treatment setting would preclude its use in a subsequent setting, as shown in Figure 10 below, except in

scenario I where patients on pemetrexed/cisplatin first-line who do not experience disease progression could continue pemetrexed maintenance treatment.

Figure 9 Patients eligible for pemetrexed treatment across all advanced, non-squamous NSCLC settings in England and Wales



Since this pool of 4,034 patients captures all patients eligible for pemetrexed in the NSCLC indication, and since receiving pemetrexed in one NSCLC setting would preclude its use in another subsequent setting (as shown in the figure below), we do not need to count patient numbers for each individual setting of NSCLC, as this would amount to counting the same patients twice.

Figure 10 Potential treatment pathways for patients receiving pemetrexed in NSCLC

NSCLC setting	Treatment pathway I	Treatment pathways II	Treatment pathway III*
1st line setting	√	X	X
Continuation maintenance setting	√		
Switch maintenance setting		√	X
2nd line setting	X	X	√

Note: Switch/continuation maintenance with pemetrexed are mutually exclusive – patients either switch to pemetrexed after non-pem chemo in the 1st line setting or continue on pemetrexed after pemetrexed/cisplatin 1st line. The option which is not valid is denoted by shaded boxes. * Pemetrexed in the 2nd line setting is not NICE recommended.

Estimated number of patients eligible for pemetrexed treatment MPM:

Pemetrexed is also licensed for unresectable MPM. Table 19 shows that there are 1,497 MPM patients in England and Wales.

Therefore the total number of patients eligible for pemetrexed treatment in both NSCLC and MPM indications is 4,034 + 1,497 = 5,531, i.e., <7,000 patients across England and Wales. Therefore pemetrexed is indicated for a small patient population and fulfils criteria 1 of the supplementary advice.

Please note that the following considerations are likely to further limit the number of patients receiving pemetrexed in clinical practice:

1) NICE guidance for first-line treatment recommends an optimised population that presents with adenocarcinoma or large cell histology, i.e not all non-squamous patients get pemetrexed in clinical practice so actual numbers are likely to be <4,034.

2) An EGFR TK inhibitor like erlotinib or gefitinib is standard of care for EGFR mutation positive non-squamous NSCLC patients. So these patients will not receive pemetrexed at any stage of the treatment pathway, which would further reduce patients from the initial 4,034.

3) Data from the NLCA (2011) show that only 52.8% of eligible patients actually receive chemotherapy. This implies that potentially only 2,130 patients would ultimately end up on pemetrexed treatment.

4) Pemetrexed is not recommended by NICE in treatment of non-squamous NSCLC in the second-line setting (TA124).

Table 19 Cumulative patient population eligible to receive pemetrexed across all licensed indications (NSCLC all settings and MPM)

Indication	Population as defined by licensed indication	Eligible patient population in England and Wales	Reference
NSCLC first-line, continuation maintenance, switch maintenance and second-line.	Patients with locally advanced or metastatic NSCLC other than predominantly squamous cell histology with Performance Status 0 or 1.	4,034 patients	NLCA audit report 2011; NICE clinical guideline CG121 See Table 5 Section 2.2 of submission for calculation.
Malignant Pleural Mesothelioma (MPM)	Chemotherapy naive patients with advanced MPM	1,497 patients with advanced MPM (calculated as proportion of advanced mesothelioma patients (88% of 1,815) in England and Wales based on audit data)	NLCA audit report 2011; Lilly submission to NICE in Mesothelioma (TA135)

Cumulative population across NSCLC and MPM indications	**5,531 patients**

Criterion 2. <u>There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment</u>

The overall survival benefit for pemetrexed continuation maintenance treatment for locally advanced or metastatic, non-squamous NSCLC, in patients who have not progressed after four cycles of pemetrexed/cisplatin first-line, in the PARAMOUNT study was **2.85 months**. The censoring rate at the end of the trial was 28.7% (i.e, 28.7% of patients had either not yet died or had been lost to follow-up). Extrapolating the trial survival data over a lifetime horizon (to a point in time when 99.9% of patients have died) to account for censoring provides a **modelled mean overall survival of 4.2 months** in the basecase analysis with a gamma distribution.

The mean OS estimates from the extrapolation exercise were within a range of **3.4 to 4.7 months** (Gompertz and Log-logistic respectively) demonstrating all estimates were in excess of 3 months additional survival compared with placebo. Table 20 shows the OS estimates obtained from all the parametric distributions in the curve-fitting exercise.

Table 20 Estimates of mean OS from the extrapolation exercise

Parametric distribution	OS gain (months)
Gamma	4.2
Exponential	4.3
Weibull	3.7
Log Normal	4.5
Log Logistic	4.7
Gompertz	3.4

Criterion 3. <u>The treatment is indicated for patients with a short life expectancy, normally less than 24 months</u>

Currently, median overall survival in patients with lung cancer is the worst among the big four cancers (lung, prostate, breast and bowel). **The median overall survival in England and Wales is only 181 days (approximately 6 months) (NLCA report 2011) with 1 year survival rates of 32%.**

The 1-year and 2-year survival rate for patients treated with pemetrexed continuation maintenance as reported in the PARAMOUNT study are 58% and 32% respectively.

7 Cost effectiveness

Definitions of terminology used within this submission

Maintenance treatment for NSCLC is a relatively recent treatment paradigm. For the purposes of this submission, the following definitions are used:

Maintenance treatment is anti-cancer treatment given to patients who **do not** experience disease progression during first-line treatment. The terms '*continuation maintenance*' and '*switch maintenance'* are used in relation to maintenance treatment referred to in this submission.

Continuation maintenance: The agent used for maintenance treatment is the same as one of the agents used for first-line treatment, e.g. pemetrexed single-agent following pemetrexed/cisplatin (pem/cis).

Switch maintenance: The agent used for maintenance treatment is different from the agent(s) used for first-line treatment, e.g. pemetrexed single-agent following gemcitabine/cisplatin or any other regimen not including pemetrexed.

A list of abbreviations used within this submission can be found at the beginning of this document.

Introduction and background information

An economic evaluation has been undertaken to assess the cost-effectiveness of pemetrexed plus BSC (referred to in this submission as 'pemetrexed') versus placebo plus BSC (referred to in this submission as 'placebo') in the continuation maintenance setting. Patients included in the economic evaluation are in line with the licensed indication i.e. advanced, stage IIIB/IV, non-squamous non-small cell lung cancer (NS NSCLC) who have not progressed following 4 cycles of induction pemetrexed/cisplatin and have a good performance status (PS 0-1).

The assessment is for continuation maintenance treatment with pemetrexed following the recent licence amendment (October 2011). The wording of the licence is:

Pemetrexed is indicated as monotherapy for the maintenance treatment of locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology in patients whose disease has not progressed immediately following platinum-based chemotherapy.

Pemetrexed was previously licensed for maintenance treatment following first-line treatment with non-pemetrexed containing regimens. Marketing authorisation for the use of pemetrexed monotherapy as maintenance treatment following first-line *pemetrexed/cisplatin* was received on 24th October 2011 after which the text of the maintenance indication was revised to reflect the licence extension. NICE has previously issued positive guidance on the use of pemetrexed as maintenance treatment following first-line regimens not including pemetrexed (TA190)

Lung cancer

Lung cancer is the second most common cancer in England and Wales and is the leading cause of cancer-related death (NICE CG121, 2011). Lung cancer is often asymptomatic in the early stages of the disease which means that patients usually present at an advanced stage

when curative treatment is not possible. As a result, prognosis is poor and the goals of treatment are to prolong survival, delay disease progression and improve quality of life.

Lung cancer treatment may be thought of in terms of lines of therapy: first-line, maintenance and second-line. First-line treatment is given following diagnosis with the aim of improving progression-free and overall survival whilst maintaining health-related quality of life (HRQL). Maintenance treatment aims to maintain the response from first-line treatment, i.e. to extend the duration of disease control thereby maintaining HRQL, improving progression-free survival and overall survival with minimal side-effects. Maintenance treatment is novel with only 6% of patients with NS NSCLC who have received first-line chemotherapy currently receiving maintenance treatment (DOF, (Lilly NSCLC SOM data) 2012). The majority of patients receive no active treatment immediately following first-line treatment, i.e. the current standard of care for patients with NS NSCLC who have received pemetrexed/cisplatin first-line is 'watch and wait' plus BSC. Second-line treatment aims to relieve symptoms due to disease progression.

Pemetrexed offers patients with NS NSCLC a well tolerated and efficacious treatment option that improves survival across all lines of therapy.

Pemetrexed continuation maintenance offers the option of an active chemotherapy for patients whose disease has not progressed, and have a good performance status (PS 0-1) immediately following induction therapy with pemetrexed. No other agents are currently licensed for continuation maintenance treatment of advanced NS NSCLC. Therefore, continuation maintenance treatment offers a beneficial alternative to 'watch and wait' following first-line pemetrexed/cisplatin in the current treatment pathway.

This submission describes an economic model comparing pemetrexed/BSC (referred to as 'pemetrexed') versus 'watch and wait' plus BSC, i.e., placebo/BSC (referred to as 'placebo').

7.1 Published cost-effectiveness evaluations

Identification of studies

7.1.1 Describe the strategies used to retrieve relevant cost-effectiveness studies from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. The search strategy used should be provided as in section 9.10, appendix 10.

A systematic literature review was conducted to identify studies that evaluated the cost-effectiveness of maintenance treatments for patients with advanced NSCLC. The search strategy was designed to inform the methodological approach for the economic evaluation and to identify data sources for relevant resources and health effects. Full details of the search are provided in Appendix11.

As some first-line studies include a maintenance component, the literature search encompassed all economic literature in first-line and maintenance interventions for NSCLC. Of the identified studies only those with a separate maintenance treatment component were included.

The initial search was conducted in February 2011 with a subsequent update in October 2011.

Databases searched were MEDLINE, Embase, NHS Economic Evaluation Database (NHS EED) and the NICE website. The search was limited to papers in English language, papers in human subjects and covering the following dates:

- 2008 to Oct 2011 - MEDLINE and Embase as recent cost studies were deemed to be relevant.
- 2000 to Oct 2011 - NHS EED to ensure no relevant studies were missed.

Additionally, a search of NSCLC maintenance appraisals conducted by NICE was also undertaken, with all associated key documents retrieved.

Inclusion and exclusion criteria were applied. Studies assessing the maintenance treatment phase were included in the review. Economic studies were included only if a full economic evaluation, (i.e., an evaluation of both benefits and costs) was reported and the study was generalisable to a UK population. Partial studies were excluded. The inclusion and exclusion criteria are presented in full in Appendix 11.

A total of 891 titles and abstracts were retrieved generating 478 records after duplicate publications were removed. 433 abstracts were excluded because they did not refer to first-line and/or maintenance treatment.

The full publications for the 48 remaining articles were reviewed. Of these, 37 were excluded for not including a maintenance component. Eight of the remaining 11 papers relating to maintenance treatment were subsequently excluded as they did not have a UK perspective, were not full economic evaluations or did not isolate the cost-effectiveness of the maintenance phase from a study that included first-line treatment. The three remaining papers were Greenhalgh et al (2010) a Health Technology Assessment (HTA) publication summarising the NICE appraisal of pemetrexed for switch maintenance (TA190), and the two

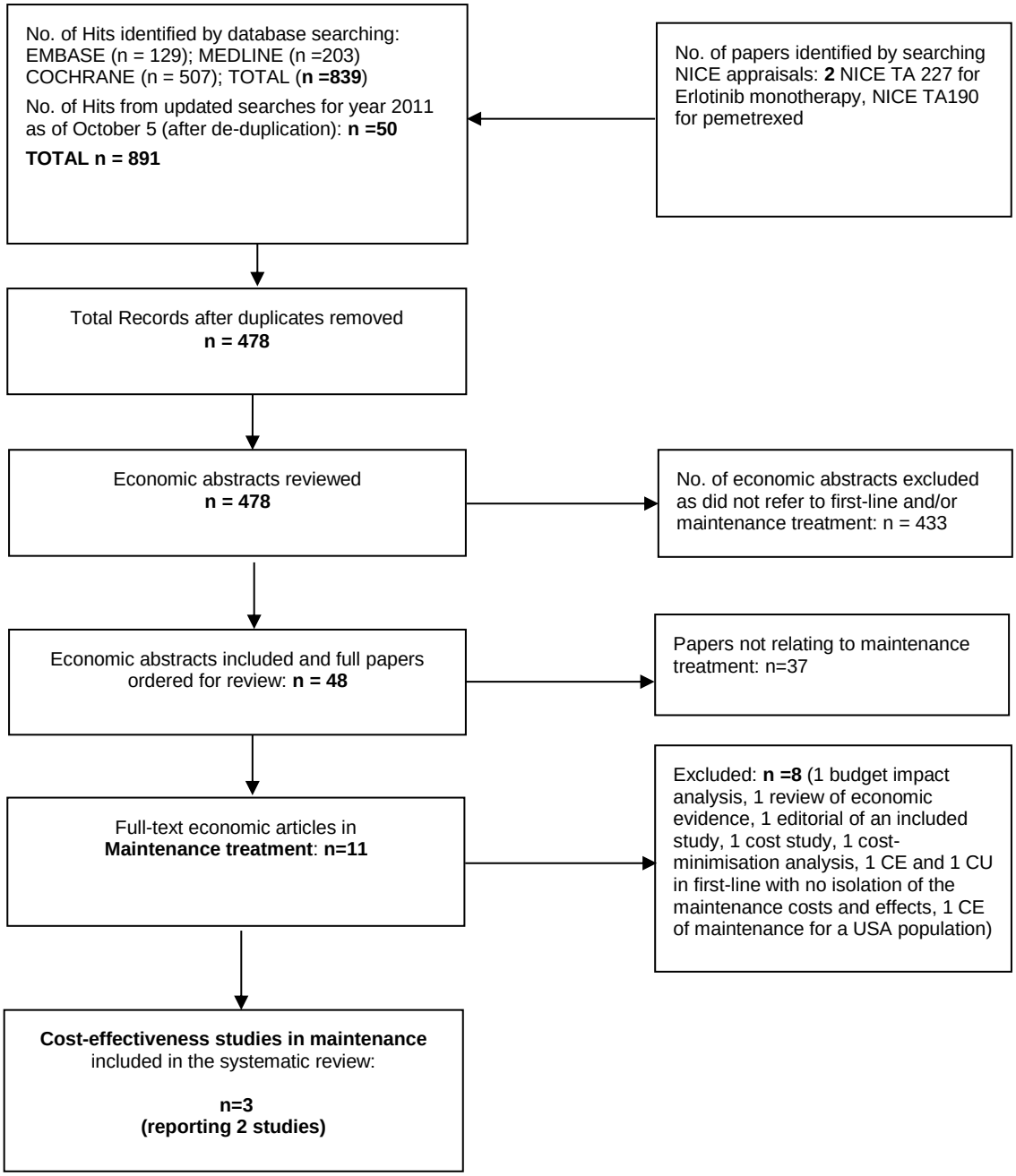
NICE technology appraisals relating to maintenance treatment of advanced NSCLC: pemetrexed (TA190) and erlotinib (TA227).

These three papers, referring to two cost-effectiveness NICE appraisals, are those included in the review to provide a greater depth of understanding of the modelling approaches used. It should be noted that the following tables are completed based on the Guidance documents and all related key documents.

Figure 11 below summarises the studies identified by the systematic searches conducted in 2011 and provides the reasons for exclusion of publications through the screening and eligibility phases of the review.

The literature search was updated in September 2012 to locate papers between October 2011 and September 2012. The same search strategy was used with the addition of the EconLit database. The same inclusion and exclusion criteria were used. This located one additional publication: Dickson et al (2011) a HTA publication summarising the NICE appraisal of erlotinib for switch maintenance.

Figure 11 PRISMA Flow Chart of Systematic Literature Review (2011 searches)



Description of identified studies

7.1.2 **Provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales. Each study's results should be interpreted in light of a critical appraisal of its methodology. When studies have been identified and not included, justification for this should be provided. If more than one study is identified, please present in a table as suggested below.**

Table 21 Summary of cost-effectiveness evaluations

Study	Year	Country where study was performed	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
NICE TA 190 (Pemetrexed in maintenance treatment of NSCLC) (Greenhalgh et al. 2010)	2010	UK	CUA, trial-based analysis with modelling component to allow extrapolation of health effects to lifetime (6 year) horizon, NHS and PSS perspective, 3.5% discount rate for both costs and outcomes.	Median age 60.6 years	**Non-squamous population**: Pemetrexed: 0.9539 Placebo: 0.6881	**Non-squamous population**: Pemetrexed: £20,925 Placebo: £8,370	**Non-squamous population**: Pemetrexed vs placebo: £47,239 (most plausible ICER accepted by Appraisal committee)
NICE TA227 (Erlotinib in maintenance treatment of NSCLC) (Dickson et al. 2011)*	2011	UK	CUA, three-state area under the curve model, UK NHS perspective, lifetime horizon (5-15 years), 3.5% discount rate for both costs and outcomes.	Not reported	**Stable disease squamous histology** Erlotinib: 0.6668 Placebo: 0.5077 **Stable disease non-squamous histology:** Erlotinib: 0.8222 Placebo: 0.6998	**Stable disease squamous histology** Erlotinib: £16,362 Placebo: £9,223 **Stable disease non-squamous histology:** Erlotinib: £18,148 Placebo: £9,808	**Stable disease squamous histology,** Erlotinib vs placebo**:** £44,812 **Stable disease non-squamous histology:** Erlotinib vs placebo: £68,120

ICER, incremental cost-effectiveness ratio; QALY(s), quality-adjusted life year(s)

**Pemetrexed not considered an appropriate comparator by the Evidence Review Group (ERG) or the Appraisal Committee (AC) within TA227.*

These studies included cost-effectiveness models from the UK NHS perspective. Greenhalgh et al. (2010) was a trial-based model with an extrapolation over a 6-year time horizon. The model had some functional limitations in relation to the extrapolation methods and was also limited to implementing OS rather than being able to use the full extent of the clinical trial data (e.g. PFS, treatment discontinuation). The Dickson et al. (2011) model, on the other hand, was a 3-state Markov model with a time horizon ranging from 5-years to 15-years (TA227). Though this model allowed for some of the limitations of Greenhalgh et al (2010) to be overcome (e.g. use of PFS, different extrapolation functions), the model did not allow for subgroups to be analysed within a single model.

Both of the previous maintenance appraisals for NSCLC utilised utility data from the literature due to a lack of suitable trial-based HRQL data. As mentioned in Section 6.5, EQ-5D data was collected throughout the PARAMOUNT trial with high rates of compliance during the maintenance phase, which made it possible for the first time to provide direct evidence of utility from patients during NSCLC maintenance treatment, therefore making it more relevant to the NICE reference case.

Therefore a *de novo* model was built that captured all the above mentioned elements of previous models for consistency with previous appraisals, as well as being able to implement new elements such as the utility data obtained directly from the PARAMOUNT trial.

7.1.3 Please provide a complete quality assessment for each cost-effectiveness study identified. Use an appropriate and validated instrument, such as those of Drummond and Jefferson (1996)[2] or Philips et al. (2004)[3]. For a suggested format based on Drummond and Jefferson (1996), please see section 10.11, appendix 11.

Quality assessments for each cost-effectiveness study identified are provided in Appendix 12.

7.2 De novo analysis

A *de novo* analysis was developed to examine the cost-effectiveness of pemetrexed plus best supportive care (BSC) compared to 'watch and wait' plus BSC for the continuation maintenance treatment of patients with advanced IIIB/IV non-squamous NSCLC PS 0-1, i.e. patients who did not progress during first-line treatment with pemetrexed/cisplatin. For reference within this submission, 'pemetrexed/BSC' will be referred to as 'pemetrexed' and 'watch and wait plus BSC' will be referred to as 'placebo'.

As mentioned above the model developed for this appraisal has additional improved functionality to allow for the impact of different survival curve parameterisations, model parameters and patient characteristics to be examined within a single model. The model is populated using individual patient-level data (IPD) from the PARAMOUNT trial using clinical data (OS, PFS and treatment discontinuation data) and EQ-5D utility data, all from the final data lock in March 2012.

The survival models developed from IPD are extrapolated and incorporated into an Excel-based state-transition Markov model. A Markov model is used to align with major clinical decision-making points. Further details of the economic model are provided in sections 7.2.2 to 7.2.6 below.

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[2] Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83.

[3] Philips Z, Ginnelly L, Sculpher M, et al. (2004) Quality assessment in decision-analytic models: a suggested checklist (Appendix 3). In: Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health Technology Assessment 8: 36.

As per the NICE Methods Guide (2008), the model implements a UK NHS perspective, specifically that of secondary care oncology budgets and uses a 2011 cost year. The model uses a lifetime time horizon, which in this model extends the extrapolation until 99.9% of the patient cohort has died as recommended by Siebert et al. (2012). This translates into an actual duration of the time horizon between approximately 6 and 20 years depending on the extrapolation method used.

As described in Section 6.3, the PARAMOUNT trial had two phases:

- Open-label, four cycles of first-line treatment with pemetrexed/cisplatin
- Double-blind, placebo-controlled, continuation maintenance treatment

Patients were randomised prior to allocation to maintenance treatment. All the economic analyses presented are from the point of randomisation onwards, focusing on difference maintenance treatment strategies: pemetrexed continuation and placebo.

Patients

7.2.1 What patient group(s) is(are) included in the economic evaluation? Do they reflect the licensed indication/CE marking or the population from the trials in sections 1.4 and 5.3.3, respectively? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem? For example, the population in the economic model is more restrictive than that described in the (draft) SPC/IFU and included in the trials.

As stated in Section 1.3. the indication relevant to this submission as per the SPC is

Pemtrexed is indicated as monotherapy for the maintenance treatment of locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology in patients whose disease has not progressed immediately following ***platinum based chemotherapy****.*

Pemtrexed was previously licensed for maintenance treatment following first-line treatment with non-pemetrexed containing regimes (i.e switch maintenance). NICE has already issued positive guidance on the use of pemetrexed as maintenance treatment following first-line regimes other than pemetrexed (TA190).

The population included in this economic evaluation is consistent with that specified in the decision problem (See Section 5) and it is in line with both the amendment to the licence for pemetrexed in the maintenance phase (October 2011) and the PARAMOUNT clinical trial. In accordance with the SPC, the patient population consists of those with locally advanced or metastatic NSCLC other than predominantly squamous cell histology whose disease has not progressed immediately following platinum-based chemotherapy and who are performance status (PS) 0-1.

The PARAMOUNT clinical trial evaluated patients who received pemetrexed single agent in the maintenance phase having received first-line treatment with pemetrexed/cisplatin (i.e. continuation maintenance). This Phase 3, randomised, double-blind, placebo controlled trial is predominantly a European-based trial that compared pemetrexed/BSC with ‘watch and wait/BSC’ (i.e.‘placebo’). Please refer to Section 6.3.2 for full details on the clinical trial design and Section 6.10 for how the evidence base from the trial corresponds with the clinical practice in the NHS.

Model structure

7.2.2 Please provide a diagrammatical representation of the model you have chosen.

See below.

7.2.3 Please justify the chosen structure in line with the clinical pathway of care identified in section 2.4.

See below.

7.2.4 Please define what the health states in the model are meant to capture.

See below.

7.2.5 How does the model structure capture the main aspects of the condition for patients and clinicians as identified in section 2 (Context)? What was the underlying disease progression implemented in the model? Or what treatment was assumed to reflect underlying disease progression? Please cross-reference to section 2.1.

See below.

Questions concerned with how the economic model represents the disease and treatment pathway, i.e. questions 7.2.2 to 7.2.5, are answered together in the section below.

The model has been designed to represent the disease progression of patients with NSCLC, the clinical pathway and clinical decision-making points consistent with UK clinical practice. The model is a state-transition Markov model developed in Excel with three health states: pre-progression, post-progression and death, the absorbing state. This is consistent with the health states used in the economic model for TA227. Patients can move from pre-progression to post-progression then post-progression to death or pre-progression directly to death (see Figure 12). The transition from pre-progression to post-progression is driven by PFS. The transition from either pre- or post-progression to death is driven by OS.

Adverse events (AEs) are not included as separate health states because pemetrexed has been shown to be well tolerated in clinical trials with low and short-lived adverse-event rates, however a statistically non-significant treatment-based utility decrement (as per EQ-5D data from PARAMOUNT) is applied in the basecase analysis to capture any potential negative impact on HRQL during maintenance treatment from adverse events (see Sections 6.5 and 7.5).

The model uses data (OS, PFS, treatment discontinuation and adverse events) from the final data lock (March 2012) from the PARAMOUNT study.

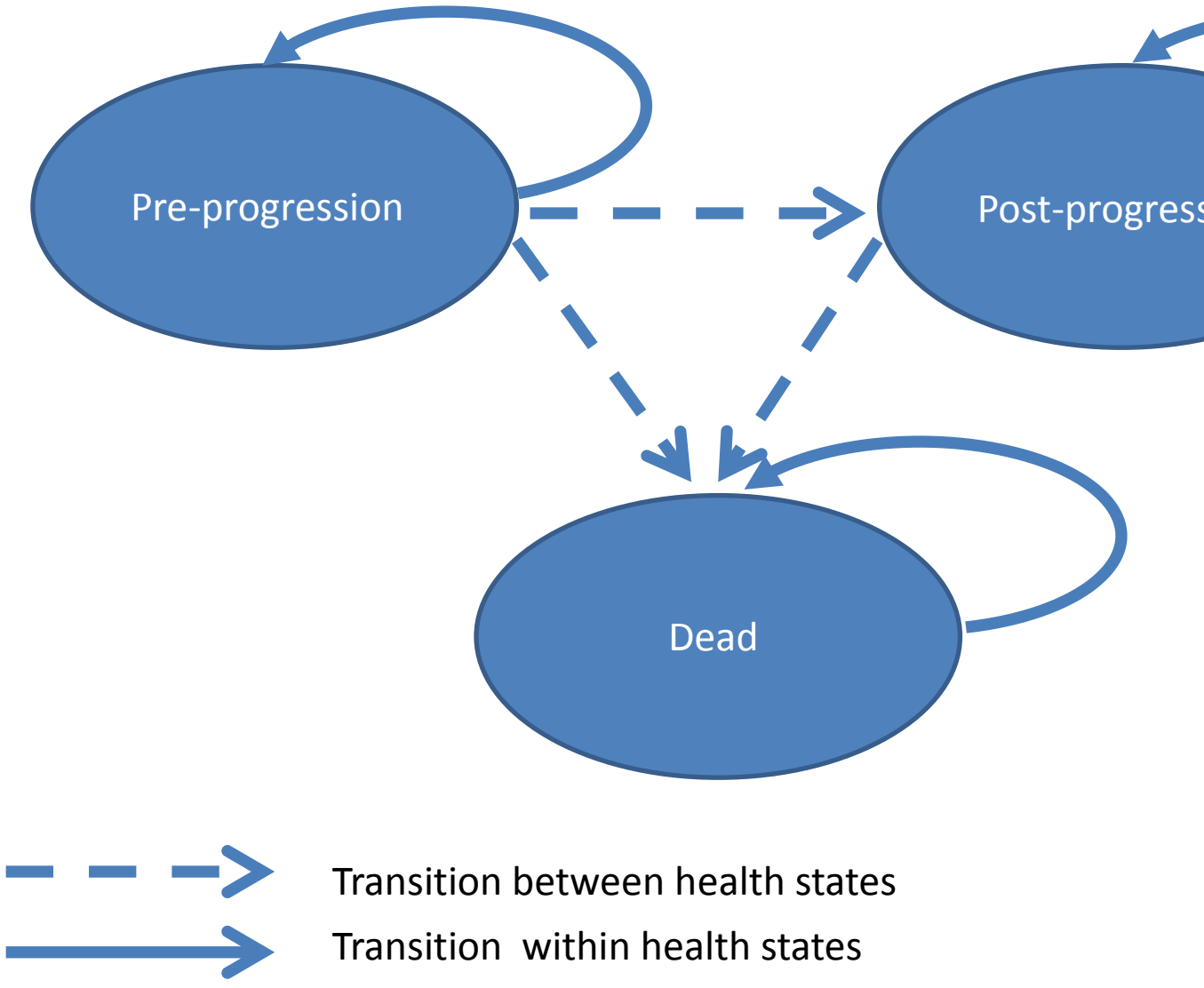
Quality-adjusted life years (QALYs) have been estimated using the OS and PFS Kaplan-Meier (KM) data and the EQ-5D IPD data from the PARAMOUNT trial. Data on the treatment discontinuation and adverse events are used to estimate the resources associated with maintenance treatment.

The economic model simulates a cohort of 359 patients in each arm and uses the observed KM data from the PARAMOUNT study to inform time-varying transition probabilities in the Markov model. 359 patients were used in the cohort to enable estimates from the Markov model to be easily validated with the pemetrexed arm KM data from PARAMOUNT. Different

sizes of cohort can be assessed in the sensitivity analyses. Model cycle length is 21 days, corresponding to the length of a pemetrexed chemotherapy treatment cycle. A half-cycle correction is applied to both costs and benefits.

A lifetime time horizon has been implemented, which corresponds to the point in time at which 99.9% of the patients in the pemetrexed arm have died (Siebert, 2012). The actual duration in years varies depending on the parameterisation used, ranging from 6 to 20 years. In the basecase gamma extrapolation this is equivalent to 15.99 years. A discount rate of 3.5% is applied per annum. Alternative time horizons and discount rates are considered within sensitivity analysis.

Figure 12 Model structure



Health states

Pre-progression

The pre-progression health state represents the maintenance phase of treatment. All patients enter the model in the pre-progression health state, corresponding to the point of randomisation in the PARAMOUNT trial following first-line treatment. In clinical practice, this reflects the point in the patient pathway when patients and clinicians decide to continue with active chemotherapy or to adopt a 'watch and wait' approach. In this health state, patients receive either pemetrexed continuation maintenance or placebo. All patients receive best supportive care (BSC). To be eligible for pemetrexed continuation treatment patients must ***not*** have progressed during first-line treatment with pemetrexed/cisplatin, i.e., they must have either complete response (CR), partial response (PR) or stable disease (SD) and have PS 0-1.

The aim of maintenance treatment is to sustain any positive response to first-line chemotherapy: CR, PR or SD. Very few patients are expected to respond further to maintenance treatment; rather their first-line response is expected to persist for longer than those patients not receiving active maintenance treatment. For this reason, the model captures only pre- and post-progression health states, which represents a conservative approach since in the PARAMOUNT trial a small proportion of patients had further responses to treatment during the maintenance phase. Best tumour response rates, (i.e., further response beyond that achieved during first-line treatment), seen in the maintenance phase of PARAMOUNT were 0.8% CR and 3.3% PR in the pemetrexed arm and 0% CR and 1.1% PR in the placebo arm, (see Table 15, Section 6.5).

Patients remain in the pre-progression health state until their disease progresses at which point they move into the post-progression health state. The duration that patients spend in the pre-progression health state is captured in the model and is driven by the PARAMOUNT PFS data. PFS censoring was relatively low, (6.7% placebo and 8.1% pemetrexed). The model uses all of the available observed PFS data in the basecase, (i.e. 47 cycles of pemetrexed and 39 cycles of placebo) and extrapolates the PFS data to account for the censored patients (n=9 in the pemetrexed arm; n=2 in the placebo arm). For the sensitivity analysis the model uses fully parameterised PFS data.

The resource use and utilities applied in the pre-progression health state relate to the maintenance phase treatment determined by the intervention received.

Utilities applied in this health state are associated with pre-progression. The utility values are derived using EQ-5D data collected during the PARAMOUNT trial. They are applied depending on the patients' treatment, pre-progression status and their proximity to death (Further details on the utilities methodology is explained in Section 7.4.3). The sensitivity analysis uses utility values derived from the literature, using a consistent method as applied in TA190 and TA227.

Resource use and costs applied in the pre-progression health state are: maintenance chemotherapy acquisition cost and delivery, monitoring associated with maintenance treatment, treatment of maintenance treatment-related grade 3/4 adverse events (AEs) and BSC. Terminal care costs are also applied to the final cycle before death for those patients who die in the pre-progression health state.

Pemetrexed or placebo treatment was administered during the maintenance phase until disease progression or treatment discontinuation, due to AEs or patient or clinician choice. Treatment was administered on day one of each 21-day cycle. The actual time on treatment was modelled using treatment discontinuation data, to capture resource use associated with pemetrexed. Treatment discontinuation data for both pemetrexed and placebo were incorporated into the model and adjusted based on actual treatment cycles to replicate as closely as possible the resource use associated with maintenance treatment in the PARAMOUNT trial.

Post-progression

This health state corresponds with clinical practice following disease progression. The post-progression health state represents the time period after maintenance treatment until death. At disease progression clinicians and patients reassess treatment options and a patient may be offered second-line treatment.

Second-line chemotherapy is modelled based on a mean number of cycles of treatment, after which patients receive BSC until death. In the basecase model mean cycles of 4.82 cycles of docetaxel and 6.27 cycles of erlotinib are used for consistency with the approach used in TA190 and TA227. These mean cycle data were originally derived from TA162 (erlotinib for second-line treatment of NSCLC) and are considered to reflect UK clinical practice. As an alternative, mean cycle data for second-line treatments from PARAMOUNT are available and are tested in the sensitivity analysis. BSC costs are applied throughout the post-progression health state and terminal care costs are also applied in the final cycle before death.

Utilities applied in this health state are associated with post-progression. The utility values are derived from the PARAMOUNT trial and are applied depending on the post-progression status and patient's proximity to death.

Death

Death is the absorbing health state. No costs or benefits are applied. However, the model uses the time point when death occurs to back calculate costs and utilities associated with the terminal phase of the disease. For simplicity in the model terminal care costs are applied in the final cycle before death (see Section 7.5.4). Based on a regression analysis, utilities are adjusted in the final six cycles before death with terminal disease utilities applied to the two cycles prior to death (see Section 7.4.3).

All-cause mortality is used in the model, i.e. cancer and non-cancer deaths, as the competing risk of a non-cancer death is assumed to be low in advanced non-squamous NSCLC.

7.2.6 Please provide a table containing the following information and any additional features of the model not previously reported. A suggested format is presented below.

The key features of the cost-effectiveness analysis are provided in Table 22.

Table 22 Key features of analysis

Factor	Chosen values	Justification	Reference
Time horizon	Lifetime, which represents when 99.9% of the modelled cohort has died in the pem/BSC arm, i.e. in the basecase, which uses the gamma distribution to extrapolate OS this equates to 15.99 years	NICE reference case criteria	NICE Guide to the Methods of Technology Appraisal. (2008)
Cycle length	21-days (3 weeks)	Consistent with the three weekly treatment administration associated with pemetrexed	Alimta SPC
Half-cycle correction	A half-cycle correction has been applied to all ongoing costs and benefits over the entire time horizon.	NICE reference case criteria.	NICE Guide to the Methods of Technology Appraisal.
Were health effects measured in QALYs; if not, what was used?	Yes, overall survival is adjusted for HRQL to estimate QALYs.	NICE reference case criteria	NICE Guide to the Methods of Technology Appraisal.
Discount of 3.5% for utilities and costs	3.5% applied per annum	NICE reference case criteria	NICE Guide to the Methods of Technology Appraisal.
Perspective (NHS/PSS)	NHS/PSS	NICE reference case criteria	NICE Guide to the Methods of Technology Appraisal.

NHS, National Health Service; PSS, personal social services; QALYs, quality-adjusted life years

Technology

7.2.7 Are the intervention and comparator(s) implemented in the model as per their marketing authorisations/CE marking and doses as stated in sections 1.3 and 1.5? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specified decision problem?

Pemetrexed is implemented in the model in line with the recent amendment to the SPC: pemetrexed can now be given as continuation maintenance treatment for patients who received pemetrexed/cisplatin first-line chemotherapy. In line with the SPC, patients included in the model have advanced NS NSCLC (stage IIIB/IV), are of good performance status (PS 0/1) and have not progressed following first-line pemetrexed/cisplatin.

The dose is consistent with the marketing authorisation, as stated in Sections 1.3 and 1.5. In the model, full licensed doses of pemetrexed are calculated based on an average body surface area (BSA) for UK patients with lung cancer (Sacco et al. 2010) weighted by gender from PARAMOUNT. Other BSA values are explored in sensitivity analysis. This assumption captures the full cost of pemetrexed and assumes no vial sharing. Vial-sharing is tested in the sensitivity analyses.

The comparator is ‘watch and wait’ and BSC, i.e. usual care that we refer to in the submission as ‘placebo’.

7.2.8 Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed? If the rule is not stated in the (draft) SPC/IFU, this should be presented as a separate scenario by considering it as an additional treatment strategy alongside the base-case interventions and comparators. Consideration should be given to the following.

- The costs and health consequences of factors as a result of implementing the continuation rule (for example, any additional monitoring required).
- The robustness and plausibility of the endpoint on which the rule is based.
- Whether the 'response' criteria defined in the rule can be reasonably achieved.
- The appropriateness and robustness of the time at which response is measured.
- Whether the rule can be incorporated into routine clinical practice.
- Whether the rule is likely to predict those patients for whom the technology is particularly cost effective.
- Issues with respect to withdrawal of treatment from non-responders and other equity considerations.

The model reflects the PARAMOUNT trial data: patients continue on treatment until disease progression or death, unacceptable adverse events, patient or physician choice. This is line with what would be expected to happen in clinical practice where patients on maintenance treatment would be treated until disease progression. Therefore, no continuation rule has been assumed in the model.

7.3 Clinical parameters and variables

When relevant, answers to the following questions should be derived from, and be consistent with, the clinical-evidence section of the submission (section 5). Cross-references should be provided. If alternative sources of evidence have been used, the method of identification, selection and synthesis should be provided as well as a justification for the approach.

In the section below the responses to questions 7.3.1 to 7.3.4 and 7.3.7 have been merged. Therefore clinical data inputs, transition probabilities, intermediate outcomes, final outcomes and extrapolation of costs and clinical outcomes beyond the trial period, including curve-fitting, are described. A list of all variables and assumptions included in the cost-effectiveness analysis are provided at the end of this section as requested in questions 7.3.6 and 7.3.8.

7.3.1 Please demonstrate how the clinical data were implemented into the model.

Questions 7.3.1 and 7.3.4 are answered below

7.3.2 Demonstrate how the transition probabilities were calculated from the clinical data. If appropriate, provide the transition matrix, details of the transformation of clinical outcomes or other details here.

Please refer to Section 7.3.5

7.3.3 Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.

Please refer to Section 7.3.5

7.3.4 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?

Questions 7.3.1 and 7.3.4 are answered below

As explained in Sections 7.2.2 to 7.2.5, all patients enter the model in the pre-progression health state. In the PARAMOUNT trial patients must not have progressed, prior to randomisation into the maintenance phase of the study. The key clinical data included in the model were derived from the PARAMOUNT trial with a March 2012 datalock (the final datalock). The key clinical outcome in the model is Overall Survival (OS) which is the gold standard outcome used in cost-effectiveness models. Therefore, it was not necessary to use any surrogate outcomes in this model as overall survival (OS) data are available.

The other key clinical/outcomes data from PARAMOUNT included in the model are: PFS, treatment discontinuation, adverse event rates and EQ-5D data. As mentioned in Sections 6.5. and 7.4 one of the strengths of this model is that the utility values are based on data from

patients in the maintenance phase of disease directly derived from the PARAMOUNT clinical trial.

Kaplan-Meier (KM) estimates from randomisation, for PFS and OS can be found in Figures 5 and 7 from Section 6.5 together with the number of patients remaining at risk. KM data as categorised by cycle in the model are provided for OS and PFS in Appendices 17 and 19.

OS was extrapolated as censoring rates at March 2012 data lock were 21.7% for the placebo arm and 28.7% for the pemetrexed arm. Therefore, curve fitting was undertaken to determine the most suitable OS parameterisation. PFS was also extrapolated as censoring rates at March 2012 data lock were 6.7% for the placebo arm and 8.1% for the pemetrexed arm. The PFS data in the model was used to estimate the time spent in the pre-progression health state. *NOTE: Please refer to Section 7.3.7 below for a full description of the extrapolation methods and the optimal choice of parametric distribution.*

Using observed PFS and OS KM trial data, the proportion of patients in each health state is reported, per cycle. Beyond the trial period, time-varying transition probabilities are taken from the extrapolated OS and PFS curves providing per cycle transition probabilities for the movement of patients between the pre- and post-progression health state and the death health state.

Based on the distribution of patients in each health state area under the curve (AUC) calculations are used to calculate mean survival and total life years (LYs). Costs and utilities are assigned per cycle. These per cycle data are summed to allow calculation of total costs and total utilities, from which total quality-adjusted life years (QALYs) and an incremental cost-effectiveness ratio (ICER) can be estimated.

Table 23 below shows how the clinical outcomes are implemented in the model.

Table 23 Implementation of clinical outcomes in the economic model

Outcome measure		Censoring	Within-trial data availability	How implemented in model
PFS	Primary outcome	6.7% for placebo/BSC 8.1% for pem/BSC	Available for: 39 cycles placebo/BSC 47 cycles pem/BSC All observed trial data used in basecase analysis. Data extrapolated beyond trial duration	Used to estimate time in the pre-progression health state.
OS	Secondary outcome but powered for significance at the 0.0499 level	21.7% for placebo/BSC: 30 patients still alive, 2 still on treatment, 7 lost to follow up 28.7% for pem/BSC: 83 patients still alive, 9 still on treatment, 10 lost to follow up, 1 discontinued but no 30-day post-discontinuation visit recorded	Available for 49 cycles placebo/BSC 50 cycles pem/BSC Observed data is used up to a common maturity stage of approx 20% of patients remaining at risk in each arm: 31 cycles pacebo/BSC and 37 cycles pem/BSC.	Used to estimate overall survival (pre- plus post-progression) for entire patient cohort.
Treatment dis-continuation	Secondary outcome	1.1% for placebo/BSC: 2 patients still on treatment and 0 patients lost to follow up 2.0% for pem/BSC: 9 patients still on treatment and 2 patients lost to follow up	Available for: 39 cycles placebo/BSC 47 cycles pem/BSC All observed trial data used in basecase analysis.	KM data used to estimate time on maintenance treatment. Converted to 21-day cycles to give a mean cycle estimate.
AE rates	Secondary outcome	N/A	Observed trial data for common grade 3-4 AEs used in basecase analysis.	Used to estimate AE rates per cycle to which costs are then applied.
EQ-5D	Secondary outcome	N/A Completeness of EQ-5D data is described in section 6.5	A mixed regression model was developed using data from the maintenance phase of the trial to estimate utility values depending on treatment, progression status and proximity to death.	Provides utility estimates for individual patients depending on treatment, progression status and proximity to death.

7.3.7 Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer term difference in effectiveness between the intervention and its comparator? For the extrapolation of clinical outcomes, please present graphs of any curve fittings to Kaplan–Meier plots.

As shown in Section 6.5. the data from the PARAMOUNT trial showed a 2.85 month median OS gain and a 1.68 month median PFS gain at the final data lock (March 2012). In order to account for the censoring data for OS and PFS an extrapolation exercise was done to evaluate the estimated mean OS and PFS from the model. The methodology and choice of distribution is explained below.

Curve-fitting of overall survival

A systematic step-wise approach to curve fitting and extrapolation of OS KM curves was undertaken as recommended in the NICE DSU Technical Support Document on survival analysis (Latimer, 2011). PARAMOUNT IPD were fitted and tested using a range of alternative parametric distributions and considered internal and external validity of the resulting models. The curve-fitting process is summarised below and additional details are provided in Appendices 1.16 to 1.19.

Step 1: Assessment of the OS hazards observed in PARAMOUNT

The KM data were explored to assess the type of hazard observed in the PARAMOUNT trial: whether the hazard function is constant over time or if the hazard increases or decreases over time (i.e accelerated failure time, AFT). In a proportional hazard (PH) model with two treatment arms the hazard of the event in one arm, at any given time point, is proportional to the hazard at the same time point in the other arm. In contrast, in an accelerated failure time (AFT) model the treatment effect is accelerated in one arm, either increasing or decreasing the hazard rate over time. The observed hazard is considered to determine whether a PH model or an AFT model is likely to be appropriate given the KM data (Latimer, 2011).[4]

The PH assumption was assessed using Schoenfeld residuals and log-log plots together with visual assessment of the KM curves. Consideration of the Schoenfeld residuals results suggests that there was no statistical evidence of PH violation. However, a log-log plot reveals some evidence of non-parallelism, suggesting possible PH violation due to the initial lack of separation of the KM curves. Schoenfeld residuals and log-log plot results are provided in Appendix 16. As a result, both PH-based and accelerated failure time (AFT) parametric distributions were considered for curve fitting and extrapolation of OS data.

Step 2: Parametric models fitted to the KM OS data

Six alternative parametric distributions were explored for OS: exponential, Weibull, log-logistic, log-normal, Gompertz and gamma.

Step 3: Parametric models compared for internal and external validity

The most appropriate distribution was determined using criteria to assess internal and external validity. For internal validity, i.e. how well they fit the observed trial data, best fit statistics (AIC, BIC and Cox-Snell goodness of fit statistics) and visual fit were considered. For external validity the plausibility of the extrapolated estimates was assessed in relation to known UK survival data.

Internal Validity

[4] PH models: exponential, Weibull and Gompertz; AFT models: exponential*, Weibull*, log-normal, gamma, log-logistic. Exponential and Weibull models may be parameterised as either a PH or AFT model.

AIC and BIC statistics provide a test of the relative fit of alternative parametric models. The smaller the value of the AIC and BIC statistics, the better the fit (Collett. 2003). Based on the AIC and BIC statistics log-logistic, log-normal and gamma distributions appear to offer the best fit for OS data (see Table 24). These models do not rely on a PH assumption. Visually, the Cox-Snell residuals for these three distributions provide a good fit (see Figure 13) and they also offer a reasonable fit to the observed KM curves (for gamma see Figure 14). Graphs for all six parametric models fitted to the KM OS data are presented in Appendix 17.

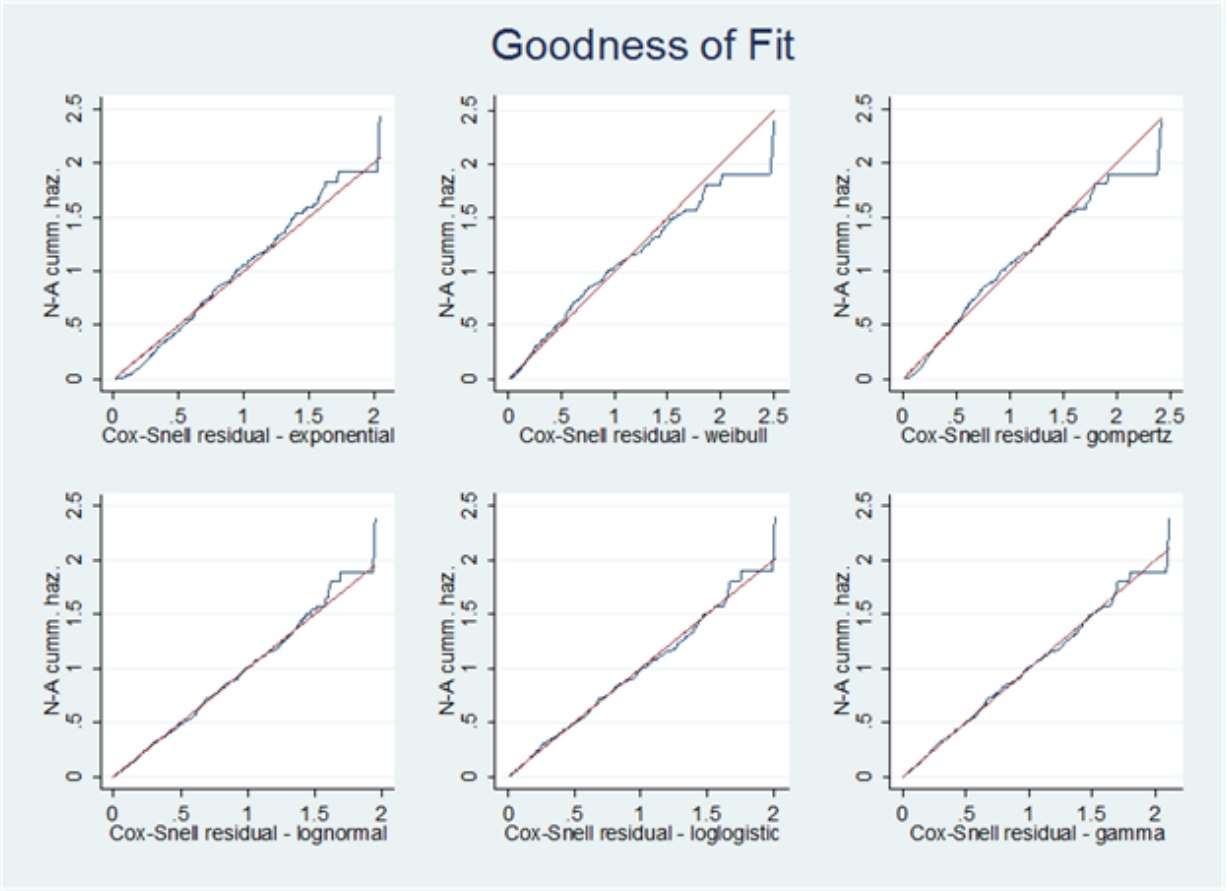
Table 24 reports the AIC and BIC statistics and Cox-Snell residuals are shown in Figure 13.

Table 24 AIC and BIC statistics for each parametric distribution

Distribution	Curve-fitting statistics	
	AIC*	BIC*
Exponential	1425.544	1434.124
Weibull	1395.023	1407.892
Gompertz	1417.424	1430.293
Log-normal	1378.888	1391.757
Log-logistic	1376.934	1389.803
Gamma	1377.652	1394.811

***** AIC: Akaike's Information Criterion; BIC: Bayesian Information Criterion.

Figure 13 OS: Cox-Snell residuals by parametric distribution



External Validity

Table 25 reports five and ten-year survival from UK cancer registry data (Cancer Research UK, 2012) and lifetime horizons estimated using each of the six parametric distributions in the economic model.

In England and Wales cancer registry survival data for 2005 to 2009 shows that approximately 8% of male and 9% of female lung cancer patients, of all ages, stages and co-morbidities, are alive five years after diagnosis. Ten-year survival rates, predicted for patients diagnosed in 2007, are 4.9% for men and 5.9% women. Since these survival estimates include patients with early stage disease, which may be amenable to curative treatment (Cancer Research UK, 2012), it is assumed that the proportion of patients with advanced NSCLC alive five or ten years after diagnosis is likely to be lower.

The log-logistic and log-normal extrapolations both result in time horizons in excess of 20 years. Coupled with the five- and ten-year survival estimates, when compared to the registry data these estimates of long term survival do not appear plausible. Gamma and exponential curves provide more conservative long-term survival estimates. Whilst the time horizons are approximately 16 and 12 years respectively, the survival estimates show that less than 1% of patients are predicted to be alive at 10-years. Weibull and Gompertz result in the lowest estimates (see Table 25). See Figure 6, Appendix 17 for visual fit of Gompertz to the observed KM data.

Table 25 Lifetime time horizon with 5-year and 10-year survival estimates (Modelled results)

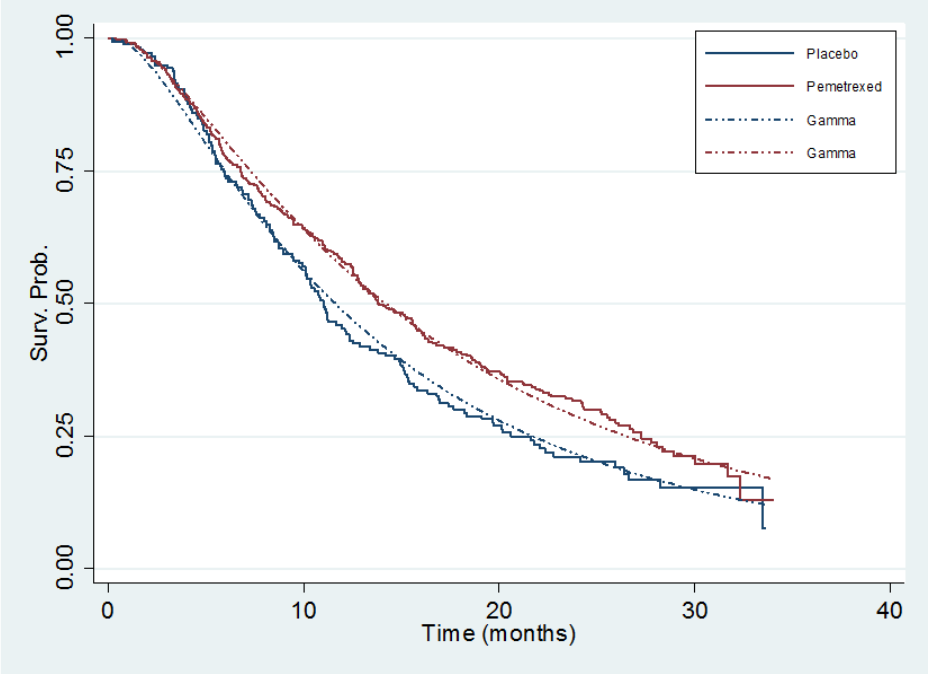
Distribution	Lifetime time horizon* (years)		5-year survival (%)		10-year survival (%)	
	Placebo/ BSC	Pem/BSC	Placebo/ BSC	Pem/BSC	Placebo/ BSC	Pem/BSC
Exponential	9.21	11.79	2.4	5.5	0.1	0.3
Weibull	6.04	7.59	0.5	1.9	0.0	0.0
Gompertz	5.29	6.16	0.2	1.0	0.0	0.0
Log-normal	20.42	20.42	4.6	7.7	0.9	1.7
Log-logistic	20.42	20.42	5.3	8.3	1.6	2.6
Gamma	12.72	15.99	3.0	5.8	0.3	0.7

Note: * **Lifetime time horizon based on time when 99.9% of patients are estimated to have died; OS extrapolation applied beyond cycle 31 placebo/BSC and 37 cycles pem/BSC of observed OS data**

Step 4: Parametric model selection

Based on the AIC, BIC and Cox-Snell residual statistics, visual fit and plausibility of the survival estimate the gamma distribution was selected as the basecase parameterisation for OS (see Figure 14). This has a lifetime time horizon of 15.99 years, which is consistent with the 15-year time horizon preferred by the ERG during the appraisal of erlotinib (TA227).

Figure 14 OS: Parametric survival model (Gamma distribution) with KM data



As described above, the log-logistic and log-normal models are not considered to have external validity. The exponential model has a poorer statistical and visual fit to the KM data but may provide plausible survival estimates when fitted to the tails. The Weibull and Gompertz models have poor internal and external validity. However, for the purposes of transparency, all six models have been implemented in the economic model to enable the impact of different alternative parametric models on survival to be shown. This demonstrates the robustness of the lifetime survival estimates presented in the basecase analysis. The exponential distribution is tested in the sensitivity analysis as a plausible alternative parametric extrapolation when fitted to the tail of the observed KM data (Latimer, 2011).

Extrapolation of overall survival using Gamma parametric distribution

Having established gamma as the basecase distribution, alternative methods of implementing the parameterisation were explored. We considered three main options:

1. Fully parameterised curves
2. Using all available OS data points and appending the extrapolation to the final observed KM data point.
3. Appending the OS extrapolation at a point on the KM curve prior to the final data point.

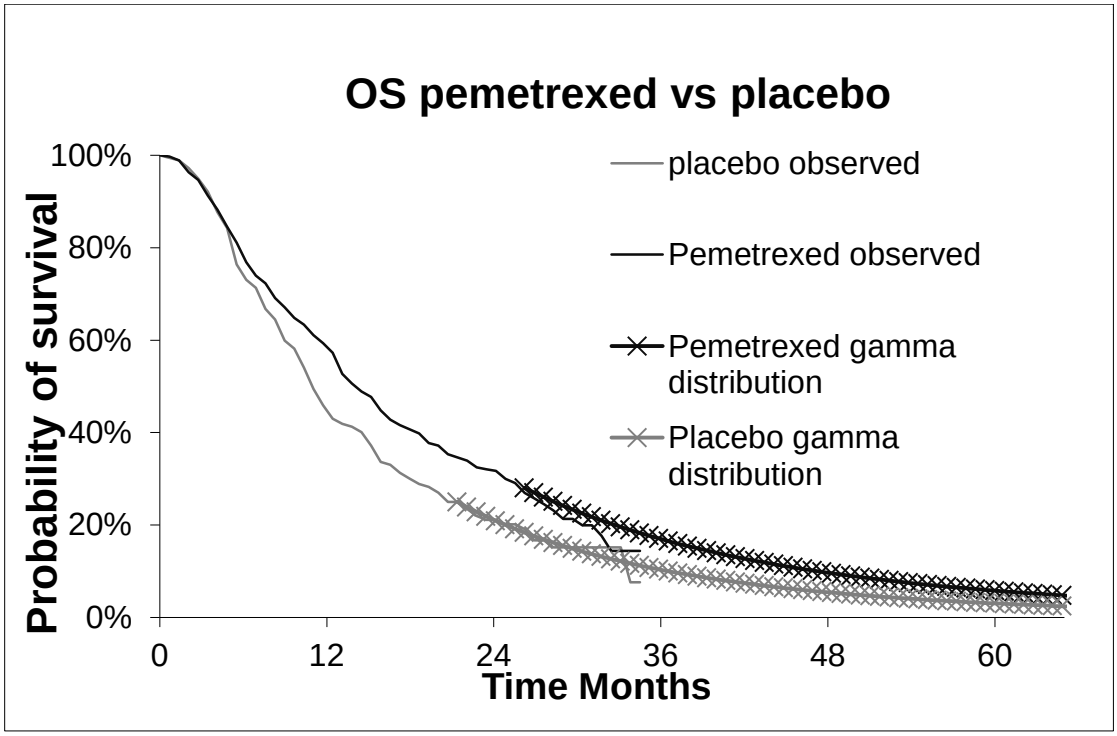
The first approach was not considered the most appropriate for the basecase analysis as it is assumed that PARAMOUNT observed data provides the most suitable estimate of mortality for the within-trial period, particularly in view of the possibility of some violation of the PH assumption, i.e. the initial lack of separation of the KM curves. However, fully parameterised curves are provided within the model for sensitivity analysis.

As for option 2, this was also not considered to provide the most accurate estimates of the long term progression given the higher degree of uncertainty associated with later data points due to fewer patients being ‘at risk’ of an event on the right-hand side of the KM curves. In

extreme cases, individual patients could 'change the shape' of the curve meaning the extension is added to a point that doesn't represent a typical survival trajectory. This approach can also result in a step in the curve at the transition point between the final observed data point and the extrapolated extension.

Therefore, the third option was chosen for the basecase appending the extension to the point on the KM curve the point where approximately 20% of patients remain at risk in each arm. Although there are no guidelines that recommend at what stage of maturity the most appropriate cut point should be, the use of a common maturity stage of KM data and the specific choice of the 20%'cut-point' was selected based on the method adopted by the ERG during TA227 (LRiG, 2010; LRiG 2011). The proportion of patients remaining at risk is used to assess the maturity of KM data (Machin et al., 2006). This equates to cycle 31 for the placebo arm (20% at risk) and cycle 37 in the pemetrexed arm (19% at risk). Truncating the arms at the same stage of KM data maturity avoids any potential bias that may occur if the KM curves were cut at a specific number of cycles for both arms (LRiG, 2010). The extrapolated survival curves are joined to the observed KM curves by applying the hazard to the last observed KM data point i.e. at the cut-points. Alternative 'cut-points' are explored in the sensitivity analysis.

Figure 15 Basecase model: OS observed KM data plus gamma parametric extension joined at 31 cycles (placebo) and 37 cycles (pemetrexed)



Curve-fitting of progression-free survival and treatment discontinuation

Curve-fitting for PFS and treatment discontinuation was undertaken using the same stepwise approach as OS, described in detail above. Results of PH assumption testing, best-fit statistics and the curve fitting exercise for PFS, together with AIC and BIC statistics for treatment discontinuation, are provided in Appendices 18 and 19. Graphs of KM data from the PARAMOUNT trial and as modelled in the basecase analysis are also provided in Appendix 19. There was some evidence of PH violation for the PFS data. The gamma distribution was also selected as the most appropriate distribution for PFS and treatment discontinuation data

providing a consistent parametric distribution in the fully parametric model. Alternative distributions can be individually selected for sensitivity analysis.

For the purpose of the sensitivity analyses fully parameterised curves are provided.

7.3.5 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[5]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

Many of the assumptions used in the model refer to previous NICE appraisals in NSCLC (TA181, TA190, TA227) therefore an extensive clinical expert input was not considered to be necessary. However, one clinical expert was consulted to validate some of the assumptions and inputs used in the model during the early stages of model development. This clinical expert was selected based on their experience and recognition as a UK leader in treating patients with NSCLC. The clinical expert was provided with a summary of the model development, a summary of the PARAMOUNT data and the preliminary statistical analyses conducted to enable a draft model to be built. The clinical expert advised on the appropriateness of the assumption for the treatment effect in the post-trial period.

Summary of selected values

7.3.6 Please provide a list of all variables included in the cost-effectiveness analysis, detailing the values used, range (distribution) and source. Provide cross-references to other parts of the submission. Please present in a table, as suggested below.

[5] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

Table 26 Summary of variables applied in the economic model

Variable	Value	CI (distribution)	Reference to section in submission
Age, median (range)	61 (32-83) years	N/A	Section 6.3.4
Gender	58% male; 42% female	N/A	Section 6.3.4
Body Surface Area (BSA) m^2	1.79m^2 based on mean UK BSA values weighted by gender from PARAMOUNT	Normal distribution of BSA by gender	Section 7.5
Clinical Outcomes:			
Overall survival	Incremental 4.21 months mean OS from randomisation. Extrapolated using gamma distribution in the basecase analysis.	Probabilistic estimates have been derived for KM data using the standard error associated with the observed failure rate per cycle. (Beta distribution) In the extrapolated period multivariable regression functions generated using KM data have been entered in the model along with Cholesky decompositions that account for correlations between parameters	Section 6.5
PFS	Incremental 3.25 months mean PFS from randomisation. Extrapolated using gamma distribution in the basecase analysis.		Section 6.5
Treatment discontinuation	5.09 cycles placebo and 7.95 cycles pemetrexed. Not extrapolated in the basecase analysis.		Section 6.5 (cycle data)
AE rates per cycle PEM/BSC	Neutropenia 0.0061	No CI available	Section 7.5.6
	Nausea & Vomiting 0.0008		
	Fatigue 0.0053		
	Anaemia 0.0066		
AE rates per cycle Placebo/BSC	Neutropenia 0.0000	No CI available	Section 7.5.6
	Nausea & Vomiting 0.0000		
	Fatigue 0.0006		
	Anaemia 0.0003		
Second-line chemotherapy use	Pem/BSC 64% Placebo/BSC 72%	Pem/BSC 58-68% Placebo/BSC 65-78% (Beta distribution)	Section 7.5.6
Utility values:			
Pre-progression >6 cycles prior to death	0.7758	Utility values derived from a mixed regression model. Multivariable regression functions generated using PARAMOUNT individual patient data have been entered in the model along with a Cholesky decomposition to account for correlated parameters. (CI for the coefficients derived from the regression model are provided in Table 28)	Section 7.4.9
Pre-progr >4 $\leq$ 6 cycles prior to death	0.7242		
Pre-progr > 2 < 4 cycles prior to death	0.6520		
Pre-progr 0-2 cycles prior to death	0.4099		
Post-progression >6 cycles prior to death	0.7028		
Post-progr >4 $\leq$ 6 cycles prior to death	0.6512		
Post-progr > 2 < 4 cycles prior to death	0.5790		
Post-progr 0-2 cycles prior to death	0.3369		

7.3.7 Provide a list of all assumptions in the *de novo* economic model and a justification for each assumption.

We have captured all assumptions incorporated into the economic model in Table 27 along with a description of the assumption and its justification. These assumptions are tested in the sensitivity analysis.

Table 27 List of assumptions used in the model

Assumption	Rationale	Comments
Structural assumptions:		
The PARAMOUNT trial results are generalisable to the UK population (e.g. advanced IIIB/IV non-squamous NSCLC PS 0-1).	PARAMOUNT was a predominantly European study with 15% of patients from UK and Nordic Europe. Patient characteristics within the trial are similar to those of UK. NICE recommends chemotherapy for patients with PS 0-1 (NICE CG121).	The age profile of the PARAMOUNT study reflects patients likely to receive active treatment in the UK based on The NHS IC, NCLA Information Sheet 2011. See Section 6.3
Parameters:		
No half-cycle correction is applied to pemetrexed costs.	Treatment costs are incurred at the start of each 21-day cycle whilst on maintenance treatment.	No mid-cycle correction is needed.
Actual cycle use in the PARAMOUNT trial assumed to be reflective of clinical practice	A proportion of patients in clinical practice will have delayed doses due to requirements of the SPC for pemetrexed (See Appendix 1).	The mean number of cycles of treatment will differ if the treatment discontinuation data are fully parameterised.
Chemotherapy and doses		
Treatment effect for pemetrexed is assumed to continue in the extrapolated tail of the OS curves.	This treatment effect, implemented in the basecase analysis using a relative time ratio for the gamma distribution to extrapolate OS is expected to continue beyond the duration of the clinical trial as patients will continue to benefit from delayed disease progression.	This assumption was verified by a clinical expert in NSCLC. An alternative assumption for treatment effect is explored in sensitivity analysis, i.e. beyond the trial duration, the treatment effect is equal to the BSC arm.
The costs of therapy are modelled to cease following disease progression.	Patients are not expected to incur treatment-related costs or AEs following treatment discontinuation. AEs are related to short-term effects from pemetrexed treatment e.g. neutropenia and nausea.	This assumption was verified by a clinical expert in NSCLC.

Any reduction in clinical benefit resulting from early treatment discontinuation, i.e. prior to disease progression, is assumed to be implicitly captured in PARAMOUNT data.	PFS and OS data are assumed to fully capture the effect of any treatment discontinuation prior to progression.	69% of patients remained on maintenance treatment until disease progression. 31% of patients discontinued treatment before progression due to AEs.
UK BSA data for patients with lung cancer, weighted by gender as per the PARAMOUNT trial are assumed to offer the most reliable data to calculate pemetrexed dose.	Consistent with ERG approach in TA190. Applied to maintenance and second-line treatments.	UK BSA data for lung cancer patients sourced from Sacco et al. 2010.
Patients are assumed to receive chemotherapy in a daycase setting.	The treatments used do not require an inpatient stay.	Alternative delivery settings are explored in sensitivity analysis.
The cost of concomitant medication used with pemetrexed (vitamins and dexamethasone) included in the HRG for chemotherapy delivery	The costs of these concomitant drugs are negligible. This assumption is consistent with TA190.	These costs are available in the model for inclusion as sensitivity analysis.
Adverse events:		
The inclusion of the most common grade 3-4 AEs are assumed to capture the impact of AEs in the model.	This assumption is consistent with TA190.	Alternative assumptions for treatment of AEs are explored in sensitivity analysis.
Costs and resources:		
Patients receiving pemetrexed are assumed to incur additional monitoring costs whilst on maintenance treatment as they are on treatment for longer and to ensure they stopped pemetrexed maintenance treatment promptly upon disease progression.	It has been assumed that patients receiving pemetrexed incur a cost for one additional consultant visit every 24 weeks (8 cycles), and 3% of patients receive one additional CT scan every 24 weeks (8 cycles).	Frequency of routine monitoring for patients following first-line treatment was determined from a recent BTOG survey of UK oncologists (Beckett et al. 2012). Alternative assumptions for monitoring of maintenance treatment are explored in sensitivity analysis.
The cost of x-rays is assumed to be captured within consultant visit costs.	The cost of x-rays is bundled in with core HRG codes.	
Utility data:		
The non-significant differences in treatment effect for EQ-5D derived from PARAMOUNT trial are implemented in the basecase model.	There was no significant difference in EQ-5D between treatment arms. However, it was considered to be more conservative to include this in the model. (See section 7.4)	The treatment effect on utilities is excluded in sensitivity analysis (i.e. utility values are assumed to be the same for both arms in the pre-progression health states).

Second-line chemotherapy:		
Patients are assumed to receive, erlotinib or docetaxel.	These are the two most common second-line treatments used in current UK clinical practice. Consistent with TA190.	Positive NICE appraisals for each of these treatments support their choice as second-line therapy in the UK. UK market share data for second-line treatment is used.
The distribution of second-line therapies reported in the PARAMOUNT trial have the same efficacy as those routinely used in UK clinical practice.	The use of second-line treatments are similar on both arms therefore overall survival data should not differ by arm. Consistent with TA190.	A number of the treatments used in the PARAMOUNT trial are not representative of UK practice.
It is assumed that the second-line therapies have equivalent efficacy and utility in the second-line setting.	Based on erlotinib second-line data (TA162). Consistent with TA190.	It is assumed no difference in efficacy or utility of second-line therapy. Therefore only a cost element needs to be applied.
The same BSA assumption is made for calculating docetaxel dose as used for pemetrexed.	In TA190 the ERG did not consider the assumption of a lower BSA of 1.7m2 for second-line to be appropriate.	
Treatment duration for second-line chemotherapy is assumed to be 4.82 cycles of docetaxel and 6.87 cycles of erlotinib.	Consistent with TA190.	Alternative treatment durations are explored in sensitivity analysis.For simplicity in the model, costs are applied as a one-off cost in the first cycle post-progression.
It is assumed that erlotinib is subject to a 14.5% discount from the list price.	Erlotinib has a patient access scheme in place (TA227).	Alternative costs for second-line treatments are explored in sensitivity analysis.
No AE costs have been applied to second-line chemotherapy.	Consistent with TA190.	
BSC and terminal care costs:		
BSC costs exclude the cost of palliative radiotherapy (RT) for patients receiving active chemotherapy (maintenance or second-line) and include the cost of RT for patients not receiving active chemotherapy.	Consistent with TA190.	Alternative assumptions are explored in sensitivity analysis.
Patients are assumed to incur one-off terminal care costs in the final cycle before death.	Consistent with TA190 and TA227.	

7.4 Measurement and valuation of health effects

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.4.

The HRQL impact of adverse events should still be explored regardless of whether they are included in cost-effectiveness analysis.

All parameters used to estimate cost effectiveness should be presented clearly in tabular form and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

Patient experience

7.4.1 Please outline the aspects of the condition that most affect patients' quality of life.

The aspects of the condition that most affect patients' HRQL are disease stage, the extent of disease progression, performance status, presence of severe symptoms and treatment-related toxicities (Nafees et al 2008, Chouaid et al 2012).

7.4.2 Please describe how a patient's HRQL is likely to change over the course of the condition.

At diagnosis, patients' HRQL is impacted by the stage and extent of disease progression, performance status and severity of symptoms. During first-line chemotherapy, patients HRQL may be negatively impacted by treatment-related toxicities. Successful first-line treatment, when disease control has been achieved, (CR, PR or SD), would be expected to improve patients' HRQL due to reduced symptom burden.

Following first-line chemotherapy, patients with advanced NSCLC would usually undergo a period of watch and wait with no active intervention. During this time they will receive BSC as necessary and will be monitored for disease progression. HRQL is usually stable in this phase of the disease, with decreasing utility as the disease begins to progress. Patients receiving pemetrexed chemotherapy in the maintenance phase are not expected to experience a decrease in HRQL. Pemetrexed maintenance chemotherapy does not have severe AEs associated with it, so there is no significant detrimental impact on HRQL (Paz-Ares, 2011). This has also been confirmed from the analyses of IPD EQ-5D in STATA.

Also, patients eligible for active treatment in the maintenance phase need to have both disease control and good performance status, therefore are likely to have a higher baseline (start of maintenance) HRQL than patients with a poorer performance status or with progressed disease.

Upon disease progression patients will be assessed and, if fit enough i.e. PS 0-1, may be offered second-line chemotherapy. As a patient's disease progresses, their HRQL is expected to worsen, due to increasing symptom burden and worsening performance status. Nafees and previous NICE technology appraisals in NSCLC (TA 190, TA181, TA 227) all document the gradual reduction in HRQL as disease progresses. Patients in the terminal stage of the

disease are expected to have a poor quality of life due to high symptom burden (Sandblom et al, 2004).

HRQL data derived from clinical trials

7.4.3 If HRQL data were collected in the clinical trials identified in section 5 (Clinical evidence), please comment on whether the HRQL data are consistent with the reference case. The following are suggested elements for consideration, but the list is not exhaustive.

- Method of elicitation.
- Method of valuation.
- Point when measurements were made.
- Consistency with reference case.
- Appropriateness for cost-effectiveness analysis.
- Results with confidence intervals.

The method of elicitation, valuation, points when measurements were made and results of the HRQL collected in the PARAMOUNT trial are described in Section 6.5. The NICE reference case requires HRQL data to be reported directly by patients preferably using the EQ-5D instrument for adult patients. In addition, these data should be based on UK public preference valuations. Therefore, the EQ-5D data reported in PARAMOUNT are consistent with the reference case.

The trial data did not provide values suitable for the pre and post-progression health states. Therefore a mixed regression analyses was undertaken in STATA. The mixed regression model considered the following covariates: treatment, disease progression and time before death. Time before death was considered for inclusion in the mixed regression model in addition to progression as HRQL is known to decline in the terminal stages of cancer (Sandblom et al, 2004).

The results of the mixed regression analysis showed a small numeric, non-significant, utility decrement associated with pemetrexed treatment (-0.0248, 95% CI -0.06-0.01, p=0.17), this is consistent with the comparison of treatment differences (See Section 6.5). Although this utility decrement was non-significant it has been applied in the pre-progression health state to capture any disutility associated with adverse events from pemetrexed. This assumption is tested in the sensitivity analyses where the treatment decrement for pemetrexed is removed.

Time before death was found to have a strong correlation with HRQL in PARAMOUNT patients in the mixed regression model. The time before death variable categorised survival time by the number of cycles prior to death, i.e., 0-2, 3-4, 5-6 and >6 cycles. Additional categories of time before death were considered, e.g. 6-8 cycles and >8 cycles, however, these were not found to have a significant effect on HRQL compared to >6 cycles. As a result, the HRQL regression equation includes covariates for disease progression and for proximity to death. This approach was chosen to enable conservative prediction of HRQL values for patients, particularly in the extrapolated post-progression period.

Coefficients derived from the mixed regression model of PARAMOUNT EQ-5D data are shown in Table 28.

Table 28 Coefficients derived from mixed regression model of PARAMOUNT EQ-5D data (valued for UK population)

HRQL parameters	Coefficient	SE	95% LCI	95% UCI
Treatment	-0.0248	0.0182	-0.06	-0.01
Time before death (3-4 cycles)	0.2421	0.0269	0.1894	0.2947
Time before death (5-6 cycles)	0.3143	0.0275	0.2604	0.3681
Time before death (>6 cycles)	0.3659	0.0273	0.3123	0.4194
Progression Free	0.0730	0.0110	0.0514	0.0946
Constant	0.3369	0.0290	0.2800	0.3938

The regression model provides a constant utility value of 0.3369 for patients in the progressed heath state who are 0-2 cycles prior to death. All other utility values in the economic model are anchored to this value using the coefficients. For example, the utility value of the *'pre-progression in the placebo arm (more than 6 cycles prior to death'* is 0.7758 which is derived from the sum of the following coefficients 0.3369 + 0.3659 + 0.0730. Similarly for the '*post-progression health state 3-4 cycles prior to death*' the utility value is 0.5790 which is derived from the sum of the 0.3369 and 0.2421 coefficients.

The complete sets of utility values applied in the economic model are shown in Table 29. These utility values are applied to each cycle in the Markov model trace according to the proportion of patients in the pre- and post-progression health states and back calculated from death to adjust for time before death increments.

Table 29 Summary of utility values used in the economic model

State	Utility value*	Derived from coefficients (see Table 28, section 7.4.3)
Pre-progression placebo/BSC >6 cycles prior to death	0.7758	0.3369 + 0.3659 + 0.0730
Pre-progression pem/BSC >6 cycles prior to death	0.7510	0.3369 + 0.3659 + 0.0730 -0.0248
Pre-progression placebo/BSC 5-6 cycles prior to death	0.7242	0.3369 + 0.3143 + 0.0730
Pre-progression pem/BSC 5-6 cycles prior to death	0.6994	0.3369 + 0.3143 + 0.0730 – 0.0248
Pre-progression placebo/BSC 3-4 cycles prior to death	0.6520	0.3369 + 0.2421 + 0.0730
Pre-progression pem/BSC 3-4 cycles prior to death	0.6272	0.3369 + 0.2421 + 0.0730 – 0.0248
Pre-progression placebo/BSC 0-2 cycles prior to death	0.4099	0.3369 + 0.0730
Pre-progression pem/BSC 0-2 cycles prior to death	0.3851	0.3369 + 0.0730 – 0.0248
Post-progression both arms >6 cycles prior to death	0.7028	0.3369 + 0.3659
Post-progression both arms 5-6 cycles prior to death	0.6512	0.3369 + 0.3143
Post-progression both arms 3-4 cycles prior to death	0.5790	0.3369 + 0.2421
Post-progression both arms 0-2 cycles prior to death	0.3369	Constant derived from regression analysis

**Note: ***No confidence interval available for the utility values due to the statistical method used. Confidence intervals for the coefficients are shown in Table 28.

Mapping

7.4.4 If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide the following information.

- Which tool was mapped from and onto what other tool? For example, SF-36 to EQ-5D.
- Details of the methodology used.
- Details of validation of the mapping technique.

No mapping was conducted.

HRQL studies

7.4.5 Please provide a systematic search of HRQL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria used. The search strategy used should be provided in section 9.12, appendix 12.

Since HRQL data were available from the PARAMOUNT trial and in accordance with the NICE reference case, these data were used in the economic analysis. To enable comparison of the trial-based utility values from PARAMOUNT with those from the literature used in previous appraisals a search for HRQL data was conducted. Full details of the literature search can be found in Appendix 14.

7.4.6 Provide details of the studies in which HRQL is measured. Include the following, but note that the list is not exhaustive.

- Population in which health effects were measured.
- Information on recruitment.
- Interventions and comparators.
- Sample size.
- Response rates.
- Description of health states.
- Adverse events.
- Appropriateness of health states given condition and treatment pathway.
- Method of elicitation.
- Method of valuation.
- Mapping.
- Uncertainty around values.
- Consistency with reference case.
- Appropriateness for cost-effectiveness analysis.
- Results with confidence intervals.
- Appropriateness of the study for cost-effectiveness analysis.

See below

7.4.7 Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

Responses to questions 7.4.6 and 7.4.7 are provided together below.

The results from the HRQL literature review did not provide specific utility values for patients in the maintenance treatment phase for NSCLC. Recent technology appraisals for maintenance treatment of advanced NSCLC (TA190 and TA227) used utility values derived from the literature for second-line treatment (Nafees et al, 2008; Berthelot, 2000). In addition, a recent publication, Chouaid et al. 2012, provided utility values for patients with NSCLC following different lines of therapy. The utility values used from these three publications can be found in Appendix 14.

As previously mentioned, PARAMOUNT is the first study to provide direct evidence of the HRQL for this patient group. Therefore, no utility values from the literature have been used in the basecase analysis. However, the utility values from TA190 have been considered in the sensitivity analyses. See Appendix 14 for details of the literature search and results.

A comparison between PARAMOUNT and the literature shows a decreasing trend in utility values as disease progresses. The main differences are

- The IPD EQ-5D data from PARAMOUNT shows that the utility values for those patients in the maintenance phase with a larger number of cycles prior to death (i.e. >6 cycles) are higher in PARAMOUNT than that used in the 'not progressed' health state from TA190 and TA227 (e.g. for placebo 0.7758 from PARAMOUNT vs 0.6628 TA190). Since the values from TA190 were for patients receiving second-line treatment, this difference is to be expected.

- The utility values derived from PARAMOUNT for patients who are closer to death (i.e. 0-2 cycles prior to death) for both the pre and post-progression health states are lower than the value used for the terminal cycle health state in TA190 (0.3851 and 0.3369 vs 0.47 respectively).

- The treatment decrement, i.e. -0.0248, included for pemetrexed in the PARAMOUNT model is larger than the treatment decrement of 0.006 applied in TA190, i.e. 0.6628 for placebo/BSC versus 0.6568 for pem/BSC during pre-progression. Thus, our inclusion of the treatment-related utility decrement from PARAMOUNT seems appropriate despite the fact that there is no statistical difference between arms.

Though there are some differences in the values for some of the health states, the granularity provided by the mixed regression model provides realistic utility values based upon treatment and proximity to death in addition to the progression status.

Adverse events

7.4.8 Please describe how adverse events have an impact on HRQL.

Using a MMRM analysis, results from the PARAMOUNT trial showed that overall there were no statistically significant differences on EQ-5D between treatment arms during maintenance treatment. Although the rates of grade 3/4 toxicities in the pemetrexed arm were statistically significantly greater than the control arm, it is important to note that the control was no active therapy and that absolute toxicity rates were low on both arms. Despite modest increases in toxicity with pemetrexed, the EQ-5D data suggest that patients are able to tolerate long-term maintenance pemetrexed without impacting on HRQL.

Quality-of-life data used in cost-effectiveness analysis

7.4.9 Please summarise the values you have chosen for your cost-effectiveness analysis in the following table, referencing values obtained in

sections 6.4.3 to 6.4.8. Justify the choice of utility values, giving consideration to the reference case.

This has already been presented in Section 7.4.3 above. Please refer to Table 29 for all the utility values used in the economic model.

7.4.10 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[6]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

It was not considered necessary for clinical experts to assess the applicability of utility values used in the economic model since the utility values were derived directly from patients during the maintenance phase of the PARAMOUNT trial and were able to be compared to previously used and accepted values in recent appraisals.

7.4.11 Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?

In the pre-progression health state during the maintenance phase, patients are expected to maintain the response achieved following first-line treatment. Following progression HRQL is expected to decrease due to increasing symptom burden as the disease progresses. See Section 7.4.3 and Tables 29 and 30 for details of how utility values change based on covariates.

[6] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

7.4.12 Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?

Utility decrements for grade 3/4 AEs were identified in the literature. The regression analysis conducted to elicit utility values for the economic model found a non-significant treatment-based utility decrement for pemetrexed which was included in the basecase analyses. As such, it was not considered appropriate to include an additional utility decrement for adverse events as this would result in double counting.

7.4.13 If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?

The methodology has been described earlier in Section 7.4.3.

7.4.14 Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.

HRQL is assumed to change over time. Utility values, derived from a mixed regression model of PARAMOUNT EQ-5D data, decrease with disease progression and proximity to death. The methodology has been described earlier in Section 7.4.3.

7.4.15 Have the values in sections 7.4.3 to 7.4.8 been amended? If so, please describe how and why they have been altered and the methodology.

The utility values were adjusted for treatment, progression status and time before death. The methodology has been described earlier in Section 7.4.3.

7.5 Resource identification, measurement and valuation

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.5.

All parameters used to estimate cost effectiveness should be presented clearly in a table and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

This section reports the resource utilisation and unit costs used in the cost-effectiveness analysis for pemetrexed continuation maintenance. The original order of questions in this section has been rearranged. To that effect, questions 7.5.3 and 7.5.4 are answered first as they relate to the identification of appropriate resource use. The remaining questions follow in order.

Resource identification, measurement and valuation studies

7.5.3 Please provide a systematic search of relevant resource data for the UK. Include a search strategy and inclusion criteria, and consider published and unpublished studies. The search strategy used should be provided as in section 9.13, appendix 13. If the systematic search yields limited UK-specific data, the search strategy may be extended to capture data from non-UK sources. Please give the following details of included studies:

- country of study
- date of study
- applicability to UK clinical practice
- cost valuations used in study
- costs for use in economic analysis
- technology costs.

In order to present a consistent approach with previous appraisals of maintenance treatment for NSCLC, relevant resources were identified from TA190 (pemetrexed) and TA227 (erlotinib). These studies were identified in the literature search documented in Section 7.1. These resources have been accepted by the ERG and the NICE appraisal committee as being representative of UK clinical practice in these previous appraisals. The NICE Guide to the Methods of Technology Appraisal (2008) states that estimates of unit costs and prices for particular resources should be used consistently across appraisals. As a result, an additional systematic literature search was not considered necessary to identify further resource utilisation data.

Unit cost data were available from NHS reference costs, HRGs or previous technology appraisals therefore no searching for bottom-up costings was required. Unit costs have been updated using the most recent NHS Reference Costs and inflation indices (UK National Statistics 2012) where necessary. All costs used are for 2011.

7.5.4 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[7]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

As mentioned in Section 7.3.5, a clinical expert was selected based on their reputation as a leading clinician with extensive experience of clinical trials and the treatment of UK patients with NSCLC as well as being familiar with the NICE appraisal process. The clinical expert was provided with a summary of the model development, a summary of the PARAMOUNT data and the preliminary statistical analyses conducted to enable a draft model to be built.

Since the majority of the assumptions used in the resource use section of the economic model are consistent with previous pemetrexed appraisals (TA181 and TA190) the clinical expert consulted for this submission was mainly focused on validating the choice of NHS reference codes for CT scans included in the model to ensure that they were appropriate for the NSCLC patient population.

Resource Identification

NHS costs

7.5.1 Please describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff. Provide the relevant Healthcare Resource Groups (HRG) and PbR codes and justify their selection. Please consider in reference to section 2.

7.5.2 Please describe whether NHS reference costs or PbR tariffs are appropriate for costing the intervention being appraised.

[7] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

The responses to questions 7.5.1 and 7.5.2 are provided together below. In line with the treatment pathway described in Section 2 the following resources are required (see Table 30):

Table 30 Resources used in the economic model

Resources	
1	Maintenance chemotherapy – acquisition and delivery
2	Monitoring of disease in the maintenance phase
3	Treatment of any adverse events
4	Second-line chemotherapy – acquisition and delivery
5	BSC – throughout the patient pathway
6	Terminal care – applicable to the final cycle only

There are Healthcare Resource Group (HRG) codes and NHS reference costs available for some of these resources, but not all. The appropriateness of using NHS reference costs has been considered and the rationale for the use of alternative costs in the economic model is described where necessary. The NHS uses core HRGs to categorise the treatment of patients with a primary diagnosis of lung cancer. The HRGs include consultant visits, surgical procedures and inpatient stays.

There are currently no national tariffs for chemotherapy or diagnostic imaging such as CT scans, with the exception of x-rays. These services, i.e. chemotherapy and diagnostic imaging, are 'unbundled', which means that multiple HRGs are created for each episode of care, e.g. each cycle of chemotherapy and each CT scan is coded and costed individually (The National Casemix Classifications Service, 2009). X-rays are included within other core HRGs such as consultant visits or inpatient stays.

Alternative methods of capturing resource utilisation using other available HRG codes and associated costs have been explored the sensitivity analysis.

HRGs for chemotherapy acquisition and delivery (Resources 1 and 4)

HRGs and NHS reference costs are available for chemotherapy acquisition and delivery.

Hospitals use OPCS (Office of Population, Censuses and Surveys) clinical codes (NHS Connecting for Health, 2012) together with the DH Chemotherapy Regimens List (DH 2012) to code each cycle of chemotherapy administered. OPCS codes group different chemotherapy regimens together into bands. Each chemotherapy band is then assigned a procurement and delivery code.

The procurement code includes the cost of the drug plus transportation, storage and pharmacy preparation. Procurement codes have not been used in the basecase as they cover a broad range of drugs with a wide disparity of costs and as such are unable to differentiate between pemetrexed and other second-line treatments accurately enough. Instead, drug acquisition costs are calculated using a bottom up approach based on estimates of body surface area (BSA). For simplicity in the model, the cost of second-line chemotherapy is applied to the first cycle following progression, in the patients who receive second-line therapy. The effect of using chemotherapy procurement codes is, however, considered in the sensitivity analysis.

The delivery code takes account of drug administration costs in different settings, i.e. daycase, regular day/night or outpatient, and are banded according to the complexity of administration (NCAT, 2010).

The above methodology is consistent with previous appraisals (TA190, TA227).

Chemotherapy delivery codes

Chemotherapy delivery codes relevant to this appraisal are provided in Table 31. These are:

- Single agent pemetrexed is coded as SB12Z ;
- Second-line treatments, erlotinib is coded as SB11Z and docetaxel is coded as SB12Z.

Table 31 Chemotherapy delivery codes (DH 2012 DH, 2011)

Code	Description
SB11Z	Deliver exclusively oral chemotherapy
SB12Z	Deliver simple parenteral chemotherapy at first attendance

HRGs for monitoring required by maintenance treatment (Resource 2)

The additional monitoring requirement for pemetrexed maintenance versus placebo are:

1. Consultant visits
2. CT scans
3. Chest x-rays

Monitoring codes

Relevant codes for monitoring maintenance treatment are consultant-led follow up attendance and CT scans. HRG codes for CT scans vary depending on the number of areas to be scanned and the inclusion or exclusion of contrast. A clinical expert advised on the selection of relevant codes for CT scans for monitoring patients with NSCLC.

As stated above, X-rays are included within the other core HRGs such as consultant visits, so are not costed separately in the model.

Table 32 Consultant Led: Follow up Attendance Non-Admitted Face to Face (DH. 2011)

Code	Description
370	Medical Oncology

Table 33 Diagnostic Imaging: (DH. 2011)

Code	Description
RA12Z	Computerised Tomography Scan, two areas with contrast

HRGs for treating maintenance therapy-related AEs (Resource 3)

There are no HRGs for the treatment of AEs. As in previous appraisals, the costs of treating common treatment-related AEs were based on data from a survey of clinical experts (Duran et al 2008, Hanna 2004). The costs are inflated for 2011.

HRGs for BSC and terminal care (Resources 5 and 6)

There are no HRGs for BSC or terminal care. For consistency, these resources have been costed using the same approach as previous appraisals. The costs for BSC and terminal care were derived from Guidance on Cancer Services Improving Supportive and Palliative Care for Adults with Cancer; Economic Review (NICE, 2004). BSC costs are assumed to capture the cost of palliative radiotherapy for patients who are not receiving active chemotherapy. Terminal care costs are applied as a one-off cost in the final cycle prior to death.

Measurement and Valuation of Resources

Intervention and comparators' costs

7.5.5 Please summarise the cost of each treatment in the following table. Cross-reference to other sections of the submission; for example, drugs costs should be cross-referenced to sections 1.10 and 1.11. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in Section 7.2.2.

Costs of chemotherapy acquisition and delivery (Resources 1 and 4)

In the PARAMOUNT trial, the study protocol required the licensed dose of 500mg/m^2 BSA of pemetrexed to be administered every 21 days with dose reductions made in accordance with the SPC.

Mean BSA values from UK lung cancer patients (Sacco et al. 2010) weighted by gender from the PARAMOUNT trial were used to calculate pemetrexed and docetaxel doses. UK list prices (BNF, 2012) have been applied to the minimum number of vials calculated based on the mean BSA. The basecase model includes drug wastage for part-used vials. Delivery costs are based on the national average NHS reference costs. See Tables 34 to 37.

Chemotherapy without wastage, alternative BSA estimates and delivery costs for alternative settings are explored in sensitivity analysis.

Table 34 BSA values for UK lung cancer patients

Gender	Gender (%)from PARAMOUNT	UK BSA values (m^2) for lung cancer patients (Sacco et al. 2010)	
		Mean BSA	95% CI
Men	58	1.89	1.87 - 1.91
Women	42	1.65	1.64 - 1.67
Mean BSA weighted by gender from PARAMOUNT		1.79	

Table 35 Chemotherapy doses (per 21-day cycle) (SPCs for Alimta, docetaxel and erlotinib)

Drug	Vial or Pack Size	SPC Dose	Mean BSA	Mean Dose	No. of vials/tabs required
Pemetrexed	500mg	500mg/m^2	1.79m^2	895mg	1
	100mg				4
Docetaxel	80mg	75mg/m^2		134mg	1
	20mg				3
Erlotinib	30 tabs	150mg/day	N/A	N/A	21

Table 36 Chemotherapy acquisition costs (per 21-day cycle) (BNF, 2012)

Drug	Vial or Pack Size	List Price (£)	No. of vials/tabs required	Cost (£) (including wastage)	Total cost per cycle (£)
Pemetrexed	500mg	800.00	1	800.00	1440.00
	100mg	160.00	4	640.00	
Docetaxel	80mg	534.75	1	534.75	1023.00
	20mg	162.75	3	488.25	
Erlotinib	30 tabs	1394.96*	21	976.47	976.47

Note:* includes 14.5% PAS discount (TA 227).

Table 37 Chemotherapy delivery costs (Daycase setting) (DH, 2011)

Drug	Code & Description	National Average Unit Cost	Lower Quartile Unit Cost	Upper Quartile Unit Cost
Pemetrexed	SB12Z: Deliver simple parenteral chemotherapy at first attendance	£208	£131	£233
Docetaxel	SB12Z: Deliver simple parenteral chemotherapy at first attendance	£208	£131	£233
Erlotinib	SB11Z: Deliver exclusively oral chemotherapy	£128*	£70*	£151*

Note: * HRG codes for erlotinib are based on a 28-day cycle. Costs have been adjusted for a 21-day cycle.

The rates of second-line chemotherapy use in PARAMOUNT are provided in Table 38. The number of cycles of second-line chemotherapy implemented in the model is consistent with TA190, which were derived from TA162 for erlotinib in second-line NSCLC (see Table 39). Alternative cycle data are explored in sensitivity analysis.

Table 38 Second-line chemotherapy use in PARAMOUNT

	Placebo/BSC (n=180)	Pem/BSC (n=359)
Number and proportion of second-line chemotherapy use (%)	129 (72%)	231 (64%)

Number of cycles of second-line chemotherapy used in the economic model

Second-line chemotherapy	Docetaxel	Erlotinib
No. of cycles	4.82	6.27

Consistent with TA190 the distribution of second-line chemotherapy agents is based on the UK market share data for docetaxel and erlotinib to reflect UK clinical practice. UK market share data for second-line chemotherapy is reported in Table 39.

Table 39 UK market share data for second-line chemotherapy (DOF, (UK NSCLC S.O.M. **Q1 2012) 2012)**

Therapy	% of patients undertaking therapy	Pro-rata % for docetaxel and erlotinib only
Docetaxel	0.17	0.20
Erlotinib	0.70	0.80
Other	0.13	
Total	**1.00**	**1.00**

The cost of concomitant medications required to be administered with pemetrexed, i.e. vitamin B12, folic acid and dexamethasone, have been excluded from the economic model as the cost of these drugs is assumed to be included within the NHS reference cost for chemotherapy delivery. These costs are however presented in Table 40 to show that they are negligible. For completeness, these are included in the sensitivity analysis.

Table 40 Concomitant medications (excluded from the basecase economic model) (Alimta SPC; BNF, 2012)

Drug	Dose	No. of vials/ tabs per cycle	List Price (£)	Cost per cycle (£)
Vitamin B12 (cyanocobalamin) injection 1mg/ml	1mg every 3 cycles	0.33	£2.90 per ampoule	0.97
Folic Acid tabs 400 micrograms	400 micrograms daily	21	£2.43/90 tabs	0.57
Dexamethasone tabs 2mg	4mg twice daily for 3 days/cycle	12 x 2mg tabs	£13.09/100 (2mg tabs)	1.57
Total Cost				**3.10**

Costs of additional monitoring for maintenance treatment (Resource 2)

A British Thoracic Oncology Group (BTOG) survey of 106 UK oncologists conducted between December 2010 and January 2011 showed that patients with NSCLC typically see a consultant four to six weeks after completing first-line treatment (Beckett et al, 2012). At this visit, 14% patients routinely receive a CT scan. X-rays are more commonly used with 46% of patients receiving them.

Further follow-up visits routinely take place at six- to 12-week intervals. Only 3% of patients receive CT scans at every visit whilst 58% receive x-rays at every visit. CT scans are mainly used only when symptoms worsen (Beckett et al, 2012).

In PARAMOUNT the mean duration of treatment was 5 cycles of placebo and 7.9 cycles of pemetrexed, i.e. approximately 15 weeks for placebo and 24 weeks for pemetrexed. Table 43 represents routine monitoring of patients following first-line chemotherapy according to UK clinical practice, with the following assumptions:

- After the first follow up, between four to six weeks, further follow ups routinely occur every nine weeks, i.e., half way between six and 12 weeks. At this visit, 14% of patients will receive a CT-scan and 46% an x-ray.

- Over the 24-week mean duration of pemetrexed maintenance treatment patients will require one additional consultant visit and additional CT scans and x-rays for 3% and 58% of the cohort respectively. This additional monitoring will ensure that patients discontinue maintenance treatment promptly following disease progression.

We have not taken into account the additional CT scans that are conducted upon worsening symptoms as we have assumed that at some point every patient will progress and so these symptom-driven CT scans will occur once for each patient, thus cancelling each other out in the two arms. This approach is conservative as it does not take into account the fact that pemetrexed patients have delayed progression. Since the use of routine CT scans is low, this would only be expected to have a small impact on the final ICER.

Table 41 Routine monitoring in UK clinical practice (Beckett et al, 2102)

Cycles	3	6	9	12	15	18	21	24
Placebo	1 x CV 14% CT scan 46% x-ray			1 x CV 3% CT scan 58% x-ray				
Pemetrexed	1 x CV 14% CT scan 46% x-ray			1 x CV 3% CT scan 58% x-ray			1 x CV 3% CT scan 58% x-ray	

Note: CV: consultant visit

In the sensitivity analysis we test alternative monitoring frequencies, including the frequency of monitoring specified in the PARAMOUNT protocol, and different proportions of patients receiving CT scans.

The cost for a CT scan has been based on the weighted cost by activity of two NHS reference costs. As stated earlier in Sections 7.5.1 to 7.5.2, x-rays are bundled in with other core HRGs, e.g. with the consultant visit, and therefore do not have a separate cost associated with use.

Unit costs for additional monitoring are shown in Tables 42 and 43 and monitoring costs per cycle are shown in Table 44.

Table 42 Consultant Led: Follow up Attendance Non-Admitted Face to Face (DH, 2011)

Code and Description	National Average Unit Cost	Lower Quartile Unit Cost	Upper Quartile Unit Cost
370: Medical Oncology	**£120**	£81	£141

Table 43 Diagnostic Imaging: Outpatient (DH, 2011)

Code and Description	Activity (No. CT scans)	National Average Unit Cost	Lower Quartile Unit Cost	Upper Quartile Unit Cost	Cost weighted by activity rate
RA12Z: CT Scan, two areas with contrast	187,559	£132.99	£102.74	£153.27	£59.20
RA13Z: CT Scan, three areas with contrast	233,749	£150.88	£115.79	£176.77	£83.71
Total	**421,308**				**£142.92**

Table 44 Additional monitoring costs per cycle for patients on pemetrexed

Monitoring Description	Unit Cost (£)	Frequency of additional monitoring	Cost per cycle (£)
Consultant follow up visit	119.99	Every 24 weeks	15.00
CT Scan for 3% cohort	142.92	Every 24 weeks	0.54
Total costs			**15.54**

Adverse-event costs

7.5.7 Please summarise the costs for each adverse event listed in section 5.9 (Adverse events). These should include the costs of therapies identified in section 2.7. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 6.2.2.

Costs of treating maintenance therapy-related AEs (Resource 3)

The cost of treating grade 3/4 AEs have been calculated using the same approach as in TA190, which included those occurring at a rate of >2% plus nausea and vomiting combined. In TA190 the costs of treating these common grade 3/4 AEs were based on data from a survey of clinical experts (Duran et al 2008; Hanna 2004). The costs used in TA190 have been inflated for 2011. These costs have been weighted according to the AE rates for each arm of the PARAMOUNT trial. In the Markov model these are adapted to estimate an AE rate per person cycle and applied whilst patients are on maintenance treatment. It is assumed that

once patients have progressed, they will no longer incur treatment-related AEs due to maintenance treatment due to the acute nature of these AEs. See Tables 45 to 46.

Table 45 Unit costs for common grade 3/4 adverse events in PARAMOUNT (Costs inflated from those used in TA190)

Grade 3-4 adverse events	Reported Cost Year	Cost per event (2009)	Cost per event inflated to 2011
Neutropenia	2009	£323.19	£345.75
Nausea and vomiting	2009	£628.04	£671.88
Fatigue	2009	£132.33	£141.57
Anaemia	2009	£570.68	£610.52

Table 46 AE rates and total costs for PARAMOUNT (Adapted from TA190; AE data PARAMOUNT)

Grade 3/4 AEs	Number of patients experiencing grade 3/4 AE	AE rate %	Rate per 21-day cycle	Cost per patient cycle PARAMOUNT
Placebo/BSC (n=180)				
Neutropenia	0	0.00%	0.0000	£0.00
Nausea / Vomiting	0	0.00%	0.0000	£0.00
Fatigue	2	1.10%	0.0006	£0.19
Anaemia	1	0.60%	0.003	£0.10
Total cost for placebo/BSC				**£0.29**
Pem/BSC (n=359)				
Neutropenia	22	6.13%	0.0061	£2.10
Nausea / Vomiting	3	0.84%	0.0008	£0.29
Fatigue	19	5.29%	0.0053	£1.82
Anaemia	24	6.69%	0.0066	£2.30
Total cost for pem/BSC				**£6.51**

Miscellaneous costs

7.5.8 Please describe any additional costs that have not been covered anywhere else (for example, PSS costs). If none, please state.

Costs of BSC and terminal care (Resources 5 and 6)

The costs of BSC and terminal care have been calculated using the same approach as in TA190. In this previous appraisal, the costs of BSC and terminal care were derived from the Guidance on Cancer Services Improving Supportive and Palliative Care for Adults with Cancer; Economic Review (NICE, 2004). The costs used in TA190 have been inflated to 2011, see Table 47.

The BSC costs have been applied to patients in each cycle depending on whether or not they are receiving active chemotherapy in that cycle. For simplicity in the model, terminal care costs are applied in the final cycle prior to death.

Table 47 Unit costs for BSC and terminal care (Adapted from TA190)

Description	Cost year	Average cost (2008 prices)	Indexed 2011 prices
BSC cost per cycle (no active chemo)	2008	£66.36	£72.44
BSC cost per cycle (active chemo)	2008	£33.18	£36.22
Terminal care	2008	£2,588.25	£2,825.29

Health-state costs

7.5.6 Please summarise, if appropriate, the costs included in each health state. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model. The health states should refer to the states in section 6.2.4.

Table 48 summarises the costs that are included in each health state. The rationale for the choice of values and the data sources have been provided in Sections 7.5.4 and 7.5.5.

Table 48 List of health states and associated costs in the economic model

Health states	Costs applied	Value (per cycle) (See Section 7.5.5)
Pre-progression with pem/BSC	Pemetrexed acquisition	£1,440
	Pemetrexed delivery	£207.88
	Pemetrexed monitoring (consultant and CT scans)	£15.54
	BSC with active chemotherapy	£36.22
	Treatment of AEs	£6.51
Pre-progression with placebo/BSC	BSC without active chemotherapy	£72.44
	Treatment of AEs	£0.29
Post-progression with second-line chemotherapy **Note**: ** These costs are only applied in those cycles when second-line chemotherapy is administered.	Docetaxel acquisition**	£1,023.00
	Erlotinib acquisition**	£976.47
	Docetaxel delivery**	£207.44
	Erlotinib delivery**	£128.44
	BSC with active chemotherapy**	£36.22
	BSC without active chemotherapy, applied to remaining cycles after second-line chemotherapy has been discontinued	£72.44
	Terminal care, applied to the final cycle before death	£2,825.29
Post-progression with no second-line chemotherapy	BSC without active chemotherapy	£72.44
	Terminal care, applied to the final cycle before death	£2,825.29
Death	N/A	N/A

7.6 Sensitivity analysis

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.1.11, 5.8, and 5.9.4 to 5.9.12.

Sensitivity analysis should be used to explore uncertainty around the structural assumptions used in the analysis. Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

The uncertainty around the appropriate selection of data sources should be dealt with through sensitivity analysis. This will include uncertainty about the choice of sources for parameter values. Such sources of uncertainty should be explored through sensitivity analysis, preferably using probabilistic methods of analysis.

All inputs used in the analysis will be estimated with a degree of imprecision. Probabilistic sensitivity analysis (PSA) is preferred for translating the imprecision in all input variables into a measure of decision uncertainty in the cost effectiveness of the options being compared.

For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

7.6.1 Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated, including a description of the alternative scenarios in the analysis.

A range of sensitivity analyses has been conducted to explore structural uncertainty:

- Alternative time horizons;
- Alternative parametric distributions;
- Alternative 'cut points' used to transition from the observed KM OS data to the extrapolated curve at different stages of KM data maturity and including the use of fully parametric models;
- Alternative assumptions for post-trial treatment effect;
- Alternative discount rates.

Further details of the structural assumptions explored in the deterministic sensitivity analysis are provided in Table 49 (Section 7.6.2).

7.6.2 Which variables were subject to deterministic sensitivity analysis? How were they varied and what was the rationale for this? If any parameters or variables listed in section 6.3.6 (Summary of selected values) were omitted from sensitivity analysis, please provide the rationale.

A series of one-way sensitivity analyses has been conducted to identify which variables are key drivers of the costs and health benefits in the model and explore uncertainty around the ICER.

Parameters have been varied over available ranges from the relevant clinical and cost data sources where the model parameter has been obtained. Where no range was available the value used in the model has been varied within a range considered appropriate. In addition, data available from alternative sources has been implemented in the model, and explored within ranges if appropriate. Details of the parameters explored in deterministic sensitivity analysis are provided in Table 49.

Table 49 Sensitivity analysis of parameter values and structural assumptions

Parameter	Basecase value	Range or alternative value(s)	Rationale and alternative data source
Pemetrexed costs			
Pemetrexed wastage	£1,440	£1,432	Assumes vial sharing
Concomitant vitamins and corticosteroid	£0	£3.10/cycle	In the basecase analysis the cost of concomitant vitamins and corticosteroid required with pemetrexed treatment are assumed to be included within the NHS reference cost for chemotherapy delivery. This sensitivity analysis assumes that these costs need to be included as a separate additional cost in the pre-progression health state. See Table 40.
Pemetrexed drug cost	£1,440	Average: £1,293 Low: £928 High: £1,611	In the basecase the cost of pemetrexed (£1,440) is based on a bottom-up costing approach. Alternative data sources: Chemotherapy daycase procurement codes (DH, Chemotherapy Regimens List 2012-2013, 2012) and national average unit costs (NHS Reference Costs, 2010-2011). Procurement HRG code for pemetrexed: SB09Z Procure Chemotherapy drugs for regimens in Band 9.
Pemetrexed delivery costs	Daycase £208	Low: £131 High: £233	Upper & lower quartile daycase costs (NHS Reference Costs, 2010-2011).
Pemetrexed delivery costs	Daycase £208	Average: £231 Low: 114 High: £279	Alternative data sources: Outpatient delivery codes/costs (NHS Reference Costs, 2010-2011).
Pemetrexed delivery costs	Daycase £208	£96 (1.5 hours of community nurse time at £64/hour)	Alternative delivery setting: deliver a proportion of cycles in a community or home setting (PSSRU, 2011).

Monitoring costs	£15.54 per cycle	£31.07 to £131.45 per cycle	Assumptions – increased frequency of monitoring ranging between current UK clinical practice and the frequency of monitoring required by the PARAMOUNT trial protocol. An increased proportion of routine use of CT scans is also tested..
AE costs	£6.51 pem/BSC £0.29 placebo/BSC	+/- 10%	Assumption
BSA based on PARAMOUNT IPD	BSA = 1.79m^2	Each patient in cohort costed based on IPD: equivalent to mean 1.8m^2	Alternative data source: PARAMOUNT was a predominantly European-based study. Thus the IPD BSA data was also considered to be an appropriate data source for BSA for estimating drug costs for the economic model. The mean BSA value from PARAMOUNT (1.8m^2) is consistent with the results of the mean BSA in UK lung cancer patients (1.79m^2).
Second-line chemotherapy costs			
Second-line chemotherapy acquisition costs	Docetaxel: £1,023 Erlotinib: £976	Docetaxel £116.40* Erlotinib £116.40, i.e. equivalent to docetaxel	Alternative data source: Electronic Market Information Tool* (eMIT) (DH CMU, 2012). Docetaxel: 80mg/2ml vial £75.84 and 20mg/0.5ml vial £13.52, thus for 134.2mg dose: 1 x 80mg vial plus 3 x 20mg vials is £116.40. Erlotinib: erlotinib was approved in TA162 on the basis of equivalent price to docetaxel, thus this is also tested at £116.40. *There is a considerable difference in the list price for docetaxel and the price available in the eMIT database as listed September 2012. The lower eMIT price reflects the average price paid by the NHS over the preceding 4 months.
Second-line chemotherapy acquisition costs	Docetaxel: £1,023 Erlotinib: £976	Docetaxel: £832 Erlotinib: £2,165	In the basecase the cost of docetaxel (£1,023) and erlotinib (£976) were based on a bottom-up costing approach. Alternative data sources: Chemotherapy daycase procurement codes (DH, Chemotherapy Regimens List 2012-2013, 2012) and national average unit costs (NHS Reference Costs, 2010-2011). Procurement HRG code for docetaxel: SB06Z Procure Chemotherapy drugs for regimens in Band 6. Procurement HRG code for erlotinib: SB10Z Procure Chemotherapy drugs for regimens in Band 10.
Second-line cycle data	Docetaxel: 4.82 Erlotinib: 6.27	3.26 Docetaxel 5.25 Erlotinib	Alternative data source: PARAMOUNT trial data.
BSC and terminal care costs			
BSC costs	£36.22/cycle if on active chemo £72.44/cycle if not on active chemo	£0 - £72.44	BSC cost for patients on active chemotherapy assumes the exclusion of the use of palliative radiotherapy and BSC cost for patients *not* on active chemotherapy assumes the inclusion of the use of palliative radiotherapy. Alternative assumptions tested include BSC costs of £36.22 for all patients irrespective of whether or not they receive active chemotherapy, BSC costs of £72.44 for all patients and BSC costs excluded from analysis, i.e. BSC costs of £0, for all patients.

AE and BSC costs	**AE costs:** £6.51 pem/BSC £0.29 placebo/BSC **BSC costs:** £36.22/cycle if on active chemo £72.44/cycle if not on active chemo	BSC drug costs applied to every cycle plus hospitalisation, blood transfusion data and palliative radiotherapy rates and associated NHS reference costs applied.	In the basecase analysis the methods for costing AE and BSC resources are consistent with TA190, with costs inflated to 2011. The cost of BSC when not on active chemotherapy is assumed to include the cost of palliative radiotherapy. Instead of AE costs we have used hospitalisations and blood transfusion data from PARAMOUNT. Instead of BSC costs we have used BSC drug use and palliative radiotherapy data from PARAMOUNT. See Appendix 20 for full details.
Terminal care costs	£2,825	£0	Assumption: terminal care costs excluded from analysis.
Utilities			
Utility values	A non-significant treatment-based utility decrement was included in the basecase. See Table 28, Section 7.4.3.	The non-significant treatment-based utility decrement is removed.	The non-significant treatment-based utility decrement was applied in the basecase to provide a conservative approach. Utility decrement was applied during pre-progression to ensure the model captured any potential utility decrement associated with maintenance treatment.
Utility values	See Table 30, Section 7.4.3.	Values used in TA190:	Alternative data source. Literature-based utility values used in previous appraisals. TA190. Not progressed pem arm: 0.6568; Not progressed placebo arm: 0.6628; Progressed, receiving 2nd-line chemo both arms: 0.58; Progressed, receiving BSC all years (placebo arm) and BSC 2nd year onwards (pem arm): 0.53; Progressed, receiving BSC in 1st year (pem arm): 0.54; Terminal cycle (both arms): 0.47
Efficacy			
HR for OS and PFS	HR derived from K-M data	Upper and lower 95% CI	PARAMOUNT data
Treatment effect	Post trial: assumes treatment effect seen during the trial continues in the extrapolation period.	Treatment effect equivalent to placebo in the extrapolation period.	Alternative assumption.

Structural assumptions			
Discounting rate	3.5%	0% - 6%	Alternative values suggested in NICE methods guide (2008).
Time horizon	15.99 years (based on gamma extrapolation and modelling until 99.9% of patients have died)	6 years 10 years Modelling until 99% of patients have died	Alternative assumptions. 6 years is consistent with the time horizon used in TA190.
Parametric distributions	Gamma	Log-logistic; log-normal; Gompertz; exponential; Weibull.	Alternative distributions.
'Cut-points'	Cut at approx 20% remaining at risk for both arms.	Cut at approx15% and 25% at risk; or fully parametric.	Alternative values for cut points at different stages of maturity – values selected as being at 5% increments on either side of the basecase cut point of approx 20% remaining at risk.

7.6.3 Was PSA undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated if different from those in section 7.3.6, including the derivation and value of 'priors'. If any parameters or variables were omitted from sensitivity analysis, please provide the rationale for the omission(s).

PSA has been undertaken with 1,000 iterations. The model has been designed to quantify uncertainty probabilistically. Multivariable regression functions generated using PARAMOUNT IPD have been entered in the model along with a Cholesky decomposition to account for correlated parameters as described in Section 7.3.6. Monte Carlo simulation has been used to generate joint distributions of total costs and QALYs that result in the model from these and other probabilistic parameters.

AE rates were not included in the PSA. The cost of treating AE rates was varied within the deterministic sensitivity analysis by changing the costs by +/- 10%. This had minimal impact on the ICER, changing the final ICER by +/- £20 per QALY. Therefore the exclusion of AE rates from the PSA is not considered to affect the probabilistic results.

NHS reference costs have not been included in the PSA. The upper and lower quartile costs have been explored in the deterministic sensitivity analysis.

7.7 Results

Provide details of the results of the analysis. In particular, results should include, but are not limited to, the following.

- Link between clinical- and cost-effectiveness results.
- Costs, QALYs and incremental cost per QALY.
- Disaggregated results such as LYG, costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment.
- A statement as to whether the results are based on a PSA.
- Cost-effectiveness acceptability curves, including a representation of the cost-effectiveness acceptability frontier.
- Scatter plots on cost-effectiveness quadrants.
- A tabulation of the mean results (costs, QALYs, ICERs), the probability that the treatment is cost effective at thresholds of £20,000–£30,000 per QALY gained and the error probability.

Clinical outcomes from the model

7.7.1 **For the outcomes highlighted in the decision problem (see Section 5), please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.**

Table 50 Summary of model results compared with clinical data

Outcome	Clinical trial results (CI)			Model results		
	Pem	Placebo	Inc*	Pem	Placebo	Inc*
Median OS	13.86 months (12.75 – 16.03)	11.01 months (9.95 –12.52)	2.85 months	14.04 months	10.95 months	3.09 months
Mean OS				20.46 months	16.24 months	4.21 Months
Median PFS	4.44 months (4.11 – 5.65)	2.76 months (2.60 – 3.02)	1.28 months	4.59 months	2.92 months	1.67 months
Mean PFS				7.68 months	4.42 months	3.25 months
QALYs				1.1743	0.9188	0.2554

Note: Numbers may not compute due to rounding; *Inc – incremental difference

The clinical section reports the median OS and median PFS results as the main the outcomes from PARAMOUNT. Since the economic model provides mean OS and mean PFS data over a lifetime horizon, the median OS and PFS results from the economic model have been calculated from the predicted survival time in the model.

These median results from the model are presented in Table 52. These are generally consistent with those from the clinical trial results (e.g. Median OS: 13.86 for placebo vs 14.04 for pemetrexed). The small differences between the clinical trial and the calculated median OS and PFS results are due to the use of a Markov model which categorises the KM survival data into 3-weekly cycles as opposed to using the exact survival times from the observed data. A linear relationship has been assumed within the 21-day cycle within which the median PFS and OS time points have been captured.

7.7.2 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

A table presenting the proportion of the cohort in each health state over time is provided in Appendix 21.

7.7.3 Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

Utility values are applied to patients in the model in each health state as reported in Section 7.4.3 using utility values adjusted for treatment, progression and proximity to death. A table presenting the discounted quality-adjusted survival time in each health state together with total LYs and QALYs for placebo and pemetrexed is provided in Appendix 22. Incremental QALYs can be calculated from the total QALYs , i.e. 1.17-0.92=0.25.

7.7.4 Please indicate the life years and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results.

Life years (LYs), QALYs and total costs are provided in Table 51. Results are provided for OS and disaggregated for the pre- and post-progression outcomes.

Table 51 Model outputs by clinical outcomes

Outcome		LYs	QALYs	Total Cost (£)
	Pemetrexed	**1.7047**	**1.1743**	**£21,682**
Overall survival	**Placebo**	**1.3537**	**0.9188**	**£9,099**
	Incremental	**0.3511**	**0.2554**	**£12,582**
	Pemetrexed	0.64	0.46	£13,584
Pre-progression	Placebo	0.37	0.27	£466
	Incremental	0.27	0.19	£13,118
	Pemetrexed	1.06	0.71	£8,098
Post-progression	Placebo	0.99	0.65	£8,633
	Incremental	0.07	0.06	-£535

Note: Numbers may not compute due to rounding; LY, life years; QALY, quality-adjusted life year

7.7.5 Please provide details of the disaggregated incremental QALYs and costs by health state, and of resource use predicted by the model by category of cost. Suggested formats are presented below.

Table 52 Summary of QALY gain by health state

Health state	QALY pemetrexed	QALY placebo	Increment	% absolute increment
Pre-progression	0.46	0.27	0.19	76%
Post-progression	0.71	0.65	0.06	24%
Total	**1.17**	**0.92**	**0.25**	**100%**

Note: Numbers may not compute due to rounding; QALY, quality-adjusted life year. Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

Table 53 Summary of costs by health state

Health state	Cost pemetrexed	Cost placebo	Increment	% absolute increment
Pre-progression	£13,584	£466	£13,118	104%
Post-progression	£8,098	£8,633	-£535	-4 %
Total	**£21,682**	**£9,099**	**£12,582**	**100%**

Note: Numbers may not compute due to rounding. Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

The categories used for costs reported in Table 55, are presented in Table 54.

Table 54 Cost categories

Cost category	Costs included	Health state(s) costs applied in
Therapy cost	Pemetrexed drug acquisition Pemetrexed delivery costs Pemetrexed monitoring costs	Pre-progression
Adverse event cost	Treatment of AE costs	Pre-progression
Follow up care costs	Second-line chemotherapy acquisition and delivery costs	Post-progression
	BSC costs	Pre- and post progression
Terminal care costs	Terminal care costs	Post-progression (applied in the final cycle before death)
Total	Therapy Adverse event cost Follow up care costs Terminal care costs	As above

Table 55 Summary of predicted resource use by category of cost

Item	Cost pemetrexed	Cost placebo	Increment	% absolute increment
Therapy cost	£13,125	£0	£13,125	104.3%
Adverse event cost	£56	£2	£54	0.4%
Follow up care costs	£5,802	£6,360	-£558	-4.4%
Terminal care costs	£2,699	£2,738	-£39	-0.3%
Total	**£21,682**	**£9,099**	**£12,582**	**100%**

Note: Numbers may not compute due to rounding

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

Base-case analysis

7.7.6 Please present your results in the following table. List interventions and comparator(s) from least to most expensive and present ICERs in comparison with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance.

The results of the deterministic basecase analysis are shown in Table 56. The deterministic results show that the mean overall survival gain is 0.35 LYG, i.e., 4.2 months, with a QALY gain of 0.26 for pem/BSC compared to standard care, i.e. placebo/BSC. The estimated ICER for pemetrexed/BSC compared to standard of care is £49,258 per QALY gained. The ICER is driven by the comparator being 'watch and wait' with low associated costs compared to active intervention with pemetrexed continuation maintenance treatment.

Table 56 Deterministic basecase results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Incremental cost/LYG	ICER (£) incremental (QALYs)
Placebo/BSC	£9,099	1.3537	0.9188					
Pem/BSC	£21,682	1.7047	1.1743	£12,582	0.3511	0.2554	£35,837	**£49,258**

Note: Numbers may not compute due to rounding; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

7.7.7 Please present results of deterministic sensitivity analysis. Consider the use of tornado diagrams.

Results of the deterministic sensitivity analysis are presented in Table 57. Deterministic and probabilistic results for the use of alternative parametric distributions are shown in Table 58.

Table 57 Deterministic sensitivity analysis

Parameter	Value or assumption in base case	Incr. cost (£)	Incr. benefit (QALY)	ICER (£)
	Base case	**12,582**	**0.2554**	**49,258**
Pemetrexed costs				
Wastage excluded (assumes vial sharing)	Wastage included	12,515	0.2554	48,995
Concomitant vitamins and corticosteroid included	Excluded	12,607	0.2554	49,354
DH HRG daycase procurement costs for pemetrexed – average £1,293	£1,440	11,422	0.2554	44,717
DH HRG daycase procurement costs for pemetrexed – lower quartile £928	£1,440	8,542	0.2554	33,442
DH HRG daycase procurement costs for pemetrexed – Upper quartile £1,611	£1,440	13,932	0.2554	54,540
Pemetrexed delivery cost – Lower quartile £131	Daycase £208	11,976	0.2554	46,883
Pemetrexed delivery cost – Upper quartile £233	Daycase £208	12,781	0.2554	50,034
Pemetrexed delivery cost – Outpatient average £231	Daycase £208	12,765	0.2554	49,972
Pemetrexed delivery cost – Outpatient lower quartile £114	Daycase £208	11,842	0.2554	46,358
Pemetrexed delivery cost – Outpatient upper quartile £279	Daycase £208	13,143	0.2554	51,455
Deliver 20% of pemetrexed in community or home setting at £96/cycle	Daycase £208	12,411	0.2554	48,586
Deliver 50% of pemetrexed in community or home setting at £96/cycle	Daycase £208	12,153	0.2554	47,579
Increase AE costs by 10%: £7.16 pem/BSC; £0.32 placebo/BSC	£6.51 pem/BSC £0.29 placebo/BSC	12,588	0.2554	49,279
Decrease AE costs by 10%: £5.86 pem/BSC; £0.26 placebo/BSC	£6.51 pem/BSC £0.29 placebo/BSC	12,577	0.2554	49,237
BSA based on PARAMOUNT IPD (Each patient in cohort costed based on IPD: equivalent to mean 1.8m^2) (**including** wastage)	Mean BSA 1.79m^2 Wastage included	13,096	0.2554	51,268

BSA based on PARAMOUNT IPD (Each patient in cohort costed based on IPD: equivalent to mean 1.8m^2) (**excluding** wastage)	Mean BSA 1.79m^2 Wastage included	12,545	0.2554	49,112
Additional monitoring for patients on pemetrexed:				
Every 12 weeks: 1 extra consultant visit for all patients and 1 extra CT scan for 3% of cohort	Over 24-week period: 1 extra consultant visit for all patients & 1 extra CT scan for 3% of cohort	12,705	0.2554	49,738
Every 12 weeks: 1 extra consultant visit for all patients and 1 extra CT scan for 20% of cohort		12,753	0.2554	49,926
Every 12 weeks: 1 extra consultant visit for all patients and 1 extra CT scan for 50% of cohort		12,837	0.2554	50,257
Every 12 weeks: 1 extra consultant visit for all patients and 1 extra CT scan for 100% of cohort		12,978	0.2554	50,809
Every 6 weeks: 1 extra consultant visit for all patients and 1 extra CT scan for 3% of cohort on pemetrexed		12,950	0.2554	50,698
Every 6 weeks: 1 extra consultant visit for all patients and 1 extra CT scan for 20% of cohort on pemetrexed		13,046	0.2554	51,073
Every 6 weeks: 1 extra consultant visit for all patients and 1 extra CT scan for 50% of cohort on pemetrexed		13,215	0.2554	51,735
Every 6 weeks: 1 extra consultant visit for all patients and 1 extra CT scan for 100% of cohort on pemetrexed		13,497	0.2554	52,839
Second-line chemotherapy costs				
Docetaxel average price from DH CMU eMIT database (accessed 15.09.2012) £116.40	£1,023	12,662	0.2554	49,572
Erlotinib & docetaxel equivalent to average docetaxel eMIT price £116.40	Erlotinib £976.47 Docetaxel £1,023	13,058	0.2554	51,121
DH HRG daycase procurement costs for erlotinib and docetaxel – average Erl: £2,165; Doc £832	Erlotinib £976.47 Docetaxel £1,023	12,052	0.2554	47,183
Cycle data from PARAMOUNT:	4.82 Docetaxel	12,696	0.2554	49,705

3.26 Docetaxel 5.25 Erlotinib	6.27 Erlotinib			
BSC and terminal care costs				
No differential BSC costs applied according to active vs no active treatment £36.22/cycle	£36.22/cycle if on active chemo £72.44/cycle if not on active chemo	12,744	0.2554	49,893
No differential BSC costs applied according to active vs no active treatment £72.44/cycle	£36.22/cycle if on active chemo £72.44/cycle if not on active chemo	12,966	0.2554	50,759
No BSC applied (terminal cost applied)	£36.22/cycle if on active chemo £72.44/cycle if not on active chemo	12,523	0.2554	49,027
No terminal or BSC costs applied	£36.22/cycle if on active chemo £72.44/cycle if not on active chemo £2,825 terminal care costs	12,562	0.2554	49,179
PARAMOUNT resource use data				
BSC drug costs, hospitalisation, blood transfusion and palliative radiotherapy rates and associated NHS reference costs. Second-line chemotherapy cycles based on PARAMOUNT data	**AE costs:** £6.51 pem/BSC £0.29 placebo/BSC **BSC costs:** £36.22/cycle if on active chemo	13,024	0.2554	50,987

	£72.44/cycle if not on active chemo **Second-line chemo cycles:** Doc:4.82 ; Erl: 6.27			
Utilities				
Assume no treatment effect associated with pemetrexed treatment during maintenance treatment (i.e. pre-progression); utilities equivalent to BSC pre-progression	Apply non-significant disutility (-0.0248)	12,582	0.2674	47,054
Utility values from TA190 (Scenario 5 JMEN values)	PARAMOUNT EQ-5D data	12,582	0.2183	57,633
Efficacy				
Post-trial treatment effect: pem/BSC is equivalent to placebo/BSC, i.e., treatment benefit for trial period only.	Treatment effect assumed to continue beyond trial duration	12,511	0.2120	59,009
OS Hazard Ratio 95% lower CI	Mean OS HR	12,518	0.2160	57,947
OS Hazard Ratio 95% upper CI	Mean OS HR	12,659	0.3018	41,940
PFS Hazard Ratio 95% lower CI	Mean PFS HR	12,583	0.2554	49,269
PFS Hazard Ratio 95% upper CI	Mean PFS HR	12,582	0.2555	49,246
Structural				
Discounting costs at 0%	3.5%	12,780	0.2554	50,032
Discounting health effects at 0%	3.5%	12,582	0.2793	45,044
Discounting costs and effects at 0%	3.5%	12,780	0.2793	45,752
Discounting costs at 6%	3.5%	12,456	0.2554	48,762
Discounting health effects at 6%	3.5%	12,582	0.2410	52,206
Discounting costs and effects at 6%	3.5%	12,456	0.2410	51,680
Time horizon - 6 years (i.e. stop Markov trace at 105 cycles)	15.99 years	12,497	0.2304	54,240

Time horizon - 10 years (i.e. stop Markov trace at 174 cycles)	15.99 years	12,566	0.2502	50,226
Time horizon – 8.97 years (i.e. stop Markov trace at 156 cycles) i.e. lifetime horizon based on when 99% of patients have died	15.99 years (99.9% patients died)	12,557	0.2476	50,724
Cut-points for extrapolation				
OS: Approx 15% at risk by arm: i.e. 34 cycles placebo/BSC (16%) & 38 cycles pem/BSC (15.9%)	20% at risk	12,574	0.2505	50,186
OS: Approx 25% at risk by arm: i.e. 29 cycles placebo/BSC (25.6%) & 33 cycles pem/BSC (26.7%)	20% at risk	12,564	0.2443	51,434
OS: using all available observed OS data i.e. 49 cycles placebo/BSC & 50 cycles pem/BSC	20% at risk	12,548	0.2363	53,091
Fully parametric OS with observed PFS & treatment discontinuation	20% OS at risk	12,509	0.2079	60,157
Fully parametric OS, PFS and treatment discontinuation	20% OS at risk; all observed PFS & treatment discontinuation	7,713	0.2076	37,157

Table 58 Sensitivity analysis: Alternative parametric distributions

Alternative parametric distribution	Parameter value or assumption in basecase	Deterministic				Probabilistic			
		Inc. cost (£)	Inc. mean OS (months)	Inc. benefit (QALY)	ICER (£)	Inc. cost (£)	Inc. mean OS (months)	Inc. benefit (QALY)	ICER (£)
	Base case	**12,582**	**4.2**	**0.2554**	**49,258**	**13,111**	**4.2**	**0.2558**	**51,249**
Exponential	Gamma	12,601	4.3	0.2583	48,784	13,138	4.3	0.2590	50,736
Weibull	Gamma	12,544	3.7	0.2236	56,093	13,121	3.7	0.2222	59,060
Gompertz	Gamma	12,512	3.4	0.2092	59,797	13,095	3.4	0.2091	62,613
Log-normal	Gamma	12,620	4.5	0.2738	46,094	13,205	4.5	0.2713	48,665
Log-logistic	Gamma	12,623	4.7	0.2842	44,415	13,188	4.6	0.2809	46,947

Overall, the majority of the results from the sensitivity analyses range from £48,000 to £51,000. This shows the model is robust and provides a high level of consistency across a wide range of alternative plausible one-way analyses.

Looking at the maximum and minimum values from the sensitivity analysis the results show that the deterministic ICERs range from £33,442 to £62,613. The £33,442 ICER is based upon the use of the lower quartile NHS reference cost for daycase procurement of pemetrexed. As discussed in Section 7.5, the procurement costs were not considered to be appropriate for costing pemetrexed in the basecase analysis due to the wide variation in chemotherapy regimens covered by the relevant NHS code and the resultant insensitivity of the associated cost of an individual drug.

If this implausible result is excluded, the remaining ICERs range from £37,157 to £62,613. The latter is the result of adopting a Gompertz parametric distribution which was considered to have a poor fit based on both internal and external validity. The lower value results from a fully parametric model for OS, PFS and treatment discontinuation.

The key drivers of the model are:

- Efficacy of pemetrexed: including both the implementation of the upper and lower confidence intervals for the OS hazard rate and changing the assumption of the post trial treatment effect.

- Use of alternative parametric distributions;

- Use of utility values from external literature as used in TA190.

The utility values used in TA190 were derived from studies in NSCLC patients being treated with second-line chemotherapy which is likely to have lower face validity than using utility data directly derived from patients with the condition being assessed.

Other variables in the sensitivity analyses have a lower impact on the ICER. For example,

- Increasing the frequency of monitoring and proportion of patients receiving CT scans from current levels of UK clinical practice within anticipated clinical practice scenarios does not impact the ICER greatly. Only when monitoring is modelled to occur every 6 weeks with all patients receiving a CT scan does the ICER increase to £52,839.

- The use of alternative chemotherapy delivery costs for pemetrexed in an outpatient or community/home setting do not impact the ICER significantly, however, delivery in a community or home setting may be preferred by some patients and free up capacity in chemotherapy units.

7.7.8 Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves.

PSA was conducted using 1,000 iterations. Cholesky decompositions have been used in the model to account for correlations between parameters. Monte Carlo simulation has been used to generate joint distributions of total costs and QALYs that result in the model from these and other probabilistic parameters (see Section 7.6.3).

The probabilistic basecase results are presented in Table 59. Since PSA results will change each time they are run, they may not be exactly replicable. The incremental cost-effectiveness plane and cost-effective acceptability curve (CEAC) are presented in Figures 16 to 17.

Table 59 Probabilistic basecase results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Incremental cost/LYG	ICER (£) incremental (QALYs)
Placebo/BSC	9,116	1.3610	0.9253					
Pem/BSC	£22,227	1.7135	1.1811	£13,111	0.3525	0.2558	£37,189	**£51,249**

Note: Numbers may not compute due to rounding

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Figure 16 Incremental cost-effectiveness plane for basecase analysis

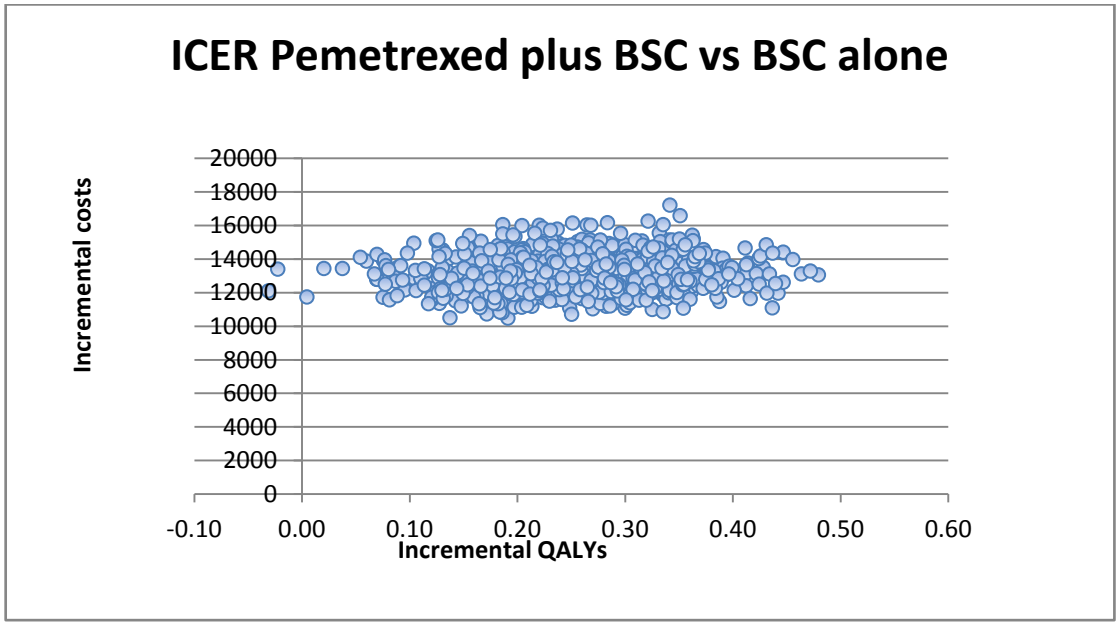
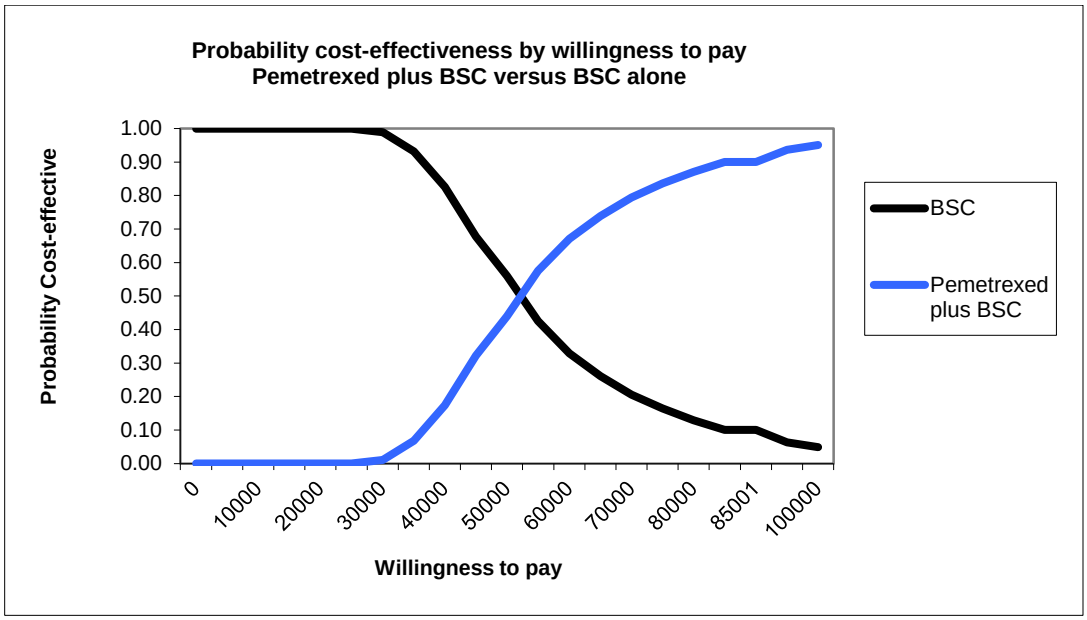


Figure 17 Cost-effectiveness acceptability curve



7.7.9 Please present the results of scenario analysis. Include details of structural sensitivity analysis.

See section 7.7.7.

7.7.10 What were the main findings of each of the sensitivity analysis?

The economic evaluation of pemetrexed continuation maintenance compared to placebo in patients with advanced NS NSCLC gives a deterministic ICER of £49,258 and a probabilistic ICER of £51,249 (see Tables 56 and 59). A wide range of one-way sensitivity analyses have been conducted which demonstrates consistent results across a range of alternative plausible data inputs. See Section 7.7.7. The results from both the deterministic and the probabilistic analyses are in the similar range showing consistency.

The CEAC shows that at a £50,000 WTP threshold pemetrexed/BSC is cost-effective in 44% of simulations. At a WTP threshold of £55,000 pemetrexed/BSC is cost-effective in 56% of simulations.

7.7.11 What are the key drivers of the cost-effectiveness results?

The key drivers of the cost-effective results are:

- Efficacy of pemetrexed: including both the implementation of the confidence interval for the OS hazard rate and changing the assumption of treatment effect post trial
- Use of alternative parametric distributions.
- Use of utility values from TA190.

7.8 Validation

7.8.1 Please describe the methods used to validate and quality assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical, quality of life and resources sections.

A draft Markov model was developed initially using data from interim analyses of PRAMOUNT. This enabled a number of errors to be identified and eliminated early on in the process and also allowed the interim results to be sense-checked. After the final data lock (March 2012) the IPD was reanalysed and the model populated with the final IPD and other data from STATA analyses such as the EQ-5D regression model. The final model was subject to a thorough validation process as detailed below.

Validation by model developers

Validation and quality assurance was conducted at several points during the modelling process to identify potential errors or bias in the model, i.e. coding and formula errors, lack of internal validity, lack of external validity and any omissions or biases from an individual analyst were addressed. The following validation tasks were conducted:

- The STATA code derived for each regression model was checked by an independent analyst not involved in the original analysis.
- The STATA code was reviewed by an independent biostatistician to verify that the most appropriate models had been developed for each clinical endpoint.
- Testing whether the model results accurately reflected PARAMOUNT observed data by comparing the predicted outcomes from the model (progression, mortality and HRQL) with observed estimates
- Undertaking a range of structural sensitivity analyses to test whether the model results were unduly affected by the model structure.
- Undertaking a range of parameter sensitivity analyses to test the robustness of results to plausible changes in values.
- Analysis of model results to ensure that the direction and magnitude of effect reflected expectations in view of the inputs used.
- Examination of each Excel worksheet for potential referencing, input and calculation errors.
- The original Markov trace was rebuilt by an independent analyst.

Independent validation

Further validation was undertaken by an independent analyst using a model validation checklist (see Appendix 23). The checklist provides a structured validation method and also includes verification of model outputs. The checklist first verifies whether the entire model is a plausible representation of the real world; then focuses on validating the model structure, timeframe, cycle length, survival distributions, input parameters and outcome measures. The model verification section of the checklist focuses on input values and references, and identification of any errors either in input values, formulae or data outputs.

Table 60 below presents a summary of the main validation issues identified during validation of the final model, and steps taken to address these issues.

Table 60 Issues identified during the model validation process

Validation issues identified	Solution
In Excel 2007 the GAMMADIST function returned #NUM for some values in the probabilistic sensitivity analysis. This caused a run time error in the PSA macro.	Kappa parameter set to a deterministic value to prevent runtime error.
Erlotinib costs not being picked up correctly.	Formulae fixed.
Cell naming errors including redundant cell names.	Cell names amended or deleted as applicable.

7.9 Subgroup analysis

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. This should be explored as part of the reference-case analysis by providing separate estimates of clinical and cost effectiveness for each relevant subgroup of patients.

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.10.

Types of subgroups that are not considered relevant are those based solely on the following factors.

- Individual utilities for health states and patient preference.
- Subgroups based solely on differential treatment costs for individuals according to their social characteristics.
- Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, when the costs of facilities available for providing the technology vary according to location).

7.9.1 Please specify whether analysis of subgroups was undertaken and how these subgroups were identified. Were they identified on the basis of an a priori expectation of differential clinical or cost effectiveness because of known, biologically plausible, mechanisms, social characteristics or other clearly justified factors? Cross-reference the response to section 5.3.7.

No subgroup analysis was undertaken as per the final decision problem for this appraisal. In addition, analyses of overall survival in patients with pemetrexed in pre-specified groups of age, smoking status, response to induction treatment, PS and histology showed that the relative treatment effect of pemetrexed was internally consistent across subgroups. Therefore, no subgroup analyses were undertaken.

7.9.2 Please clearly define the characteristics of patients in the subgroup.

N/A

7.9.3 Please describe how the statistical analysis was undertaken.

N/A

7.9.4 What were the results of the subgroup analysis/analyses, if conducted? Please present results in a similar table as in section 6.7.6 (Base-case analysis).

N/A

7.9.5 Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Please refer to the subgroups identified in the decision problem in section 4.

N/A

7.10 Interpretation of economic evidence

Pemetrexed continuation maintenance offers patients who currently have no treatment options immediately following first-line treatment with pemetrexed/cisplatin, but who are appropriate candidates for active chemotherapy, a cost-effective treatment under conventional thresholds when the end of life criteria is applied Section 6.10 (End of life criteria).

7.10.1 Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

The results from this economic evaluation are not expected to align with other economic evaluations in the published literature since this is the first cost-effectiveness analysis of continuation maintenance in NSCLC.

7.10.2 Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem in section 4?

The economic evaluation is relevant to all patients who would be eligible for pemetrexed continuation maintenance treatment, following first-line treatment with pemetrexed/cisplatin who have advanced IIIB/IV non-squamous NSCLC and PS 0-1 which is the population in line with the licensed indication and the decision problem.

7.10.3 What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

Strengths

One of the key strengths of this economic evaluation is the use of utility values obtained directly from patients during maintenance treatment in the PARAMOUNT study. The EQ-5D data collected during the PARAMOUNT trial were analysed using a regression model to provide a range of utility values for each health state over the entire time horizon. Due to a lack of available EQ-5D data from other recent NSCLC clinical trials, other appraisals have relied on utility values from the literature elicited from members of the public in the second-line NSCLC setting. As a result the utility values used in this economic evaluation are considered to be particularly robust for the decision problem.

The model uses final OS data together with other clinical data from the final data lock. This ensures that the most mature data sets have been utilised to model the clinical benefits and resources of pemetrexed continuation maintenance treatment and allow more robust extrapolation of the survival data. In addition, an extensive curve-fitting exercise has been undertaken to identify the most appropriate parametric distribution to extrapolate survival over the lifetime time horizon.

The methods used to model resource use have been implemented as consistently as possible with those used in other recent appraisals in NSCLC (TA190, TA227). As such many of the assumptions used in this model have been validated and accepted in previous appraisals. This approach provides a transparent analysis where the model inputs are readily identifiable within the model and are familiar to the ERG and the Appraisal Committee.

A wide range of sensitivity analyses have been presented, which generally provide consistent results for plausible alternative input data.

Weaknesses

For simplicity in the model, the costs of a course of second-line chemotherapy are applied as a one-off cost in the first cycle following disease progression and terminal care costs are applied in the final cycle prior to death rather than allocating these costs pro-rata over the cycles when these resources would be expected to occur. However, since these resources are given over a relatively short period of time the effect of this pragmatic approach is likely to be minimal.

The model does not capture resource use due to monitoring of patients who receive 'watch and wait' following first-line treatment. The model therefore captures only the incremental resource use and costs associated with pemetrexed maintenance treatment. As all patients are likely to have additional monitoring including a consultant visit and a CT scan when disease progression is suspected, the delay in the occurrence of this event in patients receiving pemetrexed maintenance due to the PFS benefit is not captured. Thus, any cost benefit due to discounting of these future costs is not realised. This potential weakness in the model is expected to have minimal impact on the incremental costs and biases in favour of the comparator 'watch and wait'.

7.10.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

No additional analyses were identified.

Section C – Implementation

8 Assessment of factors relevant to the NHS and other parties

The purpose of this section is to provide an analysis of any factors relevant to the NHS and other parties that may fall outside the remit of the assessments of clinical effectiveness and cost effectiveness. This will allow the subsequent evaluation of the budget impact analysis. Such factors might include issues relating to service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers.

Pemetrexed continuation maintenance in the treatment pathway

The current treatment pathway for patients with PS 0-1 and stage IIIB/IV NS NSCLC is to receive first-line chemotherapy, most typically with pem/cis, followed by a period of 'watch and wait'. The current standard of care in the NHS for maintenance treatment of NSCLC is therefore 'watch and wait' plus BSC as necessary.

The introduction of pemetrexed as a continuation maintenance treatment may replace this 'watch and wait' period and represents a new treatment paradigm which is likely to have downstream consequences in terms of what is offered in subsequent lines of treatment.

As pemetrexed is already used in the NHS as first-line standard of care or switch maintenance the services needed are in place and no additional resources, i.e. pathology, training and education, are required.

8.1 How many patients are eligible for treatment in England and Wales? Present results for the full marketing authorisation/CE marking and for any subgroups considered. Also present results for the subsequent 5 years.

It is estimated that **535** patients are eligible for treatment with pemetrexed continuation maintenance in England and Wales each year.

Eligible population

This eligible population is based on the marketing authorisation and the UK treatment pathway as per CG121, excluding those patients eligible for switch maintenance, i.e. excluding patients who **have not** received pem/cis as first-line chemotherapy, as per the final NICE scope. Pemetrexed is recommended for switch maintenance treatment in TA190.

Estimated patient numbers

However, only a small proportion of eligible patients are likely to receive pemetrexed continuation maintenance treatment. It is estimated that **37** patients will receive pemetrexed continuation maintenance in 2013 increasing to **206** patients per year from 2016 onwards.

The steps taken to estimate the number of patients eligible to receive pemetrexed continuation maintenance treatment in England and Wales are described below:

In order to estimate the number of eligible patients for this appraisal we first need to estimate the number of patients with stage IIIB and IV NS NSCLC who receive pemetrexed/cisplatin as first-line chemotherapy. NICE clinical guidelines for lung cancer state that chemotherapy should be offered to patients with stage III/IV NSCLC when they have good performance status, i.e. PS 0 – 1 (NICE CG121, 2011). Thus, we need to know what proportion of patients with PS 0-1 and stage IIIB/IV NSCLC have NS disease since pemetrexed is licensed only in patients with NS NSCLC.

- There were **32,347** new cases of lung cancer in England and Wales included in the 2011 National Lung Cancer Audit (NLCA) report. These new cases of lung cancer include NSCLC, mesothelioma, carcinoid and small cell lung cancer (The NHS IC, (NLCA Report) 2011).

- Of these 32,347 new cases, there were 5,932 patients with PS 0-1 and stage IIIB/IV NSCLC (The NHS IC, (NLCA Report) 2011).

- NS disease accounts for 68% of NSCLC (CG121, 2011).

    - Thus, **4,034** patients (68% of 5,932) with PS 0-1 and stage IIIB/IV NSCLC are estimated to have NS histology.

- Of the 5,932 patients with PS 0-1 and stage IIIB/IV, 52.8% of these patients received chemotherapy (The NHS IC, (NLCA Report) 2011).

    - Thus, **2,130** patients (52.8% of 4,034) with PS 0-1 and stage IIIB/IV NS NSCLC received chemotherapy.

- A survey of 70 UK oncologists conducted during Q2 2012 demonstrated that 43% of UK patients with stage IIIB/IV NS NSCLC received pem/cis as first-line chemotherapy (DOF, (UK NSCLC SoM Q2 2012) 2012).

    - Thus, **916** patients (43% of 2,130) with stage IIIB/IV NS NSCLC are estimated to receive pem/cis as first-line chemotherapy.

- In PARAMOUNT, patients were eligible for the maintenance phase of the trial if they had a PS of 0-1, had completed four cycles of first-line chemotherapy with pem/cis and had documented radiographical evidence of complete response (CR), partial response (PR) or stable disease (SD). Based on these criteria, of the 939 patients who received pem/cis first-line chemotherapy, 539 patients were randomised to maintenance treatment. A further nine patients were eligible for maintenance, but did not participate due to patient (n=8) or physician (n=1) decision. Thus, 548 patients (58.4%, calculated as (539+9)/939) were eligible for continuation maintenance treatment (Paz-Ares et al. 2012).

    - Thus, **535** patients (58.4% of 916) are estimated to be eligible for treatment with pemetrexed continuation maintenance in England and Wales each year.

The steps taken to estimate the number of patients eligible for pemetrexed continuation maintenance treatment in England and Wales are summarised in Table 61:

Table 61 Patients eligible for continuation maintenance with pemetrexed in England and Wales

Description	% patients	Number	References
Patients with Lung cancer	-	32,347 (reported)	The NHS IC, (NLCA Report) 2011
Patients with confirmed NSCLC	-	19,163 (reported)	The NHS IC, (NLCA Report) 2011
Patients with PS 0-1 and stage IIIB/IV NSCLC	-	5,932 (reported)	The NHS IC, (NLCA Report) 2011
Patients with NS NSCLC	68% (reported)	4,034 (calculated)	NICE CG121, 2011
Patients with PS 0-1 and stage IIIB/IV receiving chemotherapy	52.8% (reported)	2,130 (calculated)	The NHS IC, (NLCA Report) 2011
Patients receiving pem/cis first-line chemotherapy	43% (reported)	916 (calculated)	DOF, 2012
Patients eligible for pemetrexed continuation maintenance	58.4% (calculated)	535 (calculated)	Paz-Ares et al. 2012

We recognise that uptake will increase gradually as clinicians continue to familiarise themselves with maintenance treatment and identify eligible patients who are keen to choose active treatment following first-line chemotherapy.

The following market share assumptions, take account of both gradual continuation maintenance uptake and market share and are applied to the 916 patients estimated to receive pem/cis as first-line chemotherapy in England and Wales each year to provide estimates of patient numbers expected to receive pemetrexed continuation maintenance over the 5-year period following introduction into the NHS. These are shown in Table 62 below.

Table 62 Market share assumptions for pemetrexed in continuation maintenance

Year end	2013	2014	2015	2016	2017
Patients receiving pem/cis as first-line chemotherapy	916	916	916	916	916
Market share of continuation maintenance for patients receiving pem/cis as first-line chemotherapy	4%	10%	20%	22.5%	22.5%
Estimated number of patients expected to receive pemetrexed continuation maintenance	**37**	**92**	**183**	**206**	**206**

This is equivalent to a market share of approximately 7% of patients eligible for pemetrexed continuation maintenance in 2013, 17% in 2014, 34% in 2015 and 38.5% in 2016 and 2017.

8.2 What assumption(s) were made about current treatment options and uptake of technologies?

As the incidence of lung cancer appears relatively stable over the period 2001 to 2009 (Cancer Research UK, (incidence data) 2012) it has been assumed that the incidence of new lung cancers will continue to be stable from 2013 – 2017. It has also been assumed that the proportion of patients with PS 0-1 and stage IIIB/IV, the percentage of patients receiving first-line therapy, the proportion of patients with NS disease and that the proportion of patients eligible for maintenance treatment remains constant over the next five years.

Maintenance treatment of NSCLC is not yet well-established in clinical practice in England and Wales. A survey of 70 UK oncologists conducted during Q2 2012 demonstrated that only 6% of patients with NS NSCLC who had received first-line chemotherapy received maintenance treatment. (DOF, (UK NSCLC SoM Q2 2012) 2012)

8.3 What assumption(s) were made about market share (when relevant)?

Pemetrexed had 66% market share of maintenance treatment in stage IIIB/IV NS NSCLC during Q2 2012 and of these 32% of patients received pemetrexed continuation maintenance treatment (DOF, (UK NSCLC SoM Q2 2012) 2012). Thus, 3.96% (66% of 6%) of patients receiving first-line chemotherapy are currently receiving pemetrexed maintenance treatment, of which 1.27% (32% of 3.96%) of patients are receiving pemetrexed continuation maintenance treatment , which is very small and means that less than 210 patients a year are estimated to receive pemetrexed continuation maintenance treatment at its peak. These figures have informed the following assumptions regarding predictions of market share over the next five years. These assumptions take account of increasing uptake of maintenance treatment in NS NSCLC as well as pemetrexed market share of continuation maintenance based on NICE making a positive recommendation for pemetrexed continuation maintenance treatment.

The market share assumptions (see Tables 62 and 63) are based on market share of patients with NS NSCLC receiving pemetrexed/cisplatin as first-line treatment. They are based on predicted year-end market share starting with 4% by the end of 2013, increasing each year until 2016 when the market share is predicted to flatten at 22.5% in future years. For the purposes of simplicity the market shares have been applied to the entire year. As such, the budget impact estimates are an overestimate of anticipated actual use in years 2013 to 2016.

Table 63 Market share assumptions for pemetrexed in continuation maintenance

Year end	2013	2014	2015	2016	2017
Market share of patients receiving pem/cis as first-line chemotherapy	4%	10%	20%	22.5%	22.5%

8.4 In addition to technology costs, please consider other significant costs associated with treatment that may be of interest to commissioners (for example, procedure codes and programme budget planning).

The budget impact analysis below accounts for the main costs observed for the treatment pathways considered.

8.5 What unit costs were assumed? How were these calculated? If unit costs used in health economic modelling were not based on national reference costs or the PbR tariff, which HRGs reflected activity?

All unit costs included in the budget impact analysis are consistent with those included in the economic model. Full details and calculations can be found in Section 7.5.

Assumptions and costs for maintenance treatment

Pemetrexed drug costs were calculated on a per-vial basis including wastage, using average BSA values for UK male and female lung cancer patients (Sacco et al. 2010) weighted by gender from the PARAMOUNT trial population and an average of 7.9 cycles of pemetrexed. See Tables 64 and 65.

Drug administration costs using NHS reference costs from 2010-2011 for daycase delivery of chemotherapy are included for each cycle of pemetrexed in the maintenance phase. The relevant HRG code for pemetrexed is SB12Z: Deliver simple parenteral chemotherapy at first attendance, which is £207.88 for daycase delivery (DH, 2011).

Additional monitoring costs using NHS reference costs for CT scans and consultant visits are included for each cycle of pemetrexed in the maintenance phase. Incremental costs for monitoring of pemetrexed maintenance treatment are £15.54 per cycle, (see Table 44, Section 7.5.6).

Although very few grade 3/4 AEs occurred in either arm of the trial, pemetrexed was associated with a higher rate of AEs than the BSC arm. Incremental costs for treating AEs for patients receiving pemetrexed are £6.22 per cycle, (see Table 46, Section 7.5.7).

BSC and terminal care costs have not been included in the budget impact analysis, although they have been included in the economic model for assessment of cost-effectiveness. It is difficult to establish the true budget impact of BSC and terminal care due to the multi-agency nature of BSC and terminal care and the variation in practice by clinicians.

A summary of pemetrexed costs included in the budget impact analysis is provided in Table 66.

Table 64 Summary of assumptions for BSA and mean number of cycles of pemetrexed maintenance treatment (Sacco et al, 2010; PARAMOUNT)

Maintenance treatment	BSA at maintenance	No. of cycles
Pemetrexed	Mean BSA for male and female UK lung cancer patients weighted by gender from the PARAMOUNT population equivalent to a mean of 1.79m2	7.9
BSC		5.0

Table 65 Pemetrexed treatment costs per cycle (MIMS, March 2012)

Chemotherapy	Unit cost/vial (excl VAT)	Dose	Dose based on mean BSA ($1.79m^2$)	No. of vials required	Cost/cycle (excl VAT)
Pemetrexed (100mg vial)	£160	500 mg/m2	895mg	4	£1,440.00
Pemetrexed (500mg vial)	£800			1	

Table 66 Summary of pemetrexed costs included in the budget impact analysis

Costs	Pemetrexed
Chemotherapy	£1,440.00

Administration	£207.88
Adverse event costs	£6.22
Monitoring	£15.54
BSC and terminal care	Excluded
Total cost/cycle	£1,669.64
Mean no. of cycles	7.9
Total cost/patient	**£13,190**

Assumptions and costs for second-line treatments

The introduction of pemetrexed continuation maintenance treatment is likely to affect clinical practice with respect to second-line therapy. From the PARAMOUNT trial it was observed that fewer patients received second-line treatment if they had received active maintenance chemotherapy; 64% of pemetrexed patients received second-line treatment versus 72% of patients who had not received pemetrexed. Given the costs associated with second-line treatment it is important to consider these differences when estimating budget impact. It is assumed that the proportion of patients receiving second-line treatment in the UK is consistent with that observed in the PARAMOUNT trial.

Patients are assumed to receive either erlotinib or docetaxel. Market data shows that erlotinib and docetaxel are favoured as second-line therapy, accounting for 70% and 17% respectively. The remaining 13% is split between seven other chemotherapy agents (DOF, (UK NSCLC SoM Q2 2012) 2012). For simplicity, we have weighted this 13% between erlotinib and docetaxel to give market shares of 80% and 20% respectively for second-line treatment in the economic model and for the purposes of the budget impact analysis.

Costs for second-line treatment are calculated on a per-vial or per-tablet basis including wastage, and also use average BSA values for UK male and female lung cancer patients (Sacco et al. 2010) weighted by gender from the PARAMOUNT trial population per 21-day cycle of treatment as per pemetrexed maintenance treatment. Patients who received active second-line line treatment are assumed to receive an average of 4.82 cycles of docetaxel or 6.27 cycles of erlotinib therapy (TA162). See Tables 67 and 69.

Drug administration costs using NHS reference costs from 2010-2011 for daycase delivery of chemotherapy are included for each cycle of erlotinib and docetaxel. The relevant HRG code for docetaxel is SB12Z: Deliver simple parenteral chemotherapy at first attendance, which is £207.88 for daycase delivery (DH, 2011).The relevant HRG for erlotinib is SB11Z: Deliver exclusively oral chemotherapy, which is £171.25 for daycase delivery. The NHS chemotherapy regimen list (DH 2012) allocates these codes based on 21-day cycle for docetaxel and a 28-day cycle for erlotinib. Given the cycle length used in the economic model is 21 days the administration cost for erlotinib is therefore adjusted to £128.44 per 21-day cycle.

AE and monitoring costs relating to second-line therapies have not been included in the model consistent with the previous pemetrexed switch maintenance appraisal (TA190). It is likely that the introduction of pemetrexed would have an effect on the proportion of patients receiving lines of therapy subsequent to second-line, however, as the effect is unknown it has not been considered.

A summary of second-line treatment costs included in the budget impact analysis is provided in Table 69.

Table 67 Summary of assumptions for the proportion and mean number of cycles of second-line chemotherapy (DOF, (UK NSCLC SoM Q2 2012) 2012; TA162; Sacco et al, 2010)

Maintenance treatment	**Proportion of patients receiving second-line treatment** (PARAMOUNT)	**Proportion of second-line treatments received** (DOF)	**No. of cycles** (TA162)
Pemetrexed	64%	Erlotinib: 80% Docetaxel: 20%	4.82
Placebo/BSC i.e. watch and wait	72%	Erlotinib: 80% Docetaxel: 20%	6.27

Table 68 Docetaxel and erlotinib treatment costs per cycle (MIMS, March 2012)

Chemotherapy	**Unit cost/ vial or pack** (excl VAT)	**Dose**	**Dose based on mean BSA** ($1.79m^2$)	**No. of vials/tablets required per cycle**	**Cost/cycle** (excl VAT)
Docetaxel (20mg vial)	£162.75	75 mg/m2	134.25mg	3	£1,023.00
Docetaxel (80mg vial)	£534.75			1	
Erlotinib 150mg (30 tabs)	£1,394.96*	150mg	150mg	21	£976.47

*14.5% discount applied as per Patient Access Scheme (TA227)

Table 69 Summary of second-line treatment costs included in the budget impact analysis

Costs	**Docetaxel**	**Erlotinib**
Chemotherapy	£1,023.00	£976.47
Administration	£207.88	£128.44
Adverse event costs	Excluded	Excluded
Monitoring	Excluded	Excluded
Total cost/cycle	£1,230.88	£1,104.91
Mean no. of cycles	4.82	6.27
Total cost per patient receiving second-line treatment	£5,933	£6,928

We have assumed that 80% of patients receiving second-line treatment will receive erlotinib and 20% docetaxel, thus, the weighted cost of second-line chemotherapy is £6,729 per patient receiving second-line treatment. The weighted cost of second-line treatment by maintenance treatment is shown in table x.

Table 70 Weighted cost of second-line treatment by maintenance treatment

Maintenance treatment	**Proportion of patients**	**Weighted cost of second-**

	receiving second-line treatment (PARAMOUNT)	line treatment by maintenance treatment
Pemetrexed	64%	£4,307*
Placebo/BSC i.e. watch and wait	72%	£4,845**

Note: *64% x £6,729 = £4,307; **72% x £6,729 = £4,845

The cycle length and total number of mean cycles implies that maintenance therapy and second-line therapy will be completed within one year. Therefore, the budget impact analysis has assumed all costs occur within the relevant financial year. Table 71 shows the total per-patient costs according to the two different treatment pathways.

Table 71 Total costs associated with treatment

Total per patient cost with pemetrexed continuation maintenance treatment		Total per patient cost with watch and wait in the maintenance phase	
Pemetrexed	£13,190	Watch and wait	£0
64% of patients receive second-line, split 80% erlotinib/20% docetaxel	£4,307	72% of patients receive second-line, split 80% erlotinib/20% docetaxel	£4,845
Total	**£17,497**	**Total**	**£4,845**

8.6 Were there any estimates of resource savings? If so, what were they?

Fewer patients who receive pemetrexed as maintenance therapy go on to receive active second-line treatment than patients who receive BSC at the maintenance stage: 64% versus 72%. This difference represents potential resource savings which have been accounted for above.

8.7 What is the estimated annual budget impact for the NHS in England and Wales?

We have assumed a relatively modest market share in the first year as the new treatment paradigm becomes established. The estimated annual budget impact in the first 5 years following recommendation for use in the NHS in England and Wales ranges from £468,124 in 2013 to £2,606,312 in 2017. The estimated budget impact is shown in Table 72.

Table 72 Annual budget impact for pemetrexed in England and Wales in the first five years post-launch/NICE recommendation

	2013	2014	2015	2016	2017
No. of patients eligible for pemetrexed continuation maintenance	535	535	535	535	535
Cost without pemetrexed maintenance therapy	£2,592,075	£2,592,075	£2,592,075	£2,592,075	£2,592,075
Market share of eligible patients	7%	17%	34%	38.5%	38.5%
No. pemetrexed patients	37	92	183	206	206
Cost with pemetrexed	£3,060,199	£3,756,059	£4,907,391	£5,198,387	£5,198,387
Net Budget Impact	**£468,124**	**£1,163,984**	**£2,315,316**	**£2,606,312**	**£2,606,312**

Note: Small discrepancies in values are due to rounding, calculations were performed in Excel.

8.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

Extending the life of a patient with a terminal disease is unlikely to result in cost savings because of the extra duration of BSC required, even if less intensive BSC is required due to improved symptom control during active chemotherapy resulting in lower use of radiotherapy during active treatment.

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Related procedures for evidence submission

Cost-effectiveness models

NICE accepts executable economic models using standard software – that is, Excel, TreeAge Pro, R or WinBUGs. If you plan to submit a model in a non-standard package, NICE should be informed in advance. NICE, in association with the ERG, will investigate whether the requested software is acceptable, and establish if you need to provide NICE and the ERG with temporary licences for the non-standard software for the duration of the appraisal. NICE reserves the right to reject economic models in non-standard software. A fully executable electronic copy of the model must be submitted to NICE with full access to the programming code. Care should be taken to ensure that the submitted versions of the model program and the written content of the evidence submission match.

NICE will need to distribute an executable version of the model to consultees and commentators because it will be used by the Appraisal Committee to assist their decision-making. On distribution of the appraisal consultation document (ACD) or final appraisal determination (FAD), and the evaluation report produced after the first committee meeting, NICE will advise consultees and commentators by letter that the manufacturer or sponsor has developed a model as part of their evidence submission for this technology appraisal. The letter asks consultees to inform NICE if they wish to receive an electronic copy of the model. If a request is received, NICE will release the model as long as it does not contain information that was designated confidential by the model owner, or the confidential material can be redacted by the model owner without producing severe limitations on the functionality of the model. The letter to consultees indicates clearly that NICE will distribute an executable copy, that the model is protected by intellectual property rights, and can be used only for the purposes of commenting on the model's reliability and informing a response to the ACD or FAD.

Manufacturers and sponsors must ensure that all relevant material pertinent to the decision problem has been disclosed to NICE at the time of submission. There will be no subsequent opportunity to submit information unless it has been specifically requested by NICE.

When making a submission, manufacturers and sponsors should check that:

- an electronic copy of the submission has been given to NICE with all confidential information highlighted and underlined
- an executable electronic copy of the economic model has been submitted
- the checklist of confidential information (provided by NICE along with invitation to submit) has been completed and submitted.

Disclosure of information

To ensure that the appraisal process is as transparent as possible, NICE considers it highly desirable that evidence pivotal to the Appraisal Committee's decisions should be publicly available. NICE recognises that because the appraisal is being undertaken close to the time of regulatory decisions, the status of information may change during the STA process. However, at the point of issuing the FAD or ACD to consultees and commentators, all the evidence seen by the Committee should be available to all consultees and commentators.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence'). Further instructions on the specification of confidential information, and its acceptability, can be found in the agreement between the Association of the British Pharmaceutical Industry (ABPI) and NICE (www.nice.org.uk).

When data are 'commercial in confidence' or 'academic in confidence', it is the manufacturer's or sponsor's responsibility to highlight such data clearly, and to provide reasons why they are confidential and the timescale within which they will remain confidential. The checklist of confidential information should be completed: if it is not provided, NICE will assume that there is no confidential information in the submission. It is the responsibility of the manufacturer or sponsor to ensure that the confidential information checklist is kept up to date.

The manufacturer or sponsor must ensure that any confidential information in their evidence submission is clearly underlined and highlighted. NICE is assured that information marked 'academic in confidence' can be presented and discussed during the public part of the Appraisal Committee meeting. NICE is confident that such public presentation does not affect the subsequent publication of the information, which is the prerequisite allowing for the marking of information as 'academic in confidence'.

Please therefore underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and information submitted under 'academic in confidence' in yellow.

The manufacturer or sponsor will be asked to supply a second version of the submission with any information that is to remain confidential removed. The confidential information should be 'blacked out' from this version, taking care to retain the original formatting as far as possible so that it is clear which data have been removed and where from. For further details on how the document should be redacted/stripped, see the checklist of confidential information.

The last opportunity to review the confidential status of information in an STA, before publication by NICE as part of the consultation on the ACD, is 2 weeks before the Appraisal

Committee meeting; particularly in terms of ‘academic in confidence’ information. The ‘stripped’ version will be issued to consultees and commentators along with the ACD or FAD, and made available on NICE’s website 5 days later.

It is the responsibility of the manufacturer or sponsor to ensure that the ‘stripped’ version of the submission does not contain any confidential information. NICE will ask manufacturers and sponsors to reconsider restrictions on the release of data if there appears to be no obvious reason for the restrictions, or if such restrictions would make it difficult or impossible for NICE to show the evidential basis for its guidance. Information that has been put into the public domain, anywhere in the world, cannot be marked as confidential.

Confidential information submitted will be made available for review by the ERG and the Appraisal Committee. Confidential information may be distributed to all consultees with the permission of the manufacturer or sponsor. NICE will at all times seek to protect the confidentiality of the information submitted, but nothing will restrict the disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

The Freedom of Information Act 2000, which came into force on 1 January 2005, enables any person to obtain information from public authorities such as NICE. The Act obliges NICE to respond to requests about the recorded information it holds, and it gives people a right of access to that information. This obligation extends to submissions made to NICE. Information that is designated as ‘commercial in confidence’ may be exempt under the Act. On receipt of a request for information, NICE will make every effort to contact the designated company representative to confirm the status of any information previously deemed ‘commercial in confidence’ before making any decision on disclosure.

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Dear [redacted],

Re: Single Technology Appraisal – Pemetrexed for maintenance treatment following induction therapy with pemetrexed and cisplatin for non-squamous non-small-cell lung cancer

The Evidence Review Group (Liverpool Reviews and Implementation Group) and the technical team at NICE have now had an opportunity to take a look at the submission received on the 15th October by Lilly. The ERG and the NICE technical team would like further clarification relating to the clinical and cost effectiveness data.

Both the ERG and the technical team at NICE will be addressing these issues in their reports.

We request you to provide a written response to this letter to the Institute by **17:00 on the 21st November**. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

Please do not 'embed' documents (i.e. PDFs, spreadsheets) within your response as this may result in your information being displaced or unreadable. Any supporting documents should be emailed to us separately as attachments, or sent on a CD.

If you have any further queries on the technical issues raised in this letter then please contact Mark Minchin – Technical Lead (mark.minchin@nice.org.uk). Any procedural questions should be addressed to Rebecca Pye – Project Manager (rebecca.pye@nice.org.uk) in the first instance.

We will be sending a separate letter shortly regarding the data marked as confidential in the submission and the version of the economic model to be offered during consultation.

Yours sincerely

Helen Knight
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

Section A: Clarification on effectiveness data

Study conduct

A1. Section 6.3.3, page 52 of the submission states that:

patients were eligible for the study if they had……completed four cycles of induction therapy with pem/cis with documented radiographic evidence of a PR/CR/SD. The 'best observed induction response' was used, i.e., if the patient had a CR/PR or SD during cycles 2 or 3 but had a subsequent 'unknown' response at cycle 4, the patient was considered to have had SD and was eligible for randomisation.

Please clarify how many patients in the induction phase of the PARAMOUNT trial had an unknown response at cycle 4 and were randomised into each trial arm.

Patient outcomes: adverse events

A2. Please provide details (using the table below) for each hospitalisation in each arm of the trial during the maintenance period. Please indicate which of these hospitalisations is treatment related.

Pemetrexed + BSC				**Placebo + BSC**			
Reason for hospitalisation	Treatment related? Y/N	Duration of hospital stay	Treatment given in hospital	Reason for hospitalisation	Treatment related? Y/N	Duration of hospital stay	Treatment given in hospital

Randomisation and statistical analyses

A3. Please provide the statistical analysis plan for the PARAMOUNT trial.

A4. Appendix 10 includes information regarding protocol amendments relevant to the PARAMOUNT trial. Please provide further details in relation to the rationale for changing the sample size.

A5. In the published paper that describes the PARAMOUNT trial (Paz-Ares et al 2012) it is stated that 'randomisation was done with the Pocock and Simon minimisation method'; however there is no reference to minimisation in either the evidence submission or the clinical study report.

a) Please confirm if minimisation was used.

b) If minimisation was used, please provide appropriate details on the process.

Section B: Clarification on cost-effectiveness data

B1. **Priority Question**: Please provide a version of the cost-effectiveness model including the logic required to generate the results for the 'Lifetime adjusted analysis' (option 4 of the 'Base case analysis' parameter, and option 2 of the 'risk equation' parameter) shown in the range 'ResultsSubgroup2' in the 'Pop' worksheet.

a) Please provide details of the methodology used in the adjusted analysis.

b) Please provide the associated results for the adjusted analysis including sensitivity analyses.

c) Please explain why this lifetime adjusted analysis was not considered to be appropriate for consideration in this appraisal.

B2. Please provide full Kaplan-Meier analysis results (see example appended below) showing K-M survival estimates at each event time, for each treatment arm in the PARAMOUNT trial:

a) OS, and PFS using final data cut, and censoring patients using date of data cut, not date of last contact/assessment, as the time of censoring.

b) Post-progression survival (PPS) stratified by time of progression (in two categories: less then or greater than 3 months after randomization) using final data cut, and censoring patients using date of data cut, not date of last contact, as the time of censoring.

B3. Please justify the decision to use a unit cost of £55 for a blood transfusion within the analysis.

B4. Please provide an analysis of the number of progression events in each treatment arm into fatal and non-fatal events, shown separately for each 21-day cycle from randomization.

B5. Please provide a table for each treatment arm showing at the beginning of each 21 day cycle:

a) The number of patients alive and uncensored.
b) The number of patients still considered 'on treatment'.
c) The number of patients who received the allocated treatment for that cycle.

B6. EQ-5D data and analysis

a) Please provide an analysis of the number (and percentage) of patients in each maintenance arm of PARAMOUNT who returned an EQ-5D form showing numbers at each trial point (baseline, each treatment cycle and post-discontinuation)

b) Please provide the same analysis for:
- patients returning forms without any missing responses.
- patients returning forms with any of the 5 three-option ratings missing.
- patients returning forms with the visual analogue scale rating missing.
- patients returning forms with both the visual analogue scale rating and at least one of the three-option ratings missing.

c) How many patients in each arm returned completed forms without any missing items for every visit? Please provide mean (standard error) EQ-5D scores and visual analogue ratings for these patients for baseline, each treatment cycle and post-discontinuation

d) If any method was used to impute missing values prior to analysis and modelling please describe the method used, and the values imputed.

e) Please confirm that no further EQ-5D data was collected after the 30-day post-discontinuation visit.

Section C: Textual clarifications and additional points

Calculation of patients eligible for treatment

C1. Section 2.2, page 28 please provide a justification for limiting the predicted eligible patients to those NSCLC patients that have received a histological diagnosis (n=19,163).

Example of output (SAS) required from analyses specified in question B2

Product-Limit Survival Estimates						
SURVIVAL		**Survival**	**Failure**	**Survival Standard Error**	**Number Failed**	**Number Left**
0.000		1.0000	0	0	0	62
1.000		.	.	.	1	61
1.000		0.9677	0.0323	0.0224	2	60
3.000		0.9516	0.0484	0.0273	3	59
7.000		0.9355	0.0645	0.0312	4	58
8.000		.	.	.	5	57
8.000		.	.	.	6	56
8.000		0.8871	0.1129	0.0402	7	55
10.000		0.8710	0.1290	0.0426	8	54
SKIP…		0.8548	0.1452	0.0447	9	53
389.000		0.1010	0.8990	0.0417	52	5
411.000		0.0808	0.9192	0.0379	53	4
467.000		0.0606	0.9394	0.0334	54	3
587.000		0.0404	0.9596	0.0277	55	2
991.000		0.0202	0.9798	0.0199	56	1
999.000		0	1.0000	0	57	0

Section A: Clarification on effectiveness data

A1. Section 6.3.3, page 52 of the submission states that:

patients were eligible for the study if they had…completed four cycles of induction therapy with pem/cis with documented radiographic evidence of a PR/CR/SD. The 'best observed induction response' was used, i.e., if the patient had a CR/PR or SD during cycles 2 or 3 but had a subsequent 'unknown' response at cycle 4, the patient was considered to have had SD and was eligible for randomisation.

Please clarify how many patients in the induction phase of the PARAMOUNT trial had an unknown response at cycle 4 and were randomised into each trial arm.

As stated in Table 10, page 54 of the submission, a total of 17/539 (3.2%) patients in PARAMOUNT had an 'unknown' best response to induction therapy. Of these 9/359 (2.5%) were randomised to the pemetrexed plus BSC arm and 8/180 (4.4%) were randomised to the placebo plus BSC arm. Though these patients were considered protocol violations, the analysis pre-specified in the statistical analysis plan was an intent-to-treat (ITT) analysis and thus all patients were included.

A2. Please provide details (using the table below) for each hospitalisation in each arm of the trial during the maintenance period. Please indicate which of these hospitalisations is treatment related.

Pemetrexed + BSC				**Placebo + BSC**			
Reason for hospitalisation	Treatment related? Y/N	Duration of hospital stay	Treatment given in hospital	Reason for hospitalisation	Treatment related? Y/N	Duration of hospital stay	Treatment given in hospital

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Detailed hospitalisation data have been provided as a separate document (file name ncqa2) attached to this email. Please note that the 'Treatment given in hospital' has been indicated as 'Data not collected', since this data was not recorded on the hospitalisation module of the Case Record Form.

All data provided on hospitalisation is commercial-in-confidence (CIC).

A3. Please provide the statistical analysis plan for the PARAMOUNT trial.

The Statistical Analysis Plan (SAP) for PARAMOUNT has been provided as a separate attachment. The SAP was revised in response to a request from the US FDA for additional preliminary analysis of OS in November 2010. The final version of the SAP was approved on the 31st January 2011, prior to the data lock of the preliminary analysis of overall survival (OS) on the 6th June 2011. Details of these additional preliminary analyses of OS are presented in Section 8 of the SAP document provided.

A4. Appendix 10 includes information regarding protocol amendments relevant to the PARAMOUNT trial. Please provide further details in relation to the rationale for changing the sample size.

The PARAMOUNT study was initially planned as a regional study to support the first registration study for pemetrexed in maintenance treatment, JMEN (Ciuleanu et al 2010), for which the primary end point of Progression free survival (PFS) was considered appropriate. Subsequently, after it became apparent that the licensed indication for pemetrexed maintenance treatment would be restricted to patients who had received non-pemetrexed containing regimens (since pemetrexed was not given first-line in JMEN), it was decided that data from PARAMOUNT would be submitted to the regulatory authorities to support the use of pemetrexed following induction treatment with pemetrexed/cisplatin. Since the study was to be used for registration purposes, Lilly amended the protocol twice, first to include overall survival (OS) as an endpoint and second to increase the power for OS. Both of these amendments included an increase in the trial sample size. Both amendments occurred prior to data lock (30 July 2010) and analysis of the results from the study.

The original trial sample size (570 patients treated in induction, 399 patients randomised to maintenance treatment) was selected based on a power calculation for the analysis of PFS, assuming a HR of 0.70 and 25% censoring.

Amendment A: The protocol was amended on 06 October 2008 to include a power calculation for the analysis of OS. The new sample size determined that 600 patients treated in induction were needed to provide 372 patients randomised to maintenance treatment. The calculation assumed a PFS HR of 0.65 and 36% censoring for PFS, and an OS HR of 0.70 and 30% censoring for OS. The trial would be fully powered for PFS (90%) and OS (80%).

Amendment B: The protocol was amended on 30 July 2009 to increase the power of the OS analysis by increasing the number of patients entering the induction and maintenance treatment periods. The new sample size determined that 900 patients treated in induction were needed to provide 558 patients randomised to maintenance treatment. The calculation assumed a PFS HR of 0.65, and an OS HR of 0.70.

The increase in survival events to at least 390 events increased the power of the analysis from 80% to 93%; for PFS, 90% power was maintained, provided that at least 238 events were included in the analysis. The final a priori SAP (version 2) was finalised and approved (30 June 2010) prior to data lock and unblinding of the aggregate database for the final PFS analysis.

A summary of the amendments is presented in the Table below, these were also included in Appendix 10 of the Lilly submission.

Table 1 Amendments to the PARAMOUNT protocol

	N for Enrolled	N for Randomized	PFS Events/HR/Power	OS Events/HR/Power
Original (28 May 2008)	570	399	294/0.70/85%	-------
Amendment A (06 October 2008)	600	372	238/0.65/90%	260/0.70/80%
Amendment B (30 July 2009**)**	900	558	238/0.65/90%	390/0.70/93%

A5. In the published paper that describes the PARAMOUNT trial (Paz-Ares et al 2012) it is stated that 'randomisation was done with the Pocock and Simon minimisation method';

however there is no reference to minimisation in either the evidence submission or the clinical study report.

a) Please confirm if minimisation was used.

The Pocock and Simon minimisation method was not used. Randomisation was controlled by a computerised voice response unit at a central location. Randomisation was stratified for the following 3 prognostic factors after completion of the first 4 cycles of induction chemotherapy with pemetrexed and cisplatin:

- ECOG PS just prior to randomisation (0 versus 1)
- Tumor response to induction chemotherapy (CR/PR versus SD)
- Disease stage prior to administration of induction therapy (IIIB versus IV)

b) If minimisation was used, please provide appropriate details on the process.

See response to a) above.

Section B: Clarification on cost-effectiveness data

B1. Priority Question: Please provide a version of the cost-effectiveness model including the logic required to generate the results for the 'Lifetime adjusted analysis' (option 4 of the 'Base case analysis' parameter, and option 2 of the 'risk equation' parameter) shown in the range 'ResultsSubgroup2' in the 'Pop' worksheet.

a) Please provide details of the methodology used in the adjusted analysis.

The deterministic lifetime-adjusted analysis employs parametric survival models to predict PFS and OS in both the within-trial period and post-trial period. These parametric models adjust for patient baseline characteristics and are consequently capable of predicting costs and outcomes for different patient subgroups.

In this analysis individual patient characteristics from the PARAMOUNT trial population are used to estimate overall costs and QALYs for pemetrexed plus BSC versus BSC alone. Individual patient profiles (characteristics) have been applied into the PARAMOUNT adjusted risk equations in the model sequentially, one profile at a time, to estimate total costs, life years and QALYs. The estimates of costs and QALYs from each iteration are then averaged to calculate incremental cost per life year and QALYs.

In subgroup analyses the ICER is estimated using cost and outcome data from patient profiles containing the subgroup defining characteristic of interest. Thus, the model is designed to reflect heterogeneity in PARAMOUNT patients' risk factors. This approach was chosen in preference to applying average variable values into the risk equations (e.g. 0.78 to represent the proportion of patients who were past smokers) since this approach can result in some loss in accuracy due to the inherent non-linearity of cost-effectiveness models.

However, the technique of using sequential individual patient profiles is far more time consuming because 539 patient profiles must be entered into the risk equations for each Monte Carlo simulation. Consequently the deterministic sensitivity analyses and PSA have used the average variable values in the risk equations to provide a range of results based on alternative plausible inputs.

The key characteristics of this modelling approach are summarised in Table 2. These characteristics are the same as those used in the basecase model in the original submission. However, in addition to adjusting for treatment allocation, the adjusted model also adjusts for patients' baseline characteristics. In this scenario a parametric approach is used to estimate OS, PFS and treatment discontinuation over the entire time horizon. In the adjusted analysis the QoL risk equation also adjusts for treatment allocation and patient's baseline characteristics. The assumptions for resource use are consistent with the base case analysis,

i.e. consistent with TA190. However, a sensitivity analysis is available for the adjusted model in which PARAMOUNT resource use data is applied instead of JMEN data. The risk equations which predict hospitalisation rates and length of stay in this scenario adjust for patient's baseline characteristics as well as treatment allocation.

Table 2 Summary of key characteristics default within trial and lifetime adjusted analyses

Parameter	Within-trial period	Post-trial period
Country	UK	
Population	PARAMOUNT average characteristics	
CE model time horizon	Lifetime	
Pemetrexed price/cycle	Current UK list price	
Cost discount rate per annum	3.50%	
Effects discount rate per annum	3.50%	
Overall survival	Parametric regression	Parametric regression
Progression free survival	Parametric regression	Parametric regression
Utility values	Mixed regression model	Mixed regression model
Rate hospitalisation (sensitivity analysis only)	Poisson regression	Poisson regression
Length of hospitalisation (sensitivity analysis only)	Negative binomial regression	Negative binomial regression

b) Please provide the associated results for the adjusted analysis including sensitivity analyses.

Based on the AIC/BIC statistics, Cox-Snell residuals and plausibility of the lifetime time horizons, the gamma distribution is considered to offer the best fit to the K-M data in the adjusted model. The results for the adjusted analysis and sensitivity analyses are provided in Report B1b.

c) Please explain why this lifetime adjusted analysis was not considered to be appropriate for consideration in this appraisal.

The base case modelling approach employs observed Kaplan-Meier data to estimate PFS and OS during the within-trial period and parametric survival models to predict PFS and OS in the post-trial period to provide a lifetime model. The key characteristics of this approach are summarised in Table 3.

Table 3 Summary of key characteristics default within trial and lifetime unadjusted analyses used in the original submission

Parameter	Within-trial period	Post-trial period
Country	UK	
Population	PARAMOUNT average characteristics	
CE model time horizon	Lifetime	
Pemetrexed price/cycle	Current UK list price	
Cost discount rate per annum	3.50%	
Effects discount rate per annum	3.50%	
Overall survival	Kaplan-Meier data	Parametric regression
Progression free survival	Kaplan-Meier data	Parametric regression
Utility values	Mixed regression model	Mixed regression model
Rate hospitalisation (sensitivity analysis only)	Poisson regression	Poisson regression
Length of hospitalisation (sensitivity analysis only)	Negative binomial regression	Negative binomial regression

The lifetime adjusted analysis was considered alongside the unadjusted model as a potential option for the basecase analysis in this appraisal and this was included in the model to enable subgroup analyses to be conducted. The clinical data showed consistent OS benefit across all subgroups (see Figure 8 of the Lilly submission), therefore the unadjusted model was considered the most appropriate option. In addition, the NICE scope did not identify any subgroups for consideration as part of the appraisal.

Additional reasons why the unadjusted analysis was considered to be the most appropriate basecase analysis are as follows:

1. Generally it is not necessary to include covariates in survival modelling in the context of an economic model based on a single RCT as it would be expected that any important covariates would be balanced through the process of randomisation. (Latimer 2011).

2. The parametric survival estimates used in the lifetime adjusted analysis do not correspond well to the observed PFS data (in the early phase of the trial). The PFS estimates predicted using the parametric model (regardless of distribution selected) underestimated PFS in the pemetrexed arm and overestimated the PFS in the BSC arm. A review of log-log plots indicated possible evidence of proportional hazards (PH) violation. In view of potential PH violation, observed K-M data from the PARAMOUNT trial appears likely to offer the most reliable estimate of survival in the within-trial period.

3. The use of Kaplan-Meier data followed by a parametric extension is consistent with the approach used for pemetrexed in TA190 and TA181. During the appraisal of TA181, the ERG made full use of the available observed Kaplan-Meier data to minimize the contribution of the trend projections beyond available IPD and fitted a parametric extrapolation to the tail of the K-M data to calculate total mean survival. (LRIG, ERG addendum, June 2009; Latimer 2011).

4. During the appraisal of erlotinib (TA227), the ERG also stated that K-M observed data was considered to provide the best estimate of PFS for the trial duration. The ERG commented that since all patients in the stable disease population of the SATURN trial had disease which had progressed (that is, the PFS data set was complete), there was no need to model the mean duration of progression-free survival because it could be based directly on K-M data from the trial.

   Whilst not complete, in the PARAMOUNT trial the censoring rates for PFS data were low (6.7% placebo arm; 8.1% pemetrexed arm). Thus it was considered to be most appropriate to use the available K-M data for PFS rather than use a fully parametric model which did not appear to fit the data well (see response in 2. above)

B2. Please provide full Kaplan-Meier analysis results (see example appended below) showing K-M survival estimates at each event time, for each treatment arm in the PARAMOUNT trial:

a) OS, and PFS using final data cut, and censoring patients using date of data cut, not date of last contact/assessment, as the time of censoring.

Please see report: ncqb2aos.rtf, ncqb2apfs.rtf

OS was derived according to the request to extend the censoring time to date of data cut (05Mar2012).

PFS was derived according to the above request modified as follows for clarity:

In the final data set, there are 41 patients censored for the PFS events. Five of these patients had disease progression prior to the randomisation date but they were still randomised (i.e these were protocol violations). Extending the censoring time to the date of data cut, as requested, will prolong the censoring time by at least 22 months. As a result, for these 5 patients we have censored them at randomisation date but have revised the censoring time for the remaining 36 patients according to the request.

b) Post-progression survival (PPS) stratified by time of progression (in two categories: less then or greater than 3 months after randomization) using final data cut, and censoring patients using date of data cut, not date of last contact, as the time of censoring.

Please see report: ncqb2bppsgt3m.rtf, ncqb2bppsle3m.rtf. A PPS report for the ITT population (ncqb2bppsov.rtf) was not specifically requested but has been provided in addition to the stratified reports for completeness.

Not all of the ITT patients had objective disease progression (PD) date, therefore the stratification (less or equal to 3 or greater than 3 months) was conducted by either time-to-death or time-to-censoring (if no PD date was observed). All the analyses were performed according to the request and PPS definition introduced in Broglio and Berry, 2009.

B3. Please justify the decision to use a unit cost of £55 for a blood transfusion within the analysis.

A unit cost of £58 (not £55 as stated above) was used for a blood transfusion within the analysis. This was based on the NHS reference cost for a blood transfusion provided in an outpatient setting. These details were provided in Appendix 20 of our submission but are provided again below.

Table 4 Blood Transfusion Outpatient Attendances (DH, 2010-2011)

Code	Description	National Average Unit Cost
821	Blood Transfusion	£58.00

B4. Please provide an analysis of the number of progression events in each treatment arm into fatal and non-fatal events, shown separately for each 21-day cycle from randomization.

Please see report ncqb4 and B4.docx.

We have provided a statistical report (ncqb4) which presents an analysis of PFS events. These data are categorised by visit rather than 21-day cycle. Since the request asks to show this data for each 21-day cycle, we have also provided a report (B4.docx) based on data from the economic model which shows predicted PFS events in terms of 21-day cycles. Due to dose delays, which occur in a real-life setting, some patients would not have had a visit on the first day of each 21-day cycle during the clinical trial. However, the model assumes that patients do receive each cycle in 21-day increments.

The two reports also differ in the way PFS events are reported. The statistical report presents an analysis of actual PFS events only and does not report progression for censored patients. In the absence of censoring in the model, the absolute number of patients at risk in each time period will differ between the model and the trial data. The model uses transition probabilities derived from the observed data for the within-trial period to predict PFS and OS. When these data are applied to a different number of patients at risk the absolute number of events changes.

B5. Please provide a table for each treatment arm showing at the beginning of each 21 day cycle:

a) The number of patients alive and uncensored.

b) The number of patients still considered 'on treatment'.

c) The number of patients who received the allocated treatment for that cycle.

Please see the attached report B5.docx

B6. EQ-5D data and analysis

a) Please provide an analysis of the number (and percentage) of patients in each maintenance arm of PARAMOUNT who returned an EQ-5D form showing numbers at each trial point (baseline, each treatment cycle and post-discontinuation)

Please see report: Final datalock_smeq5d_2b

b) Please provide the same analysis for:

1. patients returning forms without any missing responses.
2. patients returning forms with any of the 5 three-option ratings missing.
3. patients returning forms with the visual analogue scale rating missing.
4. patients returning forms with both the visual analogue scale rating and at least one of the three-option ratings missing.

Please see reports: ncqb6b1, ncqb6b2, ncqb6b3, ncqb6b4
In each of these reports the column headed 'number of assessments' represents the number of patients who were still on treatment at each cycle and thus the patients for whom an EQ-5D assessment was expected.

c) How many patients in each arm returned completed forms without any missing items for every visit? Please provide mean (standard error) EQ-5D scores and visual analogue ratings for these patients for baseline, each treatment cycle and post-discontinuation

Please see report ncqB6c.

d) If any method was used to impute missing values prior to analysis and modelling please describe the method used, and the values imputed.

No imputation of missing values was conducted prior to analysis. The EQ-5D scoring algorithm for this study followed that given by McDowell and Newell, 1996. According to this scoring algorithm, if any of the five questions are not answered, that patient's overall score cannot be calculated (i.e., a missing answer on 1 of the dimensions will lead to the complete rejection of the questionnaire).

No imputation was conducted for the unadjusted model. However, for the adjusted analysis (for both PFS and OS clinical risk equations) where baseline EQ-5D was used as a covariate in the parametric regression equations, about 17% of values were missing and multiple imputation was used (predictive mean matching) to account for missing values.

e) Please confirm that no further EQ-5D data was collected after the 30-day post-discontinuation visit.

EQ-5D data was not collected after the 30-day post-discontinuation visit.

Section C: Textual clarifications and additional points

Calculation of patients eligible for treatment

C1. Section 2.2, page 28 please provide a justification for limiting the predicted eligible patients to those NSCLC patients that have received a histological diagnosis (n=19,163).

As per the summary of product characteristics for pemetrexed, the licensed indication for pemetrexed in maintenance NSCLC is as follows:

"Pemetrexed is indicated as monotherapy for the maintenance treatment of locally advanced or metastatic NSCLC other than predominantly squamous cell histology in patients whose disease has not progressed immediately following platinum-based chemotherapy."

In order to establish that patients have 'other than predominantly squamous' (i.e. non-squamous) histology and are eligible for pemetrexed treatment, patients are required to undergo a histological diagnosis.

The data source for number of patients with histological diagnosis (n= 19,163) is the National Lung Cancer Audit report 2011. According to the National Clinical Lung Cancer Audit (LUCADA) data manual (2010), for each patient, one of the fields recorded is the basis on which the lung cancer diagnosis was made. The manual states that if diagnosis is cytology or histology (from a primary tumour or metastases), the data item concerning pre-treatment histology must be completed, i.e, a histology code must be assigned to the patient. Prior to starting pemetrexed treatment, all patients would be required to undergo histological diagnosis to determine appropriateness of therapy, which would automatically place them in the category of patients with confirmed histological diagnosis. Some patients may be diagnosed with NSCLC without a histological diagnosis, for example, based upon X-ray, clinical findings or at post-mortem. These patients, in the absence of a histological diagnosis, i.e. their NSCLC subtype (squamous vs non-squamous) would be unknown, and therefore these patients would not be appropriate for pemetrexed treatment.

Patients who are eligible for continuation maintenance treatment with pemetrexed would also have received pemetrexed in the first-line setting. The NICE guidance on pemetrexed in the first-line setting (TA181) specifies that only patients with adenocarcinoma and large cell histology are eligible to receive pemetrexed in the NHS. This further establishes the fact that only patients with a confirmed histological diagnosis of NSCLC subtypes would be eligible for pemetrexed treatment.

References:

1. Department of Health. National Schedule of Reference Costs Year: 2010-11 - NHS Trusts and PCTs combined. 2011 http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_131140.
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3. Latimer N., NICE DSU Technical support document 14: Survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data, June 2011. http://www.nicedsu.org.uk/NICE%20DSU%20TSD%20Survival%20analysis_finalv2.pdf.

4. Liverpool Reviews and Implementation Group. ERG addendum. Pemetrexed for the first-line treatment of non-small cell lung cancer. June 2009. http://www.nice.org.uk/nicemedia/live/12045/45084/45084.pdf
5. McDowell I, Newell C. Measuring Health: A guide to rating scales and questionnaires. 2nd ed. New York: Oxford University Press; 1996.
6. NICE. Erlotinib monotherapy for maintenance treatment of non-small-cell lung cancer. TA227. London; NICE: June 2011.
7. The NHS Information Centre (The NHS IC). National Lung Cancer Audit Report 2011. (Audit period 2010) 2011. http://www.ic.nhs.uk/webfiles/Services/NCASP/audits%20and%20reports/NHS_IC_Lung_Cancer_AUDIT_2011_Interactive_PDF_V1.0.pdf..
8. The National Clinical Lung Cancer Audit (LUCADA) DATA MANUAL Title: Data Manual Version: 3.1.3 Date: Oct 2010. http://www.ic.nhs.uk/webfiles/Services/NCASP/Cancer/New%20web%20documents%20(Lung)/Latest_LUCADA_Data_Manual_V3.1.3.pdf

B1b: Results (adjusted model)

Provide details of the results of the analysis. In particular, results should include, but are not limited to, the following.

- Link between clinical- and cost-effectiveness results.
- Costs, QALYs and incremental cost per QALY.
- Disaggregated results such as LYG, costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment.
- A statement as to whether the results are based on a PSA.
- Cost-effectiveness acceptability curves, including a representation of the cost-effectiveness acceptability frontier.
- Scatter plots on cost-effectiveness quadrants.
- A tabulation of the mean results (costs, QALYs, ICERs), the probability that the treatment is cost effective at thresholds of £20,000–£30,000 per QALY gained and the error probability.

Clinical outcomes from the model

1.1.1 **For the outcomes highlighted in the decision problem (see Section 5), please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.**

Table 1 Summary of adjusted model results compared with clinical data

Outcome	Clinical trial results (CI)			Model results		
	Pem	Placebo	Inc*	Pem	Placebo	Inc*
Median OS (months)	13.86	11.01	2.85	14.52	11.76	2.76
Mean OS (months)				19.08	15.96	3.24
Median PFS (months)	4.44	2.76	1.28	4.8	3.48	1.32
Mean PFS (months)				7.56	5.04	2.52
QALYs				1.08	0.90	0.18

Note: Numbers may not compute due to rounding; *Inc – incremental difference; results reported for adjusted model - risk equations populated with average covariates; results reported for adjusted model with risk equations populated with average covariates.

The clinical section of the Lilly submission reports the median OS and median PFS results as the main the outcomes from PARAMOUNT. Since the economic model provides mean OS and mean PFS data over a lifetime horizon, the median OS and PFS results from the economic model have been calculated from the predicted survival time in the model.

1.1.2 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

A table presenting the proportion of the cohort in each health state over time is provided in Appendix 1.

1.1.3 Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

A table presenting the discounted quality-adjusted survival time in each health state together with total LYs and QALYs for placebo and pemetrexed is provided in Appendix 2.

1.1.4 Please indicate the life years and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results.

Table 2 Model outputs by clinical outcomes (adjusted model)

Outcome	Therapy	LYs	QALYs	Total Cost (£)
	Pemetrexed	**1.59**	**1.08**	**£25,522**
Overall survival	**Placebo**	**1.33**	**0.90**	**£13,859**
	Incremental	**0.27**	**0.18**	**£11,663**
	Pemetrexed	0.63	0.45	£13,164
Pre-progression	Placebo	0.42	0.31	£532
	Incremental	0.21	0.15	12632.63
	Pemetrexed	0.96	0.63	£12,358
Post-progression	Placebo	0.91	0.59	£13,328
	Incremental	0.05	0.04	-969.47

Note: Numbers may not compute due to rounding; LY, life years; QALY, quality adjusted life year; results reported for adjusted model - risk equations populated with average covariates; results reported for adjusted model with riskequations populated with average covariates.

1.1.5 Please provide details of the disaggregated incremental QALYs and costs by health state, and of resource use predicted by the model by category of cost. Suggested formats are presented below.

Table 3 Summary of QALY gain by health state (adjusted model)

Health state	QALY pemetrexed	QALY placebo	Increment	% absolute increment
Pre-progression	0.45	0.31	0.15	47%
Post-progression	0.63	0.59	0.04	7%
Total	1.08	0.90	0.18	21%

Note: Numbers may not compute due to rounding; QALY, quality-adjusted life year. Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee; results reported for adjusted model with riskequations populated with average covariates.

Table 4 Summary of costs by health state (adjusted model)

Health state	Cost pemetrexed	Cost placebo	Increment	% absolute increment
Pre-progression	£13,164	£532	£12,633	2377%
Post-progression	£12,358	£13,328	-£969	-7%
Total	£25,522	£13,859	£11,663	84%

Note: Numbers may not compute due to rounding. Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee; results reported for adjusted model - risk equations populated with average covariates.

Table 5 Summary of predicted resource use by category of cost (adjusted model)

Item	Cost pemetrexed	Cost placebo	Increment	% absolute increment
Therapy cost	£12,705	£0	£12,705	-
Adverse event cost	£62	£5	£57	1262%
Follow up care costs	£10,044	£11,116	-£1,072	-10%
Terminal care costs	£2,712	£2,738	-£27	-1%
Total	£25,522	£13,859	£11,663	84%

Note: Numbers may not compute due to rounding. Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee; results reported for adjusted model – risk equations populated with average covariates.

Base-case analysis

1.1.6 Please present your results in the following table. List interventions and comparator(s) from least to most expensive and present ICERs in comparison with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance.

The lifetime analysis (adjusted model) employs parametric survival models to predict PFS and OS in both the within-trial period and post-trial period. These parametric models adjust for treatment and patient baseline characteristics and are consequently capable of predicting costs and outcomes for different patient subgroups.

Two tables of results have been reported (see Table 6 and Table 7). In the first analysis (Table 6) average variable values have been applied into the risk equations (e.g. 0.78 to represent the proportion of patients who were past smokers). However, due to the inherent non-linearity of cost-effectiveness models this approach can result in some loss in accuracy. In a second analysis (Table 7) individual patient characteristics from the PARAMOUNT trial population have been used to estimate overall costs and QALYs for pemetrexed plus BSC versus BSC alone. In this approach individual patient profiles (characteristics) have been applied into the PARAMOUNT adjusted risk equations in the model sequentially - one profile at a time, to estimate total costs, life years and QALYs. The estimates of costs and QALYs from each iteration have been averaged to calculate incremental cost per life year and QALY. However, this technique is more time consuming because 539 patient profiles must be entered into the risk equations for each Monte Carlo simulation. Consequently, the deterministic sensitivity analyses and PSA have used the average variable values in the risk equations to provide a range of results based on alternative plausible inputs.

Table 6 Deterministic basecase results (average values for baseline variables)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Incremental cost/LYG	ICER (£) incremental (QALYs)
Placebo/BSC	£13,859	1.33	0.90					
Pem/BSC	£25,522	1.59	1.08	£11,663	0.27	0.18	£43,823	**£63,126**

Note: Numbers may not compute due to rounding; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 7 Deterministic basecase results (individual patient profiles)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Incremental cost/LYG	ICER (£) incremental (QALYs)
Placebo/BSC	£14,041	1.38	0.93					
Pem/BSC	£26,402	1.65	1.13	£12,360	0.27	0.19	£45,137	**£64,742**

Note: Numbers may not compute due to rounding; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

1.1.7 Please present results of deterministic sensitivity analysis. Consider the use of tornado diagrams (adjusted model)

Results of the deterministic sensitivity analysis, using average values for baseline chatachteristics, are presented in Table 8. Deterministic and probabilistic results for the use of alternative parametric distributions are shown in Table 9.

Table 8 Deterministic sensitivity analysis (adjusted model)

Parameter	Value or assumption in base case	Incr. cost (£)	Incr. benefit (QALY)	ICER (£)
Base case (using average values for baseline characteristics)		**£11,663**	**0.18**	**£63,126**
Pemetrexed costs				
Wastage excluded (assumes vial sharing)	Wastage included	£11,598	0.18	£62,775
Concomitant vitamins and corticosteroid included	Excluded	£11,687	0.18	£63,255
DH HRG daycase procurement costs for pemetrexed – average £1,293	£1,440	£10,540	0.18	£57,049
DH HRG daycase procurement costs for pemetrexed – lower quartile £928		£7,753	0.18	£41,960
DH HRG daycase procurement costs for pemetrexed – upper quartile £1,611		£12,969	0.18	£70,195
Pemetrexed delivery cost – Lower quartile £131	Daycase £208	£11,076	0.18	£59,948
Pemetrexed delivery cost – Upper quartile £233		£11,855	0.18	£64,165
Pemetrexed delivery cost – Outpatient average £231		£11,840	0.18	£64,082
Pemetrexed delivery cost – Outpatient lower quartile £114		£10,946	0.18	£59,245
Pemetrexed delivery cost – Outpatient upper quartile £279		£12,206	0.18	£66,066
Deliver 20% of pemetrexed in community or home setting at £96/cycle		£11,501	0.18	£62,246
Deliver 50% of pemetrexed in community or home setting at £96/cycle		£11,257	0.18	£60,925
Increase AE costs by 10%: £8.17 pem/BSC; £0.91 placebo/BSC	£7.43 pem/BSC, £0.83 placebo/BSC	£11,669	0.18	£63,157
Decrease AE costs by 10%: £6.68 pem/BSC; £0.75 placebo/BSC		£11,657	0.18	£63,095
BSA based on PARAMOUNT IPD (Based on IPD: equivalent to mean 1.8m^2 **including** wastage)	Mean BSA:1.79m2 (wastage included)	£12,160	0.18	£65,816
BSA based on PARAMOUNT IPD (Based on IPD: equivalent to mean 1.8m^2, **excluding** wastage)		£11,627	0.18	£62,931
Additional monitoring for patients on pemetrexed:				
Every 12 weeks: 1 extra consultant visit for all patients and 1 extra CT scan for 3% of cohort	Over 24-week period: 1 extra consultant visit for all patients and	£11,782	0.18	£63,769

Parameter	Value or assumption in base case	Incr. cost (£)	Incr. benefit (QALY)	ICER (£)
Every 12 weeks: 1 extra consultant visit for all patients and 1 extra CT scan for 20% of cohort	1 extra CT scan for 3% of cohort.	£11,828	0.18	£64,020
Every 12 weeks: 1 extra consultant visit for all patients and 1 extra CT scan for 50% of cohort		£11,910	0.18	£64,463
Every 12 weeks: 1 extra consultant visit for all patients and 1 extra CT scan for 100% of cohort		£12,047	0.18	£65,201
Every 6 weeks: 1 extra consultant visit for all patients and 1 extra CT scan for 3% of cohort on pemetrexed		£12,019	0.18	£65,053
Every 6 weeks: 1 extra consultant visit for all patients and 1 extra CT scan for 20% of cohort on pemetrexed		£12,112	0.18	£65,555
Every 6 weeks: 1 extra consultant visit for all patients and 1 extra CT scan for 50% of cohort on pemetrexed		£12,276	0.18	£66,441
Every 6 weeks: 1 extra consultant visit for all patients and 1 extra CT scan for 100% of cohort on pemetrexed		£12,549	0.18	£67,918
Second-line chemotherapy costs				
Docetaxel average price from DH CMU eMIT database (accessed 15.09.2012): £116.40	Erlotinib £976.47 Docetaxel £1,023	£11,797	0.18	£63,848
Erlotinib & docetaxel equivalent to average docetaxel eMIT price £116.40		£12,455	0.18	£67,412
DH HRG daycase procurement costs for erlotinib and docetaxel – average Erl: £2,165; Doc £832		£10,781	0.18	£58,354
Cycle data from PARAMOUNT: 3.26 docetaxel, 5.25 Erlotinib	4.82 Docetaxel, 6.27 Erlotinib	£11,856	0.18	£64,171
BSC and terminal care costs				
No differential BSC costs applied according to active vs no active treatment: £36.22/cycle	£36.22/cycle: active chemo, £72.44/cycle not on active chemo £2,825 terminal care costs	£11,876	0.18	£64,280
No differential BSC costs applied according to active vs no active treatment: £72.44/cycle		£12,044	0.18	£65,188
No BSC applied (terminal cost applied)		£11,709	0.18	£63,373

Parameter	Value or assumption in base case	Incr. cost (£)	Incr. benefit (QALY)	ICER (£)
No terminal or BSC costs applied		£11,735	0.18	£63,517
PARAMOUNT resource use data				
BSC drug costs, hospitalisation, blood transfusion and palliative radiotherapy rates and associated NHS reference costs. Second-line chemotherapy cycles based on PARAMOUNT data	**AE costs:** £6.51 pem/BSC. £0.29 placebo/BSC. **BSC costs:** £36.22/cycle: active chemo, £72.44/cycle not on active chemo. **Second-line chemo cycles:** Doc:4.82 ; Erl: 6.27. **Terminal care cost**: £2,825	£12,552	0.18	£67,936
Utilities				
Assume no treatment effect associated with pemetrexed treatment during maintenance treatment (i.e. pre-progression); utilities equivalent to BSC pre-progression	PARAMOUNT EQ-5D data. Apply non-significant disutility (-0.0248)	£11,663	0.20	£59,134
Utility values from TA190 (Scenario 5 JMEN values)		£11,663	0.17	£70,683
Efficacy				
Post-trial treatment effect: pem/BSC is equivalent to placebo/BSC, i.e. treatment benefit for trial period only.	Treatment effect assumed to continue beyond trial duration	£11,617	0.15	£75,926
OS Treatment effect 95% lower CI	Mean OS treatment effect	£11,382	0.02	£594,172
OS Treatment effect 95% upper CI		£11,992	0.38	£31,708
PFS Treatment effect 95% lower CI	Mean PFS treatment effect	£11,748	0.18	£66,080
PFS Treatment effect 95% upper CI		£11,561	0.19	£59,944
Structural				
Discounting costs at 0%	3.50%	£11,830	0.18	£64,028
Discounting health effects at 0%		£11,663	0.20	£58,462
Discounting costs and effects at 0%		£11,830	0.20	£59,298
Discounting costs at 6%		£11,556	0.18	£62,548
Discounting health effects at 6%		£11,663	0.18	£66,373

Parameter	Value or assumption in base case	Incr. cost (£)	Incr. benefit (QALY)	ICER (£)
Discounting costs and effects at 6%	13.29 years (99.9% patients died)	£11,556	0.18	£65,766
Time horizon - 6 years (i.e. stop Markov trace at 105 cycles)		£11,596	0.17	£67,724
Time horizon - 10 years (i.e. stop Markov trace at 174 cycles)		£11,655	0.18	£63,769
Time horizon – when 99% of patients died - 7.77 years (i.e. stop Markov trace at 135 cycles)		£11,636	0.18	£65,117

Notes: Results reported for adjusted model - risk equations populated with average covariates.

The remaining sensitivity analyses based on changes to cut-points for extrapolation that were presented for the unadjusted model are not applicable for the adjusted model since it is a fully parametric model.

Table 9 Sensitivity analysis: Alternative parametric distributions

Alternative parametric distribution	Parameter value or assumption in basecase	Deterministic				Probabilistic			
		Inc. cost (£)	Inc. mean OS (months)	Inc. benefit (QALY)	ICER (£)	Inc. cost (£)	Inc. mean OS (months)	Inc. benefit (QALY)	ICER (£)
	Base case	**£11,663**	**3.2**	**0.18**	**£63,126**	**£11,783**	**3.2**	**0.18**	**£63,760**
Exponential	Gamma	£12,134	3.8	0.22	£55,248	£12,242	3.8	0.22	£54,697
Weibull	Gamma	£12,108	3.1	0.18	£67,005	£12,177	3.0	0.18	£67,753
Gompertz	Gamma	£12,202	2.9	0.17	£72,322	£12,310	2.8	0.17	£72,777
Log-normal	Gamma	£12,160	3.3	0.19	£64,096	£12,247	3.2	0.19	£65,070
Log-logistic	Gamma	£12,114	3.3	0.19	£63,256	£12,242	3.3	0.19	£64,352

1.1.8 Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves.

PSA was conducted using 1,000 iterations. Cholesky decompositions have been used in the model to account for correlations between parameters. Monte Carlo simulation has been used to generate joint distributions of total costs and QALYs that result in the model from these and other probabilistic parameters (see Section **Error! Reference source not found.**).

The probabilistic basecase results are presented in Table 10. Since PSA results will change each time they are run, they may not be exactly replicable. The incremental cost-effectiveness plane and cost-effective acceptability curve (CEAC) are presented in Figure 1 and Figure 2.

Table 10 Probabilistic basecase results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Incremental cost/LYG	ICER (£) incremental (QALYs)
Placebo/BSC	£13,869	1.33	0.90					
Pem/BSC	£25,652	1.60	1.09	£11,783	0.26	0.18	£44,489	**£63,760**

Note: Numbers may not compute due to rounding. ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; results reported for adjusted model with risk equations populated with average covariates.

Figure 1 Incremental cost-effectiveness plane for basecase analysis

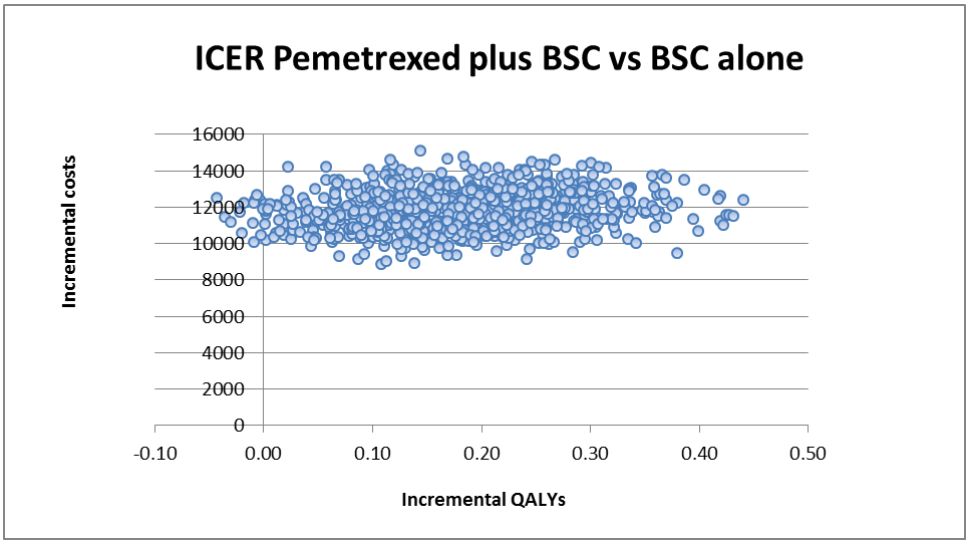
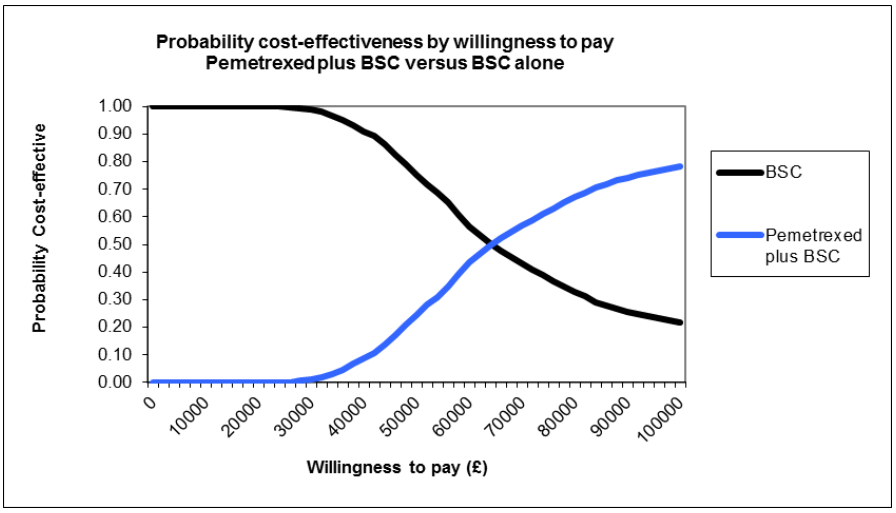


Figure 2 Cost-effectiveness acceptability curve



1.1.9 Please present the results of scenario analysis. Include details of structural sensitivity analysis.

See section 1.1.7.

1.1.10 What were the main findings of each of the sensitivity analysis?

The economic evaluation of pemetrexed continuation maintenance compared to placebo in patients with advanced NS NSCLC gives a deterministic ICER of £64,742 and a probabilistic ICER of £63,760 (see Table 8 and Table 10). One way sensitivity analyses indicate that the ICER is largely robust to changes in structural and parameter assumptions, although the model showed sensitivity to a change in the treatment effect (time ratio) within 95% confidence intervals for overall survival. In the adjusted model the lower bound 95% confidence interval for the time ratio (1.02) was very close to 1 and consequently pemetrexed resulted in little additional gain in survival compared to BSC (incremental LYs saved 0.02). In this isolated scenario the ICER rose to £594,172.

The base case ICER estimated using the adjusted analysis, which use parametric survival models to predict progression, overall survival and time on treatment both within-trial and post-trial, is higher than the ICER estimated using Kaplan-Meier data with the unadjusted parametric extrapolation. This was primarily driven by a smaller gain in QALYs (0.18 QALYs adjusted parametric model versus 0.26 QALYs Kaplan-Meier+ parametric extension). The smoothing of the survival curves in the adjusted parametric model appears to have failed to capture some of the survival benefit of pemetrexed observed in PARAMOUNT within-trial phase.

The CEAC shows that at a £50,000 WTP threshold pemetrexed/BSC is cost-effective in 27% of simulations. At a WTP threshold of £60,000 pemetrexed/BSC is cost-effective in 56% of simulations.

1.1.11 What are the key drivers of the cost-effectiveness results?

Consistent with the default base case analysis the key drivers of the cost-effective results for the adjusted model are:

- Efficacy of pemetrexed: including both the implementation of the confidence interval for the OS treatment effect and changing the assumption of treatment effect post trial
- Use of alternative parametric distributions.
- Use of utility values from TA190.

Appendix adjusted model

Appendix 1 The proportion of the cohort in each health state over time

Time			Proportion of patients at end of cycle placebo/BSC				Proportion of patients at end of cycle pem/BSC			
Years	Months	Cycles	Pre-progression	Post-progression	Dead	Check	Pre-progression	Post-progression	Dead	Check
0.06	0.69	1.00	0.95	0.05	0.00	1.00	0.98	0.01	0.00	1.00
0.11	1.38	2.00	0.79	0.20	0.02	1.00	0.90	0.09	0.01	1.00
0.17	2.07	3.00	0.63	0.33	0.04	1.00	0.79	0.18	0.03	1.00
0.23	2.76	4.00	0.51	0.42	0.07	1.00	0.69	0.26	0.05	1.00
0.29	3.45	5.00	0.42	0.48	0.10	1.00	0.60	0.33	0.07	1.00
0.34	4.14	6.00	0.35	0.51	0.14	1.00	0.52	0.38	0.10	1.00
0.40	4.83	7.00	0.30	0.53	0.18	1.00	0.46	0.41	0.13	1.00
0.46	5.52	8.00	0.25	0.53	0.21	1.00	0.40	0.44	0.16	1.00
0.52	6.21	9.00	0.22	0.53	0.25	1.00	0.36	0.45	0.19	1.00
0.57	6.90	10.00	0.19	0.53	0.29	1.00	0.32	0.46	0.22	1.00
0.63	7.59	11.00	0.17	0.51	0.32	1.00	0.29	0.46	0.25	1.00
0.69	8.28	12.00	0.15	0.50	0.35	1.00	0.26	0.46	0.28	1.00
0.75	8.97	13.00	0.13	0.48	0.39	1.00	0.23	0.45	0.31	1.00
0.80	9.66	14.00	0.12	0.47	0.42	1.00	0.21	0.45	0.34	1.00
0.86	10.35	15.00	0.10	0.45	0.45	1.00	0.19	0.44	0.37	1.00
0.92	11.04	16.00	0.09	0.43	0.47	1.00	0.18	0.43	0.39	1.00
0.98	11.73	17.00	0.09	0.41	0.50	1.00	0.16	0.42	0.42	1.00
1.03	12.42	18.00	0.08	0.40	0.53	1.00	0.15	0.41	0.44	1.00
1.09	13.11	19.00	0.07	0.38	0.55	1.00	0.14	0.39	0.47	1.00
1.15	13.80	20.00	0.07	0.36	0.57	1.00	0.13	0.38	0.49	1.00
1.21	14.49	21.00	0.06	0.35	0.59	1.00	0.12	0.37	0.51	1.00
1.26	15.18	22.00	0.06	0.33	0.61	1.00	0.11	0.36	0.53	1.00
1.32	15.87	23.00	0.05	0.32	0.63	1.00	0.10	0.35	0.55	1.00
1.38	16.56	24.00	0.05	0.30	0.65	1.00	0.10	0.33	0.57	1.00
1.44	17.25	25.00	0.04	0.29	0.67	1.00	0.09	0.32	0.59	1.00
1.49	17.94	26.00	0.04	0.27	0.69	1.00	0.09	0.31	0.60	1.00
1.55	18.63	27.00	0.04	0.26	0.70	1.00	0.08	0.30	0.62	1.00
1.61	19.32	28.00	0.04	0.25	0.71	1.00	0.08	0.29	0.64	1.00
1.67	20.01	29.00	0.03	0.24	0.73	1.00	0.07	0.28	0.65	1.00
1.72	20.70	30.00	0.03	0.23	0.74	1.00	0.07	0.27	0.66	1.00
1.78	21.39	31.00	0.03	0.22	0.75	1.00	0.06	0.26	0.68	1.00
1.84	22.08	32.00	0.03	0.21	0.77	1.00	0.06	0.25	0.69	1.00
1.90	22.77	33.00	0.03	0.20	0.78	1.00	0.06	0.24	0.70	1.00
1.95	23.46	34.00	0.03	0.19	0.79	1.00	0.05	0.23	0.72	1.00
2.01	24.15	35.00	0.02	0.18	0.80	1.00	0.05	0.22	0.73	1.00
2.07	24.84	36.00	0.02	0.17	0.81	1.00	0.05	0.21	0.74	1.00
2.13	25.53	37.00	0.02	0.16	0.82	1.00	0.05	0.20	0.75	1.00
2.18	26.22	38.00	0.02	0.16	0.82	1.00	0.04	0.20	0.76	1.00
2.24	26.91	39.00	0.02	0.15	0.83	1.00	0.04	0.19	0.77	1.00
2.30	27.60	40.00	0.02	0.14	0.84	1.00	0.04	0.18	0.78	1.00
2.36	28.29	41.00	0.02	0.14	0.85	1.00	0.04	0.18	0.79	1.00
2.41	28.98	42.00	0.02	0.13	0.85	1.00	0.04	0.17	0.79	1.00

Time			Proportion of patients at end of cycle placebo/BSC				Proportion of patients at end of cycle pem/BSC			
Years	Months	Cycles	Pre-progression	Post-progression	Dead	Check	Pre-progression	Post-progression	Dead	Check
2.47	29.67	43.00	0.02	0.12	0.86	1.00	0.04	0.16	0.80	1.00
2.53	30.36	44.00	0.02	0.12	0.87	1.00	0.03	0.16	0.81	1.00
2.59	31.05	45.00	0.01	0.11	0.87	1.00	0.03	0.15	0.82	1.00
2.64	31.74	46.00	0.01	0.11	0.88	1.00	0.03	0.14	0.82	1.00
2.70	32.43	47.00	0.01	0.10	0.88	1.00	0.03	0.14	0.83	1.00
2.76	33.12	48.00	0.01	0.10	0.89	1.00	0.03	0.13	0.84	1.00
2.82	33.81	49.00	0.01	0.10	0.89	1.00	0.03	0.13	0.84	1.00
2.87	34.50	50.00	0.01	0.09	0.90	1.00	0.03	0.12	0.85	1.00
2.93	35.19	51.00	0.01	0.09	0.90	1.00	0.03	0.12	0.85	1.00
2.99	35.88	52.00	0.01	0.08	0.91	1.00	0.03	0.12	0.86	1.00
3.05	36.57	53.00	0.01	0.08	0.91	1.00	0.02	0.11	0.86	1.00
3.10	37.26	54.00	0.01	0.08	0.91	1.00	0.02	0.11	0.87	1.00
3.16	37.95	55.00	0.01	0.07	0.92	1.00	0.02	0.10	0.87	1.00
3.22	38.64	56.00	0.01	0.07	0.92	1.00	0.02	0.10	0.88	1.00
3.28	39.33	57.00	0.01	0.07	0.92	1.00	0.02	0.10	0.88	1.00
3.33	40.02	58.00	0.01	0.06	0.93	1.00	0.02	0.09	0.89	1.00
3.39	40.71	59.00	0.01	0.06	0.93	1.00	0.02	0.09	0.89	1.00
3.45	41.40	60.00	0.01	0.06	0.93	1.00	0.02	0.09	0.90	1.00
3.51	42.09	61.00	0.01	0.06	0.94	1.00	0.02	0.08	0.90	1.00
3.56	42.78	62.00	0.01	0.05	0.94	1.00	0.02	0.08	0.90	1.00
3.62	43.47	63.00	0.01	0.05	0.94	1.00	0.02	0.08	0.91	1.00
3.68	44.16	64.00	0.01	0.05	0.94	1.00	0.02	0.07	0.91	1.00
3.74	44.85	65.00	0.01	0.05	0.95	1.00	0.02	0.07	0.91	1.00
3.79	45.54	66.00	0.01	0.05	0.95	1.00	0.02	0.07	0.92	1.00
3.85	46.23	67.00	0.01	0.04	0.95	1.00	0.02	0.07	0.92	1.00
3.91	46.92	68.00	0.01	0.04	0.95	1.00	0.01	0.06	0.92	1.00
3.97	47.61	69.00	0.01	0.04	0.95	1.00	0.01	0.06	0.92	1.00
4.02	48.30	70.00	0.01	0.04	0.96	1.00	0.01	0.06	0.93	1.00
4.08	48.99	71.00	0.01	0.04	0.96	1.00	0.01	0.06	0.93	1.00
4.14	49.68	72.00	0.01	0.04	0.96	1.00	0.01	0.06	0.93	1.00
4.20	50.37	73.00	0.01	0.03	0.96	1.00	0.01	0.05	0.93	1.00
4.25	51.06	74.00	0.00	0.03	0.96	1.00	0.01	0.05	0.94	1.00
4.31	51.75	75.00	0.00	0.03	0.96	1.00	0.01	0.05	0.94	1.00
4.37	52.44	76.00	0.00	0.03	0.96	1.00	0.01	0.05	0.94	1.00
4.43	53.13	77.00	0.00	0.03	0.97	1.00	0.01	0.05	0.94	1.00
4.48	53.82	78.00	0.00	0.03	0.97	1.00	0.01	0.05	0.94	1.00
4.54	54.51	79.00	0.00	0.03	0.97	1.00	0.01	0.04	0.95	1.00
4.60	55.20	80.00	0.00	0.03	0.97	1.00	0.01	0.04	0.95	1.00
4.66	55.89	81.00	0.00	0.03	0.97	1.00	0.01	0.04	0.95	1.00
4.71	56.57	82.00	0.00	0.02	0.97	1.00	0.01	0.04	0.95	1.00
4.77	57.26	83.00	0.00	0.02	0.97	1.00	0.01	0.04	0.95	1.00
4.83	57.95	84.00	0.00	0.02	0.97	1.00	0.01	0.04	0.95	1.00
4.89	58.64	85.00	0.00	0.02	0.97	1.00	0.01	0.04	0.96	1.00
4.94	59.33	86.00	0.00	0.02	0.98	1.00	0.01	0.03	0.96	1.00
5.00	60.02	87.00	0.00	0.02	0.98	1.00	0.01	0.03	0.96	1.00

Time			Proportion of patients at end of cycle placebo/BSC				Proportion of patients at end of cycle pem/BSC			
Years	Months	Cycles	Pre-progression	Post-progression	Dead	Check	Pre-progression	Post-progression	Dead	Check
5.06	60.71	88.00	0.00	0.02	0.98	1.00	0.01	0.03	0.96	1.00
5.12	61.40	89.00	0.00	0.02	0.98	1.00	0.01	0.03	0.96	1.00
5.17	62.09	90.00	0.00	0.02	0.98	1.00	0.01	0.03	0.96	1.00
5.23	62.78	91.00	0.00	0.02	0.98	1.00	0.01	0.03	0.96	1.00
5.29	63.47	92.00	0.00	0.02	0.98	1.00	0.01	0.03	0.96	1.00
5.35	64.16	93.00	0.00	0.02	0.98	1.00	0.01	0.03	0.97	1.00
5.40	64.85	94.00	0.00	0.02	0.98	1.00	0.01	0.03	0.97	1.00
5.46	65.54	95.00	0.00	0.02	0.98	1.00	0.01	0.03	0.97	1.00
5.52	66.23	96.00	0.00	0.01	0.98	1.00	0.01	0.02	0.97	1.00
5.58	66.92	97.00	0.00	0.01	0.98	1.00	0.01	0.02	0.97	1.00
5.63	67.61	98.00	0.00	0.01	0.98	1.00	0.01	0.02	0.97	1.00
5.69	68.30	99.00	0.00	0.01	0.98	1.00	0.01	0.02	0.97	1.00
5.75	68.99	100.00	0.00	0.01	0.98	1.00	0.01	0.02	0.97	1.00
5.81	69.68	101.00	0.00	0.01	0.99	1.00	0.01	0.02	0.97	1.00
5.86	70.37	102.00	0.00	0.01	0.99	1.00	0.01	0.02	0.97	1.00
5.92	71.06	103.00	0.00	0.01	0.99	1.00	0.01	0.02	0.97	1.00
5.98	71.75	104.00	0.00	0.01	0.99	1.00	0.01	0.02	0.98	1.00
6.04	72.44	105.00	0.00	0.01	0.99	1.00	0.01	0.02	0.98	1.00
6.09	73.13	106.00	0.00	0.01	0.99	1.00	0.01	0.02	0.98	1.00
6.15	73.82	107.00	0.00	0.01	0.99	1.00	0.01	0.02	0.98	1.00
6.21	74.51	108.00	0.00	0.01	0.99	1.00	0.01	0.02	0.98	1.00
6.27	75.20	109.00	0.00	0.01	0.99	1.00	0.01	0.02	0.98	1.00
6.32	75.89	110.00	0.00	0.01	0.99	1.00	0.01	0.02	0.98	1.00
6.38	76.58	111.00	0.00	0.01	0.99	1.00	0.01	0.01	0.98	1.00
6.44	77.27	112.00	0.00	0.01	0.99	1.00	0.01	0.01	0.98	1.00
6.50	77.96	113.00	0.00	0.01	0.99	1.00	0.01	0.01	0.98	1.00
6.55	78.65	114.00	0.00	0.01	0.99	1.00	0.00	0.01	0.98	1.00
6.61	79.34	115.00	0.00	0.01	0.99	1.00	0.00	0.01	0.98	1.00
6.67	80.03	116.00	0.00	0.01	0.99	1.00	0.00	0.01	0.98	1.00
6.73	80.72	117.00	0.00	0.01	0.99	1.00	0.00	0.01	0.98	1.00
6.78	81.41	118.00	0.00	0.01	0.99	1.00	0.00	0.01	0.98	1.00
6.84	82.10	119.00	0.00	0.01	0.99	1.00	0.00	0.01	0.98	1.00
6.90	82.79	120.00	0.00	0.01	0.99	1.00	0.00	0.01	0.98	1.00
6.96	83.48	121.00	0.00	0.01	0.99	1.00	0.00	0.01	0.98	1.00
7.01	84.17	122.00	0.00	0.01	0.99	1.00	0.00	0.01	0.99	1.00
7.07	84.86	123.00	0.00	0.01	0.99	1.00	0.00	0.01	0.99	1.00
7.13	85.55	124.00	0.00	0.01	0.99	1.00	0.00	0.01	0.99	1.00
7.19	86.24	125.00	0.00	0.01	0.99	1.00	0.00	0.01	0.99	1.00
7.24	86.93	126.00	0.00	0.00	0.99	1.00	0.00	0.01	0.99	1.00
7.30	87.62	127.00	0.00	0.00	0.99	1.00	0.00	0.01	0.99	1.00
7.36	88.31	128.00	0.00	0.00	0.99	1.00	0.00	0.01	0.99	1.00
7.42	89.00	129.00	0.00	0.00	0.99	1.00	0.00	0.01	0.99	1.00
7.47	89.69	130.00	0.00	0.00	0.99	1.00	0.00	0.01	0.99	1.00
7.53	90.38	131.00	0.00	0.00	0.99	1.00	0.00	0.01	0.99	1.00
7.59	91.07	132.00	0.00	0.00	0.99	1.00	0.00	0.01	0.99	1.00

Time			Proportion of patients at end of cycle placebo/BSC				Proportion of patients at end of cycle pem/BSC			
Years	Months	Cycles	Pre-progression	Post-progression	Dead	Check	Pre-progression	Post-progression	Dead	Check
7.65	91.76	133.00	0.00	0.00	0.99	1.00	0.00	0.01	0.99	1.00
7.70	92.45	134.00	0.00	0.00	0.99	1.00	0.00	0.01	0.99	1.00
7.76	93.14	135.00	0.00	0.00	1.00	1.00	0.00	0.01	0.99	1.00
7.82	93.83	136.00	0.00	0.00	1.00	1.00	0.00	0.01	0.99	1.00
7.88	94.52	137.00	0.00	0.00	1.00	1.00	0.00	0.01	0.99	1.00
7.93	95.21	138.00	0.00	0.00	1.00	1.00	0.00	0.01	0.99	1.00
7.99	95.90	139.00	0.00	0.00	1.00	1.00	0.00	0.01	0.99	1.00
8.05	96.59	140.00	0.00	0.00	1.00	1.00	0.00	0.01	0.99	1.00
8.11	97.28	141.00	0.00	0.00	1.00	1.00	0.00	0.01	0.99	1.00
8.16	97.97	142.00	0.00	0.00	1.00	1.00	0.00	0.01	0.99	1.00
8.22	98.66	143.00	0.00	0.00	1.00	1.00	0.00	0.01	0.99	1.00
8.28	99.35	144.00	0.00	0.00	1.00	1.00	0.00	0.01	0.99	1.00
8.34	100.04	145.00	0.00	0.00	1.00	1.00	0.00	0.01	0.99	1.00
8.39	100.73	146.00	0.00	0.00	1.00	1.00	0.00	0.00	0.99	1.00
8.45	101.42	147.00	0.00	0.00	1.00	1.00	0.00	0.00	0.99	1.00
8.51	102.11	148.00	0.00	0.00	1.00	1.00	0.00	0.00	0.99	1.00
8.57	102.80	149.00	0.00	0.00	1.00	1.00	0.00	0.00	0.99	1.00
8.62	103.49	150.00	0.00	0.00	1.00	1.00	0.00	0.00	0.99	1.00
8.68	104.18	151.00	0.00	0.00	1.00	1.00	0.00	0.00	0.99	1.00
8.74	104.87	152.00	0.00	0.00	1.00	1.00	0.00	0.00	0.99	1.00
8.80	105.56	153.00	0.00	0.00	1.00	1.00	0.00	0.00	0.99	1.00
8.85	106.25	154.00	0.00	0.00	1.00	1.00	0.00	0.00	0.99	1.00
8.91	106.94	155.00	0.00	0.00	1.00	1.00	0.00	0.00	0.99	1.00
8.97	107.63	156.00	0.00	0.00	1.00	1.00	0.00	0.00	0.99	1.00
9.03	108.32	157.00	0.00	0.00	1.00	1.00	0.00	0.00	0.99	1.00
9.08	109.01	158.00	0.00	0.00	1.00	1.00	0.00	0.00	0.99	1.00
9.14	109.70	159.00	0.00	0.00	1.00	1.00	0.00	0.00	0.99	1.00
9.20	110.39	160.00	0.00	0.00	1.00	1.00	0.00	0.00	0.99	1.00
9.26	111.08	161.00	0.00	0.00	1.00	1.00	0.00	0.00	0.99	1.00
9.31	111.77	162.00	0.00	0.00	1.00	1.00	0.00	0.00	0.99	1.00
9.37	112.46	163.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
9.43	113.15	164.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
9.49	113.84	165.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
9.54	114.53	166.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
9.60	115.22	167.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
9.66	115.91	168.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
9.72	116.60	169.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
9.77	117.29	170.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
9.83	117.98	171.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
9.89	118.67	172.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
9.95	119.36	173.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
10.00	120.05	174.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
10.06	120.74	175.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
10.12	121.43	176.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
10.18	122.12	177.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00

Time			Proportion of patients at end of cycle placebo/BSC				Proportion of patients at end of cycle pem/BSC			
Years	Months	Cycles	Pre-progression	Post-progression	Dead	Check	Pre-progression	Post-progression	Dead	Check
10.23	122.81	178.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
10.29	123.50	179.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
10.35	124.19	180.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
10.41	124.88	181.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
10.46	125.57	182.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
10.52	126.26	183.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
10.58	126.95	184.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
10.64	127.64	185.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
10.69	128.33	186.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
10.75	129.02	187.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
10.81	129.71	188.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
10.87	130.40	189.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
10.92	131.09	190.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
10.98	131.78	191.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
11.04	132.47	192.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
11.10	133.16	193.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
11.15	133.85	194.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
11.21	134.54	195.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
11.27	135.23	196.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
11.33	135.92	197.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
11.38	136.61	198.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
11.44	137.30	199.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
11.50	137.99	200.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
11.56	138.68	201.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
11.61	139.37	202.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
11.67	140.06	203.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
11.73	140.75	204.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
11.79	141.44	205.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
11.84	142.13	206.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
11.90	142.82	207.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
11.96	143.51	208.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
12.02	144.20	209.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
12.07	144.89	210.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
12.13	145.58	211.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
12.19	146.27	212.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
12.25	146.96	213.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
12.30	147.65	214.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
12.36	148.34	215.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
12.42	149.03	216.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
12.48	149.72	217.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
12.53	150.41	218.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
12.59	151.10	219.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
12.65	151.79	220.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
12.71	152.48	221.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
12.76	153.17	222.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00

Time			Proportion of patients at end of cycle placebo/BSC				Proportion of patients at end of cycle pem/BSC			
Years	Months	Cycles	Pre-progression	Post-progression	Dead	Check	Pre-progression	Post-progression	Dead	Check
12.82	153.86	223.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
12.88	154.55	224.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
12.94	155.24	225.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
12.99	155.93	226.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
13.05	156.62	227.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
13.11	157.31	228.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
13.17	158.00	229.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
13.22	158.69	230.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
13.28	159.38	231.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
13.34	160.07	232.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
13.40	160.76	233.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
13.45	161.45	234.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
13.51	162.14	235.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
13.57	162.83	236.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
13.63	163.52	237.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
13.68	164.21	238.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
13.74	164.90	239.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
13.80	165.59	240.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
13.86	166.28	241.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
13.91	166.97	242.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
13.97	167.66	243.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
14.03	168.34	244.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
14.09	169.03	245.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
14.14	169.72	246.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
14.20	170.41	247.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
14.26	171.10	248.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
14.32	171.79	249.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
14.37	172.48	250.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
14.43	173.17	251.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
14.49	173.86	252.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
14.55	174.55	253.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
14.60	175.24	254.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
14.66	175.93	255.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
14.72	176.62	256.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
14.78	177.31	257.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
14.83	178.00	258.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
14.89	178.69	259.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
14.95	179.38	260.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
15.01	180.07	261.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
15.06	180.76	262.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
15.12	181.45	263.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
15.18	182.14	264.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
15.24	182.83	265.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
15.29	183.52	266.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
15.35	184.21	267.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00

Time			Proportion of patients at end of cycle placebo/BSC				Proportion of patients at end of cycle pem/BSC			
Years	Months	Cycles	Pre-progression	Post-progression	Dead	Check	Pre-progression	Post-progression	Dead	Check
15.41	184.90	268.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
15.47	185.59	269.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
15.52	186.28	270.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
15.58	186.97	271.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
15.64	187.66	272.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
15.70	188.35	273.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
15.75	189.04	274.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
15.81	189.73	275.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
15.87	190.42	276.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
15.93	191.11	277.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
15.98	191.80	278.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
16.04	192.49	279.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
16.10	193.18	280.00	0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00

Notes: Results reported for adjusted model with risk equations populated with average covariates.

Appendix 2 Quality-adjusted survival time in cycles for each health state and total QALYs per cycle (Discounted)

Total QA Survival placebo/BSC				Total QA Survival pem/BSC			
Total life cycles (21 days)	Pre-progression	Post progression	Total QA Survival	Total life cycles (21 days)	Pre-progression	Post progression	Total QA Survival
358.38	266.04	6.04	272.08	358.62	264.17	1.61	265.78
355.24	234.18	30.03	264.21	356.57	249.03	12.31	261.34
348.58	189.91	63.48	253.39	352.02	221.93	32.77	254.71
339.15	152.25	89.61	241.85	345.28	192.72	54.09	246.81
327.86	123.38	106.93	230.31	336.93	166.50	71.81	238.32
315.45	101.48	117.51	218.99	327.44	144.27	85.29	229.56
302.43	84.69	123.30	207.98	317.20	125.72	95.02	220.74
289.18	71.60	125.76	197.36	306.52	110.27	101.69	211.97
275.95	61.24	125.92	187.16	295.62	97.36	105.97	203.33
262.94	52.90	124.49	177.40	284.66	86.49	108.39	194.88
250.25	46.12	121.97	168.09	273.77	77.28	109.39	186.67
237.98	40.52	118.71	159.23	263.04	69.42	109.29	178.71
226.18	35.84	114.98	150.82	252.54	62.66	108.37	171.02
214.87	31.91	110.94	142.85	242.31	56.81	106.81	163.63
204.06	28.57	106.74	135.31	232.39	51.72	104.79	156.52
193.77	25.71	102.47	128.17	222.80	47.27	102.43	149.70
183.98	23.24	98.19	121.43	213.55	43.35	99.81	143.16
168.78	20.38	90.79	111.17	197.72	38.53	93.75	132.28
160.26	18.57	86.79	105.36	189.46	35.55	90.95	126.50
152.19	16.99	82.89	99.88	181.53	32.89	88.09	120.99
144.55	15.58	79.12	94.71	173.92	30.51	85.20	115.72
137.31	14.34	75.48	89.82	166.64	28.37	82.32	110.69
130.46	13.23	71.98	85.21	159.67	26.44	79.45	105.89
123.98	12.24	68.62	80.87	153.00	24.69	76.62	101.31
117.86	11.36	65.41	76.76	146.63	23.10	73.85	96.95
112.06	10.56	62.33	72.89	140.53	21.66	71.13	92.79
106.57	9.83	59.40	69.23	134.71	20.34	68.48	88.82
101.39	9.18	56.60	65.78	129.15	19.13	65.91	85.04
96.48	8.58	53.93	62.52	123.83	18.02	63.41	81.43
91.83	8.04	51.39	59.43	118.76	17.00	60.99	77.99
87.44	7.55	48.97	56.52	113.91	16.06	58.65	74.71
83.28	7.09	46.67	53.77	109.28	15.19	56.39	71.58
79.33	6.68	44.49	51.17	104.86	14.39	54.22	68.60
75.60	6.29	42.41	48.70	100.63	13.64	52.11	65.76
69.63	5.74	39.06	44.80	93.33	12.51	48.40	60.91
66.39	5.43	37.25	42.67	89.60	11.89	46.52	58.41
63.33	5.13	35.52	40.66	86.04	11.31	44.71	56.02
60.42	4.86	33.88	38.75	82.64	10.77	42.97	53.74
57.66	4.62	32.35	36.96	79.38	10.28	41.33	51.60
55.04	4.39	30.91	35.30	76.27	9.82	39.78	49.59
52.56	4.18	29.54	33.72	73.30	9.39	38.29	47.67
50.20	3.98	28.24	32.22	70.46	8.98	36.85	45.84
47.97	3.80	27.00	30.79	67.74	8.60	35.48	44.08

Total QA Survival placebo/BSC				Total QA Survival pem/BSC			
Total life cycles (21 days)	Pre-progression	Post progression	Total QA Survival	Total life cycles (21 days)	Pre-progression	Post progression	Total QA Survival
45.84	3.62	25.81	29.44	65.14	8.24	34.15	42.40
43.82	3.46	24.69	28.15	62.65	7.91	32.88	40.79
41.90	3.31	23.62	26.93	60.27	7.59	31.66	39.25
40.08	3.17	22.60	25.76	57.98	7.29	30.49	37.78
38.34	3.03	21.63	24.66	55.80	7.01	29.36	36.36
36.69	2.91	20.70	23.60	53.71	6.74	28.27	35.01
35.12	2.79	19.82	22.60	51.71	6.49	27.23	33.72
33.63	2.67	18.98	21.65	49.79	6.25	26.23	32.48
32.20	2.57	18.17	20.74	47.95	6.02	25.27	31.29
29.80	2.38	16.82	19.20	44.63	5.61	23.52	29.13
28.56	2.29	16.11	18.41	43.00	5.41	22.67	28.07
27.37	2.21	15.44	17.65	41.43	5.22	21.84	27.06
26.24	2.12	14.80	16.92	39.93	5.04	21.05	26.09
25.16	2.04	14.19	16.23	38.49	4.87	20.29	25.16
24.13	1.97	13.60	15.57	37.11	4.71	19.56	24.26
23.14	1.90	13.04	14.94	35.79	4.55	18.85	23.40
22.21	1.83	12.51	14.34	34.52	4.40	18.18	22.58
21.31	1.77	12.00	13.77	33.30	4.26	17.53	21.79
20.46	1.71	11.52	13.22	32.13	4.13	16.90	21.03
19.64	1.65	11.05	12.70	31.00	4.00	16.30	20.30
18.86	1.60	10.61	12.20	29.92	3.87	15.73	19.60
18.12	1.54	10.18	11.73	28.88	3.75	15.17	18.93
17.41	1.49	9.78	11.27	27.88	3.64	14.64	18.28
16.73	1.45	9.39	10.83	26.93	3.53	14.12	17.66
16.08	1.40	9.02	10.42	26.00	3.43	13.63	17.06
15.45	1.36	8.66	10.02	25.12	3.33	13.15	16.48
14.36	1.27	8.04	9.31	23.44	3.12	12.26	15.39
13.81	1.23	7.72	8.96	22.65	3.04	11.84	14.87
13.28	1.19	7.42	8.62	21.89	2.95	11.43	14.38
12.78	1.16	7.13	8.29	21.16	2.87	11.03	13.90
12.29	1.12	6.86	7.98	20.45	2.79	10.65	13.44
11.83	1.09	6.59	7.69	19.77	2.71	10.29	13.00
11.39	1.06	6.34	7.40	19.12	2.64	9.94	12.58
10.96	1.03	6.10	7.13	18.49	2.57	9.60	12.17
10.56	1.00	5.87	6.87	17.89	2.50	9.27	11.77
10.17	0.97	5.64	6.62	17.30	2.44	8.95	11.39
9.80	0.95	5.43	6.38	16.74	2.37	8.65	11.03
9.44	0.92	5.22	6.14	16.20	2.31	8.36	10.67
9.09	0.90	5.03	5.92	15.68	2.26	8.08	10.33
8.76	0.87	4.84	5.71	15.17	2.20	7.81	10.00
8.45	0.85	4.66	5.51	14.69	2.14	7.54	9.69
8.14	0.83	4.48	5.31	14.22	2.09	7.29	9.38
7.85	0.81	4.32	5.12	13.77	2.04	7.05	9.09
7.32	0.76	4.02	4.78	12.88	1.93	6.58	8.51
7.06	0.74	3.87	4.61	12.48	1.88	6.36	8.24

Total QA Survival placebo/BSC				Total QA Survival pem/BSC			
Total life cycles (21 days)	Pre-progression	Post progression	Total QA Survival	Total life cycles (21 days)	Pre-progression	Post progression	Total QA Survival
6.81	0.72	3.73	4.45	12.09	1.83	6.15	7.99
6.57	0.70	3.59	4.29	11.71	1.79	5.95	7.74
6.34	0.68	3.46	4.14	11.35	1.75	5.75	7.50
6.12	0.67	3.33	4.00	11.00	1.71	5.56	7.27
5.91	0.65	3.21	3.86	10.66	1.67	5.38	7.05
5.70	0.64	3.09	3.73	10.33	1.63	5.20	6.84
5.51	0.62	2.98	3.60	10.01	1.60	5.03	6.63
5.32	0.61	2.87	3.48	9.71	1.56	4.87	6.43
5.14	0.59	2.77	3.36	9.41	1.53	4.71	6.24
4.96	0.58	2.67	3.25	9.13	1.49	4.56	6.05
4.79	0.57	2.58	3.14	8.85	1.46	4.41	5.87
4.63	0.55	2.48	3.04	8.59	1.43	4.27	5.70
4.48	0.54	2.40	2.94	8.33	1.40	4.13	5.53
4.33	0.53	2.31	2.84	8.08	1.37	4.00	5.37
4.18	0.52	2.23	2.75	7.84	1.34	3.87	5.21
4.04	0.51	2.15	2.66	7.61	1.31	3.74	5.06
3.78	0.48	2.00	2.48	7.14	1.24	3.50	4.74
3.65	0.47	1.93	2.40	6.93	1.22	3.39	4.61
3.53	0.46	1.87	2.32	6.72	1.19	3.28	4.47
3.42	0.45	1.80	2.25	6.53	1.17	3.17	4.34
3.31	0.44	1.74	2.17	6.34	1.15	3.07	4.22
3.20	0.43	1.68	2.11	6.15	1.12	2.97	4.10
3.09	0.42	1.62	2.04	5.98	1.10	2.88	3.98
2.99	0.41	1.56	1.97	5.80	1.08	2.79	3.87
2.90	0.40	1.51	1.91	5.64	1.06	2.70	3.76
2.81	0.39	1.46	1.85	5.48	1.04	2.61	3.65
2.72	0.39	1.40	1.79	5.32	1.02	2.53	3.55
2.63	0.38	1.36	1.74	5.17	1.00	2.45	3.45
2.55	0.37	1.31	1.68	5.02	0.98	2.37	3.35
2.47	0.36	1.26	1.63	4.88	0.96	2.30	3.26
2.39	0.36	1.22	1.58	4.74	0.95	2.23	3.17
2.31	0.35	1.18	1.53	4.61	0.93	2.15	3.08
2.24	0.34	1.14	1.48	4.48	0.91	2.09	3.00
2.10	0.33	1.06	1.39	4.21	0.86	1.95	2.82
2.03	0.32	1.03	1.35	4.09	0.85	1.89	2.74
1.97	0.31	0.99	1.30	3.98	0.83	1.83	2.67
1.91	0.31	0.96	1.26	3.87	0.82	1.77	2.59
1.85	0.30	0.92	1.23	3.76	0.81	1.72	2.52
1.79	0.30	0.89	1.19	3.66	0.79	1.66	2.46
1.74	0.29	0.86	1.15	3.56	0.78	1.61	2.39
1.69	0.29	0.83	1.12	3.46	0.76	1.56	2.33
1.64	0.28	0.81	1.09	3.37	0.75	1.51	2.26
1.59	0.28	0.78	1.05	3.28	0.74	1.46	2.20
1.54	0.27	0.75	1.02	3.19	0.73	1.42	2.14
1.49	0.27	0.73	0.99	3.10	0.71	1.37	2.09

Total QA Survival placebo/BSC				Total QA Survival pem/BSC			
Total life cycles (21 days)	Pre-progression	Post progression	Total QA Survival	Total life cycles (21 days)	Pre-progression	Post progression	Total QA Survival
1.45	0.26	0.70	0.96	3.02	0.70	1.33	2.03
1.40	0.26	0.68	0.93	2.94	0.69	1.29	1.98
1.36	0.25	0.65	0.91	2.86	0.68	1.25	1.93
1.32	0.25	0.63	0.88	2.79	0.67	1.21	1.88
1.28	0.24	0.61	0.86	2.71	0.66	1.17	1.83
1.25	0.24	0.59	0.83	2.64	0.65	1.13	1.78
1.17	0.23	0.55	0.78	2.48	0.61	1.06	1.68
1.13	0.22	0.53	0.76	2.42	0.60	1.03	1.63
1.10	0.22	0.51	0.73	2.36	0.59	1.00	1.59
1.07	0.22	0.50	0.71	2.29	0.59	0.96	1.55
1.04	0.21	0.48	0.69	2.23	0.58	0.93	1.51
1.01	0.21	0.46	0.67	2.18	0.57	0.90	1.47
0.98	0.21	0.45	0.65	2.12	0.56	0.88	1.43
0.95	0.20	0.43	0.64	2.07	0.55	0.85	1.40
0.92	0.20	0.42	0.62	2.01	0.54	0.82	1.36
0.90	0.20	0.40	0.60	1.96	0.53	0.80	1.33
0.87	0.19	0.39	0.58	1.91	0.53	0.77	1.30
0.85	0.19	0.38	0.57	1.86	0.52	0.75	1.26
0.82	0.19	0.37	0.55	1.81	0.51	0.72	1.23
0.80	0.18	0.35	0.54	1.77	0.50	0.70	1.20
0.78	0.18	0.34	0.52	1.72	0.49	0.68	1.17
0.75	0.18	0.33	0.51	1.68	0.49	0.65	1.14
0.73	0.18	0.32	0.49	1.64	0.48	0.63	1.11
0.69	0.17	0.30	0.46	1.54	0.46	0.59	1.05
0.67	0.16	0.29	0.45	1.50	0.45	0.57	1.02
0.65	0.16	0.28	0.44	1.47	0.44	0.56	1.00
0.63	0.16	0.27	0.43	1.43	0.44	0.54	0.97
0.62	0.16	0.26	0.42	1.39	0.43	0.52	0.95
0.60	0.15	0.25	0.40	1.36	0.43	0.50	0.93
0.58	0.15	0.24	0.39	1.33	0.42	0.49	0.91
0.57	0.15	0.23	0.38	1.29	0.41	0.47	0.88
0.55	0.15	0.22	0.37	1.26	0.41	0.45	0.86
0.54	0.15	0.22	0.36	1.23	0.40	0.44	0.84
0.52	0.14	0.21	0.35	1.20	0.40	0.43	0.82
0.51	0.14	0.20	0.34	1.17	0.39	0.41	0.80
0.49	0.14	0.19	0.33	1.14	0.39	0.40	0.78
0.48	0.14	0.19	0.33	1.12	0.38	0.38	0.76
0.47	0.14	0.18	0.32	1.09	0.38	0.37	0.75
0.45	0.13	0.17	0.31	1.06	0.37	0.36	0.73
0.44	0.13	0.17	0.30	1.04	0.37	0.35	0.71
0.42	0.13	0.16	0.28	0.98	0.35	0.32	0.67
0.41	0.12	0.15	0.28	0.95	0.34	0.31	0.66
0.39	0.12	0.15	0.27	0.93	0.34	0.30	0.64
0.38	0.12	0.14	0.26	0.91	0.33	0.29	0.63
0.37	0.12	0.14	0.25	0.89	0.33	0.28	0.61

Total QA Survival placebo/BSC				Total QA Survival pem/BSC			
Total life cycles (21 days)	Pre-progression	Post progression	Total QA Survival	Total life cycles (21 days)	Pre-progression	Post progression	Total QA Survival
0.36	0.12	0.13	0.25	0.87	0.33	0.27	0.60
0.35	0.12	0.13	0.24	0.85	0.32	0.26	0.58
0.35	0.11	0.12	0.24	0.83	0.32	0.25	0.57
0.34	0.11	0.12	0.23	0.81	0.31	0.24	0.56
0.33	0.11	0.11	0.22	0.79	0.31	0.23	0.54
0.32	0.11	0.11	0.22	0.77	0.31	0.23	0.53
0.31	0.11	0.10	0.21	0.75	0.30	0.22	0.52
0.30	0.11	0.10	0.21	0.73	0.30	0.21	0.51
0.29	0.11	0.10	0.20	0.72	0.29	0.20	0.50
0.29	0.10	0.09	0.20	0.70	0.29	0.19	0.49
0.28	0.10	0.09	0.19	0.68	0.29	0.19	0.47
0.27	0.10	0.09	0.19	0.67	0.28	0.18	0.46
0.27	0.10	0.08	0.18	0.65	0.28	0.17	0.45
0.25	0.10	0.08	0.17	0.62	0.27	0.16	0.43
0.24	0.09	0.07	0.17	0.60	0.26	0.15	0.42
0.24	0.09	0.07	0.16	0.59	0.26	0.15	0.41
0.23	0.09	0.07	0.16	0.57	0.26	0.14	0.40
0.23	0.09	0.07	0.16	0.56	0.25	0.14	0.39
0.22	0.09	0.06	0.15	0.55	0.25	0.13	0.38
0.21	0.09	0.06	0.15	0.54	0.25	0.13	0.37
0.21	0.09	0.06	0.14	0.52	0.25	0.12	0.37
0.20	0.09	0.05	0.14	0.51	0.24	0.12	0.36
0.20	0.09	0.05	0.14	0.50	0.24	0.11	0.35
0.19	0.08	0.05	0.13	0.49	0.24	0.11	0.34
0.19	0.08	0.05	0.13	0.48	0.23	0.10	0.34
0.18	0.08	0.05	0.13	0.47	0.23	0.10	0.33
0.18	0.08	0.04	0.13	0.46	0.23	0.09	0.32
0.18	0.08	0.04	0.12	0.45	0.23	0.09	0.31
0.17	0.08	0.04	0.12	0.44	0.22	0.08	0.31
0.17	0.08	0.04	0.12	0.43	0.22	0.08	0.30
0.16	0.08	0.03	0.11	0.40	0.21	0.07	0.28
0.15	0.07	0.03	0.11	0.40	0.21	0.07	0.28
0.15	0.07	0.03	0.10	0.39	0.21	0.07	0.27
0.15	0.07	0.03	0.10	0.38	0.20	0.06	0.27
0.14	0.07	0.03	0.10	0.37	0.20	0.06	0.26
0.14	0.07	0.03	0.10	0.36	0.20	0.06	0.26
0.14	0.07	0.03	0.10	0.35	0.20	0.05	0.25
0.13	0.07	0.02	0.09	0.35	0.20	0.05	0.25
0.13	0.07	0.02	0.09	0.34	0.19	0.05	0.24
0.13	0.07	0.02	0.09	0.33	0.19	0.04	0.24
0.12	0.07	0.02	0.09	0.32	0.19	0.04	0.23
0.12	0.07	0.02	0.08	0.32	0.19	0.04	0.23
0.12	0.07	0.02	0.08	0.31	0.19	0.04	0.22
0.11	0.06	0.02	0.08	0.30	0.18	0.03	0.22
0.11	0.06	0.02	0.08	0.30	0.18	0.03	0.21

Total QA Survival placebo/BSC				Total QA Survival pem/BSC			
Total life cycles (21 days)	Pre-progression	Post progression	Total QA Survival	Total life cycles (21 days)	Pre-progression	Post progression	Total QA Survival
0.11	0.06	0.01	0.08	0.29	0.18	0.03	0.21
0.11	0.06	0.01	0.08	0.28	0.18	0.03	0.20
0.10	0.06	0.01	0.07	0.28	0.18	0.02	0.20
0.10	0.06	0.01	0.07	0.26	0.17	0.02	0.19
0.10	0.06	0.01	0.07	0.26	0.17	0.02	0.18
0.09	0.06	0.01	0.07	0.25	0.16	0.02	0.18
0.09	0.06	0.01	0.07	0.25	0.16	0.01	0.18
0.09	0.06	0.01	0.06	0.24	0.16	0.01	0.17
0.09	0.06	0.01	0.06	0.24	0.16	0.01	0.17
0.09	0.06	0.01	0.06	0.23	0.16	0.01	0.17
0.08	0.05	0.00	0.06	0.23	0.16	0.01	0.16
0.08	0.05	0.00	0.06	0.22	0.15	0.01	0.16
0.08	0.05	0.00	0.06	0.22	0.15	0.00	0.16
0.08	0.05	0.00	0.06	0.21	0.15	0.00	0.15
0.08	0.05	0.00	0.05	0.21	0.15	0.00	0.15
0.07	0.05	0.00	0.05	0.20	0.15	0.00	0.15
0.07	0.05	0.00	0.05	0.20	0.14	0.00	0.14
0.07	0.05	0.00	0.05	0.20	0.14	0.00	0.14
0.07	0.05	0.00	0.05	0.19	0.14	0.00	0.14
0.07	0.05	0.00	0.05	0.19	0.14	0.00	0.14
0.06	0.05	0.00	0.05	0.18	0.13	0.00	0.13
0.06	0.05	0.00	0.05	0.17	0.13	0.00	0.13
0.06	0.04	0.00	0.04	0.17	0.12	0.00	0.12
0.06	0.04	0.00	0.04	0.17	0.12	0.00	0.12
0.06	0.04	0.00	0.04	0.16	0.12	0.00	0.12
0.06	0.04	0.00	0.04	0.16	0.12	0.00	0.12
0.06	0.04	0.00	0.04	0.16	0.11	0.00	0.11
0.05	0.04	0.00	0.04	0.15	0.11	0.00	0.11
0.05	0.04	0.00	0.04	0.15	0.11	0.00	0.11
0.05	0.04	0.00	0.04	0.15	0.11	0.00	0.11
0.05	0.04	0.00	0.04	0.14	0.10	0.00	0.10
0.05	0.04	0.00	0.04	0.14	0.10	0.00	0.10
0.05	0.04	0.00	0.04	0.14	0.10	0.00	0.10
0.05	0.03	0.00	0.03	0.14	0.10	0.00	0.10
0.05	0.03	0.00	0.03	0.13	0.10	0.00	0.10
0.05	0.03	0.00	0.03	0.13	0.09	0.00	0.09
0.04	0.03	0.00	0.03	0.13	0.09	0.00	0.09
0.04	0.03	0.00	0.03	0.12	0.09	0.00	0.09
0.04	0.03	0.00	0.03	0.12	0.09	0.00	0.09
0.04	0.03	0.00	0.03	0.12	0.08	0.00	0.08
0.04	0.03	0.00	0.03	0.11	0.08	0.00	0.08
0.04	0.03	0.00	0.03	0.11	0.08	0.00	0.08
0.04	0.03	0.00	0.03	0.11	0.08	0.00	0.08
0.04	0.03	0.00	0.03	0.11	0.08	0.00	0.08
0.04	0.03	0.00	0.03	0.11	0.08	0.00	0.08

Total QA Survival placebo/BSC				Total QA Survival pem/BSC			
Total life cycles (21 days)	**Pre-progression**	**Post progression**	**Total QA Survival**	**Total life cycles (21 days)**	**Pre-progression**	**Post progression**	**Total QA Survival**
0.04	0.03	0.00	0.03	0.10	0.07	0.00	0.07
0.03	0.02	0.00	0.02	0.10	0.07	0.00	0.07
0.03	0.02	0.00	0.02	0.10	0.07	0.00	0.07
0.03	0.02	0.00	0.02	0.10	0.07	0.00	0.07
0.03	0.02	0.00	0.02	0.10	0.07	0.00	0.07
0.03	0.02	0.00	0.02	0.09	0.07	0.00	0.07
0.03	0.02	0.00	0.02	0.09	0.07	0.00	0.07
0.03	0.02	0.00	0.02	0.09	0.07	0.00	0.07
0.03	0.02	0.00	0.02	0.09	0.06	0.00	0.06
0.03	0.02	0.00	0.02	0.09	0.06	0.00	0.06
0.03	0.02	0.00	0.02	0.08	0.06	0.00	0.06
0.03	0.02	0.00	0.02	0.08	0.06	0.00	0.06
Total LYs	**Total QALYs pre-prog**	**Total QALYs post-prog**	**Total QALYs**	**Total LYs**	**Total QALYs pre-prog**	**Total QALYs post-prog**	**Total QALYs**
1.33	**0.31**	**0.59**	**0.90**	**1.60**	**0.45**	**0.63**	**1.08**

Notes: Results reported for adjusted model with risk equations populated with average covariates.

Addendum to Lilly submission and audit trail

Workbook Alimta UK adaptation 181112.xlsm

Changes that have affected base case results or sensitivity analyses:

- **Worksheet "jmen_resource"**
    - Cells F17-F21, F29-F33 formula amended to reflect correct adverse event name (e.g. "=(1-EXP(-E18))*cNausea") due to name referencing error (previously all cells had referenced cNeutro), the formula was also amended to change the rate per person cycle into a probability per cycle.
    - Cells E29-E32 formula amended to reflect BSC pre-progression person cycles due to cell referencing error (previously reflected PEM pre-progression person cycles).
    - Base case ICER changes from £49,258 to £49,278
- **Worksheet "resource"**
    - Cells E332 amended to 80 from 85 to reflect PARAMOUNT data (footnote also amended) due to data input error. This change then effects C305 and F305.
    - Base case ICER changes from £49,278 to £49,679
- **Worksheet "pem" and "bsc"**
    - Columns DH-DI. The costs of docetaxel and erlotinib were missing from total cost calculations for JMEN resource use scenario (model dated 111012 columns DR, DT and DW, DX).
    - Base case ICER changes from £49,679 to £47,576

Changes that have not affected default lifetime base case results or sensitivity analyses:

- **Worksheets "pem" and "bsc" (Markov trace)**
    - Columns BE and BQ. Formula amendment to prevent negative numbers in extreme scenarios (e.g. formula amended to "=IF((BD12+BE11-BT12)>0,BD12+BE11-BT12,0)")
    - Simplification of Markov trace layout for resource use (removed separate columns for JMEN cost data - columns DK-DO in the model dated 11/10/12). Checker cell included to cross validate resource use estimates (Column DS)
- **Worksheets "results2" and "results3"**
    - NICE submission results tables added to automate results generation
    - Macros created in VBA to run NICE submission results
- **Worksheets "parameters"**
    - Cells E163-I165 - change in location of variables propCTscans, propconsults, pchemohome (previously located in "resource" worksheet cells C172, C173 and C140), added into parameters sheet to automate sensitivity analyses for NICE

submission results. Note column E directly feeds into Markov trace. Columns F-I are used to restore default analyses. Worksheet “resource” Cells C172, C173 and C140 describe these resource use items and have been left in the model for reference purposes only. They no longer directly input in the Markov trace.

- Cells E174. Addition of analysis time into parameters sheet to automate sensitivity analysis on time horizon for lifetime analysis (e.g. 99% rather than 99.9% of patients who had died).

Word document: Alimta NICE submission_Merged_15th October 2012_final.doc

The following changes have been made to the original submission as a result of the changes to the model dated 151012 as detailed in the change audit on previous page. **Note:** page numbers refer to initial submission document.

- **Executive summary**

  We have reproduced the entire text of the executive summary for comprehensive review, however, only the cost-effectiveness results detailed below have been changed, and are highlighted in pink:

  - page 15: deterministic and probabilistic ICERs, probabilities of being cost-effective at £50,000 WTP threshold

  - page 16, Table 1: Base-case cost-effectiveness results

- **7.3 Clinical parameters and variables**

  - Section 7.3.6, page 109, Table 26 AE rates per cycle Placebo/BSC (fatigue and anaemia)

- **7.5 Resource identification, measurement and evaluation**

  - Section 7.5.7, page 130, Table 45 2011 costs updated due to input error in original submission (no change to model)

  - Section 7.5.7, page 130, Table 46 AE rates and total costs for PARAMOUNT (Adapted from TA190; AE data PARAMOUNT), columns Rate per 21-day cycle (placebo - fatigue and anaemia) and Cost per patient cycle Paramount

  - Section 7.5.7, page 131, Table 48 value per cycle for Treatment with AEs (pre-progression with Pem/BSC, pre-progression with placebo/BSC)

- **7.6 Sensitivity analysis**

  - Section 7.6.2, page 135 and 136, Table 49 AE costs

  - Section 7.6.2, page 136 Table 49 Relabelled HR OS and PFS as treatment effect OS and PFS

- **7.7 Results**

  - Section 7.7.4, page 141, Table 51 Model outputs by clinical outcomes, column Total Cost

- Section 7.7.5, page 142, Table 52 Summary of QALY gain by health state, absolute increment column
- Section 7.7.5, page 142, Table 53 Summary of costs by health state, all columns
- Section 7.7.5, page 143, Table 55 Summary of predicted resource use by category of cost, all columns
- Section 7.7.6, page 143, Table 56 Deterministic basecase results, and associated text
- Section 7.7.7, pages 144-148, Table 57 Deterministic sensitivity analysis, and associated text on page 150. Final sensitivity analysis deleted because full set of results provided for adjusted analysis in response to clarification question B1b.
- Section 7.7.7, pages 147, Table 57 Deterministic sensitivity analysis. Relabelled HR OS and PFS as treatment effect OS and PFS
- Section 7.7.7, page 149, Table 58 Sensitivity analysis: Alternative parametric distributions, and associated text on page 150
- Section 7.7.8, page 151, Table 59, Figure 16
- Section 7.7.8 page 152, Figure 17
- Section 7.7.10, page 153, deterministic and probabilistic ICERs, probabilities of being cost-effective at different thresholds.

- **8 Assessment of factors relevant to the NHS and other parties**
  - Section 8.5, page 164, Incremental costs for treating AEs for patients receiving pemetrexed were updated to £6.60 per cycle to reflect the changes made to AE costs in the jmen_resource worksheet of the model as described above
  - Section 8.5, page 164 and 165, Table 66 Adverse event cost modified, total cost per cycle and total cost per patient modified based on change in AE cost
  - Section 8.7, page 167, The estimated budget impact in the first 5 years following recommendation has been updated to include the change in AE cost
  - Section 8.7, page 167, Table 72 Cost with pemetrexed and net budget impact updated include change in AE cost

Revised text, tables and figures for submission following changes to unadjusted economic model

Executive summary

Please provide an executive summary that summarises the key sections of the submission. All statements should be directly relevant to the decision problem, be evidence-based when possible and clearly reference the relevant section of the submission. The summary should cover the following items.

Executive summary

Lung cancer

Improving survival in lung cancer patients is a key government priority as shown by its inclusion in the NHS Outcomes Framework 2011/2012. Lung cancer is the leading cause of cancer-related death in England and Wales (Cancer Research UK 2010), with about a third of patients dying within one year after diagnosis. Survival in lung cancer patients is the worst among the 'big four' cancers (lung, breast, bowel and prostate).

Survival rates for lung cancer in both men and women have improved over the last two decades (Cancer Research UK). One-year survival in men increased from 15% in the 1970s to 29% in 2005-2009. 5-year and 10-year survival rates increased too though at a slower pace. These rates possibly do not reflect the technological advances that occurred later in the mid to late-2000s, i.e., availability of pharmacological treatment options like pemetrexed, and the biological agents erlotinib and gefitinib for use in the first-line setting which have since transformed the standard of care for patients with NSCLC in the UK.

Treatment of lung cancer

NSCLC is asymptomatic in the early stages of the disease. Since lung cancer is largely asymptomatic in the early stages, patients usually present at an advanced stage, by which time their cancer is likely to be inoperable. For those with non-resectable cancer, the treatment options are chemotherapy and radiotherapy. First-line chemotherapy treatment is given following diagnosis with the aim of reducing tumour size (response), improving progression-free and overall survival whilst maintaining health-related quality of life (HRQL). Maintenance chemotherapy treatment aims to prolong the response achieved in the first-line treatment setting in patients whose disease has not progressed, i.e. to extend the duration of disease control thereby maintaining HRQL, improving progression-free survival and overall survival with minimal side-effects. Second-line treatment aims to relieve symptoms due to disease progression.

Maintenance treatment in the NHS

The administration of an active maintenance treatment immediately following first-line therapy improves overall survival in NSCLC by allowing more patients to benefit from additional treatment while tumour and symptom burden is low, patient tolerance is high and before the inevitable deterioration in performance status and disease progression occurs. Market research data show that currently in the NHS only 6% of non-squamous NSCLC patients who receive first-line treatment go on to receive maintenance treatment. Although these figures appear low, they reflect the fact that active maintenance treatment for NSCLC is a relatively new concept with the first active treatment (pemetrexed for switch maintenance) being licensed for use in the NHS as recently as 2009, and has yet to become embedded within clinical practice in the NHS.

Pemetrexed in maintenance treatment of non-squamous NSCLC

Pemetrexed was previously licensed for the treatment of locally advanced, metastatic (stage IIIB/IV) non-squamous NSCLC in the first-line and second-line settings and for maintenance treatment in patients without disease progression following first-line therapy with non-pemetrexed containing regimens (i.e., "switch maintenance"). The recent (24th October 2011) amendment to the licence allows the use of pemetrexed in advanced, metastatic (stage IIIB/IV) non-squamous NSCLC in patients who have not progressed after four cycles of pemetrexed/cisplatin first-line treatment.

There are two licensed maintenance treatment options available in the NHS, pemetrexed and erlotinib. Pemetrexed has been recommended by NICE for switch maintenance treatment of non-squamous NSCLC (TA 190). Erlotinib is not recommended by NICE for maintenance treatment of NSCLC.

Pemetrexed continuation maintenance

Pemetrexed is now licensed for treatment of patients with locally advanced or metastatic, non-squamous NSCLC who have not progressed following four cycles of pemetrexed/cisplatin first-line. The current submission presents the clinical and cost-effectiveness case for pemetrexed continuation maintenance in this population.

The PARAMOUNT study

Since pemetrexed/cisplatin is the standard of care for first-line non-squamous NSCLC in the NHS, there was a clinical demand to determine whether patients receiving pemetrexed/cisplatin first-line would benefit from further treatment with pemetrexed monotherapy in the maintenance setting. The PARAMOUNT study was designed to address this question. Key results from this study are as follows:

- Pemetrexed-treated patients experienced a significantly higher PFS benefit of 1.28 months over placebo/BSC (median overall PFS at final data lock of 4.44 months compared to 2.76 months) and a 40% reduction in risk of disease progression (HR for pemetrexed/BSC vs placebo/BSC: 0.60).
- Pemetrexed-treated patients experienced significant OS benefit of 2.85 months (median overall survival of 13.86 months vs 11.01 months for pemetrexed/BSC vs placebo/BSC, log-rank p=0.0195) and a 22% reduction in the risk of death compared to placebo-treated patients (HR for pemetrexed/BSC vs placebo/BSC: 0.78). This OS benefit was in addition to that experienced by patients treated with pemetrexed/cisplatin in the first-line treatment setting.
- 1-year and 2-year survival rates for pemetrexed treated patients were 58% and 32% respectively, compared to 45% and 21% for placebo treated patients.
- EQ-5D data were collected in PARAMOUNT with compliance rates of over 80% in the maintenance phase. No statistically significant differences in changes from baseline in EQ-5D index scores were seen between pemetrexed/BSC and placebo/BSC.
- The analysis of performance status showed that patients were able to maintain their performance status and there were no between group differences in changes in performance status from baseline. These data show that patients can tolerate long-term pemetrexed continuation maintenance without significant detrimental impact on QoL.
- Pemetrexed was well-tolerated in PARAMOUNT, with an adverse events profile consistent with the known safety profile of pemetrexed given as single-agent switch maintenance treatment in the JMEN study and second-line treatment in the JMEI study. The grade 3/4 toxicities that were significantly different between pemetrexed and placebo were neutropenia (5.8% vs 0%, p=0.0002), anaemia (6.4% vs 0.6% p=0.001) and fatigue (4.7% vs 1.1%, p=0.044).

Patient perspective on pemetrexed continuation maintenance

The implications of the PARAMOUNT study for patients suffering from this terminal disease are as follows:

- Pemetrexed continuation maintenance makes it possible for clinicians to give patients the most effective treatment (pemetrexed/cisplatin) upfront, so that patients are able get the most benefit in terms of increased survival and symptom palliation (Scagliotti et al 2008). Patients can continue pemetrexed monotherapy enabling them to maintain benefit of first-line treatment and avoid cisplatin-associated toxicities like nausea, vomiting, ototoxicity and neurotoxicity as well as hospital stays for cisplatin-required hydration.
- Pemetrexed continuation maintenance improves the outlook for patients suffering from non-squamous NSCLC by providing them with an opportunity for increased survival while maintaining their performance status and without significant detrimental impact on their quality of life. Since patients are fit enough to receive treatment, this could potentially improve their chances of receiving further chemotherapy in the second-line setting.
- Pemetrexed as a single-agent treatment requires a ten-minute infusion once every three weeks and can be administered in chemotherapy units or in the community/at home. This has the added benefit of potentially moving care of these patients from the hospital into the community, which is more convenient for patients and carers.

Pemetrexed continuation maintenance fulfils all the criteria of the NICE 'End of Life' supplementary advice

Pemetrexed continuation maintenance fulfils all three criteria specified in NICE's 'Supplementary Advice for Appraising Life Extending, End of Life Treatments' and therefore the supplementary advice should be applied to this appraisal.

- Criterion 1: The cumulative population of patients eligible for pemetrexed treatment across all NSCLC indications and mesothelioma is **5,531** (4,034 NSCLC pts; 1,497 MPM pts), which is less than the population size implicitly set at < 7,000.
- Criterion 2: The overall survival benefit for patients treated with pemetrexed/BSC from the PARAMOUNT trial was 2.85 months. Due to the high censoring for OS data, an extrapolation of the trial survival data over a lifetime horizon was undertaken. This provided a modelled mean overall survival of 4.2 months in the basecase analysis (range from the parametric distributions explored: 3.4 to 4.7 months).
- Criterion 3: The median overall survival in England and Wales is lower than 24 months

Cost-effectiveness analysis

The economic analysis compared the cost-effectiveness of pemetrexed/BSC with that of placebo ("watch and wait")/BSC as continuation maintenance in patients with locally advanced, metastatic NSCLC (stage IIIB/IV) who have not progressed following four cycles of first-line pemetrexed/cisplatin. A cost-effectiveness analysis has been conducted from the perspective of the NHS in England and Wales with a lifetime horizon. The analysis is based on a Markov model populated with individual patient data (IPD) from the PARAMOUNT study.

The survival models developed from the IPD are extrapolated and incorporated into an Excel-based state-transition Markov model.

The economic evaluation gives a deterministic ICER of £47,576 and a probabilistic ICER of £48,218. A wide range of one-way sensitivity analyses have been conducted which demonstrates consistent results across a range of alternative plausible data inputs. The Cost Effectiveness Acceptability Curve (CEAC) shows that at a £50,000 WTP threshold pemetrexed/BSC is cost-effective in 54% of simulations.

Conclusion

Pemetrexed continuation maintenance offers patients who currently have no treatment options immediately following first-line treatment with pemetrexed/cisplatin, but who are appropriate candidates for active chemotherapy, a cost-effective treatment under conventional thresholds when the end of life criteria are applied.

Table 1. Base-case cost-effectiveness results

	Pemetrexed	Placebo	Incremental results
Therapy costs*	£13,125	£0	£13,125
Adverse event costs	£64	£4	£59
Follow up care costs	£10,177	£11,170	-£993
Terminal care costs	£2,699	£2,738	-£39
Total costs	**£26,064**	**£13,912**	**£12,153**
LYG	1.7047	1.3537	0.3511
QALYs	1.1743	0.9188	0.2554
ICER			**£47,576**

Note: * Therapy costs includes drug acquisition, delivery and additional monitoring costs (See table 5, Section 7.7.5 for further details of cost categories);; LYG, life years gained; QALY(s), quality-adjusted life year(s); ICER, incremental cost-effectiveness ratio

Table 26. Summary of variables applied in the economic model

Variable	Value	CI (distribution)	Reference to section in submission
Age, median (range)	61 (32-83) years	N/A	Section 6.3.4
Gender	58% male; 42% female	N/A	Section 6.3.4
Body Surface Area (BSA) m^2	1.79m^2 based on mean UK BSA values weighted by gender from PARAMOUNT	Normal distribution of BSA by gender	Section 7.5
Clinical Outcomes:			
Overall survival	Incremental 4.21 months mean OS from randomisation. Extrapolated using gamma distribution in the basecase analysis.	Probabilistic estimates have been derived for KM data using the standard error associated with the observed failure rate per cycle. (Beta distribution) In the extrapolated period multivariable regression functions generated using KM data have been entered in the model along with Cholesky decompositions that account for correlations between parameters	Section 6.5
PFS	Incremental 3.25 months mean PFS from randomisation. Extrapolated using gamma distribution in the basecase analysis.		Section 6.5
Treatment discontinuation	5.09 cycles placebo and 7.95 cycles pemetrexed. Not extrapolated in the basecase analysis.		Section 6.5 (cycle data)
AE rates per cycle PEM/BSC	Neutropenia 0.0061	No CI available	Section 7.5.6
	Nausea & Vomiting 0.0008		
	Fatigue 0.0053		
	Anaemia 0.0066		
AE rates per cycle Placebo/BSC	Neutropenia 0.0000	No CI available	Section 7.5.6
	Nausea & Vomiting 0.0000		
	Fatigue 0.0019		
	Anaemia 0.0009		
Second-line chemotherapy use	Pem/BSC 64% Placebo/BSC 72%	Pem/BSC 58-68% Placebo/BSC 65-78% (Beta distribution)	Section 7.5.6
Utility values:			
Pre-progression >6 cycles prior to death	0.7758	Utility values derived from a mixed regression model. Multivariable regression functions generated using PARAMOUNT individual patient data have been entered in the model along with a Cholesky decomposition to account for correlated parameters. (CI for the coefficients derived from the regression model are provided in Table 28)	Section 7.4.9
Pre-progr >4 $\leq$ 6 cycles prior to death	0.7242		
Pre-progr > 2 < 4 cycles prior to death	0.6520		
Pre-progr 0-2 cycles prior to death	0.4099		
Post-progression >6 cycles prior to death	0.7028		
Post-progr >4 $\leq$ 6 cycles prior to death	0.6512		
Post-progr > 2 < 4 cycles prior to death	0.5790		
Post-progr 0-2 cycles prior to death	0.3369		

Table 45. Unit costs for common grade 3/4 adverse events in PARAMOUNT (Costs inflated from those used in TA190)

Grade 3-4 adverse events	Reported Cost Year	Cost per event (2009)	Cost per event inflated to 2011
Neutropenia	2009	£323.19	£345.13
Nausea and vomiting	2009	£628.04	£670.67
Fatigue	2009	£132.33	£141.31
Anaemia	2009	£570.68	£609.41

Table 46. AE rates and total costs for PARAMOUNT (Adapted from TA190; AE data PARAMOUNT)

Grade 3/4 AEs	Number of patients experiencing grade 3/4 AE	AE rate %	Rate per 21-day cycle	Cost per patient cycle PARAMOUNT
Placebo/BSC (n=180)				
Neutropenia	0	0.00%	0.0000	£0.00
Nausea / Vomiting	0	0.00%	0.0000	£0.00
Fatigue	2	1.10%	0.0019	£0.26
Anaemia	1	0.60%	0.0009	£0.57
Total cost for placebo/BSC				**£0.83**
Pem/BSC (n=359)				
Neutropenia	22	6.13%	0.0061	£2.09
Nausea / Vomiting	3	0.84%	0.0008	£0.56
Fatigue	19	5.29%	0.0053	£0.74
Anaemia	24	6.69%	0.0066	£4.03
Total cost for pem/BSC				**£7.43**

Table 48. List of health states and associated costs in the economic model

Health states	Costs applied	Value (per cycle) (See Section 7.5.5)
Pre-progression with pem/BSC	Pemetrexed acquisition	£1,440
	Pemetrexed delivery	£207.88
	Pemetrexed monitoring (consultant and CT scans)	£15.54
	BSC with active chemotherapy	£36.22
	Treatment of AEs	£7.43
Pre-progression with placebo/BSC	BSC without active chemotherapy	£72.44
	Treatment of AEs	£0.83
Post-progression with second-line chemotherapy	Docetaxel acquisition**	£1,023.00
	Erlotinib acquisition**	£976.47
	Docetaxel delivery**	£207.44
	Erlotinib delivery**	£128.44
	BSC with active chemotherapy**	£36.22
Note: ** These costs are only applied in those cycles when second-line chemotherapy is administered.	BSC without active chemotherapy, applied to remaining cycles after second-line chemotherapy has been discontinued	£72.44
	Terminal care, applied to the final cycle before death	£2,825.29
Post-progression with no second-line chemotherapy	BSC without active chemotherapy	£72.44
	Terminal care, applied to the final cycle before death	£2,825.29
Death	N/A	N/A

Table 49. Sensitivity analysis of parameter values and structural assumptions

Parameter	Basecase value	Range or alternative value(s)	Rationale and alternative data source
AE costs	£7.43 pem/BSC £0.83 placebo/BSC	+/- 10%	Assumption
AE and BSC costs	**AE costs:** £7.43 pem/BSC £0.83 placebo/BSC **BSC costs:** £36.22/cycle if on active chemo £72.44/cycle if not on active chemo	BSC drug costs applied to every cycle plus hospitalisation, blood transfusion data and palliative radiotherapy rates and associated NHS reference costs applied.	In the basecase analysis the methods for costing AE and BSC resources are consistent with TA190, with costs inflated to 2011. The cost of BSC when not on active chemotherapy is assumed to include the cost of palliative radiotherapy. Instead of AE costs we have used hospitalisations and blood transfusion data from PARAMOUNT. Instead of BSC costs we have used BSC drug use and palliative radiotherapy data from PARAMOUNT. See Appendix 20 for full details.
Treatment effect for OS and PFS	Treatment effect derived from K-M data	Upper and lower 95% CI	PARAMOUNT data

Table 51. Model outputs by clinical outcomes

Outcome		LYs	QALYs	Total Cost (£)
Overall survival	**Pemetrexed**	**1.7047**	**1.1743**	**£26,064**
	Placebo	**1.3537**	**0.9188**	**£13,912**
	Incremental	**0.3511**	**0.2554**	**£12,153**
Pre-progression	Pemetrexed	0.64	0.46	£13,592
	Placebo	0.37	0.27	£469
	Incremental	0.27	0.19	£13,123
Post-progression	Pemetrexed	1.06	0.71	£12,472
	Placebo	0.99	0.65	£13,443
	Incremental	0.07	0.06	-£970

Note: Numbers may not compute due to rounding; LY, life years; QALY, quality-adjusted life year

Table 52. Summary of QALY gain by health state

Health state	QALY pemetrexed	QALY placebo	Increment	% absolute increment
Pre-progression	0.46	0.27	0.19	70%
Post-progression	0.71	0.65	0.06	10%
Total	**1.17**	**0.92**	**0.25**	**28%**

Note: Numbers may not compute due to rounding; QALY, quality-adjusted life year. Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

Table 53. Summary of costs by health state

Health state	Cost pemetrexed	Cost placebo	Increment	% absolute increment
Pre-progression	£13,592	£469	£13,123	2799%
Post-progression	£12,472	£13,443	-£970	-7%
Total	**£26,064**	**£13,912**	**£12,153**	87%

Note: Numbers may not compute due to rounding. Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

Table 55. Summary of predicted resource use by category of cost

Item	Cost pemetrexed	Cost placebo	Increment	% absolute increment
Therapy cost	£13,125	£0	£13,125	-
Adverse event cost	£64	£4	£59	1369%
Follow up care costs	£10,177	£11,170	-£993	-9%
Terminal care costs	£2,699	£2,738	-£39	-1%
Total	**£26,064**	**£13,912**	**£12,153**	87%

Base-case analysis

7.7.6 Please present your results in the following table. List interventions and comparator(s) from least to most expensive and present ICERs in comparison with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance.

The results of the deterministic basecase analysis are shown in Table 56. The deterministic results show that the mean overall survival gain is 0.35 LYG, i.e., 4.2 months, with a QALY gain of 0.26 for pem/BSC compared to standard care, i.e. placebo/BSC. The estimated ICER for pemetrexed/BSC compared to standard of care is £47,576 per QALY gained. The ICER is driven by the comparator being 'watch and wait' with low associated costs compared to active intervention with pemetrexed continuation maintenance treatment.

Table 56. Deterministic basecase results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Incremental cost/LYG	ICER (£) incremental (QALYs)
Placebo/BSC	£13,912	1.3537	0.9188					
Pem/BSC	£26,064	1.7047	1.1743	£12,153	0.3511	0.2554	£34,613	**£47,576**

Note: Numbers may not compute due to rounding; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 57. Deterministic sensitivity analysis

Parameter	Value or assumption in base case	Incr. cost (£)	Incr. benefit (QALY)	ICER (£)
	Base case	**12,153**	**0.2554**	**47,576**
Pemetrexed costs				
Wastage excluded (assumes vial sharing)	Wastage included	12,086	0.2554	47,313
Concomitant vitamins and corticosteroid included	Excluded	12,177	0.2554	47,672
DH HRG daycase procurement costs for pemetrexed – average £1,293	£1,440	10,993	0.2554	43,035
DH HRG daycase procurement costs for pemetrexed – lower quartile £928	£1,440	8,113	0.2554	31,760
DH HRG daycase procurement costs for pemetrexed – Upper quartile £1,611	£1,440	13,502	0.2554	52,858
Pemetrexed delivery cost – Lower quartile £131	Daycase £208	11,546	0.2554	45,201
Pemetrexed delivery cost – Upper quartile £233	Daycase £208	12,351	0.2554	48,352
Pemetrexed delivery cost – Outpatient average £231	Daycase £208	12,335	0.2554	48,290
Pemetrexed delivery cost – Outpatient lower quartile £114	Daycase £208	11,412	0.2554	44,676
Pemetrexed delivery cost – Outpatient upper quartile £279	Daycase £208	12,714	0.2554	49,773
Deliver 20% of pemetrexed in community or home setting at £96/cycle	Daycase £208	11,984	0.2554	46,918
Deliver 50% of pemetrexed in community or home setting at £96/cycle	Daycase £208	11,732	0.2554	45,930
Increase AE costs by 10%: £8.17 pem/BSC; £0.91 placebo/BSC	£7.43 pem/BSC £0.83 placebo/BSC	12,159	0.2554	47,599
Decrease AE costs by 10%: £6.68 pem/BSC; £0.75 placebo/BSC	£7.43 pem/BSC £0.83 placebo/BSC	12,147	0.2554	47,553
BSA based on PARAMOUNT IPD (Each patient in cohort costed based on IPD: equivalent to mean 1.8m^2) (**including** wastage)	Mean BSA 1.79m^2 Wastage included	12,666	0.2554	49,586
BSA based on PARAMOUNT IPD (Each patient in cohort costed based on IPD: equivalent to mean 1.8m^2) (**excluding** wastage)	Mean BSA 1.79m^2 Wastage included	12,115	0.2554	47,430

Additional monitoring for patients on pemetrexed:				
Every 12 weeks: 1 extra consultant visit for all patients and 1 extra CT scan for 3% of cohort	Over 24-week period: 1 extra consultant visit for all patients & 1 extra CT scan for 3% of cohort	12,275	0.2554	48,056
Every 12 weeks: 1 extra consultant visit for all patients and 1 extra CT scan for 20% of cohort		12,323	0.2554	48,243
Every 12 weeks: 1 extra consultant visit for all patients and 1 extra CT scan for 50% of cohort		12,408	0.2554	48,574
Every 12 weeks: 1 extra consultant visit for all patients and 1 extra CT scan for 100% of cohort		12,549	0.2554	49,126
Every 6 weeks: 1 extra consultant visit for all patients and 1 extra CT scan for 3% of cohort on pemetrexed		12,520	0.2554	49,016
Every 6 weeks: 1 extra consultant visit for all patients and 1 extra CT scan for 20% of cohort on pemetrexed		12,616	0.2554	49,391
Every 6 weeks: 1 extra consultant visit for all patients and 1 extra CT scan for 50% of cohort on pemetrexed		12,785	0.2554	50,053
Every 6 weeks: 1 extra consultant visit for all patients and 1 extra CT scan for 100% of cohort on pemetrexed		13,067	0.2554	51,157
Second-line chemotherapy costs				
Docetaxel average price from DH CMU eMIT database (accessed 15.09.2012) £116.40	£1,023	12,289	0.2554	48,109
Erlotinib & docetaxel equivalent to average docetaxel eMIT price £116.40	Erlotinib £976.47 Docetaxel £1,023	12,961	0.2554	50,742
DH HRG daycase procurement costs for erlotinib and docetaxel – average Erl: £2,165; Doc £832	Erlotinib £976.47 Docetaxel £1,023	11,252	0.2554	44,050
Cycle data from PARAMOUNT: 3.26 Docetaxel 5.25 Erlotinib	4.82 Docetaxel 6.27 Erlotinib	12,350	0.2554	48,348
BSC and terminal care costs				
No differential BSC costs applied according to active vs no active treatment £36.22/cycle	£36.22/cycle if on active chemo £72.44/cycle if not on active chemo	12,318	0.2554	48,222

No differential BSC costs applied according to active vs no active treatment £72.44/cycle	£36.22/cycle if on active chemo £72.44/cycle if not on active chemo	12,539	0.2554	49,088
No BSC applied (terminal cost applied)	£36.22/cycle if on active chemo £72.44/cycle if not on active chemo	12,097	0.2554	47,356
No terminal or BSC costs applied	£36.22/cycle if on active chemo £72.44/cycle if not on active chemo £2,825 terminal care costs	12,135	0.2554	47,509
PARAMOUNT resource use data				
BSC drug costs, hospitalisation, blood transfusion and palliative radiotherapy rates and associated NHS reference costs. Second-line chemotherapy cycles based on PARAMOUNT data	**AE costs:** £6.51 pem/BSC £0.29 placebo/BSC **BSC costs:** £36.22/cycle if on active chemo £72.44/cycle if not on active chemo **Second-line chemo cycles:** Doc:4.82 ; Erl: 6.27	13,099	0.2554	51,279
Utilities				
Assume no treatment effect associated with pemetrexed treatment during maintenance treatment (i.e. pre-progression); utilities equivalent to BSC pre-progression	Apply non-significant disutility (-0.0248)	12,153	0.2674	45,447
Utility values from TA190 (Scenario 5 JMEN values)	PARAMOUNT EQ-5D data	12,153	0.2183	55,977

Efficacy				
Post-trial treatment effect: pem/BSC is equivalent to placebo/BSC, i.e., treatment benefit for trial period only	Treatment effect assumed to continue beyond trial duration	12,083	0.2119	57,012
OS Treatment effect 95% lower CI (Time ratio: 1.02)	OS treatment effect	12,088	0.2160	55,957
OS Treatment effect 95% upper CI (Time ratio: 1.46)	OS treatment effect	12,229	0.3018	40,517
PFS Treatment effect 95% lower CI (Time ratio: 1.23)	PFS treatment effect	12,153	0.2554	47,587
PFS Treatment effect 95% upper CI (Time ratio: 1.76)	PFS treatment effect	12,152	0.2555	47,563
Structural				
Discounting costs at 0%	3.5%	12,382	0.2554	48,474
Discounting health effects at 0%	3.5%	12,153	0.2793	43,506
Discounting costs and effects at 0%	3.5%	12,382	0.2793	44,327
Discounting costs at 6%	3.5%	12,005	0.2554	46,999
Discounting health effects at 6%	3.5%	12,153	0.2410	50,423
Discounting costs and effects at 6%	3.5%	12,005	0.2410	49,811
Time horizon - 6 years (i.e. stop Markov trace at 105 cycles)	15.99 years	12,060	0.2304	52,345
Time horizon - 10 years (i.e. stop Markov trace at 174 cycles)	15.99 years	12,135	0.2502	48,502
Time horizon – 8.97 years (i.e. stop Markov trace at 156 cycles) i.e. lifetime horizon based on when 99% of patients have died	15.99 years (99.9% patients died)	12,125	0.2476	48,979
Cut-points for extrapolation				
OS: Approx 15% at risk by arm: i.e. 34 cycles placebo/BSC (16%) & 38 cycles pem/BSC (15.9%)	20% at risk	12,144	0.2505	48,471
OS: Approx 25% at risk by arm: i.e. 29 cycles placebo/BSC (25.6%) & 33 cycles pem/BSC (26.7%)	20% at risk	12,134	0.2443	49,675
OS: using all available observed OS data i.e. 49 cycles placebo/BSC & 50 cycles pem/BSC	20% at risk	12,118	0.2363	51,272
Fully parametric OS with observed PFS & treatment discontinuation	20% OS at risk	12,080	0.2079	58,091

Table 58. Sensitivity analysis: Alternative parametric distributions

Alternative parametric distribution	Parameter value or assumption in basecase	Deterministic				Probabilistic			
		Inc. cost (£)	Inc. mean OS (months)	Inc. benefit (QALY)	ICER (£)	Inc. cost (£)	Inc. mean OS (months)	Inc. benefit (QALY)	ICER (£)
	Base case	**12,153**	**4.2**	**0.2554**	**47,576**	**12,318**	**4.2**	**0.2521**	**48,866**
Exponential	Gamma	12,174	4.3	0.2583	47,133	12,340	4.3	0.2594	47,565
Weibull	Gamma	12,118	3.7	0.2236	54,187	12,335	3.7	0.2224	55,458
Gompertz	Gamma	12,082	3.4	0.2092	57,742	12,283	3.4	0.2087	58,840
Log-normal	Gamma	12,192	4.5	0.2738	44,532	12,383	4.5	0.2732	45,335
Log-logistic	Gamma	12,193	4.7	0.2842	42,902	12,370	4.6	0.2782	44,465

Overall, the majority of the results from the sensitivity analyses range from £47,000 to £50,000. This shows the model is robust and provides a high level of consistency across a wide range of alternative plausible one-way analyses.

Looking at the maximum and minimum values from the sensitivity analysis the results show that the deterministic ICERs range from £31,760 to £58,840. The £31,760 ICER is based upon the use of the lower quartile NHS reference cost for daycase procurement of pemetrexed. As discussed in Section 7.5, the procurement costs were not considered to be appropriate for costing pemetrexed in the basecase analysis due to the wide variation in chemotherapy regimens covered by the relevant NHS code and the resultant insensitivity of the associated cost of an individual drug.

If this implausible result is excluded, the remaining ICERs range from £40,517 to £58,840. The latter is the result of adopting a Gompertz parametric distribution which was considered to have a poor fit based on both internal and external validity. The lower value results from using the 95% upper CI for OS treatment effect, i.e. the time ratio for basecase gamma distribution.

The key drivers of the model are:

- Efficacy of pemetrexed: including both the implementation of the upper and lower confidence intervals for the OS treatment effect and changing the assumption of the post trial treatment effect.

- Use of alternative parametric distributions;

- Use of utility values from external literature as used in TA190.

The utility values used in TA190 were derived from studies in NSCLC patients being treated with second-line chemotherapy which is likely to have lower face validity than using utility data directly derived from patients with the condition being assessed.

Other variables in the sensitivity analyses have a lower impact on the ICER. For example,

- Increasing the frequency of monitoring and proportion of patients receiving CT scans from current levels of UK clinical practice within anticipated clinical practice scenarios does not impact the ICER greatly. Only when monitoring is modelled to occur every 6 weeks with all patients receiving a CT scan does the ICER increase to £51,157.

- The use of alternative chemotherapy delivery costs for pemetrexed in an outpatient or community/home setting do not impact the ICER significantly, however, delivery in a community or home setting may be preferred by some patients and free up capacity in chemotherapy units.

Table 59. Probabilistic basecase results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Incremental cost/LYG	ICER (£) incremental (QALYs)
Placebo/BSC	£13,890	1.36	0.92					
Pem/BSC	£26,233	1.71	1.18	£12,343	0.35	0.26	£34,995	**£48,218**

Note: Numbers may not compute due to rounding

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Figure 16. Incremental cost-effectiveness plane for basecase analysis

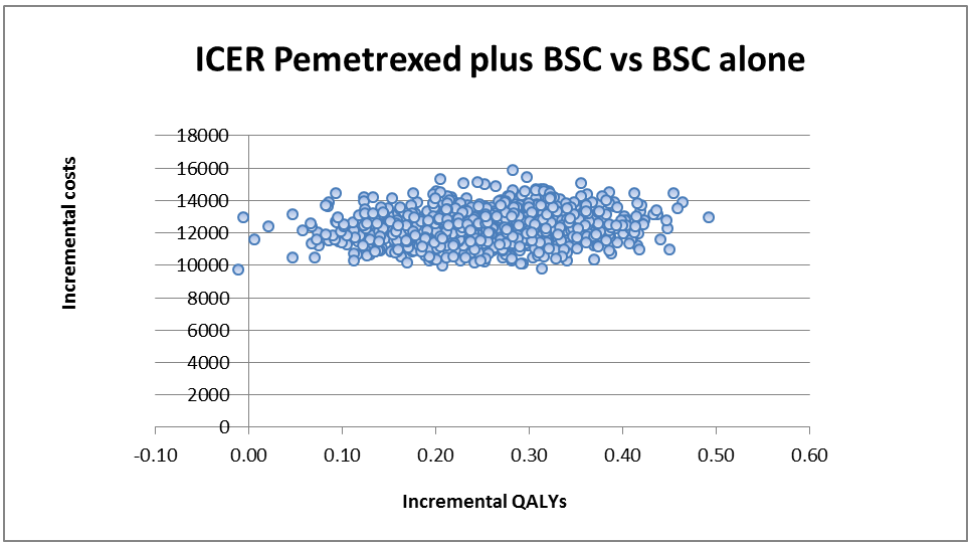
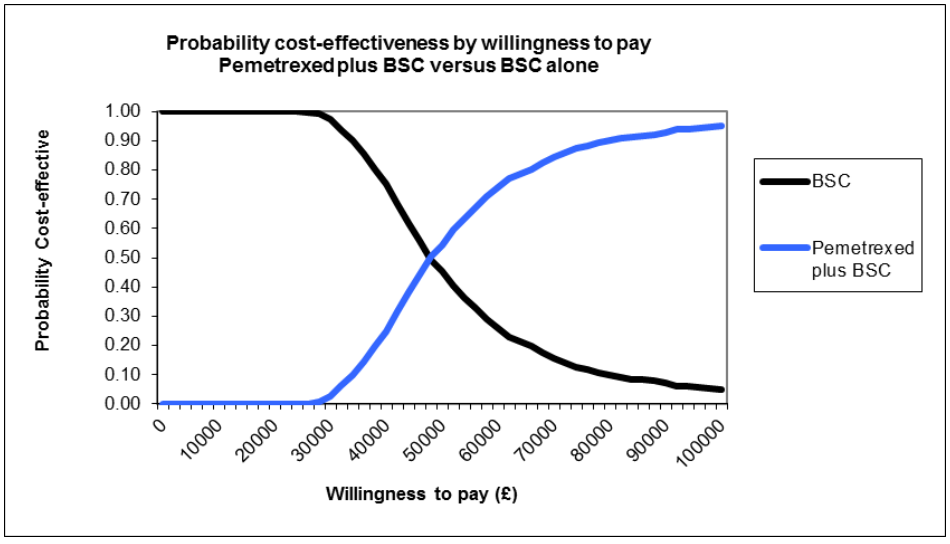


Figure 17. Cost-effectiveness acceptability curve



7.7.10. What were the main findings of each of the sensitivity analysis?

The economic evaluation of pemetrexed continuation maintenance compared to placebo in patients with advanced NS NSCLC gives a deterministic ICER of £47,576 and a probabilistic ICER of £48,218 (see Tables 56 and 59). A wide range of one-way sensitivity analyses have been conducted which demonstrates consistent results across a range of alternative plausible

data inputs. See Section 7.7.7. The results from both the deterministic and the probabilistic analyses are in the similar range showing consistency.

The CEAC shows that at a £50,000 WTP threshold pemetrexed/BSC is cost-effective in 54% of simulations.

8. Assessment of factors relevant to the NHS and other parties

8.5. Although very few grade 3/4 AEs occurred in either arm of the trial, pemetrexed was associated with a higher rate of AEs than the BSC arm. Incremental costs for treating AEs for patients receiving pemetrexed are £6.60 per cycle, (see Table 46, Section 7.5.7).

Table 66. Summary of pemetrexed costs included in the budget impact analysis

Costs	Pemetrexed
Chemotherapy	£1,440.00
Administration	£207.88
Adverse event costs	£6.60
Monitoring	£15.54
BSC and terminal care	Excluded
Total cost/cycle	£1,670.02
Mean no. of cycles	7.9
Total cost/patient	**£13,193**

8.7. **What is the estimated annual budget impact for the NHS in England and Wales?**

We have assumed a relatively modest market share in the first year as the new treatment paradigm becomes established. The estimated annual budget impact in the first 5 years following recommendation for use in the NHS in England and Wales ranges from £468,225 in 2013 to £2,606,872 in 2017. The estimated budget impact is shown in Table 72.

Table 72. Annual budget impact for pemetrexed in England and Wales in the first five years post-launch/NICE recommendation

	2013	2014	2015	2016	2017
No. of patients eligible for pemetrexed continuation maintenance	535	535	535	535	535
Cost without pemetrexed maintenance therapy	£2,592,075	£2,592,075	£2,592,075	£2,592,075	£2,592,075
Market share of eligible patients	7%	17%	34%	38.5%	38.5%
No. pemetrexed patients	37	92	183	206	206
Cost with pemetrexed	£3,060,300	£3,756,309	£4,907,888	£5,198,947	£5,198,947
Net Budget Impact	**£468,225**	**£1,164,234**	**£2,315,813**	**£2,606,872**	**£2,606,872**

Note: Small discrepancies in values are due to rounding, calculations were performed in Excel.

List of statistical reports and supporting documents provided with Lilly response to clarification questions on pemetrexed in maintenance treatment (ID489)

Question	Statistical report / other supporting documents	Description
A1	None	_
A2	ncqa2	Listing of all randomised patients with hospitalisations during the maintenance period
A3	Statistical Analysis plan version 3 31st Jan 2011	_
A4	None	_
A5	None	_
B1	None	_
B1 b	Report B1b	Results of adjusted model
B2.a)	ncqb2aos	[redacted]
	ncqb2apfs	[redacted]
B2. b)	ncqb2bppsgt3m	[redacted]
	ncqb2bpple3m	[redacted]
	ncqb2bppsov	[redacted]
B3	None	_
B4	ncqb4	Progression-free Survival Event Classification by Treatment Arm and Visit : pts With Progression-free Survival Events
B4	B4.docx	PFS data by 21-day cycle from the economic model
B5	B5.docx	Model predicted number of patients alive and uncensored, ''on treatment' and who received the allocated treatment for that cycle at the beginning of each 21 day cycle by treatment arm
B6.a)	Final datalock_smeq5d_2b	All Patients Randomized That Completed Baseline (V1-V4) and at Least One Post Baseline* EQ-5D Assessment

1 Documents containing CIC data are highlighted in turquoise

B6. b) 1	ncqb6b1	Summary of Patients Returning EQ-5D Assessments Without Any Missing Responses: all rz pts
B6. b) 2	ncqb6b2	Summary of Patients Returning EQ-5D Assessments With Any of the Five Three-option Ratings Missing: a;; rz pts
B6. b) 3	ncqb6b3	Summary of Patients Returning EQ-5D Assessments With the Visual Analog Scale Rating Missing
B6. b) 4	ncqb6b4	Summary of Patients Returning EQ-5D Assessments With Both the Visual Analog Scale Rating And At Least One of the Three-option Ratings Missing
B6. c)	ncqb6c	Summary of Visual Analog Scale Health State Scores and Index Scores
B6 e)	None	_
B6. d)	None	_
C1	None	_

Appendix G -Professional organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Pemetrexed for maintenance treatment following induction therapy with pemetrexed and cisplatin for non-squamous non-small-cell lung cancer [ID489]

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation: British Thoracic Society
Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology?
  YES

- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?

- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)?
  YES
  British Thoracic Society Lung Cancer and Mesothelioma Specialist Advisory Group

- other? (please specify)

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NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Pemetrexed for maintenance treatment following induction therapy with pemetrexed and cisplatin for non-squamous non-small-cell lung cancer [ID489]

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Currently, patients who have finished first-line palliative chemotherapy for NSCLC will not receive any maintenance therapy. Follow-up practice amongst oncologists and other healthcare professionals is variable and whilst some will review and image the patient on a regular basis, many will wait for symptoms and re-referral. As a result use of second-line treatments is relatively low as the patients are often not fit enough.

The concept of maintenance treatment is relatively new. There is good evidence that survival is improved without adversely affecting quality of life, with the latter being of key importance in this group of patients.

Treatment is likely to be based in secondary care chemotherapy units, but as this would require significantly increased capacity, it may be a driver to the development of more community/home based treatment which is not currently widespread.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for

example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Currently the alternative to maintenance therapy is best supportive care/active monitoring. Several TKIs (e.g Tarceva) have been trialled as maintenance treatment but I am not aware of the trial data. These might need to be included as a comparator.

It would be important to ensure that use of maintenance treatment outside a trial setting was not leading to increased complication rates, chemo-related mortality and hospitalisations. This will require oncologists to be vigilant in assessing their patient's fitness for treatment.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

None

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that

have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

As mentioned above, treatment is likely to be based in secondary care chemotherapy units, but as this would require significantly increased capacity, it may be a driver to the development of more community/home based treatment which is not currently widespread.

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

None

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NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

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Pemetrexed for maintenance treatment following induction therapy with pemetrexed and cisplatin for non-squamous non-small-cell lung cancer [ID489]

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation: Royal College of Pathologists

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? **Yes**
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? **No**
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)? **No**
- other? (please specify)

Appendix G -Professional organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

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What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

I foresee no further professional input from pathologists beyond what is routinely done now if this technology were approved.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Pemetrexed for maintenance treatment following induction therapy with pemetrexed and cisplatin for non-squamous non-small-cell lung cancer [ID489]

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

No Comment

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

No Comment

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within

3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

No extra pathology resources would be needed.

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

No equality issues identified.

Professional Organisation Statement

Single Technology Appraisal
Pemetrexed for maintenance treatment following induction therapy with pemetrexed and cisplatin for non-squamous non-small cell lung cancer (ID489)

Prepared by Dr Yvonne J Summers on behalf of:
National Cancer Research Institute, Lung Cancer clinical studies group, Royal College of Physicians, Royal College of Radiologists, Association of Cancer Physicians and the Joint Collegiate Council for Oncology
Role:

- Specialist in the treatment of people with the condition for which NICE is considering this technology

- Specialist in the clinical evidence base that is to support the technology (involved in clinical trials for the technology)

What is the expected place of the technology in current practice?

Lung cancer is one of the most common cancers in the UK with over 41 thousand new cases being diagnosed each year. In 2010, there were 34,859 deaths from lung cancer, a statistic that demonstrates how very poor the prognosis is for these patients[1]. Lung cancer is the most common cause of cancer mortality in the UK, accounting for more than a fifth of all cancer deaths and constitutes almost a quarter (24%) of all male deaths from cancer and is also the most common cause of cancer death in women (21%).
The majority of patients with non-small cell lung cancer (NSCLC) present with advanced disease and although treatment rates vary across the UK, an average of 55% of patients who have good performance status (PS 0-1) receive first line chemotherapy[2], with approximately 25% of all patients undergoing systemic treatment. Palliative chemotherapy modestly improves in median survival from 6 months to 8-11 months compared to best supportive care alone for patients with stage IV NSCLC[3].
NICE guidance on the diagnosis and treatment of lung cancer (CG121) suggests that patients of good performance status (PS 0-1) diagnosed with stage 3 or 4 disease should be offered platinum doublet chemotherapy (cisplatin or carboplatin plus one of the third generation drugs {docetaxel, gemcitabine, paclitaxel or vinorelbine}) in addition to supportive care.
More recently pemetrexed has been shown to improve outcomes for patients with NSCLC other than those with predominantly squamous cell histology[4,5].

Pemetrexed Treatment of NSCLC
A phase 3 trial which compared cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy naive patients with advanced NSCLC showed a 1.4 month overall survival benefit, with improved toxicity and easier administration (day 1 treatment on a 21 day cycle with pemetrexed, compared to a day 1 & 8 treatment with gemcitabine) in the pemetrexed arm for patients with non-squamous disease, but no benefit for those with squamous NSCLC[4].
Consequently NICE approved the use of pemetrexed in combination with cisplatin as first line treatment option for patients with adenocarcinoma or large cell carcinoma of lung (TA 181, September 2009) and this treatment option has been welcomed in UK practice for patients of good performance status who can tolerate a cisplatin based regimen. It should be noted that some clinicians are also using pemetrexed in combination with carboplatin as first line therapy for patients who cannot tolerate cisplatin.

Ciuleanu et al[5] reported a phase 3 study of maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for NSCLC. Patients with stage IIIB or IV disease who had not progressed after 4 cycles of non-pemetrexed containing platinum doublet chemotherapy and remained of good performance status were randomised to receive pemetrexed or placebo every 21 days until disease progression. This trial met both its primary and secondary endpoints with improvements in progression free survival of 1.9 months and overall survival of 5.2 months for the non-squamous NSCLC patient group. Predictably there was an increase in grade 3 or 4 adverse events in the pemetrexed arm (6.3% versus 2.3%) with more fatigue, anaemia and infection, although reassuringly, there were no treatment related deaths in the investigational arm.
NICE approved pemetrexed as an option for the maintenance treatment of patients with non-squamous NSCLC which has not progressed following non-pemetrexed containing platinum doublet chemotherapy (TA190) in June 2010.

There has been significantly less uptake of pemetrexed as a maintenance therapy than there was of 1st line use of pemetrexed following NICE recommendation for a practical reason: 1st line pemetrexed treatment was approved by NICE in September 2009 and was welcomed by the community of health professionals treating lung cancer as a significant advance in treatment of patients with non-squamous NSCLC. It has the added benefit of less hospital attendances for most patients, resulting in a slight reduction in pressure on chemotherapy units. Consequently 1st line pemetrexed treatment was quickly adopted into local guidelines and treatment policies which has had an effect on the use of pemetrexed maintenance therapy: patients included in the Ciuleanu study[5] had received induction therapy with 4 cycles

of non-pemetrexed containing platinum doublet chemotherapy, however by the time this trial finally reported, clinical practice had changed to incorporate pemetrexed earlier in the patient pathway. It was not possible, at that time, to determine whether the improvements in outcomes demonstrated for maintenance pemetrexed would be abrogated if patients received pemetrexed as part of their induction therapy.

The recently reported PARAMOUNT study now addresses these issues[6].
This randomised phase 3 trial enrolled 1022 PS 0-1, stage IIIB/IV non-squamous NSCLC patients prior to 1st line cisplatin and pemetrexed. 539 of these patients were randomised after completion of 4 cycles of chemotherapy (providing that they were still PS 0-1 and their CT scans had shown non-progression after chemotherapy and measurable disease) in a 2:1 fashion to receive pemetrexed or placebo maintenance every 21 days until disease progression. Patients with stable treated brain metastases were eligible for inclusion in the trial and randomisation was stratified according to PS (0 vs 1), response to induction chemotherapy (CR/PR vs SD) and stage (IIIB vs IV). There were more females in the pemetrexed arm compared to placebo (44% vs 38%) and more never-smokers (23% vs 19% respectively). Patients rated their present health condition using the standardised EuroQoL 5-dimensional scale (EQ-5D) throughout the study.

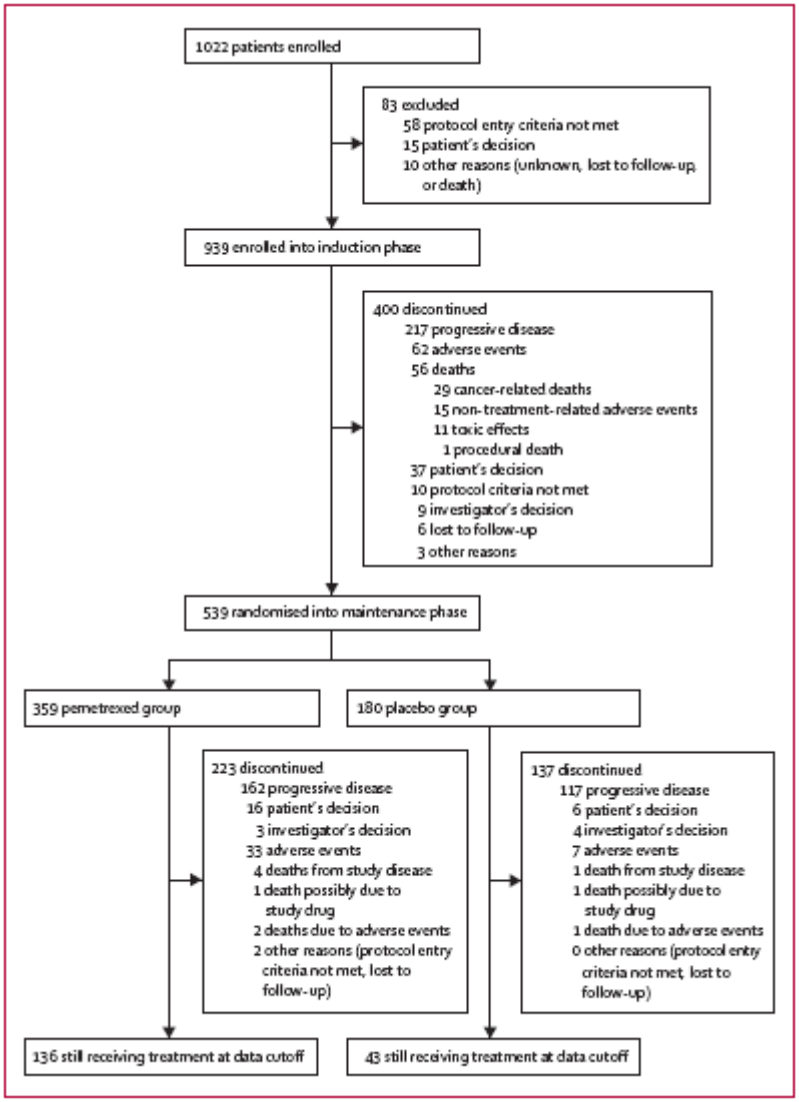

Figure 1. PARAMOUNT trial profile.
The primary end point of the study was a comparison of progression free survival (PFS) and results showed a benefit for pemetrexed of 1.3 months (hazard ratio 0.62; 95% CI 0.49-0.79; p<0.0001) compared to placebo. Overall survival (OS) was one of the secondary endpoints and analysis revealed a benefit of 2.9 months for the pemetrexed arm (13.9 vs 11.0 months

from randomisation or 16.9 vs 14.0 months from induction), (HR 0.78; 95% CI 0.64-0.96; p=0.0191) There was an impressive 1 year survival in the active treatment group of 58%. These improvements in PFS and OS were consistent across all subgroups examined and no difference in outcomes was reported according to initial response to induction chemotherapy, an important observation, as other maintenance therapy trials have demonstrated a differential improvement in survival according to whether patients have had a response or stable disease with induction therapy. Despite these analyses in other studies [6,10] not being pre-planned, it has led to a restriction in the licensing of erlotinib in the maintenance setting to those with stable disease following induction chemotherapy.

Consistent with other pemetrexed trials, toxicity was manageable with increased fatigue, blood transfusion requirements and infections in the pemetrexed arm. Grade 3/4 non-laboratory adverse events occurred in 9% and 4% in pemetrexed and placebo arms respectively and there were 2 possibly treatment related deaths in the treatment arm: one pneumonia and one endocarditis. There was no meaningful difference in quality of life according to analysis of EQ-5D questionnaires.

The majority of patients received post-discontinuation therapy, however there were some differences between the two arms: more patients in the placebo group received second line treatment (72% versus 64%) and more patients were treated with docetaxel in the placebo arm (43% versus 32%). These variations in second line treatment would, if anything, contribute to improved survival in the placebo arm of the study. The rates of subsequent treatment described for PARAMOUNT are higher than we would anticipate in standard UK practice, but reflect the rigorous selection of patients which occurred in this clinical trial.

The consistent improvement in outcomes demonstrated in PARAMOUNT for maintenance pemetrexed treatment is a very welcome treatment advance for a disease where the median survival for the majority of patients remains less than a year.

Clinical Practice

At present in the UK, patients who are eligible for 1st line therapy with cisplatin and pemetrexed receive this treatment, which, under current NICE guidance, renders them ineligible for pemetrexed maintenance treatment. In practice this means that the numbers of patients currently receiving maintenance treatment (out-with clinical trials) is low. If the data from PARAMOUNT results in a change in guidance on pemetrexed maintenance therapy it should be noted that this treatment will still not be appropriate for **all** NSCLC patients due to a number of factors:

1. approximately 30% of lung cancers have squamous histology and this histological subtype derives no benefit from pemetrexed treatment
2. many patients are poorer performance status (PS 2 or more) and have been excluded from clinical trials and are therefore likely to be excluded from treatment
3. where information has been recorded about numbers of patients starting induction therapy compared to those entering maintenance phase in clinical trials, a reproducible drop out rate of around 50% due to a variety of factors including disease progression, toxicity and patient factors e.g. deteriorating performance status, has been observed
4. some patients may prefer to have a break from treatment and regular hospital appointments following initial platinum doublet chemotherapy

Other Maintenance Treatments

Several other drugs are used for maintenance treatment and are recommended in guidelines for NSCLC. There are varying levels of evidence to support the recommendations made, however as several of these therapies are not used for this indication in standard UK practice further extensive discussion is not made. Table 1 summarises salient points from pivotal randomised phase 3 clinical trials.

Table 1: Treatments recommended for maintenance therapy on international guidelines

Treatment	Class	Indication	Trial design	Outcome Improvement (months)
Docetaxel[7]	Chemotherapy	Switch maintenance after Gem+Carbo. Non selected NSCLC	Immediate vs delayed docetaxel	3.7 PFS 2.8 OS
Gemcitabine[8]	Chemotherapy	Continuation maintenance. Non selected NSCLC	Gem+Cis followed by Gem or observation	1.9 PFS 1.3 OS (ns)
Bevacizumab[9]	VEGF Ab	Continuation maintenance. Non-squamous NSCLC	Carbo+Paclitaxel vs Carbo+Pacltaxel + Bevacizumab with maintenance Beva Did not specifically investigate maintenance component	1.7 PFS 2.0 OS
Erlotinib[10]	EGFR TKI	Switch maintenance after non-PEM platinum doublet	Erlotinib vs placebo	0.3 PFS 1.0 OS
Cetuximab[11]	EGFR Ab	Continuation maintenance. EGFR expressing NSCLC	Cisplatin+vinorelbine vs cisplatin+vinorelbine +cetuximab with maintenance cetuximab Did not specifically investigate maintenance component	No diff PFS 1.2 OS

Guidelines

There are 3 internationally recognised guidelines for the treatment of NSCLC which offer differing advice on maintenance therapy:

1. American Society of Clinical Oncology (ASCO) guidelines[12] recommend pemetrexed as an option for maintenance treatment of non-squamous NSCLC, but also recommend docetaxel and erlotinib as alternative maintenance treatment for unselected patients, and bevacizumab and cetuximab for patients who have fulfilled the trial criteria for first line therapy. Furthermore they give no priority to the different options except that erlotinib is the only treatment licensed for the group of patients with squamous cell disease.
2. European Society of Medical Oncology (ESMO) clinical practice guidelines[13] recommend pemetrexed maintenance for non-squamous NSCLC but offer erlotinib as an alternative for patients with all histologies who have stable disease following 4 cycles of platinum doublet chemotherapy. EGFR TKI maintenance is recommended for any patient with a sensitising EGFR mutation who has not received 1st line therapy.
3. National Comprehensive Cancer Network (NCCN)[14] (USA) guidelines recommend continuation maintenance with pemetrexed, bevacizumab, cetuximab or gemcitabine and switch maintenance with erlotinib, pemetrexed and docetaxel. Docetaxel is recommended for patients with squamous histology, pemetrexed for non-squamous histologies and the guideline specifically comments that close follow up of patients without therapy is an alternative to switch maintenance.

Clinical setting for technology use

The technology would be used in secondary care although and treatment delivery would be on chemotherapy units, however the nature of the patient group (those who have done well with induction chemotherapy, remain of good performance status and have tolerated chemotherapy well, with manageable toxicity) means that this treatment may used in a group

of patients who could be managed through nurse led clinics and perhaps be an example of a group of lung cancer patients who could be targeted for delivery of “chemotherapy closer to the home”.

The advantages and disadvantages of the technology

Relevance of trial data to UK population
Patients enrolled in clinical trials are usually of better performance status, with less co-morbidities and higher non-smoking rates than the average NSCLC patient and this observation is true for the PARAMOUNT study. However, the trial was conducted mainly in Europe with 16 different EU countries plus India. 94.6% of patients were Caucasian in origin and a smaller proportion of Asian patients were enrolled (4.5%). There were 6 centres within the UK who participated in study and UK patients made up 8% of the final number randomised in the maintenance phase. It is therefore reasonable to assume that the significant improvements in PFS and OS will be translated to the UK lung cancer population, with the caveats mentioned previously concerning which patients might not benefit from treatment.
There could be some concern that if patients of lower performance status are treated with maintenance therapy then the burden of toxicity may be higher and improvements in outcome less reproducible. Careful patient selection will therefore be very important with this therapy.

Resource utilisation
Disease control rates improve with maintenance therapy and this may translate into improved symptom control and less utilisation of supportive care therapies (e.g. analgesia, palliative care team consultations, radiotherapy). Furthermore, as patients on maintenance therapy are reviewed every 3 weeks rather than every 2-3 months, it is likely that disease progression may be detected at an earlier stage and result in a greater proportion of patients being suitable for second line treatment.

Inevitably, in a situation where a new treatment is being offered and the current standard of care is outpatient follow up, there is a burden on resources.
In the case of maintenance pemetrexed there will be a modest increase in resource utilisation in several areas:

1. Chemotherapy suite – the treatment is a short 15 minutes drip, however there will be a median of 4 extra cycles of treatment per patient
2. Pharmacy – time to prepare the additional cycles of treatment (median 4, mean 8)
3. Radiology – it is estimated that there will be on average an extra 1 or 2 CT scans and an extra 3-4 CXRs per patient treated
4. Pathology – it is estimated that there with be approximately 4-8 extra blood tests (FBC and Biochemical profile) per patient
5. Additional out-patient review – extra doctor and nurse time will be necessary with 3-4 additional visits
6. Cost of supportive medication – although inexpensive, additional folic acid, vitamin B12, dexamethasone and antiemetics are required
7. Extra blood transfusions
8. Extra cost of treating infections

Patient preference
There is also the issue of patient choice to be considered in relation to maintenance therapy; patients embarking on a course of palliative chemotherapy for advanced NSCLC have an initial discussion about 4 (occasionally 6) cycles of chemotherapy, after which it is hoped that there will be a few months disease stability and good quality of life. In this period they may look forward to a spell of less frequent hospital appointments and a more normal life, with less emphasis on the cancer diagnosis. They may plan for family and social events or perhaps have an opportunity for a last holiday.
The quality of life assessment tool EQ-5D did not demonstrate any meaningful difference between the patients receiving pemetrexed and placebo in the PARAMOUNT study. However it could be argued that, in order to detect a difference in quality of life caused by a change in

practice from no treatment, to regular 3 weekly treatment, the most appropriate comparator would be patients who were not returning to the hospital regularly (which the patients on the placebo arm of the trial were doing).
Many patients derive reassurance from more regular out patient follow-up and are enthusiastic about on-going treatment.
This is clearly an area of treatment where patient views vary significantly and careful discussion will be required with each individual patient in order to come to a decision about maintenance therapy.

Any additional sources of evidence

There are a number of studies which are relevant to the appraisal of maintenance pemetrexed treatment that are still enrolling patients or have closed to recruitment but have not yet been fully reported.

The AVAPERL study enrolled patients with previously untreated advanced non-squamous NSCLC to receive four cycles of cisplatin, pemetrexed and bevacizumab, and subsequently randomized those who hadn't progressed to either maintenance pemetrexed + bevacizumab or bevacizumab alone. At the European Society for Medical Oncology (ESMO) 2011 meeting, investigators presented early results that showed a very significant improvement in progression-free survival in the pemetrexed containing arm from the beginning of all treatment, at 10.2 vs. 6.6 months (HR 0.50, $p < 0.001$) and more recently initial overall survival results have also demonstrated an improvement with 15.7 months in the bevacizumab arm and median survival not yet reached for the pemetrexed + bevacizumab arm[16]. The study is not yet mature, but the initial report supports the growing body of evidence demonstrating improved survival outcomes for patients receiving pemetrexed maintenance treatment.

ECOG 5508 is a randomised phase 3 study which is currently recruiting patients and aims to assess the efficacy of maintenance therapy with bevacizumab (B) or pemetrexed (Pm) alone or both drugs in combination (BPm) following 4 cycles of induction therapy with paclitaxel, carboplatin and bevacizumab. The primary objective is to compare overall survival with B, Pm or BPm in patients with advanced stage NSCLC. Secondary objectives include progression free survival, response and toxicity. Recruitment of 1282 patients is planned and initial results may be available at the ASCO meeting in 2013.

Implementation issues

There will be an additional burden on existing services and although numbers of patients treated may be lower than anticipated, each provider of chemotherapy services will need to assess locally the potential impact of this change in the treatment pathway for patients with NSCLC and make plans accommodate the increase in demand. It is possible that some NHS trusts may chose to investigate whether this is a treatment with could be suitable for one of the VAT saving schemes utilising delivery of chemotherapy in the patients home or consider whether nurse-led clinics may be a suitable way of delivering this service.

Equality

There are no groups of patients protected by the equality legislation who would be disadvantaged by this appraisal.
However, it should be noted that patients with squamous cell NSCLC are lagging behind other groups of lung cancer patients in the development of new treatments.

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Submission from **Roy Castle Lung Cancer Foundation,** for consideration by NICE, in their review of pemetrexed (maintenance following pemetrexed and cisplatin) in the treatment of patients with non small cell, non squamous lung cancer [ID 489].

Submitting Organisation

Roy Castle Lung Cancer Foundation is a UK wide lung cancer charity. We fund lung cancer research, tobacco control initiatives and work in lung cancer patient care (information, support and advocacy activity).

The Foundation has contact with patients/carers through its UK wide network of over 45 monthly Lung Cancer Patient Support Groups, on line Forums and its Lung Cancer Information Helpline.

Clearly, our patient group members and contacts are a self-selected group, who have taken the step to seek out information or have accessed specialist support services. As most lung cancer sufferers tend to be older, from lower social class groups and with the five year survival being only 7%, less physically well, we acknowledge that our patients are perhaps not representative of the vast majority of lung cancer patients, who are not so well informed. It is, however, important that the opinions expressed to us, be passed on to NICE, as it considers the place of this product in the management of non small cell lung cancer (NSCLC).

General Points

1. For the overwhelming majority of NSCLC patients, cure is not a treatment option. In this scenario, improving quality of life and even small extensions in duration of life are of considerable significance to the individual and their family.

2. As active treatment options are limited in NSCLC and as overall outcomes remain poor, the availability of new choices, offer 'hope' for patients

3. The issue of "inverse weighting for duration of life" must be stressed. When considering the cost of treatment, it is not appropriate, for example, to give the same weighting to the final six months of life as to all other six months of life. It is important for this to be part of any numeric equation, which is looking at cost and quality of life. This point is of crucial importance to patients and relatives in this desperate situation

4. Improvement in symptoms. Patients with advanced non small cell lung cancer are often debilitated with multiple and distressing symptoms. Symptoms such as breathlessness are very difficult to manage clinically. Therapies with anti-tumour activity often provide the best option for symptom relief. The reality, however, is that few active options currently exist.

5. The potential of improving quality of life brings obvious benefits. These patients, in general, have quite limited life expectancy. It is of paramount importance, both to them and their families, that they are able to function as fully as is possible, for as long as possible.

This Appraisal

Our observations come from a combination of one-to-one discussion with lung cancer patients and from our patient information helpline.

We do not have any new research or data to add to this appraisal. However, we note the NICE recommendation in June 2010, recommending pemetrexed maintenance treatment for people with locally advanced or metastatic NSCLC, other than those with predominantly squamous cell histology, if disease has not progressed immediately following platinum containing first line chemotherapy (with a regimen containing paclitaxel, gemcitabine or docetaxel). This recommendation excluded the cisplatin and pemetrexed combination. A positive recommendation from this appraisal, would ensure maintenance treatment for patients in this group.

In the anecdotal patient experience reported to us, this maintenance therapy appears to be well tolerated.

This therapy represents a treatment option, providing benefit to a defined histological group of non small cell lung cancer patients.

Patients with advanced and metastatic lung cancer are in a particularly devastating situation. Even with the currently recommended options, the outlook for the majority is poor. It is for this reason that the availability of additional active therapy options is so important. As noted above, even relatively small benefits can be disproportionately large for these patients.

J Fox, Medical Director, RCLCF.

December 2012.

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Pemetrexed for maintenance treatment following induction therapy with pemetrexed and cisplatin for non-squamous non-small-cell lung cancer [ID489]

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: Dr Riyaz Shah

Name of your organisation Maidstone and Tunbridge Wells NHS Trust

Are you (tick all that apply):

- **a specialist in the treatment of people with the condition for which NICE is considering this technology?**
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)?
- other? (please specify)

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What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Maintenance Pemetrexed is already NICE approved in the case of patients treated with non-pemetrexed platinum doublets (TA190).

Data has demonstrated superiority of Pemetrexed as a first line partner in platinum doublets in patients with advanced non squamous non small cell lung cancer. NICE approval has already been issued on this matter (TA181).

The PARAMOUNT trial has now been presented and published. This trial gave maintenance pemetrexed or placebo to patients receiving 4 cycles of cisplatin + pemetrexed as first line therapy with advanced non squamous non small cell lung cancer. Only patients with response or stable disease were offered entry into the trial. Results show a progression free survival benefit for the addition of maintenance pemetrexed. At a subsequent meeting the overall survival data has been presented again showing a benefit for maintenance pemetrexed. The median survival was 13.9m vs 11.0m with a hazard ratio of 0.78 and confidence intervals that do not cross parity. The main publication did not include the overall survival data but this was presented at the ASCO annual meeting this year (2012).

I think that the only justification for maintenance chemotherapy in lung cancer is if there is a clear benefit in terms of overall survival. To my mind a progression free survival benefit of its own is of academic interest but would not justify routine use off trial. I was disappointed that the main publication did not include survival data but

having now seen this presented at a subsequent peer review meeting am content that this is a treatment that should not be discounted.

I think most oncologists accept that maintenance chemotherapy has a benefit in NSCLC however; I also think most of us feel that this is a strategy applicable to a select subgroup of patients. The main issue here revolves around tolerability and patient acceptance of remaining on chemotherapy for an indefinite period.

Currently, most patients who are fit with non squamous NSCLC get pemetrexed first line as per TA181 and therefore are not eligible for maintenance pemetrexed as per TA190.

Since the PARAMOUNT trial data presentation some oncologists have been successfully seeking funding for selected patients using the Cancer Drugs Fund. In my network (Kent and Medway Cancer Network) this is the case.

In terms of alternatives, there is data supporting erlotinib, docetaxel and gemcitabine in maintenance settings however I am not aware of any UK centres that would consider giving these routinely. My opinion is that the toxicity and logistics of delivery for these other agents does not lend itself to a maintenance strategy. The main advantage of pemetrexed is that it is given on day1 only (not day 1 and 8), significantly less myelosupressive than docetaxel and a short infusion.

The benefits in PARAMOUNT seemed to be across all subgroups. This technology does lend itself to delivery using novel systems such as nurse led or community based programmes (or even at home). This will critically depend on the resources available within the local health economy.

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Single Technology Appraisal (STA)

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

I think that if approved, maintenance pemetrexed will become a standard of care for selected patients. The treatment is a simple 15 minute infusion and will be easy to deliver within established chemo units. Systems will need to be in place to ensure patients continue to receive folate and B12 supplementation at the required timepoints.

There will be a **key issue** around how frequently these patients are assessed for progression. A patient who is not scanned frequently is more likely to have additional cycles of pemetrexed that are futile (due to undetected progression). Within the trial CT scans were performed every 6 weeks which is significantly more frequent than would be the case in routine NHS practice. I think the oncological community would welcome NICE giving advice on the assessment methodology and frequency through maintenance chemotherapy. Without that I think wide variation in practice will develop making it will be impossible to collect meaningful comparative data when looking at outcome measures. In addition more futile pemetrexed will be given and this could be a significant waste of resource.

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The side effect profile is as present in the published data however I would say that runny eyes and nose is a frequent complaint of patients that does not feature in the published data.

Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

I don't think there are equality or diversity issues

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Single Technology Appraisal (STA)

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

I presume the MA holder will be furnishing NICE with all the overall survival data which to my knowledge is currently unpublished.

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

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Single Technology Appraisal (STA)

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

This technology is deliverable in currently established chemotherapy units. I don't think that extra resources will be needed as this technology will only be applicable to a selected subgroup of patients.

Patients would have to have

- Non squamous NSCLC
- Advanced disease
- Response of stable disease after 4 cycles of platinum double chemotherapy
- Tolerated first line therapy well
- Be willing to continue maintenance therapy

In my experience these points are only applicable to a small section of the patient load.

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Pemetrexed for maintenance treatment following induction therapy with pemetrexed and cisplatin for non-squamous non-small-cell lung cancer [ID489]

Pléase sign and return to:
Technology Appraisals Administrator (Committee D), Donna Barnes
Email: TACommD@nice.org.uk Fax: Fax: (0)20 7061 9752
Post: NICE, Level 1A, City Tower, Piccadilly Plaza, Manchester, M1 4BT

I confirm that:

- I agree with the content of the statement submitted by the Royal College of Physicians and consequently I will not be submitting a personal statement.

Name: H Summers

Signed: [redacted]

Date: 18th Dec 2012

STA

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Pemetrexed for maintenance treatment following induction therapy with pemetrexed and cisplatin for non-squamous non-small cell lung cancer

This report was commissioned by the NIHR HTA Programme as project number 11/84/01

Completed 23rd January 2013

DOES NOT CONTAIN CIC/AIC

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Title: Pemetrexed for maintenance treatment following induction therapy with pemetrexed and cisplatin for non-squamous non-small cell lung cancer

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Declared competing interests of the authors:
None

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Rider on responsibility for report:

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contributions of authors:

Janette Greenhalgh	Project lead, drafted clinical section, supervised production of the final report
Adrian Bagust	Critical appraisal of the economic model
Michaela Blundell	Critical appraisal of the clinical statistical approach
Kerry Dwan	Critical appraisal of the clinical statistical approach
Sophie Beale	Critical appraisal of the economic sections of the manufacturer's submission
Helen Davis	Critical appraisal of the manufacturer submission
Yenal Dundar	Cross checking of the manufacturer's search strategy
Fabio Vecchio	Cross checking clinical sections of the report
Joseph Sacco	Critical appraisal of the clinical sections of the manufacturer submission
Ernie Marshall	Critical appraisal of the clinical sections of the manufacturer submission

All authors read and commented on draft versions of the ERG report.

Table of contents

Abbreviations

AC	Appraisal Committee
AE(s)	Adverse event(s)
BNF	British National Formulary
BSA	Body surface area
BSC	Best supportive care
CEAC	Cost-effectiveness acceptability curve
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CR	Complete response
CSR	Clinical study report
CTX	chemotherapy
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
e-MIT	Electronic Marketing Information Tool
EQ-5D	EuroQol 5D (a standardised instrument used as a measure of health outcome)
ERG	Evidence Review Group
FAS	Full analysis set
FDA	Food and Drug Administration
HR	Hazard ratio
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
IPD	Individual patient data
ITT	Intention- to- treat
KM	Kaplan-Meier
LYG	Life year gained
MS	Manufacturer's submission
NICE	National Institute for Health and Clinical Excellence
NLCA	National Lung Cancer Audit
NSCLC	Non-small cell lung cancer
NS	Non-squamous
OS	Overall survival
PARAMOUNT	The key trial described in the manufacturer's submission
PAS	Patient Access Scheme
PD	Progressive disease
PDT	Post-discontinuation therapy
PR	Partial response
PFS	Progression-free survival
PPS	Post-progression survival
PS	Performance status
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
QALY	Quality adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
SAP	Statistical analysis plan
SD	Stable disease
SPC	Summary of Product Characteristics
STA	Single Technology Appraisal
vs	versus
WTP	Willingness to pay

1 SUMMARY

1.1 Scope of the submission

The remit of the Evidence Review Group (ERG) is to comment on the clinical and cost-effectiveness evidence submitted to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal (STA) process. Clinical and economic evidence have been submitted to NICE from Eli Lilly and Company Ltd. in support of the use of pemetrexed (Alimta®) as maintenance treatment of locally advanced or metastatic (stage IIIB/IV) non-squamous non-small cell lung cancer (NSCLC) for people whose disease has not progressed immediately following first-line induction chemotherapy (CTX) with pemetrexed and cisplatin.

In the context of this report, two types of maintenance treatment are discussed: 'switch maintenance' and 'continuation maintenance.' Continuation maintenance is the focus of this appraisal. The manufacturer's submission (MS) provides definitions for both terms (MS, p18):

- Switch maintenance: the agent used for maintenance treatment is different from the agent(s) used for first-line treatment, e.g. pemetrexed following gemcitabine/cisplatin or any other regimen not including pemetrexed first-line
- Continuation maintenance: the agent used for maintenance treatment is the same as one of the agents used for first-line treatment, e.g. pemetrexed following pemetrexed/cisplatin first-line.

In October 2011, the European Medicines Agency (EMA) approved an extension to the existing marketing authorisation for the use of pemetrexed in the maintenance treatment of people with NSCLC other than squamous cell histology after first-line CTX. Pemetrexed can be given as maintenance therapy after first-line platinum-based CTX including a pemetrexed plus platinum combination. Formerly, pemetrexed was licensed as maintenance treatment only after first-line treatment with a platinum doublet of gemcitabine, paclitaxel or docetaxel.

1.2 Critique of the decision problem in the manufacturer's submission

The manufacturer has appropriately addressed the decision problem.

1.3 Summary of clinical effectiveness evidence submitted by the manufacturer

The evidence in the MS is derived from an international multi-centred randomised controlled trial (RCT - PARAMOUNT) that demonstrated improved progression-free survival (PFS) and overall survival (OS) for people receiving pemetrexed maintenance plus best supportive care (BSC) compared with those receiving placebo plus BSC. All participants had a complete response, partial response or stable disease following induction CTX with pemetrexed plus cisplatin. The median PFS (primary analysis July 2010) for pemetrexed plus BSC compared to placebo plus BSC was 4.11

months and 2.83 months respectively (HR=0.62; 95% CI 0.49 to 0.79). The median OS for pemetrexed plus BSC compared to placebo plus BSC was 13.86 months and 11.01 months respectively (HR=0.78; 95% CI 0.64 to 0.96). No overall treatment differences in health related quality of life (QoL) as measured by the EuroQol EQ-5D tariff score were observed between the two arms of the trial.

1.4 Summary of the ERG's critique of clinical effectiveness evidence submitted

The manufacturer conducted a literature search to identify RCTs of pemetrexed as maintenance treatment in people with advanced NSCLC. The PARAMOUNT trial was the only RCT that met the manufacturer's (appropriate) inclusion criteria. The PARAMOUNT trial was well-designed and well-conducted with a participant population predominantly from European centres. However, the ERG noted that when compared to people treated in clinical practice in England and Wales, the participants in the trial were generally younger and fitter, with a higher proportion identified as being of performance status (PS) 0, a higher proportion presented with Stage IV disease and a lower proportion were ever smokers. In addition, the trial allowed maintenance treatment until disease progression or unacceptable toxicity; a number of participants received more than six cycles of treatment. It is unclear whether this would be the case in clinical practice in England and Wales.

1.5 Summary of cost-effectiveness evidence submitted by the manufacturer

The manufacturer developed a de novo economic model. It is constructed in Microsoft Excel and structured using three patient health states (pre-progression, post progression and death). Variants of this model structure have been used in the modelling of metastatic oncology for a number of NICE STAs. The model population is based on the participants enrolled in the PARAMOUNT trial. Parametric survival models are fitted to the OS and PFS data to allow survival estimates to be made for the lifetime of the model. In the base case, the economic evaluation adopts a time horizon of 15.99 years, and the perspective is that of the UK NHS. Resource use, costs and utilities are estimated based on information from trial data and published sources.

Following receipt of the clarification letter, the manufacturer submitted a revised model and updated cost-effectiveness results. The results described in this document are those reported in the manufacturer's addendum, not those in the MS. The base-case incremental cost-effectiveness ratio (ICER) results generated by the manufacturer's model show the ICERs for the target population to be £47,576 per QALY gained and £34,613 per life year gained. The manufacturer carried out a wide range of deterministic sensitivity analyses. These generated ICERs that ranged from £31,760 to £58,091 per QALY gained. The manufacturer's probabilistic sensitivity analyses (PSA) show that, at

a threshold of £50,000 per QALY gained, pemetrexed plus BSC would be considered cost-effective in 54% of simulations compared to placebo plus BSC.

The manufacturer has also submitted a case for pemetrexed maintenance to be considered as an 'End of Life' treatment. The ERG considers that the manufacturer's case meets NICE's 'End of Life' criteria.

1.6 Summary of the ERG's critique of cost-effectiveness evidence submitted

Although the essential design of the model is very simple (two health states and death), its implementation at times seems unduly complex. A particular feature of the model is the large number of control variables provided to allow many alternative features to be explored in the analysis, although several are so specialised as to be unlikely to have much relevance in determining cost effectiveness. The main area that gave cause for concern was the parametric modelling of the PFS and OS data from the PARAMOUNT trial.

Several other modelling issues were identified including drug costs, inappropriate mid-cycle correction, suggested differences in second-line CTX rates, co-medication costs, PFS monitoring costs, terminal care costs, and covariate modelling of utility values.

1.7 ERG commentary on the robustness of evidence submitted by the manufacturer

1.7.1 Strengths

Clinical data reported in the submission are derived from a well-designed multi-centre, international RCT.

1.7.2 Weaknesses and areas of uncertainty

The uncertainty in the clinical effectiveness evidence relate to the generalisability of the trial results to the clinical population in England and Wales.

The main weakness of the economic model relates to the modelling of PFS and OS, leading to over-optimistic estimates of survival benefit. Multiple issues relating mainly to inaccurate cost estimation were also identified.

1.8 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG has developed three scenarios to be compared to the manufacturer's base-case scenario (with an ICER of £47,576 per QALY gained):

1) The manufacturer's model with eight ERG corrections implemented, resulting in an ICER of £58,092 per QALY.

2) The manufacturer's model amended as in (1), but using the manufacturer's covariate adjusted projective models for OS and PFS and the ERG's preferred method for implementing survival projections, resulting in an ICER of £68,810 per QALY.

3) The manufacturer's model amended as in (1), including the manufacturer's covariate adjusted projective model for PFS, but substituting the ERG's alternative OS projective model calibrated to reproduce the lack of continuing survival benefit observed in the PARAMOUNT trial data, resulting in an ICER of £76,344 per QALY.

2 BACKGROUND

2.1 Critique of manufacturer's description of underlying health problems

The context section of the MS (Section 2), appropriately presents the key issues related to the underlying health problem, including epidemiology, diagnosis and prognosis. A summary of these sections is presented in Box 1.

Box 1 Epidemiology and prognosis

Epidemiology

Lung cancer is the leading cause of cancer-related death in England and Wales.[1] It is also the second most common cancer in England and Wales with 35,406 new cases reported in 2009.[2]

Lung cancer consists of two main histological categories. The majority (78%) are non-small cell type (NSCLC) with the rest being small cell lung cancer.[3] Non-small cell lung cancer may be further classified into histological subtypes of squamous (32%), adenocarcinoma (26%), NSCLC not otherwise specified (NOS, 35%) and large cell carcinoma (4%).[3] The histological diagnosis rate for patients with lung cancer in England and Wales is 76%.[4]

Diagnosis and Prognosis

The prognosis for patients with lung cancer depends on the disease stage at diagnosis, i.e, the size and degree of spread of the tumour. Since lung cancer is largely asymptomatic in the early stages, patients usually present at an advanced stage. The National Lung Cancer Audit data show that 65% of patients with histologically confirmed NSCLC have advanced metastatic (stage IIIB or stage IV tumours) cancer at the time of presentation.[5] Late presentation in turn translates into lower survival rates. One-year survival rates of 32% and a 5-year survival rate of 9% have been reported.[5, 6]

For clarity, the ERG notes that the patient population of relevance to this appraisal is a subgroup of the overall NSCLC population: people with non-squamous disease that is epidermal growth factor receptor mutation negative. Non-squamous disease includes adenocarcinoma and large cell carcinoma tumours.

2.2 Critique of manufacturer's overview of current service provision

The MS provides a summary of options for the treatment of NSCLC (summarised in Box 2 to Box 4) and describes current NICE guidance relevant to treatment (summarised in Table 1). The MS also provides a schematic (MS, Figure 1) of a proposed treatment pathway for patients with non-squamous NSCLC in England and Wales that includes the use of pemetrexed within its recently extended marketing authorisation.

Box 2 Summary of treatment options

Treatment options for NSCLC depend on the stage of the disease at presentation. For stage IIIB or IV NSCLC, options include radiotherapy or CTX alone or a combination of the two. Chemotherapy may be recommended for patients with non-resectable stage III or IV disease, provided they are of good performance status (PS 0-1). Approximately 53% of NSCLC patients with advanced disease (stage IIIB/IV) and good performance status (PS 0-1) receive CTX for NSCLC in England and Wales.[5]

First-line chemotherapy treatment for non-squamous NSCLC

Pemetrexed plus cisplatin is established as the CTX regimen of choice for the first-line treatment of patients with non-squamous, EGFR mutation negative NSCLC, with a market share of 43% of all stage IIIB/IV NSCLC patients.[7] Another available option is gemcitabine in combination with cisplatin or carboplatin (2% and 12% market share respectively.[7]

Options following first-line chemotherapy

1. Watch and wait - the majority of patients who do not progress following first-line (induction) CTX are not immediately given further active treatment. Induction treatment is routinely followed by a period of 'watch and wait' during which patients undergo clinical assessment and receive best supportive care (BSC), as necessary. On disease progression, patients are usually offered second-line CTX with docetaxel or erlotinib, depending on performance status and eligibility.
2. Maintenance treatment - maintenance treatment of NSCLC is a relatively new concept which aims to maintain the clinical benefit achieved after first-line CTX, postpone disease progression and ultimately prolong overall survival along with palliation of disease symptoms. Maintenance treatment of NSCLC is not yet well-established in the NHS given that licensed and recommended treatments have only been available since 2010.

The ERG notes that, as indicated in Figure 1 of the MS (MS, p32) platinum-based CTX with docetaxel, paclitaxel or vinorelbine are also recommended by NICE as first-line treatment options for people with NSCLC.[3] However, the ERG is aware that the majority of people with non-squamous disease in England and Wales will be treated with pemetrexed plus cisplatin as a first-line treatment; these people will be ineligible for maintenance treatment with pemetrexed under current NICE guidance TA190.[8]

Clinical opinion to the ERG has highlighted that during 'watch and wait' a large proportion of people in England and Wales become unfit for second-line treatment with CTX.

Box 3 Pemetrexed as maintenance treatment

Pemetrexed switch maintenance

Pemetrexed is the first and only active treatment option to be licensed by the EMA and recommended by NICE (TA190)[8] for switch maintenance treatment of locally advanced or metastatic non-squamous NSCLC. Even after a positive NICE recommendation, the uptake of pemetrexed switch maintenance has been low, since the use of pemetrexed plus cisplatin in the first-line setting precluded the use of maintenance pemetrexed.

Box 4 Place of proposed treatment in treatment pathway

Continuation maintenance with pemetrexed

The MS (MS, p26) states that subsequent to the licence amendment allowing the use of pemetrexed as continuation maintenance in patients without disease progression after first-line pemetrexed plus cisplatin, patients who previously could not avail of pemetrexed maintenance treatment will now become eligible for this.

The ERG considers the manufacturer's overview of treatment options and the treatment pathway as described in the MS to be accurate.

Table 1 NICE guidelines and guidance

NICE Guideline/Guidance and date	**Title**	**Key recommendations**
CG121 (2011)[3]	The diagnosis and treatment of lung cancer	1.4.40. Chemotherapy should be offered to patients with stage III or IV NSCLC and good performance status (WHO 0, 1 or a Karnofsky score of 80–100), to improve survival, disease control and quality of life. 1.4.41. Chemotherapy for advanced NSCLC should be a combination of a single third-generation drug (docetaxel, gemcitabine, paclitaxel or vinorelbine) plus a platinum drug. Either carboplatin or cisplatin may be administered, taking account of their toxicities, efficacy and convenience. 1.4.42. Patients who are unable to tolerate a platinum combination may be offered single-agent CTX with a third-generation drug.
TA190 (2010)[8]	Pemetrexed for maintenance treatment of NSCLC	People who have received pemetrexed in combination with cisplatin as first-line CTX cannot receive pemetrexed maintenance treatment. 1.1Pemetrexed is recommended as an option for the maintenance treatment of people with locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology if disease has not progressed immediately following platinum-based CTX in combination with gemcitabine, paclitaxel, or docetaxel.
TA227 (2011)[9]	Erlotinib monotherapy for maintenance treatment of NSCLC	1.1Erlotinib monotherapy is not recommended for maintenance treatment in people with locally advanced or metastatic non-small cell lung cancer who have stable disease after platinum-based first-line CTX.[a]

a for clarity, the ERG adds that in the appraisal for erlotinib as a maintenance treatment (TA227), the submitted evidence was only for the population with stable disease.

The ERG notes that the MS does not include NICE guidance TA181 'Pemetrexed for the first-line treatment of NSCLC' (2009) in this section of the document.[10] However, TA181[10] is discussed extensively in the cost-effectiveness section of the MS.

The ERG agrees with the manufacturer's statement regarding NICE's clinical guideline CG121.[3]

> "The recommendations currently in CG121 were drafted before pemetrexed became standard of care for first-line treatment of NSCLC and well in advance of the licensing and positive NICE guidance for pemetrexed in switch maintenance treatment of NSCLC."

> "CG121 does not contain any recommendations on maintenance treatment and instead refers to the NICE guidance on pemetrexed (TA190), and erlotinib (TA227, in progress at the time) under the heading 'Related guidance'."

In summary, the ERG is confident that the manufacturer has accurately described the current service provision for people with non-squamous NSCLC.

2.3 Eligible population in England and Wales

In Table 4 of the MS (MS, p28) the manufacturer estimates that 535 patients in England and Wales would be eligible for maintenance treatment with pemetrexed (Table 2) as outlined in this STA. These are people with stage III/IV non-squamous NSCLC who are of PS 0 or 1. The ERG considers this to be a reasonable estimate of this population; however, it is noted that pemetrexed is currently licensed and recommended by NICE as a switch maintenance treatment (TA190)[8] and so overall, the number eligible for switch and continuation maintenance treatment with pemetrexed is higher.

Table 2 Manufacturer's estimate of number of patients in England and Wales eligible for continuation maintenance treatment with pemetrexed in this STA

Description	% patients	Number	References
Patients with lung cancer		32,347 (reported)	NLCA audit report 2011 [4]
Patients with confirmed NSCLC		19,163 (reported)	NLCA audit report 2011[4]
Patients with stage IIIB/IV NSCLC and PS 0-1		5,932 (reported)	NLCA audit report 2011[4]
Non-squamous NSCLC patients with stage IIIB/IV NSCLC and PS 0-1	68% (reported)	4,034 (calculated)	NICE CG121 (2011)[3]
Non-squamous NSCLC patients with stage IIIB/IV NSCLC and PS 0-1 receiving CTX	52.8% (reported)	2130 (calculated)	NLCA audit report 2011[4]
Patients receiving pemetrexed plus cisplatin at first-line	43% (reported)	916 (calculated)	Market research data, Q2 2012[7]
Patients eligible for pemetrexed continuation maintenance (i.e. patients without disease progression following first-line treatment)	58.4% (patients eligible for maintenance phase in PARAMOUNT)	535 (calculated)	Paz-Ares et al 2012[11]

3 CRITIQUE OF MANUFACTURER'S DEFINITION OF DECISION PROBLEM

Table 3 presents the decision problem issued by NICE[12] and the manufacturer's rationale for any deviation from this in the MS.

Table 3 Decision problem as addressed in the MS

	NICE Final scope	Decision problem addressed in MS	Rationale if different from scope
Population	People with advanced or metastatic (stage IIIIB and IV) NSCLC, other than predominantly squamous histology, whose disease has not progressed following induction treatment with pemetrexed plus cisplatin	People with advanced or metastatic (stage IIIIB and IV) NSCLC, other than predominately squamous histology, with good performance status (PS 0-1), who experience complete or partial response or stable disease after first-line treatment with pemetrexed plus cisplatin	As per the licensed population for pemetrexed continuation maintenance. As per the NICE guideline CG121, only patients with advanced disease and good PS (WHO 0, 1 or Karnofsky 80-100) should be offered CTX. The inclusion criteria for the PARAMOUNT trial specified that only patients with PS 0-1 were to be included. Accordingly, this submission presents the clinical and economic case for patients with PS 0-1 only
Intervention	Pemetrexed	Pemetrexed plus BSC	N/A
Comparator	Best supportive care (includes bisphosphonates and palliative radiotherapy)	Placebo (watch and wait) plus BSC. In the PARAMOUNT study, BSC was defined as treatment without a specific antineoplastic regimen given with the intent to maximise quality of life. Specifically excluded were: anticancer surgery, immunotherapy, radiation to intrathoracic structures, anticancer hormonal therapy, and systemic CTX in which the goal was to either eradicate or slow the progression of the study disease. Therapies considered acceptable included, but not limited to, palliative radiation to extrathoracic structures, antibiotics, analgesics, antiemetics, thoracentesis, pleurodesis, blood transfusions, and/or nutritional support (enteral or parenteral)	N/A
Outcomes	• OS • PFS • response rates • adverse effects of treatment (according to grade) • HR QoL	The primary outcome measure was PFS. Secondary outcomes included OS, response rate, HRQoL	N/A
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per QALY. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and PSS perspective.	Cost effectiveness has been expressed in terms of cost per QALY and LYG. The analysis will have a lifetime time horizon, i.e., when 99.9% patients are modelled to have died, which for the base case equates to 15.99 years for patients in the pemetrexed plus placebo arm, based on a gamma distribution for the parametric extrapolation, placebo plus BSC arm. The cost-effectiveness analysis has been conducted from an NHS and PSS perspective.	N/A

QALY=quality adjusted life year; LYG=life years gained; PSS=personal and social services

3.1 Population

The population in the final scope issued by NICE[12] and the key submitted trial (PARAMOUNT[11]) both include people with advanced or metastatic (stage IIIB or IV) NSCLC, other than predominantly squamous histology, whose disease has not progressed following induction treatment with pemetrexed plus cisplatin. In the MS, the population is further limited to people with a PS of 0 or 1. The ERG considers this limitation to be appropriate as in clinical practice in England and Wales, only patients with a PS of 0 or 1 are eligible for CTX treatment.[3] However, the ERG is aware that a substantial proportion of people with NSCLC in England and Wales are of PS 2.

3.2 Intervention

The intervention described in the MS and in the scope is pemetrexed. Pemetrexed is described in the MS (MS, p17) as a multi-targeted anti-cancer antifolate agent that disrupts crucial folate-dependent metabolic processes essential for cell replication. In the maintenance setting, pemetrexed is administered as a 10 minute intravenous infusion at a recommended dose of 500mg/m^2 of body surface area (BSA) on the first day of a 21-day cycle until disease progression. Concomitant medications required to be administered with pemetrexed include vitamin B12, folic acid and dexamethasone. In the MS, BSC is given as needed alongside pemetrexed.

In October 2012, the European Medicines Agency (EMA) approved an extension to the existing market authorisation for the use of pemetrexed in the maintenance treatment of people with NSCLC other than squamous cell histology after first-line CTX. Pemetrexed can now be given as maintenance therapy after first-line platinum-based CTX including a pemetrexed plus platinum combination.[13] Formerly, pemetrexed was licensed as maintenance treatment only after first-line treatment with a platinum doublet of gemcitabine, paclitaxel or docetaxel.

3.3 Comparators

The comparator specified in the final scope is best supportive care (BSC) which includes bisphosphonates and palliative radiotherapy. In the MS, the comparator is placebo (watch and wait) plus BSC. In the key trial (PARAMOUNT[11]) BSC is defined as treatment without a specific antineoplastic regimen given with the intent to maximise QoL. The manufacturer states that BSC specifically excluded anticancer surgery, immunotherapy, radiation to intrathoracic structures, anticancer hormonal therapy, and systemic CTX in which the goal was to either eradicate or slow the progression of the study disease. Those therapies considered acceptable included, but were not limited to, palliative radiation to extrathoracic structures, antibiotics, analgesics, antiemetics, thoracentesis, pleurodesis, blood transfusions, and/or nutritional support (enteral or parenteral). The ERG considers that the comparator defined by the manufacturer matches BSC as specified in NICE's final scope.[12]

In the definition of the decision problem, the manufacturer's stated comparator is placebo (watch and wait) plus BSC. The placebo treatment consisted of a saline solution infused over 10 minutes on day 1 every 21 days. The ERG considers that the manufacturer's comparator includes an extra element to the stated comparator in the final scope and the 'watch and wait' policy used in clinical practice. Whilst the placebo treatment adds to the robustness of the trial design, in clinical practice placebo treatment would not be offered.

3.4 Outcomes

Data are reported in the MS for all of the five outcomes specified in the scope, overall survival (OS), progression-free survival (PFS), response rate reported as objective tumour response rate, disease control rate, adverse effects of treatment (AEs) and health-related quality of life (HRQoL). In the MS, data for OS and PFS from the key trial (PARAMOUNT[11]) are reported at a number of timepoints. The HRQoL data were collected using the EQ-5D,[14] a standardised instrument for use as a measure of health outcome that is applicable to a wide range of health conditions.

3.5 Other relevant factors

No equity issues are identified in the MS or by the ERG. The ERG is unaware of any ongoing Patient Access Scheme (PAS) application.

3.6 Innovation

The manufacturer puts forward a case for pemetrexed continuation maintenance as an innovative treatment (MS, p36). The manufacturer points to the increased survival in the induction phase and then the maintenance phase, the preservation of QoL and the possibility that pemetrexed maintenance could be administered in CTX units, in the community or at home.

The ERG is of the opinion that there is limited scope for the technology to be considered as innovative. Pemetrexed is already recommended for use in the NHS by NICE as a maintenance treatment for people with locally advanced or metastatic NSCLC other than predominantly squamous histology who were previously treated with platinum-based treatment other than pemetrexed.[8] The use of pemetrexed as a continuation maintenance as described in the MS has the effect of increasing the number of eligible patients.

In addition, the ERG considers that maintenance treatment could be viewed as partially equivalent to extending first-line treatment (i.e. six cycles of first-line CTX rather than four) as is practised in the US.[15]

4 CLINICAL EFFECTIVENESS

The clinical effectiveness evidence in the MS is derived from a single trial, the PARAMOUNT trial.[11] The location of the key clinical information in the MS is described in Table 4. The manufacturer also provided the PARAMOUNT trial clinical study report[16] (CSR) as part of the submission and the PARAMOUNT trial statistical analysis plan (SAP) as part of the clarification process.

Table 4 Key clinical information in the MS

Key information	Page(s) in the MS
Description of the technology	17
Context	25-37
Statement of decision problem	38-39
Literature search main	40 and Appendix 2
Study selection	40
Clinical effectiveness evidence from key trial	48-75

4.1 Critique of the methods of review(s)

4.1.1 Searches and inclusion criteria

A systematic literature search was conducted to identify relevant Phase 3, RCTs of pemetrexed as maintenance treatment in people with advanced NSCLC. Key databases were searched, including Ovid Medline, Medline (R) In-Process and Embase. The Evidence Based Medicine Reviews database was used to search the Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials and the Cochrane Methodology Register as well as ACP Journal Club, DARE, Health Technology Assessment and NHS Evaluation database. Other databases searched were Biosys Previews and Current Contents. Searches of the American Society of Clinical Oncology website and internal Eli Lilly databases were also undertaken. All searches were conducted up to 25th July 2012. The ERG considers the range of databases included in the search to be thorough. Appropriate search strategies and inclusion criteria were utilised by the manufacturer.

The ERG has conducted its own searches and is confident that the PARAMOUNT trial, as identified by the manufacturer is the only Phase 3 RCT relevant to the decision problem.

4.1.2 Identified studies

One RCT, the PARAMOUNT trial[11] was identified by the manufacturer. Details of the PARAMOUNT trial were reported in nine publications. The main publication by Paz-Ares[11] et al was published in 2012, seven other reports were conference abstracts[17-23] and one publication described the

trial design.[24] The ERG has identified a paper published after the submission of the MS; this paper reports the safety and QoL data of participants in the PARAMOUNT trial.[25]

4.1.3 PARAMOUNT trial characteristics

The PARAMOUNT trial[11] is a randomised double-blind, placebo-controlled, Phase 3, international, multi-centre trial that compares pemetrexed maintenance treatment plus BSC (n=359) with placebo plus BSC (n=180) in people with stage IIIB or stage IV NSCLC. Treatment was given until disease progression or unacceptable toxicity. All participants in the trial had experienced complete response (CR), partial response (PR) or stable disease (SD) following induction CTX with pemetrexed plus cisplatin. Randomisation was performed on a 2:1 ratio with stratification factors including PS (0 or 1), tumour response to induction treatment and disease stage prior to randomisation.

It is stated in the MS (MS, p60) that the submission describes only the maintenance phase of the trial; however the manufacturer has provided the inclusion and exclusion criteria applied in the induction phase of the key trial (MS, p52) to which 1022 participants were enrolled. The ERG considers these criteria to be appropriate. The key trial characteristics described in the MS (MS, p51) are summarised in Table 5

Table 5 PARAMOUNT trial characteristics

Characteristic	Description
Location	83 sites located in Australia, Belgium, Canada, Finland, France, Germany, Greece, India, Italy, Netherlands, Poland, Portugal, Romania, Spain, Turkey and the UK
Design	Randomised, double-blind, placebo-controlled, Phase 3, international multi-centre
Duration	All enrolled patients received four 21-day cycles of induction CTX with pemetrexed plus cisplatin. Subsequently, eligible patients were randomised to maintenance treatment consisting of 21-day cycles of treatment with pemetrexed plus BSC or placebo plus BSC, administered until disease progression or toxicity or death due to any cause
Method of randomisation	Randomisation was carried out in a 2:1 ratio with the help of an interactive voice response system (IVRS) and stratified by PS, tumour response to induction treatment and disease stage prior to randomisation
Method of blinding (care provider, patient and outcome assessor)	Both pemetrexed and placebo IV bags appeared identical. An unblinded pharmacist or designee obtained patient's treatment allocation from the IVRS and prepared the blinded study drug for infusion. Lab investigations took place immediately before each cycle to minimise unblinding due to lab toxicities. Variables linking patients to study arm remained blinded in the database until primary data lock. Both arms received identical supplementation regimens
Intervention(s) and comparator	Intervention (N= 359): Pemetrexed 500 mg/m^2 administered IV on day 1 every 21 days, plus BSC. Placebo comparator (N=180): Normal saline (0.9% sodium chloride) administered IV on day 1 every 21 days, plus BSC. All patients received concomitant medications vitamin B12 folic acid and dexamethasone
Primary outcomes	Objective PFS
Secondary outcomes	OS, objective tumour response rate, EQ-5D, toxicity
Duration of follow-up	Median patient follow-up (measured from time of randomisation), was 12.5 months (11.1 to 13.7) for all patients

IV=intravenous; IVRS=interactive voice response system

4.1.4 PARAMOUNT participant characteristics

The key baseline characteristics of the trial participants (at randomisation) are described in Table 6. Overall, these appear to be well-balanced across the two arms of the trial. It is acknowledged in the MS (MS, p53) that the trial participants are generally younger than those seen in clinical practice in England and Wales. The ERG agrees with the manufacturer that this is a typical feature of clinical trials in this area. Clinical opinion to the ERG indicated that compared to clinical practice in England and Wales, the PARAMOUNT trial[11] included a higher proportion of patients considered to be of PS 0, a substantially higher proportion of participants with Stage IV disease and somewhat lower proportions of ever smokers.

Table 6 PARAMOUNT key participant characteristics

Characteristic	Pemetrexed + BSC N=359	Placebo + BSC N=180	Total N=539
Gender n (%)			
Male	201 (56)	112 (62.2)	313 (58.1)
Female	158 (44.0)	68 (37.8)	226 (41.9)
Age at randomisation (years)			
Mean	60.34	62.17	60.95
Median	60.95	62.35	61.39
Range	31.9 to 78.7	34.9 to 83.3	31.9 to 83.3
Age group n (%)			
Age <65 years	238 (66.3)	112 (62.2)	350 (64.9)
Age ≥65 years	121 (33.7)	68 (37.8)	189 (35.1)
Origin n **(%)**			
Caucasian	339 (94.4)	171 (95.0)	510 (94.6)
Asian	16 (4.5)	8 (4.4)	24 (4.5)
Black	4 (1.1)	1 (0.6)	5 (0.9)
Smoking status n **(%)**			
Ever smoker	274 (76.3)	144 (80.0)	418 (77.6)
Never smoker	83 (23.1)	34 (18.9)	117 (21.7)
Unknown	2 (0.6)	2 (1.1)	4 (0.7)
Histology n **(%)**			
Adenocarcinoma	310 (86.4)	161 (89.4)	471 (87.4)
Large cell carcinoma	24 (6.7)	12 (6.7)	36 (6.7)
Other/indeterminate[a]	25 (7.0)	7 (3.9)	32 (5.9)
Disease stage prior to induction n **(%)**			
Stage IIIB	31 (8.6)	18 (10.0)	49 (9.1)
Stage IV	328 (91.4)	162 (90)	490 (90.9)

Characteristic	Pemetrexed + BSC N=359	Placebo + BSC N=180	Total N=539
ECOG PS n **(%)**			
0	113 (31.5)	60 (33.3)	173 (32.1)
1	245 (68.2)	118 (65.6)	363 (67.3)
2[b]	0 (0)	1 (0.6)	1 (0.2)
3[b]	1 (0.3)	1 (0.6)	2 (0.4)
Best tumour response to induction therapy			
Complete/partial response	159 (44.3)	75 (41.7)	234 (43.4)
Stable disease	190 (52.9)	95 (52.8)	285 (52.9)
Progressive disease[b]	1 (0.3)	2 (1.1)	3 (0.6)
Not done	0 (0.3)	0 (0.0)	0 (0.0)
Unknown[b]	9 (2.5)	8 (4.4)	17 (3.2)

a Patients with primary diagnosis of NSCLC whose diagnosis did not clearly qualify as adenocarcinoma or large-cell carcinoma
b 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.

4.1.5 PARAMOUNT quality and validity assessment

The manufacturer's quality assessment of the PARAMOUNT trial[11] is presented in Appendix 1.3 of the MS. The assessment demonstrates that the trial was well designed with robust methods of randomisation and appropriate blinding. The ERG notes that the primary endpoint was PFS, but the trial was also powered for OS and that QoL was assessed using the EQ-5D utility score.

As the trial population was predominantly European, including six centres in the UK, the results of the trial are considered by the ERG to be applicable to the clinical population in England and Wales, within the limits of the trial population.

Patients were recruited from 83 centres in 16 countries (Australia, Belgium, Canada, Finland, France, Germany, Greece, India, Italy, Netherlands, Poland, Portugal, Romania, Spain, Turkey and the UK). For the results of a trial with so many centres to be meaningfully interpreted, the manner in which the protocol is implemented should be clear and similar across all centres. This is because with so many investigators in different countries, general clinical practice will always be an issue and the results of a trial can only be generalisable if it is executed efficiently. The issue of data quality assurance is addressed in the CSR.[16] It is stated that a number of quality control safeguards were put into place, including, but not limited to, instructional material provided to study sites, investigator training sessions, periodic visits to study sites, contact maintained with study sites, use of standard computer edits to detect errors in data collection. Evidence of study monitoring is provided in the CSR[16] (CSR, p79) where it is reported that during routine site monitoring, Eli Lilly identified 17 events described as 'extraordinary', 'serious and/or persistent issues' that would not have been picked up from the electronic reporting forms. Once identified, the CSR[16] states that each issue was addressed and documented.

According to the CSR,[16] a total of 69 (19.2%) patients randomised to pemetrexed plus BSC and 27 (15.0%) patients randomised to placebo plus BSC had a protocol deviation. Table 7 summarises the protocol deviations that occurred. Levels of protocol deviations were low and most were comparable across the two treatment arms and so this is not of great concern to the ERG.

Table 7 PARAMOUNT summary of protocol deviations

Protocol Deviation	Pemetrexed + BSC (n=359) n(%)	Placebo + BSC (n=180) n(%)
Protocol inclusion/exclusion criteria	25 (7.0)	21 (2.4)
Study treatment continued after PD occurred	12 (3.3)	10 (5.6)
Patient randomized but response to induction therapy was NOT a CR, PR, or SD[a]	7 (1.9)	10 (5.6)
Patient randomized had less than 4 cycles in induction treatment	6 (1.7)	2 (1.1)
Patient randomized but ECOG PS not 0 or 1 following induction treatment	1 (0.3)	2 (1.1)
Incorrect dose modification	45 (12.5)	6 (3.3)

a in the manufacturers' response to the ERG's clarification letter, the numbers specified were 9 for the pemetrexed plus BSC arm and 8 for placebo plus BSC

4.1.6 PARAMOUNT outcome selection and measurement

The outcome measures and their definitions are presented in Table 8. All outcomes and methods of measurement are standard for this disease area.

Table 8 PARAMOUNT outcomes

Outcome	Definition and measure	Time of assessment
Primary outcome		
Objective PFS	Time from date of randomisation to the maintenance phase to the first date of objectively determined PD or death from any cause Tumour imaging was done by CT scans, MRI or chest X-rays and tumour response was assessed by the RECIST guidelines • The primary analysis was based on investigator- assessed PFS • Investigator- assessed PFS was validated by independent radiologists masked to treatment assignment	Scans at cycle 4 of induction phase were mandatory to determine eligibility for and serve as baseline for the maintenance phase, subsequently, once randomised to maintenance treatment, patients were followed every other cycle (6 ±1 weeks) until progression or death. Confirmation of response was required ≤ 4 weeks from the first evidence of response.
Secondary outcomes		
OS	The time from the date of randomisation to the maintenance phase to the date of death from any cause	
Objective tumour response rate	The proportion of randomised patients having a confirmed tumour response to maintenance therapy of PR or CR Tumour measurements were carried out by CT scan, MRI or chest X-ray	At baseline and every other cycle in the maintenance phase. Confirmation required ≤ 4 weeks from the first evidence of response. Thereafter, a responding patient was followed every other cycle (6 weeks ± 1 week)
HRQoL	EQ-5D	Baseline, day 1 of each cycle of induction and maintenance therapy, and 30-day post-discontinuation visit
Toxicity	National Cancer Institute (NCI) CTCAE (Common Terminology Criteria for Adverse Events) scale, version 3.0.	Assessed before every treatment cycle
Disease control rate	The proportion of randomised patients in each treatment arm who achieved a confirmed CR, PR, or SD	

RECIST=response evaluation criteria in solid tumours

4.1.7 PARAMOUNT trial description and critique of the statistical approach

The PARAMOUNT trial[11] consisted of two phases; the first phase was a non-randomised induction phase and the second was a double blind randomised maintenance phase.

According to the published paper[11] and the SAP, patients were randomised (2:1) to receive treatment using a computer generated random sequence with a block size of three. The trial report states that the "randomisation ratio was chosen to provide sufficient comparative data to show the superiority of pemetrexed plus BSC while reducing patient exposure to the potentially inferior treatment of placebo plus BSC." Randomisation was stratified with the following baseline and prognostic factors:

- ECOG performance status just before randomisation (0 vs 1);
- tumour response to induction CTX (complete or partial response vs stable disease);
- disease stage before administration of induction therapy (IIIB vs IV).

In the published paper it is stated that randomisation was done using the Pocock and Simon minimisation method; however the ERG found no mention of minimisation in other documents that described the PARAMOUNT trial[11] methodology. In their clarification response to the ERG, the manufacturer stated that minimisation was not used. The ERG is unclear as to why the main published report of the trial refers to the Simon and Pocock minimisation method but is satisfied with the method of randomisation.

Sample size calculation

The original sample size calculation was based on the primary outcome of PFS. The MS reports two protocol amendments, the first in October 2008 (prior to study initiation in November 2008) to include a power calculation for the analysis of OS and a second amendment in July 2009 to increase the power of the OS analysis. The amendments were made in response to requests from the United States Food and Drug Administration and are summarised in Table 9.

Both revisions involved changes to the sample size calculations; first decreasing the number randomised and then increasing the number randomised, but decreasing the number of events. The power was raised from 85% to 90% and the hazard ratio for PFS was changed from 0.70 to 0.65. It is stated in Appendix 10 of the MS that both revisions were in place prior to datalock and analysis. As part of the clarification process, the ERG queried the justification for these revisions. The manufacturer provided extra information on the revisions but failed to provide any further rationale behind them.

Table 9 PARAMOUNT Summary of protocol amendments

	Number to be enrolled	**Number to be randomised**	**PFS**			**OS**		
			Events	HR	Power (%)	Events	HR	Power (%)
Original protocol (28 May 2008)	570	399	294	0.70	85	-	-	-
Amendment A (06 October 2008)	600	372	238	0.65	90	260	0.70	80
Amendment B (30 July 2009**)**	900	558	238	0.65	90	390	0.70	93

HR=hazard ratio

In summary, a total of 900 participants were estimated to be required for enrolment to the induction phase to allow 558 people to be randomised to maintenance treatment with pemetrexed plus BSC. The calculation assumed a PFS HR of 0.65 and 238 events for PFS, and an OS HR of 0.70 and 390 events for OS. This analysis was fully powered for both PFS (90%) and OS (93%). Type I (alpha) error was controlled for the analysis of both PFS and OS so as to maintain an overall two-sided alpha level of 0.05. A gate keeping and alpha spending scheme approach was introduced to control the overall alpha

error in testing both PFS and OS. Assuming a statistically significant result for the primary analysis of PFS, this approach maintained full statistical power to assess OS at the time of survival maturity, without an adjustment in sample size.
The ERG considers the manufacturer's sample size calculations to be appropriate.

Statistical analyses
According to the MS, the analysis population for primary and secondary efficacy analyses was the intention-to-treat (ITT) population, defined as all patients randomised to maintenance treatment, whether or not study treatment was received, analysed according to the treatment assigned at randomisation. The analysis population for the safety analysis was all patients enrolled in the study that were treated with at least one dose of pemetrexed plus cisplatin during the induction phase.

The statistical methods used to analyse the efficacy outcomes in the PARAMOUNT trial[11] are presented in Table 10. The ERG is satisfied that in the main, these methods of analysis are appropriate, however the ERG notes that in the MS p-values are reported in relation to AEs, suggesting that hypothesis tests were performed although no formal statistical analysis of AEs was specified in the SAP.

Table 10 PARAMOUNT efficacy analyses

Outcomes	Method of analysis
PFS and OS	Comparison of the two treatment groups, made using an unadjusted log-rank test (two-sided). Median OS and PFS times estimated using the Kaplan-Meier method. Hazard ratios and associated two-sided 95% CIs computed using the Cox proportional hazards model.
Objective tumour response rate	Tumour response rate (CR + PR) and disease control rate (DCR=CR + PR + SD) were reported. Tumour response rate to induction therapy was calculated as the proportion of patients who achieved a CR or PR (confirmed or not). Disease control rates (DCRs) to maintenance therapy were calculated as the proportion of randomised patients in each treatment arm who achieved a confirmed CR, PR, or SD. Tumour response and DCRs were reported with 95% CI and were compared between randomisation arms using the Fisher exact test.
EQ-5D quality of life	A paired t-test and mixed effects repeated measures model (MMRM) were used to analyse changes from baseline. An analysis in STATA was used to estimate mean observed index scores. This was done by clustering individual patient data across all visits during the maintenance phase i.e. including maintenance baseline, all maintenance cycles and the 30-day post-discontinuation visit.
AEs	Summarised using descriptive statistics and p-values

The ERG is unclear as to how the manufacturer dealt with missing QoL data. In the CSR[16] (CSR, p58) it is stated that 'When scoring the quality of life scales for an individual questionnaire (EQ-5D), scores were imputed if at least 50% of the items within the scale were completed, based on the mean of the completed items.' However the manufacturer's response to the ERG clarification request states that imputation was only used in the sensitivity analysis.

Log-rank tests stratified by the following three randomisation factors were run for PFS and OS to assess the robustness of the unadjusted/non-stratified analyses: ECOG performance status prior to

randomisation (0 vs 1); tumour response to induction therapy (CR/PR vs SD), disease stage prior to randomisation (stage IIIB vs IV).

Cofactor-adjusted Cox models were run for PFS and OS with the following potentially prognostic cofactors: treatment arm (pemetrexed plus BSC vs placebo plus BSC); ECOG PS just prior to randomization (0 vs 1); tumour response to induction CTX (CR/PR vs SD); disease stage prior to administration of induction therapy (IIIB vs IV); sex (female vs male); histology (adenocarcinoma vs non-adenocarcinoma or unknown histology).

Subgroup analyses

Several subgroup analyses were also performed for PFS and OS to assess the potential impact of the following factors:

- Age: <70 vs ≥70 years; <65 vs ≥65 years;
- Smoking status: non-smokers vs smokers;
- Response to induction treatment: CR/ PR vs SD;
- Pre-randomisation ECOG performance status: PS 0 vs 1;
- Gender (male vs female);
- Histology: adenocarcinoma vs large cell carcinoma vs other histology.

The ERG notes from the SAP that the only subgroups specified in advance were those relating to histology. Performance status, response to first-line treatment, and disease stage before induction were also stratification factors for randomisation and so analyses of these subgroups were confirmatory. The ERG notes that subgroup analyses of age, smoking status and gender were not pre-specified in the SAP.

Meta-analysis

As only one RCT investigating the efficacy of pemetrexed is available, it was not possible to perform a meta-analysis.

4.2 Results

The CSR[16] (CSR, p24) states that subsequent to database lock, errors in the reporting database were discovered and that the errors remained in the reporting database used for all analyses in the CSR. The errors were considered to be minor and did not affect any conclusions reported in the CSR. However the ERG notes that the CSR[16] was approved in January 2011 when only the first set of analyses had been completed and errors may have since been corrected.

The MS (MS, p61) reports that participants in both arms of the trial received a median of four treatment cycles in the maintenance phase. The mean number of cycles in the pemetrexed plus BSC arm was 7.86 compared to 4.99 (placebo plus BSC). A greater proportion of patients in the

pemetrexed plus BSC arm received ≥6 cycles of maintenance treatment (47.1%) compared with placebo plus BSC (30.0%). The ERG notes that a number of participants received at least 10 cycles of treatment in the maintenance phase, 27.6% in the pemetrexed plus BSC arm and 11.7% in the placebo plus BSC arm.

The planned primary analysis for PFS was performed in July 2010 based on a data cut from June 2010, when 184 events (51.3%) in the pemetrexed plus BSC arm and 118 events (65.6%) in the placebo plus BSC arm had occurred.

The final analysis for OS has since been performed (based on March 2012 data cut). Table 11 shows the time-points of the analyses that have been performed to date.

Table 11 PARAMOUNT timing of analyses

Data cut-off/ Data lock date	**Analyses performed**	**Reason for analysis**
June 30, 2010/ July 30 2010	Primary PFS analysis (investigator assessed and independently reviewed) Tumour response HRQoL Preliminary OS analysis safety study drug exposure	Planned
February 7, 2011/ March 8 2011	4-month safety update and study drug exposure	For submission to FDA
May 16, 2011/ June 6 2011	Second preliminary analysis of overall survival, postdiscontinuation therapy and study drug exposure	Requested at the PARAMOUNT 29 November 2010 meeting with the FDA
March 5, 2012/ March 19 2012	Final OS analysis PDT and study drug exposure Updated PFS analysis Updated safety Updated QoL	Planned

PDT=post-discontinuation treatment

Progression-free survival data are presented in Table 12. At both analysis time-points, a PFS gain for pemetrexed plus BSC compared to placebo plus BSC is reported, a median of 1.28 months in June 2010 and 1.68 months in March 2012. The CSR[16] also includes results from independently reviewed data; the results are similar and therefore support the robustness of the results of the investigator assessments.

Table 12: PARAMOUNT progression-free survival at key analysis time points

Data cut-off	Treatment	Number of events (%)	Median PFS (months) (95% CI)	HR (95% CI)
June 30, 2010	Pemetrexed + BSC	184 (51.3)	4.11 (3.15 to 4.57)	0.62 (0.49 to 0.79)
	Placebo + BSC	118 (65.6)	2.83 (2.60 to 3.12)	
March 5, 2012	Pemetrexed + BSC	Not reported	4.4 (4.11 to 5.65)	0.60 (0.50 to 0.73)
	Placebo+ BSC	Not reported	2.76 (2.6 to 3.02)	

Overall survival data are presented in Table 13. The results of the first preliminary survival analysis did not meet the predefined level of statistical significance. Survival was immature with high censoring rates (78.6% and 74.4% for the pemetrexed plus BSC arm and placebo plus BSC arms, respectively). No further data are presented for the first preliminary analysis. At the final data cut-off in 2012, a median OS benefit of 2.85 months is reported for pemetrexed plus BSC compared to placebo plus BSC.

The percentage of people surviving at 1 year was 58% (95% CI 53 to 63) in the pemetrexed plus BSC arm and 45% (95% CI 38 to 53) in the placebo plus BSC arm. At 2 years, the percentage of people surviving was 32% (95% CI 27 to 37) in the pemetrexed plus BSC arm and 21% (95% CI 15 to 28) in the placebo plus BSC arm.

Table 13 PARAMOUNT overall survival at key analysis timepoints

Data cut-off	Treatment	Number of deaths n(%)	Median OS (months) (95% CI)	HR (95% CI)
June 30, 2010	Pemetrexed + BSC	Not reported	Not reported	Not reported
	Placebo +BSC	Not reported	Not reported	
May 16, 2011	Pemetrexed + BSC	188 (52.4)	Not reported	0.78 (0.61 to 0.98)
	Placebo+ BSC	111 (61.7)	Not reported	
March 5, 2012	Pemetrexed + BSC	256 (71.3)	13.86 (12.75 to 16.03)	0.78 (0.64 to 0.96)
	Placebo + BSC	141 (78.3)	11.01 (9.95 to 12.52)	

Tumour response rate and disease control rate are presented in Table 14. The manufacturer notes (MS, p65) that a substantial increase in the tumour response rate in the maintenance setting is unlikely as participants had already responded to induction treatment.

Table 14 PARAMOUNT tumour response and disease control July 2010

	Pemetrexed + BSC	Placebo + BSC
Tumour response rate % (95% CI)	4.2 (2.36 to 6.80)	1.1 (0.13 to 3.96)
Disease control rate % (95% CI) (CR + PR + SD).	71.8 (66.53 to 76.73)	59.6 (51.47 to 67.39)

Sensitivity analyses

Stratified analyses of OS and PFS, as described in section 4.1 were performed but not reported in the MS. Co-factor adjusted analyses (also described in section 4.1) were reported as similar and consistent with the results of the main unadjusted analysis but no data were reported.

Pre-specified sensitivity analyses which used alternative censoring rules were undertaken to evaluate the robustness of the PFS results. The sensitivity analyses support the robustness of the primary analysis and results 'strongly indicate' that post-discontinuation therapy and delayed radiologic assessments did not bias the primary analysis in favour of pemetrexed.

Subgroup analyses

Subgroup analyses were performed for both OS and PFS, as described in section 4.1. Results for PFS can be found in Figure 1. Results for OS can be found in Figure 2. All results are consistent with the results of the whole population, indicating that there is no difference in the estimate of treatment effect across the different subgroups of patients.

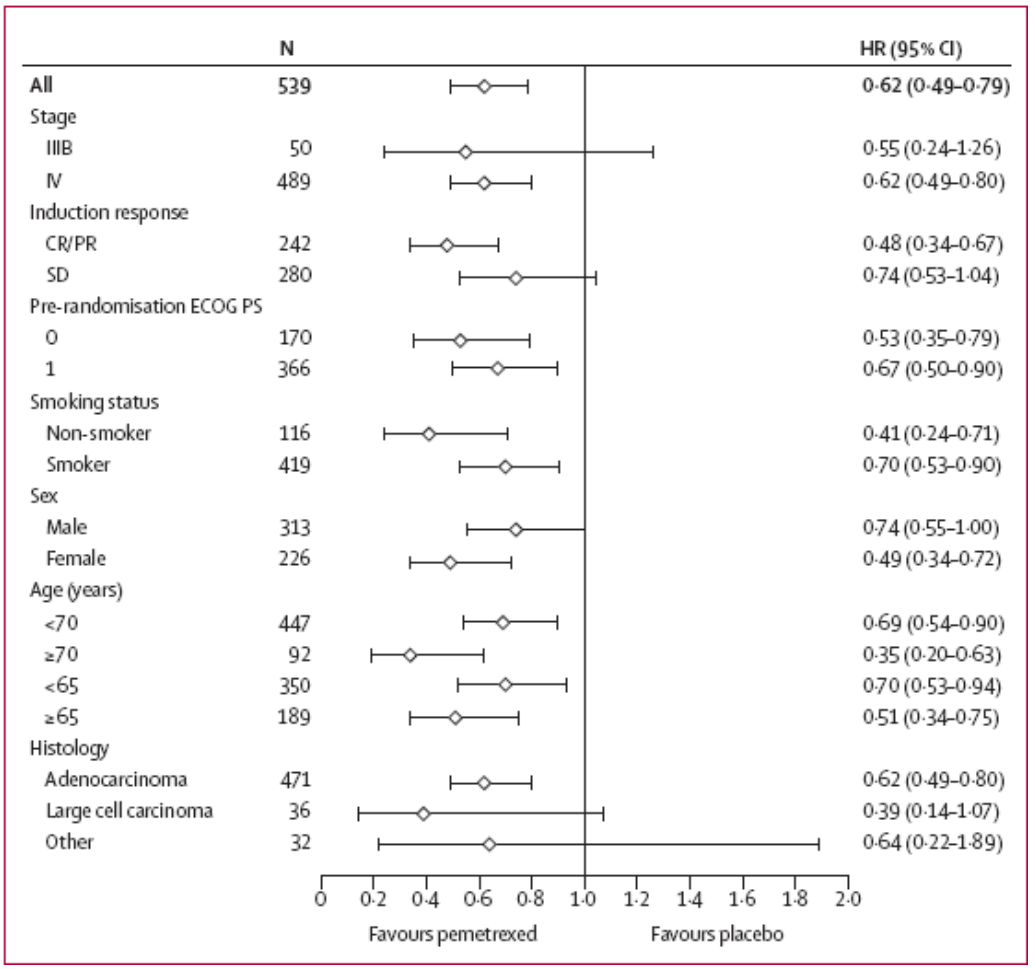

Figure 1 PARAMOUNT subgroup analyses for progression-free survival (MS, p65)

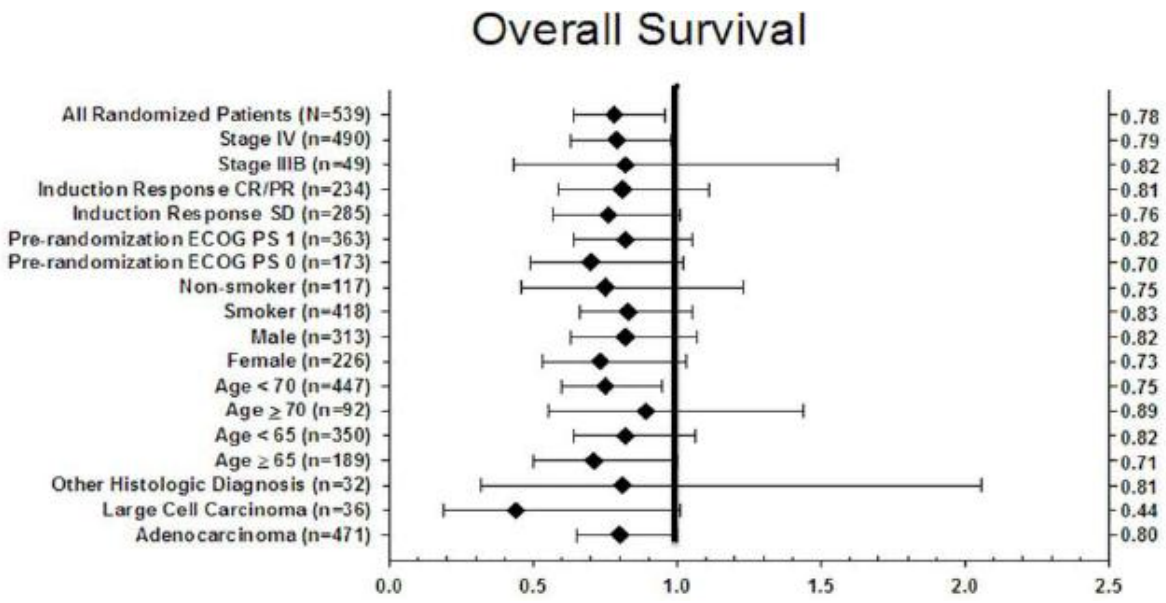

Figure 2 PARAMOUNT subgroup analyses for overall survival (MS, p68)

4.3 Health related quality of life

The EQ-5D questionnaire was used to collect HRQoL data. The MS reports that the completion rates were high, 83.6% for the pemetrexed plus BSC arm and 81.9% in the placebo plus BSC arm. Data from 325 patients in the pemetrexed plus BSC arm and 165 in the placebo plus BSC arm were included in the analysis as baseline data and at least one subsequent measurement was available during maintenance treatment. Table 15, taken from the MS, indicates that there is no difference in QoL between the two arms of the trial.

As part of the clarification process, the ERG requested extensive further details from the manufacturer regarding the conduct and analysis of the EQ-5D. The ERG is satisfied that the results of the EQ-5D exercise as reported by the manufacturer are reliable. The ERG is also aware of the difficulties in collecting HRQoL data during trials of this nature and notes that few trials report useful HRQoL outcomes.

Table 15 PARAMOUNT EQ-5D results

Measurement time points	**UK EQ-5D index scores (SD or 95% CI)**	
	Pemetrexed+BSC	**Placebo+BSC**
Prior to first-line treatment *	0.71	
N=805; single-arm open-label phase.	(SD 0.258)	
(2010 data lock reported in CSR[16])		
Maintenance baseline, i.e. prior to randomisation for maintenance treatment *	0.77	0.77
N=325 pemetrexed; N=165 placebo	(SD 0.210)	(SD 0.190)
(2012 data lock: DOF)		
Maintenance phase **		
i.e. includes EQ-5D data from maintenance baseline, all maintenance cycles and the 30-day post-discontinuation visit	0.7841* (0.7608-0.8074)*	0.8020* (0.7660-0.8381)*
30-days post-maintenance treatment discontinuation *	0.68 (SD 0.300)	0.68 (SD 0.287)
N=131 pem/BSC; N=77 placebo/BSC	(p<0.001 vs baseline)	(p=0.001 vs baseline)
(2012 data lock: DOF)		

* Analysed with paired t-test and MMRM **Analysed in STATA
DOF=data on file; SD=standard deviation;

4.4 Adverse events

The MS (MS, p74) states that the safety of pemetrexed plus BSC was evaluated at three timepoints: i) at the primary analysis for PFS (data lock 30th July 2010); ii) during a safety update (data lock 8th March 2011) and iii) at data lock for final OS (19th March 2012). All safety data reported in the MS are from the final 19th March 2012 data lock. Only the safety results for the maintenance phase are reported in the MS.

The frequency of grade 3 and 4 AEs occurring in ≥5% of trial participants reported in MS are described in Table 16. Fatigue, anaemia and neutropenia were all reported at a statistically significantly greater frequency by participants in the pemetrexed plus BSC arm compared to placebo plus BSC. The ERG notes that the figures quoted in the MS appear to be different to those in the main published paper that describes the PARAMOUNT trial[11] and are different again in the published paper that describes the safety and QoL results of that trial.[25] However, in all reports, fatigue, anaemia and neutropenia are the AEs that occur more frequently (with statistical significance) in the pemetrexed plus BSC arm of the trial.

Table 16 PARAMOUNT grade 3 and 4 adverse events

Adverse Event (Grade 3 or 4)	Pemetrexed + BSC N=359 N(%)	Placebo + BSC N=180 N(%)	p-value
Fatigue	19 (5.3)	2 (1.1)	0.017
Anaemia	24 (6.7)	1 (0.6)	<0.001
Neutropenia	22 (6.1)	0 (0.0)	<0.001

The MS provides a comparison of selected AEs between patients receiving more than six cycles of maintenance treatment and those receiving less than six cycles. This is summarised in Table 17. The manufacturer states that the incidence of all other AEs was not significantly different between the groups.

Table 17 PARAMOUNT selected adverse events for people receiving >6 or <6 cycles maintenance

Adverse Event	Treatment with > 6 cycles pemetrexed	Treatment with < 6 cycles pemetrexed	p- value
Grade 3, 4 or 5 non laboratory AEs (%)	12.4	11.3	0.867
Grade 3, 4 or 5 laboratory AEs %	11.1	16.5	0.147
Neutropenia %	9.8	4	0.039

Other selected AE data provided in the MS are summarised in Table 18. As part of the clarification process, the ERG requested from the manufacturer further information regarding the hospitalisations in the PARAMOUNT trial.[11] The ERG considers that AEs underlying the hospitalisations reported in the PARAMOUNT trial[11] reflect those generally experienced in lung cancer trials.

Table 18 PARAMOUNT selected adverse event data

Adverse Event	Pemetrexed+BSC N=359 N(%)	Placebo+BSC N=180 N(%)	p-value
Grade 3 or 4 non laboratory AEs	42 (11.7)	8 (4.4)	<0.001
Grade 3 or 4 laboratory AEs	47 (13.1)	1 (0.6)	<0.001
Treatment discontinued due to AE	43 (12)	8 (4.4)	0.005
Hospitalisations for treatment-related AE	39 (10.9)	6 (3.3)	0.003
Patients receiving transfusions	66 (18.4)	11 (6.1)	<0.001

Grade 1 and 2 adverse events

Clinical opinion to the ERG advised that in the maintenance setting, grade 1 and 2 toxicities should be considered in addition to grades 3 and 4 as grade 1 and 2 toxicities can have a significant impact on well-being and hospital resource. In addition, the ERG notes that the impact of a symptomatic grade 2 AE can be much greater than a non-symptomatic grade 4 AE.

The recently published paper describing safety and QoL in the PARAMOUNT trial[25] provides information on grades 1 and 2 treatment-related AEs reported by ≥3% of participants. This is summarised in Table 19. The rates of anaemia, neutropenia, nausea and vomiting are statistically significantly higher in the pemetrexed plus BSC arm compared to placebo plus BSC.

Table 19 PARAMOUNT Grade 1 and 2 AEs

Adverse Event Grade 1 or 2	Pemetrexed+BSC N=359 N(%)	Placebo+BSC N=180 N(%)	p-value
Anaemia	34 (10)	7 (4)	≤ 0.05
Neutropenia	17(5)	1 (0.6)	≤ 0.05
Fatigue	44 (12)	18 (10)	NS
Anorexia	13(4)	2 (1)	NS
Constipation	8 (2)	5 (3)	NS
Diarrhoea	10 (3)	3 (2)	NS
Mucositis/stomatitis	17 (5)	4 (2)	NS
Nausea	38 (11)	4 (2)	≤ 0.05
Vomiting	21 (6)	3 (2)	≤ 0.05
Edema	17 (5)	6 (3)	NS
Neuropathy: sensory	9 (3)	9 (5)	NS
Watery eye (epiphora, tearing)	9 (3)	1 (0.6)	NS
Pain	11 (3)	3 (2)	NS

In summarising the safety profile of pemetrexed maintenance therapy, the manufacturer points to data from previous RCTs, JMEI[26] in which pemetrexed was given as a second-line treatment and JMEN[27] in which pemetrexed was given as maintenance treatment. The ERG notes that pemetrexed was not given as a first-line treatment in either of these trials.

The manufacturer states that pemetrexed was well-tolerated in both JMEI[26] and JMEN[27] that the incidence of toxicities in the PARAMOUNT trial[11] was similar to the safety profile recorded in those trials and no new safety signals emerged from the PARAMOUNT trial.[11] The ERG notes that the EMA's assessment report[13] included a comparison of AEs reported in the JMEN trial,[27] JMDB trial[28] (a trial of first-line pemetrexed plus cisplatin) and the PARAMOUNT trial.[11] The EMA concluded that the safety results are consistent with the known safety profile of pemetrexed (p26).

4.4.1 Post-discontinuation treatments

The PARAMOUNT trial CSR[16] states that participants were unblinded to study treatment at disease progression and the protocol did not specify the treatments that patients should receive once they had completed their trial treatment. The post discontinuation treatments (PDT) are described in the final CSR and summarised in Table 20. As noted earlier, the manufacturer's sensitivity analysis indicates that PDT did not bias the primary analyses in favour of pemetrexed.

The ERG notes that in clinical practice in England and Wales, NICE recommends second-line CTX treatment with erlotinib or docetaxel. The majority of the participants in the PARAMOUNT trial[11] who received PDT received erlotinib or docetaxel. The ERG notes that the Royal College of Physicians/NIHR in their commentary to NICE for this appraisal, consider the rates of subsequent treatment to be higher than might be expected in clinical practice, but probably reflect the rigorous selection of patients to the trial. The ERG further notes that the patients in the placebo and BSC arm were regularly followed up with imaging to assess PFS, this means that early relapse will be detected and lead to a greater use of second-line treatment.

Table 20 PARAMOUNT summary of post-discontinuation treatment

	Pemetrexed + BSC (N=359)	Placebo + BSC (N=180)	p- value
Participants with post-discontinuation therapy n (%)	231 (64.3)	129 (71.7)	0.10
Drug name			
Erlotinib	142 (39.6)	78 (43.3)	0.41
Docetaxel	116 (32.3)	78 (43.3)	0.01
Gemcitabine	36 (10)	15 (8.3)	0.64
Vinorelbine	28 (7.8)	11 (6.1)	0.60
Investigational drug	20 (5.6)	8 (4.4)	0.68
Carboplatin	18 (5.0)	8 (4.4)	0.84
Paclitaxel	9 (2.5)	6 (3.3)	0.59
Pemetrexed	7 (1.9)	7 (3.9)	0.25
Cisplatin	5 (1.4)	4 (2.2)	0.49
Bevacizumab	6 (1.7)	1 (0.6)	0.43
Gefitinib	3 (0.8)	2 (1.1)	1.00
Afatinib	2 (0.6)	2 (1.1)	0.60
Placebo	4 (1.1)	0 (0.0)	0.31
Sorafenib	3 (0.8)	1 (0.6)	1.00
Aflibercept	1 (0.3)	1 (0.6)	1.00
Other*	18 (7)	6 (3)	-

* includes BIBF 1120, cyclophosphamide, etoposide, mitomycin, aspirin, antineoplastic agents, capecitabine, carboplatin + gemcitabine, cytarabine, doxorubicin, gemfibrozil, ifosfamide, lactoferrin, ritonavir, vincristine, vinflunine, zoledronic acid, other antineoplastic agents.

4.5 Conclusions of the clinical effectiveness section

The clinical effectiveness evidence was derived from a single well-designed and conducted trial with a participant population predominantly from European centres. However, compared to people seen in clinical practice in England and Wales, the trial participants were generally younger and fitter, a higher proportion presented with stage IV disease and there was a lower proportion of ever smokers. The mean number of cycles of active maintenance treatment given in the trial may be greater than would be the case in clinical practice in England and Wales. The data presented clearly demonstrate a statistically significant difference in favour of pemetrexed plus BSC over placebo plus BSC for both OS and PFS in a population of people of good PS who have stage IIIB/IV non-squamous NSCLC. The QoL status of trial participants was maintained and the reported AEs are consistent with the known profile of pemetrexed.

5 COST EFFECTIVENESS

This section provides a structured critique of the economic evidence submitted by Eli Lilly and Company Ltd. in support of the use of pemetrexed (Alimta®) as maintenance treatment of locally advanced or metastatic (stage IIIB/IV) non-squamous non-small cell lung cancer (NSCLC) for people whose disease has not progressed immediately following first-line induction chemotherapy (CTX) with pemetrexed and cisplatin. The two key components of the economic evidence presented in the MS are (i) a systematic review of the relevant literature and (ii) a report of the manufacturer's de novo economic evaluation. Table 21 contains details of the location of key information within the MS. The manufacturer has also provided an electronic version of their economic model which was developed in Microsoft Excel.

Following receipt of the clarification letter the manufacturer submitted a revised model and updated cost-effectiveness results. The results described in this document are those reported in the manufacturer's addendum, not those reported in the MS.

Table 21 Location of key economic information in the MS

Key information	Page number	Tables/figures
Details of the systematic review of the economic literature	87-92	
De novo analysis	92-98	Tables 22, Figure 12
Clinical evidence used in economic evaluation	99-112	Tables 23-27, Figure 13
Measurement and valuation of health effects	113-120	Tables 28-29
Resource identification, measurement and valuation	121-131	Tables 30-48
Sensitivity analysis	132-138	Table 49
Results – base case analysis	139-155	Tables 50-60
Subgroup analysis	156-157	
Interpretation of economic evidence	158-159	
Assessment of factors relevant to the NHS and other parties	160-168	Tables 61-72

5.1 ERG comment on manufacturer's review of cost-effectiveness evidence

The manufacturer's search was designed to identify studies that evaluated the cost effectiveness of maintenance treatments for patients with locally advanced or metastatic NSCLC. The search strategy was designed to inform the methodological approach for the economic evaluation and to identify data sources for relevant resources and health effects.

The literature search was performed on 4 February 2011 using NHS EED and on 7 February 2011 using MEDLINE and Embase. Subsequent searches were repeated on 5 October 2011 and 10

September 2012 to update the results. The search strategies used by the manufacturer are provided in the MS (Appendix 11, p14-15).

Hand-searching of retrieved articles and appraisals conducted by NICE was also undertaken by the manufacturer.

5.1.1 Inclusion and exclusion criteria used in study selection

The inclusion/exclusion criteria used by the manufacturer are summarised in Table 22. Full details are described in the MS (Appendix 11, p16).

Table 22 Economic review evaluation search inclusion and exclusion criteria

Parameter	Inclusion criteria	Exclusion criteria
Population	NSCLC stage IIIB-IV	Study not in the population of interest
Line of therapy	Maintenance treatment	Second-line therapy
Study design	Full economic evaluation (an evaluation of both costs and benefits)	Partial evaluation, cost minimisation, review
Other	Study findings generalisable to the UK population	Duplicates

5.1.2 Included studies

Two studies were identified by the literature search (Table 23). Both studies formed a part of NICE technology appraisals and thus details are available from the NICE website.[8, 9] The study from TA227 was subsequently published as a journal article.[29]

Table 23 Identified studies

Study ID	Study name	Year
TA190[8]	Pemetrexed in maintenance treatment of NSCLC	2010
TA227[9]	Erlotinib in maintenance treatment of NSCLC	2011

5.1.3 Conclusions of the review

The manufacturer's search to identify studies that evaluated the cost-effectiveness of maintenance treatments for patients with advanced NSCLC identified two NICE appraisals (TA190[8] and TA227[9]). The ERG is satisfied with the manufacturer's search strategy and is reasonably confident that the manufacturer did not miss any relevant published articles.

5.2 Summary and critique of manufacturer's submitted economic evaluation by the ERG

Checklists

Table 24 describes how closely the manufacturer's submitted economic evaluation accords with the requirements for a base-case analysis as set out in the NICE reference case checklist[30] and Table 25 summarises the ERG's appraisal of the economic evaluation conducted by the manufacturer using the Drummond checklist.[31]

Table 24 NICE reference case checklist

Attribute	Reference case	Does the de novo economic evaluation match the reference case?
Decision problem	The scope developed by the Institute	Yes
Comparator(s)	Alternative therapies routinely used in the NHS	Yes
Perspective costs	NHS and Personal Social Services	Yes, although the inclusion of Personal Social Service costs is limited.
Perspective benefits	All health effects on individuals	Health effects to the individual are captured via QALYs
Form of economic evaluation	Cost-effectiveness analysis	Cost-effectiveness analysis
Time horizon	Sufficient to capture differences in costs and outcomes	Yes – 15.99 years in the base case
Synthesis of evidence on outcomes	Systematic review	No - EQ-5D data were collected in the PARAMOUNT trial[11] and used in a mixed regression model to generate QALY estimates
Outcome measure	Quality adjusted life years	QALYs are used, which is appropriate
Health states for QALY	Described using a standardised and validated instrument	Yes – EQ-5D
Benefit valuation	Time-trade off or standard gamble	Yes - Time-trade off
Source of preference data for valuation of changes in HRQoL	Representative sample of the public	UK preference tariff based on public sample. Data for assigning valuation health states were collected directly from trial participants
Discount rate	An annual rate of 3.5% on both costs and health effects	Benefits and costs are discounted at the 3.5% rate
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	All QALYs estimated by the economic model have the same weight
Sensitivity analysis	Probabilistic sensitivity analysis	Yes - deterministic, scenario and probabilistic analyses are provided

QALY=quality adjusted life year

Table 25 Critical appraisal checklist of the manufacturer's economic evaluation

Question	Critical appraisal	ERG comment
Was a well-defined question posed in answerable form?	Yes	-
Was a comprehensive description of the competing alternatives given?	Yes	-
Was the effectiveness of the programme or services established?	Extent of outcome gains not secure	RCT provides direct comparison of survival and utility differences. However projection of benefits beyond the trial data is questionable
Were all the important and relevant costs and consequences for each alternative identified?	Mostly	The ERG notes social care costs are not fully considered but recognises the difficulty associated with estimating such costs.
Were costs and consequences measured accurately in appropriate physical units?	Mostly	Specific problem issues described in Section 8
Were the cost and consequences valued credibly?	Mostly	Specific problem issues described in Section 8
Were costs and consequences adjusted for differential timing?	Mostly	Specific problem issues described in Section 8
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	ICER calculated correctly
Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	Deterministic, scenario and probabilistic sensitivity analyses were undertaken
Did the presentation and discussion of study results include all issues of concern to users?	Yes	-

ICER=incremental cost-effectiveness ratio

5.2.1 Model structure

A schematic of the manufacturer's model is shown in Figure 3. It comprises three health states: pre-progression, post-progression and dead. All patients enter the model in the pre-progression health state following a course of pemetrexed plus cisplatin CTX. At the beginning of each time period patients can either remain in the same health state or progress to a 'worse' health state, i.e. move from pre-progression to post-progression or dead; or move from post-progression to dead.

The resource use and utilities applied in the pre-progression health state relate to the maintenance phase of treatment. The post-progression health state corresponds with NHS clinical practice following disease progression, representing the time period after maintenance treatment until death. On entering this state clinicians and patients reassess treatment options and a patient may be offered second-line treatment.

Variants of this model structure have been used frequently in the modelling of metastatic oncology for NICE STAs (TA227,[9] TA212,[32] Fleeman et al 2010,[33])

The model has been developed in Microsoft Excel and has a 21-day cycle length. It employs a continuity correction and the base-case time horizon is 15.99 years. A discount rate of 3.5% has been used for both costs and outcomes and the perspective is stated to be that of the NHS and Personal Social Services.

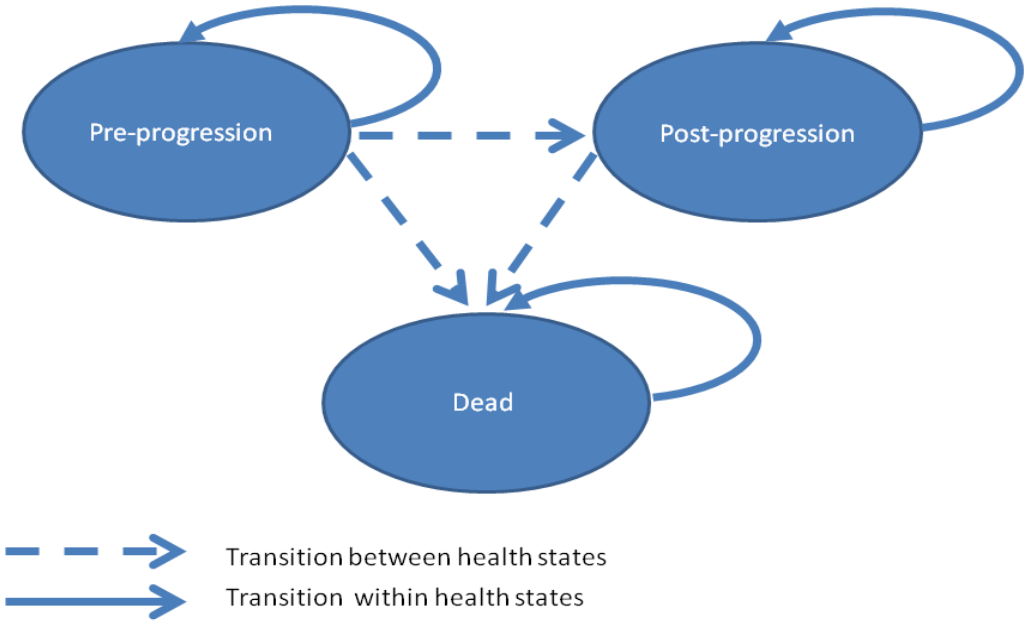

Figure 3 Model structure (MS, p95)

5.2.2 Population

The economic model was constructed to evaluate the cost effectiveness of maintenance treatments for patients with locally advanced or metastatic NSCLC in England and Wales. The base-case analysis uses PARAMOUNT trial[11] population data and assumes that the trial population is representative of the wider non-squamous stage IIIB or IV NSCLC population whose disease has not progressed following platinum-based CTX and who are of PS 0 or 1 (see Table 26 for details).

Table 26 Baseline population variables applied in the model

Variable	Value
Age, median (range)	61 (32-83) years
Gender	58% male; 42% female
Body surface area	1.79m^2 based on mean UK BSA values[34] weighted by gender observed in the PARAMOUNT trial[11]

5.2.3 Interventions and comparators

Pemetrexed is modelled as administered in the PARAMOUNT trial,[11] [i.e. at a dose of 500mg/m^2 administered by IV on day 1 of a 21-day cycle, plus BSC. Pemetrexed is administered until disease progression or death, unacceptable AEs, or withdrawal by patient or physician choice.

The comparator is placebo plus BSC. The manufacturer has assumed that BSC (and also terminal care) are delivered in line with recommendations set out in the NICE report Guidance on Cancer Services Improving Supportive and Palliative Care for Adults with Cancer: The Manual.[35]

Second-line chemotherapy

Data from the PARAMOUNT trial[11] show that 192 (72%) of placebo plus BSC patients and 231 (64%) of pemetrexed plus BSC patients received second-line CTX. Data from a UK 2012 market survey[36] suggests that of the patients who receive second-line CTX, 17% receive docetaxel, 70% receive erlotinib and 13% receive other CTX drugs. Within the model the manufacturer has ignored the use of other CTX drugs and, using a pro-rata approach, estimated that, in both arms, 20% of patients receive docetaxel and 80% of patients receive erlotinib.

Within the model the mean number of cycles of second-line CTX is 4.82 for docetaxel patients and 6.27 for erlotinib patients, consistent with the approach used in TA190. The mean numbers of cycles from the PARAMOUNT trial[11] (3.26 for docetaxel and 5.25 for erlotinib) are used in a sensitivity analysis.

5.2.4 Perspective, time horizon and discounting

The manufacturer states that the economic appraisal is undertaken from the perspective of the NHS and Personal Social Services. Outcomes are expressed in terms of gains in life years and quality adjusted life years (QALYs). The time horizon is set at between 6 and 20 years depending on the extrapolation method employed (15.99 years in the base case) and, in line with the NICE Methods Guide to Technology Appraisal,[30] both costs and benefits are discounted at 3.5%.

5.2.5 Treatment effectiveness and extrapolation

The model was developed using the final data lock (March 2012) of the PARAMOUNT trial.[11] Due to censoring (see Table 27) curves were fitted to the OS and PFS data to allow survival estimates to be made for the lifetime of the model. The PFS data were used to estimate the time in the pre-progression health state.

Table 27 Censoring of PARAMOUNT trial data at the March 2012 data lock

Variable	Pemetrexed + BSC	Placebo + BSC
Overall survival	28.7%	21.7%
Progression-free survival	8.1%	6.7%

Overall survival

Six alternative parametric distributions were explored for OS: exponential, Weibull, log-logistic, log-normal, Gompertz and gamma. The manufacturer concluded that, based on consideration of Akaike's Information Criterion (AIC), Bayesian Information Criterion (BIC) and Cox-Snell residual statistics,

visual fit and plausibility of survival estimate the gamma distribution was the most appropriate distribution. Curves were fitted to both arms at the point where approximately 20% of randomised patients remain at risk, i.e. cycle 31 for the placebo plus BSC arm (20% at risk) and cycle 37 in the pemetrexed plus BSC arm (19% at risk).

Progression free survival and treatment discontinuation

The approach taken to curve fitting for PFS and treatment discontinuation was the same as that used for fitting curves to the OS data. Again, the gamma distribution was selected as the most appropriate distribution for PFS and treatment discontinuation data.

Post-progression survival

Post-progression survival (PPS) is estimated as the difference between OS and PFS at each model timepoint.

5.2.6 Health related quality of life

Patients in the PARAMOUNT trial[11] were asked to rate their present health condition using the EQ-5D instrument. The EQ-5D questionnaire was administered and completed at the following time points:

- Prior to the first cycle of first-line CTX;
- On day one of each cycle of first-line treatment, prior to treatment administration;
- On day one of each cycle of maintenance therapy, prior to treatment administration;
- At the 30-day post-discontinuation follow-up visit, i.e. 30 days following maintenance treatment discontinuation.

Compliance was defined as the number of completed EQ-5D assessments divided by the number of visits attended and was 83.6% in the pemetrexed arm and 81.9% in the placebo arm.

Trial data did not provide values suitable to distinguish between patient experience in the pre-and post-progression health states and therefore a mixed regression analysis was carried out. The analysis considered the following covariates: treatment, disease progression and time before death. Utility values, which have been derived from adding together appropriate coefficients derived from the mixed regression model, are listed in Table 28.

Table 28 Utility values used in the model

State	Value
Pre-progression placebo + BSC >6 cycles prior to death	0.7758
Pre-progression pemetrexed + BSC >6 cycles prior to death	0.7510
Pre-progression placebo + BSC 5-6 cycles prior to death	0.7242
Pre-progression pemetrexed+ BSC 5-6 cycles prior to death	0.6994
Pre-progression placebo + BSC 3-4 cycles prior to death	0.6520
Pre-progression pemetrexed + BSC 3-4 cycles prior to death	0.6272
Pre-progression placebo + BSC 0-2 cycles prior to death	0.4099
Pre-progression pemetrexed + BSC 0-2 cycles prior to death	0.3851
Post-progression both arms >6 cycles prior to death	0.7028
Post-progression both arms 5-6 cycles prior to death	0.6512
Post-progression both arms 3-4 cycles prior to death	0.5790
Post-progression both arms 0-2 cycles prior to death	0.3369

5.2.7 Resources and costs

Chemotherapy acquisition and delivery costs

In the PARAMOUNT trial[11] the licensed dose of 500mg/m^2 BSA of pemetrexed was administered every 21 days with dose reductions made in accordance with the Summary of Product Characteristics (SPC).[37] Mean BSA values for UK lung cancer patients[34] weighted by gender from the PARAMOUNT trial[11] were used to calculate pemetrexed and docetaxel doses. UK list prices[38] were applied to the minimum number of vials required which was calculated based on the mean BSA. The base-case model includes drug wastage for part-used vials. NHS Reference Costs[39] are used to estimate delivery costs.

Erlotinib was costed in accordance with its SPC[40]. Delivery was assumed to occur every 21 days and NHS Reference Costs,[39] which were assumed are based on a 28-day cycle, were pro-rata-ed accordingly. The UK list price was reduced by 14.5% in line with the manufacturer's PAS. The cost of concomitant medications required to be administered with pemetrexed (i.e. vitamin B12 (£0.97 per cycle), folic acid (£0.57 per cycle) and dexamethasone (£1.57 per cycle)) have been excluded from the economic model as the manufacturer assumes these costs are included within the NHS Reference Cost for CTX delivery. Details are summarised in Table 29.

Table 29 Drug costs

Costs	Calculation	Value	Source
Pemetrexed			
BSA	58% male: mean BSA 1.89m^2 42% female: mean BSA 165m^2	1.79m^2	PARAMOUNT[11] Sacco et al. 2010[34]
Drug cost	SPC dose: 500mg/m^2 Vials: 1 x 500mg + 4 x 100mg Cost: 1 x £800 + 4 x £160	£1,440	BNF 2012[38]
Administration cost	SB12Z - Deliver simple parental CTX at first attendance (day case and regular day/night)	£208	NHS Reference Cost (NHS Trusts & PCTs) 2010/2011[39]
Docetaxel			
BSA		1.79m^2	
Drug cost	SPC[41] dose: 75mg/m^2 Vials: 1 x 80mg + 3 x 20mg Cost: 1 x £534.75 + 3 x £162.75	£1,023	BNF 2012[38]
Administration cost	SB12Z - Deliver simple parental CTX at first attendance (day case and regular day/night)	£208	NHS Reference Cost (NHS Trusts & PCTs) 2010/2011[39]
Erlotinib			
BSA	N/A		
Drug cost	SPC[40] dose: 150mg/day Cost (30 x 150mg tab pack): £1,631.53 14.5% PAS discount (TA227): £236.57	£976.47	BNF 2012[38]
Administration cost	SB11Z - Deliver exclusively oral CTX Cost for a 28-day cycle: £171	£128	NHS Reference Cost (NHS Trusts & PCTs) 2010/2011[39]

BSA=Body Surface Area; PAS=Patient Access Scheme; SPC=Summary of Product Characteristics

Costs of additional monitoring for patients receiving maintenance treatment

Details of maintenance treatment monitoring are presented in Table 30, with costs listed in Table 31.

Table 30 Maintenance treatment monitoring

Therapy	Time	Costs
Pemetrexed + BSC Placebo + BSC	Between weeks 4-6	Consultant visit:100% CT scan: 14% X-ray: 46%
Pemetrexed + BSC Placebo+ BSC	Between weeks 9-15	Consultant visit: 100% CT scan: 3% X-ray: 58%
Pemetrexed + BSC	Between weeks 18-24	Consultant visit: 100% CT scan: 3% X-ray: 58%

CT=computerised tomography

Table 31 Maintenance monitoring treatment costs

Costs	NHS HRG codes and assumptions (used directly or in calculation)	Value	Source
Maintenance monitoring – all patients			
370: Medical oncology	Consultant led: Follow-up attendance non-admitted face-to-face	£120	NHS Reference Cost (NHS Trusts & PCTs) 2010/2011[39]
CT scan	RA12Z: CT scan, two areas with contrast (no of scans=187,559)	£132.99	
	RA13Z: CT scan, three areas with contrast (no of scans=233,749)	£150.88	
	Average cost weighted by activity	£142.92	
X-ray	Assumed to be included in SB11Z and SB12Z. Therefore no additional cost.	N/A	NHS Reference Cost (NHS Trusts & PCTs) 2010/2011 [39]
Additional monitoring costs per cycle for patients receiving pemetrexed (every 24 weeks)			
Consultant follow-up visit	Unit cost: £119.99	£15 per cycle	NHS Reference Cost (NHS Trusts & PCTs) 2010/2011[39]
CT scan (3% of cohort)	Unit cost: £142.92	£0.54 per cycle	

HRG = Healthcare Resource Group; CT=computerised tomography

Adverse event costs

The cost of treating grade 3 and 4 AEs has been calculated using the approach that was used in TA190[8] (pemetrexed as switch maintenance) namely including all grade 3 and 4 AEs occurring at a rate of >2% plus nausea and vomiting combined. Costs were extracted from TA190[8] and inflated to 2011 prices (see Table 32).

Table 32 Key model parameters: adverse events

Adverse event	Rate per 21-day cycle		Cost per episode	Cost per cycle		Source
	Pem +BSC	Placebo + BSC		Pem +BSC	Placebo + BSC	
Neutropenia	0.0061	0.0000	£345.13	£2.09	£0.00	Rate: PARAMOUNT trial[11] Costs: TA190[8]
Nausea and vomiting	0.0008	0.0000	£670.67	£0.56	£0.00	
Fatigue	0.0053	0.0019	£141.31	£0.74	£0.26	
Anaemia	0.0066	0.0009	£609.41	£4.03	£0.57	
Total				**£7.43**	**£0.83**	

Pem=pemetrexed

Best supportive care and terminal care costs

The average drug cost for patients receiving BSC has been estimated using data from the PARAMOUNT trial[11] cohort; however, this does not apply to the base-case scenario. The cost has been derived by considering the therapies received by 10% or more of these patients and is estimated to be £3.41 per cycle. The drugs included alprazolam, amoxicillin with clavulanate, diclofenac sodium, doxycycline, furosemide, metoclopramide, morphine and omeprazole (MS, Appendix 20).

In TA190[8] the costs of BSC and terminal care were derived from information in the NICE report 'Guidance on Cancer Services Improving Supportive and Palliative Care for Adults with Cancer: Economic Review'[35, 42] These costs have been inflated to 2011 prices (see Table 33).

Table 33 Best supportive care and terminal care costs

Health state	Value used in TA190	Model revalued cost
BSC – no active CTX	£66.36 per cycle	72.44 per cycle
BSC – active CTX	£33.18 per cycle	£36.22 per cycle
Terminal care cost	£2,588.25 (one-off)	£2,825.29 (one-off)

5.2.8 Cost-effectiveness results

The base-case incremental cost-effectiveness ratio (ICER) results generated by the manufacturer's model are presented in Table 34. The ICERs for the target population are £47,576 per QALY gained and £34,613 per life year gained. A summary of predicted resource use by category of cost is presented in Table 35.

Table 34 Base-case results

Treatment	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£) (cost per LY)	ICER (£) (cost per QALY)
Pemetrexed+ BSC	£26,064	1.7047	1.1743	£12,153	0.3511	0.2554	£34,613	£47,576
Placebo + BSC	£13,912	1.3537	0.9188					

ICER=incremental cost-effectiveness ratio; LYG=life years; QALYs=quality adjusted life years

Table 35 Summary of predicted resource use by category of cost for the base case

Unit Cost	Pemetrexed + BSC	Placebo + BSC	Increment	% absolute increment
Therapy	£13,125	£0	£13,125	108.0%
Adverse events	£64	£4	£59	0.5%
Follow-up care	£10,177	£11,170	-£993	-8.2%
Terminal care	£2,699	£2,738	-£39	-0.3%
Total	£26,064	£13,912	£12,153	100%

Numbers may not compute due to rounding.

5.2.9 Sensitivity analyses

Deterministic sensitivity analyses

The manufacturer carried out 59 deterministic sensitivity analyses. The ICERs per QALY gained for these analyses ranged from £31,760 to £58,091. Further details are provided in Table 36. Results, presented in Table 37 for the ten parameters showing the greatest variability demonstrate that the ICER per QALY gained for pemetrexed + BSC in the modelled patients is most sensitive to using the lower quartile estimate (£928) for pemetrexed procurement costs (decrease in the ICER per QALY gained of £15,816) and modelling using fully parametric OS with observed PFS and treatment discontinuation (increase in the ICER per QALY gained of £10,515).

Table 36 Overview of deterministic univariate sensitivity analysis results

Parameter	Number of analyses for each parameter	ICER per QALY gained range
Pemetrexed costs	16	£31,760-£52,858
Additional monitoring for patients on pemetrexed	8	£48,056-£51,157
Second-line CTX costs	4	£44,050-£50,742
BSC and terminal care costs	4	£47,356-£49,088
PARAMOUNT resource use data	1	£51,527
Utilities	2	£45,447-£55,977
Efficacy	5	£40-517-£57,012
Structural	9	£43,506-£52,345
Cut points for extrapolation	5	£48,471-£58,091
Alternative parametric distributions	5	£42,902-£57,742
Total	59	£31,760-£58,091

ICER=incremental cost-effectiveness ratio; QALYs=quality adjusted life years

Table 37 Ten most sensitive deterministic univariate sensitivity analysis results

Parameter	Base-case value	ICER per QALY gained (base case £47,576)	Difference from base-case ICER per QALY gained
DH HRG daycase procurement costs for pemetrexed - lower quartile £928	£1,440	£31,760	£15,816
Fully parametric OS with observed PFS & treatment discontinuation	20% OS at risk	£58,091	£10,515
Post-trial treatment effect: pemetrexed + BSC is equivalent to placebo + BSC, i.e. treatment benefit for trial period only	Treatment effect assumed to continue beyond trial duration	£57,012	£9,436
OS treatment effect 95% lower CI (Time ratio:1.02)	OS treatment effect	£55,957	£8,381
OS treatment effect 95% upper CI (Time ratio:1.46)	OS treatment effect	£40,517	£7,059
DH HRG daycase procurement costs for pemetrexed - upper quartile £1,611	£1,440	£52,858	£5,282
Time horizon - 6 years (i.e. stop Markov trace at 105 cycles)	15.99 years	£52,345	£4,769
DH HRG daycase procurement costs for pemetrexed - average £1,293	£1,440	£43,035	£4,541
Discounting health effects at 0%	3.5%	£43,506	£4,070
OS: using all available observed OS data, i.e. 49 cycles placebo+BSC & 50 cycles pemetrexed +BSC	20% at risk	£51,272	£3,696

DH=Department of Health; HRG=health resource group; ICER=incremental cost-effectiveness ratio; QALY=quality adjusted life years; CI=Confidence Interval

Further sensitivity analyses were carried out using alternative parametric distribution to extrapolate OS/PFS/treatment discontinuation trial data. The results from these analyses are displayed in Table 38.

Table 38 Scenario analyses results

Alternative parametric distribution	Incremental cost (£)	Incremental mean OS (months)	Incremental benefit (QALY)	ICER per QALY gained
Gamma (base case)	£12,153	4.2	0.2554	£47,576
Exponential	£12,174	4.3	0.2583	£47,113
Weibull	£12,118	3.7	0.2236	£54,187
Gompertz	£12,082	3.4	0.2092	£57,742
Log-normal	£12,192	4.5	0.2738	£44,532
Log-logistic	£12,193	4.7	0.2842	£42,902

QALY=quality adjusted life years

Subgroup analyses

The manufacturer reported that no subgroup analyses were carried out. The ERG, however, notes that attempts have been made within the model to account for differences in subgroups but, as explained in Section 6.1.1, the ERG considers the methods used to be unreliable.

Probabilistic sensitivity analyses

The 1,000 simulations conducted by the manufacturer show that, at a threshold of £50,000 per QALY gained, pemetrexed plus BSC would be considered cost-effective in 54% of simulations. The cost-effectiveness plane and cost-effectiveness acceptability curve included in the MS are reproduced in

Figure 4 and Figure 5 respectively.

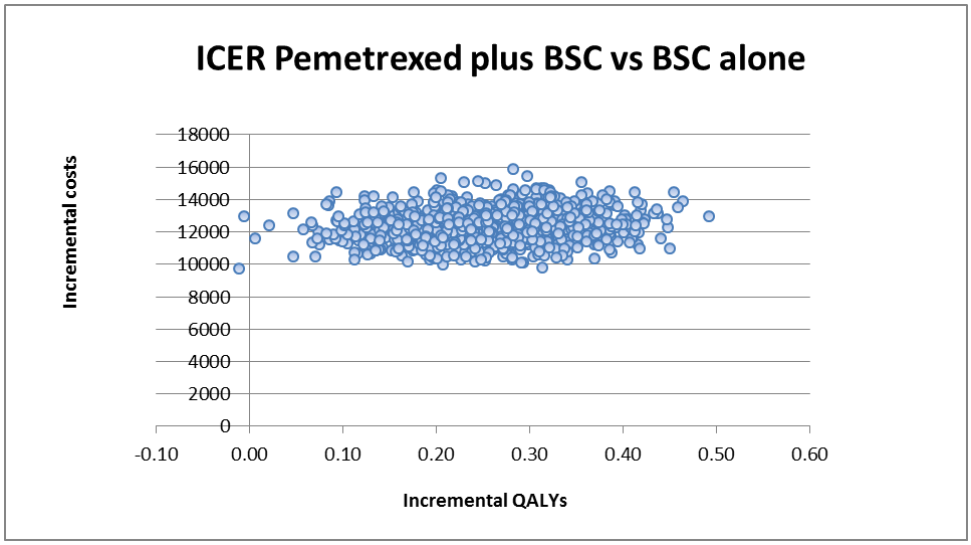

Figure 4 Incremental cost-effectiveness plane for base-case analysis (Addendum, Figure 16)

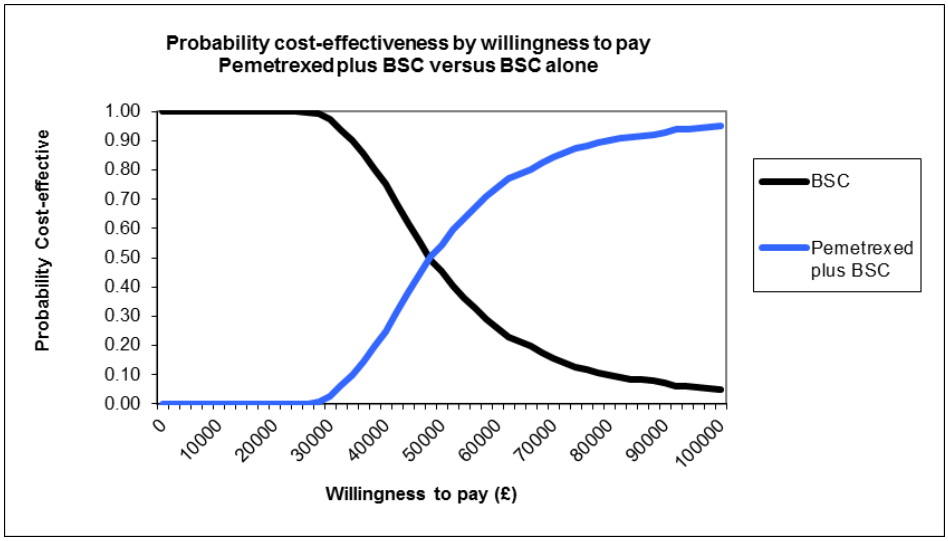

Figure 5 Cost-effectiveness acceptability curve (Addendum, Figure 17 p152)

5.2.10 Model validation and face validity check

The manufacturer states that the final model was subject to thorough validation. Further validation was undertaken by an independent analyst using a detailed model validation checklist (MS, Appendix 22). The independent verification process identified a number of errors which were subsequently resolved.

5.3 Summary of the cost-effectiveness section

The manufacturer's search to identify studies that evaluated the cost-effectiveness of maintenance treatments for patients with locally advanced or metastatic NSCLC identified two NICE appraisals (TA190[8] and TA227[9]). The ERG is satisfied with the manufacturer's search strategy and is reasonably confident that the manufacturer did not miss any relevant published articles.

The manufacturer's reported base-case ICER is £47,576 per QALY gained and £34,613 per life year gained.

6 IMPACT ON THE ICER OF ERG ADDITIONAL ANALYSES

6.1 Detailed critique of manufacturer's economic model

6.1.1 Model design and implementation

The manufacturer's model is implemented as a series of Microsoft Excel worksheets. Although the essential design of the model is very simple (two health states and death), its implementation at times seems unduly complex. Nonetheless the core of the model, which traces the progression of two cohorts of patients from initiation of maintenance therapy until death, appears to be largely sound. A particular feature of the model is the large number of control variables (41 on the 'Parameters' worksheet) provided to allow many alternative features to be explored in the analysis, although several are so specialised as to be unlikely to have much relevance in determining cost effectiveness.

The model additionally contains data and Visual Basic code to estimate cost effectiveness for a range of different subgroups. However, the results of applying this feature were not originally reported in the MS, though a full table of such results did in fact exist in the original model and showed far higher ICERs than in the manufacturer's base-case analysis. In the response to the ERG's clarification questions, the manufacturer has provided detail of the mode of operation of the subgroup analysis technique (based on modelling individual trial patients, rather than in aggregate).

The ERG has attempted to replicate this procedure for the base-case analysis to assess how well the results accord with the deterministic model results. Unfortunately, it only proved possible to activate this facility for a single preset scenario using a range of model parameter settings quite different from the submitted base case scenario. As access to the Visual Basic code was found to be password protected it was not possible for the ERG to complete this validation check.

6.1.2 Model implementation and parameter value issues (costs, resources and utility)

Method for estimating of pemetrexed costs

Pemetrexed monotherapy doses are calculated at 500mg/m^2 of BSA. In the manufacturer's base-case analysis a simple method is employed which uses a single average BSA figure for all patients, and determines the required number of vials of the drug required for such an average patient. This average BSA figure is the average of all patients (male and female) in the PARAMOUNT trial[11] and is slightly higher than the corresponding figure reported by Sacco et al[34] for UK CTX patients. However, this method of calculation ignores the effect of gender on BSA in altering the amount of drug wastage, as the wide distribution of BSA within the population (separately for males and females) typically increases the number of vials required to treat the whole population. The mean BSA figures reported

by Sacco et al[34] for UK CTX patients include those lung cancer patients whose treatment was adjuvant or neo-adjuvant rather than palliative. The ERG has therefore re-estimated the mean cost per cycle of pemetrexed acquisition, using UK distributional data for palliative CTX, and applying a maximum dose limit of 1000mg, yielding a figure of £1,481.37 per dose instead of the manufacturer's estimate of £1,440 per dose.

Mid-cycle correction error in estimating pemetrexed costs

It is conventional in state-based models which update key variables at fixed cycle times to estimate costs and outcomes which vary during the course of a cycle by averaging the value of the variable at the beginning and end of the cycle. This has been applied in the manufacturer's model to the calculation of the cost of pemetrexed CTX, by multiplying the cost per dose by the average number of patients on treatment during each cycle. However, pemetrexed is given on day one of each 21-day cycle, so the correct population receiving treatment is all those patients still on treatment at the beginning of each cycle. This contradicts the statement made on page 110 of the MS that "no half-cycle correction is applied to pemetrexed costs". This error has the effect of understating the true cost of pemetrexed treatment for every cycle of the model.

Post-progression chemotherapy

The manufacturer's model includes a parameter for the relative risk of surviving patients receiving further systemic therapy after discontinuing maintenance treatment (or 'watch and wait' BSC). This has been estimated as 0.88 indicating that pemetrexed plus BSC patients are 12% less likely to receive additional CTX than placebo plus BSC patients. However, Paz-Ares et al reported from the PARAMOUNT trial[11] that "A similar proportion of patients in both groups received post-discontinuation therapy" and indicated a p-value of 0.35 for the comparison. A chi-square test of the data used in the manufacturer's model yields a p-value of 0.44, confirming that there is no evidence of a greater propensity for further treatment in the placebo plus BSC arm. Since there is no *a priori* basis for supposing that surviving patients who have not received maintenance therapy will be any more prone to additional treatment, the ERG concludes that it is more appropriate to set the value of this model parameter to 1.0.

Method for estimating docetaxel costs

Docetaxel monotherapy doses for second-line CTX are calculated at 75mg/m^2 of BSA. The ERG has re-estimated the mean cost per cycle of docetaxel acquisition, using UK distributional data for palliative CTX as described above, arriving at a figure of £800.06 per dose based on the least expensive generic product featured in the BNF,[38] or £87.39 per dose using the corresponding average hospital contract prices reported by eMIT.[43] These costs contrast with that used in the manufacturer's model of £1,023 per dose.

Co-medication costs

Specific co-medication and vitamin supplementation are required for pemetrexed treatment (dexamethasone, folic acid and injected vitamin B12). The costs of these medications are estimated in the manufacturer's model, but omitted from the base-case results. As the specific co-medications are mandated within the SPC[37] for pemetrexed and are not required for any other CTX they represent a real differential cost beyond that normally included in the cost of administration of CTX. The targeted medications are directly relevant to treatment-related AEs. The ERG is of the opinion that these direct costs should be included in the base-case calculations.

Pre-progression monitoring costs

In the manufacturer's base-case analysis the routine monitoring of patients prior to disease progression is assumed to cost twice as much per cycle for placebo plus BSC patients as for those receiving pemetrexed maintenance therapy (apparently based on adapting the approach used by the manufacturer in TA190[8]) resulting in an extra cost per patient not receiving pemetrexed. If, instead, the follow-up pattern previously used by the ERG for the TA190[8] appraisal of pemetrexed maintenance therapy is applied to the manufacturer's model (review every 4 cycles on pemetrexed vs at 3, 6, 12, and 18 months for 'watch and wait' patients), the estimated discounted cost difference is £169.26 per patient greater for patients on pemetrexed monotherapy.

Omitted cost of blood products

The manufacturer's model shows a cost per blood transfusion of just £58. This relates to the cost of administering the transfusion in an out-patient setting, but does not include the cost of the blood product delivered. As a minimum, the ERG has increased the cost to include a unit of red blood cells priced at £125 from the NHS Blood and Transplant 2011-2012 Annual Review.[45] The cost of blood transfusions only features explicitly on a non-base case model scenario using a limited number of directly measured resources in the PARAMOUNT trial,[11] and therefore the ERG amendment does not have any effect on the base-case results.

Terminal care costs

In a recent review of first-line CTX for people with NSCLC,[46] a detailed estimate of terminal care costs for this patient population was undertaken, leading to a greater mean cost per patient than that used in the manufacturer's model (£3,906 compared to £2,825). Substituting this value leads to a slightly reduced ICER, due to the effect of discounting when death is deferred as a result of pemetrexed maintenance therapy.

Casemix adjusted utility model

Utility values have been modelled from the EQ-5D data obtained in the PARAMOUNT trial.[11] A statistical model was calibrated against the trial data, using variables to capture the influence of treatment (pemetrexed plus BSC vs placebo plus BSC), the time prior to death (measured in 21-day cycles) and the health state (pre- vs post-progression). A second model was also developed which featured four additional explanatory variables: ECOG PS, response to first-line CTX (SD vs CR/PR), historical illness, and cycle number as a proxy for time. Three of these covariate factors yielded coefficient values statistically significant at the 5% level, indicating that the adjusted model corresponds more closely to the observed trial data than the unadjusted model. However, the submitted base-case analysis uses the unadjusted model coefficients rather than those of the superior adjusted model. Although EQ-5D responses were received from all but one patient in the PARAMOUNT trial,[11] only 83% of responses were free of missing items. This introduces the opportunity for bias to influence the estimation of modelled utility values, suggesting that the adjusted model is probably the more reliable. Selecting the adjusted utility values in the model results in the ICER increasing by £1,659 per QALY gained.

Summary of ERG cost, resource use and utility changes

Table 39 summarises the effects of the amendments made by the ERG to the manufacturer's base-case model.

Table 39 Effect of cost, resource use and utility amendments made by the ERG to the base-case manufacturer's model

	Incremental cost	Incremental QALYs	ICER (£/QALY)	Change in ICER
Base-case analysis	**£12,153**	**0.2554**	**£47,576**	**-**
Pemetrexed drug cost	£12,479	0.2554	£48,854	+ £1,278
No mid-cycle correction	£12,906	0.2554	£50,524	+ £2,948
No difference in further CTX rates	£13,112	0.2554	£51,332	+ £3,756
Docetaxel drug cost*	£12,186	0.2554	£47,707	+ £131
Co-medication costs	£12,179	0.2554	£47,679	+ £103
PFS monitoring costs	£12,266	0.2554	£47,707	+ £443
Terminal care costs	£12,138	0.2554	£47,518	- £58
Adjusted utility model	£12,153	0.2468	£49,235	+ £1,659
All ERG cost, resource & utility changes	**£14,339**	**0.2468**	**£58,092**	**+ £10,516**

* using least expensive BNF prices (eMIT prices give IC = £12,293, ICER = £48,126)

6.1.3 Implementation of survival modelling and projection

Covariate adjusted survival models

For the manufacturer's base-case analysis it is assumed that the parametric models used for projecting PFS and OS beyond the available trial data should not take account of the influence of baseline covariates of patient characteristics in the PARAMOUNT trial.[11] It is suggested that taking these factors into account is unnecessary since the randomised allocation of patients should ensure that all relevant variables are fully balanced within the trial data set.

This should be the case when calculating results directly from the data, but may not be valid in relation to a parametric model fitted to those data, since any parametric model involves a number of implicit assumptions which may override the unbiased nature of the source data (not least the assumption that treatment and comparator may be modelled jointly). The use of covariate adjustment when fitting a parametric function allows the appropriateness of a selected parametric form to be tested. If significant non-zero coefficients are generated by the analysis this implies that the fit of the model can be improved with additional information, indicating that some degree of bias is present in the estimated function. The options then are either to use the covariate adjusted version of the model to correct partially for the bias, or seek an alternative parametric model formulation less prone to bias.

The submitted model contains the results of proportional hazards multivariate regression analyses of PFS and OS undertaken by the manufacturer which includes covariates drawn from the baseline patient characteristics data of the PARAMOUNT trial.[11] Most of the covariates included in the adjusted models exhibit statistically significant non-zero coefficients. This indicates that the adjusted PFS and OS models are superior to the unadjusted models, explaining significantly more of the inter-patient variation and at least partially correcting for modelling bias. The ERG is of the opinion that if

the manufacturer's preferred gamma functions are used for projecting PFS and OS beyond the observed data, then it is inappropriate to base the base-case analysis on the unadjusted models.

The effects of changing each of these assumptions are shown in Table 40, and indicate that using both adjusted models leads to a noticeable worsening of the cost effectiveness for pemetrexed maintenance.

Table 40 Effect of covariate adjusted survival models on cost effectiveness of pemetrexed maintenance therapy

	Incremental cost	Incremental QALYs	ICER (£/QALY)	Change in ICER
Base-case analysis	**£12,153**	**0.2554**	**£47,576**	**-**
PFS adjusted model	£12,155	0.2553	£44,609	+ £33
OS adjusted model	£12,135	0.2450	£49,534	+ £1,958
Both adjusted models	**£12,137**	**0.2449**	**£49,567**	**+ £1,991**

Selection of time point for projecting survival beyond Kaplan-Meier survival estimates

The manufacturer refers to the approach taken by the ERG in relation to NICE appraisal TA227[9] where a 20% maturity 'cut-point' was employed as the basis for switching from Kaplan-Meier data to projective modelling. However, it appears that the manufacturer has misunderstood the meaning of 'maturity' as it was previously applied. In TA227,[9] maturity refers to the maturity of the results obtained from Kaplan-Meier analysis of the trial data, i.e. the proportion of the original cohort who are estimated to remain event-free at a particular time, regardless of the absolute number of individuals not yet censored. By contrast, the manufacturer has sought to equalise the proportion of individuals remaining active in the dataset at the time of data cut-off, which is heavily influenced by the pattern of fall-out of subjects from the study. An analysis may be considered fully mature only when every individual has been followed through to the defined end-event, allowing for natural loss to follow-up. This precludes trials which are subject to right-censoring (early termination of the trial on a particular date), since such censoring ensures that it is impossible for a complete Kaplan-Meier estimated survival curve to be estimated, regardless of the number of individuals remaining at the date of general censoring.

In the PARAMOUNT trial,[11] the PFS data available may be considered effectively fully mature, since the estimated survival at last recorded event was only 3.7% in the placebo plus BSC arm and 4.2% in the pemetrexed plus BSC arm.

The choice of a common survival rate to determine the point at which projection takes over from Kaplan-Meier estimation is intended, as far as possible, to equalise the proportion of expected survival which is subject to modelling uncertainty in addition to sample error. The ERG has applied

this approach to the manufacturer's base case, using 'cut-off' survival thresholds of 15%, 20% and 25% as shown in Table 41. In all cases, when the same survival level is used for the transition to projective estimates, the ICER is less favourable to pemetrexed.

Table 41 Effect of applying equal OS 'cut-off' levels for transition from Kaplan-Meier estimates to projective modelling

	Cycle Placebo + BSC	Cycle Pem + BSC	Incremental cost	Incremental QALYs	ICER (£/QALY)	Change in ICER
Base-case analysis	**31**	**37**	**£12,153**	**0.2554**	**£47,576**	**-**
25% 'cut-point'	30	40	£12,140	0.2480	£48,953	+ £1,377
20% 'cut-point'	36	44	£12,093	0.2201	£54,936	+ £7,360
15% 'cut-point'	41	47	£12,043	0.1889	£63,755	+ £16,179

Pem=pemetrexed

Summary of ERG changes to manufacturer's survival model implementation

The effect of the projective survival modelling amendments made by the ERG are summarised in Table 42 and indicate that when the superior adjusted PFS and OS gamma models are applied and model projection is applied in a balanced fashioned to both arms of the model, the ICER is substantially increased to more than £56,000 per QALY.

Table 42 Effect of projective survival modelling amendments made by the ERG to the base-case manufacturer's model

	Incremental cost	Incremental QALYs	ICER (£ per QALY)	Change in ICER
Base- case analysis	£12,153	0.2554	£47,576	-
Use adjusted PFS and OS models	£12,137	0.2449	£49,567	+ £1,991
20% 'cut-point' for OS projection	£12,093	0.2201	£54,936	+ £7,360
Combined effect	£12,088	0.2155	£56,084	+ £8,508

6.1.4 ERG re-analysis of PARAMOUNT survival data

Post-progression survival

The manufacturer's base-case analysis estimates the mean additional survival for patients receiving pemetrexed plus BSC maintenance therapy as 4.6 months undiscounted (4.2 months discounted). Not all this advantage occurs in the pre-progression period when pemetrexed is administered; 27% of the undiscounted gain is generated after disease progression (23% when discounted).

To test whether this effect is evident in the PARAMOUNT trial[11] data, the ERG requested results of a Kaplan-Meier analysis of PPS. Figure 6 shows the PPS survival plot, indicating very close correspondence of survival for the two trial arms during this period, confirmed by a non-significant Log Rank test result (p = 0.759). On this basis the ERG concluded that the prognosis of patients at the time of confirmed disease progression should be considered independently of the randomised

treatment. Using the results of a single combined Kaplan-Meier analysis of pooled PPS data, the ERG was able to calibrate a Weibull projective model which accurately replicates the PARAMOUNT trial[11] data (Figure 7). This yields an estimated mean PPS (undiscounted) for all patients in the trial of 13.4 months.

If the prognosis for patients entering the post-progression state is the same for all patients, is there another cause which could justify the additional PPS gain in the manufacturer's model? This could be explained if there were a sufficient difference in the proportion of patients failing to enter the post-progression state because their progression-event was fatal. Analysis of data from the PARAMOUNT trial[11] indicates that there is no significant difference in the fatal component of progression events, and the difference detected (10.6% pemetrexed vs 7.1% placebo) would lead to worse PPS results for pemetrexed, rather than the additional survival gains produced by the manufacturer's model.

It is not possible to calculate an accurate estimate of the effect of eliminating this questionable PPS gain from the manufacturer's model since PPS is not a primary model variable, being derived from the OS and PFS models. An approximation in which the excess QALY gain is removed and a pro-rata adjustment to post-progression follow-up is applied suggests that the base-case ICER would increase from £47,576 per QALY to about £55,000 per QALY.

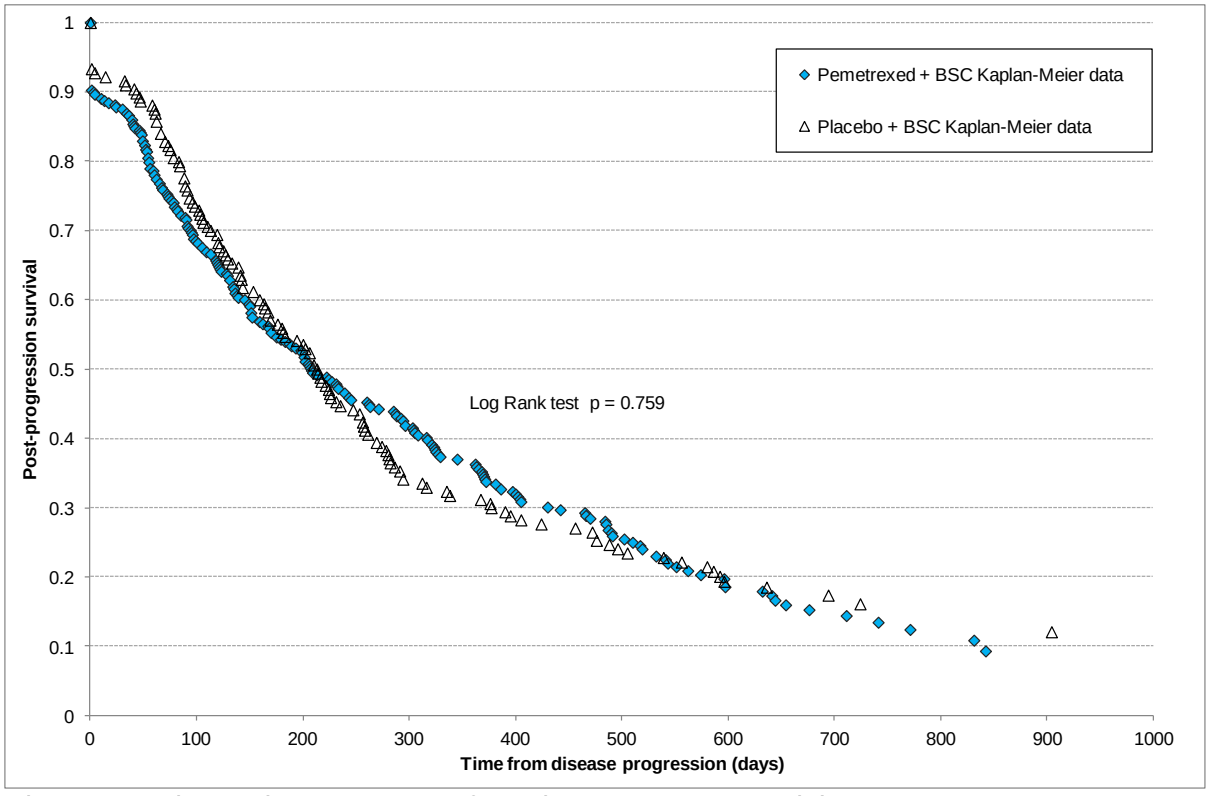

Figure 6 Kaplan-Meier PPS curves from the PARAMOUNT trial

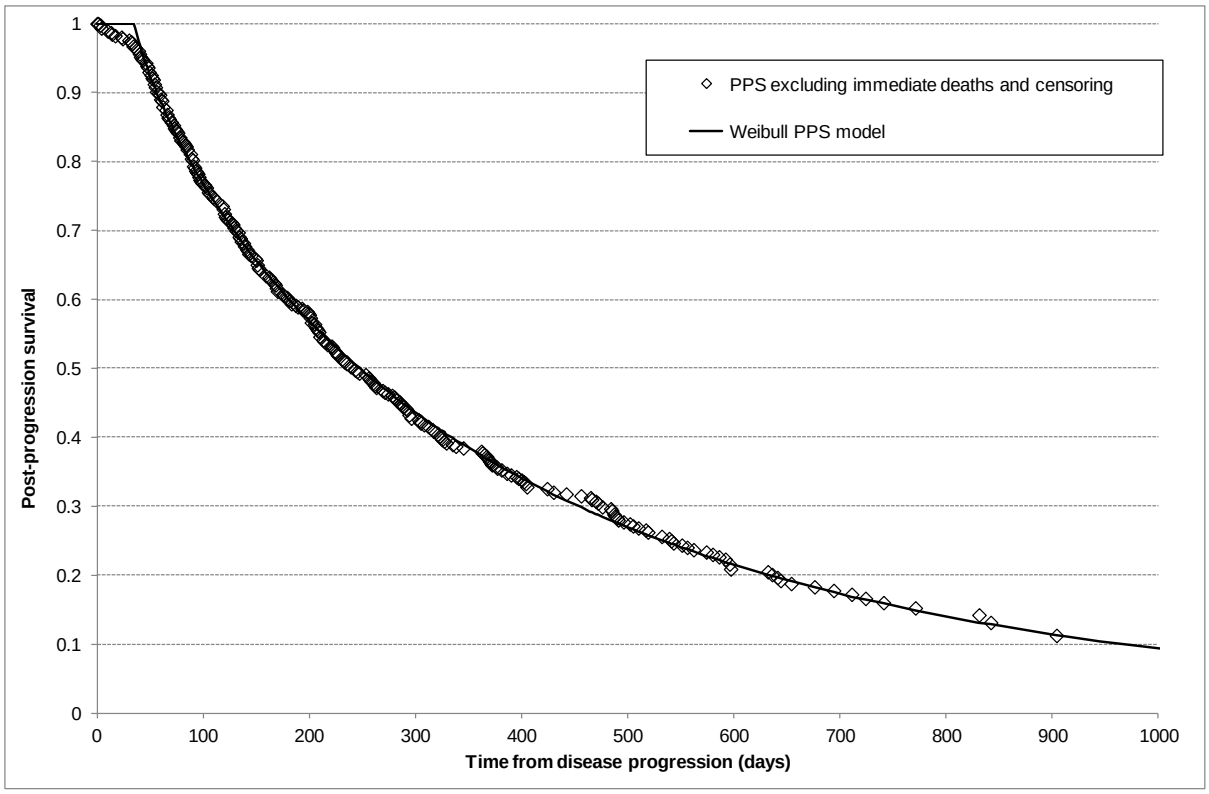

Figure 7 Pooled PPS survival curve form the PARAMOUNT trial with fitted Weibull parametric function. (Patients dying or censored on day 1 have been removed for clarity)

Overall survival

The results obtained with the manufacturer's model are strongly influenced by the method adopted for analysing time-to-event data. This is most important when modelling OS, since this determines the dominant outcome variable (quality adjusted life years), and because the OS data from the PARAMOUNT trial[11] are less mature than for other variables so greater reliance is placed on projective modelling to fill the data deficit. The approach adopted is based on using a single parametric function designed to generate OS projection estimates for both trial arms simultaneously, featuring a binary variable to alter the event hazard depending on the randomised treatment. This introduces a very strong constraint on the analysis which can easily introduce serious bias into the resulting trendlines. The manufacturer sought to justify this assumption with residual plots (MS, Appendix 16) and OS survival plots (MS, Appendix 17). In addition, the MS Appendix 18 includes AIC statistics to support the selection of the gamma function as preferable to five other standard distributions. However, the extent of the mismatch of the fitted gamma model to the observed trial data is most clearly seen when the residuals are plotted to indicate the patterns of over- and underestimation (Figure 8 and Figure 9).

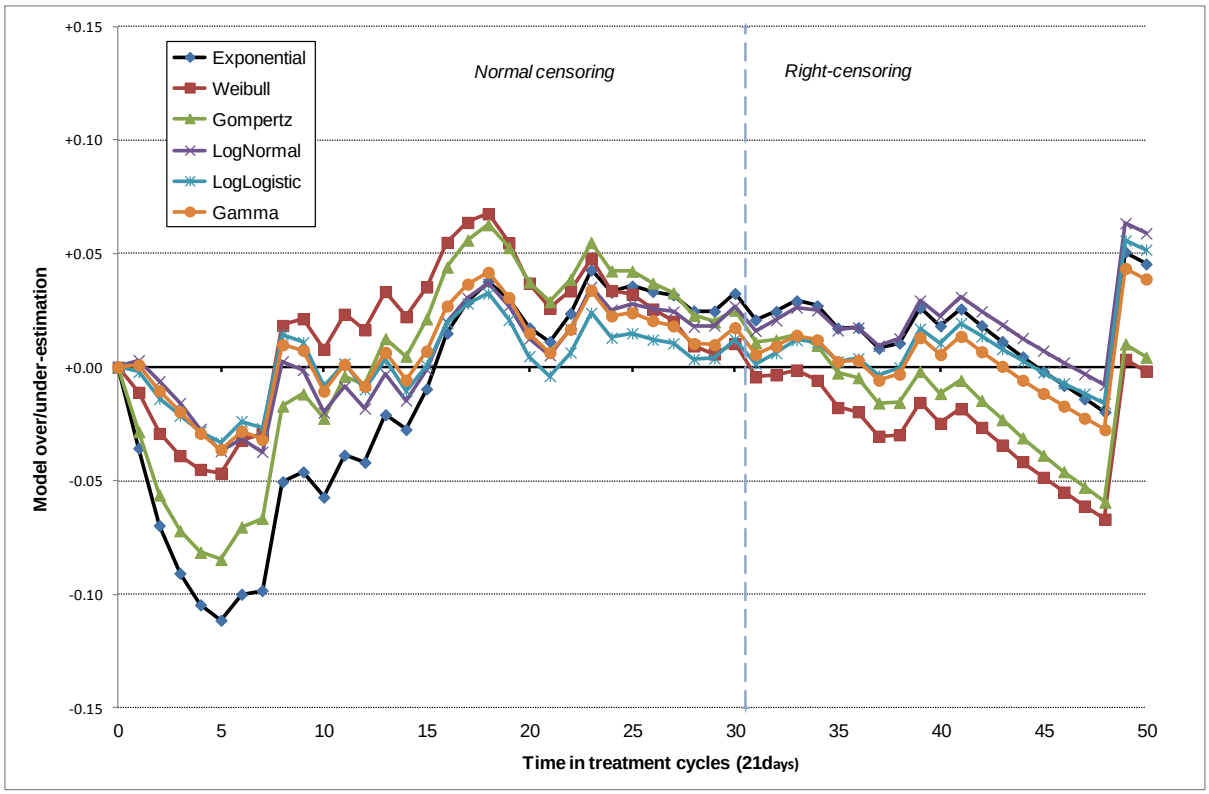

Figure 8 Over- and underestimation of OS by six standard survival functions calibrated against the placebo+BSC arm of the PARAMOUNT trial

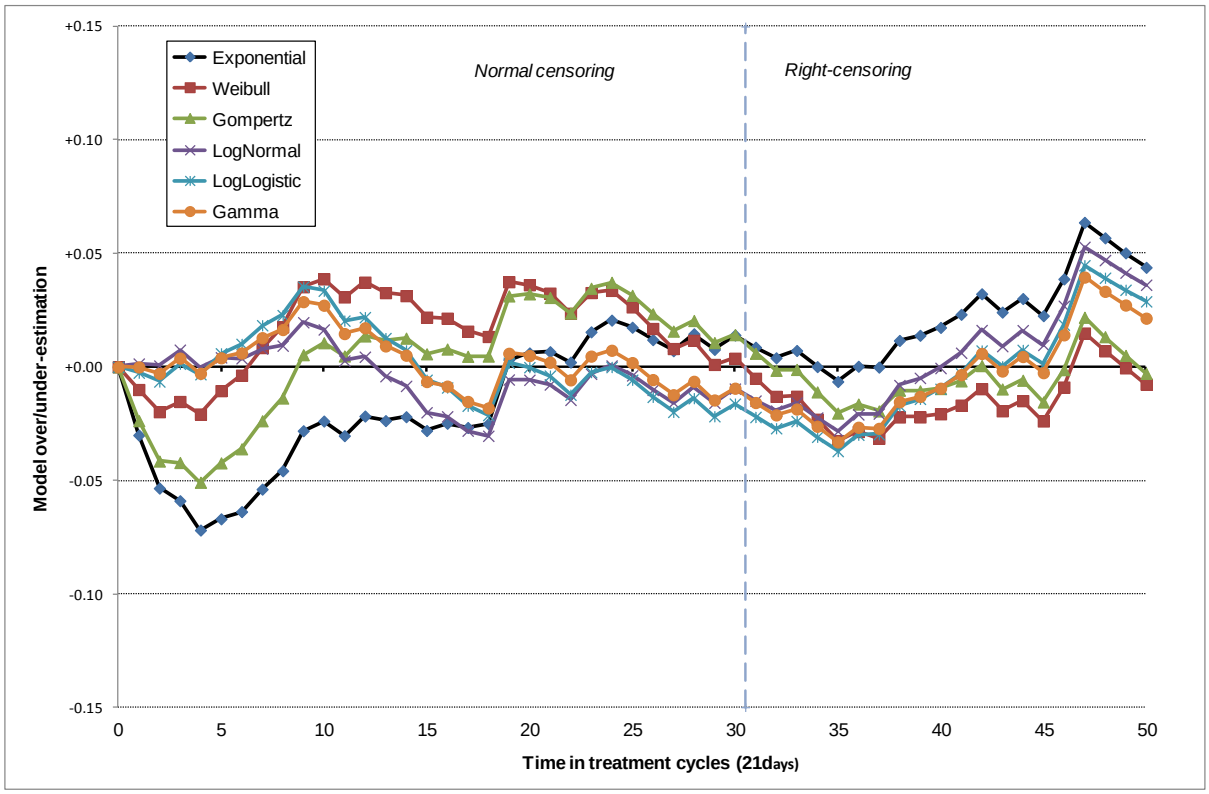

Figure 9 Over- and underestimation of OS by six standard survival functions calibrated against the pemetrexed+BSC arm of the PARAMOUNT trial

Systematic patterns of deviation from random fluctuation can be observed for both treatment arms, but are most pronounced in the placebo plus BSC arm which is based on the smaller sample size (due to 2:1 randomisation) and therefore likely to suffer double the magnitude of compensatory bias. There are general tendencies toward underestimation in the early period, followed by a smaller over-estimation in the middle period. However, most important are the contrary trends in the later trial period when right censoring is in operation. This is the phase in which it is necessary to establish a trend for use in projecting survival beyond the observed data until all patients have died. In the placebo plus BSC arm the trend is toward steadily increasing underestimation of survival, whereas in the pemetrexed plus BSC arm the gamma function trends steadily increase overestimation of OS. The consequence of this misspecification of the survival function combined with the constraint of using a single jointly estimated model is that incremental projected differences in expected OS are seriously biased in favour of pemetrexed plus BSC, and do not represent the true underlying differences attributable to pemetrexed maintenance therapy. This is the main source of the additional gain in PPS described above and shown to be unsupportable from the PPS trial data.

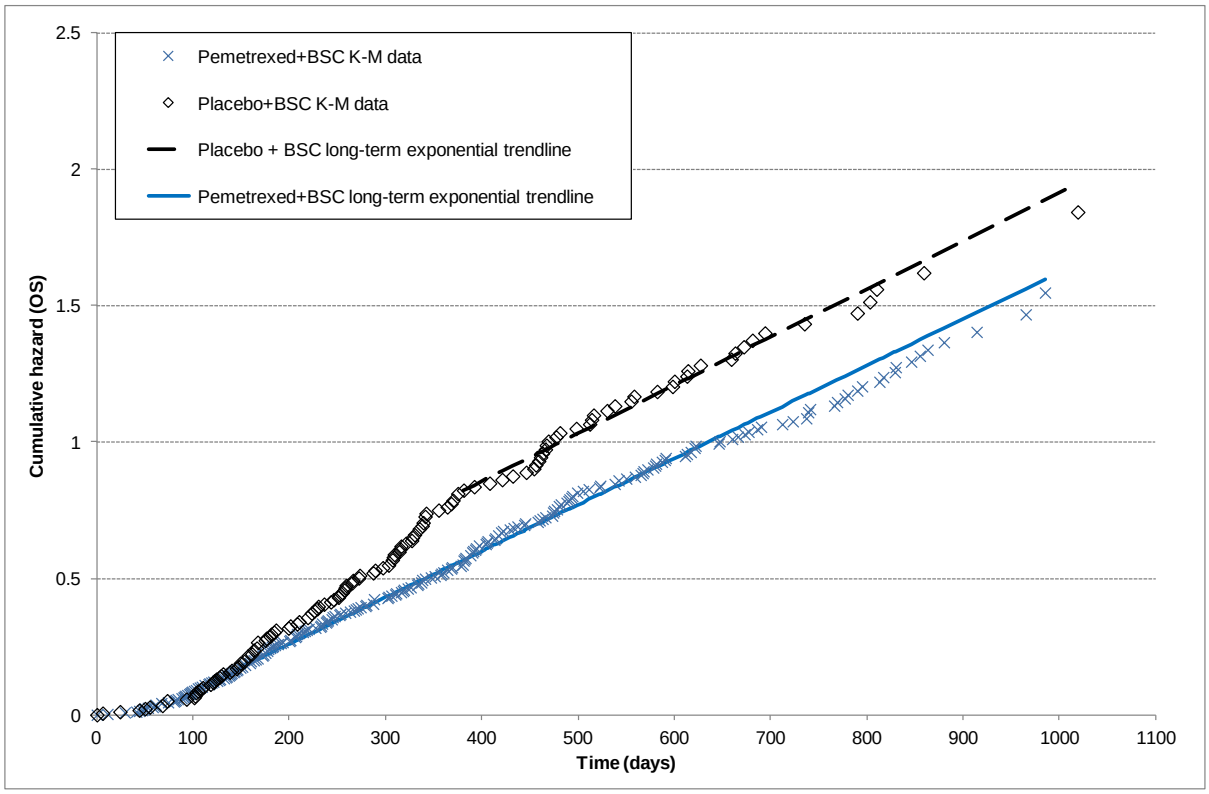

Figure 10 Comparison of cumulative OS hazards in both arms of the PARAMOUNT trial with ERG calibrated exponential trend.

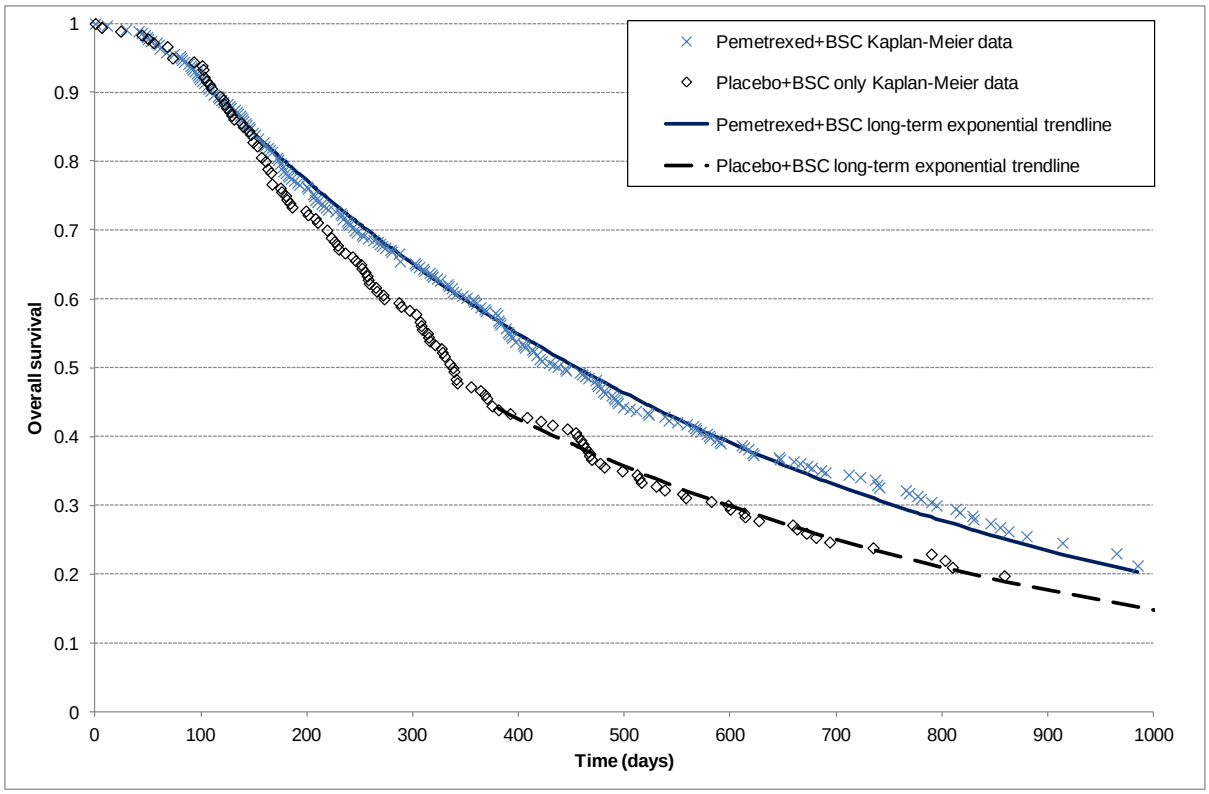

Figure 11 Comparison of OS in both arms of the PARAMOUNT trial with ERG calibrated exponential long-term models

In Figure 10 it is easily seen that the data available for the trial arms are not amenable to proportional hazards modelling. The trends run together for about 5 months and then diverge steadily for the rest of the first year. Thereafter, the two arms run parallel indicating that the long-term mortality risk is very similar, as would be expected since by this time almost all surviving patients have already suffered disease progression, and should therefore be subject to the same PPS risk as described above. Figure 11 indicates the close correspondence in both arms of the trial between the observed data and the long-term projective exponential models fitted by the ERG.

Substituting these long-term OS trends in place of the gamma function, without any other changes to the manufacturer's base case, has a significant impact on the cost effectiveness of pemetrexed maintenance therapy. Incremental costs are reduced by only £103 per patient, but incremental QALYs reduce by more than 24% so that the ICER is increased by £14,859 per QALY to £62,435 per QALY, indicating the strong influence that model-generated PPS gain has in restricting the size of the ICER in the submitted base case.

6.2 Revised model results for three alternative sets of assumptions

Results are presented for three sets of modifications to the manufacturer's decision model, defined by different sets of assumptions governing how selected alterations (as detailed above) are used in combination to produce alternative scenarios as follows:

1. Manufacturer's base-case analysis (No changes)
2. Apply only the basic set of corrections and parameter amendments detailed in Section 6.1.2 (Basic changes only)
3. Apply the basic changes, use the casemix adjusted PFS and OS projective functions provided in the model, and alter the cut-off for projective modelling to 20% of Kaplan-Meier survival in each arm (Casemix adjusted models) as detailed in 6.1.3
4. Apply the basic changes with the casemix adjusted PFS model, but replace the OS model with the ERG alternative formulation (ERG OS model) as detailed in 6.1.4

Scenario 1 is the manufacturer's base-case analysis.

Scenario 2 assumes that all structures and analyses in the manufacturer's model are appropriate, and only formula errors and parameter values need to be amended.

Scenario 3 assumes that the survival modelling using gamma functions is appropriate, adequately reflecting the trial data, provided casemix adjustments are applied and projections are applied consistently between the arms of the evaluation.

Scenario 4 rejects the use of a single OS gamma function based on the proportional hazards assumption which generates additional PPS gain for pemetrexed, and prefers the ERG approach to modelling long-term survival. The construction of each scenario is summarised in Table 43.

Table 43 Model amendments active in each ERG scenario

Scenario	Scenario 1 Base case	Scenario 2 Basic alterations only	Scenario 3 Basic + adjusted survival models	Scenario 4 Basic + adjusted PFS model + ERG OS model
Pemetrexed drug cost	No	Yes	Yes	Yes
Mid-cycle correction error	No	Yes	Yes	Yes
Later CTX use	No	Yes	Yes	Yes
Docetaxel drug cost	No	Yes	Yes	Yes
Use adjusted EQ-5D model	No	Yes	Yes	Yes
Use adjusted PFS model	No	No	Yes	Yes
Use adjusted OS model	No	No	Yes	No
Cost of co-medications	No	Yes	Yes	Yes
PFS follow-up cost	No	Yes	Yes	Yes
Terminal care cost	No	Yes	Yes	Yes
OS projection at 20% survival	No	No	Yes	No
Use ERG OS long-term model	No	No	No	Yes

Table 44 provides a detailed analysis of the individual impact of each model amendment compared to the manufacturer's base-case deterministic result. Changes affecting the way that OS is estimated have the largest impact, followed by the method used to estimate drug costs. In all scenarios the undiscounted survival gain exceeds 3 months. However all three ERG scenarios indicate an amended ICER substantially greater than £50,000 per QALY gained (Table 45).

Table 44 Cost and outcome effects of each ERG model amendment relative to the manufacturer's base case analysis

Adjustment	Placebo + BSC				Pemetrexed + BSC				Incremental				
	Therapy cost	Other costs	Survival (months)*	QALYs	Therapy cost	Other costs	Survival (months)*	QALYs	Survival (months)*	Cost	QALYs	ICER (£/QALY)	ICER change
Base case	**£0**	**£13,912**	**16.82**	**0.9188**	**£13,125**	**£12,939**	**21.46**	**1.1743**	**4.65**	**£12,153**	**0.2554**	**£47,576**	**-**
Pemetrexed drug cost	£0	£13,912	16.82	0.9188	£13,451	£12,939	21.46	1.1743	4.65	£12,479	0.2554	£48,854	+£1,278
Mid-cycle correction error	£0	£13,912	16.82	0.9188	£13,878	£12,939	21.46	1.1743	4.65	£12,906	0.2554	£50,524	+£2,948
2nd-line CTX use	£0	£13,912	16.82	0.9188	£13,125	£13,899	21.46	1.1743	4.65	£13,112	0.2554	£51,332	+£3,756
Docetaxel drug cost	£0	£13,605	16.82	0.9188	£13,125	£12,666	21.46	1.1743	4.65	£12,186	0.2554	£47,707	+£131
Use adjusted EQ-5D model	£0	£13,912	16.82	0.9103	£13,125	£13,899	21.46	1.1571	4.65	£12,153	0.2468	£49,235	+£1,659
Use adjusted PFS model	£0	£13,912	16.82	0.9188	£13,125	£12,941	21.46	1.1742	4.65	£12,155	0.2553	£47,609	+£33
Use adjusted OS model	£0	£13,870	16.31	0.8938	£13,125	£12,880	20.72	1.1388	4.41	£12,135	0.2450	£49,534	+£1,958
Cost of co-medications	£0	£13,912	16.82	0.9188	£13,151	£12,939	21.46	1.1743	4.65	£12,179	0.2554	£47,679	+£103
PFS follow-up cost	£0	£12,599	16.82	0.9188	£13,125	£11,740	21.46	1.1743	4.65	£12,266	0.2554	£48,019	+£443
Terminal care cost	£0	£14,959	16.82	0.9188	£13,125	£13,972	21.46	1.1743	4.65	£12,138	0.2554	£47,518	-£58
OS projection set at 20% survival	£0	£13,914	16.83	0.9197	£13,125	£12,882	20.79	1.1398	3.98	£12,093	0.2201	£54,936	+ £7,360
Use ERG OS long-term model	£0	£13,977	17.52	0.9585	£13,125	£12,902	20.89	1.1515	3.38	£12,050	0.1930	£62,435	+£14,859

* survival is undiscounted, all other figures are discounted

Table 45 Comparison of results from manufacturer's base-case analysis and three ERG scenarios

Adjustment	Placebo + BSC				Pemetrexed + BSC				Incremental				
	Therapy cost	Other costs	Survival (months)*	QALYs	Therapy cost	Other costs	Survival (months)*	QALYs	Survival (months)*	Cost	QALYs	ICER (£/QALY)	ICER change
Scenario 1 Base case	**£0**	**£13,912**	**16.82**	**0.9188**	**£13,125**	**£12,939**	**21.46**	**1.1743**	**4.65**	**£12,153**	**0.2554**	**£47,576**	**-**
Scenario 2 Basic alterations only	**£0**	**£13,340**	**16.82**	**0.9103**	**£14,251**	**£13,427**	**21.46**	**1.1571**	**4.65**	**£14,339**	**0.2468**	**£58,092**	**+£10,516**
Scenario 3 Basic alterations + casemix adjusted survival models	**£0**	**£13,307**	**16.39**	**0.8890**	**£14,251**	**£13,332**	**20.24**	**1.0964**	**3.85**	**£14,276**	**0.2075**	**£68,810**	**+£21,234**
Scenario 4 Basic alterations + casemix adjusted PFS model + ERG OS model	**£0**	**£13,403**	**17.52**	**0.9488**	**£14,251**	**£13,394**	**20.89**	**1.1354**	**3.38**	**£14,242**	**0.1866**	**£76,344**	**+£28,768**

* survival is undiscounted, all other figures are discounted

7 END OF LIFE

7.1 NICE End of Life treatment criteria

7.2 Introduction

This section provides an overview of the manufacturer's case for pemetrexed maintenance as an 'End of Life' treatment for patients with non-squamous NSCLC. The NICE 'End of Life' treatment criteria[47] have three key points:

(i) treatment is indicated for patients with a short life expectancy, normally less than 24 months and
(ii) there is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with NHS treatment and
(iii) the treatment is licensed or otherwise indicated for small patient populations.

7.2.1 Life expectancy of less than 24 months

The manufacturer quotes data from the 2011 NLCA report[4] that suggests median OS in England and Wales for patients with lung cancer is 181 days (approximately 6 months) with 1 year survival rates of 32%. The manufacturer further notes that the 1 and 2 year survival rates reported in the PARAMOUNT trial[11] are 58% and 32% respectively.

The ERG agrees that people with stage IIIB/IV non-squamous NSCLC have a mean life expectancy of less than 24 months.

7.2.2 Life extension of at least 3 months

The manufacturer cites the clinical evidence from the PARAMOUNT trial[11] that demonstrates an OS benefit of 2.85 months for pemetrexed plus BSC maintenance compared with placebo plus BSC. The manufacturer explains that as 28.7% of participants remained alive or were lost to follow-up at the end of the trial, the OS data from the trial were extrapolated over a lifetime horizon to reflect 99.9% participant death. The modelled mean OS data afforded an OS gain of 4.2 months in the base-case analysis (based on a gamma distribution).

Table 20 of the MS (MS, p84) presents the OS estimates from the manufacturer's extrapolation procedures. These are replicated in Table 46. The ERG's preferred approach to modelling survival indicates that the most likely gain in mean OS is 3.38 months.

Table 46 Manufacturer's estimates of mean overall survival

Parametric distribution	OS gain (months)
Gamma	4.2
Exponential	4.3
Weibull	3.7
Log normal	4.5
Log logistic	4.7
Gompertz	3.4

7.2.3 Licensed for a small population

The manufacturer estimates that the cumulative population eligible for treatment with pemetrexed is 5531. This includes the use of pemetrexed as a treatment for non-squamous NSCLC and mesothelioma. For the treatment of NSCLC, pemetrexed has a marketing authorisation for stage IIIB/IV non-squamous disease at first-line, maintenance and second-line. However, second-line treatment with pemetrexed is not recommended by NICE.

The manufacturer has provided a calculation of the size of the population of people with non-squamous NSCLC who would be eligible for treatment with pemetrexed at the first-line stage. The population is appropriately limited to patients who are of good PS (either 0 or 1). The calculations in the MS are replicated in Table 2 of the present report and for reference are partly presented in Table 47. The ERG agrees that the manufacturer's calculations demonstrate that approximately 4034 people with non-squamous NSCLC would be eligible for first-line treatment with pemetrexed.

Table 47 Manufacturer's estimate of the size of the eligible population

Population	Estimated number	Source
People with confirmed NSCLC, PS 0 or 1 and stage IIIB/IV	5932	NLCA audit report 2011[4]
People with confirmed NSCLC, PS 0 or 1, stage IIIB/IV and non-squamous histology	4034 (calculated as 68% of 5932)	CG121[3]

The manufacturer further argues that only people with non-squamous disease would ever be eligible for treatment with pemetrexed and therefore calculating separately patient numbers at first-line treatment and maintenance treatment amounts to double counting.

Mesothelioma

The manufacturer quotes data from the NLCA audit report[4] that demonstrate that 1815 people were diagnosed with mesothelioma in 2010 and NICE TA135[48] guidance that states that approximately

88% of these will have advanced disease. Thus, 1497 people with advanced mesothelioma are estimated to be eligible for treatment in England and Wales. The sum of the non-squamous NSCLC population of 4034 and the mesothelioma group of 1497 equates to 5531 people.

In the above scenario, the ERG is of the opinion that the number of patients eligible for treatment with pemetrexed falls within NICE's description of a small population.

The alternative scenario would consider numbers of people treated at each stage of the patient pathway. This is described in Table 48. The ERG notes that this scenario increases the estimated patient numbers to just above 7000.

The ERG is also aware that all scenarios are likely to over-estimate the uptake of CTX treatment in this population. For example, a proportion of people with non-squamous NSCLC will be EGFR M+ and will be treated with a tyrosine kinase inhibitor such as erlotinib or gefitinib.

In the light of these considerations, the ERG is of the opinion that the criteria for consideration of pemetrexed maintenance therapy for NSCLC following pemetrexed plus cisplatin induction under the NICE End of Life provision are satisfied.

Table 48 Estimate of patient numbers eligible for treatment with pemetrexed across treatment phases

Treatment / phase	Rationale	Numbers
NSCLC First-line	Based on published NLCA data Non-squamous, stage IIIB/IV PS 0 or 1	4034
NSCLC Maintenance	PARAMOUNT 58% of participants eligible following induction	2340
Mesothelioma	Based on published NLCA data	1497
Total		7871

8 OVERALL CONCLUSIONS

The trial data provided in the MS clearly demonstrate the efficacy of pemetrexed plus BSC as maintenance treatment for people with non-squamous NSCLC whose disease has not progressed following induction CTX with pemetrexed plus cisplatin and who are of good PS (0 or 1). The key trial was well-designed, well-conducted and notably included collection of participant QoL data. No new safety concerns regarding the use of pemetrexed were reported; the safety results were consistent with the known safety profile of pemetrexed.

Clinical advice to the ERG highlights that a large proportion of people in clinical practice in England and Wales become unfit for second-line treatment during the 'watch and wait' phase of the current clinical pathway. The QoL data from the key trial suggest that the PS of people receiving pemetrexed as continuation maintenance was maintained without significant impact on their QoL. This may increase the chances of some patients remaining fit enough to undergo further (second-line) treatment at the time of disease progression.

It is important to note the limitations of the PARAMOUNT trial[11] when considering the applicability of the results to people treated in clinical practice in England and Wales. Firstly, the participants in the trial were younger than those seen in clinical practice. Secondly, in line with the inclusion criteria for the trial, all participants were of good PS (0 or 1), whereas many people seen in clinical practice will be of PS 2. Thirdly, the greater majority of the trial population (91%) consisted of people with stage IV disease. The ERG further notes that there is a subgroup of people who have EGFR M+ NSCLC for whom first-line treatment will be with a tyrosine kinase inhibitor such as erlotinib or gefitinib. An additional consideration is the number of cycles of maintenance treatment; in the PARAMOUNT trial[11] treatment was given until disease progression or unacceptable toxicity and a number of participants received more than six cycles of treatment. It is unclear whether this would be the case in clinical practice in England and Wales.

Maintenance treatment with pemetrexed following induction treatment with pemetrexed appears to be relatively well-tolerated. However, the ERG is aware that the treatment of all clinically relevant AEs creates a significant additional burden on NHS resources. In the pemetrexed plus BSC arm of the PARAMOUNT trial,[11] there were statistically significantly more participants who experienced fatigue (grades 3 and 4), nausea (all grades) and neutropenia (all grades) compared to patients who received placebo plus BSC. In addition, statistically significantly greater numbers of people treated with pemetrexed plus BSC compared to placebo plus BSC needed blood transfusions or were hospitalised for treatment-related AEs.

The ERG notes that pemetrexed is already licensed and recommended by NICE[8] as 'switch maintenance' treatment for people with locally advanced or metastatic non-small-cell lung cancer other than predominantly squamous cell histology if disease has not progressed immediately following platinum-based CTX in combination with gemcitabine, paclitaxel or docetaxel.

The manufacturer presents a case for the cost effectiveness of pemetrexed as continuation maintenance to be considered under NICE's End of Life criteria;[47] the submitted base-case ICER is £47,576 per QALY gained. The ERG corrected a number of errors in the manufacturer's model and presented results from three scenarios. The three scenarios generated ICERs that ranged between £58,000 and £76,000 per QALY. Pemetrexed continuation maintenance may not, therefore, be considered cost effective under any of the three ERG scenarios.

Of particular note with regard to the manufacturer's submitted model, the base-case analysis estimated that almost one quarter of the survival benefit seen in the pemetrexed plus BSC arm occurred after disease progression. The ERG's re-analysis of the survival data found no evidence of any PPS benefit for people treated with pemetrexed plus BSC compared to placebo plus BSC. The removal of this unsupported PPS gain resulted in a substantial increase in the size of the ICER per QALY.

8.1 Implications for research

Maintenance therapy is a relatively new addition to the treatment pathway of people with NSCLC in the UK, and the results of several RCTs offering discrete comparisons of various CTX options are now available. A systematic review and economic evaluation of the evidence for all maintenance therapy options for NSCLC would be of value in the near future.

In considering the benefits of continuation maintenance, there is the question of whether six cycles rather than the commonly used four cycles of first-line CTX would deliver more benefit than continuation maintenance treatment given indefinitely.[15] A suitable RCT could be designed to address this question.

9 KEY POINTS OF THE ERG REPORT:

- Key clinical trial was of good design and showed clear benefits of pemetrexed plus BSC compared to placebo plus BSC. However, the trial population differed from clinical practice in England and Wales in being younger, fitter and with a very high proportion of stage IV disease

- Unlimited cycles of maintenance treatment were allowed in the trial but it is unclear if this would be realistic in clinical practice

- Re-analysis of clinical trial data indicates that there is no additional benefit provided to patients by pemetrexed once disease progression is confirmed

- After corrections and adjustments to the submitted economic model, the ERG found that estimates of the cost effectiveness of pemetrexed monotherapy as maintenance therapy are substantially less favourable than was indicated in the manufacturer's submission

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STA ERRATUM

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Pemetrexed for maintenance treatment following induction therapy with pemetrexed and cisplatin for non-squamous non-small cell lung cancer

This report was commissioned by the NIHR HTA Programme as project number 11/84/01

Completed 23rd January 2013

DOES NOT CONTAIN CIC/AIC

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LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

This document contains erratum in respect of the ERG report following the factual accuracy check by Eli Lilly and Company.

Box 1 Summary of treatment options

Treatment options for NSCLC depend on the stage of the disease at presentation. For stage IIIB or IV NSCLC, options include radiotherapy or CTX alone or a combination of the two. Chemotherapy may be recommended for patients with non-resectable stage III or IV disease, provided they are of good performance status (PS 0-1). Approximately 53% of NSCLC patients with advanced disease (stage IIIB/IV) and good performance status (PS 0-1) receive CTX for NSCLC in England and Wales.[5]

First-line chemotherapy treatment for non-squamous NSCLC

Pemetrexed plus cisplatin is established as the CTX regimen of choice for the first-line treatment of patients with non-squamous, EGFR mutation negative NSCLC, with a market share of 43% of all stage IIIB/IV NSCLC patients.[7] Another available option is gemcitabine in combination with cisplatin or carboplatin (2% and 12% market share respectively.[7]

Options following first-line chemotherapy

1. Watch and wait - the majority of patients who do not progress following first-line (induction) CTX are not immediately given further active treatment. Induction treatment is routinely followed by a period of 'watch and wait' during which patients undergo clinical assessment and receive best supportive care (BSC), as necessary. On disease progression, patients are usually offered second-line CTX with docetaxel or erlotinib, depending on performance status and eligibility.
2. Maintenance treatment - maintenance treatment of NSCLC is a relatively new concept which aims to maintain the clinical benefit achieved after first-line CTX, postpone disease progression and ultimately prolong overall survival along with palliation of disease symptoms. Maintenance treatment of NSCLC is not yet well-established in the NHS given that licensed and recommended treatments have only been available since 2010.

The ERG notes that, as indicated in Figure 1 of the MS (MS, p32) platinum-based CTX with docetaxel, paclitaxel or vinorelbine are also recommended by NICE as first-line treatment options for people with NSCLC.[3] However, the ERG is aware that the majority of people with non-squamous disease in England and Wales will be treated with pemetrexed plus cisplatin as a first-line treatment; these people will be ineligible for maintenance treatment with pemetrexed under current NICE guidance TA190.[8]

Clinical opinion to the ERG has highlighted that during 'watch and wait' a large proportion of people in England and Wales become unfit for second-line treatment with CTX.

The ERG agrees with the manufacturer's statement regarding NICE's clinical guideline CG121.[3]

> "The recommendations currently in CG121 were drafted before pemetrexed became standard of care for first-line treatment of NSCLC and well in advance of the licensing and positive NICE guidance for pemetrexed in switch maintenance treatment of NSCLC."

> "CG121 does not contain any recommendations on maintenance treatment and instead refers to the NICE guidance on pemetrexed (TA190), and erlotinib (TA227, in progress at the time) under the heading 'Related guidance'."

In summary, the ERG is confident that the manufacturer has accurately described the current service provision for people with non-squamous NSCLC.

2.3 Eligible population in England and Wales

In Table 4 of the MS (MS, p28) the manufacturer estimates that 535 patients in England and Wales would be eligible for maintenance treatment with pemetrexed (Table 1) as outlined in this STA. These are people with stage III/IV non-squamous NSCLC who are of PS 0 or 1. The ERG considers this to be a reasonable estimate of this population; however, it is noted that pemetrexed is currently licensed and recommended by NICE as a switch maintenance treatment (TA190)[8] and so overall, the number eligible for switch and continuation maintenance treatment with pemetrexed is higher.

Table 1 Manufacturer's estimate of number of patients in England and Wales eligible for continuation maintenance treatment with pemetrexed in this STA

Description	% patients	Number	References
Patients with lung cancer		32,347 (reported)	NLCA audit report 2011 [4]
Patients with confirmed NSCLC		19,163 (reported)	NLCA audit report 2011[4]
Patients with stage IIIB/IV NSCLC and PS 0-1		5,932 (reported)	NLCA audit report 2011[4]
Non-squamous NSCLC patients with stage IIIB/IV NSCLC and PS 0-1	68% (reported)	4,034 (calculated)	NICE CG121 (2011)[3]
Non-squamous NSCLC patients with stage IIIB/IV NSCLC and PS 0-1 receiving CTX	52.8% (reported)	2130 (calculated)	NLCA audit report 2011[4]
Patients receiving pemetrexed plus cisplatin at first-line	43% (reported)	916 (calculated)	Market research data, Q2 2012[7]
Patients eligible for pemetrexed continuation maintenance (i.e. patients without disease progression following first-line treatment)	58.4% (patients eligible for maintenance phase in PARAMOUNT)	535 (calculated)	Paz-Ares et al 2012[11]

According to the CSR,[16] a total of 69 (19.2%) patients randomised to pemetrexed plus BSC and 27 (15.0%) patients randomised to placebo plus BSC had a protocol deviation. Table 2 summarises the protocol deviations that occurred. Levels of protocol deviations were low and most were comparable across the two treatment arms and so this is not of great concern to the ERG.

Table 2 PARAMOUNT summary of protocol deviations

Protocol Deviation	**Pemetrexed + BSC (n=359) n(%)**	**Placebo + BSC (n=180) n(%)**
Protocol inclusion/exclusion criteria	25 (7.0)	21 (2.4)
Study treatment continued after PD occurred	12 (3.3)	10 (5.6)
Patient randomized but response to induction therapy was NOT a CR, PR, or SD[a]	7 (1.9)	10 (5.6)
Patient randomized had less than 4 cycles in induction treatment	6 (1.7)	2 (1.1)
Patient randomized but ECOG PS not 0 or 1 following induction treatment	1 (0.3)	2 (1.1)
Incorrect dose modification	45 (12.5)	6 (3.3)

a in the manufacturers' response to the ERG's clarification letter, the numbers specified were 9 for the pemetrexed plus BSC arm and 8 for placebo plus BSC

4.1.6 PARAMOUNT outcome selection and measurement

The outcome measures and their definitions are presented in **Error! Reference source not found.**. All outcomes and methods of measurement are standard for this disease area.

Table 3: PARAMOUNT progression-free survival at key analysis time points

Data cut-off	Treatment	Number of events (%)	Median PFS (months) (95% CI)	HR (95% CI)
June 30, 2010	Pemetrexed + BSC	184 (51.3)	4.11 (3.15 to 4.57)	0.62 (0.49 to 0.79)
	Placebo + BSC	118 (65.6)	2.83 (2.60 to 3.12)	
March 5, 2012	Pemetrexed + BSC	Not reported	4.4 (4.11 to 5.65)	0.60 (0.50 to 0.73)
	Placebo+ BSC	Not reported	2.76 (2.6 to 3.02)	

Overall survival data are presented in Table 4. The results of the first preliminary survival analysis did not meet the predefined level of statistical significance. Survival was immature with high censoring rates (78.6% and 74.4% for the pemetrexed plus BSC arm and placebo plus BSC arms, respectively). No further data are presented for the first preliminary analysis. At the final data cut-off in 2012, a median OS benefit of 2.85 months is reported for pemetrexed plus BSC compared to placebo plus BSC.

The percentage of people surviving at 1 year was 58% (95% CI 53 to 63) in the pemetrexed plus BSC arm and 45% (95% CI 38 to 53) in the placebo plus BSC arm. At 2 years, the percentage of people surviving was 32% (95% CI 27 to 37) in the pemetrexed plus BSC arm and 21% (95% CI 15 to 28) in the placebo plus BSC arm.

Table 4 PARAMOUNT overall survival at key analysis timepoints

Data cut-off	Treatment	Number of deaths n(%)	Median OS (months) (95% CI)	HR (95% CI)
June 30, 2010	Pemetrexed + BSC	Not reported	Not reported	Not reported
	Placebo +BSC	Not reported	Not reported	
May 16, 2011	Pemetrexed + BSC	188 (52.4)	Not reported	0.78 (0.61 to 0.98)
	Placebo+ BSC	111 (61.7)	Not reported	
March 5, 2012	Pemetrexed + BSC	256 (71.3)	13.86 (12.75 to 16.03)	0.78 (0.64 to 0.96)
	Placebo + BSC	141 (78.3)	11.01 (9.95 to 12.52)	

Tumour response rate and disease control rate are presented in **Error! Reference source not found.**. The manufacturer notes (MS, p65) that a substantial increase in the tumour response rate in the maintenance setting is unlikely as participants had already responded to induction treatment.

In summarising the safety profile of pemetrexed maintenance therapy, the manufacturer points to data from previous RCTs, JMEI[26] in which pemetrexed was given as a second-line treatment and JMEN[27] in which pemetrexed was given as maintenance treatment. The ERG notes that pemetrexed was not given as a first-line treatment in either of these trials.

The manufacturer states that pemetrexed was well-tolerated in both JMEI[26] and JMEN[27] that the incidence of toxicities in the PARAMOUNT trial[11] was similar to the safety profile recorded in those trials and no new safety signals emerged from the PARAMOUNT trial.[11] The ERG notes that the EMA's assessment report[13] included a comparison of AEs reported in the JMEN trial,[27] JMDB trial[28] (a trial of first-line pemetrexed plus cisplatin) and the PARAMOUNT trial.[11] The EMA concluded that the safety results are consistent with the known safety profile of pemetrexed (p26).

4.4.1 Post-discontinuation treatments

The PARAMOUNT trial CSR[16] states that participants were unblinded to study treatment at disease progression and the protocol did not specify the treatments that patients should receive once they had completed their trial treatment. The post discontinuation treatments (PDT) are described in the final CSR and summarised in Table 5. As noted earlier, the manufacturer's sensitivity analysis indicates that PDT did not bias the primary analyses in favour of pemetrexed.

The ERG notes that in clinical practice in England and Wales, NICE recommends second-line CTX treatment with erlotinib or docetaxel. The majority of the participants in the PARAMOUNT trial[11] who received PDT received erlotinib or docetaxel. The ERG notes that the Royal College of Physicians/NIHR in their commentary to NICE for this appraisal, consider the rates of subsequent treatment to be higher than might be expected in clinical practice, but probably reflect the rigorous selection of patients to the trial. The ERG further notes that the patients in the placebo and BSC arm were regularly followed up with imaging to assess PFS, this means that early relapse will be detected and lead to a greater use of second-line treatment.

Table 5 PARAMOUNT summary of post-discontinuation treatment

	Pemetrexed + BSC (N=359)	Placebo + BSC (N=180)	p- value
Participants with post-discontinuation therapy n (%)	231 (64.3)	129 (71.7)	0.10
Drug name			
Erlotinib	142 (39.6)	78 (43.3)	0.41
Docetaxel	116 (32.3)	78 (43.3)	0.01
Gemcitabine	36 (10)	15 (8.3)	0.64
Vinorelbine	28 (7.8)	11 (6.1)	0.60
Investigational drug	20 (5.6)	8 (4.4)	0.68
Carboplatin	18 (5.0)	8 (4.4)	0.84
Paclitaxel	9 (2.5)	6 (3.3)	0.59
Pemetrexed	7 (1.9)	7 (3.9)	0.25
Cisplatin	5 (1.4)	4 (2.2)	0.49
Bevacizumab	6 (1.7)	1 (0.6)	0.43
Gefitinib	3 (0.8)	2 (1.1)	1.00
Afatinib	2 (0.6)	2 (1.1)	0.60
Placebo	4 (1.1)	0 (0.0)	0.31
Sorafenib	3 (0.8)	1 (0.6)	1.00
Aflibercept	1 (0.3)	1 (0.6)	1.00
Other*	18 (7)	6 (3)	-

* includes BIBF 1120, cyclophosphamide, etoposide, mitomycin, aspirin, antineoplastic agents, capecitabine, carboplatin + gemcitabine, cytarabine, doxorubicin, gemfibrozil, ifosfamide, lactoferrin, ritonavir, vincristine, vinflunine, zoledronic acid, other antineoplastic agents.

4.5 Conclusions of the clinical effectiveness section

The clinical effectiveness evidence was derived from a single well-designed and conducted trial with a participant population predominantly from European centres. However, compared to people seen in clinical practice in England and Wales, the trial participants were generally younger and fitter, a higher proportion presented with stage IV disease and there was a lower proportion of ever smokers. The mean number of cycles of active maintenance treatment given in the trial may be greater than would be the case in clinical practice in England and Wales. The data presented clearly demonstrate a statistically significant difference in favour of pemetrexed plus BSC over placebo plus BSC for both OS and PFS in a population of people of good PS who have stage IIIB/IV non-squamous NSCLC. The QoL status of trial participants was maintained and the reported AEs are consistent with the known profile of pemetrexed.

The comparator is placebo plus BSC. The manufacturer has assumed that BSC (and also terminal care) are delivered in line with recommendations set out in the NICE report Guidance on Cancer Services Improving Supportive and Palliative Care for Adults with Cancer: The Manual.[35]

Second-line chemotherapy

Data from the PARAMOUNT trial[11] show that 192 (72%) of placebo plus BSC patients and 231 (64%) of pemetrexed plus BSC patients received second-line CTX. Data from a UK 2012 market survey[36] suggests that of the patients who receive second-line CTX, 17% receive docetaxel, 70% receive erlotinib and 13% receive other CTX drugs. Within the model the manufacturer has ignored the use of other CTX drugs and, using a pro-rata approach, estimated that, in both arms, 20% of patients receive docetaxel and 80% of patients receive erlotinib.

Within the model the mean number of cycles of second-line CTX is 4.82 for docetaxel patients and 6.27 for erlotinib patients, consistent with the approach used in TA190. The mean numbers of cycles from the PARAMOUNT trial[11] (3.26 for docetaxel and 5.25 for erlotinib) are used in a sensitivity analysis.

5.2.4 Perspective, time horizon and discounting

The manufacturer states that the economic appraisal is undertaken from the perspective of the NHS and Personal Social Services. Outcomes are expressed in terms of gains in life years and quality adjusted life years (QALYs). The time horizon is set at between 6 and 20 years depending on the extrapolation method employed (15.99 years in the base case) and, in line with the NICE Methods Guide to Technology Appraisal,[30] both costs and benefits are discounted at 3.5%.

5.1.5 Treatment effectiveness and extrapolation

The model was developed using the final data lock (March 2012) of the PARAMOUNT trial.[11] Due to censoring (see Table 6) curves were fitted to the OS and PFS data to allow survival estimates to be made for the lifetime of the model. The PFS data were used to estimate the time in the pre-progression health state.

Table 6 Censoring of PARAMOUNT trial data at the March 2012 data lock

Variable	Pemetrexed + BSC	Placebo + BSC
Overall survival	28.7%	21.7%
Progression-free survival	8.1%	6.7%

Overall survival

Six alternative parametric distributions were explored for OS: exponential, Weibull, log-logistic, log-normal, Gompertz and gamma. The manufacturer concluded that, based on consideration of Akaike's Information Criterion (AIC), Bayesian Information Criterion (BIC) and Cox-Snell residual statistics,

Table 7 Utility values used in the model

State	Value
Pre-progression placebo + BSC >6 cycles prior to death	0.7758
Pre-progression pemetrexed + BSC >6 cycles prior to death	0.7510
Pre-progression placebo + BSC 5-6 cycles prior to death	0.7242
Pre-progression pemetrexed+ BSC 5-6 cycles prior to death	0.6994
Pre-progression placebo + BSC 3-4 cycles prior to death	0.6520
Pre-progression pemetrexed + BSC 3-4 cycles prior to death	0.6272
Pre-progression placebo + BSC 0-2 cycles prior to death	0.4099
Pre-progression pemetrexed + BSC 0-2 cycles prior to death	0.3851
Post-progression both arms >6 cycles prior to death	0.7028
Post-progression both arms 5-6 cycles prior to death	0.6512
Post-progression both arms 3-4 cycles prior to death	0.5790
Post-progression both arms 0-2 cycles prior to death	0.3369

5.1.6 Resources and costs

Chemotherapy acquisition and delivery costs

In the PARAMOUNT trial[11] the licensed dose of 500mg/m^2 BSA of pemetrexed was administered every 21 days with dose reductions made in accordance with the Summary of Product Characteristics (SPC).[37] Mean BSA values for UK lung cancer patients[34] weighted by gender from the PARAMOUNT trial[11] were used to calculate pemetrexed and docetaxel doses. UK list prices[38] were applied to the minimum number of vials required which was calculated based on the mean BSA. The base-case model includes drug wastage for part-used vials. NHS Reference Costs[39] are used to estimate delivery costs.

Erlotinib was costed in accordance with its SPC[40]. Delivery was assumed to occur every 21 days and NHS Reference Costs,[39] which were assumed are based on a 28-day cycle, were pro-rata-ed accordingly. The UK list price was reduced by 14.5% in line with the manufacturer's PAS. The cost of concomitant medications required to be administered with pemetrexed (i.e. vitamin B12 (£0.97 per cycle), folic acid (£0.57 per cycle) and dexamethasone (£1.57 per cycle)) have been excluded from the economic model as the manufacturer assumes these costs are included within the NHS Reference Cost for CTX delivery. Details are summarised in **Error! Reference source not found.**.

Table 8 Maintenance monitoring treatment costs

Costs	NHS HRG codes and assumptions (used directly or in calculation)	Value	Source
Maintenance monitoring – all patients			
370: Medical oncology	Consultant led: Follow-up attendance non-admitted face-to-face	£120	NHS Reference Cost (NHS Trusts & PCTs) 2010/2011[39]
CT scan	RA12Z: CT scan, two areas with contrast (no of scans=187,559)	£132.99	
	RA13Z: CT scan, three areas with contrast (no of scans=233,749)	£150.88	
	Average cost weighted by activity	£142.92	
X-ray	Assumed to be included in SB11Z and SB12Z. Therefore no additional cost.	N/A	NHS Reference Cost (NHS Trusts & PCTs) 2010/2011 [39]
Additional monitoring costs per cycle for patients receiving pemetrexed (every 24 weeks)			
Consultant follow-up visit	Unit cost: £119.99	£15 per cycle	NHS Reference Cost (NHS Trusts & PCTs) 2010/2011[39]
CT scan (3% of cohort)	Unit cost: £142.92	£0.54 per cycle	

HRG = Healthcare Resource Group; CT=computerised tomography

Adverse event costs

The cost of treating grade 3 and 4 AEs has been calculated using the approach that was used in TA190[8] (pemetrexed as switch maintenance) namely including all grade 3 and 4 AEs occurring at a rate of >2% plus nausea and vomiting combined. Costs were extracted from TA190[8] and inflated to 2011 prices (see Table 9).

Table 9 Key model parameters: adverse events

Adverse event	Rate per 21-day cycle		Cost per episode	Cost per cycle		Source
	Pem +BSC	Placebo + BSC		Pem +BSC	Placebo + BSC	
Neutropenia	0.0061	0.0000	£345.13	£2.09	£0.00	Rate: PARAMOUNT trial[11] Costs: TA190[8]
Nausea and vomiting	0.0008	0.0000	£670.67	£0.56	£0.00	
Fatigue	0.0053	0.0019	£141.31	£0.74	£0.26	
Anaemia	0.0066	0.0009	£609.41	£4.03	£0.57	
Total				**£7.43**	**£0.83**	

Pem=pemetrexed

Best supportive care and terminal care costs

The average drug cost for patients receiving BSC has been estimated using data from the PARAMOUNT trial[11] cohort; however, this does not apply to the base-case scenario. The cost has been derived by considering the therapies received by 10% or more of these patients and is estimated to be £3.41 per cycle. The drugs included alprazolam, amoxicillin with clavulanate, diclofenac sodium, doxycycline, furosemide, metoclopramide, morphine and omeprazole (MS, Appendix 20).

6 IMPACT ON THE ICER OF ERG ADDITIONAL ANALYSES

6.1 Detailed critique of manufacturer's economic model

6.1.1 Model design and implementation

The manufacturer's model is implemented as a series of Microsoft Excel worksheets. Although the essential design of the model is very simple (two health states and death), its implementation at times seems unduly complex. Nonetheless the core of the model, which traces the progression of two cohorts of patients from initiation of maintenance therapy until death, appears to be largely sound. A particular feature of the model is the large number of control variables (41 on the 'Parameters' worksheet) provided to allow many alternative features to be explored in the analysis, although several are so specialised as to be unlikely to have much relevance in determining cost effectiveness.

The model additionally contains data and Visual Basic code to estimate cost effectiveness for a range of different subgroups. However, the results of applying this feature were not originally reported in the MS, though a full table of such results did in fact exist in the original model and showed far higher ICERs than in the manufacturer's base-case analysis. In the response to the ERG's clarification questions, the manufacturer has provided detail of the mode of operation of the subgroup analysis technique (based on modelling individual trial patients, rather than in aggregate).

The ERG has attempted to replicate this procedure for the base-case analysis to assess how well the results accord with the deterministic model results. Unfortunately, it only proved possible to activate this facility for a single preset scenario using a range of model parameter settings quite different from the submitted base case scenario. As access to the Visual Basic code was found to be password protected it was not possible for the ERG to complete this validation check.

6.1.2 Model implementation and parameter value issues (costs, resources and utility)

Method for estimating of pemetrexed costs

Pemetrexed monotherapy doses are calculated at 500mg/m^2 of BSA. In the manufacturer's base-case analysis a simple method is employed which uses a single average BSA figure for all patients, and determines the required number of vials of the drug required for such an average patient. This average BSA figure is the average of all patients (male and female) in the PARAMOUNT trial[11] and is slightly higher than the corresponding figure reported by Sacco et al[34] for UK CTX patients. However, this method of calculation ignores the effect of gender on BSA in altering the amount of drug wastage, as the wide distribution of BSA within the population (separately for males and females) typically increases the number of vials required to treat the whole population. The mean BSA figures reported

by Sacco et al[34] for UK CTX patients include those lung cancer patients whose treatment was adjuvant or neo-adjuvant rather than palliative. The ERG has therefore re-estimated the mean cost per cycle of pemetrexed acquisition, using UK distributional data for palliative CTX, and applying a maximum dose limit of 1000mg, yielding a figure of £1,481.37 per dose instead of the manufacturer's estimate of £1,440 per dose.

Mid-cycle correction error in estimating pemetrexed costs

It is conventional in state-based models which update key variables at fixed cycle times to estimate costs and outcomes which vary during the course of a cycle by averaging the value of the variable at the beginning and end of the cycle. This has been applied in the manufacturer's model to the calculation of the cost of pemetrexed CTX, by multiplying the cost per dose by the average number of patients on treatment during each cycle. However, pemetrexed is given on day one of each 21-day cycle, so the correct population receiving treatment is all those patients still on treatment at the beginning of each cycle. This contradicts the statement made on page 110 of the MS that "no half-cycle correction is applied to pemetrexed costs". This error has the effect of understating the true cost of pemetrexed treatment for every cycle of the model.

Post-progression chemotherapy

The manufacturer's model includes a parameter for the relative risk of surviving patients receiving further systemic therapy after discontinuing maintenance treatment (or 'watch and wait' BSC). This has been estimated as 0.88 indicating that pemetrexed plus BSC patients are 12% less likely to receive additional CTX than placebo plus BSC patients. However, Paz-Ares et al reported from the PARAMOUNT trial[11] that "A similar proportion of patients in both groups received post-discontinuation therapy" and indicated a p-value of 0.35 for the comparison. A chi-square test of the data used in the manufacturer's model yields a p-value of 0.44, confirming that there is no evidence of a greater propensity for further treatment in the placebo plus BSC arm. Since there is no *a priori* basis for supposing that surviving patients who have not received maintenance therapy will be any more prone to additional treatment, the ERG concludes that it is more appropriate to set the value of this model parameter to 1.0.

Method for estimating docetaxel costs

Docetaxel monotherapy doses for second-line CTX are calculated at 75mg/m^2 of BSA. The ERG has re-estimated the mean cost per cycle of docetaxel acquisition, using UK distributional data for palliative CTX as described above, arriving at a figure of £800.06 per dose based on the least expensive generic product featured in the BNF,[38] or £87.39 per dose using the corresponding average hospital contract prices reported by eMIT.[43] These costs contrast with that used in the manufacturer's model of £1,023 per dose.

Co-medication costs

Specific co-medication and vitamin supplementation are required for pemetrexed treatment (dexamethasone, folic acid and injected vitamin B12). The costs of these medications are estimated in the manufacturer's model, but omitted from the base-case results. As the specific co-medications are mandated within the SPC[37] for pemetrexed and are not required for any other CTX they represent a real differential cost beyond that normally included in the cost of administration of CTX. The targeted medications are directly relevant to treatment-related AEs. The ERG is of the opinion that these direct costs should be included in the base-case calculations.

Pre-progression monitoring costs

In the manufacturer's base-case analysis the routine monitoring of patients prior to disease progression is assumed to cost twice as much per cycle for placebo plus BSC patients as for those receiving pemetrexed maintenance therapy (apparently based on adapting the approach used by the manufacturer in TA190[8]) resulting in an extra cost per patient not receiving pemetrexed. If, instead, the follow-up pattern previously used by the ERG for the TA190[8] appraisal of pemetrexed maintenance therapy is applied to the manufacturer's model (review every 4 cycles on pemetrexed vs at 3, 6, 12, and 18 months for 'watch and wait' patients), the estimated discounted cost difference is £169.26 per patient greater for patients on pemetrexed monotherapy.

Omitted cost of blood products

The manufacturer's model shows a cost per blood transfusion of just £58. This relates to the cost of administering the transfusion in an out-patient setting, but does not include the cost of the blood product delivered. As a minimum, the ERG has increased the cost to include a unit of red blood cells priced at £125 from the NHS Blood and Transplant 2011-2012 Annual Review.[45] The cost of blood transfusions only features explicitly on a non-base case model scenario using a limited number of directly measured resources in the PARAMOUNT trial,[11] and therefore the ERG amendment does not have any effect on the base-case results.

Table 10 Effect of cost, resource use and utility amendments made by the ERG to the base-case manufacturer's model

	Incremental cost	Incremental QALYs	ICER (£/QALY)	Change in ICER
Base-case analysis	**£12,153**	**0.2554**	**£47,576**	**-**
Pemetrexed drug cost	£12,479	0.2554	£48,854	+ £1,278
No mid-cycle correction	£12,906	0.2554	£50,524	+ £2,948
No difference in further CTX rates	£13,112	0.2554	£51,332	+ £3,756
Docetaxel drug cost*	£12,186	0.2554	£47,707	+ £131
Co-medication costs	£12,179	0.2554	£47,679	+ £103
PFS monitoring costs	£12,266	0.2554	£47,707	+ £443
Terminal care costs	£12,138	0.2554	£47,518	- £58
Adjusted utility model	£12,153	0.2468	£49,235	+ £1,659
All ERG cost, resource & utility changes	**£14,339**	**0.2468**	**£58,092**	**+ £10,516**

* using least expensive BNF prices (eMIT prices give IC = £12,293, ICER = £48,126)

6.1.3 Implementation of survival modelling and projection

Covariate adjusted survival models

For the manufacturer's base-case analysis it is assumed that the parametric models used for projecting PFS and OS beyond the available trial data should not take account of the influence of baseline covariates of patient characteristics in the PARAMOUNT trial.[11] It is suggested that taking these factors into account is unnecessary since the randomised allocation of patients should ensure that all relevant variables are fully balanced within the trial data set.

This should be the case when calculating results directly from the data, but may not be valid in relation to a parametric model fitted to those data, since any parametric model involves a number of implicit assumptions which may override the unbiased nature of the source data (not least the assumption that treatment and comparator may be modelled jointly). The use of covariate adjustment when fitting a parametric function allows the appropriateness of a selected parametric form to be tested. If significant non-zero coefficients are generated by the analysis this implies that the fit of the model can be improved with additional information, indicating that some degree of bias is present in the estimated function. The options then are either to use the covariate adjusted version of the model to correct partially for the bias, or seek an alternative parametric model formulation less prone to bias.

The submitted model contains the results of proportional hazards multivariate regression analyses of PFS and OS undertaken by the manufacturer which includes covariates drawn from the baseline patient characteristics data of the PARAMOUNT trial.[11] Most of the covariates included in the adjusted models exhibit statistically significant non-zero coefficients. This indicates that the adjusted PFS and OS models are superior to the unadjusted models, explaining significantly more of the inter-patient variation and at least partially correcting for modelling bias. The ERG is of the opinion that if

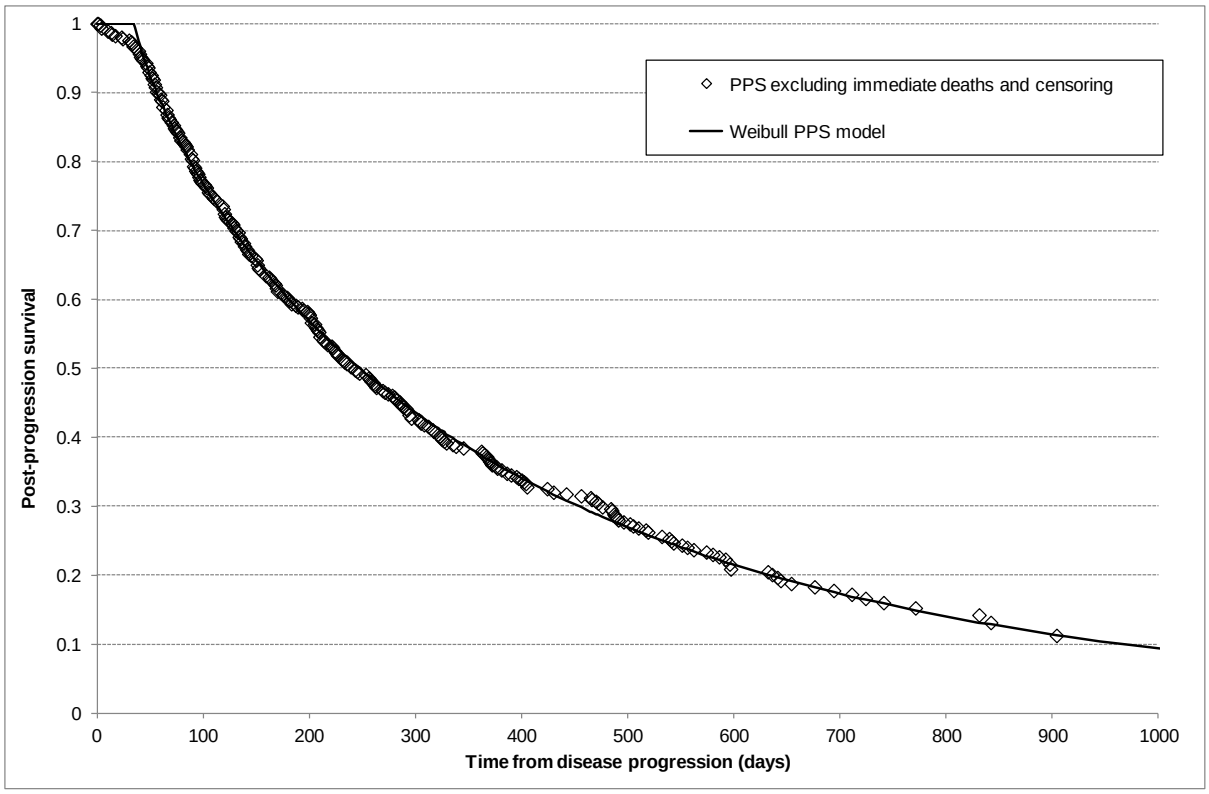

Figure 1 Pooled PPS survival curve form the PARAMOUNT trial with fitted Weibull parametric function. (Patients dying or censored on day 1 have been removed for clarity)

Overall survival

The results obtained with the manufacturer's model are strongly influenced by the method adopted for analysing time-to-event data. This is most important when modelling OS, since this determines the dominant outcome variable (quality adjusted life years), and because the OS data from the PARAMOUNT trial[11] are less mature than for other variables so greater reliance is placed on projective modelling to fill the data deficit. The approach adopted is based on using a single parametric function designed to generate OS projection estimates for both trial arms simultaneously, featuring a binary variable to alter the event hazard depending on the randomised treatment. This introduces a very strong constraint on the analysis which can easily introduce serious bias into the resulting trendlines. The manufacturer sought to justify this assumption with residual plots (MS, Appendix 16) and OS survival plots (MS, Appendix 17). In addition, the MS Appendix 18 includes AIC statistics to support the selection of the gamma function as preferable to five other standard distributions. However, the extent of the mismatch of the fitted gamma model to the observed trial data is most clearly seen when the residuals are plotted to indicate the patterns of over- and underestimation (Figure 2 and Figure 3).

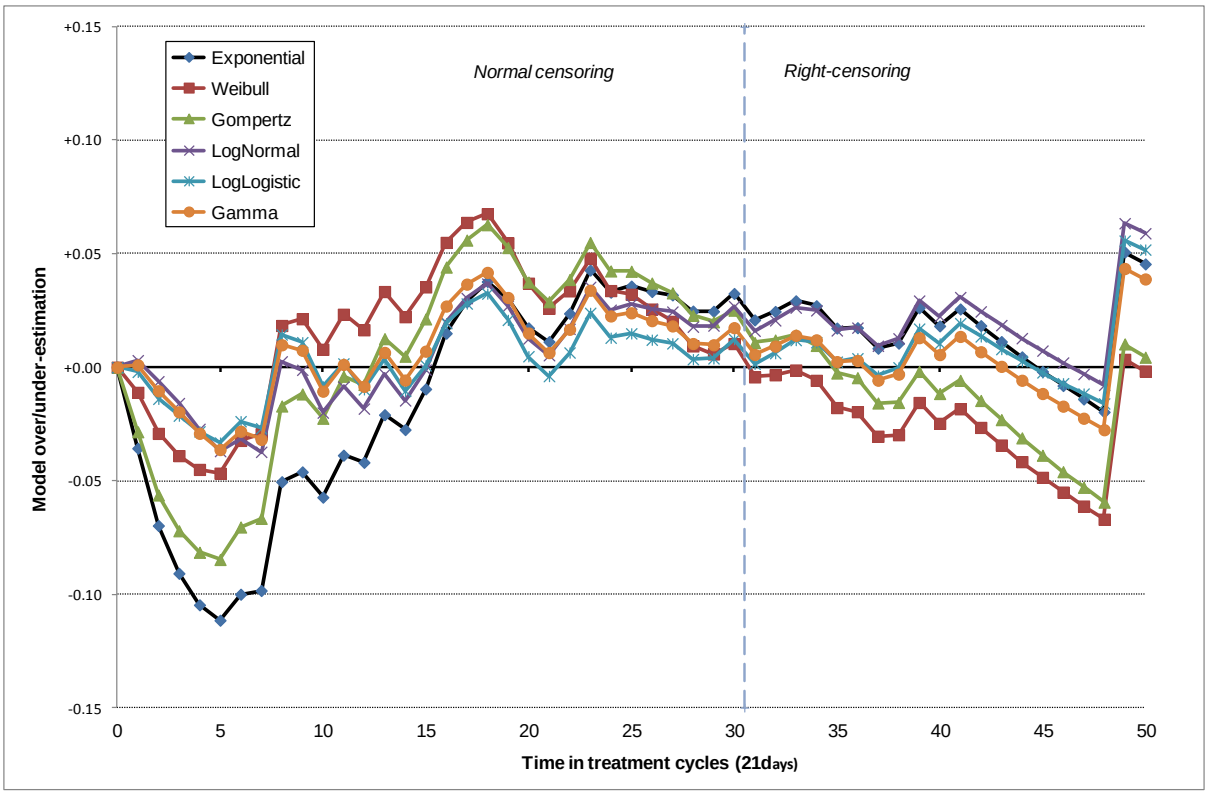

Figure 2 Over- and underestimation of OS by six standard survival functions calibrated against the placebo+BSC arm of the PARAMOUNT trial

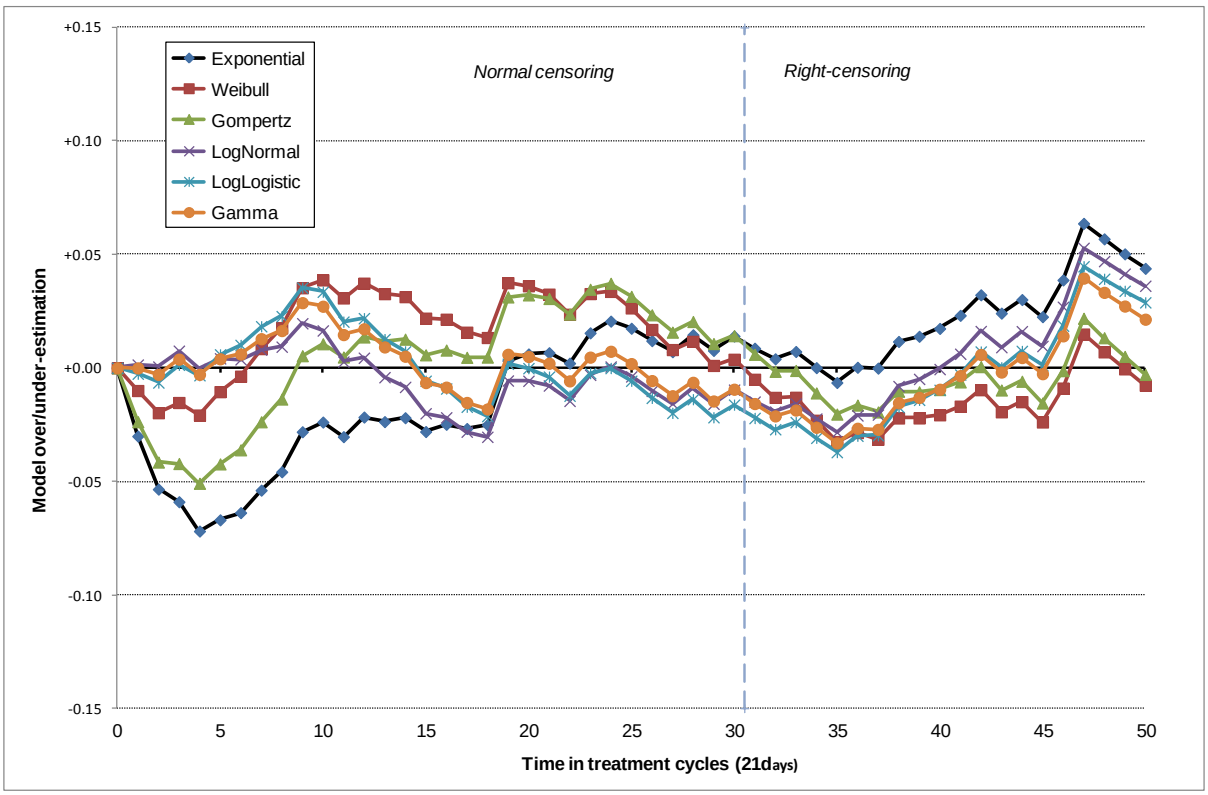

Figure 3 Over- and underestimation of OS by six standard survival functions calibrated against the pemetrexed+BSC arm of the PARAMOUNT trial

Systematic patterns of deviation from random fluctuation can be observed for both treatment arms, but are most pronounced in the placebo plus BSC arm which is based on the smaller sample size (due to 2:1 randomisation) and therefore likely to suffer double the magnitude of compensatory bias. There are general tendencies toward underestimation in the early period, followed by a smaller over-estimation in the middle period. However, most important are the contrary trends in the later trial period when right censoring is in operation. This is the phase in which it is necessary to establish a trend for use in projecting survival beyond the observed data until all patients have died. In the placebo plus BSC arm the trend is toward steadily increasing underestimation of survival, whereas in the pemetrexed plus BSC arm the gamma function trends steadily increase overestimation of OS. The consequence of this misspecification of the survival function combined with the constraint of using a single jointly estimated model is that incremental projected differences in expected OS are seriously biased in favour of pemetrexed plus BSC, and do not represent the true underlying differences attributable to pemetrexed maintenance therapy. This is the main source of the additional gain in PPS described above and shown to be unsupportable from the PPS trial data.

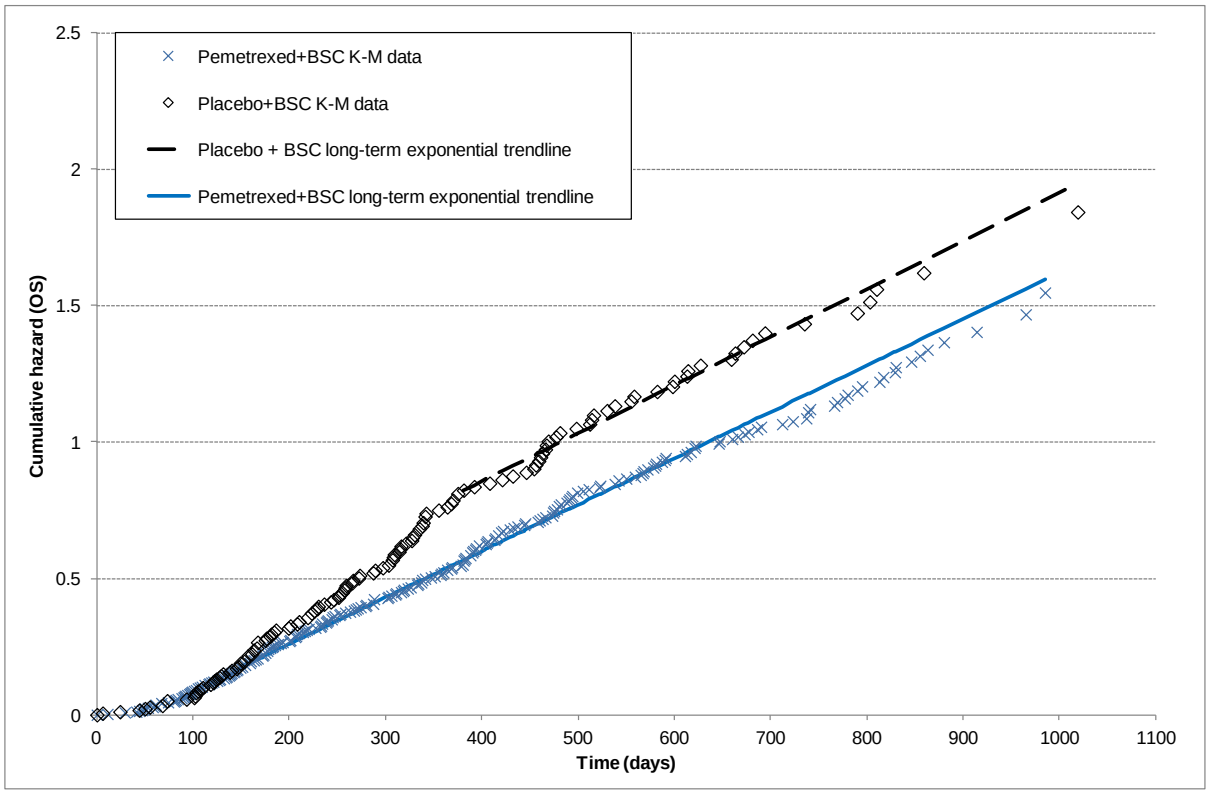

Figure 4 Comparison of cumulative OS hazards in both arms of the PARAMOUNT trial with ERG calibrated exponential trend.

Issue 1 Unadjusted versus adjusted model and subgroups

Description of problem	Description of proposed amendment	Justification for amendment
General misunderstanding and/or misinterpretation of the unadjusted versus adjusted modelling approach We note that within this report there are a number of statements referring to the use of the adjusted and unadjusted model methodology that have been misrepresented. We would like to ensure that the evidence and methodology used in the economic model is accurately represented within the NICE process and have therefore provided further clarification below to this end. Where appropriate in the form, the specific comments on the model are also reported. **Base Case Model - Lifetime Unadjusted Analysis** As reflected in the LRiG report, the key evidence for this appraisal is based upon a single RCT: PARAMOUNT. This trial includes a balanced distribution of patient characteristics between treatment arms. As a result, the PARAMOUNT base case analysis uses observed Kaplan Meier (KM) data for the within-trial period followed by a parametric extension in order to assess the cost-effectiveness of pemetrexed over a lifetime horizon. This base case analysis is therefore 'unadjusted' since it takes account of the treatment effect between arms directly from the PARAMOUNT trial and does not adjust for covariates. The base case analysis does therefore not permit subgroup analyses as it would be inappropriate to adjust the parametric model extension without first stratifying KM data by the same characteristic(s) of interest. **Alternative Analysis - Lifetime Adjusted Analysis** Since the model development was started prior to both the final decision problem being published by NICE and the final data lock of the PARAMOUNT trial, the model was designed with additional functionality, i.e., the adjusted model options, to enable subgroup analyses to be conducted should this have been considered appropriate based on final trial results. This alternative analysis adjusts for patient baseline characteristics and is fully parametric rather than using an extrapolation from the tail of the KM curve (as per the approach for the unadjusted analysis above). A fully-parametric survival model consequently may be used to extrapolate right censored survival data to a lifetime time horizon and readily facilitate subgroup analyses. **Choice of the Unadjusted analysis for the Base Case Model** The LRiG report refers to the reason for the manufacturer not using the adjusted model for the base-case analysis on the basis that the subgroup analysis technique (ie. the adjusted model) was more time-consuming to run. This statement is based on the response to Clarification Questions. We would like to clarify that the adjusted model has two different methods of calculating the base-case results: a) using individual patient data (IPD) and b) using average covariates in the risk equation. The time consuming statement in the clarification question was referring to the IPD method for the adjusted model compared to the average covariate method only and it had no bearing on the selection of adjusted versus unadjusted model. In addition, it is stated that the adjusted model is a more accurate representation of the base-case results and therefore should have been used instead of the unadjusted. Similarly to the rationale above, the accuracy comment in the Clarification Questions response refers to the accuracy between the two different		

methods used in the adjusted model, i.e. IPD versus average covariate, rather than between the adjusted versus the unadjusted model methodology.

The reasons for the choice of the unadjusted model were presented in the manufacturer's submission (MS) and also in response to the Clarification Questions. An extract of this rationale is described below. No subgroup analyses were considered necessary for the base case analysis in the original MS for a number of reasons:

- The NICE final decision problem did not identify any specific subgroup analyses for consideration during this appraisal.
- Analyses of overall survival in the PARAMOUNT trial showed that the relative treatment effect of pemetrexed was internally consistent across a range of pre-specified subgroups, including: response to induction treatment, performance status, histology and age.

In our response to Clarification Question B1c, we also provided the following additional reasons why the unadjusted analysis was considered to be the most appropriate base case analysis:

1. Generally it is not necessary to include covariates in survival modelling in the context of an economic model based on a single RCT as it would be expected that any important covariates would be balanced through the process of randomisation. (Latimer 2011). Therefore it follows that if the baseline characteristics are evenly distributed across treatment groups then the estimates of treatment effect generated from the unadjusted model would be expected to be unbiased.
2. The parametric survival estimates used in the lifetime adjusted analysis do not correspond well to the observed PFS data (in the early phase of the trial). The PFS estimates predicted using the parametric model (regardless of distribution selected) underestimated PFS in the pemetrexed arm and overestimated the PFS in the BSC arm. A review of log-log plots indicated possible evidence of proportional hazards (PH) violation. In view of potential PH violation, observed KM data from the PARAMOUNT trial appears likely to offer the most reliable estimate of survival in the within-trial period.
3. The use of KM data followed by a parametric extension is consistent with the approach used for pemetrexed in TA190 and TA181. During the appraisal of TA181, the ERG made full use of the available observed KM data to minimize the contribution of the trend projections beyond available IPD and fitted a parametric extrapolation to the tail of the KM data to calculate total mean survival. (LRIG, ERG addendum, June 2009; Latimer 2011).
4. During the appraisal of erlotinib (TA227), the ERG also stated that KM observed data was considered to provide the best estimate of PFS for the trial duration. The ERG commented that since all patients in the stable disease population of the SATURN trial had disease which had progressed (that is, the PFS data set was complete), there was no need to model the mean duration of progression-free survival because it could be based directly on KM data from the trial.

   Whilst not complete, in the PARAMOUNT trial the censoring rates for PFS data were low (6.7% placebo arm; 8.1% pemetrexed arm). Thus it was considered to be most appropriate to use the available KM data for PFS rather than use a fully parametric model which did not appear to fit the data well (see bullet 2. above).

On the basis of the above, the KM data was considered to be most appropriate for the within-trial period, meaning the unadjusted OS and PFS extrapolations

should be implemented together and a combination approach of the unadjusted KM data with an adjusted extrapolation for different survival parameters was not considered methodologically appropriate. A detailed list of factual inaccuracies, and/or clarifications as a result of the misrepresentation of the model methodology explained above, are detailed below.		
Section 6.1.1, page 50 states: *However, the results of applying this feature were not originally reported in the MS, though a full table of such results did in fact exist in the original model and showed far higher ICERs than in the manufacturer's base-case analysis.*	We suggest amending this statement as follows: *However, the results of applying this feature were not originally reported in the MS, since no subgroups were described in the decision problem and the clinical data did not suggest that there were any differences in relative efficacy by different subgroups.*	Though the statement is not inaccurate we believe it leads to misinterpretation on the reasons for the selection of the unadjusted model and for not showing the results of the subgroups in the original submission. The original basecase model uses the unadjusted analysis, which does not report a table of subgroup results since it was not designed to investigate subgroups. Please refer to the text above for detailed explanation on this element. The subgroup results, which are only reported when the adjusted model is selected, will show a range of ICERs both above and below the ICER for the ITT population from the adjusted model. I.e., the subgroup results are relative to the adjusted ITT ICER, rather than the base-case (unadjusted) ICER.
Section 6.1.1, page 50 states: *In the response to the ERG's clarification questions,* ***the manufacturer has suggested that the subgroup analysis technique*** *(based on modelling individual trial patients, rather than in aggregate)* ***was not employed to generate base-case results as, although more accurate, it is more time consuming.*** *The ERG does not find this argument to be convincing.*	This text should be removed or changed to reflect that it refers to the alternative methods of analysing the subgroups/adjusted model only.	The time-consuming statement provided in response to the Clarification Question B1a refers to the choice between the two adjusted model methodologies used in the subgroup analyses, i.e., IPD versus average covariates in the risk equations, and had no bearing on the choice of adjusted versus unadjusted models. The adjusted model has two alternative methods of calculating ICERs with covariate adjustment to enable subgroup analyses • Option 1 applies individual patient characteristics in the risk equations, sequentially one at a time. The model generates estimates of the underlying risk and pemetrexed treatment effect using these patient characteristics for each relevant parameter in the cost-effectiveness model (i.e. PFS, OS, QoL). The overall costs and effects for each patient profile

		are then estimated as if the patient was treated with pemetrexed plus BSC or BSC alone. Cost and effects are then averaged over the patient profiles with the subgroup characteristic of interest. • Option 2 applies average covariates in the risk equations

Section 6.1.1, page 50 states: *In particular, if the subgrouping technique is indeed more accurate, then the use of the unadjusted deterministic base-case results in the MS is seriously misleading.*	We suggest this text to be removed.	The statement relating to the subgrouping technique being more accurate referred to the accuracy of the IPD subgroup method in direct comparison to the average covariate subgroup method, not versus the unadjusted model as stated in the ERG Report.
Section 6.1.1, page 50 states: *Using subgroup average characteristics is the only reliable method, and leads to subgroup results consistent with the deterministic base-case scenario.*	We suggest this text to be removed.	The method of using IPD (as in Option 1 described above) is a reliable method of generating results for the subgroup analysis due to the inherent non-linearity of cost-effectiveness models.
Section 6.1.2., page 53 states: *Three of these covariate factors yielded coefficient values statistically significant at the 5% level, indicating that the adjusted model corresponds more closely to the observed trial data than the unadjusted model. However, the submitted base-case analysis uses the unadjusted model coefficients rather than those of the superior adjusted model.*	This text should be removed or changed to reflect that the results show little difference between the two models.	Examination of the regression coefficients associated with these variables using the adjusted and unadjusted models indicates there is very little difference in the mean estimate of effect or precision between the two models. The adjusted model therefore offers little (or no) improvement and no genuine change in predicted utility estimates compared to the unadjusted model.
Section 6.1.2., page 53 states: *Although EQ-5D responses were received from all but one patient in the PARAMOUNT trial,[11] only 83% of responses were free of missing items. This introduces the opportunity for bias to influence the estimation of modelled utility values, suggesting that the adjusted model is probably the more reliable.*	This text should be removed or changed to reflect that the results show little difference between the two models.	Examination of the regression coefficients associated with these variables using the adjusted and unadjusted models indicates there is very little difference in the mean estimate of effect or precision between the two models. The adjusted model therefore offers little (or no) improvement and no genuine change in predicted utility estimates compared to the unadjusted model. Therefore, the unadjusted model provides an unbiased estimate of the treatment effect.

Issue 2 Implementation of survival modelling and projection

Description of problem	Description of proposed amendment	Justification for amendment
Section 6.1.3. Page 54 states: *(not least the assumption of proportional hazards)*	We suggest deletion of the statement: (*not least the assumption of proportional hazards)*	A PH assumption was not made in the basecase model.
Section 6.1.3. Page 54 states: *If significant non-zero coefficients are generated by the analysis this implies that the fit of the model can be improved with additional information, clearly indicating that some degree of bias is present in the estimated function.* *… This indicates that the adjusted PFS and OS models are superior to the unadjusted models, explaining significantly more of the inter-patient variation and at least partially correcting for modelling bias.*	We suggest amending the text to reflect that the adjusted model is not superior to the unadjusted model.	Examination of the log treatment coefficients (time ratio) estimated using the unadjusted and adjusted models indicates that there is very little difference in the mean estimates of effect and precision between the unadjusted and adjusted models (Time ratio unadjusted: 1.22, 95% CI 1.02-1.46, Time ratio adjusted model: 1.21, 95% CI: 1.02-1.44). This suggests that the addition of baseline characteristics did little to improve estimates of the treatment effect in PARAMOUNT. Therefore, the adjusted model is not superior to the unadjusted model for OS and PFS.

Issue 3 ERG re-analysis of PARAMOUNT survival data

Description of problem	Description of proposed amendment	Justification for amendment
Overall survival		
Section 6.1.4., Page 58 states that: *'The approach adopted is based on using a single parametric function designed to generate OS projection estimates for both trial arms simultaneously. This is achieved*	We suggest the following text is deleted: *This is achieved by using a proportional hazards formulation including a binary variable to scale up or down the event hazard depending on the randomised treatment'.*	A proportional hazard (PH) model has not been used for the base case analysis. The base case analysis uses an accelerated failure time model (gamma distribution); AFT models do not rely on a PH assumption. Page 102 of MS states that Schoenfeld residual plot showed no evidence of PH violation, however, a log-log plot revealed

by using a proportional hazards formulation including a binary variable to scale up or down the event hazard depending on the randomised treatment'. The proportional hazards assumption is a very strong constraint on the analysis, which can easily introduce serious bias into the resulting trendlines. The manufacturer has sought to justify this assumption with residual plots.	*The proportional hazards assumption is a very strong constraint on the analysis, which can easily introduce serious bias into the resulting trendlines. The manufacturer has sought to justify this assumption with residual plots.*	some evidence of non-parallelism, suggesting possible PH violation due to the initial non-separation of the KM curves.
Section 6.1.4., page 58 states that: *In addition, the MS Appendix 18 includes AIC statistics to support the selection of the gamma function as preferable to **six other** standard distributions.*	This statement should read: *In addition, the MS Appendix 18 includes AIC statistics to support the selection of the gamma function as preferable to **five** other standard distributions.*	The Lilly submission considered six parametric distributions in total.
Section 6.1.4., page 58 states that: ***'**However, the mismatch of the fitted gamma model to the observed trial data is most clearly seen when the residuals are plotted to indicate the patterns of over- and underestimation (Figure 8 and Figure 9).'*	Suggest statement is deleted.	Figures 8 and 9 show that it is the exponential model which demonstrates the greatest mismatch compared to observed KM data, particularly in the early phase of the trial.
Figures 8 and 9 (p 59) refer to *'**seven**' standard survival functions*	These headings should read *'**six**' standard survival functions.*	The Lilly submission considered six parametric distributions in total.

Section 6.1.4., Page 60 states that: *The consequence of this misspecification of the survival function combined with the constraint of using a single proportional hazards model...*	We suggest the following statement is deleted.	The model was not constrained to PH
Section 6.1.4., Page 60 states that *... is that incremental projected differences in expected OS are seriously biased in favour of pemetrexed plus BSC, and do not represent the true underlying differences attributable to pemetrexed maintenance therapy. This is the main source of the additional gain in PPS described above and shown to be unsupportable from the PPS trial data.*	We suggest the following statement is deleted.	This statement does not appear to be supported by the evidence presented in Figures 8 and 9. The figures presented by the ERG suggest that exponential and gamma models are very similar in the placebo plus BSC arm and it is the exponential model which demonstrates the greatest overestimation of observed KM data, compared to the gamma model, particularly in the latter phase of the trial. Therefore the statement that [the use of the gamma model] seriously biases in favour of pemetrexed does not seem valid. Given the scale of the residual plots (figures 8 and 9) the differences between the gamma and exponential model appear minimal and preclude a clear choice between the two. Therefore our sensitivity analysis has tested the basecase ICERs using six different survival distributions.
The ERG states (p61) that: *'Substituting these long-term OS trends in place of the gamma function,* ***without any other changes to the manufacturer's base case****, has a significant impact on the cost effectiveness of pemetrexed maintenance therapy….. the ICER is increased by £14,859 per QALY to £62,435 per QALY…'*	We suggest the following statement is amended to: ***'****Substituting these long-term OS trends in place of the gamma function, without any other changes to the manufacturer's base case, has* ***minimal*** *impact on the cost effectiveness of pemetrexed maintenance therapy….. the ICER is* ***decreased to £47,133***	When an exponential parametric model is used in place of the gamma model and all other assumptions remain consistent with the base case (as suggested in ERG comments), the ICER actually decreases from £47,576 to £47,133, as reported in the sensitivity analyses in the Lilly submission, rather than increasing to £62,435.

Issue 4 ERG re-estimation of pemetrexed acquisition costs using UK distributional data

Description of problem	Description of proposed amendment	Justification for amendment
Section 6.1.2, page 50 of the ERG report: *This ignores the effect of gender on BSA, and fails to recognise the wide distribution of BSA within any population.*	We suggest that this statement be deleted	As stated in the ERG report on page 43, Section 5.2.7 UK BSA values for men and women with lung cancer are weighted by gender from the PARAMOUNT trial. I.e. the base case model adjusts the estimates of BSA according to the proportion of males and females modelled in any given analysis. In addition, one of the sensitivity analyses varying pemetrexed costs uses PARAMOUNT IPD, which takes account of both BSA distribution and gender.
Section 6.1.2, page 51 it states: *The manufacturer has used the mean BSA figures reported by Sacco et al for UK CTX patients. However, these published totals for lung cancer patients include people whose treatment was adjuvant or neo adjuvant rather than palliative in nature.*	We suggest that this statement is supported with additional reference(s).	The paper by Sacco et al (2010) states: *Treatment intent (i.e. neo/adjuvant or palliative) was also recorded for* ***all patients with breast or colorectal cancer***, (page 3). I.e. lung cancer data was reasonably assumed to only have been collected for palliative patients. To support this Appendix S3 of this paper lists IPD for BSA by cancer and gender and only provides separate neo/adjuvant versus palliative data for breast and colorectal cancer. In addition, in Appendix S1 of this paper the authors use $1.89m^2$ mean BSA for males & $1.65m^2$ mean BSA for females with lung cancer to recalculate drug costs in a palliative setting. I.e. Average BSA = $1.79m^2$ using Sacco et al data, weighted by gender from PARAMOUNT.

Section 6.1.2, page 51 states: *This contradicts the statement made on page 110 of the MS that "no half-cycle correction is applied to pemetrexed costs". This error has the effect of understating the true cost of pemetrexed treatment for every cycle of the model.*	We suggest that the statement that "*This error has the effect of understating the true cost of pemetrexed treatment for every cycle of the model.*" is amended to reflect the fact that this error has minimal impact on the cost of pemetrexed	The statement made on page 110 of the MS that "no half-cycle correction is applied to pemetrexed costs" was correctly identified by the ERG as an error in the Lilly submission. In the basecase analysis, the model estimates 7.95 cycles of pemetrexed, which is very close to the observed mean number of cycles on treatment from PARAMOUNT, i.e. 7.86 cycles (95% CI 7.00- 8.72 cycles). However the exclusion of a half-cycle correction actually overestimates the number of cycles and subsequent costs of pemetrexed and placebo in the model. Therefore, the statement by the ERG that this error understates the true cost is factually incorrect. If the half-cycle correction is removed, as suggested by the ERG, the model over estimates time on treatment at 8.41 cycles which then also over estimates the associated cost of pemetrexed treatment. Using this approach patients will be modelled to receive more cycles of pemetrexed therapy than observed in PARAMOUNT and, contrary to ERG observations, costs will be overstated. The half cycle correction improves the Markov approximation of the number of cycles of therapy received relative to observed PARAMOUNT data.

Issue 5 Miscellaneous factual inaccuracies in the ERG report

Description of problem	Description of proposed amendment	Justification for amendment
Section 5.2.7, page 43 states: *The UK list price was reduced by 14% in line with the manufacturer's PAS.*	We suggest that the statement be amended as follows: *The UK list price was reduced by 14.5% in line with the manufacturer's PAS.*	As per Table 36 of the Lilly submission, the erlotinib list price includes a 14.5% PAS discount (TA227).
Section 5.2.7, page 43 states: *Delivery was assumed to occur every 21 days and NHS Reference Costs which **were assumed to be** based on a 28-day cycle, were pro-rata-ed accordingly.*	We suggest that the statement be amended as follows: *Delivery was assumed to occur every 21 days and NHS Reference Costs which **are** based on a 28-day cycle, were pro-rata-ed accordingly.*	As per Table 37 of the Lilly submission, the HRG code for erlotinib is based on a 28-day cycle. Costs were therefore adjusted for a 21-day cycle. (Reference: DH Chemotherapy Regimens List (DH 2012) as per pages 123 and 124 of the Lilly submission).
Section 5.2.7, page 45 states: *The average drug cost for patients receiving BSC has been estimated using data from the PARAMOUNT trial cohort.*	We suggest that the statement be amended as follows: *The cost of BSC drugs only features explicitly in a non-base case model scenario using a limited number of directly measured resources in the PARAMOUNT trial.*	Suggested amendment aligns statement in ERG Report with ERG comments on changes to blood transfusion costs on page 52 of ERG report.
Section 6.1.2, page 52 states: *In the manufacturer's base-case analysis the monitoring of patients prior to disease progression is assumed to cost twice as much per cycle for placebo plus BSC patients as for those receiving pemetrexed maintenance therapy (apparently based on adapting the approach used in TA190,[8] resulting in an extra discounted cost per patient not receiving pemetrexed of £858. This directly contradicts the calculations detailed in Tables 42-44 of the MS which conclude (based on figures drawn from the*	If this paragraph in the ERG Report is still deemed necessary we suggest that this statement be amended: *In the manufacturer's base-case analysis the **BSC costs** are assumed to cost twice as much per cycle for patients **not on active chemotherapy as for those receiving active chemotherapy, i.e. either pemetrexed maintenance therapy or second-line agents post-progression.*** In addition, we suggest that this statement is deleted: ***This directly contradicts** the calculations detailed in Tables 42-44 of the MS which conclude (based on figures drawn from*	It appears that the ERG has confused BSC costs (which are applied to all patients in all cycles) with additional monitoring costs applied only to patients receiving pemetrexed maintenance treatment. As a result, some of the statements in this section of the ERG report are factually incorrect. The ERG's initial observations appear to relate to general BSC costs per cycle. However, the latter paragraph appears to relate to the costs of monitoring for pemetrexed, which were modelled separately to the BSC costs.

BTOG survey report[44] that monitoring costs prior to progression are £15.54 per cycle greater for patients receiving pemetrexed plus BSC than for patients receiving placebo plus BSC, due to more frequent out-patient consultant reviews and CT scans.	*the BTOG survey report[44] that monitoring costs prior to progression are £15.54 per cycle greater for patients receiving pemetrexed plus BSC than for patients receiving placebo plus BSC, due to more frequent out-patient consultant reviews and CT scans.*	BSC costs are modelled consistently with the accepted approach used in TA190. I.e. BSC costs have been applied to patients in each cycle (both pre- and post-progression) depending on whether or not they are receiving active chemotherapy (maintenance or second-line chemotherapy) in that cycle. BSC costs for patients not receiving active chemotherapy (£72) are twice as much per cycle as those patients receiving active chemotherapy (£36) irrespective of whether the patient is in the pre- or post-progression health state. This is reported on page 130-131 of MS and the difference in BSC costs assumes that patients receiving active chemotherapy will not receive additional palliative radiotherapy. This assumption is stated in Table 27 on page 112 of the MS. Additional monitoring costs for patients receiving pemetrexed are £15.54 per cycle as stated, due to additional consultant visits and CT scans compared to patients not receiving maintenance treatment.
Section 6.1.2, Table 39 Co-medication costs have been reported as: Incremental cost: £12,179 ICER: £48,785 Change in ICER: £1,209	These costs should read as follows: Incremental cost: £12,177 ICER: £47,672 Change in ICER: £96	The results reported in the ERG Report are incorrect.
Section 5.2.3, page 41 states: *Within the model the mean number of cycles of second-line CTX is 4.82 for docetaxel patients and 6.27 for erlotinib*	We suggest that this sentence should be amended as below: Within the model the mean number of cycles of second-line CTX is 4.82 for docetaxel patients and 6.27 for erlotinib patients, **which is consistent with the approach used in**	The number of cycles of second-line CTX are derived from TA162 (STA of erlotinib in second-line NSCLC) and were used in TA190 as they were considered to reflect UK clinical

*patients **reflecting the results of the JMEN trial**.*	**TA190**.	practice.

Issue 6 Factual inaccuracies in the clinical section

Description of problem	Description of proposed amendment	Justification for amendment
Page 11, Section 2.2 of ERG report: The following statement regarding the eligible patient population of pemetrexed appears to have inadvertently been left in the document: *However, the ERG is aware that the majority of people with non-squamous disease in England and Wales will be treated with pemetrexed plus cisplatin as a first-line treatment; these people will be ineligible for maintenance treatment with pemetrexed.*	The phrase '*these people will be ineligible for maintenance treatment with pemetrexed*' needs to be removed or an additional clarification should be added that patients were ineligible under the TA190.	Pemetrexed is now licensed for use as continuation maintenance, so patients who have used pem/cis first line are eligible to receive pemetrexed as maintenance treatment.
Page 13, Section 2.3 of ERG report: It is not sufficiently clear that the 'overall' patient population referred to in the following statement includes switch and maintenance treatment. *The ERG considers this to be a reasonable estimate of this population; however, it is noted that pemetrexed is currently licensed and recommended by NICE as a switch maintenance treatment (TA190) and so **overall**, the number eligible for maintenance pemetrexed is higher.*	We suggest that the sentence be modified as follows: The ERG considers this to be a reasonable estimate of this population; however, it is noted that pemetrexed is currently licensed and recommended by NICE as a switch maintenance treatment (TA190) and so overall, the number eligible for switch and continuation maintenance treatment with pemetrexed is higher.	The indication relevant to this submission is continuation maintenance, so only the number of patients eligible for pemetrexed continuation maintenance (N=535) is relevant to this submission. It should also be noted that patients who may be eligible for switch maintenance with pemetrexed would also have to be part of the pool of 4,034 patients described in the Lilly submission, i.e., these would be patients who were eligible for pem/cis first-line but did not receive it and are therefore eligible for pem switch maintenance at maintenance stage. With pem/cis

		becoming standard of care, the number of patients who would receive switch maintenance is very small. As stated in the Lilly submission, market data from Q2 2012 show that only 24 patients currently receive pemetrexed switch maintenance.
Table 7 on page 22, Section 4.1.5 of ERG report, the percentage of patients violating inclusion/exclusion criteria in the placebo + BSC arm is incorrect. Protocol inclusion/exclusion criteria, n(%) (for placebo + BSC arm)=8 (2.4).	We suggest the following amendment: Protocol inclusion/exclusion criteria, n (%) (for placebo + BSC arm)= 21 (11.7).	As specified in the PARAMOUNT CSR, page 78 Table S124.10.4.
Section 4.1.7, page 26 of ERG report: *The ERG notes that subgroup analyses of age, smoking status and gender were not pre-specified in the SAP.*	We suggest that the statement be amended as follows; *The ERG notes that subgroup analyses of smoking status was not pre-specified in the SAP.*	The population to be used for each analysis (and therefore pre-specified) including age and gender is stated in the SAP, version 3, page 21. This document was provided in response to the clarification questions. The subgroup analysis results for age and gender should therefore be considered as confirmatory, not exploratory.
Section 4.2, page 28 of the ERG report states: *At 2 years, the percentage of people **surviving at 1 year** was 32% (95% CI 27 to 37) in the pemetrexed plus BSC arm and 21% (95% CI 15 to 28) in the placebo plus BSC arm."*	We suggest deleting the words in bold '*at 1 year*'	This appears to be a typographical error.
Table 20, Section 4.4, page 35 of ERG	We suggest that the PDT values from the final OS datalock	This inaccurate reflection of the clinical data

report presents values from a previous (PFS) datalock: *The summary of PDT has been taken from the published paper (Paz-Ares et al 2012) and is from the July 30th 2010 (primary PFS) datalock. The updated numbers from the March 19th datalock (final OS) are reported in the final CSR, page 21, Table S124.4.7, provided with the Lilly submission*.	(final CSR, Table S124.4.7, page 21) be presented since these values are incorporated in the economic model.	used as input for the economic model could cause unnecessary reader confusion.
Section 4.4, page 32 of ERG report: *The ERG notes that the figures quoted in the MS appear to be different to those in the main published paper that describes the PARAMOUNT trial and are different again in the published paper that describes the safety and QoL results of that trial. However, in all reports, fatigue, anaemia and neutropenia are the AEs that occur more frequently (with statistical significance) in the pemetrexed plus BSC arm of the trial.*	No amendment required	The reason for the difference is because the values in the submission are from the most recent datalock (final OS) while those in the published paper (Gridelli et al 2012) are from the PFS datalock. As the ERG mentions, the AE results are consistent.

Issue 1 Unadjusted versus adjusted model and subgroups

General misunderstanding and/or misinterpretation of the unadjusted versus adjusted modelling approach

We note that within this report there are a number of statements referring to the use of the adjusted and unadjusted model methodology that have been misrepresented. We would like to ensure that the evidence and methodology used in the economic model is accurately represented within the NICE process and have therefore provided further clarification below to this end. Where appropriate in the form, the specific comments on the model are also reported.

Base Case Model - Lifetime Unadjusted Analysis

As reflected in the LRiG report, the key evidence for this appraisal is based upon a single RCT: PARAMOUNT. This trial includes a balanced distribution of patient characteristics between treatment arms. As a result, the PARAMOUNT base case analysis uses observed Kaplan Meier (KM) data for the within-trial period followed by a parametric extension in order to assess the cost-effectiveness of pemetrexed over a lifetime horizon. This base case analysis is therefore 'unadjusted' since it takes account of the treatment effect between arms directly from the PARAMOUNT trial and does not adjust for covariates. The base case analysis does therefore not permit subgroup analyses as it would be inappropriate to adjust the parametric model extension without first stratifying KM data by the same characteristic(s) of interest.

Alternative Analysis - Lifetime Adjusted Analysis

Since the model development was started prior to both the final decision problem being published by NICE and the final data lock of the PARAMOUNT trial, the model was designed with additional functionality, i.e., the adjusted model options, to enable subgroup analyses to be conducted should this have been considered appropriate based on final trial results. This alternative analysis adjusts for patient baseline characteristics and is fully parametric rather than using an extrapolation from the tail of the KM curve (as per the approach for the unadjusted analysis above). A fully-parametric survival model consequently may be used to extrapolate right censored survival data to a lifetime time horizon and readily facilitate subgroup analyses.

Choice of the Unadjusted analysis for the Base Case Model

The LRiG report refers to the reason for the manufacturer not using the adjusted model for the base-case analysis on the basis that the subgroup analysis technique (ie. the adjusted model) was more time-consuming to run. This statement is based on the response to Clarification Questions. We would like to clarify that the adjusted model has two different methods of calculating the base-case results: a) using individual patient data (IPD) and b) using average covariates in the risk equation. The time consuming statement in the clarification question was referring to the IPD method for the adjusted model compared to the average covariate method only and it had no bearing on the selection of adjusted versus unadjusted model.

In addition, it is stated that the adjusted model is a more accurate representation of the base-case results and therefore should have been used instead of the unadjusted. Similarly to the rationale above, the accuracy comment in the Clarification Questions response refers to the accuracy between the two different methods used in the adjusted model, i.e. IPD versus average covariate, rather than between the adjusted versus the unadjusted model methodology.

The reasons for the choice of the unadjusted model were presented in the manufacturer's submission (MS) and also in response to the Clarification Questions. An extract of this rationale is described below. No subgroup analyses were considered necessary for the base case analysis in the original MS for a number of reasons:

- The NICE final decision problem did not identify any specific subgroup analyses for consideration during this appraisal.
- Analyses of overall survival in the PARAMOUNT trial showed that the relative treatment effect of pemetrexed was internally consistent across a range of pre-specified subgroups, including: response to induction treatment, performance status, histology and age.

In our response to Clarification Question B1c, we also provided the following additional reasons why the unadjusted analysis was considered to be the most appropriate base case analysis:

1. Generally it is not necessary to include covariates in survival modelling in the context of an economic model based on a single RCT as it would be expected that any important covariates would be balanced through the process of randomisation. (Latimer 2011). Therefore it follows that if the baseline characteristics are evenly distributed across treatment groups then the estimates of treatment effect generated from the unadjusted model would be expected to be unbiased.
2. The parametric survival estimates used in the lifetime adjusted analysis do not correspond well to the observed PFS data (in the early phase of the trial). The PFS estimates predicted using the parametric model (regardless of distribution selected) underestimated PFS in the pemetrexed arm and overestimated the PFS in the BSC arm. A review of log-log plots indicated possible evidence of proportional hazards (PH) violation. In view of potential PH violation, observed KM data from the PARAMOUNT trial appears likely to offer the most reliable estimate of survival in the within-trial period.
3. The use of KM data followed by a parametric extension is consistent with the approach used for pemetrexed in TA190 and TA181. During the appraisal of TA181, the ERG made full use of the available observed KM data to minimize the contribution of the trend projections beyond available IPD and fitted a parametric extrapolation to the tail of the KM data to calculate total mean survival. (LRIG, ERG addendum, June 2009; Latimer 2011).
4. During the appraisal of erlotinib (TA227), the ERG also stated that KM observed data was considered to provide the best estimate of PFS for the trial duration. The ERG commented that since all patients in the stable disease population of the SATURN trial had disease which had progressed (that is, the PFS data set was complete), there was no need to model the mean duration of progression-free survival because it could be based directly on KM data from the trial.

   Whilst not complete, in the PARAMOUNT trial the censoring rates for PFS data were low (6.7% placebo arm; 8.1% pemetrexed arm). Thus it was considered to be most appropriate to use the available KM data for PFS rather than use a fully parametric model which did not appear to fit the data well (see bullet 2. above).

On the basis of the above, the KM data was considered to be most appropriate for the within-trial period, meaning the unadjusted OS and PFS extrapolations should be implemented together and a combination approach of the unadjusted KM data with an adjusted extrapolation for different

survival parameters was not considered methodologically appropriate.

A detailed list of factual inaccuracies, and/or clarifications as a result of the misrepresentation of the model methodology explained above, are detailed below.

ERG response to issue 1

The parametric survival models used in the submitted model were calibrated on data covering the whole trial period, including the early 6-9 months when both PFS and OS models do not fit the data well. The manufacturer's argument for not needing to adjust for baseline characteristics is justified for Kaplan-Meier data (provided the initial trial analysis confirms that there are no imbalances in patient characteristics between the trial arms), but only apply to parametric models where these can be shown to be well-fitted to the data (i.e. with well balanced residuals of similar magnitude across the whole trial period). There are plainly problems satisfying this requirment for the six models considered in this case, especially for the PFS models.

There are two options available in such situations:

1) Attempt to improve the fit of the model by adjusting the model through use of a range of patient baseline characteristics which may act directly or by proxy to correct some of the misspecification bias;

2) Seek a better functional form for modelling the data.

The ERG's Scenario 3 follows Option 1 by attempting to ameliorate at least some of the problems associated with the gamma functions.

The ERG's Scenario 4 follows Option 2 in returning to the original Kaplan-Meier data to respecify survival models which are less prone to biased residuals.

If no adjusted models had been developed by the manufacturer the ERG would have proceeded directly to Scenario 4.

For clarity we set out below principles always used by the ERG to guide survival projection:

- Kaplan_Meier data should be used directly from the beginning of a trial until there is evidence of a long-term stable survival trend becoming established and/or the Kaplan-Meier data becoming unstable due to attrition of the number of trial subjects remaining at risk

- long-term trends should be calibrated only on the segment of the Kaplan-Meier data over which the long-term trend is evident

- if all patients have experienced the outcome event (with only truly uninformative censoring) then the Kapln-Meier data should not be modelled without strong cause.

Detailed list of factual inaccuracies			
Section and page reference of ERG report	**Manufacturer suggested amendment**	**Justification for amendment**	**ERG response**
Section 6.1.1, page 50 states: *However, the results of applying this feature were not originally reported in the MS, though a full table of such results did in fact exist in the original model and showed far higher ICERs than in the manufacturer's base-case analysis.*	We suggest amending this statement as follows: *However, the results of applying this feature were not originally reported in the MS, since no subgroups were described in the decision problem and the clinical data did not suggest that there were any differences in relative efficacy by different subgroups.*	Though the statement is not inaccurate we believe it leads to misinterpretation on the reasons for the selection of the unadjusted model and for not showing the results of the subgroups in the original submission. The original basecase model uses the unadjusted analysis, which does not report a table of subgroup results since it was not designed to investigate subgroups. Please refer to the text above for detailed explanation on this element. The subgroup results, which are only reported when the adjusted model is selected, will show a range of ICERs both above and below the ICER for the ITT population from the adjusted model. I.e., the subgroup results are relative to the adjusted ITT ICER, rather than the base-case (unadjusted) ICER.	This statement is an accurate reflection of the manufacturer's submission and the submitted decision model.

Section 6.1.1, page 50 states: *In the response to the ERG's clarification questions,* ***the manufacturer has suggested that the subgroup analysis technique*** *(based on modelling individual trial patients, rather than in aggregate)* ***was not employed to generate base-case results as, although more accurate, it is more time consuming.*** *The ERG does not find this argument to be convincing.*	This text should be removed or changed to reflect that it refers to the alternative methods of analysing the subgroups/adjusted model only.	The time-consuming statement provided in response to the Clarification Question B1a refers to the choice between the two adjusted model methodologies used in the subgroup analyses, i.e., IPD versus average covariates in the risk equations, and had no bearing on the choice of adjusted versus unadjusted models. The adjusted model has two alternative methods of calculating ICERs with covariate adjustment to enable subgroup analyses • Option 1 applies individual patient characteristics in the risk equations, sequentially one at a time. The model generates estimates of the underlying risk and pemetrexed treatment effect using these patient characteristics for each relevant parameter in the cost-effectiveness model (i.e. PFS, OS, QoL). The overall costs and effects for each patient profile are then estimated as if the patient was treated with pemetrexed plus BSC or BSC alone. Cost and effects are then averaged over the patient profiles with the subgroup characteristic of interest. • Option 2 applies average covariates in the risk equations	The ERG has revised the text of the report. The revision is also detailed at the end of this document
Section 6.1.1, page 50 states:	We suggest this text to be removed.	The statement relating to the	The ERG has revised the text of the

In particular, if the subgrouping technique is indeed more accurate, then the use of the unadjusted deterministic base-case results in the MS is seriously misleading.		subgrouping technique being more accurate referred to the accuracy of the IPD subgroup method in direct comparison to the average covariate subgroup method, not versus the unadjusted model as stated in the ERG Report.	report. The revision is also detailed at the end of this document.
Section 6.1.1, page 50 states: *Using subgroup average characteristics is the only reliable method, and leads to subgroup results consistent with the deterministic base-case scenario.*	We suggest this text to be removed.	The method of using IPD (as in Option 1 described above) is a reliable method of generating results for the subgroup analysis due to the inherent non-linearity of cost-effectiveness models.	The ERG has revised the text of the report. The revision is also detailed at the end of this document.
Section 6.1.2., page 53 states: *Three of these covariate factors yielded coefficient values statistically significant at the 5% level, indicating that the adjusted model corresponds more closely to the observed trial data than the unadjusted model. However, the submitted base-case analysis uses the unadjusted model coefficients rather than those of the superior adjusted model.*	This text should be removed or changed to reflect that the results show little difference between the two models.	Examination of the regression coefficients associated with these variables using the adjusted and unadjusted models indicates there is very little difference in the mean estimate of effect or precision between the two models. The adjusted model therefore offers little (or no) improvement and no genuine change in predicted utility estimates compared to the unadjusted model.	There are no factual inaccuracies in this section. The manufacturer is suggesting that the additional significant variables may not add very much to the accuracy of the estimates. This is a matter of opinion, and the inclusion of this information in the ERG report allows the committee to consider the issue. No action required
Section 6.1.2., page 53 states: *Although EQ-5D responses were received from all but one patient in the PARAMOUNT trial,[11] only 83% of responses were free of missing items. This introduces the opportunity for bias to*	This text should be removed or changed to reflect that the results show little difference between the two models.	Examination of the regression coefficients associated with these variables using the adjusted and unadjusted models indicates there is very little difference in the mean estimate of effect or precision between	See above

influence the estimation of modelled utility values, suggesting that the adjusted model is probably the more reliable.		the two models. The adjusted model therefore offers little (or no) improvement and no genuine change in predicted utility estimates compared to the unadjusted model. Therefore, the unadjusted model provides an unbiased estimate of the treatment effect.	

Implementation of survival modelling and projection

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**ERG response**
Section 6.1.3. Page 54 states: *(not least the assumption of proportional hazards)*	We suggest deletion of the statement: (*not least the assumption of proportional hazards)*	A PH assumption was not made in the basecase model.	The proportional hazards assumption does apply to some of the projection functions used in the model (i.e. exponential and Weibull, which are both PH and AFT models), but does not apply to the base case gamma function. The ERG has mended the text to read: "(not least the assumption that treatment and comparator may be modelled jointly)"
Section 6.1.3. Page 54 states: *If significant non-zero coefficients are generated by the analysis this implies that the fit of the model can be improved with additional information, clearly indicating that some degree of bias is present in the estimated function.* *… This indicates that the adjusted PFS and OS models are superior to the unadjusted*	We suggest amending the text to reflect that the adjusted model is not superior to the unadjusted model.	Examination of the log treatment coefficients (time ratio) estimated using the unadjusted and adjusted models indicates that there is very little difference in the mean estimates of effect and precision between the unadjusted and adjusted models (Time ratio unadjusted: 1.22, 95% CI 1.02-	Where the arms of the trial are inappropriately modelled jointly, then the time treatment coefficient reflects the constraint imposed on the data (i.e. the loss of one degree of freedom). Under these circumstances the time ratio coefficient may not show any noticeable response to adding adjustment variables which reflect the

models, explaining significantly more of the inter-patient variation and at least partially correcting for modelling bias.		1.46, Time ratio adjusted model: 1.21, 95% CI: 1.02-1.44). This suggests that the addition of baseline characteristics did little to improve estimates of the treatment effect in PARAMOUNT. Therefore, the adjusted model is not superior to the unadjusted model for OS and PFS.	unaccounted variance under the joint estimation constraint. True measures of fit are those based on residuals between the raw data values and the constrained model estimates. The significance of the adjusting variables indicates the overall deviation between model and data is reduced resulting in superior model fit. No action required.

ERG re-analysis of PARAMOUNT survival data

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**ERG response**
Overall survival			
Section 6.1.4., Page 58 states that: *'The approach adopted is based on using a single parametric function designed to generate OS projection estimates for both trial arms simultaneously. This is achieved by using a proportional hazards formulation including a binary variable to scale up or down the event hazard depending on the randomised treatment'. The proportional hazards assumption is a very strong constraint on the analysis, which can easily introduce serious bias into the resulting trendlines. The manufacturer has sought to justify this assumption with residual plots.*	We suggest the following text is deleted: *This is achieved by using a proportional hazards formulation including a binary variable to scale up or down the event hazard depending on the randomised treatment'. The proportional hazards assumption is a very strong constraint on the analysis, which can easily introduce serious bias into the resulting trendlines. The manufacturer has sought to justify this assumption with residual plots.*	A proportional hazard (PH) model has not been used for the base case analysis. The base case analysis uses an accelerated failure time model (gamma distribution); AFT models do not rely on a PH assumption. Page 102 of MS states that Schoenfeld residual plot showed no evidence of PH violation, however, a log-log plot revealed some evidence of non-parallelism, suggesting possible PH violation due to the initial non-separation of the KM curves.	The ERG has amended the text to remove reference to proportional hazards.
Section 6.1.4., page 58 states that: *In addition, the MS Appendix 18 includes AIC statistics to support the selection of the gamma function as preferable to* ***six other***	This statement should read: *In addition, the MS Appendix 18 includes AIC statistics to support the selection of the gamma function*	The Lilly submission considered six parametric distributions in total.	The ERG has corrected the text accordingly

standard distributions.	*as preferable to **five** other standard distributions.*		
Section 6.1.4., page 58 states that: ***'**However, the mismatch of the fitted gamma model to the observed trial data is most clearly seen when the residuals are plotted to indicate the patterns of over- and underestimation (Figure 8 and Figure 9).'*	Suggest statement is deleted.	Figures 8 and 9 show that it is the exponential model which demonstrates the greatest mismatch compared to observed KM data, particularly in the early phase of the trial.	This is not a factual error. The sentence is not saying that the gamma function has the largest residuals compared to other functions. It is focussing the readers attention on the gamma function as the base case scenario. No action required
Figures 8 and 9 (p 59) refer to *'**seven'** standard survival functions*	These headings should read *'**six'** standard survival functions.*	The Lilly submission considered six parametric distributions in total.	The ERG has amended the text to read 'six'
Section 6.1.4., Page 60 states that: *The consequence of this misspecification of the survival function combined with the constraint of using a single proportional hazards model...*	We suggest the following statement is deleted.	The model was not constrained to PH	The ERG has amended the text to read " *The consequence of this misspecification of the survival function combined with the constraint of using a single jointly estimated model...*
Section 6.1.4., Page 60 states that *... is that incremental projected differences in expected OS are seriously biased in favour of pemetrexed plus BSC, and do not represent the true underlying differences attributable to pemetrexed maintenance therapy. This is the main source of the additional gain in PPS described above and shown to be unsupportable from the PPS trial data.*	We suggest the following statement is deleted.	This statement does not appear to be supported by the evidence presented in Figures 8 and 9. The figures presented by the ERG suggest that exponential and gamma models are very similar in the placebo plus BSC arm and it is the exponential model which demonstrates the greatest overestimation of observed KM data, compared to the gamma model, particularly in the latter phase of the trial. Therefore the statement that [the use of the gamma model] seriously biases in favour of pemetrexed does	This is not a factual error, but a matter of interpretation. The residual charts (Figures 8 & 9) are only presented to aid readers' appreciation of the nature ot the bias implicit to the use of contrained joint modelling of pemetrexed and BSC data. The primary argument is that there is no evidence of PPS benefit, indicated by the PPS trial data (figures 6 & 7), and the confirmatory parallel hazard trends Figure 10.

		not seem valid. Given the scale of the residual plots (figures 8 and 9) the differences between the gamma and exponential model appear minimal and preclude a clear choice between the two. Therefore our sensitivity analysis has tested the basecase ICERs using six different survival distributions.	
The ERG states (p61) that: *'Substituting these long-term OS trends in place of the gamma function, **without any other changes to the manufacturer's base case**, has a significant impact on the cost effectiveness of pemetrexed maintenance therapy….. the ICER is increased by £14,859 per QALY to £62,435 per QALY…'*	We suggest the following statement is amended to: *'Substituting these long-term OS trends in place of the gamma function, without any other changes to the manufacturer's base case, has **minimal** impact on the cost effectiveness of pemetrexed maintenance therapy….. the ICER is **decreased to £47,133*** 	When an exponential parametric model is used in place of the gamma model and all other assumptions remain consistent with the base case (as suggested in ERG comments), the ICER actually decreases from £47,576 to £47,133, as reported in the sensitivity analyses in the Lilly submission, rather than increasing to £62,435.	The statement on page 61 is accurate, as it relates specifically to the manufacturer's base case analysis using the gamma projective model. It has no relevance to any sensitivity analyses, and the suggested amendment would be completely misleading.

ERG re-estimation of pemetrexed acquisition costs using UK distributional data

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**ERG response**
Section 6.1.2, page 50 of the ERG report: *This ignores the effect of gender on BSA, and fails to recognise the wide distribution of BSA within any population.*	We suggest that this statement be deleted	As stated in the ERG report on page 43, Section 5.2.7 UK BSA values for men and women with lung cancer are weighted by gender from the PARAMOUNT trial. I.e. the base case model adjusts the estimates of BSA according to the proportion of males and females modelled in any given analysis.	The ERG recognises that this section does not provide full detail of the differences in method between the manufacturer and the ERG. The section has therefore been modified to make the differences in approach clearer. However, the ERG maintains that its method is more accurate and is consistent with that used in other

		In addition, one of the sensitivity analyses varying pemetrexed costs uses PARAMOUNT IPD, which takes account of both BSA distribution and gender.	appraisals. The ERG has revised the text for this section of the report. The revision is also detailed at the end of this document.
Section 6.1.2, page 51 it states: *The manufacturer has used the mean BSA figures reported by Sacco et al for UK CTX patients. However, these published totals for lung cancer patients include people whose treatment was adjuvant or neo adjuvant rather than palliative in nature.*	We suggest that this statement is supported with additional reference(s).	The paper by Sacco et al (2010) states: *Treatment intent (i.e. neo/adjuvant or palliative) was also recorded for **all patients with breast or colorectal cancer***, (page 3). I.e. lung cancer data was reasonably assumed to only have been collected for palliative patients. To support this Appendix S3 of this paper lists IPD for BSA by cancer and gender and only provides separate neo/adjuvant versus palliative data for breast and colorectal cancer. In addition, in Appendix S1 of this paper the authors use $1.89m^2$ mean BSA for males & $1.65m^2$ mean BSA for females with lung cancer to recalculate drug costs in a palliative setting. I.e. Average BSA = $1.79m^2$ using Sacco et al data, weighted by gender from PARAMOUNT.	The full dataset for this paper is available to researchers on request from the corresponding author. In the study the treatment intention was recorded similarly for all types of cancer, but was only reported selectively in the publication. No action required.
Section 6.1.2, page 51 states: *This contradicts the statement made on page 110 of the MS that "no half-cycle correction is applied to pemetrexed costs". This error has the effect of understating the true cost of pemetrexed treatment for every cycle of the model.*	We suggest that the statement that "*This error has the effect of understating the true cost of pemetrexed treatment for every cycle of the model."* is amended to reflect the fact that this error has minimal impact on the cost of pemetrexed	The statement made on page 110 of the MS that "no half-cycle correction is applied to pemetrexed costs" was correctly identified by the ERG as an error in the Lilly submission. In the basecase analysis, the model estimates 7.95 cycles of pemetrexed, which is very close to the observed mean number of cycles on treatment	This is not a factual error. The effect of correcting the error is reported in Table 39 alongside seven other amendments and has the largest effect of the ICER of any of this group of issues. If the manufacturer considers that correcting this error exposes additional

		from PARAMOUNT, i.e. 7.86 cycles (95% CI 7.00- 8.72 cycles). However the exclusion of a half-cycle correction actually overestimates the number of cycles and subsequent costs of pemetrexed and placebo in the model. Therefore, the statement by the ERG that this error understates the true cost is factually incorrect. If the half-cycle correction is removed, as suggested by the ERG, the model over estimates time on treatment at 8.41 cycles which then also over estimates the associated cost of pemetrexed treatment. Using this approach patients will be modelled to receive more cycles of pemetrexed therapy than observed in PARAMOUNT and, contrary to ERG observations, costs will be overstated. The half cycle correction improves the Markov approximation of the number of cycles of therapy received relative to observed PARAMOUNT data.	inconsistencies in the model, then it suggests that more substantial changes are required to ensure the reliability of the model. It is noted that despite including a parametric model formulation within the model, this has no logical connection to the cost estimation for pemetrexed therapy. The ERG is required to report on model errors identified, but it is not within the ERG's remit to restructure the submitted model.

Miscellaneous factual inaccuracies in the ERG report

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**ERG response**
Section 5.2.7, page 43 states: *The UK list price was reduced by 14% in line with the manufacturer's PAS.*	We suggest that the statement be amended as follows: *The UK list price was reduced by 14.5% in line with the manufacturer's PAS.*	As per Table 36 of the Lilly submission, the erlotinib list price includes a 14.5% PAS discount (TA227).	The ERG has amended text as suggested by the manufacturer.
Section 5.2.7, page 43 states: *Delivery was assumed to occur every 21*	We suggest that the statement be amended as follows:	As per Table 37 of the Lilly submission, the HRG code for erlotinib	The ERG has amended text as suggested by the manufacturer.

*days and NHS Reference Costs which **were assumed to be** based on a 28-day cycle, were pro-rata-ed accordingly.*	*Delivery was assumed to occur every 21 days and NHS Reference Costs which **are** based on a 28-day cycle, were pro-rata-ed accordingly.*	is based on a 28-day cycle. Costs were therefore adjusted for a 21-day cycle. (Reference: DH Chemotherapy Regimens List (DH 2012) as per pages 123 and 124 of the Lilly submission).	
Section 5.2.7, page 45 states: *The average drug cost for patients receiving BSC has been estimated using data from the PARAMOUNT trial cohort.*	We suggest that the statement be amended as follows: *The cost of BSC drugs only features explicitly in a non-base case model scenario using a limited number of directly measured resources in the PARAMOUNT trial.*	Suggested amendment aligns statement in ERG Report with ERG comments on changes to blood transfusion costs on page 52 of ERG report.	The ERG has amended text to read: 'The average drug cost for patients receiving BSC has been estimated using data from the PARAMOUNT trial cohort; however, this does not apply to the base case scenario.'
Section 6.1.2, page 52 states: *In the manufacturer's base-case analysis the monitoring of patients prior to disease progression is assumed to cost twice as much per cycle for placebo plus BSC patients as for those receiving pemetrexed maintenance therapy (apparently based on adapting the approach used in TA190,[8] resulting in an extra discounted cost per patient not receiving pemetrexed of £858. This directly contradicts the calculations detailed in Tables 42-44 of the MS which conclude (based on figures drawn from the BTOG survey report[44] that monitoring costs prior to progression are £15.54 per cycle greater for patients receiving pemetrexed plus BSC than for patients receiving placebo plus BSC, due to more frequent out-patient consultant reviews and CT scans.*	If this paragraph in the ERG Report is still deemed necessary we suggest that this statement be amended: *In the manufacturer's base-case analysis the **BSC costs** are assumed to cost twice as much per cycle for patients **not on active chemotherapy as for those receiving active chemotherapy, i.e. either pemetrexed maintenance therapy or second-line agents post-progression.*** In addition, we suggest that this statement is deleted: ***This directly contradicts** the calculations detailed in Tables 42-44 of the MS which conclude (based on figures drawn from the BTOG survey report[44] that monitoring costs prior to progression are £15.54 per cycle greater for*	It appears that the ERG has confused BSC costs (which are applied to all patients in all cycles) with additional monitoring costs applied only to patients receiving pemetrexed maintenance treatment. As a result, some of the statements in this section of the ERG report are factually incorrect. The ERG's initial observations appear to relate to general BSC costs per cycle. However, the latter paragraph appears to relate to the costs of monitoring for pemetrexed, which were modelled separately to the BSC costs. BSC costs are modelled consistently with the accepted approach used in TA190. I.e. BSC costs have been applied to patients in each cycle (both pre- and post-progression) depending on whether or not they are receiving active chemotherapy (maintenance or second-line chemotherapy) in that	The ERG has revised the text of the report. The revision is also detailed at the end of this document

	patients receiving pemetrexed plus BSC than for patients receiving placebo plus BSC, due to more frequent out-patient consultant reviews and CT scans.	cycle. BSC costs for patients not receiving active chemotherapy (£72) are twice as much per cycle as those patients receiving active chemotherapy (£36) irrespective of whether the patient is in the pre- or post-progression health state. This is reported on page 130-131 of MS and the difference in BSC costs assumes that patients receiving active chemotherapy will not receive additional palliative radiotherapy. This assumption is stated in Table 27 on page 112 of the MS. Additional monitoring costs for patients receiving pemetrexed are £15.54 per cycle as stated, due to additional consultant visits and CT scans compared to patients not receiving maintenance treatment.	
Section 6.1.2, Table 39 Co-medication costs have been reported as: Incremental cost: £12,179 ICER: £48,785 Change in ICER: £1,209	These costs should read as follows: Incremental cost: £12,177 ICER: £47,672 Change in ICER: £96	The results reported in the ERG Report are incorrect.	The ERG has amended Table 39 to read: Incremental cost: **£12,179** ICER: **£47,679** Change in ICER: **£103**
Section 5.2.3, page 41 states: *Within the model the mean number of cycles of second-line CTX is 4.82 for docetaxel patients and 6.27 for erlotinib patients* ***reflecting the results of the JMEN trial***.	We suggest that this sentence should be amended as below: Within the model the mean number of cycles of second-line CTX is 4.82 for docetaxel patients and 6.27 for erlotinib patients, **which is consistent with the approach used in TA190**.	The number of cycles of second-line CTX are derived from TA162 (STA of erlotinib in second-line NSCLC) and were used in TA190 as they were considered to reflect UK clinical practice.	The ERG has amended the text accordingly.

Factual inaccuracies in the clinical section

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 11, Section 2.2 of ERG report: The following statement regarding the eligible patient population of pemetrexed appears to have inadvertently been left in the document: *However, the ERG is aware that the majority of people with non-squamous disease in England and Wales will be treated with pemetrexed plus cisplatin as a first-line treatment; these people will be ineligible for maintenance treatment with pemetrexed.*	The phrase '*these people will be ineligible for maintenance treatment with pemetrexed*' needs to be removed or an additional clarification should be added that patients were ineligible under the TA190.	Pemetrexed is now licensed for use as continuation maintenance, so patients who have used pem/cis first line are eligible to receive pemetrexed as maintenance treatment.	The ERG has amended the report to reference to TA190.
Page 13, Section 2.3 of ERG report: It is not sufficiently clear that the 'overall' patient population referred to in the following statement includes switch and maintenance treatment. *The ERG considers this to be a reasonable estimate of this population; however, it is noted that pemetrexed is currently licensed and recommended by NICE as a switch maintenance treatment (TA190) and so* ***overall****, the number eligible for maintenance pemetrexed is higher.*	We suggest that the sentence be modified as follows: The ERG considers this to be a reasonable estimate of this population; however, it is noted that pemetrexed is currently licensed and recommended by NICE as a switch maintenance treatment (TA190) and so overall, the number eligible for switch and continuation maintenance treatment with pemetrexed is higher.	The indication relevant to this submission is continuation maintenance, so only the number of patients eligible for pemetrexed continuation maintenance (N=535) is relevant to this submission. It should also be noted that patients who may be eligible for switch maintenance with pemetrexed would also have to be part of the pool of 4,034 patients described in the Lilly submission, i.e., these would be patients who were eligible for pem/cis first-line but did not receive it and are therefore eligible for pem switch maintenance at maintenance stage. With pem/cis becoming standard of care, the number of patients who would receive switch maintenance is very small. As stated in the Lilly	The ERG has added 'switch and continuation' to the statement

		submission, market data from Q2 2012 show that only 24 patients currently receive pemetrexed switch maintenance.	
Table 7 on page 22, Section 4.1.5 of ERG report, the percentage of patients violating inclusion/exclusion criteria in the placebo + BSC arm is incorrect. Protocol inclusion/exclusion criteria, n(%) (for placebo + BSC arm)=8 (2.4).	We suggest the following amendment: Protocol inclusion/exclusion criteria, n (%) (for placebo + BSC arm)= 21 (11.7).	As specified in the PARAMOUNT CSR, page 78 Table S124.10.4.	The ERG has corrected the error.
Section 4.1.7, page 26 of ERG report: *The ERG notes that subgroup analyses of age, smoking status and gender were not pre-specified in the SAP.*	We suggest that the statement be amended as follows; *The ERG notes that subgroup analyses of smoking status was not pre-specified in the SAP.*	The population to be used for each analysis (and therefore pre-specified) including age and gender is stated in the SAP, version 3, page 21. This document was provided in response to the clarification questions. The subgroup analysis results for age and gender should therefore be considered as confirmatory, not exploratory.	On page 21 of the SAP a list of tables presenting the data split by age and gender are provided but the manufacturer did not state that any formal analyses would be performed on either of these subgroups. No action required
Section 4.2, page 28 of the ERG report states: *At 2 years, the percentage of people **surviving at 1 year** was 32% (95% CI 27 to 37) in the pemetrexed plus BSC arm and 21% (95% CI 15 to 28) in the placebo plus BSC arm."*	We suggest deleting the words in bold '*at 1 year'*	This appears to be a typographical error.	The ERG has deleted 'at 1 year' from statement as suggested
Table 20, Section 4.4, page 35 of ERG report presents values from a previous (PFS) datalock: *The summary of PDT has been taken from the published paper (Paz-Ares et al 2012) and is from the July 30th 2010 (primary PFS) datalock. The updated numbers from*	We suggest that the PDT values from the final OS datalock (final CSR, Table S124.4.7, page 21) be presented since these values are incorporated in the economic model.	This inaccurate reflection of the clinical data used as input for the economic model could cause unnecessary reader confusion.	The ERG has updated Table 20 in accordance with Table S124.4.7 presented in the final CSR.

the March 19th datalock (final OS) are reported in the final CSR, page 21, Table S124.4.7, provided with the Lilly submission.			
Section 4.4, page 32 of ERG report: *The ERG notes that the figures quoted in the MS appear to be different to those in the main published paper that describes the PARAMOUNT trial and are different again in the published paper that describes the safety and QoL results of that trial. However, in all reports, fatigue, anaemia and neutropenia are the AEs that occur more frequently (with statistical significance) in the pemetrexed plus BSC arm of the trial.*	No amendment required	The reason for the difference is because the values in the submission are from the most recent datalock (final OS) while those in the published paper (Gridelli et al 2012) are from the PFS datalock. As the ERG mentions, the AE results are consistent.	No action required.

REVISED SECTION IN 6.1.2 (PAGE 50)

Method for estimating of pemetrexed costs

Pemetrexed monotherapy doses are calculated at 500mg/m^2 of BSA. In the manufacturer's base-case analysis a simple method is employed which uses a single average BSA figure for all patients, and determines the required number of vials of the drug for such an average patient. This average BSA figure is the average of all patients (male and female) in the PARAMOUNT trial, and is slightly higher than the corresponding figure reported by Sacco et al[34] for UK CTX patients. However, this method of calculation ignores the effect of gender on BSA in altering the amount of drug wastage, as the wide distribution of BSA within the population (separately for males and females) typically increases the number of vials required to treat the whole population. The mean BSA figures reported by Sacco et al[34] for UK CTX patients include those lung cancer patients whose treatment was adjuvant or neo-adjuvant rather than palliative. The ERG has therefore re-estimated the mean cost per cycle of pemetrexed acquisition, using UK distributional data for palliative CTX, and applying a maximum dose limit of 1000mg, yielding a figure of £1,481.37 per dose instead of the manufacturer's estimate of £1,440 per dose.

REVISED SECTION IN 6.1.2 (PAGE 52)

Pre-progression monitoring costs

In the manufacturer's base-case analysis the routine monitoring of patients prior to disease progression is assumed to cost twice as much per cycle for placebo plus BSC patients as for those receiving pemetrexed maintenance therapy (apparently based on adapting the approach used in TA190[8]), resulting in an extra cost per patient not receiving pemetrexed. If, instead, the follow-up pattern previously used by the ERG for the TA190[8] appraisal of pemetrexed maintenance therapy is applied to the manufacturer's model (review every 4 cycles on pemetrexed vs at 3, 6, 12, and 18 months for 'watch and wait' patients), the estimated discounted cost difference is £169.26 per patient greater for patients on pemetrexed monotherapy.

REVISED SECTION IN 6.1.4 (PAGE 58)

Overall survival

The results obtained with the manufacturer's model are strongly influenced by the method adopted for analysing time-to-event data. This is most important when modelling OS, since this determines the dominant outcome variable (quality adjusted life years), and because the OS data from the PARAMOUNT trial[11] are less mature than for other variables so greater reliance is placed on projective modelling to fill the data deficit. The approach adopted is based on using a single parametric function designed to generate OS projection estimates for both trial arms simultaneously, featuring a binary variable to alter the event hazard depending on the randomised treatment. This introduces a very strong constraint on the analysis, which can easily introduce serious bias into the resulting trendlines. The manufacturer has sought to justify this assumption with residual plots (MS, Appendix 16) and OS survival plots (MS, Appendix 17). In addition, the MS Appendix 18 includes AIC statistics to support the selection of the gamma function as preferable to six other standard distributions. However, the extent of the mismatch of the fitted gamma model to the observed trial data is most clearly seen when the residuals are plotted to indicate the patterns of over- and underestimation.

REVISED SECTION IN 6.1.1 (PARAGRAPHS 2 & 3 PAGE 50)

The model additionally contains data and Visual Basic code to estimate cost effectiveness for a range of different subgroups. However, the results of applying this feature were not originally reported in the MS, though a full table of such results did in fact exist in the original model and showed far higher ICERs than in the manufacturer's base-case analysis. In the response to the ERG's clarification questions, the manufacturer has provided detail of the mode of operation of the subgroup analysis technique (based on modelling individual trial patients, rather than in aggregate).

The ERG has attempted to replicate this procedure for the base case analysis to assess how well the results accord with the deterministic model results. Unfortunately, it only proved possible to activate this facility for a single preset scenario using a range of model parameter settings quite different from the submitted base case scenario. As access to the Visual Basic code was found to be password protected it was not possible for the ERG to complete this validation check.