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

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DOES NOT CONTAIN CIC/AIC

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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

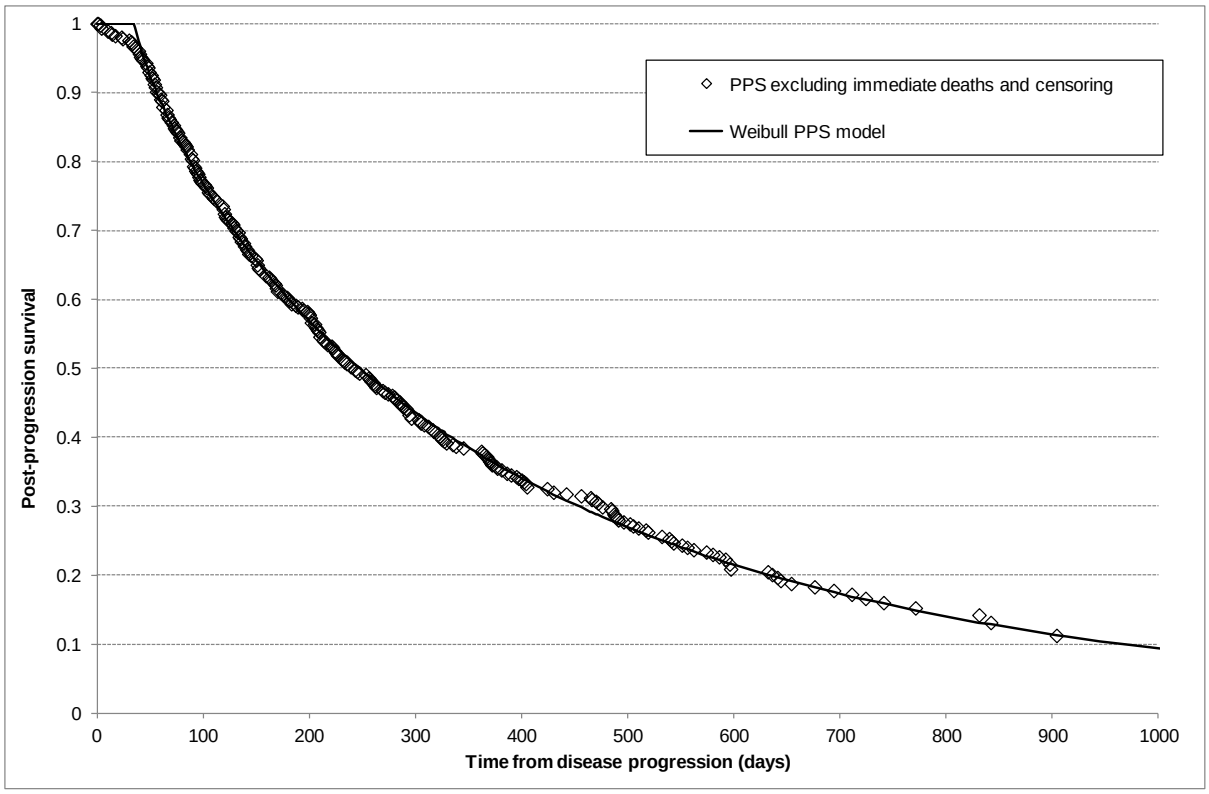

Figure 1 Pooled PPS survival curve form the PARAMOUNT trial with fitted Weibull parametric function. (Patients dying or censored on day 1 have been removed for clarity)

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).

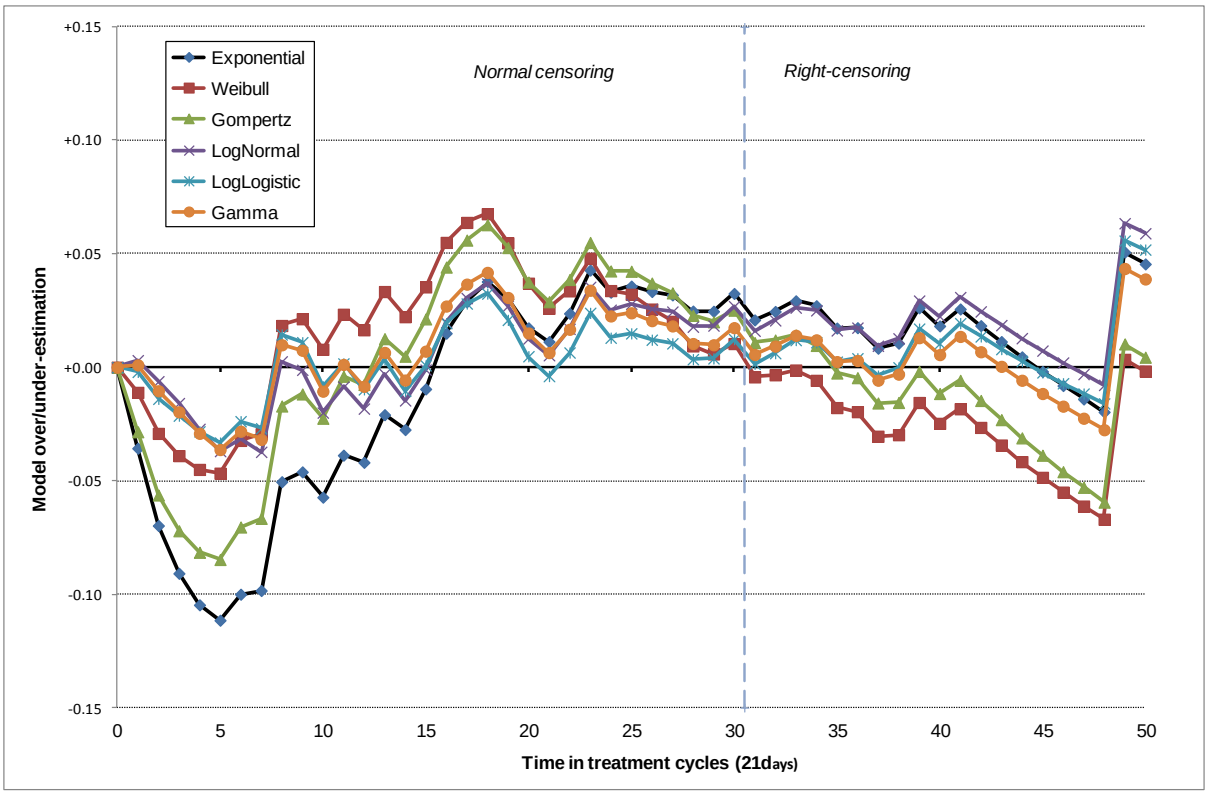

Figure 2 Over- and underestimation of OS by six standard survival functions calibrated against the placebo+BSC arm of the PARAMOUNT trial

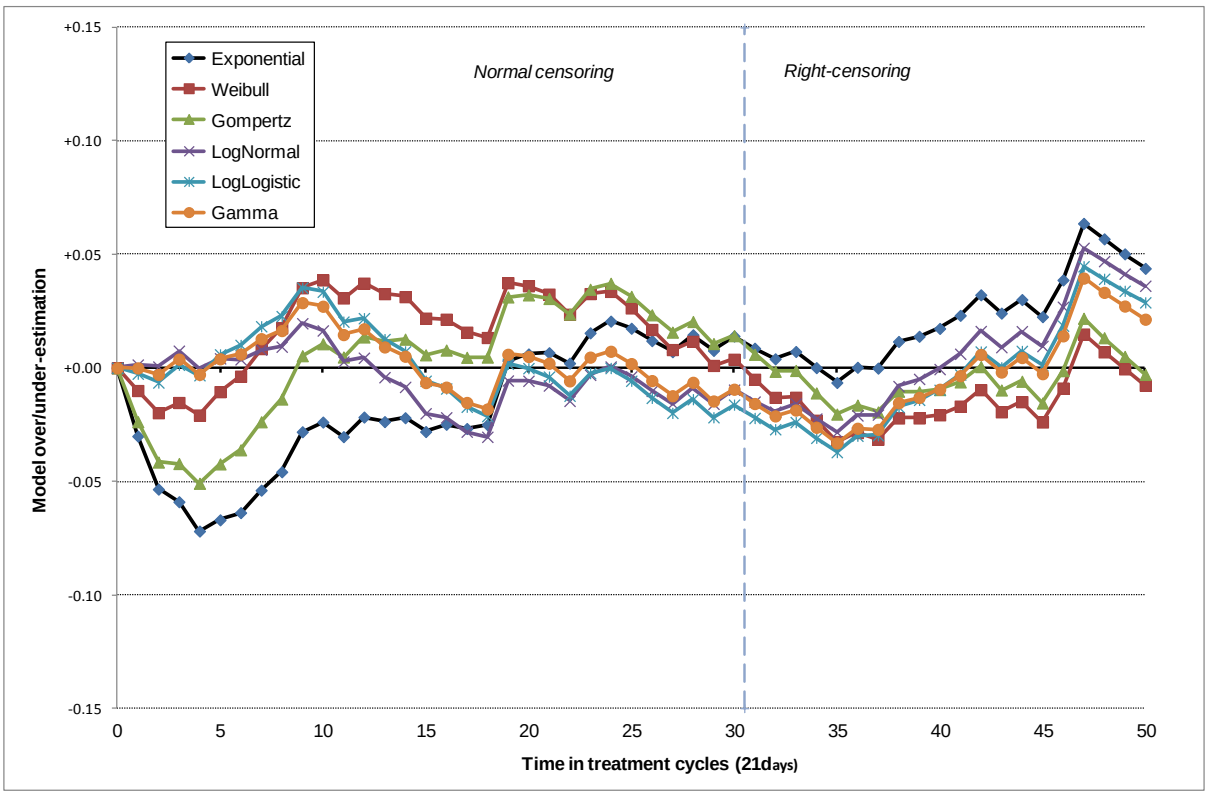

Figure 3 Over- and underestimation of OS by six standard survival functions calibrated against the pemetrexed+BSC arm of the PARAMOUNT trial

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.

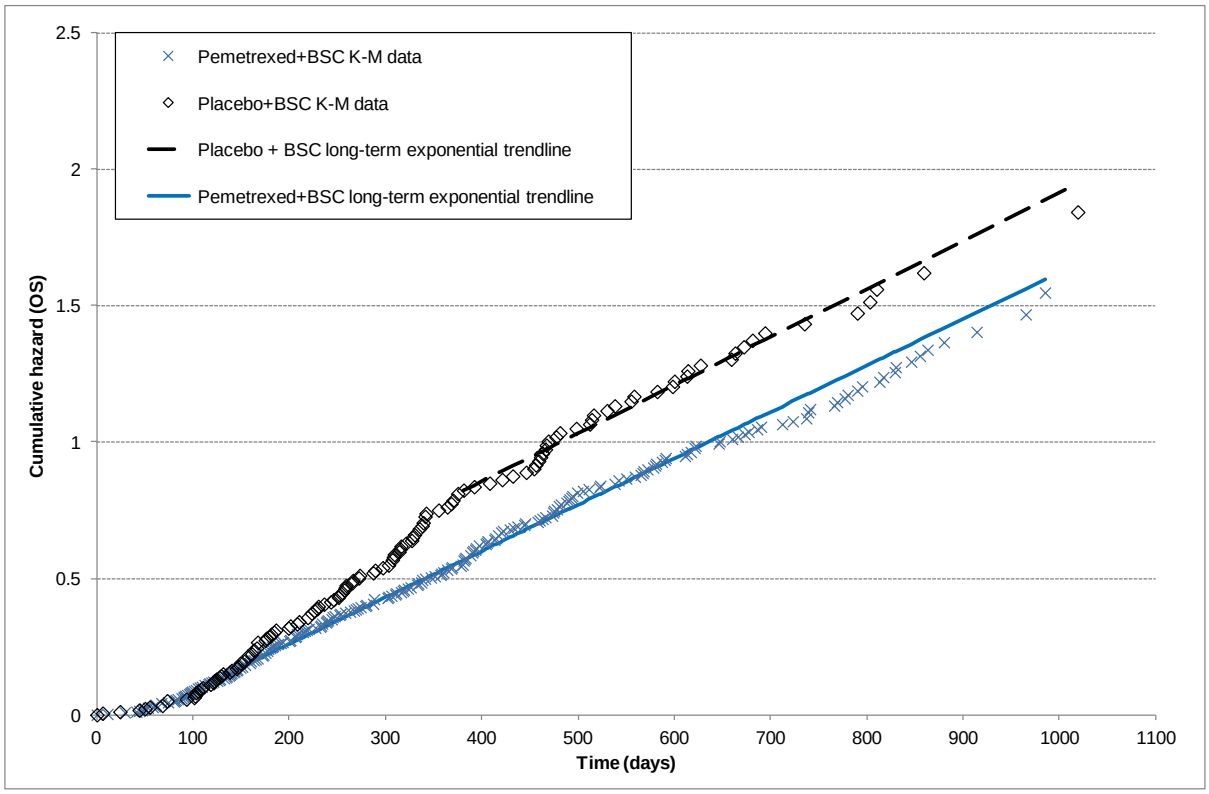

Figure 4 Comparison of cumulative OS hazards in both arms of the PARAMOUNT trial with ERG calibrated exponential trend.