STA 2nd Addendum

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

SECOND ADDENDUM

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DOES NOT CONTAIN CIC/AIC

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LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

1 INTRODUCTION

In August 2013, the National Institute for Health and Care Excellence (NICE) issued a second Appraisal Consultation Document (ACD) for the appraisal of pemetrexed for maintenance treatment following induction therapy with pemetrexed and cisplatin for non-squamous NSCLC to consultees in preparation for a reconsideration of the Appraisal Committee's (AC) provisional decision on 25th September 2013. Only two responses were received, the most extensive of which was from the manufacturer of pemetrexed and concerned the modelling of overall survival (OS) from the PARAMOUNT trial, and the estimation of patient numbers eligible for pemetrexed treatment. The former discussion included several criticisms of the approach taken by the Evidence Review Group (ERG), who considered it important that the AC should receive a careful response to the issues raised for consideration on the 25th September. Due to the very short time interval between the manufacturer's response being received by the ERG and the AC meeting, it was not practicable to prepare a detailed response document for prior circulation to the committee members and the consultees. Therefore the ERG prepared a short verbal presentation based on four PowerPoint slides, which were provided in advance to the manufacturer.

This addendum presents the content of that presentation with supporting technical details of the methods used to derive the results shared with the AC members on 25th September 2013, and discussed by the committee in public session. It is important to emphasise that this contribution by the ERG does not involve new data not previously seen by the AC, but seeks only to address the central concerns expressed in the manufacturer's response document. This is done by re-assessing the available evidence in a manner which is believed to be helpful to the AC in considering the most appropriate estimate of the likely gain in OS which could be expected to be obtained from pemetrexed maintenance treatment in the eligible population.

2 RECONSIDERATION OF PARAMOUNT COST-EFFECTIVENESS RESULTS

Issues raised

The manufacturer's response did not address the central concern raised by the ERG; that Kaplan-Meier analysis of post-progression survival data from the PARAMOUNT clinical trial shows no evidence of any patient survival benefit accruing after disease progression. This led the ERG to consider that the cost-effectiveness estimates generated by the manufacturer's decision model were unrealistic since they indicate that a substantial proportion of the indicated extension in OS occurs after disease progression. Instead, the manufacturer's comments relate to questioning aspects of the way the ERG modified the decision model in estimating alternative OS gains and incremental cost-effectiveness ratios (ICERs). Firstly, the ERG observation that in the latter period of the trial analysis

patients in the control and intervention arms of the trial were experiencing similar mortality risks, and therefore following the same survival trajectory. In addition it was claimed that the parametric function (exponential) employed by the ERG to model survival beyond the available trial data was inappropriate.

Long-term survival

In the original ERG report, the ERG concluded that there is a common long-term survival trajectory for both arms of the PARAMOUNT trial, based on a visual comparison of the cumulative hazard plots of the trial arms (Figure 10 of the ERG report). Linear trendlines were then fitted to the latter portion of each arm's data with a common hazard rate.

The ERG has revisited this analysis from a different perspective to test whether the approach described in the original ERG report was robust and the conclusions justified. The ERG now focus attention on the OS Kaplan-Meier data directly (rather than the cumulative hazard). This involves comparing the patient experience in the latter part of the two survival curves after realigning those curves over time to obtain the best possible correspondence in survival trends, prior to carrying out a statistical test of equivalence. Figure 1 shows the effect of advancing the timing of control arm events (deaths) by 200 days so that the closest correspondence was obtained between the two data sequences in the last 400-500 days. This procedure is necessary as it has been clearly demonstrated that there is a statistically significant PFS gain for pemetrexed patients, so that deaths can be expected to be delayed substantially in the pemetrexed OS survival curve. Visual examination appears to show very close correspondence of the pemetrexed arm and the shifted control arm over an extended period of time.

To test this observation further, The ERG carried out a landmark Kaplan-Meier analysis of all patients remaining alive and at risk with an estimated OS less than 0.367 (i.e. cumulative hazard > 1.0). Figure 2 shows clearly the close correspondence of the two survival curves, with a non-significant Log-rank test result ($p = 0.754$) confirming the visual assessment in indicating that there is no support in the PARAMOUNT data for any parametric model which generates continuing additional OS gain beyond the available data. This result is fully consistent with the post-progression survival analysis previously reported in the ERG report (pages 56-57).

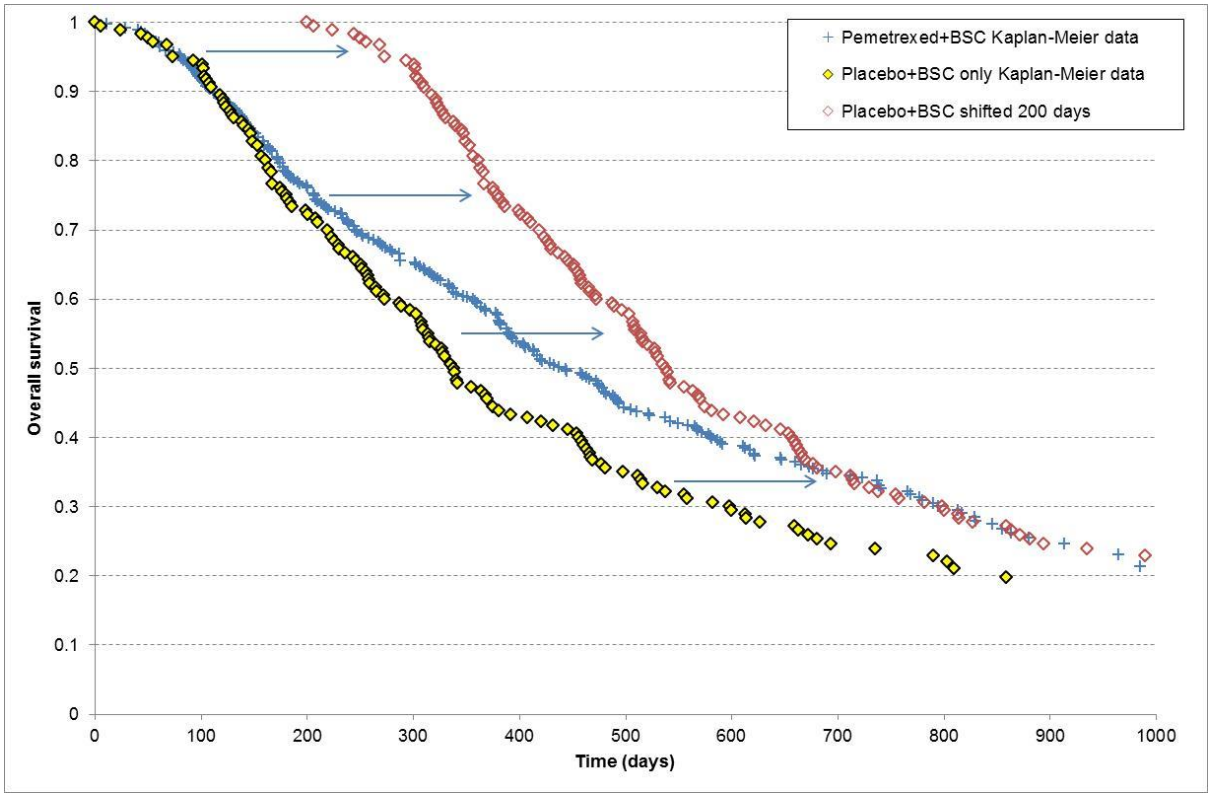

Figure 1 Comparison of OS in both arms of the PARAMOUNT trial after shifting the control arm forward by 200 days

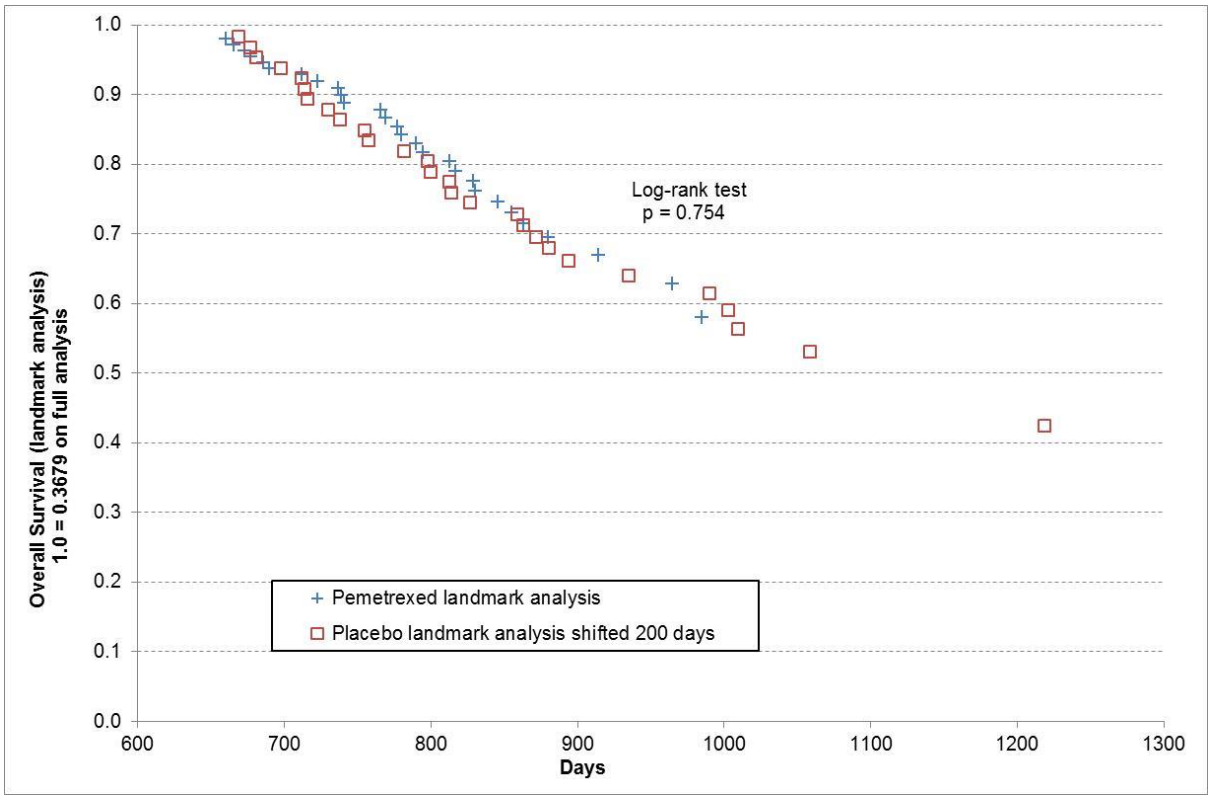

Figure 2 Landmark Kaplan-Meier analysis pemetrexed OS and placebo OS shifted by 200 days

There being no reason to distinguish between trial arms, we repeated the analysis pooling data from both arms of the PARAMOUNT trial, and examined the resulting cumulative hazard plot (Figure 3). A simple linear regression trendline fits these data very closely (r^2 = 0.9948) confirming the appropriateness of using a common exponential model to extrapolate OS in both trial arms.

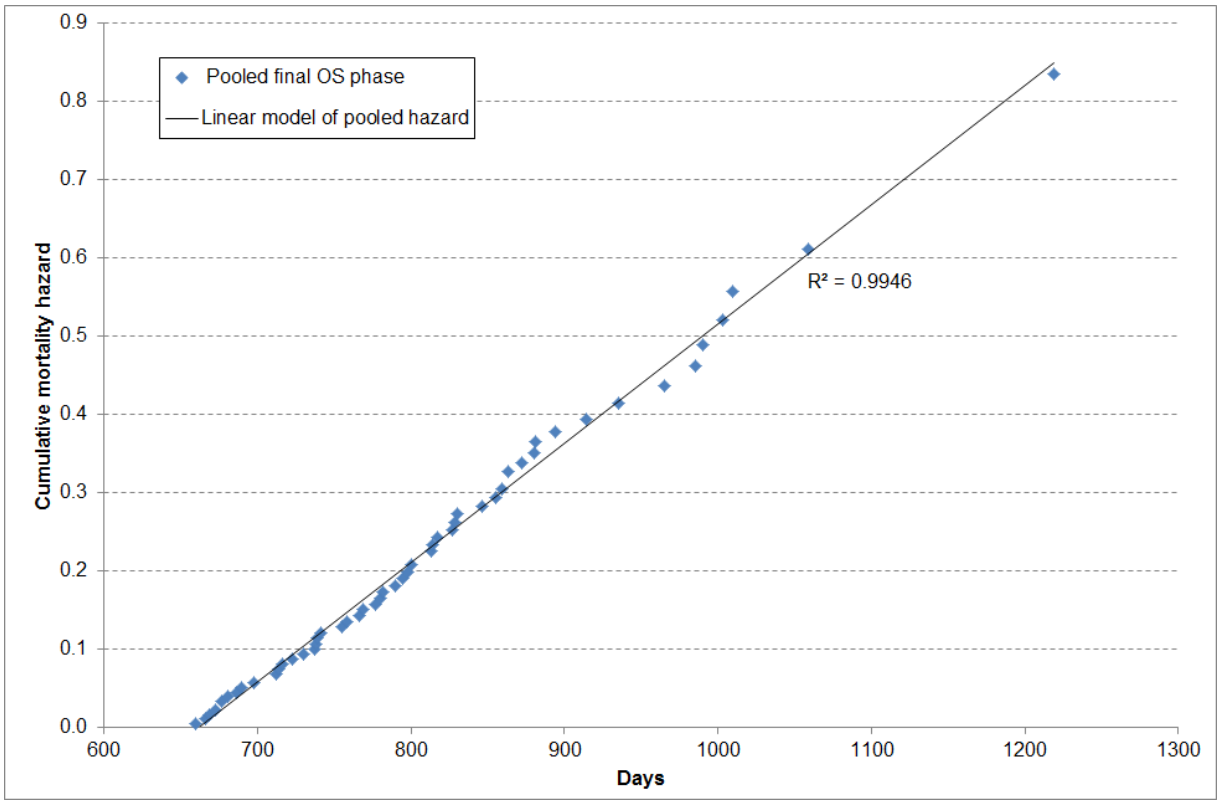

Figure 3 Cumulative hazard plot from landmark Kaplan-Meier analysis (pooled pemetrexed OS and placebo OS shifted by 200 days data), for patients alive and at risk ≥ 669 days

Re-estimation of OS gain

Confirmation of the equivalence of long-term OS trends in both arms of the PARAMOUNT trial data has suggested an alternative method for estimating the mean OS gain due to pemetrexed maintenance treatment.

In Figure 4, any projection of OS beyond point D in the pemetrexed arm or in the shifted control arm will provide the same OS value (equivalent to the area under the curve from the line DE until all patients have died). However, this value is identical to the unshifted control arm from line BC until all patients have died. Thus there is no need to carry out projective modelling of OS in either arm to obtain a reliable estimate of the OS gain attributable to pemetrexed, since the late phase of survival in both arms yields the same mean OS contribution and so has no net effect on OS gain. Instead there is

only a need to compare the area under each Kaplan-Meier curve prior to the final phase. The result of this calculation (using SPSS 21 Kaplan-Meier survival analysis routine) is shown in Figure 4 and indicates that the best estimate for mean OS gain is 106 days or 3.49 months.

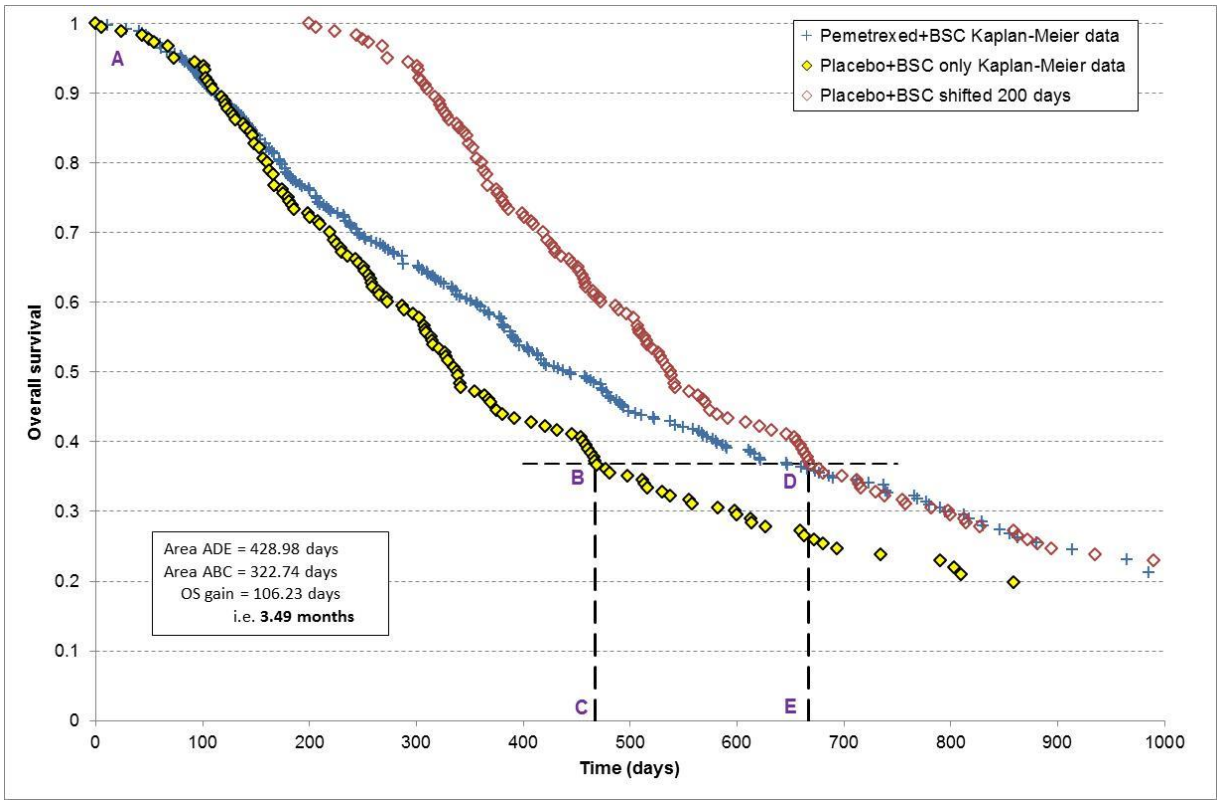

Figure 4 Calculation of OS gain directly from Kaplan-Meier analysis

Re-estimation of ICER

It is not possible to accommodate this revised estimate of OS gain by simple substitution of parameters or data within the manufacturer's decision model without substantial restructuring of the model. However, as the differences in OS gain are attributable predominantly to the different estimates of post-progression survival gain (since there is very little difference in PFS estimates) any changes in ICER, when OS gain is altered, are largely reflected in changes in post-progression health state costs and post-progression QALYs. This allows straightforward estimation of a revised ICER, by interpolation between existing ICERs obtained using the model for scenarios which differ only in the amount of OS gain generated in the model, namely the revised base case, revised base case + ERG OS option 1 and revised base case + ERG OS option 2, details of which may be found in the first ERG Addendum.

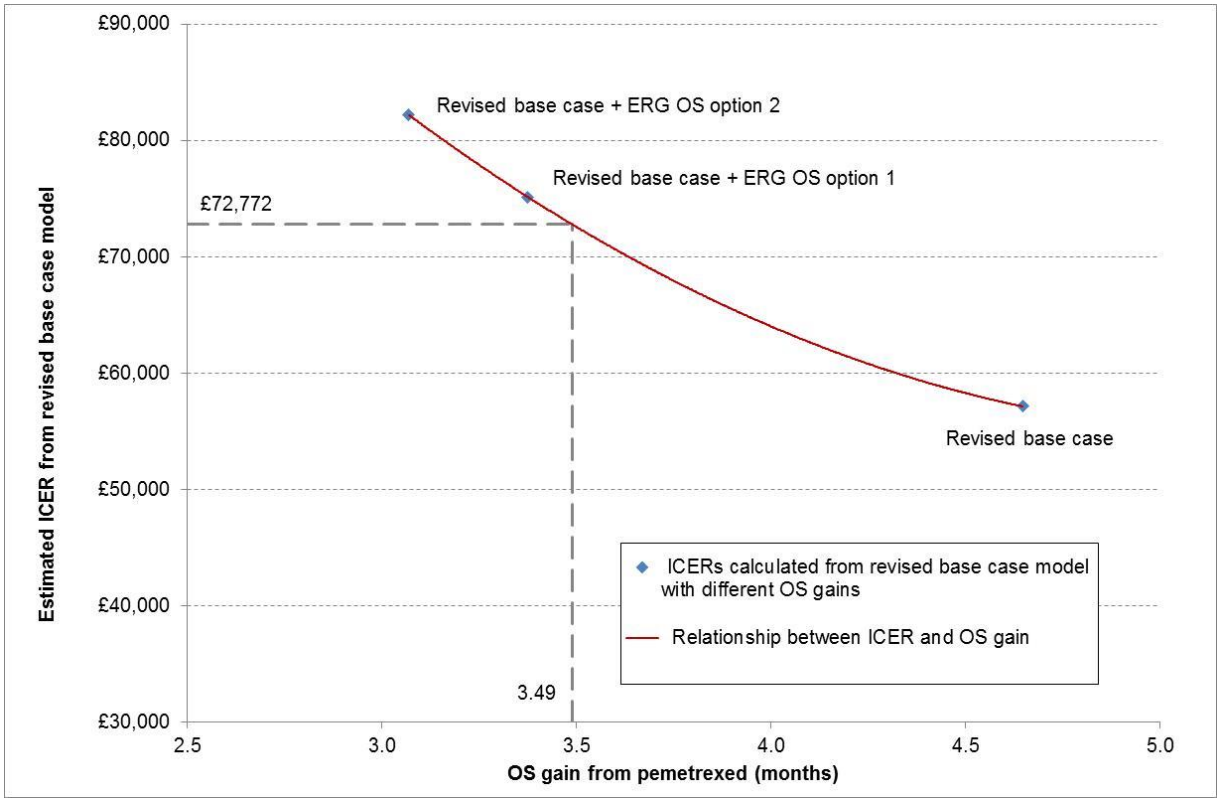

Figure 5 Estimation of revised ICER by univariate interpolation of previous model results differing only by estimated OS gain.

[polynomial trendline: estimated ICER = 5629.1 * ΔOS^2 - 59325 * ΔOS + 211257.4]

Based on the best estimate of OS gain due to pemetrexed continuation maintenance therapy in the PARAMOUNT trial, a revised base case ICER is obtained of £72,772 per QALY gained.

Modelling of resource use data

In addition to the issue of OS estimation, the ERG's first addendum also reported cost-effectiveness results relating to the method by which resource use both before and after disease progression are estimated in the manufacturer's model. Although the model includes logic and parameter values derived from the PARAMOUNT trial to estimate supportive care costs in the categories of hospitalisations, transfusions, radiotherapy treatments and palliative medications, the manufacturer prefers to use the results from the earlier JMEN trial uprated for inflation. The balance of uncertainty between the reliability of some PARAMOUNT data, and the appropriateness of using inflation measures to update data from a different trial is unclear and not well argued by the manufacturer. To maintain consistency, the ERG prefers the use of PARAMOUNT resource data with the PARAMOUNT outcome data to populate the model in the absence of a convincing argument to the contrary.

Including this additional model amendment raises the estimated ICER to £74,500 per QALY gained (Figure 6), which represents the ERG's preference as the most plausible assessment of the cost-effectiveness of pemetrexed continuation maintenance therapy in this population.

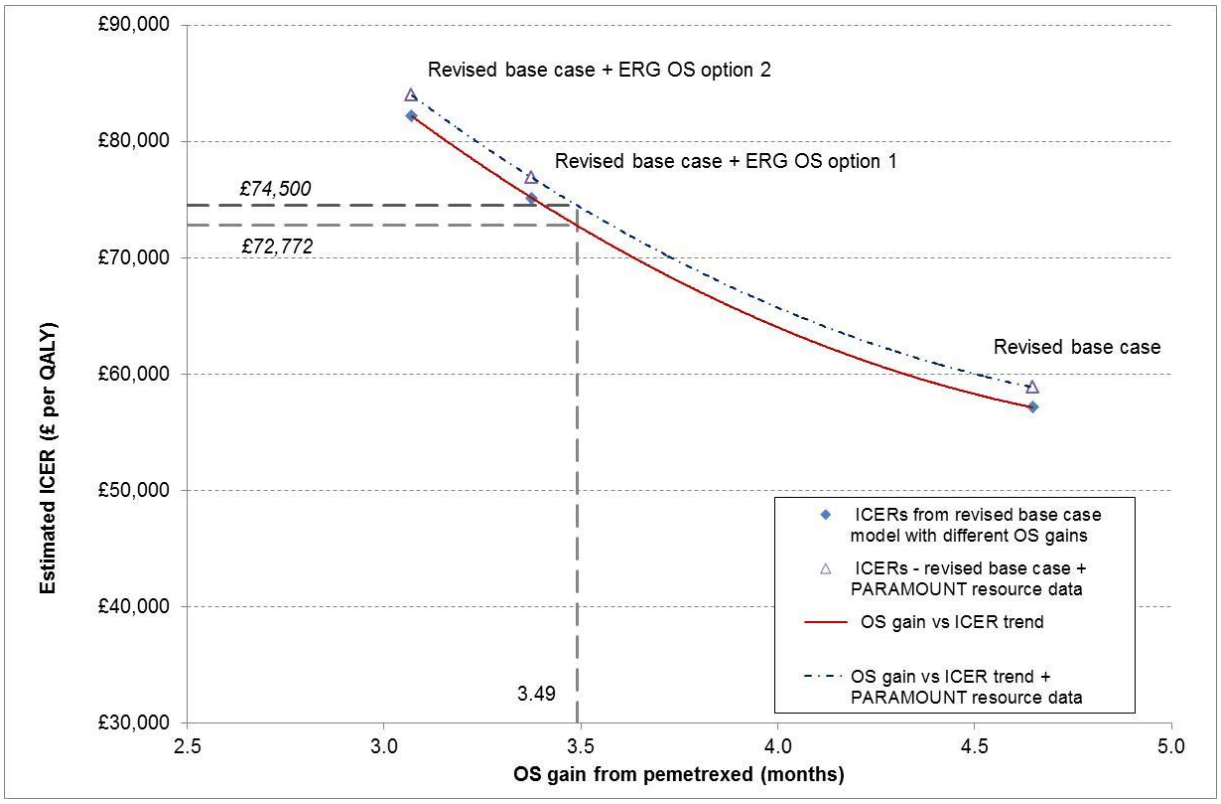

Figure 6 Estimation of revised ICER by univariate interpolation of previous model results differing only by estimated OS gain, including use of PARAMOUNT resource data.

[polynomial trendline: estimated ICER = $5732.3 * \Delta OS^2 - 60156 * \Delta OS + 214628.4$]

3 SUMMARY OF FINDINGS

The manufacturer's response to the second ACD has prompted the ERG to re-examine the PARAMOUNT survival data previously considered, with a view to addressing the issues raised by the manufacturer that questioned the ERG's approach to OS estimation. A straightforward graphical procedure was applied to the Kaplan-Meier analysis results to test the ERG's previous observation that the long-term hazard trends in the trial arms appear parallel. This approach clearly confirmed the ERG's original conclusion that hazards are parallel, as is implied by the absence of evidence of any additional survival benefit accruing after patients disease has progressed. In addition, this re-examination of the data also supported the ERG's choice of the exponential function for long-term extrapolation.

However, the new perspective taken to the trial data suggested a simpler and more reliable method of estimating the OS gain attributable to pemetrexed using only Kaplan-Meier data, without recourse to any projective survival modelling. In general, direct use of trial data will always be associated with less uncertainty than attempting to apply an appropriate projective model to the data, as no parametric assumptions are required to modify the original trial data. Use of this direct approach indicated that the best estimate for OS gain is 3.49 months, which corresponds to an **ICER of £72,772 per QALY gained**.

The other disputed issue considered in the ERG's first addendum was the choice of resource data (PARAMOUNT data vs inflated JMEN cost results). The ERG has reconsidered this issue and does not see a convincing reason why PARAMOUNT data should not be used consistently throughout the decision model. When this amendment is also applied, the estimated **ICER increases to £74,500 per QALY gained**.

Appendix

The polynomial trend

Polynomial interpolation is the simplest mathematical method for estimating intermediate points in a non-linear series. The non-linearity is evident from the charts, and is to be expected because the y variable (ICER) is a ratio, and the x-axis variable is the driver of the denominator of the ICER ratio. Even if linear interpolation were (incorrectly) used instead, the estimated ICERs would be very similar, albeit slightly higher than the estimates made by the polynomial method.

Polynomial trendline in Figure 5

Create scatterplot in Excel using the following data from the ERG 1st Addendum:

x-axis OS gain (months)	*y-axis ICER*
3.07	82,183
3.376	75,133
4.647	57,133

Click on any data point, then right-click and select 'Add trendline'.
Select the polynomial option (order 2)
Select 'Display equation on chart'
The following equation will appear as "$\mathbf{y = 5629.1x^2 - 59325x + 211256}$"

This equation was checked for correspondence with the original data and a small displacement bias was found in the estimates. A correction was estimated by least squares minimisation, adding 1.4 to the constant which then becomes **211257.4**

Polynomial trendline in Figure 6

Create scatterplot in Excel using the following data (obtained by using the same model settings as above but with the resource use parameter set to PARAMOUNT instead of JMEN):

x-axis OS gain(months)	*y-axis ICER*
3.07	83,876
3.376	76,875
4.647	58,870

Follow the same procedure to add a polynomial trendline to this data series.
The following equation will appear as "$\mathbf{y = 5732.3x^2 - 60156x + 214630}$"

This equation was checked for correspondence with the original data and found a small displacement bias in the estimates. A correction was estimated by least squares minimisation, subtracting 1.6 from the constant which then becomes **214628.4**

Finally, these equations were used to estimate the new ICERs, by substituting the estimated survival gain (3.490201) as the x variable.

With the first equation the estimated ICER is **£72,772.17**

With the second equation the estimated ICER is **£74,499.90**

Replicating the OS gain

The ERG best estimate of the OS gain is based on using the OS data provided in the manufacturer's clarification response, using the ERG specified censoring rule (which removes informed censoring bias). Truncated estimates of mean survival by the AUC method were obtained by censoring all cases in the pemetrexed arm still at risk at 669 days, and in the placebo arm at 469 days.

The estimated mean OS (in days) using SPSS 21 Kaplan-Meier procedure is:

Arm	*Estimate*	*Standard error*
Pemetrexed	428.977	11.853
Placebo	322.744	10.859
Difference	**106.233**	

Re-estimation of the ICER

The manufacturer and the ERG agree quite closely on the amount of PFS gain attributable to pemetrexed. So the difference in opinion about OS gain is essentially a disagreement about how much (if any) PPS gain is consistent with the trial evidence. So when we compare different estimates of OS gain, we are essentially comparing different estimates of PPS gain, and it is predominantly post-progression QALYs and costs that are the source of difference in model estimated ICERs.

Resource costing

The primary difference in the method of costing resources applies to the cost of AEs (other small differences cancel out). The PARAMOUNT method is composed of four components: hospital in-patient episodes before and after disease progression costed at an average cost per day, and blood transfusion costs before and after disease progression.

The JMEN method involves a single component which uses an average cost per patient cycle based on using PARAMOUNT AE event numbers for 4 specific AEs (neutropenia, nausea / vomiting, fatigue, anaemia) combined with average costs per event adapted from papers by Duran (2008) and Hanna (2004), uplifted for inflation. The difference this makes to incremental costs is about £440 per patient.

Reasons to prefer PARAMOUNT approach:

- It is more detailed and uses PARAMOUNT resource use data directly
- JMEN approach limits AE coverage to just 4 types, whereas PARAMOUNT covers all causes of resource use
- Tables in the model for the JMEN method carry this note – "JMEN method inaccurate not estimated using rate per person cycle"