STA 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

ADDENDUM

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1 INTRODUCTION

On 29th January 2013, the National Institute for Health and Clinical Excellence (NICE) Appraisal Committee (AC) considered the use of pemetrexed as a maintenance treatment of locally advanced or metastatic non-squamous, non-small cell lung cancer (NSCLC) for people whose disease has not progressed immediately following first-line induction chemotherapy with pemetrexed and cisplatin.

As part of the appraisal process, the ERG carried out an independent critique of the manufacturer's submission of evidence to NICE which was considered by the AC. The ERG identified 12 issues where they considered the decision model prepared by the manufacturer required amendment. The Appraisal Consultation Document (ACD) issued by NICE following the AC meeting commented on these points and used them to inform their provisional decision.

In response to the ACD the manufacturer has responded in detail to the model amendments proposed by the ERG, accepting several but arguing against others. This addendum to the ERG report:

1. describes attempts made by the ERG to validate the manufacturer's implementation of the proposed model amendments which the manufacturer has accepted
2. provides a discussion of the outstanding issues on which the ERG and the manufacturer continue to differ
3. presents the ERG's updated cost-effectiveness results for the use of pemetrexed in continuation maintenance therapy, showing a revised base case analysis with additional results when ERG preferred approaches to the outstanding disputed issues are implemented.

2 VALIDATING THE MANUFACTURER'S IMPLEMENTATION OF AGREED MODEL AMENDMENTS

2.1 Method for estimating pemetrexed acquisition costs

The ERG indicated that the cost of an average dose of pemetrexed should be estimated on the basis of the body surface area of individual patients rather than from a notional average patient. This increases the mean cost per dose of pemetrexed from £1440.00 to £1481.37, and increases the manufacturer's base case ICER from £47,576/QALY to £48,854/QALY. This amendment has been accurately implemented in the manufacturer's revised decision model.

2.2 Correction of mid-cycle adjustment logic error

The ERG noted that the manufacturer's original decision model applied a mid-cycle adjustment (averaging patient numbers over each treatment cycle) to all treatment-related costs (drug acquisition and administration as well as periodic CT scans and out-patient

consultations). The ERG commented that this is inappropriate for pemetrexed treatment cycles which are always given on day 1 of the cycle, whereas scans and monitoring are carried out less frequently and may be more flexibly scheduled meaning that a mid-cycle adjustment may reasonably be applied. However, the manufacturer has removed the adjustment to scanning and out-patient costs as well as that to the treatment cost, leading to a small discrepancy between the ERG's revised ICER (£50,524/QALY) and the manufacturer's implementation (£50,552/QALY).

2.3 Cost of post-progression chemotherapy

The manufacturer's original model employed a differential rate of second-line chemotherapy favouring pemetrexed patients, which is not supported by trial evidence. Removing this difference increases the base case ICER from £47,576/QALY to £51,332/QALY. This amendment has been accurately implemented in the manufacturer's revised decision model.

2.4 Method for estimating docetaxel acquisition costs

The required alteration to the estimation of the mean cost per dose for pemetrexed applies also to docetaxel used in second-line chemotherapy. This adjustment reduces the mean cost per dose of docetaxel from £1,023 to £800.06, and reduces the manufacturer's base case ICER from £47,576/QALY to £47,707/QALY. This amendment has been accurately implemented in the manufacturer's revised decision model.

2.5 Cost of concomitant medications

The manufacturer claims that concomitant medications required for pemetrexed have previously been considered part of the NHS reference cost for drug administration and should not therefore be included as a cost amendment, citing appraisals TA181[1] and TA190[2] as precedents. This is incorrect: since the need for supplementation was identified as essential in the appraisal of pemetrexed for treatment of mesothelioma (TA135[3] January 2008) the ERG has included the costs of co-medications as part of their re-estimation of chemotherapy costs in all subsequent pemetrexed technology appraisals. This was implicit in the ERG report for TA181,[1] but mentioned explicitly in the ERG report for TA190.[2]

The manufacturer further states:

> "In addition, during 2012, Lilly introduced a free 'supplementation pack' service to hospitals in the UK (including vitamins, dexamethasone and patient information leaflets). The packs can be ordered by any hospital ordering pemetrexed at no additional charge. For both these reasons we do not agree they should be included in the revised basecase."

This information has not been widely disseminated, and may not be in the public domain. The extent to which these packs are being ordered and used in UK treatment centres is unclear. However, as the impact of this amendment on the ICER is relatively small the ERG is content to assume the amendment is not required provided the manufacturer can provide evidence of general take-up of this new provision in the UK.

2.6 Increased frequency of monitoring

The manufacturer's decision model does not employ explicit schedules of the frequency of disease monitoring for the two arms of the model. Instead, it includes parameters to govern the extra frequency of monitoring required by patients receiving pemetrexed maintenance therapy. This covers both out-patient consultations and additional CT scans.

The ERG lacked convincing evidence on which to base an estimate of the need for additional scans for pemetrexed maintenance patients and so made no adjustment to the manufacturer's model for scanning. However, the ERG applied an adjustment to the frequency of out-patient consultations using a schedule from a previous appraisal, although this could not be readily implemented through the parameters available within the manufacturer's model, and had to be applied as a revision to the model output.

In the manufacturer's revised model, both the frequency of additional consultations and of additional CT scans have been increased to reflect the concerns expressed in the ACD. These changes have been implemented through three model parameters:

- increasing the frequency of additional consultant visits from once every 24 weeks (8 cycles) to once every 12 weeks (4 cycles)
- increasing the frequency of additional CT scans from once every 24 weeks (8 cycles) to once every 12 weeks (4 cycles)
- increasing the proportion of patients needing additional scans from 3% to 100%.

If it is assumed that patients not receiving continuation maintenance pemetrexed will be assessed every 6 months, then these alterations to frequency parameters have the effect of increasing monitoring in those patients receiving additional cycles of pemetrexed to once every 2 months with CT scanning carried out on all patients. This approach goes beyond the limited ERG amendment and appears to represent full compliance with the intentions of the committee expressed in the ACD. It results in the base case ICER increasing from

£47,576/QALY to £49,126/QALY. The ERG confirms that these changes have been accurately implemented in the manufacturer's revised decision model.

2.7 Amended cost of terminal care

The ERG noted that a recent review of first-line chemotherapy in patients with NSCLC estimated a greater mean cost of terminal care than that used by the manufacturer, leading to a small reduction in the incremental cost of pemetrexed maintenance therapy due to differential discounting. Employing the updated care cost decreases the manufacturer's base case ICER from £47,576/QALY to £47,518/QALY. This amendment has been accurately implemented in the manufacturer's revised decision model.

2.8 Inclusion of blood product costs

The ERG noted that the manufacturer's original model included the cost of administering blood transfusions but did not include the cost of the blood products themselves. Adding in this additional cost does not affect the base case ICER at all (which relies on data from a different trial (JMEN) for resource costing), but is still required for sensitivity analysis using PARAMOUNT trial data as the source for estimating costs. This amendment has been accurately implemented in the manufacturer's revised decision model.

2.9 Combined effect of agreed amendments

The model amendments on which there is agreement between the manufacturer and the ERG all affect aspects of the costing of patient care; none have an effect on patient outcomes. A summary is shown in Table 1, indicating that taken together these changes raise the manufacturer's submitted base case scenario ICER from £47,576/QALY to £57,133/QALY.

Table 1 Revised cost effects of each agreed model amendment relative to the manufacturer's original 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
Original 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
Monitoring costs	£0	£13,912	16.82	0.9188	£13,521	£12,939	21.46	1.1743	4.65	£12,549	0.2554	£49,126	+£1,550
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
Cost of blood products	£0	£13,912	16.82	0.9188	£13,125	£12,939	21.46	1.1743	4.65	£12,153	0.2554	£47,576	£0
Updated base case	**£0**	**£14,652**	**16.82**	**0.9188**	**£14,619**	**£14,627**	**21.46**	**1.1743**	**4.65**	**£14,594**	**0.2554**	**£57,133**	**+£9,557**

* survival is undiscounted, all other figures are discounted

3 MODEL AMENDMENTS ON WHICH THE MANUFACTURER AND THE ERG DISAGREE

3.1 Utility models

In the manufacturer's base-case analysis, the preferred method for estimating patient utility employs a regression analysis of trial EQ-5D patient utility data which features only three explanatory factors (type of maintenance treatment – pemetrexed or none, pre- or post-progression health state, and time prior to death). However, an extended regression model was also provided in the decision model, alongside several other alternatives. The extended regression features three additional baseline variables (ECOG status, response to induction therapy and historical illness) to adjust the utility estimates. No explanation was provided by the manufacturer in their submission for selecting the unadjusted version for their base case analysis and, in the absence of further information, the ERG made the reasonable assumption that since two of these new variables yielded statistically significant parameter estimates the adjusted version was likely to yield improved estimation. The manufacturer has provided further information indicating that the extended regression model resulted in counterintuitive results, and was therefore not considered reliable. The ERG accepts this as a justifiable basis for preferring the unadjusted utility model, but does not accept that the unadjusted regression model is suitable for estimating patient utility.

The manufacturer's submitted model includes seven different methods of estimating patient utility values. Of these, three are of primary interest:

A) Unadjusted mixed model based on PARAMOUNT EQ-5D index score IPD data (updated base case ICER = £57,133/QALY)
B) Covariate-adjusted mixed model based on PARAMOUNT EQ-5D index score IPD data (updated base case ICER using this option = £59,125/QALY)
C) Nafees[4] (2008) mixed model analysis for NSCLC patients (base case ICER using this option = £68,891/QALY)

The first of these is the manufacturer's preferred (base case) option. The manufacturer's contention that the addition of covariates to the unadjusted utility model resulted in counter-intuitive results and was deemed implausible has led the ERG to question whether the manufacturer's approach to modelling utility from the PARAMOUNT[5] trial patient-reported EQ-5D data is well-founded and robust, and whether the Nafees[4] model (used in previous

appraisals and discarded by the manufacturer as an option for this appraisal) may be more reliable.

3.1.1 Utility model formulation

The option A model attempts to replicate the body of EQ-5D observed data (involving multiple responses per patient and spanning an extended period of time) from the PARAMOUNT trial using just three explanatory factors:

- treatment arm (pemetrexed vs. placebo);
- whether the patient's disease has progressed or not; and
- the time between the observation and the patient's death.

Individually, each factor is plausible in terms of known differences in patient experience. However, the ERG has serious concerns as to whether their use together is meaningful and reliable.

The main difficulty is that a single analysis is attempting to model both pre-progression and post-progression health states simultaneously. The treatment arm variable distinguishes between patients in both health states but is only relevant to the pre-progression health state as pemetrexed is withdrawn at disease progression. The time before death variable is predominantly focussed on the post-progression phase since only a very small number of patients die prior to confirmed progression (only eight in the pemetrexed arm and four in the placebo arm). The progression variable is therefore correlated with the treatment arm variable prior to progression and with the time to death variable after progression. This means that these three factors are inevitably subject to substantial collinearity, so that it is not surprising that including additional variables leads to instability and uninterpretable results. A clear pointer to collinearity is that in both the adjusted and unadjusted versions of the manufacturer's mixed model the treatment factor does not achieve statistical significance ($p = 0.137$ and $p = 0.172$ respectively) indicating that both the utility models are over-parameterised.

In view of these important shortcomings it is clear that a more robust utility model design is necessary before the use of these EQ-5D data could be considered useful for decision analysis. In particular, the ERG would recommend employing separate models to estimate the pre- and post-progression health states, introducing explicit adverse event variables or appropriate proxies (such as hospital admissions) to represent disutilities.

3.1.2 Application of utility and cost estimates

The ERG is also concerned about the way that the utility models are implemented in the manufacturer's submitted decision model. The manufacturer's utility options based on EQ-5D PARAMOUNT[5] trial data (A & B above) do not make direct use of adverse event (AE) data collected

during this trial. Instead, it is assumed that the detrimental effect of AEs is implicitly included in the results generated by the utility model. The frequency of AEs in the trial is only used explicitly by the Nafees[4] option (C), and the accompanying disutility factor calculated by that model is only used when the Nafees[4] option is selected.

In several previous NICE technology appraisals including TA227[6](erlotinib), TA192[7](gefitinib) and TA190(pemetrexed), the Nafees[4] mixed methods model has been used, and provides some consistency between appraisals. In view of the serious problems associated with options A and B, the ERG's preferred approach to utility estimation is the Nafees[4] method (option C) since it explicitly incorporates the disutility effects of key adverse events, whereas the manufacturer's utility regression models used in their submitted economic model do not employ any adverse event factors.

When the Nafees[4] utility model option is employed in the manufacturer's revised decision model (with a minor ERG logic correction), the updated base case ICER increases from £57,133/QALY to £68,891/QALY indicating that the manufacturer's modelling of utility may be inconsistent with evidence used in previous NSCLC appraisals.

3.2 Resource use data source

A related issue concerns the cost of AEs. The manufacturer's decision model does not use AE data at all for costing purposes. Hospitalisation rates from the PARAMOUNT trial are used to represent the general cost of continuing care, and it is assumed that these include the cost of treating AEs. This means that there is no way to test the sensitivity of model results to uncertainty in the incidence of specific AEs, since neither the utility estimates nor the cost estimates are driven by AE model parameters.

However, there is a wider issue. In the manufacturer's base case analysis, the source of most resource use data is not in fact the PARAMOUNT[5] trial, but selected average costs taken from the earlier JMEN[8] trial which assessed treatment effect in a different patient population (non-squamous patients not progressing after non-pemetrexed platinum doublet chemotherapy). This suggests that neither of the available methods of estimating the cost of on-going patient care are appropriate for use in a decision model. However, on balance the ERG is most concerned with importing resource data and costs from a different trial, and therefore would favour the PARAMOUNT[5] trial data option. If the updated base case is re-calculated using PARAMOUNT[5] resource use data the ICER increases from £57,133/QALY to £58,870/QALY.

3.3 Survival projection

3.3.1 Adjusted vs unadjusted projection models

The manufacturer did not accept the ERG comment that models adjusted for covariates are likely to provide a more reliable basis for extrapolation of progression-free survival (PFS) and overall survival (OS). Without access to the patient level data set from the PARAMOUNT[5] trial and full diagnostics of the model-fitting analysis undertaken by the manufacturer, the ERG is unable to comment further on this issue. In practical terms the difference to the estimated ICER from using the adjusted PFS model is very small (£33/QALY) and can be safely ignored in the context of the other issues being considered. The use of the adjusted OS model is overridden by the ERG's preferred approach to modelling OS, and therefore would only have any significance if the ERG exploratory OS modelling is not adopted. On this basis the ERG is content not to pursue this matter any further.

3.3.2 The manufacturer's objections to the ERG's projection modelling of overall survival

The manufacturer takes issue with the ERG in relation to:

1) the ERG's criticism that an inappropriate parametric (gamma) function has been fitted to the trial data;
2) the ERG's opinion that jointly fitting a single parametric function to both trial arms is inappropriate;
3) that the ERG's approach concentrates the curve-fitting analysis on the latter part of the survival plot where fewer patients remain at risk and to which greater uncertainty applies.

Underlying these points is the essential difference between the manufacturer's preferred approach and the ERG's exploratory projections: the question of whether or not patients receiving pemetrexed maintenance treatment receive additional survival gains after their disease has progressed and pemetrexed treatment is discontinued. The manufacturer makes no explicit claim in this regard but relies on extrapolation of overall survival trial results which implicitly generate a substantial extra survival gain in the post-progression phase in addition to the gains already apparent whilst receiving pemetrexed prior to progression.

3.3.3 The ERG's position

The ERG's approach is unashamedly data-driven, since the PARAMOUNT[5] trial provides the only reliable randomized evidence source available at this time. There are two ways to approach this question:

- directly by considering a landmark survival analysis of PARAMOUNT[5] patients surviving a disease progression event

- indirectly by comparing the trial evidence of overall survival in the PARAMOUNT[5] trial when almost all surviving patients have already suffered disease progression; any indication of differential mortality rates from this point onward will confirm differential post-progression survival

Figure 6 of the ERG report presents the results of a post-progression Kaplan-Meier survival analysis which strongly indicates that there are no grounds on which the PARAMOUNT[5] trial data can be used to support any claim that additional survival gains accrue once treatment is discontinued.

Figure 10 of the ERG report compares the cumulative mortality hazard for the two PARAMOUNT[5] trial arms and strongly indicates that the hazard trends after about 400 days are parallel, suggesting that from this point onwards (when most patients have suffered disease progression) surviving patients are subject to the same mortality risk. Figure 10 also provides a clear indication that if the whole period of the trial is used when fitting a smooth parametric function to the OS data then it is not realistic to fit the same functional form to both arms of the trial since at least one arm shows clear evidence of a sharp change in trend which is not present in the other – this disqualifies both proportional hazards and accelerated failure time parametric models from consideration, including all the 'standard parametric models'.

Given this disjunction in hazard trends, it is only reasonable to limit curve-fitting to the segment of the survival plot where a long-term trend is clearly established. Moreover, this segment of the available data is the only part which is relevant to the primary issue – what is most likely to happen to surviving patients beyond the end of the trial? Of course, it is regrettable that diminishing numbers of patients at risk increase the uncertainty attached to any extrapolation, but this is true of any projection modelling. The benefit of selecting the portion of evidence most clearly related to the projection of long-term trends is that it minimises the risk of bias driven by the larger bulk of early evidence which is of limited relevance to the consideration of prognosis for the minority of patients with extended survival.

Regardless of speculative suggestions as to why pemetrexed could engender additional long-term benefit after discontinuation, the results of the randomised trial do not support the reality of such gains, but equally do not indicate that any of the survival gain achieved in the pre-progression phase is subsequently lost. The ERG, therefore, believes that their interpretation of the trial evidence should not be considered either optimistic or pessimistic, but a measured, realistic assessment of empirical data.

3.3.4 Implementation of the ERG approach

In the ERG report it was pointed out that the manufacturer had misunderstood the method for avoiding bias which had been described in the ERG's report for TA227.[6] The ERG's approach

involves selecting time points on the Kaplan-Meier plot at which the same proportion of patients in each arm are estimated to remain alive. The most appropriate choice of the surviving proportion is a matter of judgement and involves balancing the benefits of minimising quantity of the patient experience exposed to the uncertainty of extrapolation with selecting a starting point which is unrepresentative and thereby introduces an additional source of bias.

To illustrate the potential effect of applying this approach, the ERG exemplified three scenarios in Table 41 of the ERG report showing the effects using 15%, 20% and 25% extrapolation starting points and recommending 20% as a reasonable scenario to use in this case.

The manufacturer has accepted the principle of this approach to extrapolation, but chose to use the 25% starting point which gives the smallest increase in the estimated ICER.

The results included in the ERG report for the ERG's preferred OS projection model did not in fact apply this method, but extrapolated from the point at which the long-term trend was considered to have been established.

Subsequent to the first AC the ERG has been able to implement an OS extrapolation with a common survival level (37.2%). This level was chosen to equalise the projective portion of patient survival in both arms, and also to ensure that, in both arms, the Kaplan-Meier estimate and the OS projective model estimate correspond precisely (thus eliminating the second potential source of bias). This occurs after 462 days (22 cycles) in the comparator arm and after 609 days (29 cycles) in the pemetrexed arm.

For clarity, cost-effectiveness results are presented for two scenarios: following the method originally used in the ERG report, and applying the improved bias-limiting method outlined in the previous paragraph. Using the former increases the updated ICER from £57,133/QALY to £75,103/QALY, whilst the latter yields an ICER of £82,183/QALY.

3.4 The effect of the contested ERG changes

The impact of each of the ERG model amendments discussed in this section are set out in Table 2, starting from the updated base case analysis derived in Table 1. The use of PARAMOUNT[5] resource use data has only a minor effect on the ICER, whereas the use of the Nafees[4] utility model and the use of the ERG approach to OS extrapolation both increase the ICER substantially. When combined, the ERG's best estimate of the ICER for pemetrexed as continuation maintenance treatment following pemetrexed+cisplatin induction chemotherapy is £93,361/QALY.

Table 2 Revised cost effects of each agreed model amendment relative to the manufacturer's original 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
Updated base case	**£0**	**£14,652**	**16.82**	**0.9188**	**£14,619**	**£14,627**	**21.46**	**1.1743**	**4.65**	**£14,594**	**0.2554**	**£57,133**	**+£9,557**
Nafees utility model	£0	£14,652	16.82	0.7108	£14,619	£14,627	21.46	0.9226	4.65	£14,954	0.2118	£68,891	+£11,758
PARAMOUNT resource use data	£80	£9,301	16.82	0.9188	£14,721	£9,699	21.46	1.1743	4.65	£15,038	0.2554	£58,870	+£1,737
ERG original OS extrapolations	£0	£14,715	17.52	0.9585	£14,619	£14,591	20.89	1.1515	3.38	£14,495	0.1903	£75,103	+17,970
ERG amended OS extrapolations	£0	£14,699	17.33	0.9484	£14,619	£14,545	20.40	1.1244	3.07	£14,466	0.1760	£82,183	+£25,050
Combined effects (original OS)	**£84**	**£9,428**	**17.52**	**0.7374**	**£14,719**	**£9,630**	**20.89**	**0.9072**	**3.38**	**£14,837**	**0.1697**	**£87,407**	**+£30,273**
Combined effects (amended OS)	**£83**	**£9,395**	**17.33**	**0.7306**	**£14,716**	**£9,543**	**20.44**	**0.8889**	**3.07**	**£14,782**	**0.1583**	**£93,361**	**+£36,228**

* survival is undiscounted, all other figures are discounted

4 REFERENCES

1. National Institute for Health and Clinical Excellence. Pemetrexed for the first-line treatment of non-small cell lung cancer: Technology Assessment TA181. 2009 [cited 2012 December]; Available from: http://guidance.nice.org.uk/TA181/Guidance/pdf/English.
2. National Institute for Health and Clinical Excellence. Pemetrexed for the maintenance treatment of NSCLC: Technology Assessment TA190. London: NICE; 2010 [cited 2012 November]; Available from: http://www.nice.org.uk/nicemedia/live/13028/49355/49355.pdf.
3. National Institute for Health and Clinical Excellence. Pemetrexed for the treatment of malignant pleural mesothelioma: TA135. NICE; 2008 [cited 2013 April]; Available from: http://guidance.nice.org.uk/TA135.
4. Nafees B, Stafford M, Gavriel S, Bhalla S, J. W. Health state utilities for non small cell lung cancer. Health Qual Life Outcomes. 2008; 21.
5. Paz-Ares L, de Marinis F, Dediu M, Thomas M, Pujol JL, Bidoli P, *et al.* 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 Oncology. 2012; 13:247-55.
6. National Institute for Health and Clinical Excellence. Erlotinib monotherapy for the maintenance treatment of non-small cell lung cancer: Technology Assessment TA227. NICE; 2011 [cited 2012 November]; Available from: http://guidance.nice.org.uk/TA227.
7. National Institute for Health and Clinical Excellence. Gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer:TA192. NICE; 2010 [cited 2013 April]; Available from: http://www.nice.org.uk/Search.do?searchText=TA192&newsearch=true&x=0&y=0#/search/?reload.
8. Ciuleanu T, Brodowicz T, Zielinski C, Kim JH M, Krzakowski M, Laack E Y-L, *et al.* Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomised, double-blind, phase 3 study. Lancet 2009; 24:1432-40.