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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

CDF Rapid Reconsideration

Pemetrexed maintenance treatment following induction therapy with pemetrexed and cisplatin for non-squamous non-small-cell lung cancer (review of TA309)

The following documents are made available to Consultees and Commentators;

1. **CDF rapid reconsideration committee meeting slides** prepared by NICE project team

2. **Company submission** from Eli Lilly

3. **Consultee submission from National Cancer Research Institute – Royal College of Physicians - Association of Cancer Physicians** (joint submission)

4. **Expert statement from Dr Riyaz Shah** (Clinical expert nominated by NCRI-ACP-RCP-RCR)

5. **Evidence Review Group report** prepared by LRiG

6. **Evidence Review Group report – company factual accuracy check & ERG responses**

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

Presentation and public slides

NICE National Institute for Health and Care Excellence

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

Rapid reconsideration of TA309

25 May 2016

CDF reconsideration – Issues for consideration

- Have all the Committee's preferred assumptions been sufficiently addressed?
- Are the company's and ERG's estimates of the ICER plausible?
- Taking into account the commercial access agreement, can pemetrexed be recommended for use in the NHS?

Lung cancer

- ~45,000 people diagnosed with lung cancer in 2013, with 35,371 deaths registered in the UK in 2012
- Most common cause of cancer mortality in the UK, accounting for almost a fifth of all cancer deaths
- Lung cancer falls into two main histological categories:
  - Non-small-cell lung cancer (NSCLC)
  - Small-cell lung cancer
- Non-small-cell lung cancer can be divided into further subgroups, one of them non-squamous

Decision problem

	Final scope issued by NICE
Population	People with advanced or metastatic (stage IIIB and IV) NSCLC, other than predominantly squamous histology, whose disease has not progressed following induction treatment with pemetrexed and cisplatin
Intervention	Pemetrexed
Comparators	Best supportive care (includes bisphosphonates and palliative radiotherapy)
Outcomes	• Overall survival • Progression-free survival • Response rates • Adverse effects of treatment (according to grade) • Health-related quality of life
Economic evaluation	Cost-utility analysis

Pemetrexed Marketing Authorisation

- ‘Pemetrexed is indicated as monotherapy for the maintenance of locally advanced or metastatic NSCLC, other than predominantly squamous histology, in patients whose disease has not progressed immediately following platinum-based chemotherapy’
- Reconsideration is only for pemetrexed following induction therapy with pemetrexed and cisplatin in line with trial and the extension to the MA (continuation maintenance)
  - TA190 recommends pemetrexed maintenance following induction therapy with platinum-based chemotherapy in combination with gemcitabine, paclitaxel or docetaxel (switch maintenance)

TA309 Evidence: PARAMOUNT trial

- Pemetrexed (n = 359) compared with placebo (n = 180)
- Inclusion criteria: ECOG of 0 or 1
- Primary outcome: median progression free survival (PFS)
  - 4.4 months compared with 2.76 months (benefit of 1.68m)
- Median overall survival (OS)
  - 13.86 months compared with 11.01 months (benefit of 2.85m)
- Committee concluded:
  - Although the licensed indication does not specify performance status for maintenance pemetrexed, it would not be usual clinical practice for a patient with a PS other than 0 or 1 to receive pemetrexed maintenance treatment following induction therapy with pemetrexed plus cisplatin
  - Pemetrexed provides a statistically significant gain in PFS and OS
  - Pemetrexed is associated with clinically significant but acceptable adverse reactions

TA309: Original cost-effectiveness model

- De novo analysis of a Markov model
- 3 health states: pre-progression, post-progression and death
- Lifetime horizon
- 21-day cycle length
- Comparator: Placebo + best supportive care

TA309: Summary of appraisal

- Committee concluded that extrapolation of survival data was not required, so cost-effectiveness based on the actual data
- Company's ICER estimate: £58,918 to £68,771/QALY
- ERG's ICER estimate: £74,500/QALY
- Committee's most plausible ICER £74,500/QALY
- Committee considered that End of Life criteria were met
- Pemetrexed was not recommended

TA309: Committee's preferred assumptions

- Equal rates of post-progression chemotherapy for pemetrexed and placebo
- Utility values available from the PARAMOUNT trial instead of those from Nafees model
- PARAMOUNT approach to sourcing resource data preferred over 'JMEN methods' approach
- Committee concerned that the unadjusted mixed model to estimate utility values did not appropriately reflect the effect of treatment on utility
- Disutility associated with adverse effects of treatment should not be estimated from an average of the on-treatment and off-treatment times because they were applied to the pre-progression state only
- No evidence to support a post-progression benefit for pemetrexed over placebo
- Extrapolation of PARAMOUNT data for survival modelling was not necessary because PARAMOUNT data were sufficiently mature

CDF reconsideration – Overview (1)

- Company submitted a Commercial Access Agreement (CAA)
- No new clinical evidence was submitted
- Company's original model structure was used
- Committee's preferred use of PARAMOUNT data for survival estimates would have required substantial re-structuring of the model
- It was therefore not possible to bridge the gap between the company's and the ERG's ICERs
- The company therefore used gamma distribution to extrapolate from survival data and noted that the use of PARAMOUNT data would add approximately £4000 to the ICER, based on the scenario analysis performed by the ERG during the appraisal process

CDF reconsideration – Overview (2)

- Utility data from PARAMOUNT was used
- Resource use data from PARAMOUNT was used
- The post-treatment benefit is still reflected in the model (accounts for approximately £4,000 in the ICER)
- The company still uses the unadjusted mixed model for estimating utilities
- The disutility associated with adverse effects of treatment is still estimated from an average of the on-treatment and off-treatment times
- Company base case ICER of £70,538 per QALY gained (list price)

CDF reconsideration: ERG critique

- ERG notes a clearly defined baseline scenario with a precise ICER was never established and refinements to the original ICER of £74,500 per QALY were needed
- Committee's most plausible ICER in TA309 was based on a rough estimate made by the ERG (£74,500 per QALY)
- ERG attempts to establish a baseline scenario in which the ICER closely reflects the most plausible ICER in TA309 by:
  - Selecting one survival projection option that most closely matches the expected value of 3.49 months of additional overall survival with pemetrexed maintenance therapy (based on PARAMOUNT data)
  - And adjusting the resulting ICER by a correction factor
- ERG amends 3 assumptions not thought to be correctly applied
- Resulting ICER of £74,371 per QALY based on the list price
- ERG sensitivity analyses considers changes in costs of other drugs (second-line treatments docetaxel and erlotinib) and inflation

CDF reconsideration – the CAA (1)

- Formally agreed with NHS England
- XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX
- XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX

CDF reconsideration – the CAA (2)

- Patients who fulfil the following criteria are covered by the CAA:
  - Application made by and first cycle of systemic anti-cancer therapy to be prescribed by a consultant specialist specifically trained and accredited in the use of systemic anti-cancer therapy.
  - The patient is being treated for non-squamous non-small cell lung cancer
  - Pemetrexed is given as maintenance therapy following 1st line chemotherapy with Cisplatin and Pemetrexed for disease not progressing after 4 cycles of such chemotherapy
  - PS 0 or 1 at time to commence maintenance pemetrexed.

CDF reconsideration – Company's results with CAA

	Pemetrexed + BSC	Placebo + BSC
Intervention cost (£)	**£XXXX**	**£79**
Other costs (£):		
• Adverse event costs	£2,694	£2,319
• Follow up costs	£4,125	£4,207
• Terminal care costs	£2,706	£2,739
Total costs (£)	**£XXXX**	**£9,344**
Difference in total costs (£)	N/A	£XXXX
LYG	1.6266	1.3376
LYG difference	N/A	0.2890
QALYs	1.1192	0.9075
QALY difference	N/A	0.2116
ICER (£)	N/A	**£XXXX**

CDF reconsideration – Company's probabilistic sensitivity analysis

CDF reconsideration: ERG exploratory analyses

Scenario	ICER	
	Original pemetrexed price	CAA pemetrexed price
Pragmatic baseline scenario	£74,371	£XXXXX
Baseline + changes in drug costs	£74,405	£XXXXX
Baseline + NHS cost inflation	£76,688	£XXXXX
Baseline + changes in drug costs + NHS cost inflation	£76,701	£XXXXX

CDF reconsideration – Issues for consideration

- Have all the Committee's preferred assumptions been sufficiently addressed?
- Are the company's and ERG's estimates of the ICER plausible?
- Taking into account the commercial access agreement, can pemetrexed be recommended for use in the NHS?

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technology appraisals

Revised submission
with formally agreed CAA
for the re-consideration of TA309 – Pemetrexed maintenance treatment following induction therapy with pemetrexed and cisplatin for non-squamous non-small-cell lung cancer under the new proposed CDF criteria

Please note that this submission contains commercial in confidence data.

May 2016

1 Introduction

1 All cancer drugs that were previously appraised by NICE and are currently funded through the current Cancer Drugs Fund (CDF) will be re-considered by NICE in line with Guide to the methods of technology appraisal (2013) and modifications to incorporate the proposed new CDF criteria outlined in the CDF consultation paper.

2 In order to allow for the transition of drugs currently in the CDF to take place before 31 March 2017, NICE needs to prepare for re-considering those drugs. This preparation is taking place in parallel with the consultation on the new CDF arrangements, without prejudging the outcome of that consultation. This content of this submission template is therefore provisional and may change if the proposed CDF arrangements are amended after the consultation. Companies will have the opportunity to change their evidence submissions to NICE if substantial changes are made to the proposals after the CDF consultation.

3 The scope for re-consideration remains the same as the final scope used for the published technology appraisal guidance.

4 The company evidence submission should focus on cost effectiveness analyses using a new patient access scheme, an amendment to the existing patient access scheme agreed with the Department of Health (see Appendix 5.1) or as a commercial access arrangement with NHS England (for a definition of commercial access arrangement please see the CDF consultation paper).

5 A new patient access scheme, an amendment to an existing patient access scheme, or a commercial access arrangement, must have been formally agreed with the relevant organisation (that is, the Department of Health for a patient access scheme or NHS England for a commercial access arrangement by the time the Appraisal Committee meets for the first Committee meeting.

6 Some details of patient access schemes or commercial access arrangements, submitted through the rapid re-consideration process, can be treated by NICE as commercial in confidence if the company requests this.

7 The cost-effectiveness analyses included in the company evidence submission must use the assumptions that determined the most plausible incremental cost-effectiveness ratio(s) as identified in the published guidance. If the published guidance refers to more than one plausible ICER, analyses relating to all plausible ICERs should be included in the submission.

8 Only in exceptional circumstances and with prior written agreement from NICE should new clinical evidence be included. New clinical evidence is acceptable only when it addresses uncertainties identified previously by the Appraisal Committee. Submission of new clinical evidence must not lead to structural changes in the company's cost-effectiveness model.

9 The submission should take account of the proposed changes to NICE's methods of technology appraisal set out in the CDF consultation paper, in particular those concerning the appraisal of life-extending products at the end of life.

2 Instructions for companies

If companies want the National Institute for Health and Care Excellence (NICE) to re-consider a NICE recommendation for a drug currently funded through the CDF, they should use this template.

The template contains the information NICE requires to assess the impact of a patient access scheme or commercial access agreement on the clinical and cost effectiveness of a technology, in the context of this re-consideration, and explains the way in the evidence should be presented. If you are unable to follow this format, you must state your reasons clearly. You should insert 'N/A' against sections that you do not consider relevant, and give a reason for this response.

In addition to the CDF consultation paper, please refer to the following documents when completing the template:

- 'Guide to the methods of technology appraisal'
- 'Specification for company submission of evidence' and
- Pharmaceutical Price Regulation Scheme 2014.

For further details on the technology appraisal process, please see NICE's 'Guide to the processes of technology appraisal'. The 'Specification for company submission of evidence' provides details on disclosure of information and equality issues.

Make the submission as brief and informative as possible. Only mark information as confidential when absolutely necessary. Sufficient information must be publicly available for stakeholders to comment on the full content of the technology appraisal, including details of the proposed patient access scheme or commercial access agreement. Send submissions electronically via NICE docs: https://appraisals.nice.org.uk.

Appendices may be used to include additional information that is considered relevant to the submission. Do not include information in the appendices that

has been requested in the template. Appendices should be clearly referenced in the main submission.

When making a submission, include:

- an updated version of the checklist of confidential information, if necessary
- an economic model with the patient access scheme or commercial access agreement incorporated, in accordance with the 'Guide to the methods of technology appraisal'.

Executive Summary

Following the original appraisal of pemetrexed in the continuation maintenance (CM) indication (TA309), the most plausible ICER as determined by the Appraisal Committee was approximately £74,500, which corresponded to a mean OS gain of 3.49 months. In addition, it was determined that pemetrexed in the continuation maintenance indication could be considered under the supplementary advice to the Committee on end-of-life treatments.

A pragmatic approach has been taken to align the assumptions in the economic model with those preferred by the Appraisal Committee since the preferred OS modelling approach could not be implemented without extensive restructuring of the original model. Retaining Lilly's original approach to OS modelling resulted in a mean OS gain of 3.48 months and a corresponding ICER of £70,538 with the remaining assumptions aligned. The revised base-case analysis, with the commercial access agreement agreed with NHS England, results in an ICER of [redacted]

The details of this commercial access agreement (CAA) are commercially sensitive information to Lilly, [redacted]

We hope the details of the CAA and subsequent cost-effectiveness results provided in this submission will help the Appraisal Committee support a positive recommendation for pemetrexed, as continuation maintenance treatment, to be made available for patients through routine commissioning.

3 Details of the patient access scheme/ commercial access agreement

3.1 Please give the name of the technology and the disease area to which the patient access scheme/ commercial access agreement applies.

For the purposes of this submission, the CAA applies to Alimta (pemetrexed) for patients who are treated with Alimta monotherapy for the maintenance treatment of locally advanced or metastatic non squamous non-small cell lung cancer following Alimta in combination with cisplatin first line treatment (known as continuation maintenance “CM”).

The details of this CAA are commercially sensitive information to Lilly, [redacted]

3.2 Please outline the rationale for developing the patient access scheme/ commercial access agreement.

Pemetrexed (Alimta) was launched in the UK in November 2004 and is licensed in 4 indications:

<u>Malignant pleural mesothelioma:</u>

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

<u>Non-small cell lung cancer:</u>

2. ALIMTA in combination with cisplatin is indicated for the first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology.

3. ALIMTA 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. 4. ALIMTA is indicated as monotherapy for the second-line treatment of patients with locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology.

The following populations have been appraised by NICE and are cost-effective: mesothelioma (TA135), first-line treatment of non-small-cell lung cancer (TA124) and pemetrexed for the maintenance treatment of non-small-cell lung cancer following platinum-based chemotherapy in combination with gemcitabine, paclitaxel or docetaxel (switch maintenance - TA190).

CM represents a small proportion of the total number of patients treated with Alimta. [redacted]

Please describe the type of patient access scheme (as defined by the PPRS)/ commercial access agreement.

[redacted]

[redacted]

[redacted]

3.3 Please provide specific details of the patient population to which the patient access scheme/ commercial access agreement applies. Does the scheme apply to the whole licensed population or only to a specific subgroup (for example, type of tumour, location of tumour)? In case of the latter, please state:

- How is the subgroup defined?

- If certain criteria have been used to select patients, why have these have been chosen?
- How are the criteria measured and why have the measures been chosen?

The patient subgroup is defined as patients who fulfil each of the following 4 conditions (http://www.blueteq.com/cdf - accessed 4 February 2016):

(1) Application made by and first cycle of systemic anti-cancer therapy to be prescribed by a consultant specialist specifically trained and accredited in the use of systemic anti-cancer therapy.

(2) The patient is being treated for non-squamous non-small cell lung cancer

(3) Pemetrexed is given as maintenance therapy following 1st line chemotherapy with Cisplatin and Pemetrexed for disease not progressing after 4 cycles of such chemotherapy

(4) PS 0 or 1 at time to commence maintenance pemetrexed.

In order to provide a fixed fee per patient central rebate it will be necessary for NHS trusts to continue to register patients eligible for Alimta CM using the existing Blueteq (CDF) registration form as detailed above.

3.4 Please provide details of when the scheme/ commercial access agreement will apply to the population specified in 3.4. Is the scheme dependent on certain criteria, for example, degree of response, response by a certain time point, number of injections? If so:

- Why have the criteria been chosen?
- How are the criteria measured and why have the measures been chosen.

It is intended that the CAA will apply from the day after NICE publishes its guidance recommending CM for routine commissioning as a result of this rapid review process.

3.5 What proportion of the patient population (specified in 3.4) is expected to meet the patient access scheme/ commercial access agreement criteria (specified in 3.5)?

Only the patient population identified in 3.4 who receive Alimta (pemetrexed) will be eligible for a fixed fee payment. This will be determined as outlined in 3.7 below. For the avoidance of doubt, Lilly will only provide the fixed fee per patient central rebate for Alimta and will not provide the fixed fee per patient to NHSE for any patients who receive pemetrexed supplied by any other company.

3.6 Please explain in detail the financial aspects of the patient access scheme/ commercial access agreement. How will any rebates be calculated and paid?

Lilly will provide a fixed fee per patient central rebate set out below based on a [redacted]

[redacted]

[redacted]				[redacted]	
[redacted]				[redacted]	
[redacted]					
[redacted]				[redacted]	

[redacted]

3.7 Please provide details of how the patient access scheme/ commercial access agreement will be administered. Please specify whether any additional information will need to be collected, explaining when this will be done and by whom.

[redacted]

3.8 Please provide a flow diagram that clearly shows how the patient access scheme/ commercial access agreement will operate. Any funding flows must be clearly demonstrated.

Please note: the entire flow diagram above, including all text in boxes, is commercial in confidence.

3.9 Please provide details of the duration of the patient access scheme/ commercial access agreement.

It is intended that the CAA will apply from the day after NICE publishes its guidance recommending CM for routine commissioning as a result of this rapid review process for the duration of the published NICE guidance.

The details of this commercial access arrangement proposal are commercially sensitive information to Lilly,

3.10 Are there any equity or equalities issues relating to the patient access scheme/ commercial access agreement,

taking into account current legislation and, if applicable, any concerns identified during the course of the appraisal? If so, how have these been addressed?

There are no equity or equality issues relating to this commercial access agreement.

Lilly has consulted with two key pharmacists within the NHS in Wales to understand which systems were in place and how rebate mechanisms work on a Local Health Board (LHB) and District General Hospital level; then to understand whether the proposed CAA would be replicable in the NHS in Wales

Both pharmacists confirmed that they were the key individuals within the NHS in Wales with respect to the management and implementation of PAS/ rebates. They both concluded the proposed fixed fee per patient rebate is implementable in Wales.

3.11 If available, please list any patient access scheme/ commercial access agreement forms, patient registration forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians and patient information documents. Please include copies in the appendices.

The patient registration form is as currently used in the CDF (http://www.blueteq.com/cdf - accessed 4 February 2016).

3.12 In the exceptional case that you are submitting an outcome-based scheme, as defined by the PPRS, please also refer to appendix 5.2.

N/A

4 Cost effectiveness

4.1 Please show the changes made to the original company base case to align with the assumptions that determined the most plausible incremental cost effectiveness ratio(s) as determined by the Appraisal Committee and presented in the published guidance. A suggested format is presented in table 1. Provide sufficient detail about how the Appraisal Committee's preferred assumptions have been implemented in the economic model. Provide sufficient detail to allow the replication of the changes made to the original base case. For example, include sheet and cell references and state the old and new cell values. No other changes should be made to the model.

Plausible ICER - Alignment with assumptions

During the original appraisal, Lilly submitted a state-transition Markov model with 3 health states: pre-progression, post-progression and death. The model was populated with the observed progression-free survival (PFS) and overall survival (OS) from the PARAMOUNT trial. Having explored a range of alternative parametric distributions, Lilly considered the gamma distribution to provide plausible survival estimates for the lifetime of the model (1 Sections 3.8-3.9).

The original base case was amended during the appraisal in line with the Appraisal Committee's preferred assumptions resulting in two scenario analyses being presented in response to the consultation on the second appraisal consultation document (ACD). These scenario analyses reflected two alternative assumptions concerning the benefit of pemetrexed over placebo in the post-trial period. The scenario where a 'one-time benefit of treatment' with pemetrexed was assumed resulted in a mean OS gain of 3.48 months and a corresponding ICER of £68,771 (1 Section 3.27).

The ERG proposed an alternative approach to OS modelling that did not rely on projective modelling, which was conducted separately to the Lilly model. This approach resulted in a mean OS gain of 3.49 months. Since implementation of this alternative OS approach would have required substantial restructuring of Lilly's model, a corresponding ICER of £72,772 was estimated by interpolation between existing ICERs previously considered during the appraisal (1 Section 3.28, 2).

The Appraisal Committee considered the most plausible ICER to be approximately £74,500 based upon the ERG's alternative OS modelling approach combined with the use of the PARAMOUNT approach for costing adverse events (AEs) (1 Section 4.17).

The rapid re-consideration process requires the submitting company to "use the assumptions that determined the most plausible ICER as presented by the Appraisal Committee in the published guidance" (3 paragraph 7).

Since the ERG was unable to implement their alternative OS approach in the original model, Lilly requested a decision problem meeting with NICE. During this meeting the NICE team advised Lilly that a pragmatic approach would be acceptable in this instance since restructuring of the original model was to be avoided except in exceptional circumstances when new clinical evidence was to be included. As such, NICE advised Lilly to present the model with the £68,771 ICER as the original base case for the purposes of the rapid re-consideration process since this model presented the closest match for mean OS gain to the ERG's alternative OS approach.

When the PARAMOUNT approach for costing AEs is implemented in Lilly's model, in combination with the 'one-time benefit of treatment' scenario, the resulting ICER is £70,538, i.e. approximately £4,000 less than the most plausible ICER determined by the Appraisal Committee. These assumptions are summarised below in Table 1.

Table 1 Assumptions in the economic model

Assumption	Original company model	Appraisal Committee's preferred assumption
Overall survival (OS) modelling	The original company model extrapolated the observed OS data to estimate the mean OS benefit for pemetrexed plus best supportive care (BSC) vs placebo plus BSC. The updated revised basecase submitted in response to the second ACD included an assumption of a one-time benefit for pemetrexed in the post-trial period.	The Appraisal Committee preferred the ERG's alternative approach to survival modelling, which did not rely on projective OS modelling.
	This approach resulted in: • ***a mean OS gain of 3.48 months*** • ***an ICER of £68,771***	This approach resulted in: • ***a mean OS gain of 3.49 months*** • ***an ICER of £72,772***
Resource use data for costs of adverse events (AEs)	The original company model used the 'JMEN methods' approach for costing AEs.	The Appraisal Committee preferred the PARAMOUNT method for costing AEs.
	This approach resulted in: • ***a mean OS gain of 3.48 months*** • ***an ICER of £70,538***	This approach resulted in: • ***a mean OS gain of 3.49 months*** • ***an ICER of approximately £74,500***

The PARAMOUNT option is implemented in the original company model using the following steps:

1. From the 'Main' worksheet select 'Customise general' button
2. Within the 'Model parameters' menu go to the 'Other resource use data' (found towards the bottom of the right hand list of options)
3. 'Resource use data' is the first item in this section. Select 'PARAMOUNT' from the drop down list rather than 'JMEN methods'

No other changes have been made to the Lilly model.

End-of-life considerations

The Appraisal Committee concluded that pemetrexed in the continuation maintenance indication could be considered under the supplementary advice to the Committee on end-of-life treatments (1 Section 4.26).

When the end-of-life criteria are met, the Appraisal Committee is able to consider applying a weighting of up to 1.7 to the QALY benefits for the cost-effectiveness to fall within the normal range of maximum acceptable ICERs considered by NICE to represent a cost-effective use of NHS resources, (4) i.e. approximately £50,000 per QALY ICER threshold.

4.2	If the population to whom the patient access scheme/ commercial access agreement applies (as described in sections 3.4 and 3.5) is not the same as that in the published technology appraisal (for example, the population is different as there has been a change in clinical outcomes or a new continuation rule), please (re-)submit the relevant sections from the 'Specification for company submission of evidence' (particularly sections 5.5, 6.7 and 6.9). You should complete those sections both with and without the patient access scheme/ commercial access agreement. You must also complete the rest of this template.

N/A – The population to whom the commercial access agreement applies is the same as that in TA309.

4.3	Please provide a summary of the clinical effectiveness parameters (resulting from the Committee's preferred evidence synthesis) which are used in the economic model which includes the patient access scheme/ commercial access agreement.

Table 23 from Lilly's original submission (October 2012) has been updated to provide a summary of the clinical effectiveness parameters used in the

revised economic model submitted for the rapid re-consideration process. The OS and AE rate assumptions have been updated to align with the preferred assumptions of the Appraisal Committee. The remaining parameters have not been amended.

Table 2 Implementation of clinical outcomes in the economic model (adapted from Table 23 in Lilly's original submission)

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 25% of patients remaining at risk in each arm: 31 cycles placebo/BSC and 37 cycles pem/BSC. A 'one-time benefit' assumption is applied in the post-progression period.	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	BSC drug costs applied to every cycle plus hospitalisation, blood transfusion data and palliative radiotherapy rates from the PARAMOUNT study and associated NHS reference costs applied. (Full details in Appendix 20 of original submission)	Used to estimate AE rates per cycle to which costs are then applied.
EQ-5D	Secondary	N/A	A mixed regression	Provides utility

	outcome	Completeness of EQ-5D data is described in section 6.5	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.	estimates for individual patients depending on treatment, progression status and proximity to death.

4.4 Please list any costs associated with the implementation and operation of the patient access scheme/ commercial access agreement (for example, additional pharmacy time for stock management or rebate calculations). A suggested format is presented in table 2. Please give the reference source of these costs. Please provide sufficient detail to allow the replication of changes made to the original base case. For example, include sheet and cell references and state the old and new cell values. Please refer to section 6.5 of the 'Specification for company submission of evidence'.

N/A [redacted]

4.5 Please provide details of any additional treatment-related costs incurred by implementing the patient access scheme/ commercial access agreement. A suggested format is presented in table 3. The costs should be provided for the intervention both with and without the patient access scheme. Please give the reference source of these costs.

N/A – There are no additional treatment-related costs incurred as a result of implementing the commercial access agreement.

Summary results

New base-case analysis

Since we cannot implement the OS modelling approach preferred by the Appraisal Committee, we acknowledge the difference (approximately £4,000) in ICERs between the final Lilly basecase submitted for the rapid re-consideration and the most plausible ICER as determined by the Appraisal Committee and presented in the published guidance (£70,538 and approximately £74,500 respectively).

[redacted]

We hope that this pragmatic approach will be considered to meet the requirements of the rapid re-consideration process.

4.6 Please present in separate tables the cost-effectiveness results as follows.[1]

- the results for the intervention without any (new) patient access scheme/ commercial access agreement; that is with the price for the technology considered in the published guidance.
- the results for the intervention with the patient access scheme/ commercial access agreement.

[1] For outcome-based schemes, please see section 5.2.8 in appendix B.

Table 3a New base-case cost-effectiveness results using the price as in the published technology appraisal

	Pemetrexed + BSC	Placebo + BSC
Intervention cost (£)	**£14,746**	**£79**
Other costs (£):		
• Adverse event costs	£2,694	£2,319
• Follow up costs	£4,125	£4,207
• Terminal care costs	£2,706	£2,739
Total costs (£)	**£24,272**	**£9,344**
Difference in total costs (£)	N/A	£14,927
LYG	1.6266	1.3376
LYG difference	N/A	0.2890
QALYs	1.1192	0.9075
QALY difference	N/A	0.2116
ICER (£)	N/A	**£70,538**

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

Table 3b New base-case cost-effectiveness results using the commercial access agreement

	Pemetrexed + BSC	Placebo + BSC
Intervention cost (£)	[redacted]	**£79**
Other costs (£):		
• Adverse event costs	£2,694	£2,319
• Follow up costs	£4,125	£4,207
• Terminal care costs	£2,706	£2,739
Total costs (£)	[redacted]	**£9,344**
Difference in total costs (£)	N/A	[redacted]
LYG	1.6266	1.3376
LYG difference	N/A	0.2890
QALYs	1.1192	0.9075
QALY difference	N/A	0.2116
ICER (£)	N/A	[redacted]

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

4.7 Please present in separate tables the incremental results as follows. [2]

- the results for the intervention without the (new) patient access scheme/ commercial access agreement, that is with the price for the technology considered in the published appraisal.
- the results for the intervention with the patient access scheme/ commercial access agreement.

List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental analysis ranking technologies in terms of dominance and extended dominance. A suggested format is presented in table 5.

N/A since there is only one comparator.

Sensitivity analyses with the relevant PAS/CAA

4.8 Please refer to the published guidance to identify the key sensitivity and scenario analyses (that is, analyses that were discussed in the 'considerations' section and which alter the ICER). Present the results of these sensitivity and scenario analyses with the patient access scheme/ commercial access agreement.

The majority of the key sensitivity analyses that were discussed during the original appraisal and summarised in the 'considerations' section (1 paragraphs 4.10 – 4.13) were addressed within the final company model (basecase ICER £68,771). The Appraisal Committee was satisfied that the preferred assumptions had been implemented appropriately in this model.

[2] For outcome-based schemes, please see section 5.3.9 in appendix 5.3.

At the end of the original appraisal, there were two areas of outstanding uncertainty:

- the use of the JMEN methods vs PARAMOUNT approach to costing adverse events (1, paragraph 4.14)
- the survival modelling approach (1, paragraphs 4.15-4.16)

The PARAMOUNT approach to costing adverse events has now been implemented in the basecase model submitted for this Rapid Reconsideration process, resulting in a £70,538 ICER. As stated previously, the ERG was not able to implement their alternative OS modelling approach within the Lilly model (See response to question 4.1). Since we have presented the results from our most plausible OS projection, which results in a very similar incremental OS gain to the Committee's preferred ERG OS approach (3.48 m vs 3.49 m respectively), we do not believe any additional sensitivity analyses conducted in the original model would provide more relevant ICERs to inform decision making in this case.

4.9 Please present any probabilistic sensitivity analysis results, and include scatter plots and cost-effectiveness acceptability curves.

Table 4 PSA results using the commercial access agreement

	Pemetrexed + BSC	**Placebo + BSC**
Intervention cost (£)	[redacted]	**£80**
Other costs (£):		
• Adverse event costs	£2,736	£2,356
• Follow up costs	£4,119	£4,203
• Terminal care costs	£2,706	£2,738
Total costs (£)	[redacted]	**£9,376**
Difference in total costs (£)	N/A	[redacted]
LYG	1.6317	1.3461
LYG difference	N/A	0.2857
QALYs	1.1229	0.9145
QALY difference	N/A	0.2085
ICER (£)	N/A	[redacted]

Figure 1 Incremental cost-effectiveness plane using the commercial access agreement (Please note the actual figure is CIC)

[redacted]

Figure 2 Cost-Effectiveness Acceptability Curve using the commercial access agreement (Please note the actual figure is CIC)

The CEAC shows that there is a 68.7% probability that pemetrexed plus BSC is cost effective if the incremental cost-effectiveness ratio ICER is £50,000 per QALY gained.

4.10 If any of the criteria on which the patient access scheme/ commercial access agreement depends is a clinical variable (for example, choice of response measure, level of response, duration of treatment), sensitivity analyses around the individual criteria should be provided, so that the Appraisal Committee can determine which criteria are the most appropriate to use.

N/A, the commercial access agreement does not depend on any clinical variables.

5 Appendices

5.1 Information about patient access schemes

5.1.1 The 2014 Pharmaceutical Price Regulation Scheme (PPRS) is a non-contractual scheme between the Department of Health and the Association of the British Pharmaceutical Industry. The purpose of the 2014 PPRS is to ensure that safe and cost-effective medicines are available on reasonable terms to the NHS in England and Wales. One of the features of the 2014 PPRS is to improve patients' access to medicines at prices that better reflect their value through patient access schemes.

5.1.2 Patient access schemes are arrangements which may be used on an exceptional basis for the acquisition of medicines for the NHS in England and Wales. Patient access schemes propose either a discount or rebate that may be linked to the number, type or response of patients, or a change in the list price of a medicine linked to the collection of new evidence (outcomes). These schemes help to improve the cost effectiveness of a medicine and therefore allow the National Institute for Health and Care Excellence (NICE) to recommend treatments which it would otherwise not have found to be cost effective. More information on the framework for patient access schemes is provided in the 2014 PPRS.

5.1.3 Patient access schemes are proposed by a pharmaceutical company and agreed with the Department of Health, with input from the Patient Access Schemes Liaison Unit (PASLU) within the Centre for Health Technology Evaluation at NICE.

5.2 Additional documents

5.2.1 If available, please include copies of patient access scheme agreement forms/ commercial access agreement, patient registration forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians, patient information documents.

Response

5.3 Details of outcome-based schemes

5.3.1 If you are submitting a proven value: price increase scheme, as defined in the PPRS, please provide the following information:

- the current price of the intervention
- the proposed higher price of the intervention, which will be supported by the collection of new evidence
- a suggested date for when NICE should consider the additional evidence.

Response

5.3.2 If you are submitting an expected value: rebate scheme, as defined in the PPRS, please provide the following details:

- the current price of the intervention (the price that will be supported by the collection of new evidence)
- the planned lower price of the intervention in the event that the additional evidence does not support the current price
- a suggested date for when NICE should consider the additional evidence.

Response

5.3.3 If you are submitting a risk-sharing scheme, as defined in the PPRS, please provide the following details:

- the current price of the intervention (the price that will be supported by the collection of new evidence)
- the proposed relationship between future price changes and the evidence to be collected.

Response

5.3.4 For outcome-based schemes, as defined in the PPRS, please provide the full details of the new information (evidence) planned to be collected, who will collect it and who will carry the cost associated with this planned data collection. Details of the new information (evidence) may include:

- design of the new study
- patient population of the new study
- outcomes of the new study
- expected duration of data collection
- planned statistical analysis, definition of study groups and reporting (including uncertainty)
- expected results of the new study
- planned evidence synthesis/pooling of data (if applicable)
- expected results of the evidence synthesis/pooling of data (if applicable).

Response

5.3.5 If you are submitting a risk-sharing scheme, please specify the period between the time points when the additional evidence will be considered.

Response

5.3.6 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic modelling of the patient access scheme at the different time points when the additional evidence is to be considered.

Response

5.3.7 Please provide the other data used in the economic modelling of the patient access scheme at the different

time points when the additional evidence is to be considered. These data could include cost/resource use, health-related quality of life and utilities.

Response

5.3.8 Please present the cost-effectiveness results as follows.

- For proven value: price increase schemes, please summarise in separate tables:
  - the results based on current evidence and current price
  - the anticipated results based on the expected new evidence and the proposed higher price.
- For expected value: rebate schemes, please summarise in separate tables:
  - the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)
  - the results based on the current evidence and the lower price (if the new evidence is not forthcoming).
- For risk-sharing schemes, please summarise in separate tables:
  - the results based on current evidence and current price
  - the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)
  - the results based on the current evidence and the lower price (if the new evidence is not forthcoming)
  - the anticipated results based on the expected new evidence and the proposed higher price.

A suggested format is shown in table 3, section 4.7.

5.3.9 Please present in separate tables the incremental results for the different scenarios as described above in section 5.2.8 for the type of outcome-based scheme being submitted.

List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental analysis ranking technologies in terms of dominance and extended dominance. A suggested format is presented in table 4, section 4.8.

References

1. NICE. Pemetrexed maintenance treatment following induction therapy with pemetrexed and cisplatin for non-squamous non-small-cell lung cancer. TA309. April 2014. http://www.nice.org.uk/guidance/ta309

2. 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. September 2013. http://www.nice.org.uk/guidance/TA309/documents/lung-cancer-non-small-cell-non-squamous-pemetrexed-maintenance-following-pemetrexed-cisplatin-evaluation-report4

3. NICE. Rapid reconsideration of drugs currently funded through the Cancer Drugs Fund. Jan 2016.

4. NHS England/NICE. Consultation on proposals for a new cancer drugs fund (CDF) operating model from 1st April 2016. November 2015 https://www.engage.england.nhs.uk/consultation/cdf-consultation/supporting_documents/cdfconsultationdoc.pdf

Appendix F - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

CDF Rapid reconsideration process

TA309 - Pemetrexed maintenance treatment following induction therapy with pemetrexed and cisplatin for non-squamous non-small-cell lung cancer

Thank you for agreeing to make a submission 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 submission, 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 Andrew Goddard, RCP registrar, submitting on behalf of:

Name of your organisation: NCRI-RCP-RCR-ACP

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: None

Appendix F - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

CDF Rapid reconsideration process

TA309 - Pemetrexed maintenance treatment following induction therapy with pemetrexed and cisplatin for non-squamous non-small-cell lung cancer

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.

The use of cisplatin pemetrexed as a first line treatment is also NICE approved for non squamous non small cell lung cancer (NS-NSCLC) with evidence of superiority over the most commonly used first line chemotherapy treatment (platinum, gemcitabine doublets) in the UK.

There is clinical evidence for the benefit of maintenance pemetrexed in carefully selected patients with NS-NSCLC. The evidence supports maintenance treatment in both patients who have had pemetrexed in the first setting (continuation) and those who have received an alternative platinum based doublet (switch maintenance) as their initial systemic treatment. Both strategies are licensed but only switch maintenance has NICE approval though continuation maintenance is currently accessible in England via the CDF. This raises a concern that the current NICE strategy of approval for the switch maintenance strategy encourages clinicians to use an inferior non-pemetrexed doublet as the induction treatment so as to allow an easier access to maintenance treatment.

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CDF Rapid reconsideration process

TA309 - Pemetrexed maintenance treatment following induction therapy with pemetrexed and cisplatin for non-squamous non-small-cell lung cancer

There have been no head to head comparison trials of switch vs continuation maintenance but pemetrexed is a well-tolerated treatment when either approach is used, and oncologists feel both approaches offer similar benefits to patients as documented by the data from the 2 registration trials.

The other consideration for current NICE guidance in the maintenance setting is the lack of stipulations about the frequency of radiological assessments. The registration trials mandated the frequency of imaging and it would be expected that a different protocol / frequency will alter the median durations of response and hence treatment which would change cost effectiveness calculations. Therefore, we would recommend an update include guidance on imaging schedules.

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?

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.

Implementation issues

The NHS is required by the Department of Health 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 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)?

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.

Appendix F - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

CDF Rapid reconsideration process

TA309 - Pemetrexed maintenance treatment following induction therapy with pemetrexed and cisplatin for non-squamous non-small-cell lung cancer

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CDF Rapid reconsideration process

TA309 - Pemetrexed maintenance treatment following induction therapy with pemetrexed and cisplatin for non-squamous non-small-cell lung cancer

Thank you for agreeing to give us a statement on your 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? YES
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? YES
- 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, Fellow of RCP
- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

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CDF Rapid reconsideration process

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.

Continuation maintenance pemetrexed is a standard of care. Switch maintenance is NICE approved. However, continuation maintenance is not.

Continuation maintenance is available via CDF.

The issue is not if maintenance pem works. The issue is whether the induction regimen makes any difference. Most oncologists would think not and see this as a moot point.

We know first line pemetrexed combination chemo is the best (NICE approved) however the approval of switch maintenance has forced some oncologists to treat patients with a non-pemetrexed doublet initially and then give pemetrexed.

This seems a perversity of the current NICE guidelines.

The price of pemetrexed is probably going to fall soon as a result of patent expiry.

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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?

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Patients live longer if offered maintenance pemetrexed. However the critical thing is to ensure that the scan frequency during maintenance is mandated. Progression is picked up on scans so if a doctor does scans less frequently, he/she will pick up fewer progression events compared to a doctor doing more frequent scans.

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'm not aware of any issues

Any additional sources of evidence

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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.

Several presentations at BTOG meetings have confirmed that the use of maintenance pemetrexed in “real life” environments results in efficacy outcomes in keeping with the published evidence.

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)?

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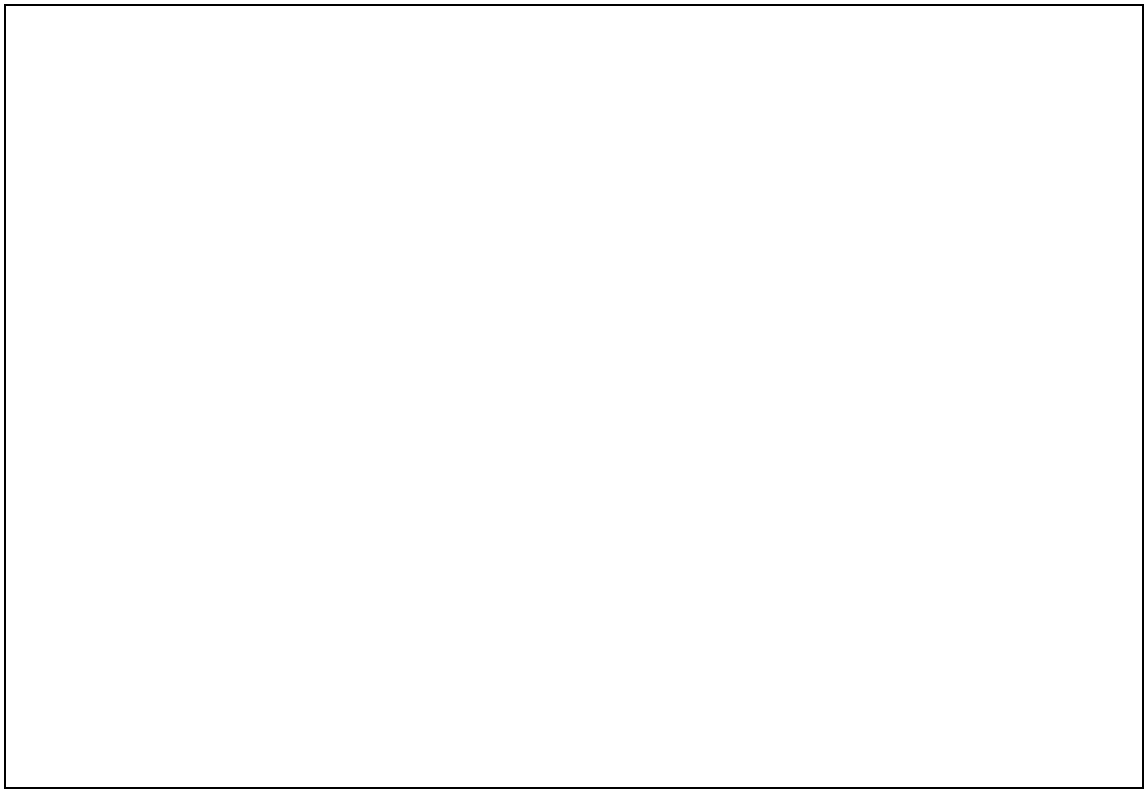

ERG REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Cancer Drugs Fund rapid review of NICE Guidance TA309

Pemetrexed for the maintenance treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC)

Confidential until published

This report was commissioned by the NIHR HTA Programme as project number 14/206/64

Completed 24th May 2016

CONTAINS CIC/AIC

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

1 INTRODUCTION

The National Institute for Health and Care Excellence (NICE) is in the process of assuming responsibility for the Cancer Drugs Fund (CDF). The CDF provided a mechanism for some cancer treatments, which failed to receive a positive recommendation when originally appraised for clinical and cost effectiveness for general use in the NHS, to be provided on a case by case basis to selected patients referred to the CDF by their clinician. As part of the transition, a number of historic technology appraisal decisions are being rapidly reviewed to determine the future status of treatments currently provided only through the CDF, i.e. whether they may now be recommended for general use, continue within the scope of the revised CDF scheme, or not be provided at all through the NHS. The Liverpool Reviews and Implementation Group (LRiG) at the University of Liverpool has been commissioned to review the company submission to assist a NICE Appraisal Committee (AC) in reconsideration of NICE Guidance TA309. The original Single Technology Appraisal (STA) was conducted in 2013-14 and final NICE guidance was issued in April, 2014 and did not recommend pemetrexed maintenance treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) following previous treatment with pemetrexed and cisplatin for use in the NHS.[1]

2 CONTEXT AND APPROACH TO RAPID REVIEWS

To allow these rapid reviews to proceed with the minimum risk of delay, the expected procedures have been restricted in scope for the company making a resubmission and for the Evidence Review Group (ERG) who is tasked with providing an independent assessment of the company submission. It is assumed that the primary clinical effectiveness data will remain essentially unchanged from the original appraisal and therefore no additional clinical evidence will be accepted by NICE. The cost-effectiveness analyses included in the company evidence submission needs to reflect the assumptions that determined the most plausible incremental cost-effectiveness ratio(s) ICER(s) as identified in the published guidance. It is anticipated that the main areas to be considered by the AC will relate to changes in the costs associated with treatment including any special NHS pricing agreements agreed since the original appraisal was carried out.

3 SPECIFIC DIFFICULTIES WITH THIS RAPID REVIEW

An unusual feature of the original appraisal concerns the late clinical evidence presented to the AC by the ERG at the meeting during which the content of the Final Appraisal Determination (FAD) was decided (25th September, 2013). The ERG highlighted a controversy related to the estimation of overall survival (OS) gain attributable to pemetrexed

maintenance therapy and was particularly concerned about how survival beyond the clinical trial data should be estimated. The ERG presented results of a new analysis of the PARAMOUNT trial data,[2] which demonstrated that parametric survival modelling in this instance was unnecessary to obtain a reliable value for survival gain, since the long-term life expectancy of patients beyond disease progression was independent of prior treatment and could be disregarded (other than for minor adjustment to differential timing). On this basis it was estimated that pemetrexed maintenance therapy was associated with about 3.5 months of additional life years per patient (ERG 2nd Addendum 27 September, 2013). Due to the lack of time available prior to the AC meeting it was not possible for the ERG to fully develop this scenario for use within the structure of the decision model and it was only possible to indicate a rough estimate of the expected ICER of approximately £74,500 per QALY gained, which the AC considered sufficiently robust to form a basis for their decision. This presents a particular difficulty in relation to the current rapid reconsideration of TA309, since a clearly defined baseline scenario with a precise ICER was never previously established directly from the decision model.

4 METHODS

4.1 Establishing a baseline scenario

The company has submitted a version of their original decision model, which has been modified in an attempt to reflect the various amendments, corrections and options considered appropriate by the AC at the time of the original appraisal. This model has been carefully reviewed by the ERG and the ERG notes that some of the recommended changes have not been fully or correctly implemented by the company. These relate to:

- The assumption that fewer pemetrexed continuation patients receive post-progression chemotherapy, than best supportive care (BSC) patients (referred to as Mod_3)

- Use of ERG generic docetaxel treatment cost estimates (referred to as Mod_6)

- ERG survival models (referred to as Mod_13).

The ERG has introduced these changes to the recently submitted model to ensure consistency with the model logic that was previously used by the ERG and accepted by the AC, following the model formula amendments previously reported (see Appendix B for details of these changes, and Appendix C for the ERG assessment of the company's implementation of specified changes in their revised base case model). Mod_3 increases the

estimated ICER by £1,924 per QALY gained, and Mod_6 increases the ICER by £182 per QALY gained.

The main difficulty in achieving an estimated ICER similar to that used in the preparation of the final decision (£74,500 per QALY gained) within the limitations of the resubmitted decision model is that it is necessary to apply appropriate lifetime survival extrapolations beyond the trial data to allow long-term treatment and care costs to be estimated. In reality it will never be possible to reconcile accurately results of a model structured around the assumption of parametric survival models, and the more accurate estimate of survival gain which requires only the evidence from the clinical trial data that there is no difference in post-progression survival attributable to continuation of pemetrexed monotherapy. The ERG had demonstrated that the same long-term projective function should be used for both treatment arms, but there are a wide variety of ways in which this can be introduced into the model depending on the time at which extrapolation is introduced into each arm, and any rules adopted to govern how this is implemented.

The ERG had developed two different approaches to this procedure which gave quite different results and neither precisely matched the most reliable estimated survival gain attributable to continuation therapy (+3.49 months). These were implemented in the company model through a logic modification (referred to as Mod_13). When Mod_13 is set to value 1 (option 1) the ERG OS exponential model is applied as detailed in the original ERG report. When Mod_13 is set to value 2, the time when the ERG OS model is introduced is governed by the time in each arm at which the same proportion of trial patients remain alive (in this case 37%).

In order to achieve a reasonably representative base case scenario against which to test the marginal effect of any additional relevant changes to non-clinical model parameters, the ERG selected the survival projection option giving the estimated survival gain closest to the expected value. Using Option 1 results in an estimated OS gain of 3.376 months under-estimating gain by 0.114 months, whereas Option 2 results in a lower OS gain of 3.071 months (under-estimating by 0.419). Therefore Option 1 provides a closer match to the non-parametric estimate. The remaining underestimate was then corrected by applying a correction factor to the model ICER proportional to the ratio of the target ICER to the uncorrected model ICER (x 1.037). The resulting base case ICER is then £74,371 per QALY gained, which is sufficiently close to the ‘approximately £74,500’ quoted in the AC documentation to allow the likely impact of changes to the NHS price of pemetrexed, and to other relevant costs, to be assessed with some confidence.

The application of the adjustment factor is through a simple post-hoc multiplier applied to the model estimate of incremental quality adjusted life years (QALYs), without altering the model logic in any way. Given the finding that there is no difference in post-progression survival between treatments in the PARAMOUNT trial, all the incremental survival benefit occurred prior to disease progression, so the health-state utility value applied to both trial arms is identical and has no differential influence on the size of the estimated ICER.

4.2 Relevant changes

Three changes affecting model cost parameters need to be considered when updating the original model results:

- The Commercial Access Agreement (CAA) proposed by the company which reduces the net cost of pemetrexed treatment acquisition to the NHS.

- Changes in the cost of other drugs received by NSCLC patients following disease progression identified by the ERG. These are of two types: a second-line treatment (docetaxel) which was off patent at the time of the original STA and for which much cheaper generic versions are available and generally used in the NHS, and a Patient Access Scheme for another second-line treatment (erlotinib) has been amended subsequent to the original STA to further reduce its price to the NHS.

- The ERG has identified model parameters for which inflation has significantly increased the cost to the NHS of administering drug treatments, responding to treatment-related adverse events and providing on-going patient care.

The details of the ERG's changes to cost parameters, including sources of information, are presented in Appendix A. The sensitivity of the estimated ICER relative to the baseline scenario for each of these types of change is reported separately and in combination.

5 RESULTS

Table 1 summarises the results of taking **all** of these factors into account in the model. The additional cost changes result in relatively small increases in the size of the estimated ICER to no more than £77,000 per QALY gained. By contrast, the inclusion of the CAA price for pemetrexed reduces the estimated ICER substantially to fall within the range of £[redacted] to £[redacted] per QALY gained.

Table 1 Sensitivity of estimated deterministic ICER to cost variations **and** proposed company CAA price of pemetrexed

Scenario	Original pemetrexed price	CAA pemetrexed price
Pragmatic baseline scenario	£74,371	£[redacted]
Baseline + changes in drug costs	£74,405	£[redacted]
Baseline + NHS cost inflation	£76,688	£[redacted]
Baseline + changes in drug costs + NHS cost inflation	£76,701	£[redacted]

ICER=incremental cost effectiveness ratio; CAA=Commercial Access Agreement

6 CONCLUSION

The approach taken by the ERG to recalibrate the company model to reflect the decision scenario previously employed by the AC as the basis for the published guidance is not ideal. However, the ERG considers that it appears to be generally robust to the inclusion of the full range of previous model amendments, and also to the cost and price parameter changes that have occurred since the company model was originally developed.

It appears that NHS cost inflation is more influential on cost effectiveness than the changes in NHS drug acquisition prices. However, neither is sufficient alone or in combination to increase the estimated ICER by more than £2,500 per QALY gained. The estimated ICERs, when the proposed CAA price for pemetrexed is applied, fall within the narrow range of £[redacted] to £[redacted] per QALY gained, whilst the best available estimate for mean survival gain exceeds 3 months (+3.49 months).

APPENDIX A: Details of ERG alterations to model cost parameters

Item	Detail	Old value	New value	Source
Chemotherapy delivery	HRG SB11Z day case oral	£192.32	£171.25	NHS Reference Costs 2014/15[3]
Chemotherapy delivery	HRG SB12Z day case simple parenteral	£207.88	£257.11	NHS Reference Costs 2014/15[3]
Chemotherapy delivery	At home by community nurse (hourly rate)	£64.00	£67.00	Inflated by HCHS inflation index (PSSRU 2015)
CT scan	Outpatient 2 areas with contrast	£132.99	£121.68	NHS Reference Costs 2014/15[3]
CT scan	Outpatient 3 areas with contrast	£150.88	£124.10	NHS Reference Costs 2014/15[3]
Clinical oncology consultation	Specialty 370 consultant-led	£119.99	£167.12	NHS Reference Costs 2014/15[3]
Clinical oncology consultation	Specialty 370 not consultant-led	£91.00	£103.37	NHS Reference Costs 2014/15[3]
Hospitalisation costs	Various	Various	Uplifted by 5.93%	Inflated by HCHS inflation index (PSSRU 2015)[4]
Radiotherapy preparation	HRG SC47Z Preparation for simple RT with imaging & simple calculation	£240.00	£288.13	NHS Reference Costs 2014/15[3]
Radiotherapy delivery	HRG SC22Z Deliver a fraction of treatment on a megavoltage machine	£91.00	£113.51	NHS Reference Costs 2014/15[3]
Docetaxel acquisition cost	80mg vial – replace with generic product 20mg vial – replace with generic product	£534.75 £162.75	£25.73 £7.47	eMIT 2015[5]
Erlotinib acquisition cost	Confidential PAS prices	Original	Modified	Details are confidential
Terminal care costs	Various	Various	Uplifted by 5.93%	Inflated by HCHS inflation index (PSSRU 2015)[4]

CT=computed tomography; PSSRU=Personal and Social Services Research Unit; eMIT=electronic market information tool; HCHS=Hospital and Community Health Service: PAS=Patient Access Scheme; RT=radiotherapy

APPENDIX B: MODEL AMENDMENTS

Details of amendments made by the ERG to the manufacturer's decision model submitted to the NICE Single Technology Appraisal of pemetrexed as maintenance therapy for NSCLC in April 2013

1) *Recalculation of mean pemetrexed acquisition cost per cycle*
This amendment is activated by a binary switch variable (Mod_1) with value 1 to apply the amendment and value 0 to use the original model logic.
Replace the formula in cell 'Resource!N47' with the following:

=IF(Mod_1=0,SUM(N45:N46),1481.37)

The mean cost per dose was obtained as follows:
For Males create a table of 100mg dose units equivalent to steps of 0.2m^2 BSA. Use a cumulative normal distribution function to calculate the proportion of patients who can be treated up to the maximum dose available in that step. Determine the number of 100mg and 500mg vials required to deliver the dose for that step. Use a SUMPRODUCT function to calculate the mean number of 100mg and 500mg vials required by Males, and multiple these by the vial unit costs to obtain the overall mean cost for Males. Note that a dose cap of 1000mg is applied on clinical advice. The same procedure is used for Females and then a weighted average cost for all patients is calculated using the balance between Males and Females in the population.
The BSA distribution parameters are derived from the Sacco survey data excluding adjuvant and neoadjuvant patients, as follows:

Males - mean 1.88568, standard deviation 0.17933

Females - mean 1.65503, standard deviation 0.17249

Males: Females ratio based on PARAMOUNT trial (313:226)

2) *Removal of inappropriate continuity correction applied to pemetrexed acquisition costs*
This amendment is activated by a binary switch variable (Mod_2) with value 1 to apply the amendment and value 0 to use the original model logic.
Replace the formula in cell 'Pem!DM11' with the following:

```
=IF(Mod_2=0,AVERAGE(CW10,CW11),$D$4*BH10*PemCost
+$D$4*AVERAGE(BH10,BH11)*(propCTscans*pCTscans*cCTscan
+propconsults*pConsults*cConsult))
+IF(JMENcosts=1,AVERAGE(CX11,CX10)+AVERAGE(DD10,DD11))
```

Copy this formula into cells 'Pem!DM12:DM366'

3) *Removal of differential use of second-line systemic therapies following disease progression*
The amendment is activated by a binary switch variable (Mod_3) with value 1 to apply the amendment and value 0 to use the original model logic.
Replace the formula in cell 'Resource!N305' with the following:

=IF(Mod_3=0,IF(PSA=1,M305,F305),pBSCSyst)

Replace the formula in cell 'Resource!N306' with the following:

=IF(Mod_3=0,IF(PSA=1,M306,F306),pBSCSyst)

Replace the formula in cell 'Resource!F307' with the following:

=IF(Mod_3=0,F305/F304,1)

4) *Recalculation of mean docetaxel acquisition cost per cycle*
This amendment is activated by a 3-way switch variable (Mod_6) taking value 0 to use the original model logic, value 1 to apply the amendment using BNF prices and value 2 using eMIT prices.
Replace the formula in cell 'Resource!M376' with the following:

=CHOOSE(Mod_6+1,SUM(M373:M375),M375+800.06,M375+87.39)

The method of calculation is similar to that used for pemetrexed (see (1) above), with the following alterations:
- dosing steps are at 20mg intervals

- three vial sizes are used - 20mg, 80mg and 140mg

- the lowest generic BNF list prices are used (£154.61, £508.01 and £720.10 respectively)

- the best eMIT average contract prices are used (£11.13, £47.24 and £86.10 respectively)

5) *Use of the covariate adjusted EQ-5D model to determine utility values*
This amendment is applied by setting range 'QoLdata' to value 2.

6) *Use of the covariate adjusted PFS model*
This amendment is applied by setting range 'PFSdata' to value 2.

7) *Use of the covariate adjusted OS model*
This amendment is applied by setting range 'OSdata' to value 2.

8) *Inclusion of re-estimated costs of vitamin supplementation required for patients receiving pemetrexed*
This amendment is activated by a binary switch variable (Mod_10) with value 1 to apply the amendment and value 0 to use the original model logic.
Replace the formula in cell 'Resource!V57' with the following:

=IF(Mod_10=0,SUM(V55:V56),1.778275)

This amendment is based on assigning protocol supplementation doses to each cycle, and applying this to the number of PARAMOUNT pemetrexed patients per cycle as shown in CSR addendum Table S124.4.8.

9) *Re-estimation of PFS follow-up costs*
This amendment proved difficult to implement within the main logic of the model. Therefore, the necessary alterations were implemented directly into cells in the Results spreadsheet. This involved calculating an estimated revised follow-up cost for both BSCand pemetrexed, and also the net discounted cost of PFS follow-up care in each arm.
The amendment is activated by a binary switch variable (Mod_11) with value 1 to apply the amendment and value 0 to use the original model logic.
Replace the formula in cell 'Results!F50 with the following:

=IF(Mod_11=0,bscTFC,bscTFC-1550.64611+238.33899)

Replace the formula in cell 'Results!M50 with the following:

=IF(Mod_11=0,pemTFC,pemTFC-1606.71508+407.59520)

The calculation of follow-up costs is based on out-patient assessment every 4 cycles for pemetrexed patients, and at 3, 6, 12 and 18 months for BSC patients. The same number of CT scans are assumed in each arm, spread out pro-rata to the number of

patients attending each assessment. Patient numbers used are taken from the PFS Kaplan-Meier estimates. The cost per OP appointment is £119.99, and the cost perCT scan is £142.92, and are discounted.

10) *Re-estimation of terminal care costs*
This amendment is activated by a binary switch variable (Mod_12) with value 1 to apply the amendment and value 0 to use the original model logic.
Replace the formula in cell 'JMEN_Resource!H45 with the following:

=IF(Mod_12=0,(E45/UKCPI_08)*UKCPI_11,3906.31)

This estimate is taken directly from an HTA report recently completed by the ERG for first-line chemotherapy for NSCLC, and encompasses costs of care for patients dying in hospital, in a hospice and at home, with all supportive community and voluntary services.

11) *Selecting alternate starting points for projection of OS*
This amendment is applied by setting ranges 'KMstopOSBSC' and 'KMstopPem' to the appropriate values:

For 15% survival use 41 & 47

For 20% survival use 36 & 44

For 25% survival use 41 & 47

12) *Substitution of ERG long-term model for OS projection*
This amendment is activated by a binary switch variable (Mod_13) with value 1 to apply the amendment and value 0 to use the original model logic.
The modification to the BSC worksheet requires the following changes:
- Set Cell AZ7 to " =0.00176541033416705 * 21 (This is the exponential risk parameter for a 21-day cycle)

- Set Cell AZ10 to "= AN10", then copy this formula to the range AZ11:AZ28

- Set Cell AZ29 to " =AZ28*EXP(-$AZ$7)" and copy this formula to range AZ30:AZ366

Replace the formula in cell AW11 as follows:
=IF(Mod_13=0, IF(Cycles<=IF($D$4=0,KMstopOSBSC,KMstopOSPem), 1-AN11/AN10, IF(OSModel=1, AQ11, IF(OSModel=2,AR11 ,IF(OSModel=3,AS11 ,IF(OSModel=4,AT11, IF(OSModel=5,AU11,AV11)))))), 1-AX11/AX10)
Replace the formula in cell AX11 as follows:

=IF(Mod_13=0,(1-AW11)*AX10,AZ11)

Copy the range AW11:AX11, and paste the formula to the range AW12:AX366

The modification to the Pem worksheet requires similar changes:
- Set Cell AZ7 to "=0.00170103676595399 * 21

- Set Cell AZ10 to "= AN10", then copy this formula to the range AZ11:AZ17

- Set Cell AZ18 to " =AZ17*EXP(-$AZ$7)" and copy this formula to range AZ19:AZ366

All other changes are identical to those in the BSC worksheet.

APPENDIX C: ASSESSMENT OF IMPLEMENTATION OF SPECIFIED ERG MODEL AMENDMENTS IN THE LATEST COMPANY REVISED BASE CASE MODEL

ERG mod#	ERG specified change	Company implemented change	Assessment
Mod_1 Pem cost per patient	Resource!N47 = IF(Mod_1=0,SUM(N45:N46),1481.37)	New cost applied directly to Resource!E32 combined with CAA discount in Resource!F31	Correctly applied.
Mod_2 Mid-cycle correction error in Pem cost	Pem!DM11..(DM366) =IF(Mod_2=0,AVERAGE(CW10,CW11), $D$4*BH10*PemCost +$D$4*AVERAGE(BH10,BH11) *(propCTscans*pCTscans*cCTscan +propconsults*pConsults*cConsult)) +IF(JMENcosts=1, AVERAGE(CX11,CX10) +AVERAGE(DD10,DD11))	Pem!DM11..(DM366)=CW10 +IF(JMENcosts=1, AVERAGE(CX11,CX10) +AVERAGE(DD10,DD11))	Correctly applied for PARAMOUNT resource data option.
Mod_3 Remove differential in 2nd line systemic Tx use	Resource!N305 =IF(Mod_3=0,IF(PSA=1,M305,F305), pBSCSyst) Resource!N306 =IF(Mod_3=0, IF(PSA=1,M306,F306),pBSCSyst) Resource!F307 =IF(Mod_3=0, F305/F304,1)	Resource!F305 unchanged Resource!F306 unchanged Resource!F307 = 1	**Incorrectly applied. Amends costs of 2nd line treatment but does not change the cost of follow-up or the associated utility.**
Mod_4 Add missing blood product cost	Resource!F293 =IF(Mod_4=0,58,58+125)	Resource!H293 =F293+125	This is correctly applied (only relevant for PARAMOUNT resource data option)

Mod_6 Include generic cost of docetaxel	Resource!M376 =CHOOSE(Mod_6+1,SUM(M373:M375),M375+800.06,M375+87.39)	None	**Not applied at all. This prevents use of generic docetaxel price.**
Mod_11 Re-estimated monitoring costs	Parameters!E163 =IF(Mod_11=0,3%,100%) Resource!C163 =IF(Mod_11=0, IF(CTscanNumber=1,1, IF(CTscanNumber=2,0.5, IF(CTscanNumber=3,0.25, IF(CTscanNumber=4,0.125, IF(CTscanNumber=5,0))))),0.25) Resource!C164 =IF(Mod_11=0, IF(ConsVisitNumber=1,1, IF(ConsVisitNumber=2,0.5, IF(ConsVisitNumber=3,0.25, IF(ConsVisitNumber=4,0.125, IF(ConsVisitNumber=5,0))))),0.25)	Parameters!E163=100% Resource!C163= IF(CTscanNumber=1,1, IF(CTscanNumber=2,0.5, IF(CTscanNumber=3,0.25, IF(CTscanNumber=4,0.125, IF(CTscanNumber=5,0))))) Resource!C164 = IF(ConsVisitNumber=1,1, IF(ConsVisitNumber=2,0.5, IF(ConsVisitNumber=3,0.25, IF(ConsVisitNumber=4,0.125, IF(ConsVisitNumber=5,0)))))	Correctly applied
Mod_12 Terminal care costs	Resource!H45 =IF(Mod_12=0,(E45/UKCPI_08) *UKCPI_11,E46) Resource!!E46 = 3906.31	Resource!H45 = 3906	Applied correctly with very minor variation (31p per patient)
Mod_13 ERG survival models	Changes to BSC worksheet AZ7, AZ10:AZ366, AW11:AW366, AX11:AX366 Changes to Pem worksheet AY7, AZ10:AZ366, AW11:AW366, AX11:AX366	None	**Not implemented at all**

7 REFERENCES

1. National Institute for Health and Care Excellence (NICE). NICE Technology Appraisal Guidance[TA309]. 2014 [April]; Available from: https://www.nice.org.uk/guidance/ta309/chapter/1-Guidance.
2. 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.
3. Department of Health. National Schedule of reference costs 2014 to 2015. 2015 [April 2016]; Available from: https://www.gov.uk/government/publications/nhs-reference-costs-2014-to-2015.
4. Curtis L. Unit costs of health and soical care 2013. Canterbury, Kent: Personal Social Services Research Unit 2013.
5. Department of Health. Electronic Market Information Tool. Commercial Medicines Unit; 2014; Available from: http://cmu.dh.gov.uk/electronic-market-information-tool-emit (Accessed 07/04/2016).

ERG Response to Factual Inaccuracy Check

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Cancer Drugs Fund rapid review of NICE Guidance TA309

TA309 Pemetrexed maintenance treatment following induction therapy with pemetrexed and cisplatin for non-squamous non-small cell lung cancer

ERG response to Lilly's Factual Inaccuracy Check of the ERG's updated report (dated May 2016)

This report was commissioned by the NIHR HTA Programme as project number 14/206/64

Completed May 23rd 2016

DOES CONTAIN CIC/AIC

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Issue 1 Incorrect statement regarding CIC data

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Cover page: Statement that ERG Report 'Contains no AIC or CIC' is incorrect	Replace with 'Contains CIC'	The ERG Report refers to with-CAA ICERs, which were marked up in the Company Submission as CIC. Whilst the ERG Report has conducted further analyses, and thus presented different with-CAA ICERs in their report compared to those presented in the company submission, the same approach to CIC marking must be reflected in the ERG Report.	All ICERs based on the CAA pemetrexed cost have been marked CiC.

Issue 2

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 2 Section 4 - METHODS: In ***4.1 Establishing a baseline scenario***, the ERG Report states: "The company has submitted a version of their original decision model, which has been modified in an attempt to reflect the various amendments, corrections and options considered appropriate by the AC at the time of the original appraisal. "This model has been carefully reviewed by the ERG and the ERG notes that four of the recommended	Replace with: "This model has been carefully reviewed by the ERG and the ERG notes that **one** of the recommended changes **has** not been implemented by the company. **This relates** to: - ERG re-estimation of terminal care costs (referred to as Mod_12)"	This statement is factually incorrect since the other three changes highlighted in the ERG Report were included in the revised company model. All ***four*** changes were included in the amended company model submitted to NICE in response to the (1st) ACD. However, at that time, the terminal care costs were only updated in the previous model in relation to the 'JMEN resource' approach, since this assumption was used in the company basecase analysis	All model modifications have been reviewed and updated in the text and described in detail in the new Appendix C. All estimated ICERs have been updated accordingly.

changes have not been implemented by the company. These relate to: - The assumption that fewer pemetrexed continuation patients receive post-progression chemotherapy, than BSC patients (referred to as Mod_3) - The non-inclusion of product cost of red blood cell transfusions (referred to as Mod_4) - Use of ERG docetaxel treatment cost estimates (referred to as Mod_6) - ERG re-estimation of terminal care costs (referred to as Mod_12)"		(submitted April 2013). Details of these, and other, changes made at that time are detailed in the company response to the (1st) ACD (See Appendix 2 of Lilly response to ACD, dated 3rd April 2013). Indeed, the ERG acknowledged this during the original appraisal. In their STA Addendum, the ERG states in relation to all four changes: "This amendment has been accurately implemented in the manufacturer's revised decision model." (See STA Addendum pages 3 and 5, dated 18th April 2013). Subsequently, the NICE Committee reviewed these changes and also accepted that the changes had been made (See TA309, paragraph 3.21.) To avoid confusion, it is noted that the cost of blood product is only used in the model with the 'PARAMOUNT resource use' approach. As such, this amendment did not affect the previous basecase ICER (£68,771), but this change was incorporated into the £70,538 ICER presented in this submission, when the preferred 'PARAMOUNT resource use' approach was implemented. The inadvertent omission of the ERG's preferred terminal care cost from the 'PARAMOUNT resource use' approach	

		has a minimal impact on the ICERs submitted for this CDF re-consideration. When the terminal care costs are also updated in the 'PARAMOUNT resource use' approach, the ICER is reduced by £60 from £70,538 to £70,478. In turn, the with-CAA ICER is reduced from [redacted].	

Issue 3 Incorrect statement regarding CIC data

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pages 2-3 Section 4 - METHODS: In 4.1 Establishing a baseline scenario, the ERG Report states: The ERG has introduced these four changes to the recently submitted model to ensure consistency with the model logic that was previously used by the ERG and accepted by the AC, following the model formula amendments previously reported.(see Appendix B for details of these changes). Mod_3 increases the estimated ICER by about £1,500 per QALY, Mod_4 increases the ICER by £235/QALY, Mod_6 increases the ICER by £40/QALY, and Mod_12 has no detectable effect.	Replace with: The ERG has introduced **this** change~~s~~ to the recently submitted model to ensure consistency with the model logic that was previously used by the ERG and accepted by the AC, following the model formula amendments previously reported.(see Appendix B for details of these changes). Mod_12 reduces the ICER by £60/QALY.	Please refer to detail in Issue 2 above: With the exception of the impact of implementing the preferred terminal care cost (as per Issue 2 above), it is assumed that the other three changes have resulted in double counting. Without access to the ERG model, this cannot be verified.	All model modifications have been reviewed and updated in the text and described in detail in the new Appendix C. All estimated ICERs have been updated accordingly.

Issue 4

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pages 3-4 Section 4 – METHODS: The ERG had developed two different approaches to this procedure which give quite different results and neither precisely matches the most reliable estimated survival gain attributable to continuation therapy (+3.49 months). These were implemented in the company model through a logic modification (referred to as Mod_13). When Mod_13 is set to value 1 (option 1) the ERG overall survival (OS) exponential model is applied as detailed in the original ERG report. When Mod_13 is set to value 2, the time when the ERG OS model is introduced is governed by the time in each arm at which the same proportion of trial patients remain alive (in this case 37%). In order to achieve a reasonably representative		Following a decision problem meeting with NICE, the company understood that such changes to the model were unnecessary as part of the CDF re-consideration process and rather, a pragmatic approach was preferred by NICE. The manufacturer was unable to fully replicate the ERG analyses, based on the details provided in Appendix B, at the time of the original appraisal. Due to the short timelines for providing a response to the ERG Report fact check, and coupled with the need to check the remaining document, the company has not had sufficient time to re-attempt the replication of the ERG analyses. As such, the company is not in a position to conduct a fact check on these statements.	No amendment proposed, but noted that the company could not check this.

base case scenario against which to test the marginal effect of any additional relevant changes to non-clinical model parameters, the ERG selected the survival projection option giving the estimated survival gain closest to the expected value. Using Option 1 results in an estimated OS gain of 3.376 months under-estimating gain by 0.114 months, whereas Option 2 results in a lower OS gain of 3.071 months (under-estimating by 0.419). Therefore Option 1 provides a closer match to the non-parametric estimate. The remaining understatement was then corrected by applying a correction factor to the model ICER proportional to the ratio of the target ICER to the uncorrected model ICER (x 1.037). The resulting base case ICER is then £74,371 per QALY gained, which is sufficiently close to the 'approximately £74,500' quoted in the AC documentation to allow the likely impact of changes in the NHS price of pemetrexed, and of other relevant costs, to be assessed with some			

confidence. The application of the adjustment factor is through a simple post-hoc multiplier applied to the model estimate if incremental quality-adjusted life-years (QALYs), without altering the model logic in any way. Given the finding that there is no difference in post-progression survival between treatments in the PARAMOUNT trial, all the incremental survival benefit occurred prior to disease progression, so the health-state utility value applied to both trial arms is identical and has no differential influence on the estimated ICER.			

Issue 5

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 4 – Relevant changes, and APPENDIX A Three changes affecting model cost parameters need to be considered when updating the original model results: - The Commercial Access Agreement (CAA) proposed by the	Two changes affecting model cost parameters need to be considered when updating the original model results: - The Commercial Access Agreement (CAA) proposed by the company which reduces the net	Following a decision problem meeting with NICE, the company understood that such changes to the model were unnecessary as part of the CDF re-consideration process and rather, a pragmatic approach was preferred by	NICE did not inform the ERG that a decision problem meeting was to be held, did not invite the ERG to participate, and did not inform the ERG of the topics discussed or any conclusions reached in the meeting. The ERG takes the view that changes in NHS costs between the initial appraisal and the current reconsideration have the

company which reduces the net cost of treatment acquisition to the NHS. - Changes in the cost of other drugs received by NSCLC patients following disease progression identified by the ERG. These are of two types: a second-line treatment (docetaxel) is now off patent and much cheaper generic versions of this drug are available and widely used in the NHS and a PAS for another second-line treatment (erlotinib) has been amended to further reduce its price. - The ERG has identified model parameters for which inflation has significantly increased the cost to the NHS of administering drug treatments, responding to treatment-related adverse events and providing on-going patient care. The details of the ERG's changes to cost parameters, including sources of information, are presented in Appendix A. The sensitivity of the estimated ICER relative to the baseline scenario for each of these types of change are reported separately and in combination.	cost of treatment acquisition to the NHS. - The re-estimation of terminal care costs APPENDIX A should be deleted.	NICE. As such, the following changes to the original model were deemed to be out of scope and in the interests of time, the company has not checked the following changes and associated results for factual accuracy: - Changes in the cost of other drugs received by NSCLC patients following disease progression identified by the ERG. These are of two types: a second-line treatment (docetaxel) is now off patent and much cheaper generic versions of this drug are available and widely used in the NHS and a PAS for another second-line treatment (erlotinib) has been amended to further reduce its price. - The ERG has identified model parameters for which inflation has significantly increased the cost to the NHS of administering drug treatments, responding to treatment-related adverse events and providing on-going patient care. The details of the ERG's	potential to be influential in the AC's consideration. Moreover, there is inconsistency in updating one cost (the CAA price of pemetrexed) and not updating all other costs, which could result in inaccurate, contradictory and misleading results. For example, if in an initial appraisal the comparator is an active treatment protected by patent but at later reconsideration was out of patent and available in generic form at much reduced price, the cost to the NHS of the generic alternatives would have to be incorporated into the cost effectiveness analysis. In this appraisal two drug prices are at issue involving second-line treatments within the decision model - one related to a generic drug cost (which was previously accepted in the previous appraisal decision) and one to a subsequent change in a PAS agreed price - and it is appropriate that the AC should have access to information on the potential effect of these and other cost changes through sensitivity analyses. Conceptually, there are two hypothetical scenarios available for conducting a reconsideration of the earlier appraisal recommendation: 1) *As if at the time of the original appraisal* - this assumes that the original clinical evidence (survival, health-related utility and incidence of relevant adverse events) is unchanged, and that all relevant costs are also unchanged from those originally

		changes to cost parameters, including sources of information, are presented in Appendix A. The sensitivity of the estimated ICER relative to the baseline scenario for each of these types of change are reported separately and in combination.	used. The only model parameter to be altered is the acquisition cost of the new intervention. This scenario is based on the assumption that pemetrexed had been made available at the same reduced CAA price as is currently being proposed and had been approved for general NHS use at that time. 2) *As at the time of the current reconsidered appraisal* - this assumes that the original appraisal had taken place at the current time according to the normal standards applicable to STAs. The clinical evidence is the same as in the original appraisal as no new evidence is available, but all other model parameters (i.e. costs and prices) would be assessed at currently available levels. This scenario is internally consistent with all evidence considered at a single time point. A logical consequence of adopting Scenario 1 ('As if at the time of the original appraisal') is that the CAA price now proposed by the company would have been available to all qualifying NHS patients at the reduced price for the whole the time between the two appraisals. However, in fact a restricted number of referred patients were given access to pemetrexed treatment paid for through the NHS Cancer Drugs Fund. A natural inference of Scenario 1 would therefore be that the company would agree to rebate to the NHS the excess costs incurred by the CDF (i.e. the difference between the price charged to the CDF

			and the newly proposed CAA price) between the two appraisals. The ERG has seen no indication that the company intends to offer such a retrospective rebate to the CDF upon a positive recommendation from the Reconsideration appraisal.

Issue 6 Unmarked CIC data

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 4 – Section 5 RESULTS, and Page 5 – Section 6 DISCUSSION: The following statements have not been marked as CIC as per the approach taken in the company submission. In addition, the ERG has conducted unnecessary additional analyses that were out of scope for this CDF re-consideration. 'By contrast the inclusion of the price for pemetrexed reduces the estimated ICER substantially within the range of [redacted] to [redacted] per QALY gained. The estimated ICERs fall within the narrow range of [redacted] to [redacted] per QALY gained when the proposed CAA price for pemetrexed is applied.	The statements should be amended and marked up as CIC as follows: By contrast the inclusion of the price for pemetrexed reduces the estimated ICER substantially to [redacted] per QALY gained. The estimated ICER is £XX,000 per QALY gained when the proposed **CAA** price for pemetrexed is applied	Lack of CIC marking for the ICERs which take account of the proposed CAA is not aligned with the CIC mark-up within the company submission .i.e. all with-CAA ICERs were marked up as CIC. Please also refer to issues 2-5 above. The ICERs which incorporate 'out of scope' changes to the basecase analysis should be deleted. Instead a single with-CAA ICER should be presented, rather than a range.	See Issues 1 & 2 above.

Issue 7 Unmarked CIC data and incorrect use of PAS

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>ERG response</th></tr>
<tr>
<td>Page 5 – Section 5 RESULTS Table 1

The ICER range in Table 1 have not been marked as CIC as per the approach taken in the company submission. In addition, the ERG has conducted unnecessary additional analyses that were out of scope for this CDF re-consideration.</td>
<td>The revised basecase ICER should be marked as CIC. The other ICERs should be deleted.

<table>
<tr><th>CAA pemetrexed price</th></tr>
<tr><td>[redacted]</td></tr>
<tr><td>[redacted]</td></tr>
<tr><td>[redacted]</td></tr>
<tr><td>[redacted]</td></tr>
</table>
</td>
<td>Lack of CIC marking for the ICERs which take account of the proposed CAA is not aligned with the CIC mark-up within the company submission .i.e. all with-CAA ICERs were marked up as CIC.

Please also refer to issues 2-5 above. The ICERs which incorporate ‘out of scope’ changes to the basecase analysis should be deleted.</td>
<td>See Issues 1 & 2 above.</td>
</tr>
</table>