www.lilly.co.uk

Eli Lilly and Company Limited
Lilly House
Priestley Road
Basingstoke
Hampshire
RG24 9NL
Tel: +44 (0) 1256 315000

HTA Strategy

Medical and Product Information: +44 (0) 1256 315999

8th August 2006

Dr Meindert Boysen
Associate Director – Single Technology Appraisals
National Institute for Health and Clinical Excellence
MidCity Place
71 High Holborn
London
WC1V 6NA

Dear Dr.Boysen

Single Technology Appraisal – Pemetrexed for the Treatment of Non-small Cell Lung Cancer

Thank you for forwarding the questions/queries from the Evidence Review Group based on the above appraisal. Please find attached our responses to your questions.

As per your email of 26/07/06, we have deleted the duplicate question (A4) and amended the questions numbers accordingly.

Please be advised that our response contains confidential data which has been highlighted in red and underlined.

We trust that this is satisfactory. Should you have any further queries, please do not hesitate to contact me.

Yours sincerely

'Confidential Information removed'

Encl:

1. **'Commercial in Confidence information removed'**
2. Lloyd A, van Hanswijck de Jonge P, Doyle S et al. Health state utility scores in lung cancer: a community survey. Presented at 27th Annual Meeting of the Society for medical Decision Making, October 21-25, 2005 – San Francisco, California
3. **'Academic in Confidence information removed'**

Section A: Clarifications of the effectiveness data

A1) JMEI trial protocol

Please provide a copy of the JMEI trial protocol.

The protocol for this study was approved on 07 November 2000 and was amended on 27 November 2000 (Amendment (a)) and again on 03 August 2001 (Amendment (b)). The major issues addressed in these amendments are outlined below. The study protocol, provided in confidence, is enclosed with this letter.

Amendment A

- Use of oral dexamethasone was encouraged
- Treatment was allowed to continue until unacceptable toxicity, disease progression, physician believes discontinuation from study therapy is in the patient's best interest, or patient requests discontinuation from study therapy.
- Prior chemotherapy allowed in the desired patient population was more clearly defined.
- A randomization factor was added to balance randomization with regard to number of prior chemotherapy regimens.
- Partial response in nonmeasurable disease (PRNM) was better defined.
- It was clarified that "follow-up" begins upon discontinuation from study therapy.
- Timing for the first baseline ECG from "Approximately 1 to 2 weeks prior to study enrollment" changed to "Recommended timing… approximately 1 week prior to the first ALIMTA dose."

Amendment B

- Liquid formulation of pemetrexed was replaced with lyophilized preparation.
- Statistical methodology was explained in further detail.
- Language was amended to reflect that an independent review of each patient's response status was optional for this study.

The JMEI protocol was written based on the CPMP recommendation of a fixed hazard ratio margin, while the US FDA recommended that the JMEI study incorporate a margin based on a 50% retention of the docetaxel survival benefit over BSC. After initiating enrollment for JMEI, two oncolytic drugs received US regulatory approval based on a percent retention method (capecitabine in first-line colorectal cancer, and docetaxel plus cisplatin in first-line NSCLC).

Because the pivotal study JMEI was planned for registration in both Europe and the United States, recommendations from both the CPMP and FDA were taken into consideration, and the 50% retention methodology was included prospectively as part of the Statistical Analysis Plan (SAP), after the database had been locked but before unblinding. The percent retention method was added, not as a protocol amendment, but as part of the approved JMEI SAP following publication of the paper in January 2003 (Rothmann et al. 2003).

As described in the Lilly STA submission, the Rothmann method (2003) is a **recently** developed method that allows the efficacy of an experimental treatment to be more easily evaluated by estimating the percentage of benefits preserved from the reference treatment compared to a historical control.

According to ICH E9, such modification of analyses in this way are acceptable provided that the method is sufficiently appropriate, predefined before unblinding of randomization assignments, and fully described in the report. These conditions were satisfied for this study because the JMEI SAP was approved on 24 January 2003, and the database was unblinded on 30 January 2003.

The following are the changes or additions to the prospectively defined statistical analysis plan (SAP):

- In the original SAP, there were 5 categories of significant protocol deviations. A sixth category, "Inclusion / Exclusion Criteria**",** was added to highlight enrolment (with or

without continued participation) of a patient who did not satisfy eligibility criteria or for whom not all criteria were assessed at the time of enrollment.

- In order to have adequate power to perform the survival analysis on the randomised and treated population, the criterion to stop the study when 385 randomized patients were dead was changed to stop the study when at least 385 randomised and treated patients were dead.
- An indirect comparison of pemetrexed to best supportive care was performed using the historical data as a consequence of Rothmann's Z calculation.
- A repeated measures analysis was performed on the average symptom burden index using the same methodology as the individual patient scales.
- A compound symmetry variance-covariance matrix was used and considered sufficient for treatment group inferences in the repeated measures model for LCSS patient scores.

A2) Patient Disposition (JMEI trial)

The paper by Hanna et al (JMEI) does not give a complete breakdown of survival data for patients in each arm receiving crossover agents and other chemotherapy post disease progression. Please provide full details of patient flows and the associated survival statistics as follows:

In response to email from NICE (28/07/06) regarding this question, we have provided (1) for those who died, the mean/median time to death, (2) for those censored, the mean/median time to being censored, and (3) or those who were LTFU, the mean/median time to being LTFU.

Patient Disposition (JMEI trial): Summary of Mean and Median Time (weeks) – ITT population

			Survival (weeks)	
Pathway	**Number**	**Percent (%)**	**Mean**	**Median**
Pemetrexed only - dead	105	37.1	23.0	18.7
Pemetrexed only - lost to follow up	5	1.8	11.7	7.4
Pemetrexed only - censored	29	10.2	49.8	46.1
Pem then Doc - dead	63	22.3	35.1	36.1
Pem then Doc - lost to follow up	0	0.0	.	.
Pem then Doc - censored	22	7.8	51.8	47.8
Pem then Other - dead	24	8.5	33.7	31.5
Pem then Other - lost to follow up	0	0.0	.	.
Pem then Other - censored	17	6.0	51.5	48.3
Pem arm but not received	18	6.4	18.8	7.4
Pem arm total	283	100.0	37.2	36.1
Docetaxel - dead	132	45.8	20.9	15.0
Docetaxel - lost to follow up	3	1.0	24.5	25.2
Docetaxel - censored	34	11.8	43.2	41.7
Doc then Pem - dead	0	0.0	.	.
Doc then Pem - lost to follow up	0	0.0	.	.
Doc then Pem - censored	0	0.0	.	.
Doc then Other - dead	66	22.9	39.0	37.2
Doc then Other - lost to follow up	0	0.0	.	.
Doc then Other - censored	41	14.2	49.9	48.3
Doc arm but not received	12	4.2	8.0	1.3
Doc arm total	288	100.0	38.0	34.4

A3) Treatment duration and Intensity (JMEI trial)

Please provide details of the numbers of patients receiving chemotherapy at each cycle in the JMEI trial as follows

	Pemetrexed								Docetaxel							
		Full Dose		Reduced Dose		Not Treated		Dead		Full Dose		Reduced Dose		Not Treated		Dead
Cycle No.	No. of Pts	N	(%)	N	(%)	N	(%)		No. of Pts	N	(%)	N	(%)	N	(%)	
1	265	265	(100.0)	0	(0.0)	0	(0.0)	3	276	276	(100.0)	0	(0.0)	0	(0.0)	12
2	239	232	(97.1)	7	(2.9)	0	(0.0)	6	238	201	(84.5)	37	(15.5)	0	(0.0)	6
3	153	149	(97.4)	4	(2.6)	0	(0.0)	2	160	151	(94.4)	9	(5.6)	0	(0.0)	4
4	136	135	(99.3)	1	(0.7)	0	(0.0)	4	139	134	(96.4)	5	(3.6)	0	(0.0)	4
5	100	100	(100.0)	0	(0.0)	0	(0.0)	1	102	95	(93.1)	7	(6.9)	0	(0.0)	1
6	90	90	(100.0)	0	(0.0)	0	(0.0)	0	88	88	(100.0)	0	(0.0)	0	(0.0)	2
7	50	50	(100.0)	0	(0.0)	0	(0.0)	1	30	28	(93.3)	2	(6.7)	0	(0.0)	1
8	38	37	(97.4)	1	(2.6)	0	(0.0)	1	24	24	(100.0)	0	(0.0)	0	(0.0)	0
9	20	20	(100.0)	0	(0.0)	0	(0.0)	0	10	9	(90.0)	1	(10.0)	0	(0.0)	0
10	15	15	(100.0)	0	(0.0)	0	(0.0)	0	7	7	(100.0)	0	(0.0)	0	(0.0)	0
11	14	14	(100.0)	0	(0.0)	0	(0.0)	0	5	5	(100.0)	0	(0.0)	0	(0.0)	1
12	12	12	(100.0)	0	(0.0)	0	(0.0)	0	3	3	(100.0)	0	(0.0)	0	(0.0)	0
13	9	9	(100.0)	0	(0.0)	0	(0.0)	0	2	2	(100.0)	0	(0.0)	0	(0.0)	1
14	6	6	(100.0)	0	(0.0)	0	(0.0)	0	1	1	(100.0)	0	(0.0)	0	(0.0)	0
15	6	5	(83.3)	1	(16.7)	0	(0.0)	0	.	.		.		.		.
16	4	4	(100.0)	0	(0.0)	0	(0.0)	0	.	.		.		.		.
17	3	3	(100.0)	0	(0.0)	0	(0.0)	0	.	.		.		.		.
18	2	2	(100.0)	0	(0.0)	0	(0.0)	0	.	.		.		.		.
19	1	1	(100.0)	0	(0.0)	0	(0.0)	0	.	.		.		.		.
20	1	1	(100.0)	0	(0.0)	0	(0.0)	0	.	.		.		.		.
Post Treat-ment[*1]	.	.		.		.		13	.	.		.		.		8

*1 Within 30 days of study drug discontinuation

A4) Treatment Response by Cycle (JMEI trial)

Please provide a cycle-by-cycle analysis of numbers of patients whose health status was confirmed as a response / stable / confirmed progression / dead.

Treatment response by Cycle, Summary of CR/PR by cycle – Patients qualified for response

	Pemetrexed (N=264)				Docetaxel (N=274)			
	Cumulative patients showing any CR/PR		Cumulative patients achieving CR/PR as best response		Cumulative patients showing any CR/PR		Cumulative patients achieving CR/PR as best response	
Cycle No.	n	(%)	n	(%)	n	(%)	n	(%)
1	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
2	12	(4.5)	10	(3.8)	18	(6.6)	13	(4.7)
3	12	(4.5)	10	(3.8)	21	(7.7)	14	(5.1)
4	24	(9.1)	20	(7.6)	31	(11.3)	21	(7.7)
5	24	(9.1)	20	(7.6)	32	(11.7)	22	(8.0)
6	30	(11.4)	23	(8.7)	36	(13.1)	24	(8.8)
7	30	(11.4)	23	(8.7)	36	(13.1)	24	(8.8)
8	30	(11.4)	23	(8.7)	36	(13.1)	24	(8.8)
9	30	(11.4)	23	(8.7)	36	(13.1)	24	(8.8)
10	31	(11.7)	24	(9.1)	36	(13.1)	24	(8.8)
11	31	(11.7)	24	(9.1)	36	(13.1)	24	(8.8)
12	31	(11.7)	24	(9.1)	36	(13.1)	24	(8.8)
13	31	(11.7)	24	(9.1)	36	(13.1)	24	(8.8)
14	31	(11.7)	24	(9.1)	36	(13.1)	24	(8.8)
15	31	(11.7)	24	(9.1)	.		.	
16	31	(11.7)	24	(9.1)	.		.	
17	31	(11.7)	24	(9.1)	.		.	
18	31	(11.7)	24	(9.1)	.		.	
19	31	(11.7)	24	(9.1)	.		.	
20	31	(11.7)	24	(9.1)	.		.	

A6) Superiority test (JMEI trial)

Section 2.3.5 states that "Superiority of pemetrexed in overall survival was defined by HR <1.00" (pg 38). Please provide details of the P value for this test.

The superiority test was indeed originally performed exactly as specified in the protocol. Strictly speaking, the test was based on the 95% confidence interval for the overall survival hazard ratio in the ITT population: If the upper bound of the 95% confidence interval for HR is not only less than 1.11 but also less than 1 then there is evidence of superiority in terms of statistical significance at 5% level ($p<0.05$). This approach is described in a CPMP points to consider (Points to consider on switching between superiority and non-inferiority, July 2000).

The calculation of a p-value was not necessary (and not pre-specified) to determine the statistical significance for this test. The test was not statistically significant (i.e. the confidence interval did not exclude a hazard ratio value of 1.00.). Retrospectively, the p-value associated with this superiority (ITT) test has been calculated as 0.93.

A7) Cox multiple regression modelling

Please provide details of all explanatory variables used in the model (including those which did not have an effect on the hazard ratio point estimate). Please also provide clarification of the variables included in the final model.

There were 4 explanatory variables in the final model:

- Study treatment arm (pemetrexed over docetaxel)
- ECOG performance status (0 over 1/2)
- Time since last (prior) chemotherapy (>= 3 months over <3 months)
- Stage of Disease (III over IV)

The three variables included above (other than study treatment arm) were chosen based on a stepwise regression procedure. The stepwise regression procedure started with a list of seven potential prognostic factors, using entry and exit p-values of 0.20 and 0.10, respectively. Upon convergence of the stepwise procedure (after using largest score chi square selection criteria at each step), only the three variables listed above remained as significant prognostic factors. The variable for study treatment arm was then added as a fourth covariate, so as to estimate the survival hazard ratio between study arms in the presence of the three significant prognostic factors.

The four variables from the original list of seven that were not found to be significant prognostic factors by this procedure are the following:

- Best response to prior chemotherapy (CR/PR/SD over PD)
- Prior taxane use (Yes over No)
- Prior platinum use (Yes over No)
- Number of prior chemotherapies (1 over 2)

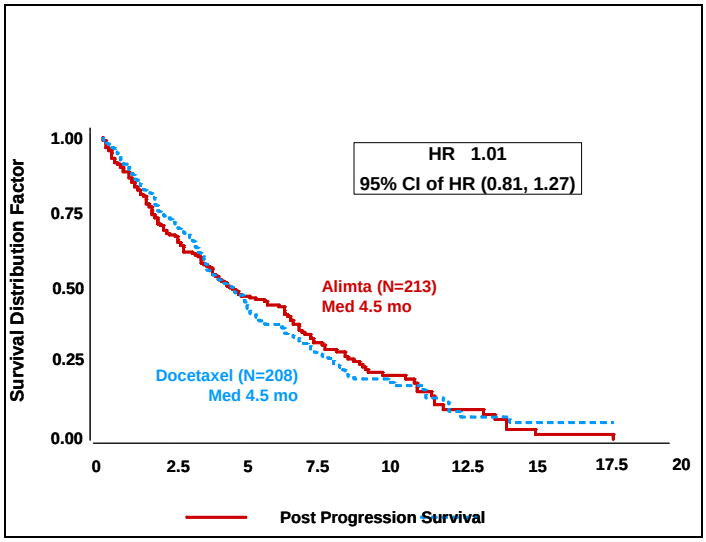
A8) Cross-over effect (JMEI trial)

Please provide details of how the cross-over effect was accounted for within the analysis.

Overall survival and other efficacy endpoints were analyzed without consideration of potential effects of post-study-treatment anti-cancer therapy. However, an additional exploratory analyses were undertaken by Lilly to examine whether there was any evidence of one treatment arm or the other receiving a differential benefit due to post-study-treatment anti-cancer therapy. Our conclusion was that while it is possible that post-study-treatment therapies may have provided additional benefits for those patients who received them, there was no evidence of a differential advantage from these therapies gained by one study arm relative to the other.

When considering the potential effect on overall survival of additional lines of therapies, the first consideration is whether there is a different outcome for those secondary efficacy measures that apply only to the study treatment period. Results for best tumour response and progression-free survival show very similar results to overall survival (in terms of the numerical comparisons between pemetrexed and docetaxel), which does not suggest any evidence of a differential benefit due to additional lines of therapy. If, for example, patients on the pemetrexed arm received additional benefit from cross-over to docetaxel, we would expect to see relatively better survival (at least numerically) on the pemetrexed arm --- some degree of improvement over the progression-free survival hazard ratio. Since we do not see any difference between the survival and progression-free survival hazard ratios, there is no evidence from these analyses of any systematic bias in the survival comparison due to additional lines of therapy.

A second, exploratory analysis of post-progression survival was also conducted. With few exceptions, patients received additional therapies only after progressive disease. So if there was any differential survival benefit between arms due to the additional lines of therapy, we might expect to see some differences in the data for post-progression survival (Kaplan-Meier analysis of the time from progressive disease to the date of death, among all trial patients experiencing progressive disease). The analysis of post-progression survival in fact showed no evidence of such a differential effect. Below is the Kaplan-Meier graph for post-progression survival:



Section B: Economic Analysis

B1) Utilities estimates (JMEI trial)

Please confirm the correct reference for the health-related utility values included in the analysis. The submission states this was Lloyd et al 2005 "Health state utility scores in lung cancer: a community survey". However, the reference in section 4 (References) of the submission and the copy provided was for "Health state utilities for metastatic breast cancer". Since this article appears not to have been published yet could you please provide the correct reference so the ERG can confirm the utility values.

The reference Lloyd et al 2005 referring to the utility study in metastatic breast cancer was provided in error. The correct reference by is as follows:

Lloyd A, van Hanswijck de Jonge P, Doyle S et al. Health state utility scores in lung cancer: a community survey. Presented at 27th Annual Meeting of the Society for medical Decision Making, October 21-25, 2005 – San Francisco, California.

The correct reference is enclosed.

Please provide details of 95% confidence intervals and ranges around the mean health-related utilities for the adverse events (Table 56, page 114 of submission).

The mean utility values, used in the economic model, were taken directly from the NSCLC utility study reported by Nafees et al., (2006), as detailed in the main submission document. The utility values were based on a multivariate regression model linked to the key health state descriptors and a set of basic demographic variables. The source data for this were the standard gamble results obtained from a representative sample of the general public. The table below presents these data, where a normal distribution to the mean utility values is assumed.

Descriptive Statistics for the utility values used within the cost utility analysis.

	Mean Utility Values*	Estimated SE**	Lower 95% CI**	Upper 95% CI**
Response	0.67	**0.0230**	0.6249	0.7151
Stable	0.65	**0.0215**	0.6079	0.6921
Progression	0.47	**0.0317**	0.4078	0.5322
Response with				
Febrile neutropenia	0.58	**0.0280**	0.5251	0.6349
Neutropenia	0.58	**0.0275**	0.5261	0.6339
Nausea/ Vomiting	0.62	**0.0273**	0.5665	0.6735
Fatigue	0.6	**0.0300**	0.5413	0.6587
Diarrhea	0.63	**0.0266**	0.5778	0.6822
Rash	0.64	**0.0253**	0.5905	0.6895
Alopecia (Hair loss)	0.63	**0.0268**	0.5775	0.6825
Stable with				
Febrile neutropenia	0.56	**0.0273**	0.5064	0.6136
Neutropenia	0.56	**0.0276**	0.5060	0.6140
Nausea/ Vomiting	0.61	**0.0275**	0.5561	0.6639
Fatigue	0.58	**0.0301**	0.5210	0.6390
Diarrhea	0.61	**0.0263**	0.5585	0.6615
Rash	0.62	**0.0251**	0.5707	0.6693
Alopecia (Hair loss)	0.61	**0.0275**	0.5561	0.6639

* Based on the Nafees et al 2006 utility study

** At the time of creating the cost utility model the actual standard errors were not available. Therefore the standard errors were estimated to provide estimated 95% confidence intervals. The standard errors were calculated by repeatedly sampling each coefficient from an assumed independent normal distribution, based on the available coefficient standard error vales. This was done by repeatedly sampling each coefficient from an assumed independent normal distribution, based on the available coefficient standard error values. The simulation was run 2,000 times for each defined health state. The result of this was to provide a sample distribution for each mean utility state. This in turn then provided a data set with which the standard errors could be estimated for each mean utility value.

The analysis of the utility values from the Nafees et al (2006) study has since been completed. The actual standard errors are now available and shown in the table below. As can be seen, estimated standard errors used within the cost utility analysis (shown above) are similar to the actual standard errors from Nafees et al 2006 (shown below).

Descriptive Statistics for the actual utility values based on Nafees et al 2006

Effect	Coefficient Estimate	S.E.
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	'Academic in Confidence information removed.	

Please provide a copy of the paper or report that details the study in which the data on health-related utilities associated with adverse events were collected (page 114).

The abstract by Nafees et al (Health state utilities in UK for second-line advanced non-small cell lung cancer) been submitted and recently accepted for the ISPOR 9th Annual European Congress to be held 28-31 October 2006 at the Radisson SAS Falconer Hotel & Conference Centre in Copenhagen, Denmark. This abstract has been provided with the Lilly submission.

As requested a copy of the draft manuscript is included in this response. Please note, this manuscript has not yet been submitted to a journal and must be considered academic-in-confidence. The manuscript is targeted for a peer-reviewed clinical journal.

References

1. ICH Harmonised Tripartate Guideline: Statistical Principles for Clinical Trials E9. Available on http://www.ich.org/LOB/media/MEDIA485.pdf

2. Rothmann et al. (2003) Design and analysis of non-inferiority mortality trials in oncology. *Stats in Med*, 22: 239-264.

3. Points to consider on switching between superiority and non-inferiority, July 2000. http://www.emea.eu.int/pdfs/human/ewp/048299en.pdf

4. Nafees et al (2006). Health state utilities in UK for second-line advanced non-small cell lung cancer. Abstract submitted and accepted for the ISPOR 9th Annual European Congress to be held 28-31 October 2006 at the Radisson SAS Falconer Hotel & Conference Centre in Copenhagen, Denmark. (abstract included in the original Lilly submission)