# Comments by ERG on additional economic results presented by Eli Lilly and Company in support of the cost effectiveness of pemetrexed as maintenance therapy for locally advanced or metastatic non squamous non-small cell lung cancer – (revised 9th February 2010)

## 1. Background

Following the issuing of the appraisal consultation document (ACD) relating to the use of pemetrexed for the maintenance treatment of non-small cell lung cancer (NSCLC), the manufacturer (Eli Lilly and Company) has provided a detailed argument for revising the draft recommendation, supported by six scenario analyses based on an updated version of the computer model used in their submission. A number of amendments and enhancements have been made to the model logic, most notably the inclusion of code to facilitate probabilistic sensitivity analysis (PSA) on the model results. The ERG (Liverpool Reviews and Implementation Group, University of Liverpool) were asked to examine this additional economic evidence and to provide further comments to assist the Appraisal Committee in its deliberations. Unfortunately only a short time was available from receipt of the new scenarios to allow scrutiny and assessment by the ERG. The ERG therefore took a decision to concentrate on just one of the six scenarios; the most appropriate appeared to be Scenario 5 which was closest to the ERG's preferred base case as presented in the original ERG report. The cost-effectiveness results from this scenario also indicated that it was one of the most favourable to pemetrexed, and therefore might be seen as representing a 'best case' for the use of pemetrexed.

## 2. ERG investigation and findings

The amended model (Scenario 5) has been examined as thoroughly as time would allow. Most of the changes made were those required in order to accommodate the new PSA routine, both in terms of new functionality, and including measures of parameter uncertainty. Generally the changes appear to have been implemented appropriately, and operate correctly. However, very few of the corrections and amendments originally identified by the ERG as necessary to the model have been incorporated. Therefore, the ERG implemented and tested all corrections and amendments as described in the ERG report, into the new model prior to generating the new results shown below.

# 3. ERG modified results for Scenario 5

Table 1 and Table 2 summarise both deterministic and probabilistic model results for both the exponential and Weibull projection versions of the model. In addition to the initial and ERG modified versions, three intermediate results are shown where the net impact of implementing similar types of changes is given: technical model corrections, revisions to data values, and additional model features.

Initially, the probabilistic results are less favourable to pemetrexed (show higher ICER values) and the use of Weibull projections also lead to higher ICERs than when exponential projections are employed. The technical model corrections and revised data changes implemented by the ERG generate only minor alterations to the results. However, the additional model features result in significant reductions in ICER values indicating improved performance for pemetrexed. In addition, it appears that the differential caused by use of different projection methods largely disappears.

The principle source of this marked change in cost-effectiveness results is attributable to the ERG's use of differential survival estimates for post-progression survival between patients who did and did not receive second- line chemotherapy in the clinical trial. In particular the direction of this differential in patients treated with pemetrexed is reversed for placebo patients, leading to a larger incremental utility per patient. A further factor contributing to the large change in probabilistic results may be due to the greater uncertainty (wider confidence limits) associated with each disaggregated survival estimate due to the smaller patient numbers in each subgroup.

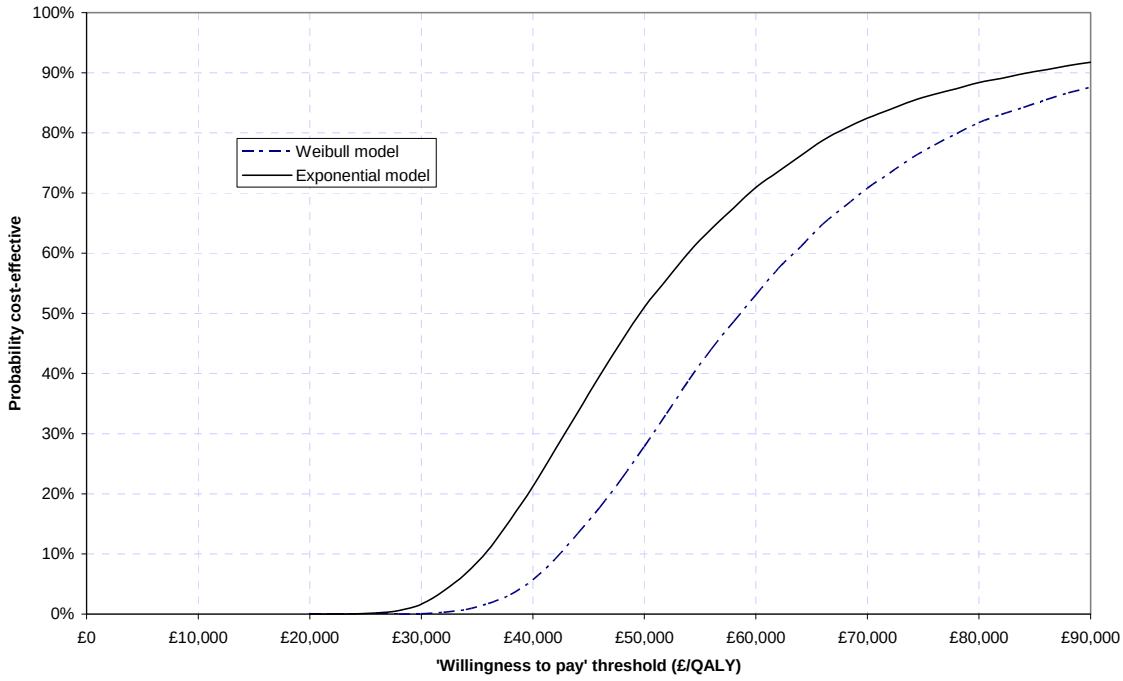


Figure 1 Cost-effectiveness acceptability curve for Scenario 5 without ERG changes

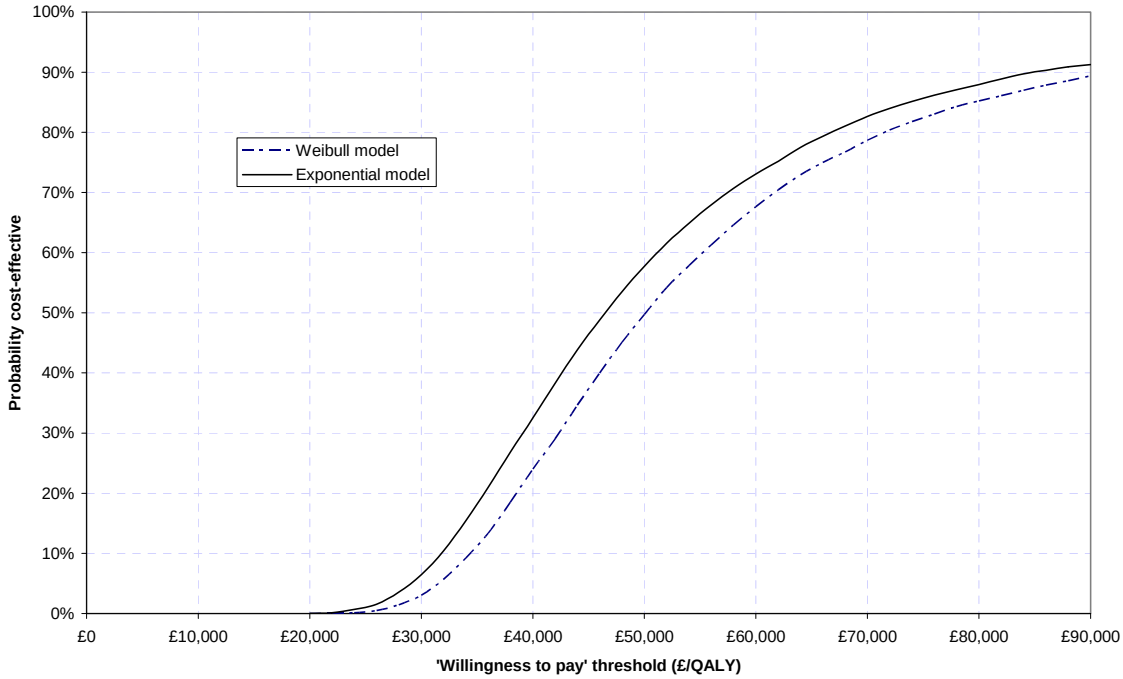


Figure 2 Cost-effectiveness acceptability curve for Scenario 5 with all ERG changes

Table 1 Cost-effectiveness estimates for pemetrexed compared to placebo –Scenario 5 with and without ERG modifications using exponential population projections

| | Deterministic | | | Probabilistic | | | Probability cost-effective at threshold | | |
|---|---|---|---|---|---|---|---|---|---|
| | IC | IQ | ICER | IC | IQ | ICER | £30k/QALY | £40k/QALY | £50k/QALY |
| **Scenario 5** | **£12,136** | **0.2591** | **£46,841** | **£12,115** | **0.2433** | **£49,800** | **1.63%** | **21.24%** | **51.02%** |
| + technical corrections | £12,083 | 0.2627 | £45,992 | £12,078 | 0.2448 | £49,329 | 3.53% | 25.36% | 51.17% |
| + data changes | £12,348 | 0.2586 | £47,752 | £12,386 | 0.2411 | £51,381 | 1.12% | 18.70% | 47.64% |
| + model enhancements | £12,292 | 0.2190 | £56,114 | £12,404 | 0.2683 | £46,236 | 5.07% | 31.01% | 58.13% |
| **All changes** | **£12,497** | **0.2196** | **£56,903** | **£12,527** | **0.2656** | **£47,168** | **6.46%** | **32.53%** | **57.71%** |

IC = incremental cost; IQ = incremental QALYs; ICER = incremental cost-effectiveness ratio (IC/IQ)

Technical corrections = continuity correction, and discounting of costs and outcomes

Data changes = number of treatment cycles, chemotherapy costs and utility in terminal care

Model enhancements = pre-progression monitoring costs and differential survival for patients with/without 2nd line chemotherapy as in clinical trial

Table 2 Cost-effectiveness estimates for pemetrexed compared to placebo –Scenario 5 with and without ERG modifications using Weibull population projections

| | Deterministic | | | Probabilistic | | | Probability cost-effective at threshold | | |
|---|---|---|---|---|---|---|---|---|---|
| | IC | IQ | ICER | IC | IQ | ICER | £30k/QALY | £40k/QALY | £50k/QALY |
| **Scenario 5** | **£12,052** | **0.2311** | **£52,157** | **£11,989** | **0.2052** | **£58,437** | **0.07%** | **5.70%** | **27.82%** |
| + technical corrections | £12,020 | 0.2299 | £52,276 | £11,969 | 0.2057 | £58,189 | 0.39% | 9.50% | 32.25% |
| + data changes | £12,267 | 0.2306 | £53,203 | £12,257 | 0.2019 | £60,704 | 0.06% | 5.26% | 24.63% |
| + model enhancements | £12,311 | 0.2190 | £56,272 | £12,496 | 0.2516 | £49,663 | 2.22% | 22.33% | 50.66% |
| **All changes** | **£12,532** | **0.2195** | **£57,082** | **£12,632** | **0.2493** | **£50,673** | **3.03%** | **23.99%** | **49.70%** |

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# 4. Conclusion

On the basis of this limited examination and reworking of the amended model (Scenario 5) it appears that the likely cost effectiveness of pemetrexed for maintenance therapy compared to placebo may be rather better than estimated in the ERG report (where it was not possible to consider probabilistic sensitivity analyses). The ERG considers that the estimated ICER most probably falls within the range £47,000 - £51,000 per QALY gained.