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**VIA EMAIL**

27 August 2010

**Re: Erlotinib monotherapy for the maintenance treatment of non-small cell lung cancer**

Dear Helen,

As requested the results of following analyses are provided within this document:

1. Probabilistic Sensitivity Analysis for:
    a. Stable Disease Patients (Erlotinib Vs BSC)
    b. Stable Disease Squamous Histology Patients (Erlotinib Vs BSC)
    c. Stable Disease Non-Squamous Histology Patients (Erlotinib Vs BSC)
    d. Stable Disease Non-Squamous Histology Patients (Erlotinib Vs Pemetrexed)

Whilst implementing probabilistic functionality into the Stable Disease model it was noted that a minor error had been made in replicating the logical cap placed by the ERG on the early stage of the erlotinib OS curve. A minus sign was mistakenly ommitted within the model which resulted in the cap being effectively redundant. This ommission was corrected prior to the commencement of probabilistic analysis with a resutant £70 increase in the deterministic base-case ICER of erlotinib compared to BSC in patients with stable disease as best response to induction (from £39,936 to £40,007).

Yours sincerely,

[redacted]

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# 1. Probabilistic Sensitivity Analysis

## 1.1. Erlotinib compared to BSC in Patients with Stable Disease as best response to induction

In order to facilitate probabilistic sensitivity analysis and the estimation of a probabilistic mean estimate the ammended SD model submitted in July 2010 was further updated with probabilistic functionality.

Where a model parameter's mean value was subject to uncertainty a distribution relating to that parameters characteristics was fitted around the base-case estimate of that parameter. All uncertain costs (i.e. the cost of BSC in PFS, BSC in PD, adverse events, erlotinib pharmacy preparation, terminal care, cost of 2$^{nd}$ line treatment) were fitted with a gamma-distribtion in order to account for the impossibility of negative costs and to simulate potential high cost outliers. A beta-pert distribution was chosen to simulate the uncertainty of the mean utility values utilised as all base-case values were sufficiently far away from zero to warrant a transformed lognormal distribution uneccessary (as discussed in Briggs et al., 2006). A log-normal distribution was utilised to inform stochastic estimation of the PFS and OS curves. A beta-distribution was utilised to simulate the uncertainty surrounding the relationship between progression free survival and time to complete treatment cessation curves (with a logical limit preventing the number of patients yet to cease treatment increasing over time) and to make the proportion of patients going on to receive second line probabilistic.

Where a standard error was not available to inform the construction of the distributions a standard error was estimated via repeated simulation of the parameter of interest. For each parameter subject to this issue; the 'trace' of the simulated value over 1,000 simulations was graphed in excel and assessed for face validity given the uncertainty believed to surround that parameter's mean. Where the trace was determined to have too wide a spread (i.e. regularly produced unfeasibly high and low estimates of a parameter's mean value) the standard error of the parameter was reduced and where there was found to be too little spread the standard error was increased. For example if in probabilistic analysis a distribution applied to erlotinib pharmacy perperation costs suggested unfeasibly low values (i.e. £0.01) or unfeasibly high values (£400) the standard error surrounding that parameter would be reduced until the values were in a range deemed plausible.

In the case of the PFS and OS parameters (to which PSA was applied to each of the individual components of the 'spline' curves fitted utilising a common random number across both model arms) the above approach was taken with the resultant progression free and overall survival durations graphed as a 'trace' rather than the individual parameters themselves (with the assumed standard errors varied accordingly).

Whilst the estimation of a standard error in this manner is subject to uncertainty (and would for example not be capable of informing a robust value of information analysis) it represents a pragmatic methodology on which to base probabilistic analysis in the absence of the required formally derived standard errors.

5,000 simulations with random sampling from the afformentioned distributions were then carried out within the model in order to simulate a range of potential estimates of the cost-effectiveness of erlotinib compared to BSC. The total costs and QALYs associated with each simulation were then utilised to calculate a mean probabilistic ICER of erlotinib compared to BSC in patients with stable disease as best response to induction.

Each simulation was plotted in Excel© in order create an incremental cost/QALY scatter plot. The incremental cost/QALY results for each simulation were then combined with a range of potential cost-effectiveness thresholds in order to determine the net health benefit of erlotinib in each simulations at each of the thresholds. The proportion of simulations in which erlotinib was cost-effective at each threshold tested (i.e. the proportion of simulations in which net health benefit was positive) was then recorded and utilised to construct a cost-effectiveness acceptability curve (CEAC)).

The probabilistic mean results are provided in table 1 below. The probabilistic mean ICER estimated (£40,816) is just over £800 higher than the corrected deterministic estimate (£40,007).

Table 1. SD Model Probabilistic Mean Results

| *Regimen* | *Cost* | *QALYs* | *Cost per QALY gained* |
|---|---|---|---|
| *Erlotinib* | *£17,486* | *0.8003* | *£40,816* |
| *BSC* | *£9,584* | *0.6067* | |

Figure 1. Stable Disease Model Probabilistic Incremental Cost/QALY Scatter plot

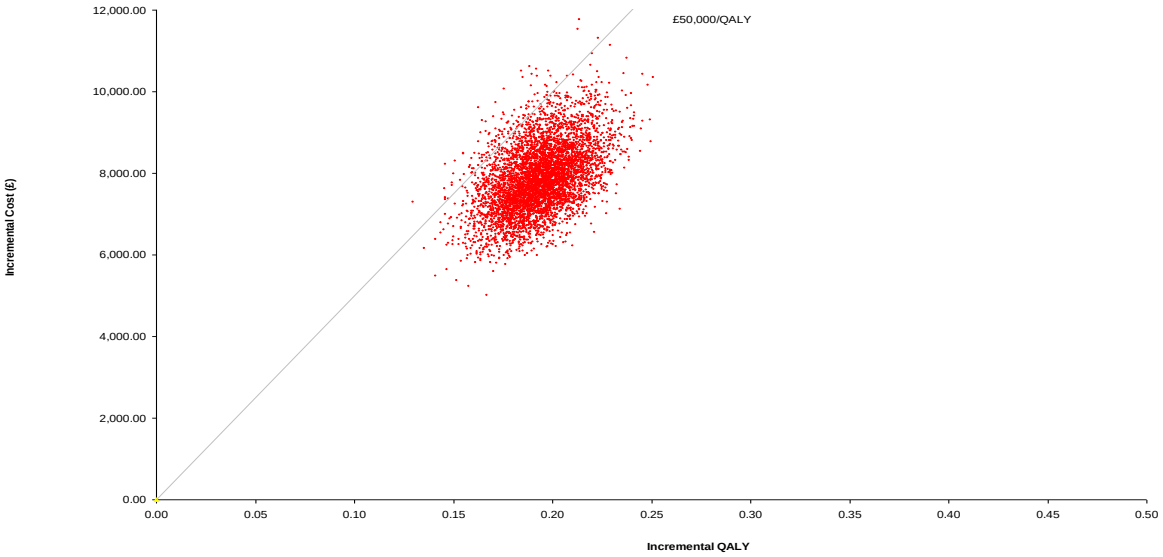
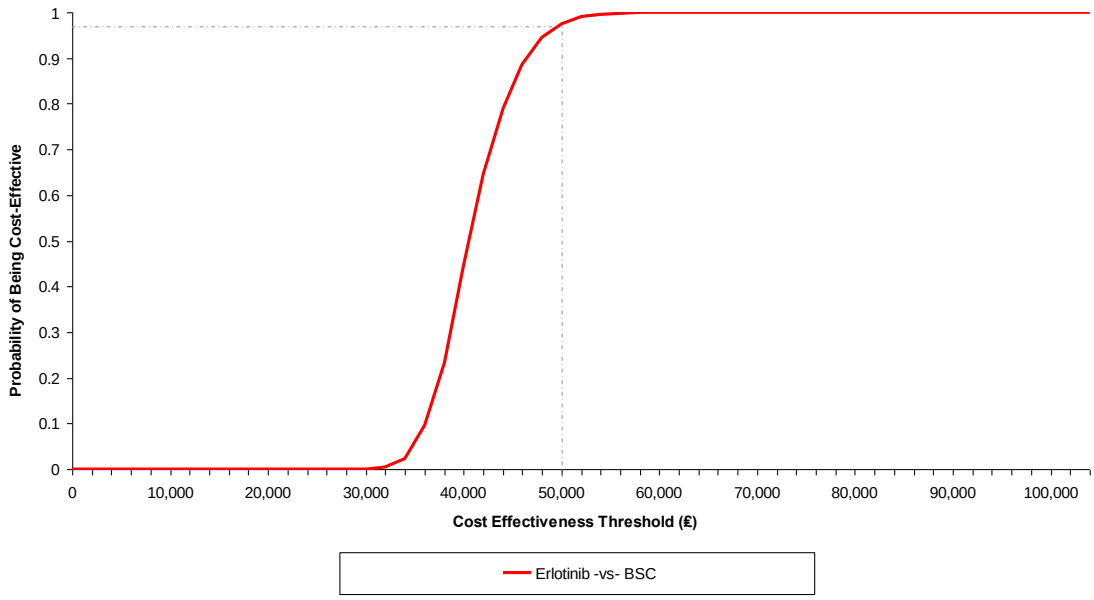


Figure 2. Stable Disease Model Cost Effectiveness Acceptability Curve




The above CEAC demonstrates that at a cost effectiveness threshold of £50,000 per QALY gained, erlotinib would be considered cost-effective in over 97% of simulations with 0% of simulations being deemed cost-effectivene at a threshold of £30,000 per QALY.

The methdology/distributions utilised for the SD model were similarly utilised for the comparisons of erlotinib and BSC in squamous histology stable disease patients and in non-squamous stable disease patients. As the PFS KM curves for the NSQ SD and SQ SD populations were utilised directly in the histological split stable disease models rather than the utilisaion of parametrically fitted curves the PFS curves within the models were made probabilistic via the introduction of a beta distribution to the proportion of patients experiencing an event in a given month.

The results of these further erlotinib vs BSC analyses are provided below.

## 1.2. Erlotinib compared to BSC in Patients with Squamous Histology Stable Disease as best response to induction

Table 2 below demonstrates the probabilistic means cost, QALYs and ICERs produced by the Stable Disease Squamous Histology model. The mean probabilistic ICER produced was just over £700 higher than the deterministic base case ICER (£36,200 rather than £35,491). At a cost-effectiveness threshold of £50,000/QALY erlotinib would be considered 'cost-effective' in this patient population in 99% of the 5,000 simulations conducted (see the CEAC in figure 4).

Table 2. SQ SD Model PSA Mean Results

| *Regimen* | *Cost* | *QALYs* | *Cost per QALY gained* |
|---|---|---|---|
| *Erlotinib* | *£16,621* | *0.721* | *£36,200* |
| *BSC* | *£9,269* | *0.516* | |

Figure 3. Stable Disease Squamous Histology Model Probabilistic Incremental Cost/QALY Scatter plot (erlotinib vs BSC)

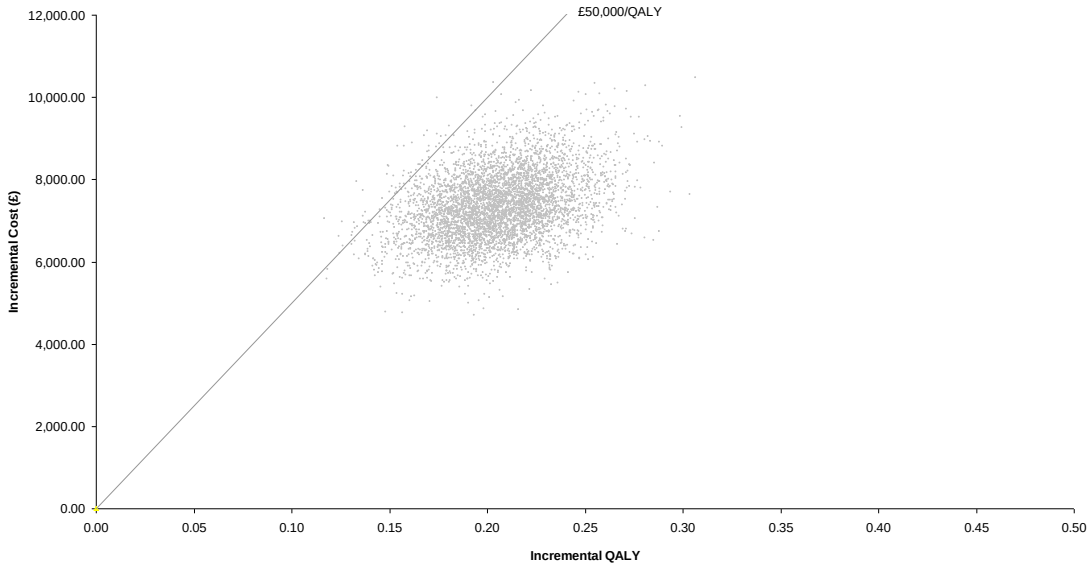
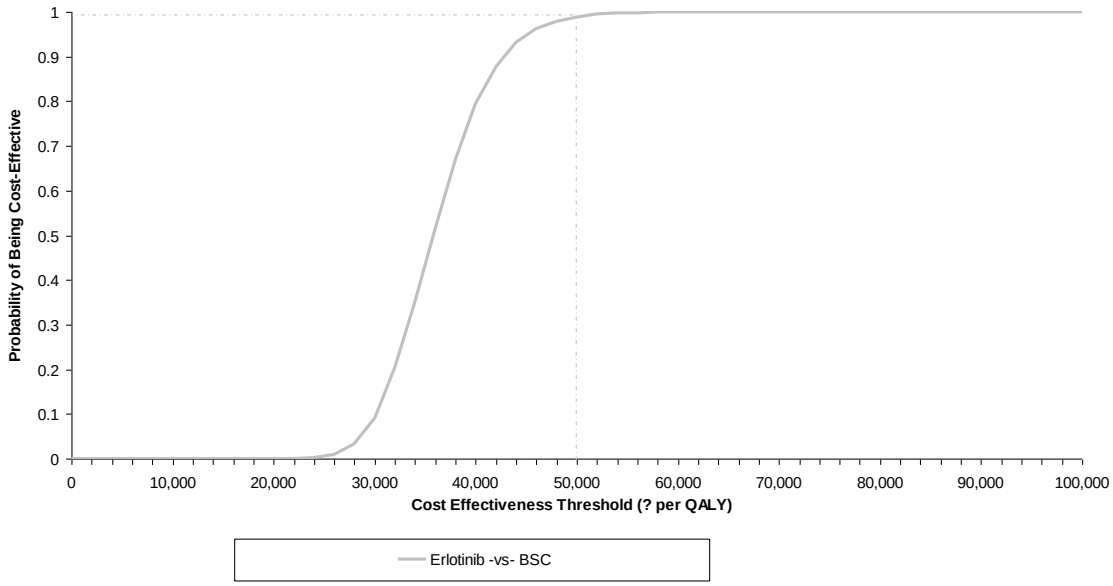


Figure 4. Stable Disease Squamous Histology Model Cost Effectiveness Acceptability Curve




## 1.3. Erlotinib compared to BSC in Patients with Non-Squamous Histology Stable Disease as best response to induction in patients unsuitable for pemetrexed

Table 3. NSQ SD Pemetrexed Unsuitable Model PSA Mean Results

| *Regimen* | *Cost* | *QALYs* | *Cost per QALY gained* |
|---|---|---|---|
| *Erlotinib* | *£17,821* | *0.883* | *£37,479* |
| *BSC* | *£9,760* | *0.668* | |

Figure 5. Stable Disease Non-Squamous Histology Erlotinib vs BSC incremental cost/QALY scatterplot

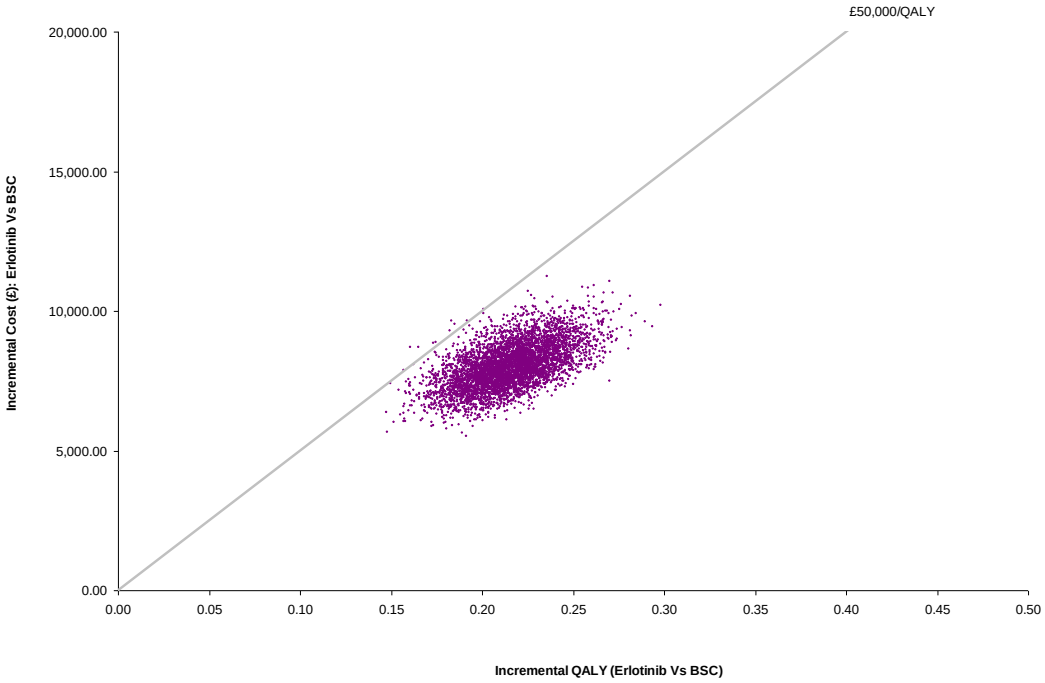
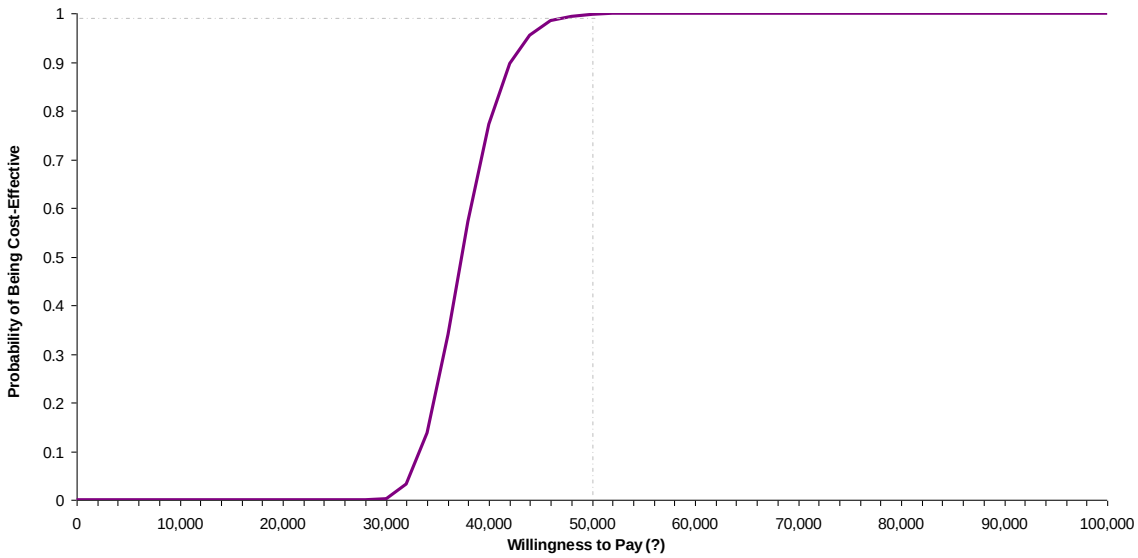



Figure 6. Stable Disease Non-Squamous Histology Erlotinib vs BSC cost effectiveness acceptability curve



### 1.4. Erlotinib compared to BSC in Patients with Non-Squamous Histology Stable Disease as best response to induction in patients unsuitable for pemetrexed

Table 4. NSQ SD Pemetrexed suitable Model PSA Mean Results

| *Regimen* | *Cost* | *QALYs* | *Cost per QALY gained* |
|---|---|---|---|
| *Pemetrexed* | *£26,298* | *0.887* | *£2,561,690* |
| *Erlotinib* | *£17,821* | *0.883* | |

The incremental cost/QALY probabilistic scatterplot below demonstrates clearly that in the 5,000 simulations undertaken erlotinib was considerably cheaper than pemetrexed with approximately the same mean health outcomes achieved given either of the regimens of interest. Whilst the mean probabilistic estimates suggest a marginal (0.004 QALY) advantage to pemetrexed this gain comes at a cost of over £2.5 million per QALY gained.

Figure 7. Stable Disease Non-Squamous Histology Erlotinib vs Pemetrexed incremental cost/QALY scatterplot

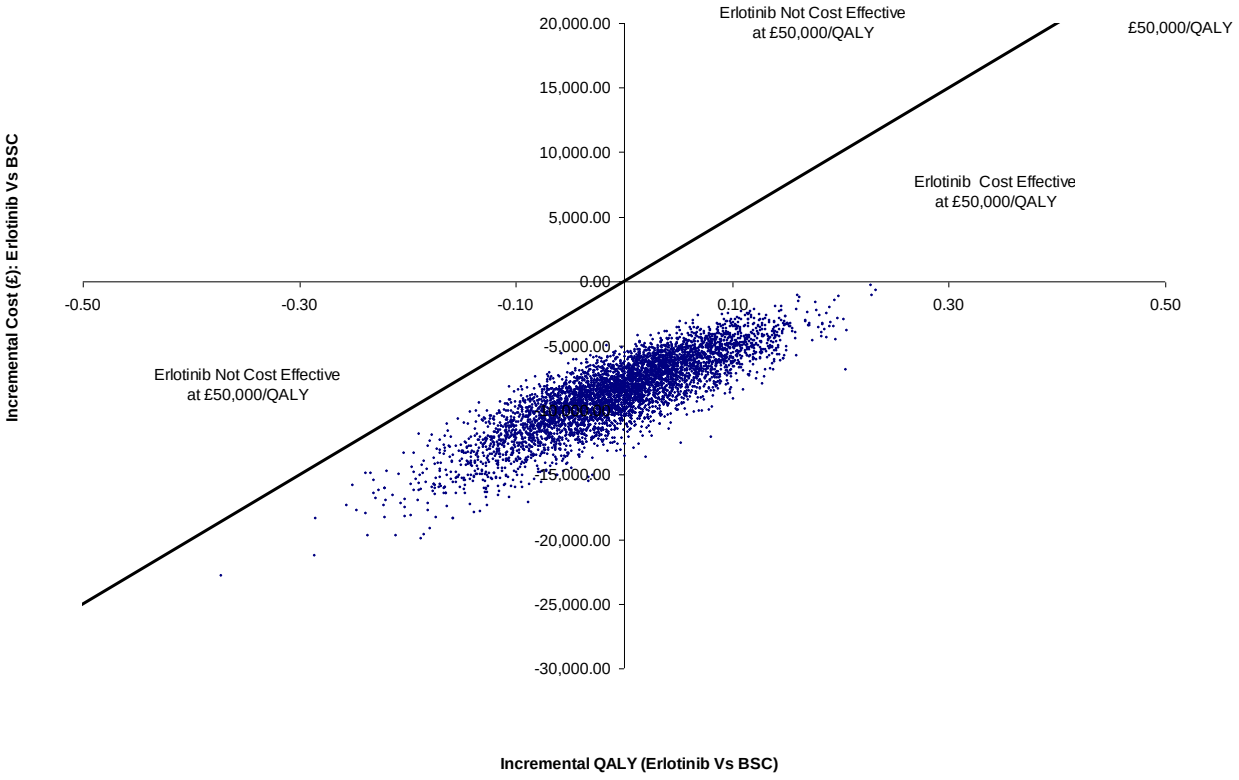



Figure 8. Stable Disease Non-Squamous Histology Erlotinib vs Pemetrexed cost-effectiveness acceptability curve