Gefitinib for the first-line treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC)

ERG Report

LRiG comments on additional information provided by the manufacturer-addendum

Produced by: *Liverpool Reviews and Implementation Group (LRiG)*

Correspondence to: Ms. Rumona Dickson
University of Liverpool
Room B05
Whelan Building
The Quadrangle
Brownlow Hill
Liverpool
L69 3GB
Tel:
Fax:
Email:

Date completed: March 9th 2010

Source of funding: This report was commissioned by the NIHR HTA Programme as 09/59/01

Declared competing interests of authors: None

Modelling problem identified in AZ Gefitinib STA submitted model

Shortly before the NICE Appraisal committee meeting on 4th March 2010, in which responses to the ACD issued for gefitinib as first-line therapy for advanced non-small cell carcinoma, an anomaly was detected in the results generated by the economic model submitted by the manufacturer, which has an important impact on the cost-effectiveness estimates for gefitinib.

This relates specifically to the estimation of the mean progression-free survival (PFS) for EGFR mutation positive patients receiving treatment with gefitinib. Examination of the summary outcomes produced by the model (see below), indicates an unusually high PFS estimate (10.22 months) leading to apparently substantial increases in PFS relative to the gain in overall survival (OS), amounting to about double the OS gain compared to treatment with a gemcitabine doublet. In the comparison with pemetrexed the anomaly is even more extreme, since the model suggests a substantial PFS gain at the same time as a reduction in OS. In the light of experience with several previous appraisals of chemotherapy for NSCLC, these results appear to be unlikely; in previous Appraisal Committee meetings discussions have focussed on the likely proportion of observed PFS gains which might reasonably be expected to translate into OS gains in the range of 0% - 100%, but has not previously been presented with evidence suggesting >200% ratio of effects.

Markov model results

	Mean PFS (mths)	Mean PPS (mths)	Mean OS (mths)
Gefitinib EGFR M+	10.22	13.87	24.08
Gem/carb EGFR M+	5.98	14.88	22.11
Gem/cis EGFR M+	7.09	15.51	22.60
Pem/cis EGFR M+	7.77	16.83	24.60

PFS = Progression Free Survival, PPS = post progression survival, OS = Overall survival

Pairwise comparison of the incremental cost-effectiveness results

	Δ PFS (months)	Δ PPS (months)	Δ OS (months)
Gefitinib EGFR M+ versus:	-	-	-
Gem/carb EGFR M+	4.24	-1.01	1.98
Gem/cis EGFR M+	3.13	-1.64	1.49
Pem/cis EGFR M+	2.45	-2.97	-0.51

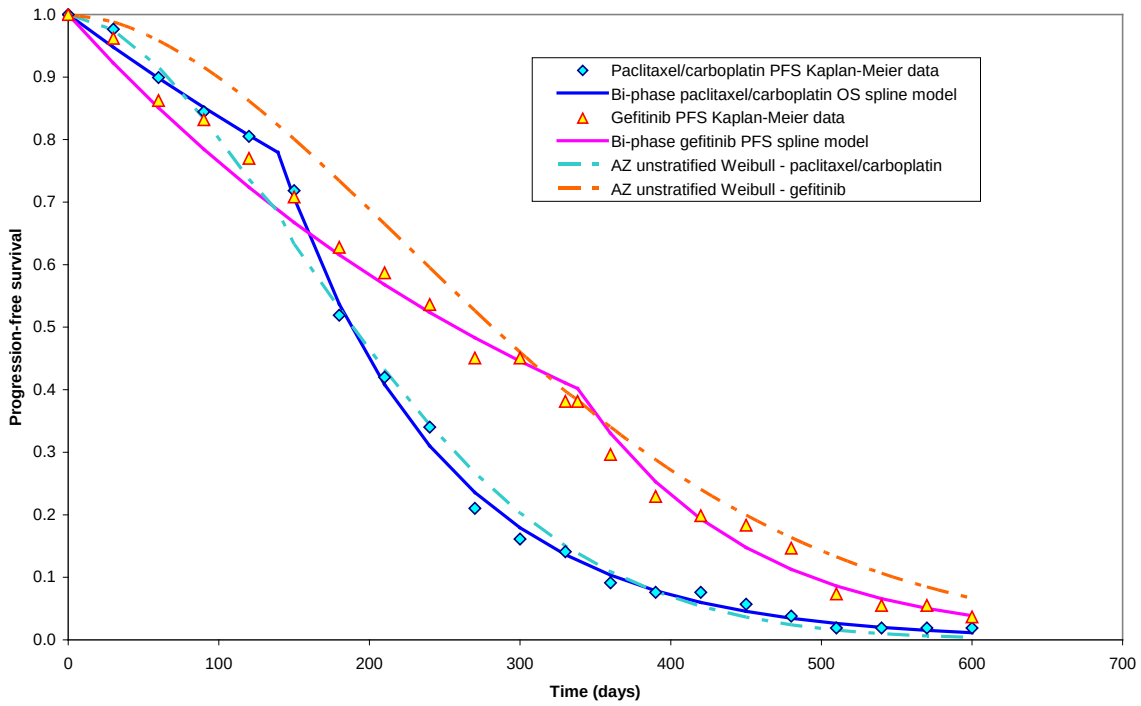
PFS = Progression Free Survival, PPS = post progression survival, OS = Overall survival

Since all these unexpected results would be explained if the estimate of mean PFS in the gefitinib were found to be faulty, the ERG examined the information made available by the manufacturer from the IPASS trial. Using the output from the Kaplan-Meier analysis of PFS in the two treatment arms, the area under the survival curve (AUC) was calculated. This is a very close approximation to the true value of PFS since the trial is very mature, with less than 4% of patients still unprogressed at the end of data collection. This was then compared with the mean PFS estimated by the ERG's own PFS model, and the output from the manufacturer's model.

Mean PFS (months)	Gemcitabine/carboplatin	Gefitinib	Gain in mean PFS
AUC estimate	6.84	8.81	+1.97
ERG model estimate	6.85	8.76	+1.91
Manufacturer's model	5.98	10.22	+4.24

Although the manufacturer's model gives a rather low estimate of PFS in the comparator arm, the major anomaly is clearly the larger overestimation of PFS in the gefitinib arm, leading directly to more than doubling of the gain attributable to gefitinib shown by the IPASS data.

This discrepancy is readily revealed in the chart below. The minor under-estimation in the comparator arm arises in the period 100-200 days where the Weibull model (dashed blue line) in noticeably lower than the observed trial data (blue diamonds). The larger over-estimation in the gefitinib arm is due to a consistent mismatch between Weibull model used by the manufacturer (dashed gold line) and the trial data (yellow/red triangles), which is in favour of gefitinib across the whole trial period. The solid lines show the much closer correspondence of the ERG's own models to the observed data.



There are two possible explanations for these discrepancies: either the imposition of joint estimation of Weibull models (unstratified analysis) has generated these effects directly, or the statistical model has been incorrectly implemented in the Excel decision model. The ERG has not had available the necessary time and resources to determine which explanation are correct.