AstraZeneca UK Ltd
600 Capability Green
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11th March 2010

Dear Dr George

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

Thank you for giving AstraZeneca the opportunity to clarify the situation regarding the anomaly the Evidence Review Group (ERG) detected in the revised economic model, developed in response to the Appraisal Committee's request for further information.

The root cause of the anomaly is a typographical error in the gefitinib EGFR M+ progression-free survival (PFS) Kaplan Meier (KM) data that was included in the background worksheets of the revised economic model.

The AstraZeneca statistician who worked on the issues relating to model selection and fit had identified and corrected this error. The statistical analyses and models presented in the response to the Appraisal Committee meeting are therefore correct and based on the right PFS KM curve data (see page 5 Figure 2).

It is regretable that, due to an oversight and time pressures, this error was not also corrected in the PFS background worksheet that was supplied with the revised economic model. However, the Appraisal Committee should note the PFS KM data played no part in the cost-effectiveness calculations.

A copy of the SAS PFS output for the EGFR mutation positive treatment arms of IPASS has been included as an Appendix to this letter. To correct the gefitinib EGFR M+ PFS data in the model a value of 1 should be inserted between cells F69 and F70 in the "Eqns PFS" worksheet and a value of 0.037 should be inserted at the end of the data column in cell F91. The effect of the missing value was to shift the gefitinib PFS KM data to the left by 30 days. This error contributed to the reduction in the PFS advantage for gefitinib reported by the ERG.

You will note that the mean PFS for geftinib EGFR mutation positive of 10.22 months (310.9 days) estimated using the revised economic model is consistent with the mean of 9.83 months (299.0 days) reported in the SAS KM PFS output (Appendix).

AstraZeneca would like to apologise to NICE, the Appraisal Committee and the ERG for the confusion and additional work this typographical error has caused.

It is unfortunate that time constraints limited the opportunity for the ERG to corroborate the gefitinib PFS KM data in the revised economic model before the additional analyses were conducted and presented to the Appraisal Committee. This could have been done by either contacting AstraZeneca directly, reviewing the PFS

KM curves in the NEJM IPASS publication or comparing the spline models fitted to these data to those fitted to the PFS data in the original ERG report.

I look forward to contacting you on Monday to discuss the way forward.

Yours faithfully

[redacted]

APPENDIX

IRESSA, IPASS study

SAS output for progression-free survival for the gefitinib EGFR M+ subgroup

The LIFETEST Procedure

Stratum 2: TRTRAND = Gefitinib

Product-Limit Survival Estimates

PROGDAYS	Survival	Failure	Survival Standard Error	Number Failed	Number Left
0.000	1.0000	0	0	0	132
40.000	0.9924	0.00758	0.00755	1	131
41.000	0.9848	0.0152	0.0106	2	130
42.000	.	.	.	3	129
42.000	0.9697	0.0303	0.0149	4	128
42.000*	.	.	.	4	127
43.000	0.9621	0.0379	0.0166	5	126
65.000	0.9544	0.0456	0.0182	6	125
70.000	0.9468	0.0532	0.0196	7	124
75.000	.	.	.	8	123
75.000	0.9315	0.0685	0.0220	9	122
78.000	0.9239	0.0761	0.0231	10	121
80.000	.	.	.	11	120
80.000	0.9086	0.0914	0.0251	12	119
81.000	0.9010	0.0990	0.0261	13	118
81.000*	.	.	.	13	117
82.000	0.8933	0.1067	0.0270	14	116
83.000	0.8856	0.1144	0.0278	15	115
84.000	.	.	.	16	114
84.000	0.8702	0.1298	0.0294	17	113
85.000	0.8625	0.1375	0.0301	18	112
108.000	0.8548	0.1452	0.0308	19	111
113.000	0.8471	0.1529	0.0315	20	110
114.000	0.8394	0.1606	0.0321	21	109
120.000	0.8317	0.1683	0.0327	22	108
122.000	.	.	.	23	107
122.000	0.8163	0.1837	0.0339	24	106
126.000	.	.	.	25	105
126.000	.	.	.	26	104
126.000	.	.	.	27	103
126.000	0.7855	0.2145	0.0359	28	102
138.000	0.7778	0.2222	0.0364	29	101
150.000	0.7701	0.2299	0.0369	30	100
164.000	0.7624	0.2376	0.0373	31	99
168.000	.	.	.	32	98
168.000	0.7470	0.2530	0.0381	33	97
169.000	.	.	.	34	96
169.000	0.7316	0.2684	0.0388	35	95
170.000	0.7239	0.2761	0.0392	36	94

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Product-Limit Survival Estimates

PROGDAYS	Survival	Failure	Survival Standard Error	Number Failed	Number Left
172.000	0.7162	0.2838	0.0395	37	93
173.000*	.	.	.	37	92
175.000	0.7084	0.2916	0.0398	38	91
181.000	0.7006	0.2994	0.0402	39	90
199.000	0.6928	0.3072	0.0405	40	89
202.000*	.	.	.	40	88
203.000*	.	.	.	40	87
203.000*	.	.	.	40	86
204.000	0.6848	0.3152	0.0408	41	85
204.000*	.	.	.	41	84
206.000	.	.	.	42	83
206.000	0.6684	0.3316	0.0414	43	82
207.000	0.6603	0.3397	0.0417	44	81
209.000	.	.	.	45	80
209.000	.	.	.	46	79
209.000	0.6358	0.3642	0.0425	47	78
210.000	0.6277	0.3723	0.0427	48	77
211.000	.	.	.	49	76
211.000	.	.	.	50	75
211.000	0.6032	0.3968	0.0433	51	74
213.000	0.5951	0.4049	0.0435	52	73
213.000*	.	.	.	52	72
217.000	0.5868	0.4132	0.0437	53	71
245.000	0.5786	0.4214	0.0438	54	70
247.000	0.5703	0.4297	0.0440	55	69
249.000	0.5620	0.4380	0.0441	56	68
249.000*	.	.	.	56	67
249.000*	.	.	.	56	66
252.000	.	.	.	57	65
252.000	0.5450	0.4550	0.0444	58	64
252.000*	.	.	.	58	63
256.000	0.5363	0.4637	0.0445	59	62
257.000*	.	.	.	59	61
258.000*	.	.	.	59	60
259.000*	.	.	.	59	59
276.000	0.5273	0.4727	0.0447	60	58
284.000*	.	.	.	60	57
286.000	0.5180	0.4820	0.0448	61	56
286.000*	.	.	.	61	55

The LIFETEST Procedure

Stratum 2: TRTRAND = Gefitinib

Product-Limit Survival Estimates

PROGDAYS	Survival	Failure	Survival Standard Error	Number Failed	Number Left
287.000	0.5086	0.4914	0.0450	62	54
288.000	0.4992	0.5008	0.0451	63	53
292.000*	.	.	.	63	52
293.000	.	.	.	64	51
293.000	0.4800	0.5200	0.0454	65	50
293.000*	.	.	.	65	49
294.000	.	.	.	66	48
294.000	0.4604	0.5396	0.0456	67	47
295.000	0.4506	0.5494	0.0457	68	46
330.000*	.	.	.	68	45
330.000*	.	.	.	68	44
331.000	0.4403	0.5597	0.0458	69	43
331.000*	.	.	.	69	42
332.000*	.	.	.	69	41
332.000*	.	.	.	69	40
335.000*	.	.	.	69	39
336.000*	.	.	.	69	38
337.000	0.4288	0.5712	0.0460	70	37
339.000	0.4172	0.5828	0.0462	71	36
340.000*	.	.	.	71	35
341.000	0.4052	0.5948	0.0464	72	34
348.000	0.3933	0.6067	0.0465	73	33
349.000	0.3814	0.6186	0.0466	74	32
365.000	0.3695	0.6305	0.0467	75	31
369.000	0.3576	0.6424	0.0467	76	30
371.000	.	.	.	77	29
371.000	0.3337	0.6663	0.0465	78	28
371.000*	.	.	.	78	27
372.000	0.3214	0.6786	0.0464	79	26
375.000	0.3090	0.6910	0.0462	80	25
379.000	0.2966	0.7034	0.0460	81	24
382.000*	.	.	.	81	23
402.000*	.	.	.	81	22
413.000	.	.	.	82	21
413.000	0.2697	0.7303	0.0456	83	20
417.000	0.2562	0.7438	0.0453	84	19
418.000	0.2427	0.7573	0.0448	85	18
420.000	0.2292	0.7708	0.0443	86	17
420.000*	.	.	.	86	16

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Product-Limit Survival Estimates

PROGDAYS	Survival	Failure	Survival Standard Error	Number Failed	Number Left
420.000*	.	.	.	86	15
423.000	0.2139	0.7861	0.0439	87	14
424.000	0.1987	0.8013	0.0434	88	13
461.000	0.1834	0.8166	0.0426	89	12
477.000*	.	.	.	89	11
500.000*	.	.	.	89	10
508.000	.	.	.	90	9
508.000	0.1467	0.8533	0.0413	91	8
511.000	0.1284	0.8716	0.0400	92	7
515.000	0.1100	0.8900	0.0382	93	6
539.000	0.0917	0.9083	0.0360	94	5
540.000	0.0734	0.9266	0.0331	95	4
546.000	0.0550	0.9450	0.0295	96	3
629.000	0.0367	0.9633	0.0247	97	2
636.000*	.	.	.	97	1
670.000*	.	.	.	97	0

NOTE: The marked survival times are censored observations.

Summary Statistics for Time Variable PROGDAYS

Quartile Estimates

Percent	Point Estimate	95% Confidence Interval [Lower	Upper)
75	418.000	371.000	508.000
50	288.000	245.000	341.000
25	168.000	122.000	206.000

Mean	Standard Error
298.981	15.516

NOTE: The mean survival time and its standard error were underestimated because the largest observation was censored and the estimation was restricted to the largest event time.