Further Clarification to Roche of ERG model amendments and other analyses undertaken in relation to Single Technology Appraisal of Erlotinib for NSCLC maintenance therapy

ERG modifications to Roche model

Modification F: Cost of 2nd line chemotherapy

Roche have pointed out a potential error in the implementation of this ERG modification. The ERG have investigated this matter and can confirm the error, and thank Roche for pointing this out. Implementing this alteration leads to a small reduction in the costs of 2nd line chemotherapy for both arms of the evaluation, and a minor reduction in the estimated ICER as a result. An updated version of Table 6-2 from the ERG report, taking account of this correction, is shown below. For the revised base case, the ICER remains above £59,000 per QALY gained.

Modifications D & E: ERG modelling of PFS & OS

The ERG approach to modelling survival was based on the general observation that in both trial arms and for both PFS and OS the cumulative hazard profile indicated a steady (i.e. linear) long-term trend preceded by a transient initial effect (high risk in PFS and low risk in OS). This is consistent with long-term trends observed in several previous advanced NSCLC NICE appraisals undertaken by this ERG. To achieve a good fit to the observed data whilst preserving the long-term trend, a decision was made to apply a 2-part model (transient + long-term) rather than conventional statistical functions for reasons discussed in the ERG report. In the case of OS, a single formulation proved appropriate at all time with the only modification being a constraint imposed in the first few weeks to avoid survival values greater than 100% due to an effective initial death-free period (probably originating I from the protocol exclusion criteria).

For PFS, the changes in event risk are more rapid and it proved necessary to adopt a 2-phase spline model to achieve an acceptable fit to the trial data.

In phase 1 the formulation described above for OS was used, involving a short-term (transient) component which diminishes steadily with time and a long-term fixed (exponential) component. In phase 2 a simple parsimonious exponential function is employed. The timing of the spline point, and the assumption of long-term constant risk may be tested jointly by fitting a regression model including both linear and non-linear terms to data points beyond a given time point. As the spline point is increased the significance of the non-linear term diminishes, while the value of the linear term converges to a stable value. An optimal range can be defined within which the linearity assumption is valid, the estimated linear term is stable, but the uncertainty in the estimate has not increased sufficiently (with reduced data points) to render meaningful estimation infeasible. This analysis suggests an optimal range of 10-12 months for the SATURN data, and 12 months was selected as convenient for modelling.

Model-fitting was carried out by OLS minimization for the model compared to Kaplan-Meier cumulative hazard data. The formulae employed and estimated parameter values are as follows:

Phase 1

Cumulative hazard = A * { 1 – exp(- B * months) } + (C * months)

Phase 2 (PFS only)

Cumulative hazard = P + Q * months

	A	B	C	P	Q
PFS erlotinib	0.432279	0.225179	0.150780	0.921091	0.109304
PFS placebo	12.619596	0.026037	0.000000	2.110823	0.098147
OS erlotinib	-0.109676	1.109700	0.064724	N/A	N/A
OS placebo	-0.245697	0.368852	0.093994	N/A	N/A

The estimated survival is given as exp (- cumulative hazard). The fitted models and K-M data points are shown graphically below.

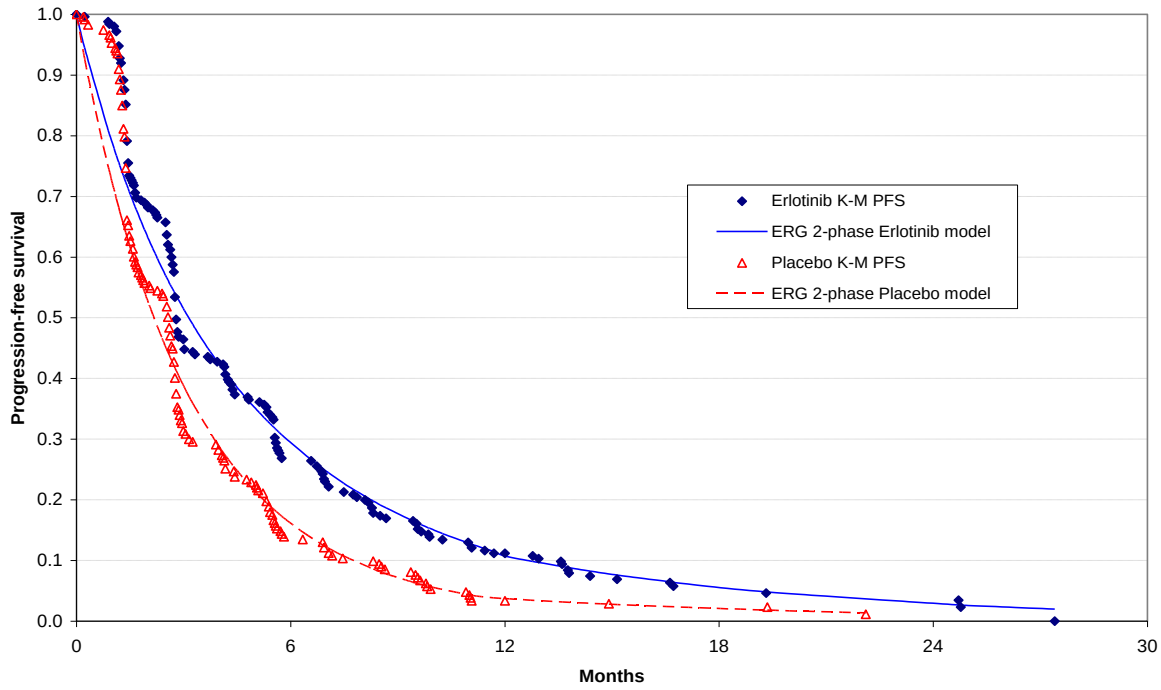
Table **Error! No text of specified style in document.**-1 (Modified) Effect of corrections/amendments made by the ERG to submitted SD model for the base case analysis

Stable disease population

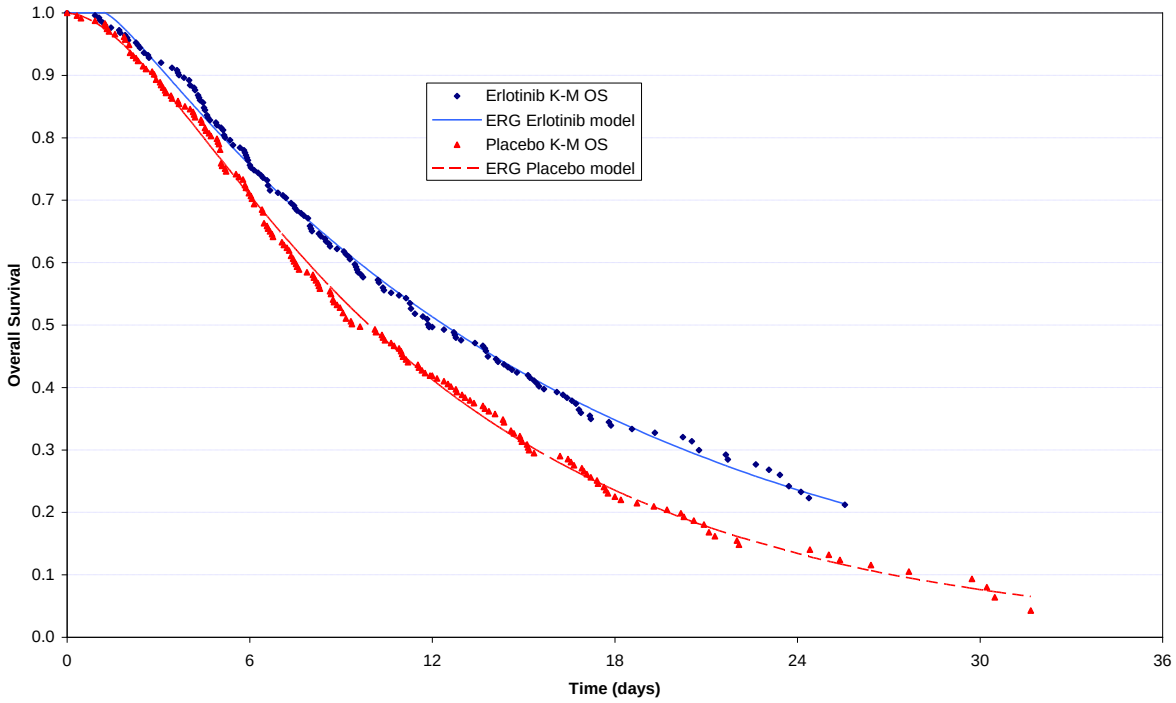
Erlotinib vs placebo

	Costs per patient			QALYs per patient				Difference from initial base case		
	Erlotinib	Placebo	Increment	Erlotinib	Placebo	Increment	ICER	Inc cost	Inc QALY	ICER
Manufacturer base case	**£24,129**	**£16,382**	**£7,747**	**0.7497**	**0.5875**	**0.1623**	**£47,743**	-	-	-
Extended time horizon	£25,001	£16,771	£8,230	0.7739	0.5972	0.1768	£46,557	£483	0.0145	-£1,186
Discounting logic corrected	£24,266	£16,476	£7,790	0.7538	0.5900	0.1638	£47,559	£43	0.0015	-£184
Cost of erlotinib corrected	£26,119	£16,382	£9,738	0.7497	0.5875	0.1623	£60,012	£1,991	0.0000	£12,269
Cost of 2nd line CTX corrected	£25,288	£16,543	£8,745	0.7497	0.5875	0.1623	£53,895	£998	0.0000	£6,152
Unit costs updated	£25,918	£17,872	£8,046	0.7497	0.5875	0.1623	£49,584	£299	0.0000	£1,842
Revised utility values	£24,129	£16,382	£7,747	0.7998	0.6284	0.1714	£45,197	£0	0.0091	-£2,545
ERG PFS model	£23,954	£16,460	£7,493	0.7505	0.5863	0.1642	£45,649	-£253	0.0019	-£2,094
ERG OS model	£23,803	£15,672	£8,132	0.7407	0.5698	0.1709	£47,574	£385	0.0087	-£169
Revised base case	**£29,203**	**£17,666**	**£11,536**	**0.8075**	**0.6120**	**0.1955**	**£59,017**	**£3,790**	**0.0332**	**£11,274**

Values altered by logic correction are shaded



ERG 2-phase spline PFS models fitted to SATURN Kaplan-Meier data



ERG OS models fitted to SATURN Kaplan-Meier data

ERG preferred estimates of long-term survival

Here we provide more details of the derivation of the lifetime estimates of survival shown in Tables 5-11, 5-12 and 5-13 of the ERG report, which were estimated primarily to assess the extent of likely survival gain for use in considering the NICE 'end of life' criteria (i.e. gain of greater than 3 months). Although the full models developed by the ERG appeared to show satisfactory correspondence to the trial data as a whole, it was evident that the protocol-driven periodicity during the first year (especially in PFS) could not be reproduced accurately by any model. In general the observed data should have primacy over any derived modelling, we decided that the most reliable estimates would result from direct use of the Kaplan-Meier area-under-curve values for the first twelve months, adding our model projections only from 12 months onwards, thus limiting any uncertainty due to the choice of projective model.

By contrast, the amendments made to the submitted model involve direct substitution of the full ERG survival estimates, as this required the minimum of recoding and avoided any restructuring of the submitted model. Full implementation of hybrid K-M/projection estimates within the model was deemed infeasible within the time constraints of the STA process, and probably beyond the ERG's remit.

Estimates based on PFS and OS models

Estimates of survival and survival gain based on projective model beyond 12 months are shown below. The lifetime projection was calculated as the modelled proportion of patients still at risk at 12 months divided by the relevant long-term exponential parameter shown above (C or Q). In this case post-progression survival is only available indirectly as the difference between OS and PFS.

		PFS (lifetime)		**OS (lifetime)**		**PPS (= OS – PFS)**	
	Estimate	**days**	**years**	**days**	**years**	**days**	**years**
Erlotinib	AUC	139.70		279.65			
	Projection	29.86		241.36			
	Total	**169.56**	**0.4642**	**521.01**	**1.4264**	351.45	0.9622
Placebo	AUC	102.35		259.99			
	Projection	11.57		133.62			
	Total	**113.92**	**0.3119**	**393.61**	**1.0776**	279.69	0.7658
Gain	**Total**	**55.64**	**0.1532**	**127.40**	**0.3488**	71.75	0.1964

Estimates based on PFS and PPS models

Details provided by Roche relating to PPS separately for patients who did and did not receive second line chemotherapy allowed the ERG to fit models suitable for projection. In this case, for all four groups the Weibull function proved to be the most appropriate since the hazard either increased steadily (for those having further CTX) or decreasing steadily (for those not receiving further CTX) without evidence of long-term stability. The parameter values of the fitted models are as follows:

Subgroup	alpha	beta
Erlotinib – 2nd line CTX	1.21869	449.633
Erlotinib – no 2nd line CTX	0.84094	154.965
Placebo – 2nd line CTX	1.37308	368.580
Placebo – no 2nd line CTX	0.84175	122.226

where Cumulative hazard = (days / alpha) ^ beta

The results of combining the PFS and PPS estimates are shown below:

		PFS (lifetime)		**PPS (lifetime)**		**OS (= PFS + PPS)**	
	Estimate	**days**	**years**	**days**	**years**	**days**	**years**
Erlotinib – 2nd line CTX [redacted]	AUC			267.33			
	Projection			157.21			
	Total			**424.54**	**1.1623**		
Erlotinib – No 2nd line CTX [redacted]	AUC			140.56			
	Projection			28.97			
	Total			**169.53**	**0.4641**		
Erlotinib overall	AUC	139.70		232.66			
	Projection	29.86		122.13			
	Total	**169.56**	**0.4642**	**354.79**	**0.9714**	**524.36**	**1.4356**
Placebo – 2nd line CTX [redacted]	AUC			250.79			
	Projection			85.85			
	Total			**336.64**	**0.9217**		
Placebo – No 2nd line CTX [redacted]	AUC			121.04			
	Projection			14.86			
	Total			**135.90**	**0.3721**		
Placebo overall	AUC	102.35		216.58			
	Projection	11.57		67.14			
	Total	**113.92**	**0.3119**	**283.72**	**0.7768**	**397.64**	**1.0887**
Gain	**Total**	**55.64**	**0.1523**	**71.07**	**0.1946**	**126.72**	**0.3469**

Post-progression values were estimated as before by a combination of AUC to 12 months and estimated lifetime projection thereafter. The relative proportions of patients within each treatment group who did/did not receive further CTX ([redacted] for erlotinib and [redacted] for placebo) were used to weight the separate estimates to obtained overall estimates for each arm of the trial. Addition of PFS and PPS then provided a second estimate for OS, which proved to be very similar to that based on PFS and OS data.

LRiG, University of Liverpool 13th May 2010