LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Osimertinib for treating locally advanced or metastatic EGFR T790M mutation-positive non-small cell lung cancer [ID1559]

Cancer Drugs Fund update of TA416

ERRATUM v2

This report was commissioned by the NIHR Systematic Reviews Programme as project number 129027

Completed 18 December 2019

CONTAINS **********

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

ERRATUM

The ERG identified an error in their amendments to the company model and accompanying instructions. In the LUME-Lung 1 utility values scenario, the utility value for the post-progression health state for platinum doublet chemotherapy (PDC) was set to 0.67, instead of 0.64.

The ERG has corrected this error and has included p10, p35, pp37-38, pp51-52 from the ERG report with the amendments in red text.

1.1 Summary of key issues in cost effectiveness evidence

Two models are included in the CDF Review CS (Model A and Model B). The basic structure of Models A and B and the model submitted as part of the TA416 CS were the same. Model A differed from that submitted as part of the TA416 CS only in that it included estimates of OS, PFS and TTD from the most up to date pooled AURAext/2 data. The key differences between Model A and Model B were that Model A was populated with OS, PFS and TTD estimates from the most up to date pooled AURAext/2 dataset whilst Model B was populated with OS, PFS and TTD estimates from the most up to date AURA3 trial data.

During TA416 the company concluded that the most likely utility estimates fell between optimistic values used by the company (derived from data collected during the AURA2 trial) and less optimistic values derived from data collected during the LUME-Lung 1 trial. Health-related quality of life data were collected as part of the AURA3 trial. Utility values derived from these data are very similar to the AURA2 values.

1.2 Summary of exploratory and sensitivity analysis undertaken by the ERG

Following discussion with the NICE technical team, the ERG created a hybrid model (Model A/B) which meets the ToE for this review better than either Model A or Model B. Model A/B has been constructed by replacing the OS, PFS and TTD data in Model A with OS, PFS, TTD data from the AURA3 trial (Model B). Using the CAA price for treatment with osimertinib and list prices for pemetrexed and cisplatin, the ERG has made four amendments to Model A/B, namely revised OS, PFS and TTD estimates (generated using AURA3 trial data) and use of the LUME-Lung 1 trial utility values. The ERG has also presented results from two scenarios:

- Scenario 1: changes to OS, PFS and TTD
- Scenario 2: changes to OS, PFS, TTD and using LUME-Lung 1 trial[1] utility values.

Model A/B base case results and results from these two scenarios are provided in the table below.

Exploratory analyses undertaken by the ERG

ERG amendment/scenario	Incremental			*ICER*	
	Cost	Life years	QALYs	£/QALY	Change from base case
A. Model A/B base case	£68,792	1.030	0.817	£84,209	
Scenario 1: R1)+R2)+R3)	£66,011	1.106	0.897	£73,565	-£10,644
Scenario 2: R1)+R2)+R3)+R4)	£66,011	1.106	0.755	£87,380	£3,171

ERG=Evidence Review Group; ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year

Table 1 Cost effectiveness analysis (Model A/B)

Treatment	Total cost	Total LYG	Total QALYs	Incremental			ICER per QALY gained
				Cost	LYG	QALYs	
Osimertinib*	£92,560	3.082	2.284				
PDC	£23,769	2.052	1.468	£68,792	1.030	0.817	£84,209

ICER=incremental cost effectiveness ratio; LYG=life year gained; PAS=patient access scheme; QALY=quality adjusted life year
* Confidential discounted prices used to estimate the cost of treatment

Table 2 Mean PFS, TTD and OS in Model A/B

Treatment	PFS months (mean)	TTD months (mean)	OS months (mean)
Osimertinib	11.531	[redacted]	36.980
PDC	5.704	[redacted]	24.624

PDC=platinum doublet chemotherapy; PFS=progression-free survival; OS=overall survival; TTD=time to treatment continuation

1.3 Exploratory and sensitivity analyses undertaken by the ERG

1.3.1 Utility values

The utility estimates generated from data collected during the AURA3 trial are very similar to those generated from data collected during the AURA2 trial. The ERG TA416 report[11] includes alternative cost effectiveness results generated using utility values from the LUME-Lung 1 trial[1] (pre-progression=0.67, post-progression=0.64). The NICE AC concluded that the true utility values associated with the pre-progression and post-progression health states are likely to lie somewhere between the estimates from the AURA2 trial and the LUME-Lung 1 trial.[1] The ERG has, therefore, also generated cost effectiveness results using LUME-Lung 1 trial[1] utility values in Model A/B.

Compared with Model A/B base case, this leads to a (0.12) decrease in incremental QALYs (from 0.82 to 0.70) and no change to incremental costs, increasing the ICER per QALY gained for the comparison of osimertinib versus PDC from £84,209 to £98,530.

1.3.2 Survival and treatment costs

For OS, PFS and TTD the company has estimated parametric curves based upon AURA3 trial data. The ERG preferred approach is to use K-M data from trials directly followed by extrapolation of the K-M data after the point at which the K-M data become heavily censored and unreliable. In choosing distributions for extrapolation, cumulative hazard plots of AURA3 trial K-M data for OS, PFS and TTD for osimertinib and PDC were built (cumulative hazard plots are provided in Appendix C). In each case, a constant hazard trend (i.e., a straight line) became evident before the end of the K-M data and so it was appropriate to extrapolate the available K-M data in all cases using exponential functions.

2 IMPACT ON COST EFFECTIVENESS OF ERG ADDITIONAL ANALYSES

A summary of the impact of the ERG's amendments to Model A/B on the cost effectiveness of osimertinib versus PDC for the treatment of patients with advanced or metastatic EGFR T790M mutation-positive disease in the second-line setting after failure of an EGFR-TKI is provided in Table 13.

Using the CAA[2] price for treatment with osimertinib and list prices for pemetrexed and cisplatin, the ERG has made four amendments to Model A/B as detailed in Section 3.2. The ERG presents the results of each amendment individually in Table 13. The ERG also presents the results of two scenarios:

- Scenario 1: changes to OS, PFS and TTD
- Scenario 2: changes to OS, PFS, TTD and using LUME-Lung 1 trial[1] utility values.

Details of all Microsoft Excel revisions carried out by the ERG to Model A/B are presented in Appendix D of this ERG report.

2.1 Conclusions of the cost effectiveness section

The company's submitted ICERs per QALY gained (CDF Review CS, Table 17) ranged from £68,015 to £104,536.

The ERG's hybrid Model A/B yields a base case ICER per QALY gained of £84,209. Compared with PDC, Model A/B base case cost effectiveness results show that treatment with osimertinib generates more QALYs but at an additional cost.

Using Model A/B as the base case, the ERG's revised ICERs per QALY gained range between £73,565 and £98,530. When all of the ERG amendments are combined, the ICER per QALY gained is £87,380.

Table 3 ERG adjustments to Model A/B base case: osimertinib (Commercial Access Agreement price) versus PDC (list prices)

ERG amendment/scenario	Osimertinib			PDC			Incremental			*ICER*	
	Cost	Life years	QALYs	Cost	Life years	QALYs	Cost	Life years	QALYs	£/QALY	Change from base case
A. Model A/B base case	£92,560	3.082	2.284	£23,769	2.052	1.468	£68,792	1.030	0.817	£84,209	
R1) ERG modelling of OS	£91,003	2.808	2.089	£21,348	1.702	1.217	£69,655	1.106	0.871	£79,942	-£4,267
R2) ERG modelling of PFS	£91,130	3.082	2.311	£23,761	2.052	1.468	£67,369	1.030	0.843	£79,925	-£4,284
R3) ERG modelling of TTD	£90,321	3.082	2.284	£24,027	2.052	1.468	£66,295	1.030	0.817	£81,153	-£3,057
R4) LUME-Lung 1 utility values	£92,560	3.082	1.996	£23,769	2.052	1.298	£68,792	1.030	0.698	£98,530	£14,320
Scenario 1: R1)+R2)+R3)	£87,585	2.808	2.115	£21,575	1.702	1.218	£66,011	1.106	0.897	£73,565	-£10,644
Scenario 2: R1)+R2)+R3)+R4)	£87,585	2.808	1.830	£21,575	1.702	1.075	£66,011	1.106	0.755	£87,380	£3,171

ERG=Evidence Review Group; ICER=incremental cost effectiveness ratio; OS=overall survival; PFS=progression-free survival; QALYs=quality adjusted life years; TTD=time to treatment discontinuation

ERG revision number and description	Modification name	Sheet	Cells	Modified formulae
R4) Use ERG suggested utility values	Mod_A	CountryData Add modification to three utility options in this sheet	G680	Use ERG suggested utility value for pre-progression =IF(mod_A=1,0.67,0.833)
			H680	Use ERG suggested utility value for pre-progression =IF(mod_A=1,0.67,0.891)
			I680	Use ERG suggested utility value for pre-progression =IF(mod_A=1,0.67,0.831)
			G681	Use ERG suggested utility value for pre-progression for stable disease also =IF(mod_A=1,0.67,0.753)
			H681	Use ERG suggested utility value for pre-progression for stable disease also =IF(mod_A=1,0.67,0.825)
			I681	Use ERG suggested utility value for pre-progression for stable disease also =IF(mod_A=1,0.67,0.751)
			G682	Use ERG suggested utility value for post-progression =IF(mod_A=1,0.64,((0.751+0.679)/2))
			H682	Use ERG suggested utility value for post-progression =IF(mod_A=1,0.64,0.821)
			I682	Use ERG suggested utility value for post-progression =IF(mod_A=1,0.64,((0.751+0.679)/2))
			G688	Use ERG suggested utility value for pre-progression =IF(Mod_A=1,0.67,0.833)
			H688	Use ERG suggested utility value for pre-progression =IF(Mod_A=1,0.67,0.891)
			I688	Use ERG suggested utility value for pre-progression =IF(Mod_A=1,0.67,0.831)
			G689	Use ERG suggested utility value for pre-progression for stable disease also =IF(Mod_A=1,0.67,0.753)
			H689	Use ERG suggested utility value for pre-progression for stable disease also =IF(Mod_A=1,0.67,0.825)
			I689	Use ERG suggested utility value for pre-progression for stable disease also =IF(Mod_A=1,0.67,0.751)
			G690	Use ERG suggested utility value for post-progression =IF(Mod_A=1,0.0.64,((0.751+0.679)/2))

ERG revision number and description	Modification name	Sheet	Cells	Modified formulae
			H690	Use ERG suggested utility value for post-progression =IF(Mod_A=1,0. 0.64,0.821)
			I690	Use ERG suggested utility value for post-progression =IF(Mod_A=1,0. 0.64,((0.751+0.679)/2))
R2) Use ERG re-modelled PFS data from AURA3	Mod_B	ResSurv_B	E22 copy down to E802	Use AURA3 ERG re-modelled PFS for osimertinib =IF(Mod_B=1,'ERG - PFS'!A4,IF(OR(analysis_nr=1,INDEX(surv_model_nr,E$13)=1,SUM(E$17:E$20)=0),0,Survival_func(E$16:E$20,$C22)))
			G22 copy down to G802	Use AURA3 ERG re-modelled PFS for PDC =IF(Mod_B=1,'ERG - PFS'!B4,IF(OR(analysis_nr=1,INDEX(surv_model_nr,G$13)=1,SUM(G$17:G$20)=0),0,Survival_func(G$16:G$20,$C22)))
R1) Use ERG re-modelled OS data from AURA3	Mod_D	ResSurv_B	F22 copy down to F802	Use AURA3 ERG re-modelled OS for osimertinib =IF(Mod_D=1,'ERG - OS'!A3,IF(OR(analysis_nr=1,INDEX(surv_model_nr,F$13)=1,SUM(F$17:F$20)=0),0,CHOOSE(surv_param_model,Survival_func(F$16:F$20,$C22),ClinicalData_B!DV22)))
			H22 copy down to H802	Use AURA3 ERG re-modelled OS for PDC =IF(Mod_D=1,'ERG - OS'!B3,IF(OR(analysis_nr=1,INDEX(surv_model_nr,H$13)=1,SUM(H$17:H$20)=0),0,CHOOSE(surv_param_model,Survival_func(H$16:H$20,$C22),ClinicalData_B!DX22)))
R3) Use ERG re-modelled TTD data from AURA3	Mod_C	PatFlow_B	NB: PDC then OS in this sheet DE13 copy down to DE792	Use AURA3 ERG re-modelled TTD for osimertinib =IF(Mod_C=1,'ERG - TTD'!A3,'AURA3_TTD'!A2)
			DD13 copy down to DD792	Use AURA3 ERG re-modelled TTD for PDC =IF(Mod_C=1,'ERG - TTD'!B3,'AURA3_TTD'!B2)