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Evidence Review Group Report commissioned by the NIHR HTA Programme on behalf of NICE

Necitumumab for untreated advanced, metastatic, squamous non-small-cell lung cancer

ADDENDUM

Additional information requested by the National Institute for Health and Care Excellence

Produced by Southampton Health Technology Assessments Centre (SHTAC)

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Key to colour highlighting used in report

Commercial in confidence (CIC) information in blue

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1 Introduction

This is an addendum to the Evidence Review Group (ERG) report for the single technology appraisal (STA) of necitumumab for untreated advanced, metastatic, squamous non-small-cell lung cancer (NSCLC). At the request of the National Institute for Health and Care Excellence (NICE), the ERG has provided the following additional information to inform the Appraisal Committee Meeting:

- The modelled mean overall survival (OS) benefit associated with necitumumab in combination with gemcitabine plus cisplatin (GCis + N) compared with cisplatin in combination with gemcitabine (GCis) alone in patients with epidermal growth factor receptor (EGFR)-expressing NSCLC from the whole SQUIRE trial population, derived from the ERG's economic model when applying a log-logistic extrapolation to the Kaplan-Meier (KM) curves. The ERG's base case, presented in our original report, used a Weibull extrapolation, and NICE was interested in the results of our analyses when a log-logistic extrapolation was used instead.
- The results (ICERs and modelled mean OS benefits) of sensitivity analyses that explore the effect of different extrapolation start points (i.e. with different numbers of patients remaining at risk) on the Kaplan-Meier (KM) curves, when using a log-logistic extrapolation on data from patients with EGFR-expressing NSCLC from the whole trial population in the ERG's economic model.
- The modelled mean OS benefit for the EGFR-expressing (whole trial) population when no extrapolation has been used, when using the ERG's economic model.

In response to a query from NICE, we have corrected Table 50 on page 143 of the ERG report, which contained errors in the 'Comparison' column. In addition, we include a corrected version of Table 49 of the ERG report (p. 141), in which we reported the modelled estimates of mean OS, PFS, costs and QALYs from the company model with discounting applied. The undiscounted estimates in the corrected table below provide a better comparison between the clinical outcomes from the company and SHTAC base case versions of the model, in the whole trial population with EGFR expressing tumours.

2 Additional information

Table 1 shows the estimated ICERs and modelled mean and median OS benefits associated with GCis + N compared with GCis for patients with EGFR-expressing NSCLC from the total trial population when using different extrapolation assumptions in the ERG's economic model (scenarios **S0a to S17**). For comparison, we have also provided the results of the company's preferred analysis (base case direct analysis) when using data from the EGFR-expressing Western Europe population (**C0a**) and when using data from the EGFR-expressing (total trial, intention-to-treat; ITT) population (**C0b**).

Scenario **S0a** is our base case, as presented in the ERG report, that used Weibull extrapolations from the points on the OS KM curves with more than 20 patients remaining per arm (from week 126 in the GCis + N arm and from week 129 in the GCis arm). Scenario **S4a** is our scenario S4 reported in the ERG report. As shown in Table 1, the results of this scenario demonstrate that when a log-logistic extrapolation is used with more than 20 patients remaining in each arm, the modelled mean benefit for the EGFR-expressing patients from the whole trial population is 2.84 months, favouring GCis + N. Altering the point at which the log-logistic extrapolation was applied to the KM curves (in sensitivity analyses), to either one patient (scenario **S4b**) or more than 30 patients (scenario **S4c**) left at risk, resulted in modelled mean OS benefits of 4.16 and 3.57 months, respectively, favouring GCis + N. The associated ICERs were £110,567 and £123,905, respectively.

We note that the direction of impact on the ICER from reducing the time to extrapolation is not consistent or obviously predictable: a reduction from full trial follow-up (scenario S4b: extrapolation from week 161 and 168 for GCis + N and GCis respectively) to the point where at least 20 patients remain in each arm (scenario S4a: from weeks 126 and 129) leads to an increase in the ICER; but a further reduction to the point where at least 30 patients remain in each arm (scenario 4c: from weeks 122 and 115) then leads to a decrease in the ICER. This can be understood with reference to the graphs reproduced from the company model in Figure 8 of the ERG report (p. 99). It can be seen that the vertical distance between the OS KM curves from the two SQUIRE trial arms is variable, particularly after about two years of follow up. This means that attaching the extrapolated tails at different times might either increase or decrease the total area between the modelled OS curves, and hence increase or decrease the estimated QALY difference.

The modelled mean OS benefit for the EGFR-expressing (whole trial) population when no extrapolation was used (scenario **S17**) was 2.04 months. As might be expected, this three year time horizon provided a higher estimated ICER (£183,649 per QALY gained) compared with that for the five year time horizon reported in scenario S1 in the ERG report (£170,755 per QALY gained).

Table 1. Modelled mean and median OS benefits and associated ICERs from the company's and the ERG's economic model when using different extrapolation assumptions

Base scenario	Population	OS model	Extrapolated from n left (week)		ICER GCis+N vs GCis (£ per QALY)	Incremental Modelled OS (months, undiscounted)	
			GCis+N	GCis		Median	Mean
C0a	WE (EGFR)	Log-logistic	n=1 (160)	n=1 (163)	£57,725	[redacted]	7.53
C0b	ITT (EGFR)	Log-logistic	n=1 (161)	n=1 (168)	£110,248	[redacted]	4.16
S0a	ITT (EGFR)	Weibull	n>20 (126)	n>20 (129)	£169,612	[redacted]	2.25
S4a	ITT (EGFR)	Log-logistic	n>20 (126)	n>20 (129)	£138,018	[redacted]	2.84
S4b	ITT (EGFR)	Log-logistic	n=1 (161)	n=1 (168)	£110,567	[redacted]	4.16
S4c	ITT (EGFR)	Log-logistic	n>30 (122)	n>30 (115)	£123,905	[redacted]	3.57
S17	ITT (EGFR)	3 year time horizon (no extrapolation)			£183,649	[redacted]	2.04

Note: all ICERs and survival estimates are from deterministic analyses. Our base case and scenario analysis results (S0 to S16) presented in our original ERG report were stated to be from a Probabilistic Sensitivity Analysis, but this is an error, and the results were from deterministic analyses. Scenario S17 is a new, additional scenario analysis to those reported in the ERG report, which we ran in response to NICE's additional information request. Scenarios S4b and S4c were new sensitivity analyses that we also carried out in response to NICE's request for additional information. EGFR, epidermal growth factor receptor; GCis, cisplatin in combination with gemcitabine; GCis + N, necitumumab in combination with gemcitabine plus cisplatin; ICER, Incremental cost-effectiveness ratio; ITT, intention-to-treat; QALY, quality-adjusted life year; OS, overall survival; WE, Western Europe.

3 Corrected Table 49

The results of the company model reported in Table 49 of the ERG report (p. 141) were incorrect: we reported discounted estimates of the modelled mean OS, PFS, costs and QALYs for the company model, rather than the undiscounted estimates that were reported for the SHTAC base case model. The corrected table with undiscounted results for both versions of the model is show below (Table 2).

Table 2 Model outputs (undiscounted): ITT EGFR expressing population (amended Table 49 from ERG report p141).

	Company model			SHTAC base case		
	GCis + N	GCis	Difference	GCis + N	GCis	Difference
Modelled OS						
Median (months)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (months)	[redacted]	[redacted]	4.16	[redacted]	[redacted]	2.25
One year OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Two year OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Five year OS	4.9%	2.4%	2.5%	0.5%	0.3%	0.3%
Modelled PFS						
Median (months)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (months)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
One year PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Two year PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Five year PFS	0.5%	0.4%	0.1%	0.0%	0.0%	0.0%
QALYs (undiscounted)						
Pre-progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Costs (undiscounted)						
Pre-progression (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-progression (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

4 Corrected Table 50

Table 3 below is a corrected table to replace Table 50 in the ERG report. The original Table 50 contained errors. In the original table, DCis was described as 'dominated' and we have now amended this to 'extendedly dominated'. We have also corrected the table to show that GCis was compared to carboplatin in combination with paclitaxel (PCarb) and not with cisplatin in combination with docetaxel (DCis).

Table 3. SHTAC base case – ITT EGFR subgroup (amended Table 50 from the ERG report)

Technologies	Total		Incremental		ICER (£ per QALY)	Comparison
	Costs	QALYs	Costs	QALYs		
PCis	[redacted]	[redacted]			-	
DCis	[redacted]	[redacted]	[redacted]	[redacted]	-	Ext. dominated
PCarb	[redacted]	[redacted]	£1,001	0.135	£7,429	vs PCis
GCarb	[redacted]	[redacted]			-	Dominated
GCis	[redacted]	[redacted]	£1,579	0.013	£124,663	vs PCarb
GCis+N	[redacted]	[redacted]	£19,993	0.118	£169,612	vs GCis

DCis, cisplatin in combination with docetaxel; GCarb, carboplatin in combination with gemcitabine; GCis, cisplatin in combination with gemcitabine; GCIs + N, necitumumab in combination with gemcitabine plus cisplatin; ICER, incremental cost-effectiveness ratio; PCarb, carboplatin in combination with paclitaxel; PCis, cisplatin in combination with paclitaxel; QALY, quality-adjusted life year.