MTA REPORT ADDENDUM 2 ID620

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Erlotinib and gefitinib for treating non-small cell lung cancer that has progressed following prior chemotherapy (review of NICE technology appraisals 162 and 175)

ID620

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1 INTRODUCTION

At the first Appraisal Committee (AC) meeting for this appraisal (7th January 2014), the committee members concluded that "Erlotinib is not recommended for treating locally advanced or metastatic non-small cell lung cancer in people with EGFR-TK mutation-negative tumours after the failure of at least 1 prior non-targeted chemotherapy regimen."

In their comments on the subsequent Appraisal Consultation Document (ACD) issued 4th February 2014, some consultees stated that they considered the incidence rate of grade 3/4 febrile neutropenia (FN) reported in a key trial (the TAILOR[1] trial) appeared to be unduly optimistic and may have distorted the economic results against erlotinib.

At the second AC meeting (5th March 2014), an Assessment Group (AG) Addendum was considered which provided information on the sensitivity of the cost-effectiveness results to the incidence of FN, and offered an alternative scenario based on the subgroup of patients in the TAILOR[1] trial who received docetaxel once every 3 weeks at a dose of 75mg/m^2. (This regimen reflects clinical practice in England and Wales). On the basis of this evidence (deterministic ICER of £31,039 per QALY gained, probabilistic ICER of £28,328 per QALY gained for docetaxel vs erlotinib) and noting concerns from consultees that the incidence of FN in clinical practice may be higher than that reported in clinical trials, the AC altered the previous decision and issued a second ACD for consultation (28th March 2014) recommending erlotinib as an option for treating NSCLC M- disease in people for whom docetaxel is a suitable treatment.

During consultation on the second ACD, the manufacturer of erlotinib communicated to NICE that they believed they had detected an error in the AG economic model, which could lead to a significant over-estimation of the cost associated with the treatment of FN.

The AG can confirm the presence of a previously undetected error in the model used to compare the cost effectiveness of erlotinib and docetaxel in the M- population. The error has now been corrected and revised cost-effectiveness results are provided in this Addendum. These include the use of the FN adverse event rate (6.35%) relating to the subgroup of patients in the TAILOR[1] trial who received 3-weekly treatment with docetaxel, as preferred by the AC at their second meeting on this topic. An extensive sensitivity analysis is also provided to explore a wide range of possible values for the incidence of FN in the EGFR M- population.

The results of the other analyses included in the AG report (erlotinib vs best supportive care [BSC] in the BR.21[2] trial EGFR M- subgroup, and erlotinib vs BSC in the BR.21[2] trial EGFR

M-unknown population) are unaffected by this error, as none of the patients in these groups experienced grade 3/4 FN in the BR.21[2] clinical trial.

2 DECISION MODEL ERROR AND CORRECTION

The detected error in the AG model was located in the 'Parameters' worksheet, and relates to the resource intensity parameter for FN. The model assumes that the costs of treating treatment-related adverse events occur in the first 12 weeks (four 3-weekly cycles) of treatment. The parameter for grade 3/4 FN in cell M34 correctly applied the mean number of episodes per patient (1.4) as reported in the DSU 2007[3] report, but omitted to divide this number by 12 to apportion the resource use per week for use in the weekly cycles of the model calculations. The effect of this omission was to multiply the true estimated cost per patient of treating FN by 12. This problem only affects the calculation of costs for docetaxel, as there is no FN attributed to erlotinib in the base case scenario. The previously reported cost-effectiveness results therefore disproportionately overestimate the cost effectiveness of erlotinib relative to docetaxel when used in the EGFR M- patient population.

3 AMENDED COST-EFFECTIVENESS RESULTS COMPARING ERLOTINIB AND DOCETAXEL IN AN EGFR M- POPULATION

The deterministic cost-effectiveness results shown in Table 1 include the FN adverse event rate (6.35%) for the subgroup of patients in the TAILOR[1] trial who received 3-weekly treatment with docetaxel, as well as the corrected calculation of the cost of treating FN. Erlotinib is found to be dominated by docetaxel in the EGFR M- population, yielding a reduced mean survival and fewer QALYs whilst also involving a greater net cost of treatment.

A probabilistic sensitivity analysis (PSA) yields a similar result: an estimated ICER of -£7,709 per QALY gained, indicating that at a cost-effectiveness threshold of £0 per QALY, there is a probability greater than 99% that erlotinib is less cost effective than docetaxel (Figure 1).

Univariate sensitivity analysis for the deterministic base case indicates that the use of generic docetaxel in place of the branded product is the major factor in establishing docetaxel as the preferred option. The incidence rate of FN has a larger influence on the estimated ICER than other model parameters, but for none of model parameters is the known parameter uncertainty sufficient to alter the conclusion that erlotinib is dominated by docetaxel in the EGFR M- population. The only model input which could alter this conclusion is the incidence rate of FN in docetaxel treated patients; this is considered below.

Table 1 Base case deterministic cost-effectiveness results for erlotinib vs docetaxel 2nd-line treatment in the EGFR M- population using evidence from the TAILOR trial

	Docetaxel		**Erlotinib**		**Incremental**	
SURVIVAL	Years	Months	Years	Months	Years	Months
PFS	0.409	4.91	0.287	3.45	-0.122	-1.46
PPS	0.731	8.77	0.641	7.70	-0.089	-1.07
Terminal	0.038	0.46	0.038	0.46	0.000	0.00
OS	**1.178**	**14.13**	**0.967**	**11.60**	**-0.211**	**-2.53**
QALYs	Not discounted	*Discounted*	Not discounted	*Discounted*	Not discounted	*Discounted*
PFS	0.2537	*0.2526*	0.1853	*0.1850*	-0.0684	*-0.0676*
PPS	0.3459	*0.3311*	0.3036	*0.2920*	-0.0423	*-0.0392*
Terminal	0.0095	*0.0092*	0.0095	*0.0093*	0.0000	*+ 0.0001*
OS	**0.6091**	***0.5930***	**0.4984**	***0.4863***	**-0.1107**	***-0.1067***
COSTS	Not discounted	*Discounted*	Not discounted	*Discounted*	Not discounted	*Discounted*
Drugs	£342	*£340*	[redacted]			
Admin	£2,314	*£2,305*				
AEs	£585	*£585*				
BSC in PFS	£1,531	*£1,524*				
BSC in PPS	£5,148	*£4,928*				
Terminal	£3,917	*£3,820*				
Total	**£13,837**	***£13,504***	**£14,302**	***£14,049***	**+£465**	***+£545***
ICER	**Cost per QALY**		**Erlotinib vs docetaxel (dominated)**		***-£5,112* per QALY (disounted)**	
Net Benefit	**£ per patient (£30,000 per QALY)**		**Erlotinib vs docetaxel (dominated)**		***-£3,746 per patient***	

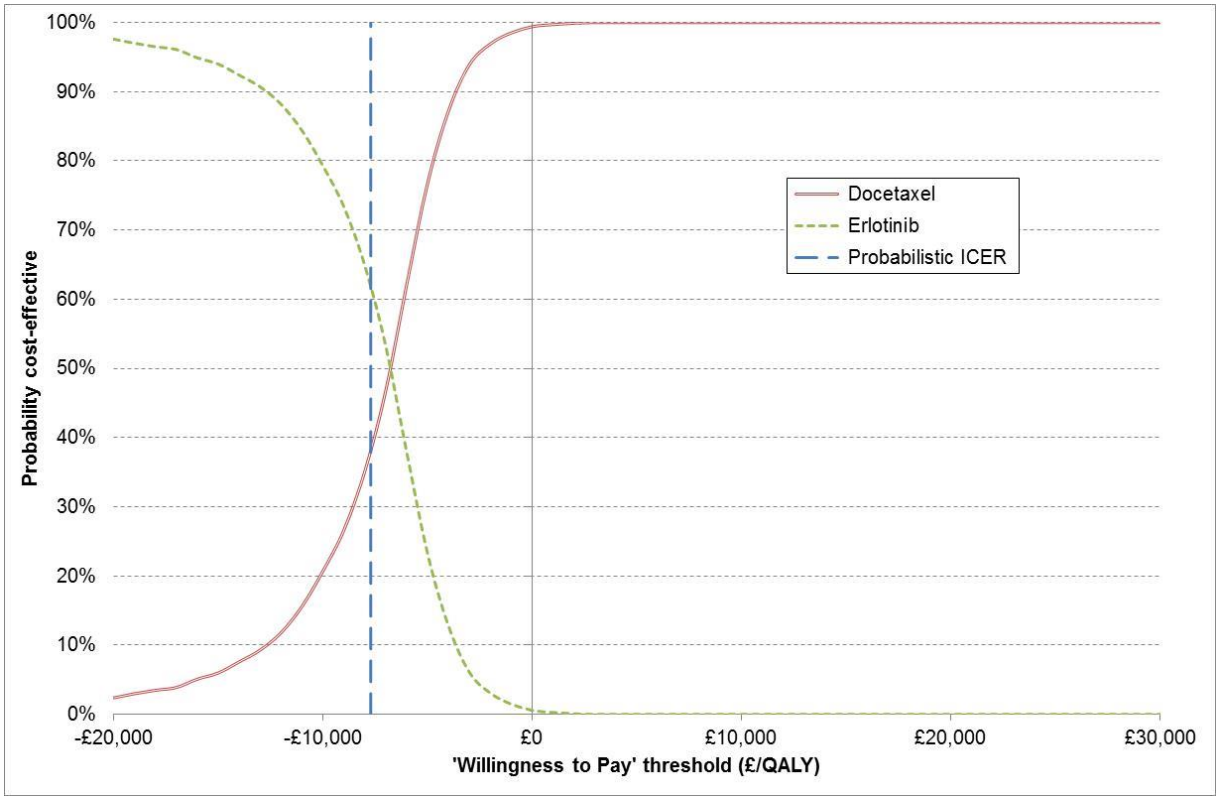

Figure 1 Cost effectiveness acceptability curves for the comparison of erlotinib and docetaxel 2nd-line treatment in the EGFR M- population using evidence from the TAILOR trial

4 INCIDENCE OF GRADE 3/4 FEBRILE NEUTROPENIA

Evidence from published trials

Several approaches can be taken to the estimation of the proportion of patients treated with docetaxel monotherapy who will experience one or more episodes of grade 3/4 FN as a result of treatment. A total of eight different estimated incidence rates were identified as follows:

AG base case (TAILOR[1] trial) – four patients in the TAILOR[1] trial were reported to have experienced grade 3/4 FN in the docetaxel arm, all of who were in the subgroup of 63 patients treated 3-weekly with high dose docetaxel (75mg/m^2 BSA). This corresponds to an incidence rate of ***6.35%*** (1.79% to 13.50%), and relates to the dose and frequency of docetaxel administration most commonly used in the UK.

Decision Support Group Report[3] – during the first appraisal of erlotinib vs docetaxel in 2nd line chemotherapy for NSCLC (TA162[4]), the DSU was asked to investigate the incidence of FN and its associated treatment costs. They conducted a meta-analysis of reported trials and estimated the incidence as ***5.95%*** (5.3% to 7.7%).

TAILOR[1] trial (all patients) – if no distinction is made between high dose (3-weekly) and low dose (weekly docetaxel 35mg/m^2 BSA), the FN incidence rate is ***3.85%*** (1.07% to 8.28%).

Other trials (pre-EGFR testing) – data from 17 randomised clinical trials,[1,5-20] which included high dose 3-weekly docetaxel monotherapy as one treatment arm, were combined to provide a weighted average incidence rate (see Appendix). It was not possible to carry out a formal meta-analysis due to the diversity of comparators, populations and settings of these trials. The weighted average estimate is ***7.3%*** (6.3% to 8.3%). Heterogeneity testing of trial incidence values identified two of the larger trials exhibited significantly higher incidence rates than the remaining 15 trials. Therefore, two weighted average values were selected for sensitivity testing: ***10.8%*** (8.9% to 12.8%) and ***5.0%*** (4.0% to 6.2%) corresponding to these distinct data subsets. The maximum estimated incidence among all 17 trials, ***12.7%*** (9.0% to 16.8%) was also selected for exemplification in the decision model.

Extreme sensitivity analysis – in order to explore the impact of a very high incidence rate, the value of the greatest upper confidence level of any of these 17 trial arms was selected – ***25%***.

Comment on RCP suggested incidence rates

In the Royal College of Physicians submission document it is stated that:

> "In clinical practice, admission rates for neutropaenic sepsis and treatment complications are 25-50% with docetaxel compared to <5% with erlotinib"

Unfortunately no supporting evidence was cited for this statement. Subsequently the RCP responded to the ACD citing a conference abstract by Sharma[21] of an observational study of admissions in three trusts, to support a figure of 41%. The abstract shows that 41% is the total number of hospital admissions in 2nd-line docetaxel treatment (9 out of 22), whereas only four of these were due to neutropenic sepsis (i.e. 18%). In addition it should be noted that admission rates are necessarily higher than incidence rates as the DSU estimated that affected patients require an average of 1.4 admissions per patient. Using this factor to adjust admission rate to incidence rate, the best estimate from the Sharma[21] study is an incidence rate of 13.0% (2.7% to 29.5%). The small numbers involved and the wide confidence interval (which encompasses all the eight estimates listed above) indicates that these data add nothing useful to the consideration of FN incidence rates.

5 SENSITIVITY ANALYSIS FOR FEBRILE NEUTROPENIA INCIDENCE

Table 2 summarises the cost-effectiveness results for the AG revised base case and seven alternative FN scenarios described above. In all cases erlotinib is not cost effective compared to docetaxel, because the cost and utility effect of varying FN incidence is not sufficient to counteract the estimated survival advantage of docetaxel. The incremental cost is zero for an FN rate of 16.2% (equal cost, but QALY gain for docetaxel). The ICER for erlotinib vs docetaxel only exceeds £30,000 cost savings per QALY lost for docetaxel FN incidence rates above 63%.

Table 2 Sensitivity analysis of AG revised base case scenario, with alternate assumed values of the incidence rate of grade 3/4 FN during 2nd line docetaxel 3-weekly monotherapy

Scenario	Febrile neutropenia incidence	Erlotinib		Docetaxel		Incremental		ICER
		Total cost	Total QALYs	Total cost	Total QALYs	Cost	QALYs	£/QALY
AG revised base case	6.35%	£14,049	0.4863	£13,504	0.5930	+£545	-0.1067	-£5,112 Dominated
Decision Support Unit estimate	5.95%	£14,049	0.4863	£13,482	0.5931	+£567	-0.1067	-£5,312 Dominated
TAILOR trial (all patients)	3.85%	£14,049	0.4863	£13,365	0.5939	+£684	-0.1076	-£6,353 Dominated
Weighted average (all trials)	7.26%	£14,049	0.4863	£13,554	0.5926	+£495	-0.1063	-£4,654 Dominated
Weighted average (2 high trials)	10.80%	£14,049	0.4863	£13,749	0.5913	+£300	-0.1050	-£2,854 Dominated
Weighted average (15 low trials)	5.03%	£14,049	0.4863	£13,431	0.5934	+£618	-0.1072	-£5,768 Dominated
Maximum trial	12.68%	£14,049	0.4863	£13,853	0.5906	+£196	-0.1044	-£1,876 Dominated
Extreme value	25.00%	£14,049	0.4863	£14,534	0.5861	-£485	-0.0998	+£4,853 Favours Docetaxel

6 SUMMARY

Table 3 provides an overview of the three estimated AG base case ICERs made available to the AC during this appraisal.

Table 3 Estimated base case cost-effectiveness estimates of erlotinib vs docetaxel for the EGFR M- population provided by the AG during the appraisal

	Incremental cost	Incremental QALYs	Deterministic ICER	Probabilistic ICER
AG report estimate	-£1,653	-0.1076	£15,359 / QALY	£12,719 / QALY
Amended for FN incidence rate (6.35%) (Addendum 1)	-£3,311	-0.1076	£31,039 / QALY	£28,328 / QALY
Amended for FN incidence rate & corrected FN cost calculation (Addendum 2)	**+£545**	**-0.1076**	**-£5,112 / QALY (dominated)**	**-£7,709 / QALY (dominated)**

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APPENDIX

17 RCTS reporting FN rates for patients treated at 2nd-line with high dose docetaxel

Trial	Patients	FN patients	Rate
Gridelli[11] (DISTAL01)	110	5	4.55%
Gervais[10]	63	4	6.35%
Schuette[18]	100	2	2.00%
Camps[5]	131	10	7.63%
Lilenbaum[14]	52	4	7.69%
Ciuleanu[7] (TITAN)	116	2	1.72%
Cufer[8] (SIGN)	63	2	3.17%
Garassino[1]	63	4	6.35%
Kim[13] (INTEREST)	715	72	10.07%
Hanna[12]	276	35	12.68%
Shepherd[19]	55	1	1.82%
Chen[6]	33	4	12.12%
Fossella[9]	121	10	8.26%
Pectasides[15]	65	3	4.62%
Quoix[16]	89	6	6.74%
Ramlau[17]	401	11	2.74%
Wachters[20]	56	3	5.36%
Combined	**2509**	**178**	**7.09%**