ERRATUM

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Erlotinib for the first-line treatment of EGFR-TK mutation positive non-small cell lung cancer

This report was commissioned by the NIHR HTA Programme as project number 11/08

Completed 6th January 2012

DOES NOT CONTAIN CIC/AIC

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

1 SUMMARY

1.1 Scope of the submission

The remit of the Evidence Review Group (ERG) is to comment on the clinical and cost-effectiveness evidence submitted to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal (STA) process. Clinical and economic evidence has been submitted to NICE from Roche Ltd in support of the use of erlotinib (Tarceva®) as a first-line treatment for patients with epidermal growth factor (EGFR) tyrokinase (TK) mutation positive (M+) locally advanced or metastatic non-small cell lung cancer (NSCLC). The manufacturer's submission (MS) describes the use of erlotinib compared with doublet chemotherapy (CTX) and with gefitinib for people with previously untreated EGFR M+ locally advanced or metastatic NSCLC.

In September 2011, the European Medicines Agency (EMA) granted an extension to the existing marketing authorisation for erlotinib to include the first-line treatment of patients with locally advanced or metastatic NSCLC with EGFR activating mutations.

1.2 STA process

The ERG identified very early in the process of this STA that there was a significant issue with the submission received from the manufacturer, namely:

- The manufacturer does not compare erlotinib vs pemetrexed as advised in the final scope issued by NICE;
- The incomplete indirect comparison (IC) fails to provide the appropriate links between the intervention and the comparator;
- The patient treatment pathways used in the model are not in line with current NICE guidance;
- The economic model indicates survival gain that is not demonstrated by the clinical evidence available.

The ERG's concerns were relayed to the NICE technical team. A joint ERG, NICE and manufacturer teleconference failed to result in any agreed way forward. Following discussions internally at NICE the ERG was asked to proceed with their critique of the submission. Due to the limitations identified by the ERG, the ERG was unable to formulate any clarification questions to put to the manufacturer and only a limited critique of the evidence has been possible.

1.3 Key points identified from the critique of submitted clinical-effectiveness evidence

The manufacturer does not compare erlotinib vs pemetrexed as advised in the final scope issued by NICE. This raises the following issues:

The manufacturer correctly states that gefitinib is the current standard of care in England and Wales for patients with EGFR M+ NSCLC due to the fact that it was recommended by NICE. However, the manufacturer does not comment on the fact that at the time of the gefitinib appraisal only immature clinical data from the IPASS trial were available to the Appraisal Committee. Nor does the manufacturer mention in the MS that the recently updated IPASS results now confirm that there is no OS gain for gefitinib vs third-generation CTX.

1. NICE's recommendation of gefitinib as a treatment for EGFR M+ NSCLC does not preclude the use of pemetrexed. Pemetrexed is the only drug that yields a statistically significant OS benefit over a third-generation CTX (gemcitabine) in patients with non-squamous lung cancer and patients who are EGFR M+ are predominantly patients with non-squamous disease. The ERG acknowledges that there is no RCT which investigates the use of pemetrexed in an EGFR M+ population and that it is uncertain whether erlotinib would be cost effective compared with pemetrexed in this patient population. However, until the matter has been fully explored firm conclusions cannot be reached.

2. The assumption that all third-generation CTX treatments are equally clinically effective for EGFR M+ patients must be carefully investigated as there is no single trial or group of trials which explore the validity of this assumption.

1.4 Key points identified from the critique of submitted cost-effectiveness evidence

The manufacturer's economic model:

1. Generates results that are uncertain in the sense that they do not provide incremental cost-effectiveness ratios (ICERs) for the full list of available treatments for patients with NSCLC who are EGFR M+;

2. Has a structure which means that in order to explore additional treatment pathways it would need to be rebuilt;

3. Yields OS gains for the first-line treatment of EGFR M+ patients with erlotinib and gefitinib that are not demonstrated by the published RCT evidence;

4. Fails to include the costs and benefits of second-line treatments (second-line treatments are a standard feature of lung cancer economic models).

1.5 Conclusion

As noted above, the ERG is only able to offer a limited critique of the evidence submitted. Further information and analyses are required in order to allow a fair assessment of the cost effectiveness of erlotinib as a first-line treatment for patients with EGFR M+ locally advanced or metastatic NSCLC.

3.1 Population

The manufacturer's statement of the decision problem describes the relevant patient population as people with previously untreated EGFR M+ locally advanced or metastatic NSCLC. This is in line with the final scope issued by NICE.[7]

The patient population in the main trial presented in the MS (EURTAC[8]), is described as patients with previously untreated stage IIIB/IV NSCLC with tumours that have EGFR exon 19 deletion or exon 21 L858R mutation.

The patients in the EURTAC[8] trial are described as Caucasian and the trial was carried out in 42 centres in European countries. The ERG notes that the major RCTs in the same clinical area have all been conducted in centres in East Asia.

3.2 Intervention

The intervention in the MS is erlotinib. This matches the intervention stated in the final scope issued by NICE.[7] Erlotinib is an orally administered inhibitor of EGFR which is over-expressed in various solid tumours including NSCLC. Erlotinib is licensed in Europe for the first-line treatment of patients with locally advanced or metastatic NSCLC with EGFR activating mutations. In the EURTAC[8] trial, erlotinib was given at a dose of 150mg daily until disease progression, unacceptable toxicity or death.

3.3 Comparators

Two comparators to erlotinib are described in the final scope[7] issued by NICE. Firstly, gefitinib for adults with previously untreated EGFR-TK mutation positive locally advanced or metastatic non-small-cell lung cancer. Secondly, pemetrexed in combination with cisplatin or carboplatin for those adults with previously untreated EGFR-TK mutation positive locally advanced or metastatic non-small-cell lung cancer who also have non-squamous NSCLC of adenocarcinoma or large cell carcinoma histology. (The ERG notes that pemetrexed is licensed and recommended by NICE for use as a first-line treatment only in combination with cisplatin).

Comparator 1 - gefitinib

In the EURTAC[8] trial, patients were randomised to receive either erlotinib or platinum-based CTX (docetaxel or gemcitabine). The EURTAC[8] trial did not include gefitinib as a comparator and no head to head trial exists that compares erlotinib with gefitinib. To allow such a comparison to be made the manufacturer has conducted a systematic review and indirect comparison (IC).

Comparator 2 - pemetrexed

In the MS, the manufacturer has not included pemetrexed as a comparator to erlotinib. The manufacturer justifies this approach with the following statements (MS, pg 47):

> "Market research indicates that an EGFR TKI (either erlotinib or gefitinib) is currently used in the first line treatment of 95% of UK patients with an EGFR M+ tumour. Only around 5% of patients receive doublet chemotherapy. Whilst pemetrexed/platinum may have been an appropriate comparator to gefitinib in TA192[5] the sizeable uptake in first line use of an EGFR TKI in the 12 months following the issuance of that guidance indicates that this is no longer the case. A UK patient with an EGFR M+ tumour is nearly 20 times more likely to receive an EGFR TKI than doublet chemotherapy as a first line treatment (with that likelihood increasing rapidly in an extremely short period of time following approval of gefitinib).
>
> In addition it should be noted that in TA192 it was found that an indirect comparison of 'traditional doublet chemotherapy' and pemetrexed/cisplatin in an EGFR M+ population was not possible due to a lack of data on the efficacy of pemetrexed/cisplatin in this group. In light of this declining relevance of pemetrexed/cisplatin in this group and the difficulty/impossibility in conducting such a comparison (as concluded in TA192) the pemetrexed based doublet CTX regimens detailed in the scope are not addressed as comparators within the submission."

The ERG understands the manufacturer's view that few patients appear to be treated with pemetrexed and therefore gefitinib is the key comparator of interest. However, the remit of the ERG is to assess all the clinical and economic information available. It is the view of the ERG that appropriate consideration of the decision problem requires consideration of erlotinib vs pemetrexed. The rationale underlying the ERG's position is outlined below.

Pemetrexed is listed as a comparator in the final scope[7] issued by NICE. The manufacturer has failed to provide a persuasive argument that pemetrexed is not a valid comparator. The manufacturer has simply stated that few patients are treated with pemetrexed and that it would be difficult or impossible to conduct a comparison of pemetrexed/cisplatin in an EGFR M+ population as there are no pemetrexed data available for the EGFR M+ population.

At the Appraisal Committee (AC) meeting for gefitinib, the AC considered the results of a mixed treatment comparison (MTC) conducted by the manufacturer of gefitinib. The MTC included standard CTX therapy with a platinum drug and paclitaxel, docetaxel, gemcitabine or vinorelbine and pemetrexed for patients with non-squamous histology. It is stated in the guidance document (TA192[5]) that "the Committee accepted that there was uncertainty in these comparisons but concluded that it was likely that gefitinib was no less efficacious than pemetrexed with cisplatin, and that pemetrexed in combination with cisplatin was the relevant comparator for gefitinib." The ERG considers that, as gefitinib and pemetrexed are believed to be equally efficacious, both treatments should be compared

with erlotinib as stated in the final scope[7] issued by NICE in order to fully address the decision problem.

In its appraisal of gefitinib, the ERG demonstrated that pemetrexed dominated gefitinib (i.e. it was cheaper and more clinically effective). This comparison of pemetrexed with gefitinib is clearly restricted to the context of the gefitinib STA appraisal given the clinical and economic assumptions used by the manufacturer of gefitinib. It is the opinion of the ERG that erlotinib should be compared with gefitinib and pemetrexed within a single framework where consistent and transparent assumptions are made in order to fully address the decision problem set out by NICE.

Pemetrexed is the only first-line treatment for patients with non-squamous lung cancer which demonstrates a statistically significant OS gain when compared with a third generation treatment (gemcitabine).[9] Recently published updates from the IPASS[10] trial have reported that there is no overall survival (OS) gain for gefitinib vs third generation CTX treatment. A recently published meta-analysis[11] of RCTs that compared gefitinib with CTX also failed to demonstrate any OS benefit for treatment with gefitinib. This means that the efficacy gap between pemetrexed and gefitinib has grown wider in favour of pemetrexed. The ERG considers pemetrexed is a valid comparator since almost all EGFR M+ patients have non-squamous lung cancer.

The proportions of patients with non-squamous disease in the six clinical trials of EGFR TKI drugs, as cited by the manufacturer, are illustrated in Table 2.

Table 2 Proportion of patients in major trials of EGFR TKI drugs with non-squamous disease

Trial Name	Proportion of patients with non-squamous disease
IPASS[10, 12]	99.8-100%
First - SIGNAL[13]	100%
NEJGSG002 [14]	95.2-97.8%
WJTOG3405[15]	97.7-99.4%
OPTIMAL[16]	94.8%
EURTAC[8]	100%

In formulating its TA192[5] guidance for gefitinib, NICE considered a range of interventions for the treatment of EGFR M+ patients including pemetrexed; the ERG notes that NICE recommended gefitinib as an option for this population but did not exclude the use of pemetrexed for this group of patients. Not all hospitals throughout England and Wales have easy access to EGFR M+ testing. Clinical advisors to the ERG have noted that EGFR testing is not routinely performed in all hospitals. The manufacturer's own market research has demonstrated that over 90% of UK clinicians have access to EGFR mutation testing. This means that there are centres (10%) that still do not have routine access to EGFR testing. The ERG considers that it is reasonable to assume that some patients who are EGFR M+ will be treated with pemetrexed if (i) the hospital does not routinely test for EGFR (ii) delaying treatment (e.g. waiting for test results) would be detrimental to the patient's health.

In summary, the ERG is of the opinion that without appropriate consideration of pemetrexed as a comparator, the evidence presented by the manufacturer in the MS is incomplete and does not allow a full evaluation of erlotinib as set out in the decision problem.

3.4 Outcomes

The outcomes addressed in the MS are those listed in the final scope issued by NICE, namely OS, PFS, response rates, adverse events (AEs) and health-related quality of life (QoL). These outcomes are standard in this disease area.

The primary outcome of the EURTAC[8] trial was PFS, defined as the time between randomisation and the first occurrence of progressive disease (both radiological and clinical progression) or death from any cause, whichever occurred first.

The ERG notes that the OS results for EURTAC[8] are immature at both the interim and the updated analysis.

3.5 Other relevant factors

In order for a patient to receive gefitinib, the EGFR mutation status of the patient must be known. It is unclear whether all patients in England and Wales will have timely access to EGFR testing.

4 CLINICAL EFFECTIVENESS

As noted in the previous section of this report, the ERG is of the opinion that the evidence presented in the MS is incomplete as it does not include pemetrexed as a comparator. In this section, the ERG provides a commentary on i) the main clinical trial (EURTAC[8]) presented in the MS in support of the efficacy of erlotinib in patients with EGFR M+ NSCLC and ii) the IC conducted by the manufacturer to compare the clinical effectiveness of erlotinib with gefitinib.

The manufacturer has provided extensive detail in respect of two RCTs, EURTAC[8] and OPTIMAL.[16] However, the manufacturer states (MS, p58) that it considers that clinical evidence from EURTAC[8] forms the basis of the submission.

Table 3 Key clinical information in the MS

Key information	Section in the MS (page)
Description of the technology	Section A (28)
Context	2 (36)
Equity and equality	3 (46)
Statement of decision problem	4 (47)
Literature search main	5.1 (51)
Literature search indirect comparison and IC	5.7 (123)
Search strategies	Appendix 2 (289)
Study selection	5.2 (53)
Clinical effectiveness evidence key trial:	
Trial information	5.3 (55)
Results: main	5.5 (94)
Results: subgroups	5 (101)
Results: safety	5.8.3.1(173)
Clinical effectiveness evidence meta-analysis	5.6 (114)
Clinical effectiveness evidence IC:	
Trial information	5.7.2.1 (126)
Results: main	5.7.6 (167)
Results: safety	5.8.3.3 (182)
Results: non-RCT evidence	5.8 (170)

IC= indirect comparison

4.1 Description of manufacturer's search strategy and ERG comment on the search strategy

The aim of the literature search described in the MS was to identify evidence from RCTs on the efficacy of erlotinib in the first-line treatment of patients with activating mutations of the EGFR tyrokinase (MS, p51).

4.4 Indirect comparison and/or multiple treatment comparison

In the absence of any head to head trial data comparing erlotinib with gefitinib, the manufacturer conducted a systematic review and IC. The search strategy used to identify randomised evidence of the efficacy of erlotinib was repeated for gefitinib (gefitinib OR IRESSA replaced erlotinib or TARCEVA). This search identified three RCTs (IPASS,[10, 12] WJT0G3405,[15] NEJGSG002[14]); a fourth RCT (First-SIGNAL[13][abstract only]) was identified following a manual search of TA192.[5] The inclusion and exclusion criteria for the IC are described in Table 10.

Table 10 Key inclusion and exclusion criteria for the indirect comparison

Inclusion	Exclusion
Randomised controlled trials	Observational data, registry analyses, single arm studies, meta-analyses
Previously untreated NSCLC (metastatic) patients whose tumours harbour an activating mutation of the EGFR tyrosine kinase	Early NSCLC patients, small-cell patients, patients previously treated for their metastatic NSCLC (i.e. maintenance treatment, second and later line treatment), patients with tumours that do not contain a mutation of the EGFR tyrosine kinase or have unknown EGFR mutation status non-metastatic NSCLC
Gefitinib monotherapy	Gefitinib combination therapy, non-erlotinib therapy
Any comparator capable of informing the relative efficacy of erlotinib to gefitinib	Investigational agents
Outcomes of PFS, OS, AEs	

Indirect comparison network

The manufacturer created a network of RCTs to compare the clinical effectiveness of erlotinib with gefitinib. Data were extracted and analysed for clinical efficacy (PFS, OS and best overall response). The manufacturer pooled the data from four gefitinib trials (IPASS,[10,12] WJT0G3405,[15] NEJGSG002,[14] First-SIGNAL[13]) on the assumption that the doublet CTX arms in each of the trials are of equal efficacy. This assumption is based on a recent meta-analysis by Ku and colleagues[11] and commentary in the STA submission underpinning TA192.[5] The manufacturer has further assumed that the CTX arms of EURTAC[8] and OPTIMAL[16] can be linked to the network using doublet CTX as the anchor point. This is depicted in Figure 3. For reference, Table 11 describes the key characteristics of the RCTs for erlotinib and gefitinib. More extensive and detailed information for all the trials is presented in the MS.

However, the manufacturer then points out that the decision problem set by NICE requires an assessment of the relative effectiveness of erlotinib compared with gefitinib in a European population (MS, pg165). The manufacturer goes on to report the results of four possible indirect comparisons. All four indirect comparisons were conducted by using the values in Table 13 and applying the adjusted indirect comparison methodology developed by Bucher.[23] Whilst this methodology is valid, it is the ERG's view that it would have been preferable to use an IC utilising the individual hazard ratios available from each of the relevant studies. The outcomes of the comparisons are described in Table 14.

The manufacturer notes that all of the results of the indirect analyses demonstrate that compared with gefitinib, erlotinib is superior (or has a trend to superiority). The manufacturer further notes that none of the analyses answers the specific question of whether erlotinib is more effective than gefitinib in a European population; however the manufacturer states that the results of the analyses provide 'the best available evidence upon which to assess the relative effectiveness of erlotinib and gefitinib in a European population'(MS, pg166).

Table 13 Summary of data used in the indirect comparisons

	PFS HR	Lower confidence limit	Upper confidence limit	Scenario
OPTIMAL	0.162	0.102	0.256	1
FE Pooling EURTAC/OPTIMAL	0.26	0.2	0.35	2
RE Pooling EURTAC/OPTIMAL	0.25	0.11	0.56	3
EURTAC	0.37	0.25	0.54	4
Ku	0.45	0.38	0.55	1,2,3,4

FE= fixed effects; RE=random effects

Table 14 Indirect comparisons

	Comparison	Indirect PFS HR erlotinib vs gefitinib
1	OPTIMAL compared with IPASS/First-SIGNAL/WJTOG3405/NEJGSG002	0.36 (0.22 to 0.59)
2	Fixed effects pooled estimate of EURTAC/OPTIMAL compared with IPASS/First-SIGNAL/WJTOG3405/NEJGSG002	0.58 (0.41 to 0.81)
3	Random effects pooled estimate of EURTAC/OPTIMAL compared with IPASS/First-SIGNAL/WJTOG3405/NEJGSG002	0.56 (0.24 to 1.28)
4	EURTAC and IPASS/First-SIGNAL/WJTOG3405/NEJGSG002	0.82 (0.54 to1.26)

No further tests of heterogeneity beyond those described for the pooling of EURTAC and OPTIMAL[16] data were undertaken by the manufacturer. The manufacturer states that in the recent appraisal of gefitinib, the ERG had recommended that the results of the key gefitinib studies be pooled and highlights that the four studies have been pooled in the published meta-analysis by Ku.[11]

The ERG notes that the results of only three studies were available at the time of the appraisal of gefitinib, IPASS,[12] First-SIGNAL[13] and NEJGSG.[14] The ERG has reviewed the methods used in the meta-analysis by Ku[11] and is satisfied that they are appropriate.

In relation to the safety and tolerability of erlotinib and gefitinib, the manufacturer states that the two treatments are broadly similar. (MS, p182).

Critique of indirect treatment comparison

In principle, the correct approach to IC has been used by the manufacturer. However a robust IC should include the maximum amount of relevant data and not impose external assumptions, i.e. in this case, the IC should not restrict the inclusion of data to trials involving only EGFR M+ patients. An extended evidence network is required incorporating erlotinib, gefitinib and pemetrexed linked via RCTs to the four third-generation CTX doublets. Ideally this should be a comprehensive evidence review and should avoid assumptions of direct clinical equivalence between third-generation agents. Without these extra comparisons any resulting treatment differences between erlotinib and gefitinib are unlikely to accurately reflect those that would have resulted from a more comprehensive network comparison. While the ERG agrees that the IC performed by the manufacturer is important, a comprehensive IC should have been the primary approach and the restricted analysis should have been performed only as a sensitivity analysis.

One of the key assumptions underlying the manufacturer's IC is that all third generation drugs are equally equivalent in an EGFR M+ population as demonstrated by Figure 41 in the MS. The ERG is not aware of any clinical evidence to support this assumption. In an undifferentiated NSCLC patient population evidence suggests that no significant pairwise differences exist, nonetheless there are consistent trends suggesting gemcitabine is probably the most beneficial and paclitaxel the least efficacious. Therefore in an EGFR M+ population, more careful investigation is needed since differences between third generation regimens may accumulate to influence the indirect comparisons between erlotinib and pemetrexed and gefitinib. In order to decrease heterogeneity and improve the reliability of the results, key specific data are required: individual HRs for the comparators in the EURTAC[8] trial (e.g. erlotinib vs docetaxel, erlotinib vs gemcitabine) and individual HRs from all third generation first-line trials (undifferentiated population) in order to expand the network used in the IC.

The ERG also has concerns regarding the methods used to estimate HRs in RCTs of gefitinib. The ERG is aware that K-M plots of PFS gefitinib and erlotinib have a different pattern to those applying to third generation drugs. It appears that the proportional hazards assumption may be invalid for all PFS comparisons between TKIs and standard chemotherapy, and the ERG considers that the use of conventional proportional hazards methods to estimate HRs in gefitinib and erlotinib trials compared