NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Erlotinib for the treatment of non-small-cell lung cancer that has progressed following prior chemotherapy

MTA Submission

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1. Executive Summary

In NICE TA162 positive guidance was restricted to patients who are suitable for docetaxel, with the requirement that erlotinib was provided at an overall cost that was equivalent to docetaxel. The patent on docetaxel has subsequently expired and it is now available in generic form at a cost that is less than 10% of the list price of docetaxel in TA162.

Despite this erlotinib has remained the dominant second line treatment with seven out of ten patients treated for advanced non-small cell lung cancer benefiting from it (Kantar Health on behalf of Roche 2013). It is not possible to demonstrate that erlotinib is cost effective compared to docetaxel at this heavily reduced acquisition cost and therefore no economic evaluation is presented.

This submission provides a comparison of erlotinib to **best supportive care** in patients who are **unsuitable for docetaxel**. In this population erlotinib is the only active treatment option following progression on 1L chemotherapy for patients who are either unsuitable for docetaxel, or who have previously received docetaxel.

1.1. Non-small cell lung cancer

More than one in five cancer deaths in the UK are from lung cancer. It is the most common cause of cancer death in the country - almost 34,900 people died of lung cancer in the UK in 2010 alone (Cancer Research UK 2013). This is equivalent to one death every 15 minutes. The prognosis of UK patients diagnosed with lung cancer is extremely poor and survival rates remain low; approximately 70% of people die within one year of diagnosis and five year survival rates are lower than 10% (Cancer Research UK 2013).

These survival rates are not only extremely poor in absolute terms but extremely poor relative to similar countries. A recent study by Walters et al. found that the UK had the lowest one year survival compared to Australia, Canada, Denmark, Norway and Sweden. In this publication it was noted that one year survival in the UK is 30% with the equivalent figure in Sweden 16% higher (Walters et al 2013) – this equates to a 50% greater one year survival percentage in a country comparable to the UK. Estimates show that if UK survival were to be brought in line with the European average up to 3,500 deaths from lung cancer could be avoided each year (United Kingdom Lung Cancer Coalition 2013).

When considering these one-year survival figures it should be noted that the UK is a low user of lung cancer treatments. A 2010 study by the Department of Health found that the UK

ranked 13th out of 14 European countries for use of three of the most commonly used lung cancer treatments (erlotinib, gemcitabine and paclitaxel) and 10th for use of two of the other most commonly used (docetaxel and vinorelbine) (Department of Health 2010) (see Table 1 below).

Table 1: UK ranking for lung cancer treatment compared to EU (DOH 2010)

	UK % use compared to EU 5	**UK % use compared to EU 10**	**UK ranking**
Erlotinib	31%	33%	13/14
Gemcitabine	54%	54%	13/14
Docetaxel	57%	63%	10/14
Paclitaxel	48%	53%	13/14
Vinorelbine	53%	43%	10/14

Whilst long-term (e.g. 5-year) survival rates are most likely to be impacted by the proportion of patients receiving surgical resection of their tumours requiring an emphasis on early disease recognition, it is similarly likely that 1-year survival rates are most likely to be influenced by access to and use of systemic drug therapy for advanced disease.

Lung cancer falls into two main histological categories: around 85% – 90% of people are diagnosed with non-small-cell lung cancer (NSCLC) and the remainder are diagnosed with small-cell lung cancer (SCLC). NSCLC can be further divided by histology (squamous cell and adenocarcinomas being the main types) and by the presence or absence of specific “biomarkers” such as mutations in the epidermal growth factor receptor (EGFR). Thus tumours can be classified as harbouring the EGFR mutation (EGFR M+) or not, known as EGFR wild-type (EGFR WT). Patients with EGFR M+ make up around 10% of the total population of NSCLC and are almost exclusively of non-squamous histology. Histological type and EGFR mutation status are important as they predict outcome with and, hence, suitability for, different drug therapies.

This submission deals with patients with advanced (inoperable stage IIIB or IV) NSCLC eligible for erlotinib treatment following prior chemotherapy.

1.2. Current clinical practice

The prognosis of people with advanced NSCLC is extremely poor and the intention of treatment is not curative, but to extend survival, improve quality of life and palliate disease related symptoms. Good clinical care involves reaching agreement with the patient on a course of treatment that balances the likely gains in these areas with the negative impacts of treatment (inconvenience and side-effects) and that reflects the circumstances and priorities of the patient. For example, some will accept high levels of toxicity for a small gain in overall survival whilst others prioritise quality of life such as convenience of treatment at home and fewer adverse events. For this reason patients and clinicians value having a choice of therapies available.

The limitations of current treatment choices are illustrated by low UK treatment rates for advanced NSCLC. Almost two-thirds of patients do not receive systemic drug therapy 1L and of those that do, under 40% receive 2L therapy (Roche data on file 2012 RXUKDONF00270).

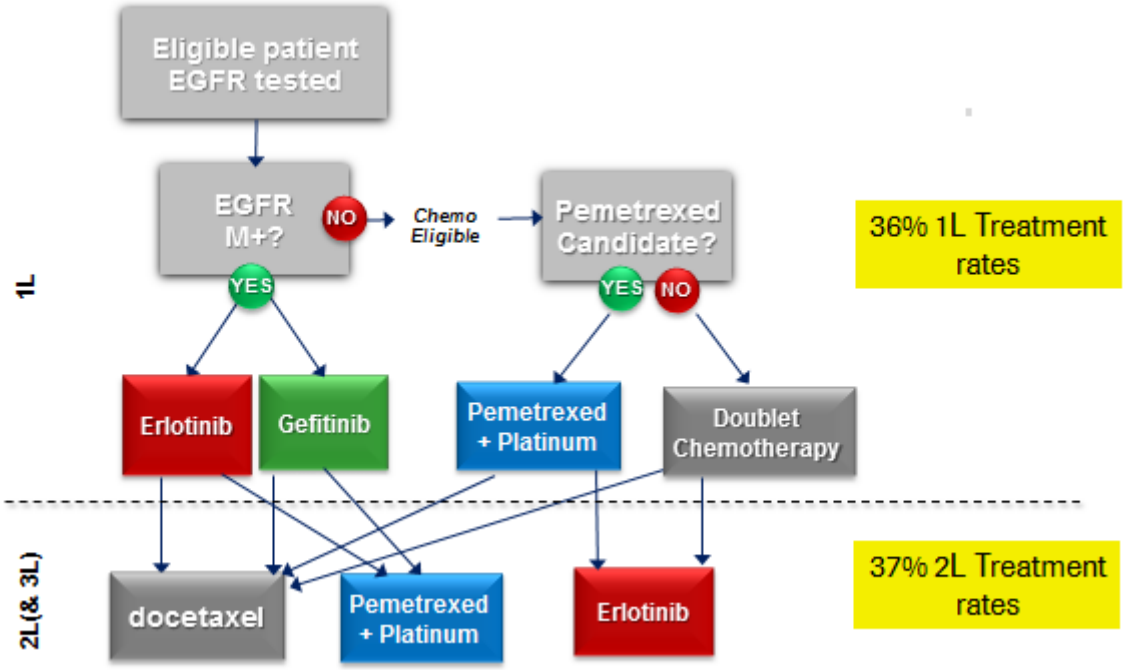
The introduction of targeted EGFR tyrosine kinase inhibitors (TKI's) such as erlotinib and gefitinib has certainly increased choice in recent years and complicated the standard treatment pathway shown in Figure 1.

When launched in 2005, erlotinib offered an alternative to cytotoxic chemotherapy for patients with disease relapsing after first-line chemotherapy – it offered a convenient oral therapy with better tolerability than the standard second-line chemotherapy (docetaxel) and similar efficacy in a broad second-line (2L) population. Evidence that it represented an important 2L treatment option that did not impose an additional financial burden on the NHS was recognised in TA162 which recommended it as a 2L treatment option for patients who would otherwise have received docetaxel. It has since become **the treatment of choice for around three-quarters of patients at 2L** (Kantar Health on behalf of Roche 2013), with most of the rest receiving docetaxel.

More recently, the clinical picture has been complicated by the finding that a small sub-group of patients with EGFR M+ disease (around 10% of the total) are extremely sensitive to EGFR TKIs. For these patients, erlotinib or gefitinib offer a much better balance of efficacy and toxicity/inconvenience than first line (1L) chemotherapy, with NICE recommending both drugs in this setting. Subsequent to this guidance, EGFR mutation testing has become

standard diagnostic practice, with known EGFR M+ patients universally treated with erlotinib or gefitinib at 1L.

Figure 1: Treatments in clinical practice



Such treatment is continued until disease progression, so that for M+ patients an EGFR TKi is not an appropriate 2L treatment option. Thus the 2L patient pool available for erlotinib consists of EGFR WT patients who will have received chemotherapy 1L plus a smaller group (perhaps 20-30%) whose EGFR status is unknown and, for practical purposes, unknowable because of a lack of archival tissue to test and an unfitness or unwillingness to undergo repeat tumour biopsy. In other words, the 2L group potentially treatable with erlotinib consist of a majority of WT patients, who might be expected to benefit somewhat less from erlotinib than the unselected population which are covered by the original 2L NICE guidance for erlotinib (TA162).

Despite the eligible population consisting of a majority of WT patients, and some recent evidence that in WT patients docetaxel may be a somewhat more active treatment in terms of response rates (RR) and progression-free survival (PFS), erlotinib remains the dominant 2L treatment in the UK, with a very consistent market share of around 70% of treated patients (Kantar Health on behalf of Roche 2013). This almost certainly reflects the fact that UK clinicians consider the alternative – docetaxel, to be sufficiently toxic and inconvenient

that they consider it to be either an unacceptable option or the least suitable treatment for many of their patients.

Despite the original NICE recommendation that erlotinib should only be used for patients suitable for docetaxel, the reality is that, **were erlotinib not available, many patients currently receiving erlotinib at second-line would no longer receive active 2L therapy**.

1.3. The Technology – Erlotinib

Erlotinib (Tarceva) is an oral tyrosine kinase inhibitor (TKI) of the human epidermal growth factor receptor (EGFR, HER1). The EGFR is a cell surface receptor which controls cell growth and differentiation. It became a target for anticancer drug development when it was observed that many cancer cells have abnormalities in EGFR signalling. Around 70% of NSCLC samples show protein overexpression often with amplification of the EGFR gene and overexpression is associated with poor prognosis. It was these observations that made NSCLC the major focus of erlotinib clinical trials.

It was subsequently found that a small group of NSCLC tumours (around 10% in Caucasian patients but 30% in those from SE Asia) harbour an activating EGFR mutation. In these tumours EGFR signalling is continuous and does not require the binding of a signalling molecule to the receptor. Cells with the mutation become “oncogene addicted” meaning that they cannot survive if signalling in this pathway is turned off. This explains why, when such tumours are treated with an EGFR TKI, tumour shrinkage can be rapid and dramatic.

In EGFR WT patients the effect of EFGR TKIs is more subtle – turning off EGFR signalling does not result, generally, in dramatic tumour cell death but does block the stimulus for cell growth and division, thus stabilising the tumour rather than producing high response rates.

In both EGFR WT and M+ patients the mechanism of action of erlotinib is the same – it binds to the phosphate binding site of the intracellular portion of the receptor preventing it from phosphorylating downstream signalling molecules.

Erlotinib has the following Marketing Authorisations for NSCLC. This submission relates to the third indication listed.

1. First-line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with EGFR activating mutations.

2. Monotherapy for maintenance treatment in patients with locally advanced or metastatic NSCLC with stable disease after 4 cycles of standard platinum-based first-line chemotherapy.
3. Treatment of patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen.

In addition erlotinib has an EMA Marketing Authorisation for the treatment of metastatic pancreatic cancer in combination with gemcitabine. However, it has never been promoted for this indication in the UK and usage is minimal.

1.4. Clinical Effectiveness

Erlotinib originally received regulatory approval and NICE endorsement as a 2L treatment for advanced NSCLC based on the results of the BR.21 study comparing erlotinib plus Best Supportive Care (BSC) with placebo plus BSC (Shepherd et al 2005). BR.21 was designed to assess erlotinib in patients with no further standard treatment options by reason of being too unfit for 2L docetaxel or having already received the drug. As shown in Table 2, this study carried out by the National Cancer Institute of Canada showed **significant improvements in OS** (the primary end-point), **PFS and Quality of Life (QoL)** (both the primary QoL end-points of time to deterioration of pain, cough and dyspnoea, but also global QoL).

Table 2 Summary of BR.21 trial results

	Erlotinib	**BSC**	**Incremental Gain**	**Additional data**
ITT Population	N= 488	N = 243		
Objective response rate	8.9%	<1%		
Overall survival (median)	6.7 months	4.7 months	2 months	HR 0.79 p < 0.001
Median time to deterioration:				
Cough	4.9 months	3.7 months	1.2 months	p = 0.04
Dyspnoea	4.7 months	2.9 months	1.8 months	p = 0.03
Pain	2.8 months	1.9 months	0.9 months	P = 0.04

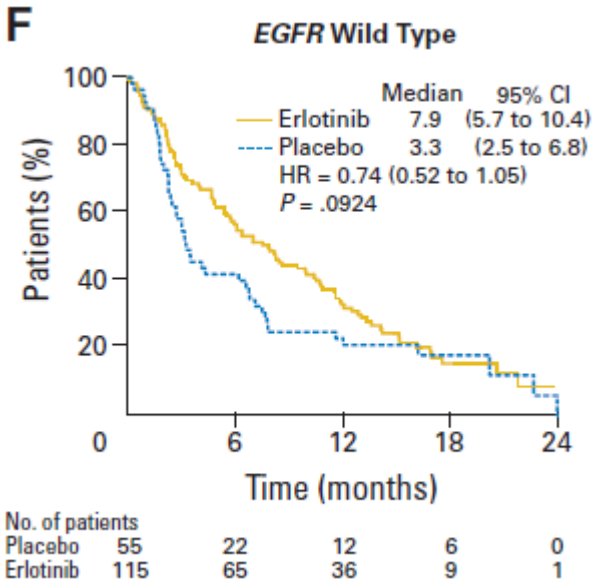
Of the candidate biomarkers for predicting sensitivity to erlotinib at the time of BR.21, none were considered sufficiently robust for clinical selection of patients for treatment and this was not a requirement of either the Marketing Authorisation or NICE guidance.

Since TA162, EGFR mutation status has emerged as a viable predictor of degree of benefit to EGFR TKIs. Again, as explained in the previous section, this has had two consequences. Firstly, erlotinib and gefitinib have become the treatments of choice at 1L for EGFR M+ tumours. Secondly, candidates for 2L erlotinib are, in the main, EGFR WT with some of unknown status. Thus the important question for this re-review is the extent to which erlotinib retains useful 2L activity in the changed 2L population.

Activity versus Best Supportive Care in WT patients

Although the significance of EGFR mutation was not known when BR.21 was started, a retrospective analysis of outcomes according to mutation status was carried out on remaining tumour samples from the study (Zhu et al 2008). Among 204 patients assessable for EGFR mutation status, 170 patients (83%) were wild type, 115 of which received erlotinib. Median OS for the WT subgroup was 7.9 m with erlotinib compared with 3.3 m in the placebo arm (HR 0.74; 95% CI, 0.52 to 1.05; P 0.0924). Despite not being statistically significant, based as it was on a small sample size, this finding suggests a beneficial trend in survival for WT patients when treated with erlotinib. Moreover the magnitude of benefit from erlotinib compared with placebo, among patients with wild-type EGFR (HR 0.74) was similar to that observed in the population as a whole (HR 0.70), with survival curves for WT group similar to those in the overall BR.21 population (see Figure 2).

Figure 2: EGFR WT overall survival (Zhu et al)



A similar OS benefit for WT patients receiving erlotinib after first-line platinum-based chemotherapy was seen in the SATURN study, where patients with at least stable disease after completion of first-line chemotherapy were assigned to maintenance erlotinib or

placebo. Patients were prospectively tested for EGFR mutation status. In the WT subgroup of patients with SD (stable disease) after 1L chemotherapy (n = 217), both PFS and OS were significantly prolonged with erlotinib (HR = 0.72 [95% CI 0.54–0.96]; P = 0.0231 and HR = 0.65 [95% CI 0.48–0.87]; P = 0.0041, respectively).

The WT data from SATURN and BR.21 have recently been the subject of a pooled analysis by Osarogiagbon et al (2013). Combined analyses resulted in an HR for PFS of 0.72 (95% CI: 0.60–0.87; p<0.01) and an HR for OS of 0.71 (95% CI: 0.58–0.87; p=0.044). Thus there is good evidence that, as would be expected from the pharmacology of erlotinib, it retains useful clinical activity in purely wild-type patients.

Activity versus chemotherapy in WT patients

Since the publication of TA162, two studies (TITAN (Ciuleanu et al 2012) and the HORG study (Karampeazis et al 2013)) have confirmed one of the underpinning assumptions of TA162 – that erlotinib has similar efficacy to 2L chemotherapy. However, these do not account for the changing characteristics of 2L patients, which raises the question of the efficacy of erlotinib compared with chemotherapy in WT patients. No study addressing this question has yet been the subject of a peer-reviewed publication, but two have been the subject of congress presentations (refer to section **Error! Reference source not found.** for further detail of both studies). The first of these, TAILOR (Garassino et al; 2012), had significant methodological deficiencies. The second, DELTA (Okano et al. 2013), although conducted in an Asian population, appears to be more robust (on the basis of limited information). Both suggest that 2L docetaxel produces somewhat higher RR and leads to slightly prolonged PFS in WT patients than erlotinib. However, in the only study to report this end-point (DELTA) both erlotinib and docetaxel appear to produce the same OS.

Taken together these results suggest that for 2L WT patients who are sufficiently fit to tolerate it and who are happy to receive further chemotherapy, docetaxel may be the preferred option. However, for WT patients, erlotinib remains a valid and valued treatment option and, for the substantial group who are unsuitable for docetaxel, with its aggressive toxicity profile and inconvenient IV administration schedule, erlotinib remains the only treatment option.

It is for these docetaxel unsuitable WT patients, that we propose that erlotinib should be a NICE-endorsed treatment option.

1.5. Cost Effectiveness

The scope of this re-review specifies erlotinib should be compared with docetaxel, gefitinib and best supportive care. However the economic evaluation conducted is focused on a comparison with best supportive care alone – in this population erlotinib is the only active treatment available. The justification for this approach is provided below.

Docetaxel

In NICE TA162, positive guidance was restricted to patients who are suitable for docetaxel, with the requirement that erlotinib was provided at an overall cost that was equivalent to docetaxel. The patent on docetaxel has subsequently expired and it is now available in generic form at a cost less than 10% of the list price of docetaxel in TA162.

As a consequence of this patent expiry we do not believe it is possible to demonstrate erlotinib is cost-effective compared to docetaxel even without the change in patient population referred to above to a predominantly WT group. For this reason we have not provided any economic evidence in support of this comparison.

Gefitinib

The majority of patients with EGFR mutation positive advanced NSCLC will have received either gefitinib or erlotinib (one of the EGFR TKIs) in the first line setting. It is not currently standard practice to retreat a patient with a subsequent EGFR TKI and EGFR M+ patients typically receive 2L treatment with doublet chemotherapy (likely pemetrexed/cisplatin), as this is, for them, their first chemotherapy. Following progression on this chemotherapy it is not expected that these patients will be retreated with a TKI (as progression on an EGFR TKI previously suggests that their disease has become resistant to this class of drug).

As a result, it is expected that the vast majority of patients with EGFR M+ disease will not be eligible for erlotinib or gefitinib after receipt of chemotherapy (which will typically take place as a second, rather than first, line treatment in this group) leaving only patients who are EGFR WT (plus a few with undeterminable mutation status) as candidates for 2L erlotinib. As gefitinib is no licensed in patients with EGFR WT disease, a comparison of erlotinib to gefitinib has not been made in this group.

Methods

A cost-utility analysis was conducted to compare erlotinib to best supportive care alone in the treatment of advanced NSCLC, in patients unsuitable for docetaxel (i.e. those who cannot tolerate docetaxel or those who have received it previously). An economic model was developed using data from BR.21 intent-to-treat population, which included mixed EGFR mutation status since EGFR mutation testing was not conducted prospectively in the study. A limitation of this analysis is acknowledged in this respect, since UK patients treated for advanced NSCLC will be almost entirely EGFR WT for reasons already described. As described more fully in Section **Error! Reference source not found.**, there are limitations to the data from a retrospective analysis of the EGFR WT population; therefore the original BR.21 analysis is thought to provide a more robust evidence base for the base case analysis. A wide range of sensitivity analyses (including subgroup analysis of those patients with retrospectively identified EGFR WT disease) was conducted to explore the uncertainty associated with the base-case ICER estimate. In addition a 5,000 simulation PSA was conducted and a CEAC produced.

Results

The base case ICER estimated for erlotinib compared to docetaxel in patients unsuitable for docetaxel was **£51,036**/QALY gained. Sensitivity analysis indicates that the key uncertainties in the model include utility values of PFS and PD, cost of progressed disease, cost of progression free disease and erlotinib dose reduction. Variation of these individual parameters produced the following results.

Table 3: Key uncertainties identified through sensitivity analysis

Parameter varied	Highest ICER £	Lowest ICER £
Nafees utility values PFS and PD	61,317	51,036
PFS Utility	59,116	44,900
PD Utility	54,487	47,997
Progressed disease costs	53,415	48,657
Progression free costs	52,647	49,425
Progression free costs reduced for erlotinib arm	51,036	45,565
Erlotinib dose reduction in 19% of patients and PFS cost reduction	51,036	44,121
Erlotinib dose reduction in 19% of patients	51,036	49,593

In the analysis using the EGFR WT data from BR.21 (n=170) the estimated ICER increased by approximately 14% to £58,579. In the base case, PSA indicates that erlotinib has a 0% probability of being cost-effective at a threshold of £30,000/QALY gained – at a threshold of £50,000/QALY gained this increases to 44%.

1.6. Conclusion

Due to the expiry of the patent of docetaxel, it is no longer possible to demonstrate that erlotinib is cost effective compared to docetaxel in patients who are able to tolerate docetaxel.

For those patients unsuitable for docetaxel, or who have previously received docetaxel, there is only one active treatment option available following progression on 1L chemotherapy - erlotinib. In this group, erlotinib has been demonstrated to provide a median survival benefit of 2 months, a PFS benefit of 0.4 months and a significant improvement in time to symptom deterioration which is a key marker of quality of life (all outcome measures of importance to people with high unmet need and burden of illness).

In this population, the cost-effectiveness of erlotinib is above the range typically accepted. It therefore appears that NICE approval of erlotinib at cost-effectiveness estimates of this magnitude will require consideration of the value wider society places upon the treatment of patients with a high burden of illness, a high unmet need and no alternative treatment options.

It should be noted that **restricting funding of erlotinib on the basis of this re-review would represent a substantial backwards step in the treatment of advanced NSCLC**, worsen the poor survival of people with relapsed lung cancer in the UK and remove the only treatment option available to many in this patient group. It would also have a significant impact upon the future treatment options available for UK NSCLC patients (given the fact that a significant number of technologies currently in development are designed to be combined with erlotinib).