Healthcare Improvement Scotland

NICE Health Technology Appraisal - Assessment Report **Erlotinib and Gefitinib for treating NSCLC that has progressed following prior chemotherapy (review of NICE technology appraisals 162 and 175)**	
TO: NICE **03 December 2013**	**FROM: Healthcare Improvement Scotland**

1. Comments provided to HIS by [redacted], [redacted], [redacted], [redacted], [redacted]

1. Gefitinib
Report addressed use of erlotinib only as gefitinib not licensed for second line systemic therapy

2. EGFR Testing
Evidence evaluated in Report and associated NICE appraisals predate widespread uptake of EGFR mutation testing at diagnosis in advance stage patients. The target population considered in this report therefore are large numbers patients all with EGFR mutation status unknown who have not had these drugs first line. Such a population no longer exists.

Patients with positive mutation will get these drugs as first line therapy so the only candidates for second line are mutation negative or unknown.

3. Mutation negative/unknown relapsing after chemo
This is the population currently for whom TKIS might be considered second line.

Cost benefit analysis undertaken in this Report shows that with price reductions having taken place for docetaxel, then docetaxel single agent is more cost-effective than erlotinib.

Best supportive care is also more cost-effective than erlotinib.

On criterion of cost-effectiveness alone then second line erlotinib not indicated.

4. Other Clinical Considerations
Issues raised in report to favour use of erlotinib in spite of straight cost-benefit lack of efficacy are advantage of oral over systemic therapy when comparing against docetaxel and also use in borderline performance status patients.

These possible ‘advantages’ are true in that most patients will prefer oral therapy and it does reduce hospital resources. Also patients with ECOG PS 2 might be able to

tolerate erlotinib but cannot manage docetaxel.

5. Further Research

I would totally endorse conclusion of report that further research needed – specifically:

If patients have had TKI first line for mutation positive tumour, what is optimal second line therapy ?
In confirmed EGFR negative patients what is expected QOL/OS benefit for second line therapy with TKI ?

2. Comments provided to Healthcare Improvement Scotland by Allan Price Consultant in Clinical Oncology NHS Lothian & Honorary Professor of Radiation Oncology University of Edinburgh Edinburgh Cancer Centre

The review concludes that epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKI) are not cost effective in patients with EGFR-unknown or EGFR-mutant tumours and that patients with EGFR-mutant tumours should already have received these agents first line. There will be a few patients in whom this status only becomes known at relapse but no trials were identified which examined this situation. It is also the case that those patients with EGFR–unknown tumours are different from those in the trials. In contemporary practice these are patients in whom adequate tissue for testing cannot be obtained; in the trials these were patients in whom no attempt at testing was made. Accordingly, and remarkably, 15 years into the development of EGFR TKIs in patients with non-small cell lung cancer the available data defines a group who should not be treated with these agents, those with EGFR-wild type tumours, but does not define the group who should be so treated, and there were no data to assess cost effectiveness. This is contrary to current SMC and NICE recommendations, where any patient may receive EGFR TKI after first line chemotherapy, and these recommendations will require revision. I think it likely this would fit with current practice, that most oncologists would not give an EGFR TKI unless there was evidence of an activating mutation in the tumour.

The search technique appears appropriate and thorough. There is a difficulty in comparing differing trial designs and in the differing molecular techniques as the field has evolved. Moreover the field is largely driven by pharmaceutically-sponsored trials (5400 participants) rather than academic studies (770 participants). The authors do not provide a detailed analysis of the relative primary outcomes or design of the individual trials considered. I also think some analysis of the quality of the economic trials could have been carried out.

The review rejects the use of meta-analysis on the available data, but the question remains whether an individual patient data meta-analysis would be worth pursuing. The review also raises the problem of the recommendations for treatment at relapse when EGFR TKI have been used first line; I would assume most patients in this setting receive cisplatin and pemetrexed second line and docetaxel third line – ie that the first line EGFR TKI is ignored.

I was unconvinced by the toxicity costings, and I didn’t understand (or recognise) the admission rates for toxicities (p104), and would question the use of the Big Lung Trial data, largely from the 1990s, as a comparator (see Table 46).

The argument from Roche that patients with EGFR-wild type tumours should receive erlotinib (response rate 3%, median survival 5 months) not chemotherapy because of

a preference for tablets over injections seems perverse given the inactivity of the drug in this setting – by analogy this would argue for using penicillin V not tazocin for neutropaenic sepsis even though the first drug is ineffective and many patients would die as a result.

As indicated above the recommended research questions reflect existing practice, and I think the third line trial would be difficult to recruit to although the question is valid.

In summary I think this is a valuable review indicating a need to revise current guidelines, although I think the reality of contemporary practice would be EGFR-TKI -> cisplatin-pemetrexed-> docetaxel in patients with EGFR-mutant tumours and cisplatin-pemetrexed-> docetaxel in all others. The areas of rechallenge with previously used drugs is un(der)-explored in patients with non-small cell lung cancer.