Nicole Fisher
Appraisal Project Manager
National Institute for Health and Care Excellence
Level 1A, City Tower
Piccadilly Plaza
Manchester
M1 4BT
BY EMAIL

24 February 2014

RE: Erlotinib and gefitinib for treating non-small-cell lung cancer that has progressed following prior chemotherapy (Review of TA162 and TA175) [ID620]

Dear Nicole,

Thank you for giving us the opportunity to comment on the above ACD. We believe this appraisal raises an important issue – an issue which must be addressed if the final recommendation is to be considered a sound and suitable basis for the issuance of guidance to the NHS.

Under the terms of the Pharmaceutical Price Regulation Scheme 2014, the total spend on branded medicines in the UK is capped. The scheme caps the budget with annual growth limited to 0% in 2014 through to 1.9% in 2018.

Forecast growth is significantly higher at 3.87% in 2014 – when the expected growth rates are compounded, by 2018 the uncapped spend on branded medicines will be 17.59% above the current level whilst the agreed spend level with the cap will be only 5.6% above the current level.

Roche Products Limited
6 Falcon Way
Shire Park
Welwyn Garden City
Hertfordshire
AL7 1TW
Market Development
Directorate
Tel. +44(0)1707 360000
Fax +44(0)1707 384123

This will result in an anticipated overspend above the cap in the region of £386m in 2014 rising to £1202m in 2018*. All expenditure which exceeds the cap will be rebated by industry.

This PPRS agreement raises an interesting question. If expenditure on branded medicines remains above the agreed cap level in the scenario of a positive or negative NICE decision (as it will in the case of erlotinib) is it reasonable for an Appraisal Committee to make a decision under the assumption that funding the medicine in question will come at an additional cost to society?

In the case of this appraisal, decommissioning erlotinib in patients unsuitable for docetaxel will result in a reduction in spending by the NHS; however this will result in an equivalent reduction in the PPRS rebate paid by industry. There is an opportunity cost associated with this loss in rebate which must be considered by the Committee.

We appreciate this is a complex issue that has not been discussed in an Appraisal to date and one that may need to be considered further by the Institute. However, we feel this is something which must be addressed if the Committee's decision is to be considered a sound and suitable basis for guidance to the NHS.

We also believe the Committee has not fully considered all relevant information on the incidence of febrile neutropenia and other treatment-related infections in patients treated with docetaxel.

Our clinical advisors strongly believe the Committee's preferred scenarios underestimate the incidence of this adverse event in clinical practice, a view supported by published literature.

Kind Regards

[redacted]

* This estimate is based upon an assumed capped branded drugs budget of £11bn in 2014 rising to £11.7 by 2018, with estimated PPRS rebates of 3.74% in 2014 increasing to 9.92% in 2018 (PPRS 2014)

Has all the relevant evidence been taken to account?

No. As outlined above the impact of the 2014 PPRS scheme has not yet been considered by the Committee. We believe that this issue must be addressed if the decision reached is to be reasonable. If the PPRS rebate lost via decommissioning of erlotinib in included in the economic model the ICER for the EGFR WT population compared to best supportive care is £5,884 per QALY gained.

In addition, the Committee has not taken into account all relevant information on the incidence of febrile neutropenia and other treatment-related infections in patients treated with docetaxel. This point is outlined below.

(1) The Committee have underestimated the incidence of treatment related infection when treating with docetaxel

We are pleased that the Assessment Group (AG) analysis reflects the considerable indirect costs associated with docetaxel use, such that, in their estimation, the costs of docetaxel treatment are greater to the NHS than those associated with erlotinib. A major element of these costs is associated with toxicity management. Because docetaxel is considered slightly more effective but more costly to the NHS, the cost-effectiveness of docetaxel relative to erlotinib is crucially dependent on the costs of toxicity management which we believe were underestimated by the AG.

The dominant toxicity with docetaxel is damage to the bone marrow and blood leading to immunosuppression with a predisposition to infection. When the level of specific white blood cells (neutrophils) drops below a critical level (0.5×10^9/L) even trivial infections can rapidly become overwhelming and life-threatening. Because of this, patients with neutrophil counts below this level who develop a high temperature (or other signs of infection) are deemed as requiring urgent treatment with broad-spectrum antibiotics This condition is described as febrile neutropenia (de Naurois J *et al*. 2010). For most patients in England, febrile neutropenia results in admission to hospital for intravenous therapy (Okera *et al.* 2011). Despite such treatment, febrile neutropenia is still a very serious problem and in a published audit from England's largest Cancer Centre, the mortality rate for patients with febrile neutropenia associated with chemotherapy for solid tumours was 4.2% (Okera *et al.* 2011).

However, patients receiving immunosuppressive chemotherapy for cancer are also more vulnerable to infection on days when their neutrophil count is not low enough for any infective episode to be classified as febrile neutropenia, but when they are still relatively immunosuppressed. Systemic infections in debilitated lung cancer patients whose immune system is depressed by chemotherapy often also results in hospitalisation (Cullen *et al.* 2005).

We believe that important relevant information on infective episodes during docetaxel treatment has not been taken into account in the formulation of this guidance. This information pertains to:

- the rates of febrile neutropenia in clinical trials
- the rates of febrile neutropenia in routine clinical practice
- the rates of docetaxel-related infections that do not meet the criteria for febrile neutropenia

We consider that the evidence outlined below demonstrates that docetaxel is cost ineffective in comparison to erlotinib.

(2) Rates of febrile neutropenia in clinical trials are higher than estimated by the Committee

The ACD states that the Committee believes the true rate of febrile neutropenia to lie somewhere between 3.85% from TAILOR (Garassino *et al.* 2013) and 5.95% from the DSU 2008 analysis of clinical trials (Wailoo *et al.* 2009).

The Committee appear to have disregarded the AG pooled AE rate of 7.6% (Greenhalgh *et al*. 2013) and provided no justification for doing so, even though this represents the most recent, independent pooled analysis and was conducted specifically to inform this Appraisal.

The febrile neutropenia rate from either pooled analysis seems more relevant than the 3.6% rate from the TAILOR study. The TAILOR febrile neutropenia rate would rank 10th out of 14 in the trials included in the DSU meta-analysis. In a large part, this low rate is due to the weekly docetaxel schedule that was used in a significant proportion of the TAILOR subjects. A schedule that the clinical expert at the Committee meeting confirmed is not used in this country and would be very costly to deliver if it was.

It is unclear how the Committee has taken into account either the issues outlined regarding TAILOR dosing and consequent febrile neutropenia rates or the AG pooled AE rates.

(3) Rates of febrile neutropenia in clinical practice are higher than estimated by the Committee

The Committee has also omitted to consider the written estimate from the NCRI/RCP/RCR/ACP/JCCO which suggest that admission rates for neutropenic sepsis and treatment complications are up to 10 times higher for docetaxel compared to erlotinib (25-50% with docetaxel compared to <5% with erlotinib) in clinical practice. This accords with Yvonne

Summers's view, given at the Committee meeting that rates of febrile neutropenic fever and complications ranged from 25% up to 50% (in less fit patients) in clinical practice.

At a recent advisory board, clinicians continued to express that rates of febrile neutropenia experienced in trials are a significant underrepresentation of those seen in clinical practice.

Moreover, during the original appraisal of erlotinib in this setting, Professor Nick Thatcher (2008) referred to an audit conducted in his department at the Christie Hospital in Manchester showing a febrile neutropenia rate of 15% in this setting

It is unsurprising that febrile neutropenia rates in clinical practice are reported as being much higher than in trials. Only the fittest patients general satisfy the selection criteria for clinical trials, with few accepting poor Performance Status patients (PS 2 or 3). The SIGNIFICANT (Cullen *et al,*2007) study also showed that poor physical fitness (performance status; PS 2+) approximately doubles the risk of being hospitalised for infection during chemotherapy.

The Committee has failed to consider available evidence on febrile neutropenia rates in clinical practice.

(4)Febrile neutropenia rates alone underestimate the total hospitalisations for infection

As stated above, patients hospitalised with infection do not always satisfy the blood count criterion for febrile neutropenia, so that febrile neutropenia rates alone underestimate hospitalisation rates for infection and hospitalisation rates for toxicity are not often reported in clinical trials. One exception is the phase III randomised comparison of docetaxel and pemetrexed as second-line chemotherapy for relapsed non-small-cell lung cancer reported by Hanna *et al* (2004). In this study, prophylactic G-CSF usage was rare (1.4%) with G-CSF only allowed after previous febrile neutropenic episodes and the rates of hospitalisation for docetaxel-related toxicity were correspondingly high with 13.4% of patients hospitalised at least once for neutropenic fever and 10.5% of recipients admitted at least once for other docetaxel-related toxicities, which would include non-neutropenic infections.

These figures are mirrored by the findings of the SIGNIFICANT study (Cullen *et a*l 2005, 2007). This was a large randomised, placebo-controlled study of levofloxacin as prophylaxis against febrile neutropenia and hospitalisation for infection in patients receiving cyclical chemotherapy for solid tumours and lymphomas. This investigator-led study was carried out in the UK and is particularly pertinent to clinical practice since there were no restrictions on patients receiving

chemotherapy – they were recruited from the general cancer population and received chemotherapy as clinically indicated. In this study, 10.8% of patients in the levofloxacin group and 15.2% of placebo patients experienced a febrile episode but the rates of hospitalisation for the treatment of infection (again as clinically indicated) were 15.7% and 21.6% in the levofloxacin and control groups respectively. It should be noted that "febrile episodes" in this study were recorded independent of blood count and are almost certainly higher than the febrile neutropenia rate (not reported) but are an important measure as febrile episodes in chemotherapy recipients need to be treated as febrile neutropenia until such time as neutropenia can be excluded by an urgent blood test requiring hospital attendance and even without a very low blood count may represent a clinically important infection.

Although SIGNIFICANT was not conducted specifically in lung cancer patients, it is noteworthy that rates of hospitalisation were in the range 18.9% to 31.5% for all tumour groups with 29.1% for small-cell lung cancer. Given that docetaxel in 2L NSCLC is notorious for its myelotoxicity and related problems, the overall figures in SIGNIFICANT would seem to be a minimum that might be expected were docetaxel to be studied separately.

It is reasonable to propose that the rate of hospitalisation for docetaxel-related infection in clinical practice is in the region of approx. 15-20%.

(5) Increased hospitalization rates for infection result in docetaxel becoming cost ineffective compared to erlotinib

Taking the available clinical trial data together, it is reasonable to propose that the most plausible clinical trial rate of febrile neutropenia with docetaxel is around 7%, whilst the rate of hospitalisation for docetaxel-related infection in clinical practice is likely to be much higher – in the region of approx. 15-20%. Whether patients admitted with infections formally satisfy the requirement for febrile neutropenia makes little difference to their experience, neither is it likely to make much difference to the burden their admission places on the NHS.

A hospitalisation rate in the plausible range of 3.85% to 15% produces ICERs ranging from £15,359 (AG base case) through to £87,371 for docetaxel compared to erlotinib (Table 1). Our analysis revealed that at any rate above 6.2%, docetaxel can be considered cost-ineffective.

Table 1: Hospitalisation rates for infection higher than 6.2% results in docetaxel being cost ineffective compared to erlotinib

Rate of hospitalisation for infection	Docetaxel	Erlotinib	Incremental Cost £ / QALY	ICER (docetaxel v erlotinib)
	Total Cost £ / Total QALY	Total Cost £/ Total QALY		

Base Case 3.85%	15,702 / 0.5949	14,049 / 0.4863	1,653 / 0.1076	£15,359
DSU 5.95%	17,096 / 0.5931	14,049 / 0.4863	3,047 / 0.1068	£28,520
AG Pooled AE rates 7.6%	18,189 / 0.5925	14,049 / 0.4863	4,140 / 0.1062	£38,976
Roche estimate 15%	23,092 / 0.5898	14,049 / 0.4863	9,043 / 0.1035	£87,371

(6)Intended and unintended consequences of removing access to erlotinib at second-line

The situation that the current ACD will produce, if reflected in the final guidance is, Roche believes, unique in several ways:

- It will remove access to the most widely used active therapy in a serious medical condition without allowing a replacement
- It accepts docetaxel as standard of care (which therefore does not need to prove its cost-effectiveness) even though it is less widely used than erlotinib. In doing so it is requiring a higher standard of evidence of erlotinib than docetaxel
- It removes from patients and clinicians the choice of a treatment which by the AGs calculation, costs the NHS less than docetaxel. Were docetaxel toxicity to be more accurately reflected in the calculation, docetaxel would not meet NICE's criteria for cost-effectiveness

As well as the consequences of reducing treatment choice for fitter patients and removing any active treatment choice for less fit patients, the guidance outlined in the ACD is likely to have other unintended and undesirable consequences:

- **Unsuitable patients will receive docetaxel.**

As detailed above, docetaxel is a very toxic therapy, currently reserved by clinicians for their very fittest patients. Less fit patients for whom active therapy is still deemed appropriate generally receive erlotinib. There is a real danger that if erlotinib is not available clinicians will feel a pressure to treat patients with borderline fitness with docetaxel. Such patients are likely to experience disproportionate and sometimes fatal toxicity. This is not good for either patients, clinicians or the NHS. A recent UK audit showed that the median duration of a hospital stay with febrile neutropenia is 5 days. Moreover, the same audit demonstrated that despite prompt treatment 4.2% of patients admitted to hospital with febrile neutropenia died as a result.

- **There will be increased use of unlicensed, cost-ineffective and unproven alternatives**

Because clinicians feel that they still need to be able to offer active palliative anti-cancer therapy to relapsed NSCLC patients unsuitable for docetaxel, they will seek better tolerated alternatives, which they currently believe that they will have access to. Those mentioned to us at an Advisory Board include: single agent oral vinorelbine, single agent IV gemcitabine and single-agent weekly paclitaxel. Of these, none has been the subject of a Phase III comparative study in this setting, none has a UK Marketing Authorisation in this indication and none has been subject to any sort of appraisal of cost-effectiveness by NICE. Appropriately, they were not included as comparators in this appraisal as they are currently rarely used and clinicians will only turn to them if they have no alternative. Given that oral vinorelbine is a patented product and the other two require weekly IV infusions they are unlikely to be more cost-effective than erlotinib.

- **There will be increased use of fluoroquinolone antibiotics with associated drug resistance problems**

As stated above docetaxel is highly toxic to white blood cells and its use is associated with high rates of serious infection which clinicians are anxious to avoid. NICE guidance precludes them from using haematopoetic growth factors like G-CSF to protect the white cell count and many resort to the use of prophylactic fluoroquinolone broad-spectrum antibiotics (Cullen *et al,* 2005, 2007, Okera *et al* 2011). These have been shown to reduce infection rates during chemotherapy. However, the unnecessary use of effective antibiotics is likely to lead to bacterial resistance, which is already a huge problem for the NHS and described as recently as last year by England's Chief Medical Officer, Sally Davies as "a bigger threat than terrorism" (Independent, February 2014).

In summary, the guidance in the ACD, if implemented is likely to reduce patient choice, remove the only active treatment option for a gravely ill patient group. At the same time it is likely to increase the use of a highly toxic treatment, that is almost certainly not cost-effective if its toxicity is properly accounted for, as well as other treatments with a minimal evidence base and high associated resource use. As a result emergency admissions to hospital for treatment of infection are likely to increase as are deaths from treatment-related infection and the incidence of fluoroquiniolone resistance. Taken in the broader context, the draft guidance is bad for patients, bad for clinicians, bad for the NHS and bad for the future health of the nation.

Are the summaries of clinical and cost-effectiveness reasonable interpretations of the evidence?

No, for the reasons identified above.

Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

No. As outlined above the impact of the PPRS must be considered is the provisional recommendations are to be considered sound and a suitable basis of the issuance of guidance to the NHS.

We also believe the recommendations will result in patients receiving less suitable treatments of uncertain clinical and cost-effectiveness.

References

Cullen MH, Steven N, Billingham L, Gaunt C *et al.* Antibacterial prophylaxis after chemotherapy for solid tumours and lymphomas. *New Engl J Med.* 2005; **353**: 988-998.

Cullen MH, Billingham LJ, Gaunt CH, Steven NM. Rational selection of patients for antibacterial prophylaxis after chemotherapy. *J Clin Oncol.* 2007; **25**: 4821-4828

De Naurois J, Novitzky-Basso I, Gill MJ, Mart Marti F *et al.* Management of febrile neutropenia: ESMO clinical practice guidelines. *Ann Oncol.* 2010; **21** (suppl. 5): v252-256.

Garassino MC, Martelli O, Broggini M, Farina G et al. Erlotinib versus docetaxel as second-line treatment of patients with advanced non-small-cell lung cancer and wild-type *EGFR* tumours (TAILOR): a randomized controlled trial. *Lancet Oncology* 2013 XXXX

Greenhalgh J, Bagust A, Boland A, Dwan K *et al.* (2013) *Erlotinib and gefitinib for treating non-small cell lung cancer that has progressed following prior chemotherapy (review of NICE technology appraisals 162 and 175).* The Liverpool Reviews and Implementation Group, University of Liverpool.

Hanna N, Shepherd FA, Fossella FV, Pereira JR *et al* Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated witrh chemotherapy. *J Clin Oncol.* 2004; 22: 1589-1597

The Independent, 11 March 2013. Chief Medical Officer Dame Sally Davies: Resistance to antibiotics risks health 'catastrophe' to rank with terrorism and climate change

Okera M, Chan S, Dernede U, Larkin J et al. A prospective study of chemotherapy-induced febrile neutropenia in the South West London Cancer Network. Interpreatation of study results in light of NCAG/NCEPOD findings. *Br J Cancer.* 2011; **104**: 407-412

Shepherd FA, Dancey J, Ramlau R XXXX *et al.* Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. *J Clin Oncol.* 2000; **18:** 2095-2103.

Thatcher N. *Single Technology Appraisal: Erlotinib for the treatment of non-small cell lung cancer. Estimate of costs of treating Docetaxel associated Febrile Neutropaenia at the Christie in NSCLC patients*. (Evidence submitted to NICE, 2008) www.nice.org.uk/nicemedia/live/11714/39169/39169.pdf (*accessed 18.02.14*)

Wailoo A, Sutton A and Morgan A. The risk of febrile neutropenia in patients with non-small-cell lung cancer treated with docetaxel: a systematic review and meta-analysis. *Br J Cancer.* 2009: **100**: 436-441.