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From The Registrar
[redacted]

Meindert Boysen
Programme Director, Centre for Health Technology Evaluation
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24 February 2014

Dear Mr Boysen

Re: Erlotinib and gefitinib for treating non-small-cell lung cancer that has progressed following prior chemotherapy (Review of TA162 and TA175) [ID620] – Appraisal Consultation Document (ACD)

The Royal College of Physicians (RCP) plays a leading role in the delivery of high quality patient care by setting standards of medical practice and promoting clinical excellence. We provide physicians in the United Kingdom and overseas with education, training and support throughout their careers. As an independent body representing over 29,000 Fellows and Members worldwide, we advise and work with government, the public, patients and other professions to improve health and healthcare.

I write on behalf of the NCRI/RCP/RCR/ACP/JCCO with regard to the above consultation. We are grateful for the opportunity to comment on the ACD and would like to submit the following comments.

We accept preliminary recommendations 1.1 and 1.2.

With regard to recommendations 1.3 and 1.4 we would make the following observations:

- **Has all of the relevant evidence been taken into account?**

Recommendation 1.3 – No. The committee have not adequately considered the possibility of a false negative EGFR mutation test result. This may arise due to genotyping of a tumour specimen with inadequate tumour tissue, resulting in failure of the EGFR genotyping technology applied to detect the EGFR mutation.

Recommendation 1.4 – No. The committee have not determined what is classified as an unobtainable EGFR mutation test due to inadequate sample or poor DNA quality. This is a subjective measure of sample or DNA quality, and would be contingent on subjective evaluation, and is therefore prone to considerable bias nationally.

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

No; the DSU meta-analysis of febrile neutropenia rates for docetaxel grossly under-estimates true incidence. Moreover, in the trials pooled, prophylaxis with GCSF was available. Due to implementation of NICE CG151, GCSF prophylaxis is no longer recommended in the UK, and febrile neutropenia rates (and associated management costs) will be considerably higher, as has been reported in England at 41% (Sharma, Lung

Cancer (2009) vol 63, suppl1;S6). Furthermore, if docetaxel is the only NICE approved 2nd line therapy for EGFR wild type (negative) NSCLC the febrile neutropaenia rates are likely to be higher than those currently observed, as patients of poorer performance status (who currently receive erlotinib) may be treated with docetaxel to ensure that they have access to second line therapy. ***This is the most important flaw in the analysis with the most significant consequences for quality of lung cancer care in the NHS.***

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

No; to suggest that for patients with unknown genotype, that response is the only indicator to continue therapy goes directly against the clinical data, which clearly demonstrate a radiological response rate of 56% (LUX 3 trial) to 80% (OPTIMAL trial). Therefore at least 20% of patients with unknown genotype and EGFR mutation positive would have erlotinib withdrawn inappropriately. For these patients, withdrawal inappropriately could lead to tumour flare (Riely et al Clinical Cancer Research 2007; Chaft et al. Clinical Cancer Research 2011), and poor outcomes, especially if further systemic therapy was not possible.

- **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?**

Yes; with respect to recommendation 1.4. Considerable evidence supports the fact that EGFR mutation is commoner in never-smokers, females, and East Asian ancestry. However, considerable evidence demonstrates that this relationship is not robust and multiple patient series have demonstrated EGFR mutations occur in patients with current or ex-smoking backgrounds, and not of East Asian ancestry (30% in one series; Leary Eur J Canc 2012;48:61-7). Therefore, to recommend possible erlotinib use in a sub-group selected by gender, race, or smoking status is discriminatory.

Yours sincerely

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