NICE ID620 response

The BTOG steering comittee~~l~~ agree with the preliminary recommendations 1.1 and 1.2

The BTOG steering committee~~l~~ disagree with recommendations 1.3 and 1.4

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

No; the committee have not adequately considered the possibility of a false negative EGFR mutation test result. This would 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.

No: for recommendation 1.4, 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 implantation of NICE CG151, GCSF prophylaxis is not longer recommended, and febrile neutropenia rates (and associated management costs) will be considerably higher, and has been reported in England at 41% (Sharma Lung Cancer (2009) vol 63, suppl1;S6).

No: The committee has put considerable weight on the Tailor data in reaching its recommendation. Further, flaws in the study and the caveats in interpretation of the data were not included in the consultation document. The Tailor study was conducted over many years, with changes to the primary outcome and without appropriate protocol-driven assessments of end points, particularly the lack of regular tumour response rate assessment for PFS data. The response rate in the Tailor study was grossly different to data from other studies. It was the conclusion of ASCO that "the results of the Tailor study should not be used to make decisions about second line therapy in NSCLC".

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

No: trial data documented in the ERG report (IPASS trial, Mok et al NEJM) clearly demonstrated that despite clinical selection, only 60% of patients harboured EGFR mutation. As a consequence, routine EGFR genotyping regardless of clinical features has been routinely implemented in the UK (and globally) following from NICE guidance TA192 and TA258. To suggest that clinical selection should be employed for genotyping is contrary to study data.

No: to suggest that for patients with unknown genotype, that response is an indicator to continue therapy goes directly against the clinical data, which clearly demonstrate a radiological response rate of 56% (LUX 3 trial) - 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 inappropriate would 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.

No: the recommendation 1.4 to allow erlotinib to patients with tissue unsuitable for genotyping will perversely drive clinical decision making to artefactually increase the number of tumour samples from patients deemed (subjectively) unsuitable for EGFR genotyping.

- 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 wholly discriminatory.