British Thoracic Oncology Group

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Dr Carole Longson
Director
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NICE

Dear Dr Longson

NSCLC – Gefitinib Appraisal Consultant Document (ACD)

The following comments are made on behalf of the British Thoracic Oncology Group (BTOG) with regard to the NICE ACD 'gefitinib for the first line treatment of locally advanced or metastatic non-small cell lung cancer' issued January 2010.

The organisation would like to express its disappointment that NICE was not minded to recommend gefitinib for the appraised indication.

In rapidly moving fields where clinical trials of drugs with novel mechanisms of action are under development it is always possible for more research to be undertaken or for existing data to become more mature. The problems are multiplied when the new treatment is targeted at a new genetically defined disease such as activating mutations of EGFR which essentially define a previously unknown disease entity. Thus an analysis of survival of NSCLC patients with activating mutations of EGFR before and after introduction of gefitinib showed a doubling of median survival in these patients, but no change in mutation negative patients (Takano et al, J Clin Oncol, 2009). This situation hasn't arisen since mutations in c-kit defined most gastrointestinal tumours (GISTs) as a disease definable by sensitivity to imatanib. It is easy to retreat into the cul du sac of claiming more data is needed but not very sympathetic to a rapidly evolving field.

In these situations the addition of the novel therapy adds to standard treatments in terms of PFS and survival. The question of 'comparator' is not so easy to define. In the available data the chemotherapy comparator was chemotherapy with carboplatin and taxol. This chemotherapy is widely used in the USA, often for 6 cycles or even until disease progression. In Europe and the UK first line treatment has generally not included a taxane and we tend to favour cisplatin over carboplatin because of the meta analysis superiority of cisplatin over carboplatin. Most patients with EGFR mutations (> 95%) are non-squamous cancers thus the UK/European comparator would be cispaltin 75 mg/m^2 plus pemetrexed 500 mg/m^2 given for up to 6 cycles with a median of probably 4-5. This chemotherapy is well tolerated with a febrile neutropaenia rate of 1.4%. Other regimens such as cisplatin/navelbine have such high febrile neutropaenia rates (around 10-17%) that clinicians rarely use them and are no longer real world comparators. Thus the most realistic comparator for gefitinib first line would be cisplatin/pemetrexed.

It is of interest that NICE in point 1.5 comment about the shape of the survival curves and exploration of alternative probability distributions. I am sure that the provision of patient level data will resolve this red herring and it is very unlikely that Weibull distribution curve will be statistically bettered.

As ever the very blunt quality of life assessments made by NICE undermine the real quality of life benefits for patients who receive gefitinib first line. The Expert Review Group seems to have been confused about these points. Thus in 4:13 (page 30 of 47) they analyse the data by inappropriate measures such as hazard ratios so as cross study comparisons could be made. It is a constant disappointment to clinicians that the diligent collection of quality of life (QoL) data is not fully taken into account by NICE who rely of generic QoL tools such as EQ5D, rather than validated disease specific models.

We would urge NICE to take account of the large benefit which gefitinib brings to patients with activating mutations of EGFR in the first line setting. These patients have significantly increased objective tumour response rates and prolonged progression free survival if they receive gefitinib first line. These observations correlate with improved disease specific symptom control. We accept that overall survival has not yet been convincingly demonstrated in a randomised controlled trial but are optimistic that in the near future additional information will be available from clinical trials to make the case for first line gefitinib in this indication overwhelming. This is underpinned by the data of Takano et al discussed earlier which indicate that when a large benefit is associated with any given treatment it is clinically obvious.

Yours sincerely
For and on behalf of British Thoracic Oncology Group

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BTOG President

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