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Robert Fernley
By email: TACommD@nice.org.uk

From [redacted]
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Dear Mr Fernley

Re: Single Technology Appraisal (STA) Bevacizumab in combination with capecitabine for the first-line treatment of metastatic breast cancer [ID54] - Appraisal consultation document

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 26,000 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 National Clinical Research Institute (NCRI), Royal College of Physicians (RCP), Royal College of Radiologists (RCR), Association of Cancer Physicians (ACP) and Joint Collegiate Council for Oncology (JCCO). These organisations work jointly to respond to NICE oncological consultations and would like to make the following comments.

Has all of the relevant evidence been taken into account?

There is only one directly relevant published clinical trial: RIBBON-1, and this has been discussed and analysed in detail. More data available is in the second-line setting: the RIBBON-2 trial (Brufsky et al, J Clin Oncol 29:4286-4293). Whilst not directly applicable this does provide additional information regarding efficacy and tolerability of capecitabine/bevacizumab. However the patient numbers are small and in the second line setting.

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

The summaries of clinical effectiveness appear accurate. Our experts would emphasise the challenge of the treatment of women with triple negative breast cancer for whom there are limited treatment options. In this sub-group of patients could bevacizumab/capecitabine fall within the life-extending, end-of-life treatment category? Certainly in a retrospective analysis of second-line data there was an increase in median PFS in this group of women (6 vs 2.7 months, p=0.0006), and a non-significant improvement in overall survival of 5 months (17.9 vs 12.6 months, p=0.0534) (Brufsky et al, J Clin Oncol 29: 2011 (suppl; abstr 1010)). Regarding applicability to UK clinical practice; capecitabine is not an uncommon choice as first-line treatment for metastatic (HER2 negative) breast cancer: for the reasons outlined (oral, no hair loss). This is even when a taxane has not previously been administered. Some clinicians start at a dose lower than the

original licensed dose (often 1000mg/m2 bd) even in fitter patients. Therefore this combination of treatments is of relevance to UK practice.

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

The evidence reviewed is a sound basis on which to base guidance to the NHS. Our experts wish to emphasise the value of the health state in which a patient is not-progressing as a positive one (congruent with the comments of patient expert, section 4.2). In other words the value of progression-free survival as an outcome measure, particularly give the difficulties with cross-over and interpretation of overall survival data elaborated in the document.

Yours sincerely

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