Lapatinib and trastuzumab in combination with an aromatase inhibitor for the first-line treatment of metastatic hormone receptor positive breast cancer which over-expresses HER2

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Comments coordinated [redacted]

Metastatic breast cancer is a fatal disease. The objectives of treatment are to control symptoms and to prolong life whilst at the same time minimising the burden of treatment to the patient. The majority of women who develop metastatic disease have hormone receptor positive (HR +ve) disease. It is well understood by oncologists that in general, endocrine therapy offers a more sustained remission with a superior quality of life than can be achieved with chemotherapy. This is recognized by the NICE Guidance on the Diagnosis and Treatment of Advanced Breast Cancer (CG81), which advises that initial endocrine treatment should be the norm unless the disease is immediately life-threatening in which case chemotherapy is preferred. HER2 +ve metastatic breast cancer has historically presented a particular problem to oncologists because it tends to be rapidly progressive, is frequently life-threatening at presentation and is HR –ve in approximately 50% of cases. Because of this, there is reluctance by oncologists to offer hormonal therapy to women with HR +ve HER2 +ve disease.

The usual treatment offered to women with HER2 +ve metastatic breast cancer in the UK is chemotherapy in combination with trastuzumab (administered 3-weekly), followed by trastuzumab monotherapy until disease progression. The NICE guidance on trastuzumab in advanced disease (TA34) is for combination therapy with paclitaxel in the first-line setting in patients who have had prior anthracycline treatment. Subsequent data from a randomised controlled trial supports the combination of trastuzumab and docetaxel; this combination, which is licensed by the MHRA and is clearly in the spirit of TA34, is preferred by most UK oncologists. TA34 also supports trastuzumab monotherapy in patients who have received 2 prior lines of chemotherapy. However because the RCT evidence shows an overall survival benefit for first-line trastuzumab-taxane combination therapy, this strategy is rarely used in practise. As taxane chemotherapy, particularly docetaxel 3-weekly is toxic and weekly paclitaxel is burdensome, in practise many elderly or less fit patients are treated with alternative less-toxic chemotherapy-trastuzumab combinations. The most widely used drugs for such patients are vinorelbine and more recently capecitabine. High-quality RCT evidence to support this practise is lacking but the available evidence is convincing. Anthracycline-trastuzumab combinations, although supported by RCT, are not used because of the unacceptable incidence of cardiac toxicity.

The publication of the TAnDEM trial of trastuzumab in combination with anastrozole and EGF30008 trial of oral lapatinib in combination with letrozole offer the welcome prospect of combining aromatase inhibitor and HER-targeted therapy in patients with HR +ve HER2 +ve disease. There is some evidence that disease with these characteristics may follow a somewhat more indolent course than HR –ve HER2 +ve disease which lessens the imperative for chemotherapy for these patients. This will give confidence to oncologists to use an approach that may offer a better quality of life in selected patients, particularly those who may find chemotherapy difficult to tolerate by virtue of

frailty or co-morbidity. The number of patients treated with this combination ab initio is likely to be small because of the widely held view that patients with HER2 +ve disease should be treated with chemotherapy. Were NICE to recommend aromatase inhibitor and HER-targeted therapy combinations, it is likely that there would be a gradual uptake of this approach.

In conducting the appraisal of lapatinib and trastuzumab in combination with an aromatase inhibitor, the most clinically relevant outcomes are progression-free and overall survival achieved with combination therapy in combination to monotherapy. The only clinical trials that inform this question that we are aware of are the TAnDEM and EGF30008 trials in which the comparator was an aromatase inhibitor. No trial has used HER2-targeted therapy as a comparator. An indirect economic analysis comparing lapatinib-letrozole with trastuzumab-anastrozole has been presented by the EGF30008 trialists at ASCO 2010. Randomised trials addressing the question of endocrine therapy and HER2-targeted therapies currently in progress include NCT00390455 (fulvestrant & lapatinib in HR +ve disease) and NCT00688194 (4 arm study of fulvestrant with aromatase inhibitor & lapatinib in HR +ve HER2 –ve disease). Additional trials are examining lapatinib and trastuzumab in combination with aromatase inhibitors. The HERA trial of adjuvant trastuzumab also in effect provides indirect evidence relating to trastuzumab-endocrine therapy combinations in a chemotherapy pre-treated population.

One important potential use of combination endocrine and HER2-targeted therapy that has not yet been addressed by clinical trials is maintenance treatment in metastatic disease following chemotherapy. It is standard practise in patients with HR +ve HER2 –ve disease who require treatment with chemotherapy but who are believed to have endocrine responsive disease to start endocrine treatment as maintenance on completion of a course of chemotherapy. The TAnDEM and EGF30008 trial results raise the possibility that a similar approach could be used HR +ve HER2 +ve disease. We are not aware of any trials in progress to study this question.