some comments:

first, what looks like an error: section 4.2.21:

gain of 316 days pre-progression survival with lapatinib treatment

I think should be

gain of 316 days pre-progression survival with trastuzumab treatment

Some comments - though I don't know how sensitive the conclusions are to the following data/assumtpions!

The various models (including that done by the independent group) all use slightly different utlity values for progression-free and post-progression states. given that utility values are a very inexact science this is, in my personal view,giving greater weight to small differences in utilities too far. Similarly for the disutilities - we ascribe a greater value (1.2) to alopecia than to diarrhoea -

Section 4.3.3 - the committee's view on the indirect comparison between the two main studies. Given that both are modest sized trials, the confidence intervals of the data are wide- so I don't see that any clinical statistician would allow such a difference to be drawn. Furthermore, in the one trial that compares the two aromatase inhibitors there was no real difference (letrozole was only marginally better, and the trial was not conduced in the HER2+ population). Therefore I don't think the data support the committee's view;

The Committee concluded that any apparent benefit in mean progression-free survival with trastuzumab compared with lapatinib was based on the difference between the aromatase inhibitor arms in the two trials.

In reality, it would be better to say that the apparent differnences betweent the trials may reflect diffferent patient populations as well as the natural imprecision in modest-sized clinical trials, and don't in my view offer any robust evidence in differences in efficacy between any of the agents (either for or against a real difference)

4.3.5 - I would really value the view of an independent statistician with expertise in cancer meta-analysis here. Every trial has different populations - the question is whether the differences are such that they invalidate a meta-analysis which has the advantage of increasing the precision of the estimate of the effect - after all, clinical trials only provide an ESTIMATE of the effect, they rarely produce the precise figure that would be seen in a full population! Sections 4.3.4, 4.3.12 & 4.3.14 highlight concerns as to which trials is the better estimate of the AI treated alone population in "real life": it is not clear to me how they conclude that EGF30008 is the better estimate, other than "clinical impression". So, again, why not meta-analyse the two? Indeed, since this is an MTA asking the question as to whether it is cost-effective to add an anti-HER2 therapy to an aromatase inhibitor, it would seem more logical to me to start with a meta-analysis and then see what the data show….and this might allow a more precise estimate of the difference, if there is any, in the overall survival !

finally - the whole question of the survival gain - it is extremely unclear what survival gain there would be as the post-progression treatments are not specified, nor protocol mandated (other than in Tandem allowing post-progression cross-over to trastuzumab): in particular patients may well have gone on to get chemo+trastuzumab in any of the4 arms of the trial. In most cases, the post-progression survivals are ~2 years, which suggests that the patients have had several more treatments, an I would suggest that models that depend on the estimated overall survivals are give less weight than those that use the primary PFS data!

I would agree however that the data in the trials suggest that the 2 year "end-of-life" criteria are probably not met!

4.3.23 - I don't understand. if either of these indications was approved, the likely population of patients is the same - why is it relevant that there are other patients for whom trastuzumab licensed? Or is that just a "NICE rule" with no real clinical relevance to the population being looked at in the MTA?

Finally the statement

The Committee concluded that neither lapatinib nor trastuzumab would be a cost-effective use of NHS resources when combined with an aromatase inhibitor for the first-line treatment of metastatic hormone-receptor-positive breast cancer that overexpresses HER2.

should it not read

The Committee concluded that neither lapatinib nor trastuzumab would be a cost-effective use of NHS resources when combined with an aromatase inhibitor for the first-line treatment of metastatic hormone-receptor-positive breast cancer that overexpresses HER2 as compared to the use of an aromatase inhibitor alone.

since that is the question that has been addressed - as the committee acknowledges, the question as to whether it would be cost-effective compared to chemotherapy+trastuzumab, which is clinicaly sometimes the more relevant comparison, cannot be addressed from the data in the three trials considered?

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