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BY EMAIL

19 May 2014

RE: Trastuzumab emtansine for treating HER2-positive, unresectable locally advanced or metastatic breast cancer after treatment with trastuzumab and a taxane

Dear Janet,

Thank you for giving us the opportunity to comment on the above ACD. We believe this appraisal raises an important issue – an issue which must be addressed if the final recommendation is to be considered a sound and suitable basis for the issuance of guidance to the NHS.

Under the terms of the Pharmaceutical Price Regulation Scheme 2014, the total spend on branded medicines in the UK is capped.

The scheme caps the budget with annual growth limited to 0% in 2014 through to 1.9% in 2018. Forecast growth is significantly higher at 3.87% in 2014 – when the expected growth rates are compounded, by 2018 the uncapped spend on branded medicines will be 17.59% above the current level whilst the agreed spend level with the cap will be only 5.6% above the current level.

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This will result in an anticipated overspend above the cap in the region of £386m in 2014 rising to £1202m in 2018*. All expenditure which exceeds the cap will be rebated by industry.

This agreement raises an important question. If expenditure on branded medicines remains above the agreed cap level in the scenario of a positive or negative NICE decision (as it will in the case of trastuzumab emtansine) is it reasonable for an Appraisal Committee to make a decision under the assumption that funding the medicine in question will come at an additional cost to society?

In the case of this appraisal, NICE approval of trastuzumab emtansine will result in an additional cost; however this will result in an equivalent reduction in the PPRS rebate paid by industry.

This issue must be considered by Committee if the decision reached is to be 'reasonable'.

In addition to the above we are concerned with the Committee's conclusion that trastuzumab emtansine does not meet the "End of Life" criteria. The conclusion was reached as the survival of patients treated with lapatinib in combination with capecitabine is regarded as being above two years.

Lapatinib is not NICE approved and is only funded via the Cancer Drugs Fund.

We believe it is unreasonable to conclude that trastuzumab emtansine does not meet the End of Life criteria due to a comparison against a medicine which is not subject to standard NHS funding.

We are committed to finding a long term solution to ensure women continue to receive trastuzumab emtansine and look forward to working with NICE, NHS England and the Department of Health on this issue.

Kind Regards

[redacted]

Jennifer Cozzone
Head of Health Economics and Strategic Pricing

1. Has all the relevant evidence been taken into account?

No. When considering whether the 'End of Life' criteria apply to trastuzumab emtansine the Committee has not considered the median overall survival observed for patients who received lapatinib in combination with capecitabine in the EGF104009 study (Cameron 2010).

In addition we believe the evidence of trastuzumab emtansine demonstrating a substantially improved tolerability profile compared to lapatinib in combination with capecitabine has been underemphasised. Details of this are identified in section 3.2 of this response.

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

The summaries are reasonable.

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

3.1 The Committee's conclusion on double-counting of the disutility of adverse events is incorrect

In section 4.11 the ACD states that:

'the Committee considered that applying a higher utility value for trastuzumab emtansine could result in the benefit of treatment being double-counted and overestimated, because the utility decrements for adverse events already capture part of this benefit'

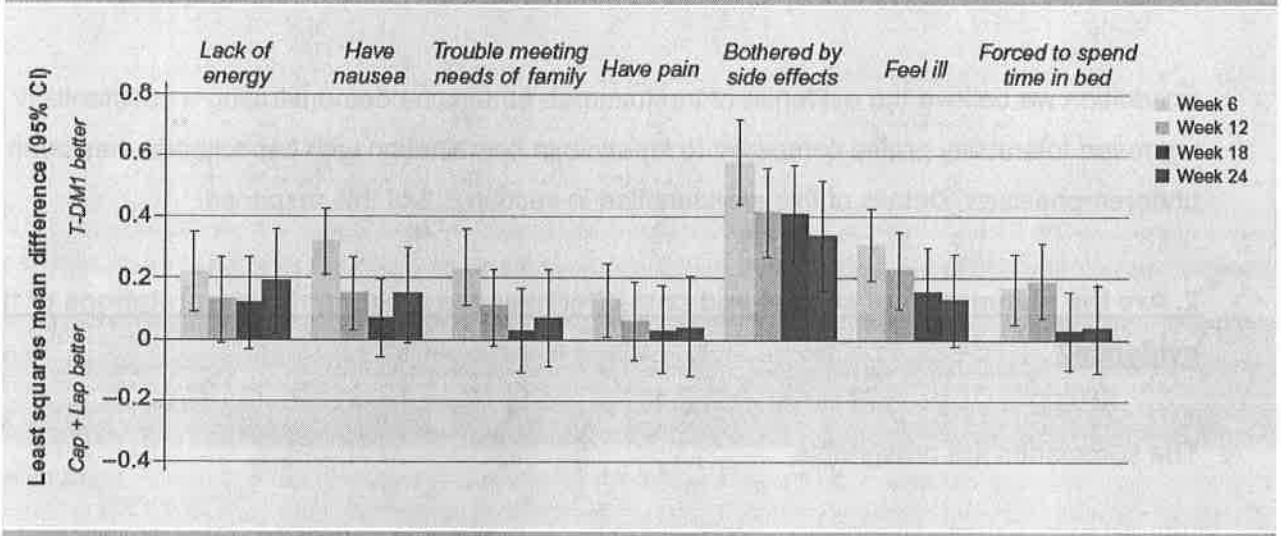
This is incorrect. The utility values presented for PFS contain the disutility of adverse events. These disutilities are only applied once and so no double-counting occurs within the model.

3.2 The Committee's conclusion that there is consistent utility across all treatments is unreasonable in light of the evidence available

Trastuzumab emtansine has been demonstrated to have a substantially improved tolerability profile compared to lapatinib in combination with capecitabine. It unreasonable to ignore the impact of this upon the utility of patients and subsequently the cost-effectiveness of trastuzumab emtansine.

The EMILIA study included the 'FACT-B' patient reported outcome tool. The figure below demonstrates the results of the physical well-being subscale of the FACT-B results from EMILIA.

Figure 3. Mean physical well-being scores (T-DM1 vs capecitabine plus lapatinib).



Cap, capecitabine; CI, confidence interval; Lap, lapatinib; T-DM1, trastuzumab emtansine.

These results demonstrate a clinically meaningful improvement in the item "Bothered by side effects" for patients in the trastuzumab emtansine arm compared with patients in the capecitabine-plus-lapatinib arm which is maintained through week 24 (Figure 3) (Welslau 2012).

This result is highly supportive of the use of a higher PFS utility value for patients receiving trastuzumab emtansine (something strongly supported by our clinical experts).

In addition the EMILIA study included the "Diarrhea Assessment Scale" (DAS) tool. Although similar at baseline, the number of patients reporting diarrhea symptoms increased 1.5- to 2-fold during treatment in the capecitabine-plus-lapatinib arm, whereas the number reporting diarrhea symptoms remained near baseline levels in the trastuzumab emtansine arm (Fig. 4). At cycle 2, more patients in the capecitabine-plus-lapatinib arm versus the trastuzumab emtansine arm had more than 1 stool per day (60.5% versus 31.7%), had unformed stools (75.1% versus 39.5%), developed urgency (60.2% versus 27.5%), and had abdominal discomfort (51.0% versus 27.3%) (Welslau 2013).

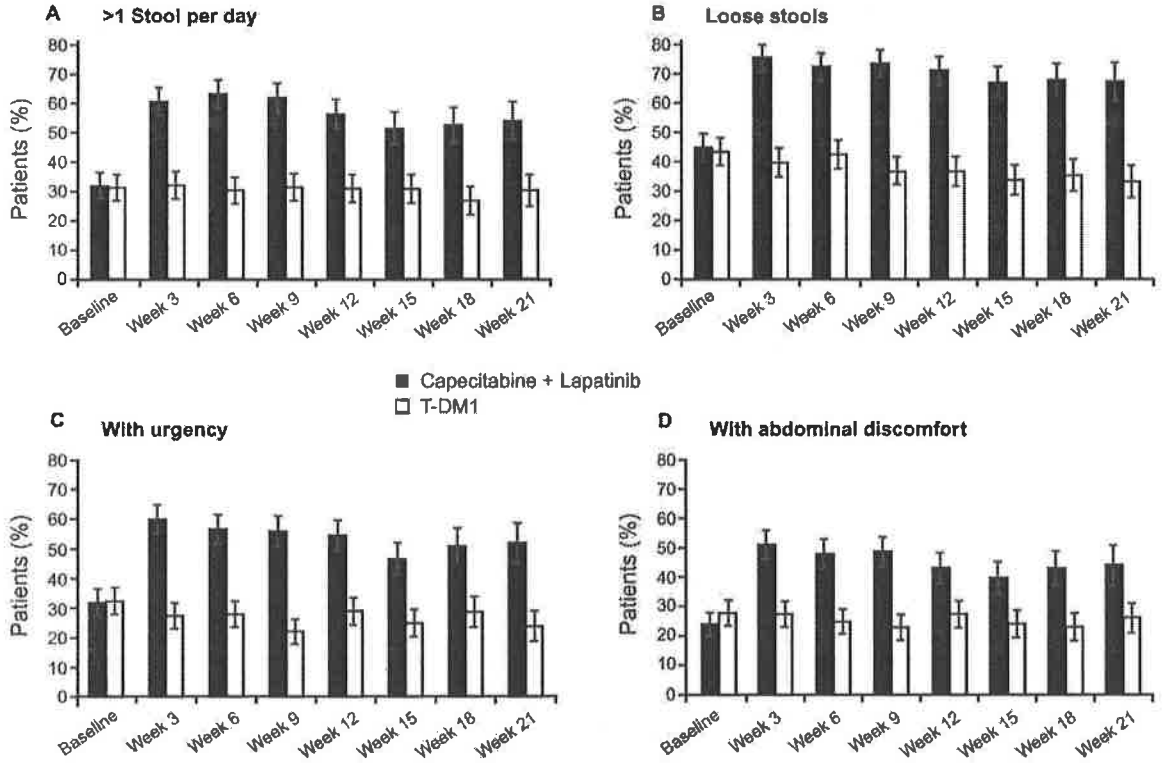


Figure 4. Diarrhea Assessment Scale results are shown. Error bars indicate 95% confidence intervals. Abbreviation: T-DM1, trastuzumab emtansine.

The combination of the EMILIA FACT-B data, the DAS data and the reduced number of symptomatic adverse events experienced with trastuzumab emtansine strongly support the use of a higher utility value for trastuzumab emtansine compared to lapatinib in combination with capecitabine.

3.3 It is unreasonable for the Committee to fail to consider the impact of the PPRS medicines cap upon this Appraisal

In the context of a capped medicines budget it is unreasonable to continue to operate as if the medicines budget is not capped. This argument is detailed further in the cover letter for this response.

3.4 It is unreasonable to conclude that trastuzumab emtansine does not meet the 'End of Life' criteria due to the estimated survival of patients treated with a medicine only available via the Cancer Drugs Fund

In Section 4.18 of the ACD the Committee concluded that patients treated with lapatinib are likely to live beyond 2 years. On the basis of this it was determined that trastuzumab emtansine did not meet the 'End of Life' criteria.

We believe this conclusion is fundamentally unreasonable. Lapatinib is only available via the Cancer Drugs Fund (CDF) and is not NICE approved. We do not believe it is reasonable to consider a medicine funded via the CDF as a comparator for the evaluation of whether or not 'End of Life' is met.

If lapatinib plus capecitabine is considered to be an appropriate comparator for determining whether trastuzumab emtansine meets the end of life criteria then it appears unreasonable to not consider the totality of evidence available on the expected survival with this regimen.

It should be noted that in the final survival analysis of lapatinib plus capecitabine in women with HER-2-positive advanced breast cancer (Cameron D. *et al.* 2010) the median overall survival for the combination arm was 75 weeks.

References

The Pharmaceutical Price Regulation Scheme 2014 (https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/282523/Pharmaceutical_Price_Regulation.pdf)

Cameron D. *et al.* 2010, Oncologist. 2010;15(9):924-34.

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