Chair's presentation

Trastuzumab emtansine for treating HER2-positive, unresectable locally advanced or metastatic breast cancer after treatment with trastuzumab and a taxane
Rapid reconsideration of TA371

3rd Appraisal Committee meeting

Committee A

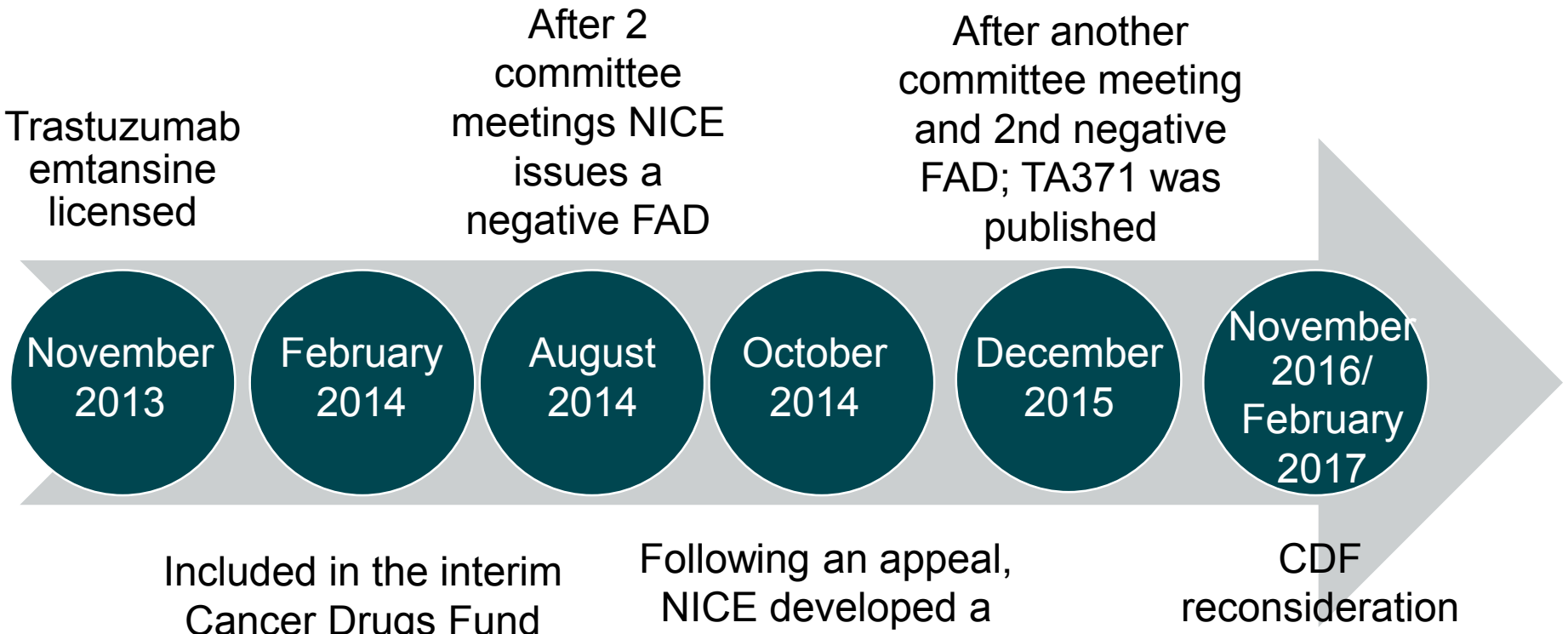
ERG/AG: School of Health and Related Research, University of Sheffield

NICE technical team: Boglarka Mikudina

Company: Roche

9th May 2017

A potted history



Summary of developments since the original appraisal in 2014

- Trastuzumab emtansine has been funded by the CDF for 3 years (most widely used treatment 2nd line in 2015 according to company)
- Was discussed by the CDF reconsideration committee 2 times – no FAD issued
- Lapatinib + capecitabine (lap/cap):
  - Was the comparator in the original clinical trial (EMILIA), and the main comparator in the appraisal (TA371)
  - Was funded by the CDF at the time of appraisal,
  - Was delisted in January 2015, no longer routinely used in the NHS
- Trastuzumab + capecitabine (tras/cap):
  - Consultees say this should now be the comparator
  - No direct clinical evidence in this population vs trastuzumab emtansine, indirect comparison only
- 2 further PAS offers from company (Roche)

Summary of developments since the original appraisal in 2014

- End of life criteria (EoL):
  - Originally considered for lap/cap
  - Slightly over 24 months in EMILIA trial (median 25.1 months with lap/cap)
  - Other trials of lap/cap show less, e.g. 18.8 months (Cameron et al. 2010)
  - Committee accepted that after the failure of trastuzumab in the metastatic setting life expectancy is limited, therefore end of life applicable
  - Updated EMILIA data shows median 25.9 months with lap/cap
  - ‘New' main comparator tras/cap - **Does EoL need to be revisited?**

Reminder of clinical evidence EMILIA + Theresa

Trial	Population	Intervention	Outcomes
EMILIA • Randomised open-label phase III • Study treatment given as 1st (12%), 2nd (36%), or 3rd or subsequent (52%) line	Adults with HER2-positive locally advanced or metastatic breast cancer who have received prior trastuzumab and a taxane	Trastuzumab emtansine (n=495) **Comparator** Lapatinib plus capecitabine (n=496)	**Primary** • Progression-free survival (independent) • Overall survival • Adverse events **Secondary** • Progression-free survival (investigator) • Objective response rate (independent) • Duration of objective response • Time to treatment failure • Time to symptom progression • Quality of life (FACT-B TOI)
TH3RESA • Randomised open-label phase III • Patients had previously received, on average, 4 lines of therapy for locally advanced or metastatic disease	Adults with metastatic or unresectable locally advanced/ recurrent HER2-positive breast cancer who have received prior trastuzumab, a taxane and *lapatinib*	Trastuzumab emtansine (n=404) **Comparator** Treatment of physician's choice (n=198) • Chemotherapy • Hormonal therapy • Biologic drug • HER2-directed therapy	**Primary** • Progression-free survival (investigator) • Overall survival **Secondary** • Objective response rate (investigator) • Duration of objective response • 6-month and 1-year survival rate • Time to pain symptom progression (EORTC QLQ-BM22)

TA371

1.1 Trastuzumab emtansine is not recommended, within its marketing authorisation, for treating adults with human epidermal growth factor 2 (HER2) positive, unresectable locally advanced or metastatic breast cancer previously treated with trastuzumab and a taxane.

- The company's base-case ICER for trastuzumab emtansine compared with lapatinib + capecitabine was £167,236 per QALY gained (incr. costs: £111,162; incr. QALYs 1.91)
- A simple discount patient access scheme (PAS) was submitted at the ACD stage, but this did not reduce the ICER to an acceptable value

CDF reconsideration of trastuzumab emtansine

- First committee meeting 29 November, 2016
- Company submitted new long-term evidence for trastuzumab emtansine and a new complex PAS scheme
  - More than 2 additional years of follow-up data from the EMILIA trial vs Lap/cap (December 2014 cut-off) used to model overall survival, time on treatment and adverse events
  - Network meta-analysis updated
  - The way in which adverse events and treatment duration are incorporated into the model has been changed
  - Complex PAS incorporated, which has been improved by the company prior to this meeting
- Second committee meeting 1 February, 2017
  - No ACD was issued
  - Company was requested to update its probabilistic sensitivity analyses based on the critique provided by the ERG

In clinical use/comparators: current status

- Trastuzumab emtansine was the most commonly used second-line therapy for HER2-positive breast cancer in 2015 (company data)
- Lapatinib + capecitabine (lap/cap):
  - Lapatinib appraisal previously suspended by NICE (October 2010)
  - Licensed and was included in the original scope as CDF funded at the time
  - Head to head trial results available (EMILIA trial)
  - Lapatinib was removed from the CDF January 2015
- Trastuzumab + capecitabine (tras/cap):
  - Trastuzumab is not licensed in combination with capecitabine for this indication
  - However, consultees consider it to become established practice in the NHS if trastuzumab emtansine not available
- Capecitabine alone
  - Not routinely used according to clinicians

Updated evidence

	EMILIA ITT population	
	Trastuzumab emtansine	Lapatinib + capecitabine
Median progression-free survival (months)	9.6	6.4
	Difference: 3.2	
	Hazard ratio (95% CI) 0.65 (0.55 to 0.77)	
Median overall survival (months)	29.9	25.9
	Difference: 4.0	
	Hazard ratio (95% CI) 0.75 (0.64 to 0.88)	

Source: Table 1, page 12 of the company submission

- Bayesian mixed treatment comparison was developed to estimate hazard ratios for trastuzumab emtansine relative to the comparators for which no head-to-head evidence existed

ACD preliminary recommendations

- Trastuzumab emtansine is not recommended, within its marketing authorisation, for treating HER2 positive, unresectable locally advanced or metastatic breast cancer in adults after trastuzumab and a taxane

- Taking into account all factors, including the end of life criteria, the committee concluded that trastuzumab emtansine was not cost effective at the price agreed in the original patient access scheme.

ACD consultation

- Comments received consultees
  - Roche (manufacturer)
  - UK Breast cancer group
  - Breast Cancer Now
- Web comments received from
  - Patients
  - Members of Parliament
- Petition submitted by Breast Cancer Now
  - Signed by 115,000 people in 3 weeks
  - Urging NICE and Roche to reach an agreement and ensure that trastuzumab emtansine remains available in England

ACD consultation comments availability of trastuzumab emtansine

- Has been widely used in the NHS via the CDF
- Not recommending would mean a withdrawal of the technology
- Effective treatment option, not only extends life, but also improves quality of life
- Much more tolerable AE profile than the other alternatives currently available for this population
- Allows patients to continue working and live a normal life, two factors that are valued very highly by patients
- Is the standard of care in many European countries

ACD consultation comments comparator

- Lapatinib + capecitabine is not routinely used in the NHS as it was not recommended by NICE and not available via the CDF since 2015

- Trastuzumab + capecitabine is the most relevant comparator

ACD consultation comments other comments

- Women under the age of 45 should be considered as a separate subgroup
  - Breast cancer in younger population has different pathological features
  - HER2 negative breast cancer is more prevalent in younger women
  - Worse prognosis and higher proportion of high grade and late stage tumours.

New evidence

- Improved PAS
- Updated base case analysis in line with the committee's preferred assumptions:
  - using patient level data to calculate vial use
  - excluding an additional adjustment for wastage
- The new evidence has been considered by the previous CDF reconsideration committee and now by this committee
- In addition, as a response to a request by the CDF committee, the company updated its probabilistic sensitivity analysis (PSA)
- Critique of new evidence by ERG:
  - The new PAS has been incorporated appropriately
  - Error highlighted by the ERG around the calculation of post-progression treatment costs has been corrected by the ERG
  - The ERG was in general satisfied with the updated PSA by the company, but also tested alternative prior distributions to determine the impact its impact on the results
  - As a results the ICERs of the latest analyses presented by the company and the ERG, are very similar

Impact of choice of comparator on the cost per QALY gained

Included comparators	Latest probabilistic ICER from company	Probabilistic ICER from ERG using alternative priors for NMA parameters	Notes
If capecitabine is a comparator	XXXXX vs cap	XXXXX vs cap	Lap/cap and trast/cap are extendedly dominated by cap and trastuzumab emtansine
If capecitabine is not a comparator, but lap/cap is a comparator	XXXXX vs lap/cap	XXXXXvs lap/cap	Trast/cap is extendedly dominated by lap/cap and trastuzumab emtansine
If both capecitabine and lap/cap are not comparators	XXXXXvs trast/cap	XXXXX vs trast/cap	Trast/cap is not estimated to be good value for money compared with existing treatments, but trast/cap is not being assessed in this STA

Source: ERG response to company additional analyses, Table 6

End of life criteria

- Trastuzumab emtansine met the end of life criteria during the original appraisal based on lap/cap being the standard of care
- At the 1st meeting, the committee agreed to uphold the end-of-life decision from the original appraisal, because the CDF reconsideration of trastuzumab emtansine is a continuation of the original appraisal
- In a clinical trial of lap/cap compared with capecitabine alone (Cameron et al. 2010) the median survival with lap/cap was 18.8 months
- Company's response to ACD:
  - In the CEREBEL study (Pivot et al. 2015), the median overall survival on the tras/cap arm was 27.3 months, however 45% of the patients were being treated first line
  - Further evidence from the GBG26/BIG 3-05 (von Minckwitz et al. 2011) shows a median overall survival of 24.9 months for tras/cap in the second line setting.

Key issues for consideration

- Which are the appropriate comparators?
- Given that there is no direct trial comparison with tras/cap in this population how robust are the ICERs?
- Does the committee wish to revise its view that patients on second line therapy, taking combinations other than trastuzumab emtansine have a short life expectancy?
- Does the committee consider that they can take into account in their evaluation of uncertainty that the NHS been funding this treatment i.e. disinvestment rather than a new investment decision
- Would this have implications for drugs now entering the CDF?