BY EMAIL

6 March 2012

RE: Multiple Technology Appraisal – 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

Thank you for giving us the opportunity to comment on the ACD for the above technology appraisal. Our response is provided under the standard headings below.

Whilst we acknowledge that our response will not change the decision of the Committee to recommend trastuzumab in this setting, we feel the need to provide a comprehensive response to specific assertions made within the ACD which we do not believe are evidence-based. These assertions are a cause for concern given that we believe they set a precedent for future appraisals and undermine the credibility of the Institute in making objective conclusions on the basis of the clinical evidence presented.

If any clarification or further analyses would aid the Committee in their deliberations we would be more than happy to provide it.

Yours Sincerely,

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

No. The Committee has not taken into account several pieces of evidence that must be appropriately considered if a sound conclusion on the clinical and cost-effectiveness of trastuzumab is to be reached.

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This includes the different prognostic status of patients in the TAnDEM and EGF30008 trials, the different modes of action of trastuzumab and lapatinib, and the wealth of data supporting the assumption of increased survival associated with trastuzumab.

Point 1: Cross-trial comparisons of progression-free survival experienced in Tandem and EGF30008

In Section 4.3.3. of the ACD it is stated that “The Committee noted that the curves showing the percentages of people alive without progression for the treatment arms were similar to each other between the trials. It understood from clinical specialists that this would be expected in clinical practice (that is, that there would be no difference in the clinical effectiveness of lapatinib and trastuzumab).”

A naïve cross-trial comparison of this kind is subject to clear bias against trastuzumab. The EGF30008 population is a better prognostic group than the TAnDEM population.

HER2/hormone receptor co-positive disease is particularly aggressive. The TAnDEM population had a heavier burden of metastatic disease than the EGF30008 population and as a consequence had a poorer prognosis, ie the rates of metastases at a number of different sites are greater in the TAnDEM study than they are in the EGF30008 study for bone (56.5 vs 15.2%), lung (44.0% vs 37.9%) and soft tissue (43.5 vs 30.1%), and the number of lesions per patient is higher in the TAnDEM study (median of 4 with a range up to 14). The median time from diagnosis of metastatic disease in TAnDEM is particularly short at 1.4 months supporting the population having more advanced and aggressive disease.

Indeed, the assessment group had already identified differences in the patient populations in EGF30008 and TAnDEM when they concluded that “key differences in the trials led the AG to the conclusion that it would not be appropriate to pool data or make meaningful comparisons, directly or indirectly, across the two completed trials.” (page 37, Liverpool Assessment Report). This was their conclusion as a consequence of the fact that the “EGF30008 trial excluded patients in which the disease was considered by the investigator to be rapidly progressing or life threatening” (page 36, Liverpool Assessment Report).

For ease of reference the characteristics of patients in TAnDEM and EGF30008 are reproduced below.

Table1. TAnDEM Baseline Patient Characteristics

Table 1. Baseline Patient Demographics and Clinical Characteristics

Characteristic	Trastuzumab + Anastrozole (n = 103)		Anastrozole Alone (n = 104)	
	No. of Patients	%	No. of Patients	%
Age, years				
Median	56		54	
Range	31-85		27-77	
Hormone receptor status*				
Primary and/or metastatic lesion ER and/or PgR positive (local)	103	100.0	104	100.0
Primary and/or metastatic lesion ER and/or PgR positive (central)	77	74.8	73	70.2
Time from diagnosis of primary disease, months				
Median	25.6		27.3	
Range	0.6-419		0.6-154.3	
Time from diagnosis of metastatic disease, months				
Median	1.6†		1.2	
Range	0.3-67.1		0.3-19.3	
No. of metastatic sites per patient				
Median	2		2	
Range	1-5		1-5	
No. of lesions per patient				
Median	4		4	
Range	1-14		1-13	
Site of metastases				
Lung	43	41.7	48	46.2
Liver	33	32.0	29	27.9
Bone	64	62.1	53	51.0
Soft tissue	46	44.7	44	42.3
Other	72	69.9	65	62.5
Previous therapy				
Hormonal	62	60.2	69	66.3
Tamoxifen for metastatic disease	5	4.9	3	2.9
Chemotherapy	55	53.4	62	59.6
Anthracycline	46	44.7	53	51.0
Bisphosphonate	28	27.2	27	26.0
LVEF, %				
Median	62		63	
Range	50-82		51-89	

Abbreviations: ER, estrogen receptor; PgR, progesterone receptor; LVEF, left ventricular ejection fraction.
*Hormone receptor status determined locally as defined by institutional criteria.
†n = 101; two patients were not considered as having metastatic disease but, instead, were considered as having local recurrence.

Table 2. EGF30008 Baseline Patient Characteristics

Table 1. Baseline Patient Demographics and Clinical Characteristics

	HER2 Positive				ITT			
	Letrozole + Placebo (n = 108)		Letrozole + Lapatinib (n = 111)		Letrozole + Placebo (n = 644)		Letrozole + Lapatinib (n = 642)	
Demographic or Clinical Characteristic	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Age, years*								
Median	59		60		63		62	
Range	45-87		44-85		35-95		31-94	
ECOG performance status*								
0	51	47	59	53	349	54	370	58
≥ 1	57	53	51	46	286	44	268	42
Hormone receptor status*								
ER/PgR positive	69	64	74	67	414	64	420	65
ER positive/PgR negative	20	19	19	17	90	14	91	14
Disease stage								
IIIB or IIIC	7	6	5	5	30	5	25	4
IV	101	94	106	95	613	95	616	96
No. of metastatic sites*								
Median	2		2		2		2	
Range	1-7		1-7		0-7		0-7	
Disease stage								
Bone only	18	17	16	14	85	13	94	15
Visceral or soft tissue	90	83	95	86	559	87	548	85
Liver	37	34	33	30	171	27	146	23
Lung	40	37	43	39	242	38	248	39
Lymph node	43	40	57	51	304	47	312	49
Soft tissue	31	29	35	32	218	34	212	33
Other	18	17	19	17	127	20	125	19
Previous therapy								
Endocrine*	62	57	60	54	317	49	313	49
Tamoxifen or toremifene only	60	56	59	53	302	47	300	47
Aromatase inhibitor only	1	< 1	1	< 1	3	< 1	5	< 1
Chemotherapy*	51	47	61	55	280	43	281	44
Anthracycline only	38	35	41	37	172	27	171	27
Anthracyclines and taxanes	9	8	9	8	41	6	42	7
Other	4	4	11	10	66	10	68	11
Biologic therapy (any)	1	< 1	1	< 1	1	< 1	2	< 1
Interval since prior adjuvant antiestrogen therapy*								
≥ 6 months or no prior therapy	67	62	73	66	487	76	501	78
< 6 months	41	38	38	34	157	24	141	22

Abbreviations: HER2, human epidermal growth factor receptor 2; ITT, intent to treat; ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; PgR, progesterone receptor.
*Indicates prespecified baseline prognostic factors used in predefined stepwise Cox regression model. Additional factors included treatment, disease-free interval, and serum HER2 (extracellular domain) at baseline.

It is important that the Committee appropriately consider these differences and the implications that this has for the assessment of the relative effectiveness of lapatinib and trastuzumab. In the current ACD these differences do not appear to be considered appropriately.

Section 4.3.3 of the ACD continues with the statement “Conversely, the Committee noted that the percentages of people alive and progression free for the comparator arms were different, and that this was the explanation for the difference in gain between treatment and comparator between the two trials. 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.”

Given the differences in patient population provided in Tables 1 and 2 above, we disagree that the reason for a worse PFS in the AI arm in TAnDEM is due to “underperformance” as suggested in the ACD. There is a clear rationale why we would expect a difference in the AI arms in the two trials and this can be seen in the difference in baseline characteristics between the two trials.

Furthermore, the Committee’s suggestion that the trastuzumab+AI arm is ‘accurate’ whilst the AI monotherapy arm is ‘underperforming’ would suggest the Committee is questioning the validity of the randomisation procedure in the TAnDEM trial. TAnDEM was a high quality, robust study run to

regulatory submission standards. In conclusion, if the Committee believe that the anastrozole arm from TAnDEM is not representative of the clinical benefit that would be observed in real-world practice (that it would instead be even better), if they accept that randomisation was accurately performed, then it must also be believed that the trastuzumab+anastrozole arm is also underperforming relative to what would be expected in real-world practice.

This issue appears again in Section 4.3.12 of the ACD which states “On the basis of previous discussions regarding the aromatase inhibitor data from the TAnDEM trial (section 4.3.4), the Committee concluded that the estimates of progression-free survival from the manufacturer of trastuzumab and the Assessment Group were likely to underestimate progression-free survival for the aromatase inhibitor group.” As noted above, this logic dismisses the difference of patient prognosis between the two RCTs and assumes that randomisation was not correctly performed in the TanDEM trial. If it is accepted that randomisation was performed correctly, it should also be concluded that Roche has underestimated progression-free survival for the trastuzumab+AI group.

Finally, in Section 4.3.14 of the ACD it is concluded that “The Committee accepted that the manufacturer’s estimate was too low given that people in the aromatase inhibitor group appeared to progress much quicker than would be expected in clinical practice (sections 4.3.4 and 4.3.12)”. Following the arguments provided above, if it is assumed that both arms are underperforming in the TanDEM trial, then the incremental QALY gain would actually be larger if these were adjusted to reflect a better-prognostic population.

A comparison of laptinib and trastuzumab – mode of action, half-life and head to head evidence

While the question of potentially comparable effectiveness between the two HER2 targeted therapies has been unknown since the launch of lapatinib, recent evidence has suggested that it cannot be assumed that lapatinib is equally as efficacious as trastuzumab. These two treatments have different modes of action that translates to different clinical efficacy and different tolerability profiles.

Trastuzumab is a recombinant humanised IgG1 monoclonal antibody against the human epidermal growth factor receptor 2 (HER2). It binds with high affinity and specificity to sub-domain IV, a juxta-membrane region of HER2's extracellular domain. Binding of trastuzumab to HER2 inhibits ligand-independent HER2 signalling and prevents the proteolytic cleavage of its extracellular domain, an activation mechanism of HER2. Additionally, trastuzumab is a potent mediator of antibody-dependent cell-mediated cytotoxicity (ADCC).In contrast, lapatinib is an inhibitor of the intracellular tyrosine kinase domains of both EGFR (ErbB1) and of HER2 (ErbB2) receptors which inhibits ErbB-driven tumour cell growth. As a small molecule, lapatinib does not mediate ADCC and has a short half-life and wash out period. In short there is a biological rationale for greater effectiveness with trastuzumab as it has mechanisms of action not available to lapatinib.

The KM curve from TAnDEM shows a later PFS gain but the benefit is sustained. In contrast, the KM curve from EGF30008 demonstrates an earlier PFS gain but the benefit is not sustained.

Figure 1. TanDEM Kaplan-Meier curves showing estimated (A) progression-free survival (PFS) for the intent-to-treat (ITT) population

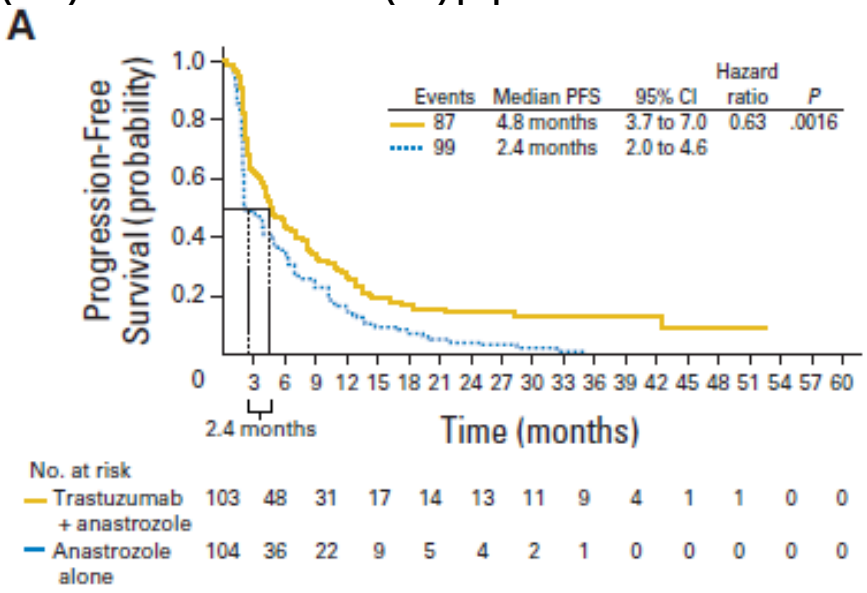
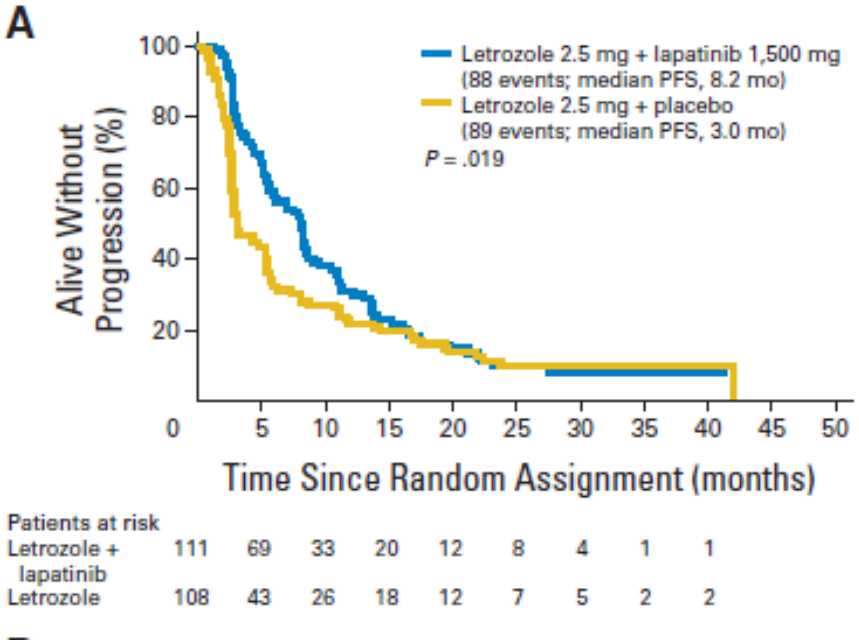


Figure 2. EGF30008 Kaplan-Meier estimates of progression-free survival (PFS)



Furthermore, trastuzumab and lapatinib are not equally effective in the treatment of early breast cancer. Trastuzumab is licensed in both the adjuvant and neoadjuvant settings. Treatment with trastuzumab for one year, following or concurrent with chemotherapy improves disease free and overall survival (Smith et al, 2007; Perez et al, 2011; Slamon et al, 2011). In the NOAH study, the addition of trastuzumab to neoadjuvant chemotherapy resulted in significant improvement in event-free survival (Gianni et al, 2010).

Conversely, on August 18th 2011 the lapatinib monotherapy arm of the ALTTO (Adjuvant Lapatinib And/Or Trastuzumab Treatment Optimisation) study was discontinued, because the comparison of this arm with the trastuzumab alone arm crossed the futility boundary, indicating that the lapatinib monotherapy arm was unlikely to meet the pre-specified criteria to demonstrate non-inferiority to trastuzumab alone with respect to disease-free survival (DFS) (ALTTO study, details available from clinicaltrials.gov).

Additionally, the authors of the GeparQuinto, GBG 44 study (lapatinib versus trastuzumab in combination with neoadjuvant anthracycline-taxane-based chemotherapy) concluded that because **pathological complete response rate with chemotherapy and lapatinib was significantly lower than that with chemotherapy and trastuzumab,** lapatinib should not be used as single anti-HER2-treatment in combination with neoadjuvant chemotherapy, outside of clinical trials (Untch et al, 2012).

Given these differences in mode of action and efficacy in the early breast cancer setting, we do not agree it is reasonable to conclude that there is no difference in the clinical effectiveness of trastuzumab and lapatinib.

Point 2: Overall survival gain estimates for trastuzumab

In Section 4.3.14 of the ACD, it is stated that "The Committee heard from the Assessment Group that this does appear to be an anomaly but that it is caused by a problem in the data in the control arm of the trial, raising further questions of uncertainty in the data. For the same reason as discussed for lapatinib (section 4.3.9) the Committee concluded that the likely impact on post-progression survival with trastuzumab was most likely to be nearer to zero."

Firstly, we have not seen any explanation/evidence of this anomaly in the TAnDEM data as suggested by the AG. We believe this is unacceptably vague wording and should be clarified for the purposes of appropriate decision making. Furthermore, the assumption on no impact of trastuzumab post-progression does not take into account the half-life of trastuzumab which is 28-38 days and subsequently the washout period is up to 27 weeks (190 days or 5 elimination half-lives) (Herceptin Summary of Product Characteristics). In contrast, the half-life of lapatinib is 24 hours (Tyverb Summary of Product Characteristics).

This is supported by a wealth of evidence across several RCTs for trastuzumab which suggests that OS gains are consistently larger than PFS gain for trastuzumab containing regimens.

Table 3 Comparison of median PFS and OS gains from several trastuzumab pivotal studies

Population/Intervention	Median PFS gain (mths)	Median OS gain (mths)	Reference
1st Line HER2+ metastatic breast cancer: paclitaxel +/- trastuzumab	2.8	4.8	Slamon 2001
1st line HER2+ metastatic breast cancer : docetaxel +/- trastuzumab	5.5	8.5	Marty 2005
1st line HER2+/HR+ metastatic breast cancer : anastrozole +/- trastuzumab	2.4	4.6	Kaufmann 2009
Advanced Gastric or Gastro Oesophageal Junction Cancer: chemotherapy +/- trastuzumab	1.2	2.7	Bang 2010

However, even if the Committee assumes that there is zero impact of trastuzumab post-progression as stated in Section 4.3.14 of the ACD, this would still translate the observed mean PFS advantage of 8 months from TanDEM into a mean OS advantage of 8 months.

Point 3: End of Life 3-month survival criterion

Section 4.3.19. of the ACD describes the deliberation on the extension of life criterion. "The Committee noted that the estimates of survival gain based on the economic model were higher than 3 months. However, these estimates of overall survival were subject to considerable uncertainty because of limited availability of follow up data." We are unclear precisely what is

considered so limited about the availability of follow-up data in TAnDEM. This trial was completed several years ago, and the final data cut-off of April 2008 represents a median follow-up of 3.1 years (and maximum follow-up of 6.2 years). This is considerably longer than most metastatic cancer RCTs reviewed by NICE, given the length of time that has passed in this particular instance between the marketing authorisation in September 2008 and the current assessment of this data by NICE.

Section 4.3.19. of the ACD continues by stating that "The Committee considered that the level of uncertainty in the estimates of survival gain was so great that there was insufficient evidence of a survival gain of at least 3 months. The Committee reiterated its view that the most robust evidence of efficacy is provided by a statistical significant survival gain. The Committee concluded the evidence was not sufficient or robust to indicate that trastuzumab plus an aromatase inhibitor provided a 3-months survival gain and so it did not fulfil the criteria for life extension."

Whilst we do agree that statistical significance is one of the most important measures used in frequentist statistics, we do not agree that it should be considered as the only measure of robustness in NICE appraisals. The 5% significance level represents an arbitrary rule of inference and has been argued by some to be irrelevant to the decisions which clinical and economic evaluations claim to inform (Claxton, 1999). The OS estimates provided when adjusting for cross-over as reported in section 4.1.10 of the ACD may not have been *significant* at a 5% level as the upper bounds of the 95% confidence interval marginally exceeded 1 (OS HR = 0.73, 95% CI 0.51 to 1.04) but it would have been *significant* at a 10% level (90% CI 0.54 to 0.98) had an arbitrary 10% significance level been chosen instead.

Furthermore, the lack of statistical significance at the 5% level can largely be attributed to the fact that, like many other trials for end of life treatments, the TAnDEM trial was not powered to show statistically significant difference in overall survival and suffers from extensive cross-over onto the intervention arm in the placebo arm.

All the figures presented to the Appraisal Committee over the course of this appraisal have suggested a greater than 3 month gain in overall survival and, in the spirit of the Bayesian approach which the NICE Guide to Methods is based, should be considered despite the lack of statistical significance at the 5% level.

Table 4. All overall survival gain estimates provided to the Committee for trastuzumab

Analysis	Overall survival gain	Reference
TAnDEM ITT analysis (ignoring 70% cross-over)	4.6 months gain (median)	Kaufmann et al. 2009
TAnDEM post-hoc censoring analysis	11.3 months (median)	Kaufmann et al. 2009
Roche cross-over method (RPSFT – medians from adjusted OS curves)	6.5 months (median)	Roche submission
Roche cross-over method in economic model (undiscounted)	12.4 months (mean)	Roche submission
Liverpool cross-over method in economic model (undiscounted)	8.4 months (mean)	LRiG Assessment Report – economic model

The Committee has previously also referred to the evidence for progression-free survival gain and commented that this appeared convincing, and could be taken as a surrogate measure for overall survival. Whilst it is possible in some situations that PFS may be required as a surrogate for OS, this is not necessarily appropriate when mature randomised control trial OS data are available. Furthermore the Committee focused on the median PFS gain of 2.4 months rather than the mean PFS gain of 8.6 months (undiscounted mean PFS gain from the TAnDEM Kaplan-Meier PFS curves). The mean PFS figure is more appropriate to consider than the median PFS from

TAnDEM, given that at the point of data cut-off (April 2008), all patients had progressed and therefore the PFS curve is complete (and requires no extrapolation).

There are also previous examples where a new intervention (e.g. pazopanib for renal cell carcinoma TA215) has been accepted under the End of Life criteria without a significant OS benefit. One of the key differences between pazopanib and trastuzumab, though, would be the wealth of evidence spanning several RCTs where trastuzumab has demonstrated again and again a clinically and statistically significant OS benefit. We present below a number of overall survival Kaplan-Meier plots for pivotal metastatic trastuzumab RCTs.

Figure 3. Marty. Comparison of estimated overall survival between trastuzumab plus docetaxel and docetaxel-alone arms (Kaplan-Meier plots

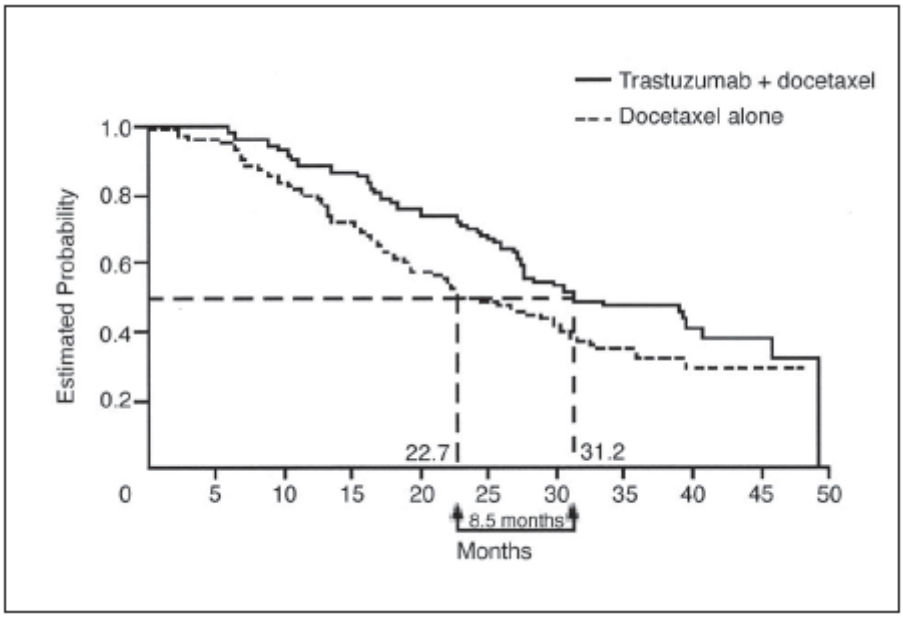
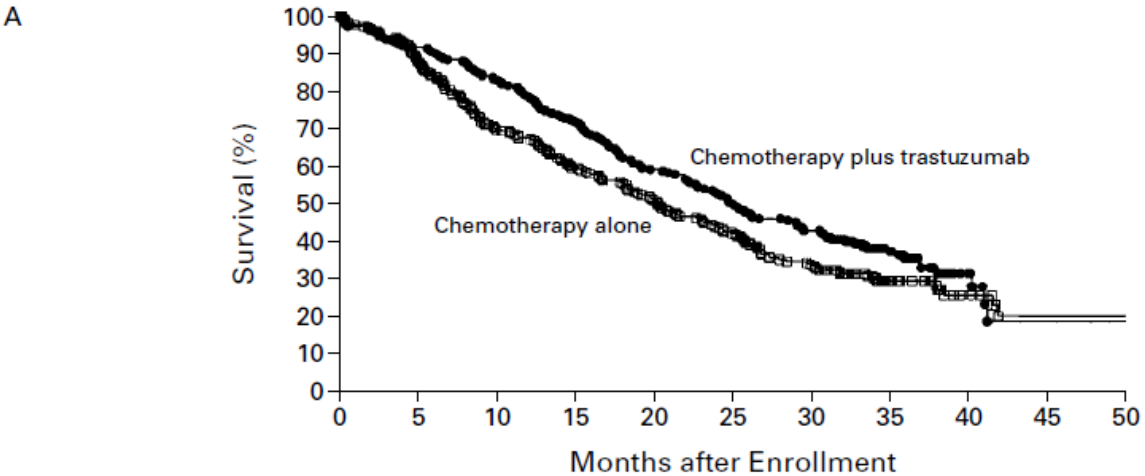


Figure 4. Slamon. OS KM curve between chemotherapy plus trastuzumab vs chemotherapy alone



No. at Risk									
Chemotherapy plus trastuzumab	235	214	192	165	134	114	96	47	11
Chemotherapy alone	234	205	160	136	116	97	76	37	13

Figure 5. RPSFT adjusted Tandem OS curves

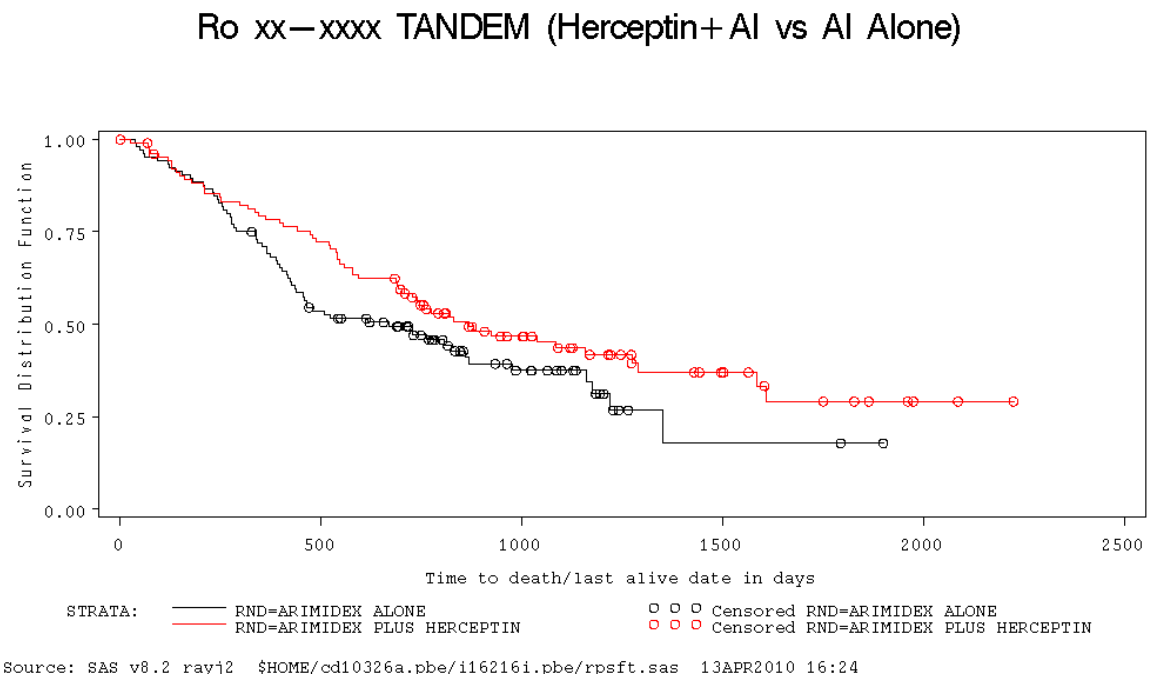
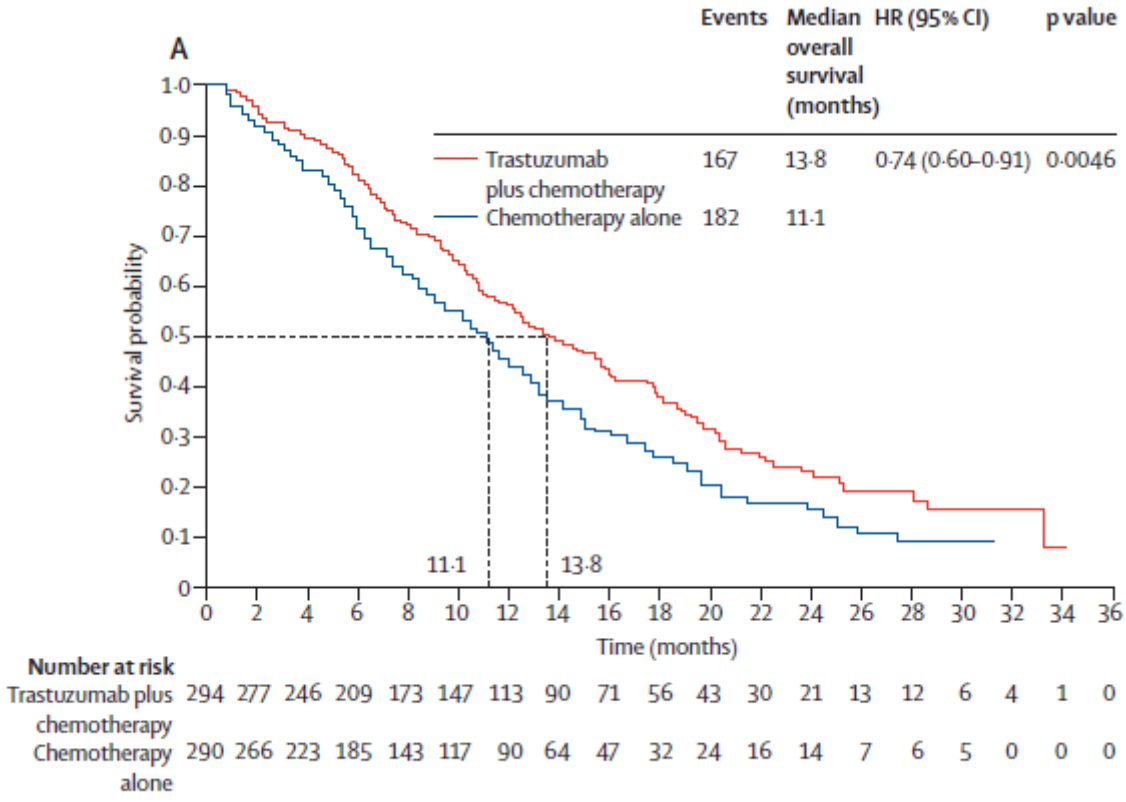


Figure 6. Bang et al. Median OS



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

Section 2.4 states "Tumours that overexpress the HER2 protein (HER2+) grow and divide more quickly." Similar to the paragraph 2.3 above which describes the prognosis associated with hormone receptor status, this section should also clarify that overexpression of HER2 is associated with a worse prognosis. We would suggest the following wording adjustment:

> "Tumours that overexpress the HER2 protein (HER2+) grow and divide more quickly and as a consequence, women with HER2 overexpression generally have a worse prognosis than women who do not have HER2 overexpression."

Section 3.5 states "The SPC states that the most common adverse events associated with trastuzumab therapy are cardiotoxicity, infusion-related reactions, haematotoxicity (in particular neutropenia) and pulmonary events." These adverse events are associated with trastuzumab when given in combination with chemotherapy and this should be reflected in the above sentence. We would recommend the following amendment to this sentence:

> "The SPC states that the most common adverse events associated with trastuzumab when given in combination with chemotherapy are cardiotoxicity, infusion-related reactions, haematotoxicity (in particular neutropenia) and pulmonary events."

Section 3.6. "The recommended dosage of trastuzumab is a loading dose of 4 mg/kg by intravenous infusion, followed by a weekly maintenance dose of 2 mg/kg until disease progression. Alternatively, a loading dose of 8 mg/kg can be given, followed by 3-weekly maintenance doses of 6 mg/kg until disease progression." This language may suggest that the former described schedule is recommended/preferred above the latter described schedule. To correct this, we would suggest the following amendment to this section:

> "The recommended dosage of trastuzumab is either a loading dose of 4 mg/kg by intravenous infusion, followed by a weekly maintenance dose of 2 mg/kg until disease progression or a loading dose of 8 mg/kg by intravenous infusion, followed by 3-weekly maintenance doses of 6 mg/kg until disease progression."

Section 4.3.4 states "The Committee considered the differences in progression-free survival between the aromatase inhibitor groups in the trials….. The Committee further noted the protocol amendment to allow people in the aromatase inhibitor alone group in TAnDEM to receive trastuzumab. It considered that this amendment may add additional uncertainty to the validity of the data from the aromatase inhibitor group in this trial, particularly if fitter people left the group earlier than they otherwise might, although no data were available to confirm if this was the case." This is an incorrect flow of thought given that this protocol amended only to allow for cross-over to occur post-progression, which therefore would not impact on PFS results. Please can this be re-considered.

Section 4.3.4 also states "….this added to the uncertainty in the estimation of meal survival." Meal should be replaced with mean, assuming this was the Committee's intention however, please see above the clarification which may remove this assumed uncertainty.

Section 4.3.18 states "The Committee noted that a range of overall survival estimates were presented, from the median survival in the ITT population of 23.9 months, median survival in the centrally confirmed population of 28.6 months and the Assessment Group and manufacturer's

estimates of mean survival of 29 and 31 months respectively…The Committee concluded that all the evidence on survival indicated that patients receiving current standard NHS treatment would have an expected survival greater than 24 months." For completeness, these estimates presented here do not include the RPSFT median (the median from the TanDEM trial which attempts to take into account the post-progression trastuzumab received in the AI (placebo) arm) which was 22 months survival.

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

No comment.

4. Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief?

This population represents untreated metastatic breast cancer patients who are older (e.g. post-menopausal), overexpressing HER2 (e.g. poorer prognosis than their HER2-negative counterparts), and who are not appropriate for chemotherapy (e.g. not eligible for the NICE-approved standard of care of trastuzumab in combination with chemotherapy). We are therefore concerned that this may represent discrimination against a very small population of elderly patients who would otherwise not have access to a proven effective treatment.

5. Are there any equality-related issues that need special consideration and are not covered in the appraisal consultation document?

No comment.

References:

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Tyverb (lapatinib) Summary of Product Characteristics, July 2011

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