National Institute for Health and Care Excellence

Draft for Consultation

Early and locally advanced breast cancer: diagnosis and management

[F] Evidence reviews for adjuvant biological therapy

NICE guideline tbc

Evidence reviews

January 2018

Draft for Consultation

These evidence reviews were developed by the National Guideline Alliance hosted by the Royal College of Obstetricians and Gynaecologists

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Adjuvant biological therapy

This evidence report contains information on 1 review relating to adjuvant biological therapy.

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Review question 6.1 Which people with T1N0 human epidermal growth receptor 2 (HER2)-positive breast cancers benefit from adjuvant trastuzumab in combination with chemotherapy?

Introduction

The standard of care for adjuvant treatment of human epidermal growth factor receptor 2 (HER2) positive breast cancer is chemotherapy and trastuzumab. Large adjuvant trials demonstrated that the addition of trastuzumab to chemotherapy reduced the risk of recurrence by about 50% compared to chemotherapy alone and increased disease-free survival by about 40%. However, the large adjuvant trials only included people who had cancers that were at least 1 cm in diameter but there are now data from cohort studies that suggest that tumour size 1 (T1) HER2-positive cancers have a much higher risk of recurrence than equivalently sized HER2-negative cancers. Patients with T1 HER2-positive cancers are therefore likely to gain reasonable benefit from trastuzumab.

The aim of the review was to determine the role of trastuzumab and chemotherapy in people with T1 node-negative (N0) HER2-positive breast cancer, and to identify if there are any subsets of people in whom this combination may be particularly beneficial.

PICO table

See Table 1: Summary of the protocol (PICO table)Table 1 for a summary of the population, intervention, comparison and outcome (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

Population	Adults (18 or over) with invasive human epidermal growth receptor 2-positive (HER2+) breast cancer (T1, N0, M0) who have undergone surgery
Intervention	Trastuzumab with chemotherapy
Comparison	• No adjuvant trastuzumab or chemotherapy • Chemotherapy alone
Outcome	**Critical** • Treatment-related morbidity • Disease-free survival • Overall survival **Important** • Treatment-related mortality • HRQoL

HER2, human epidermal growth factor receptor 2; HRQoL, health-related quality of life; T1, tumour size 1, N0, node negative; M0, no distant metastases

For full details see review protocol in appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual; see the methods chapter for further information.

Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy.

Clinical evidence

Included studies

Eight articles (number of participants, N=10,079) identified by the literature search were included in the review (Cadoo, 2016; Gori, 2015; McArthur, 2011; O'Sullivan, 2015; Rodrigues, 2013; van Ramshorst, 2016; Vici, 2014; Webster, 2012), which report data from 7 retrospective cohort studies and 1 systematic review of 5 randomised controlled trials: HERA, NCCTG N9831, NSABP B31 , PACS-04 and FinHER.

All of the trials included in the systematic review compared adjuvant chemotherapy and trastuzumab with adjuvant chemotherapy alone, as did 3 of the cohort studies. The remaining 4 cohort studies compared adjuvant chemotherapy and trastuzumab against no adjuvant chemotherapy or trastuzumab.

Two studies (van Ramshorst, 2016; Vici, 2014) reported data for critical outcomes by subgroups of interest: T1a (number of publications, k=1), T1b (k=1) and T1c (k=2). Further, two studies (McArthur, 2011; Vici, 2014) reported data for T1a and T1b subgroups combined. No studies reported subgroup data based on tumour grade or oestrogen receptor status; however, the systematic review (O'Sullivan, 2015) reported data separately for those that were hormone-receptor (oestrogen and/or progesterone) positive and negative.

The clinical studies included in this evidence review are summarised in Table 2 and evidence from these are summarised in the clinical GRADE evidence profiles below (Table 3 and Table 4). See also the study selection flow chart in appendix C, forest plots in appendix E, and study evidence tables in appendix D.

This review updates a question from the previous guideline CG80 (NICE 2009). Therefore, studies for this topic identified by the previous guideline would usually be incorporated into forest plots, GRADE evidence profiles, and evidence statements. However, studies are not incorporated where there is more recent data available from the same trial, unless different outcomes are reported, or where a change in protocol from the previous guideline means that studies no longer meet inclusion criteria. None of the 9 papers included in the previous guideline were incorporated into the current results as they did not include, or report data separately, for individuals with invasive, HER2-positive, T1N0M0 breast cancer.

Excluded studies

Studies not included in this review with reasons for their exclusions are provided in appendix K.

Summary of clinical studies included in the evidence review

Table 2: Summary of included studies

Study	Additional inclusion/exclusion criteria	Interventions/comparison
Cadoo 2016	Age ≥55 years	• Intervention arm (CT+T): adjuvant trastuzumab and chemotherapy (50% taxane-based, 34% taxane and anthracycline-based) - 54% also received adjuvant hormonal therapy • Control arm (CT-T): no adjuvant trastuzumab - 53% received chemotherapy and 66% received adjuvant hormonal therapy
Gori 2015	No additional criteria	• Intervention arm (CT+T): 93% received adjuvant chemotherapy (75% anthracycline-based) and trastuzumab; 7% received trastuzumab only

Study	Additional inclusion/exclusion criteria	Interventions/comparison
		• Control arm (no treatment)
McArthur 2011	No additional criteria	• Intervention arm (CT+T): adjuvant trastuzumab (mean duration 52 weeks; range 1-68) and chemotherapy (61% anthracycline and taxane; 26% taxane) - 61% also received hormone therapy • Control arm (CT-T): no adjuvant trastuzumab following breast conserving surgery - 66% received adjuvant chemotherapy (64% anthracycline; 19% anthracycline and taxane); 59% also received hormone therapy
O'Sullivan 2015	Articles published between 1995 and 2013	• Intervention arm (CT+T): Adjuvant trastuzumab (duration 9 weeks to 2 years; 73% 1 year) and chemotherapy (96% anthracycline based) • Control arm (CT-T): no further details reported
Rodrigues 2013	No additional criteria	• Intervention arm (CT+T): trastuzumab was given in a 3-weekly schedule after an anthracycline-based regimen (29%), concomitantly with a taxane after an anthracycline-based regimen (43%), concomitantly with a taxane-only regimen (28%), and after the completion of concomitant anthracycline–taxane (1%). The median duration of trastuzumab therapy was 12 months (range: 2–12). • Control arm (no treatment)
van Ramshorst 2016	No additional criteria	• Intervention arm (CT+T): 92% received chemotherapy and trastuzumab, 5% received chemotherapy only, 3% trastuzumab only - 55% also received endocrine therapy. • Control arm (no treatment)
Vici 2014	No additional criteria	• Intervention arm (CT+T): adjuvant chemotherapy (16% anthracycline-based, 65% anthraxycline+taxane-based) + trastuzumab (58% concurrent with chemotherapy) for median of 52 weeks (range 1-104) • Control arm (CT-T): adjuvant chemotherapy (49% anthracycline-based, 20% anthraxycline+taxane-based)
Webster 2012	No additional criteria	• Intervention arm (CT+T): No details reported specifically for stage I patients - 24% of whole sample received taxane containing chemotherapy regimen; 81% completed full course of trastuzumab • Control arm (no treatment)

CT, chemotherapy; T, trastuzumab

See appendix D for full evidence tables.

1 Quality assessment of clinical studies included in the evidence review

2 **Table 3: Summary clinical evidence profile: Comparison 1. Adjuvant trastuzumab and**
3 **chemotherapy versus adjuvant chemotherapy only**

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: CT-T	Corresponding risk: CT+T			
Disease-free survival - Whole sample (3 year follow-up)	3 yr DFS 82%	3 yr DFS 98% (93% to 99%)	HR 0.13 (0.05 to 0.37)	261 (1 study)	Very low[1,2,6]
Disease-free survival - T1a/b (3 year follow-up)	3 yr DFS 78%	3 yr DFS 95% (88% to 98%)	HR 0.19 (0.07 to 0.51)	158 (2 studies)	Very low[2,3,6]
Disease-free survival - T1c (5 year follow-up)	5 yr DFS 81%	5 yr DFS 94% (87% to 98%	HR 0.28 (0.12 to 0.65)	224 (1 study)	Very low[2,6]
Disease-free survival - HR+ (RCT; 8 year follow-up)	8 yr DFS 81%	8 yr DFS 87% (84% to 90%)	HR 0.64 (0.48 to 0.85)	1,092 (1 study)	Not possible to GRADE this outcome due to lack of information presented in review
Disease-free survival - HR- (RCT; 8 year follow-up)	8 yr DFS 74%	8 yr DFS 79% (74% to 84%)	HR 0.77 (0.59 to 1.00)	1,040 (1 study)	Not possible to GRADE this outcome due to lack of information presented in review
Overall survival - Whole sample (3 year follow-up)	3 yr OS 97%	3 yr OS 99% (95% to 100%)	HR 0.27 (0.04 to 1.83)	261 (1 study)	Very low[1,2,6]
Overall survival - T1a/b (3 year follow-up)	3 yr OS 98%	3 yr OS 99% (81% to 100%)	HR 0.64 (0.04 to 10.50)	99 (1 study)	Very low[1,2,6]
Overall survival - HR+ (RCT; 8 year follow-up)	8 yr OS 93%	8 yr OS 95% (92% to 97%)	HR 0.68 (0.42 to 1.10)	1,092 (1 study)	Not possible to GRADE this outcome due to lack of information presented in review
Overall survival - HR- (RCT; 8 year follow-up)	8 yr OS 88%	8 yr OS 92% (88% to 94%)	HR 0.69 (0.46 to 1.04)	1,040 (1 study)	Not possible to GRADE

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: CT-T	Corresponding risk: CT+T			
					this outcome due to lack of information presented in review
Overall survival - T1c (5 year follow-up)	5 yr OS 84%	5 yr OS 97% (91% to 99%)	HR 0.20 (0.07 to 0.55)	224 (1 study)	Very low[2,6]
Treatment-related morbidity: congestive heart failure (4 year follow-up)	9 per 1000	31 per 1000 (4 to 276)	RR 3.62 (0.41 to 31.97)	244 (1 study)	Very low[4,5,6]
Treatment-related morbidity: secondary cancer (4 year follow-up)	26 per 1000	16 per 1000 (4 to 288)	RR 0.60 (0.10 to 3.55)	244 (1 study)	Very low[2,6]

Rates of disease-free survival and overall survival in the control group correspond to the trial with the shortest follow-up period
CI: Confidence interval; CT: chemotherapy; DFS, disease-free survival; HR: Hazard ratio; HR+: hormone receptor positive; HR-: hormone receptor negative; OS, overall survival; RCT, randomised controlled trial; RR: Risk ratio; T: trastuzumab
[1] Comparison: only 66% of comparison arm received chemotherapy
[2] <300 events
[3] Comparison: study with greatest weight only 66% of comparison arm received chemotherapy
[4] Comparison: only 53% of comparison arm received chemotherapy
[5] events <300 and 95%CI crosses boundaries for no effect (1) and minimally important differences (0.80 and 1.25) based on GRADE default values
[6] Groups not comparable due to differences in chemotherapy regimens

Table 4: Summary clinical evidence profile: Comparison 2. Adjuvant trastuzumab and chemotherapy versus no adjuvant chemotherapy or trastuzumab

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: no treatment	Corresponding risk: CT+T			
Disease-free survival (3 year follow-up)	3 yr DFS 84%	3 yr DFS 98% (95% to 99%)	HR 0.12 (0.04 to 0.32)	582 (3 studies)	Low[1,2]
Overall survival - Whole sample (3 year follow-up)	3 yr OS 96%	3 yr OS 99% (98% to 99%)	HR 0.29 (0.20 to 0.40)	3604 (2 studies)	Moderate[3]
Overall survival - T1a (8 year follow-up)	8 yr OS 85%	8 yr OS 99% (99% to 100%)	HR 0.05 (0.03 to 0.09)	385 (1 study)	Moderate[1,2]
Overall survival - T1b (8 year follow-up)	8 yr OS 89%	8 yr OS 98% (89% to 100%)	HR 0.14 (0.02 to 0.99)	800 (1 study)	Very low[1]
Overall survival - T1c (8 year follow-up)	8 yr OS 80%	8 yr OS 95% (93% to 97%)	HR 0.23 (0.16 to 0.33)	2327 (1 study)	Low[1,3]

Rates of disease-free survival and overall survival in the control group correspond to the trial with the shortest follow-up period
CI: Confidence interval; DFS, disease-free survival; CT, chemotherapy; HR: Hazard ratio; OS, overall survival; RR: Risk ratio; T, trastuzumab
[1] <300 events
[2] Estimated HR <0.20
[3] Estimated HR <0.50

See appendix F for full GRADE tables.

Economic evidence

A systematic review of the economic literature was conducted but no relevant studies were identified which were applicable to this review question.

Economic model

An economic analysis was undertaken to estimate the cost-effectiveness of adjuvant trastuzumab in combination with chemotherapy in people with T1N0 HER2-positive breast cancer (see appendix J for the full report of the economic analysis).

Methods

The analysis was developed in Microsoft Excel® and was conducted from the perspective of the NHS and Personal Social Services (PSS) as outlined in the NICE Reference Case (see Developing NICE guidelines: the manual). The model considered a fifty year time horizon with future costs and benefits discounted at a rate of 3.5% (as recommended in the NICE reference case).

Clinical data and model approach

The economic analysis was based on overall survival and progression free survival estimates for each of the treatments included in the analysis. The analysis essentially took the form of a simple partitioned survival analysis, in which three mutually exclusive health states were derived from the overall survival and progression free survival estimates:

- alive without progressed disease
- alive with progressed disease
- dead.

Overall survival (OS) and disease-free survival (DFS) for each of the interventions was estimated using data on absolute risk combined with data on treatment effects from the Herceptin Adjuvant (HERA) trial (Cameron 2017; Piccart-Gebhart 2005). Absolute OS and DFS for people with HER2-positive T1 tumours was sourced from Vas-Luiz 2014. The study included 257 HER2-positive people with T1a-b tumours who had not received chemotherapy or trastuzumab. The study reported an average overall survival of 94.9% and disease-free survival of 84.4% at five years.

In order to estimate baseline risk in people receiving adjuvant chemotherapy, a treatment effect associated with adjuvant chemotherapy was applied to the absolute risks in the observation arm. An Early Breast Cancer Trialists' Collaborative Group (EBCTCG 2012) review estimated ten year relative risks (RRs) of 0.73 for recurrence and 0.84 for overall mortality in people receiving anthracycline based chemotherapy in comparison to no chemotherapy. This gives an estimated OS of 95.8% and DFS of 88.9% at 5 years (compared to 94.9% and 84.4% in no treatment group)

OS and DFS values for the adjuvant chemotherapy and trastuzumab arm were derived based on treatment effects from the long-term results of the HERA trial (Cameron 2017). Hazard ratios (HRs) of 0.74 and 0.76 for OS and DFS respectively. Applying these relative

effects to the absolute risk estimated in the adjuvant chemotherapy arm results in an OS estimate of 96.9% and a DFS estimate of 91.5% at five years.

Mortality from other causes was captured using 2013-2015 life tables for England and Wales from the office of national statistics (ONS). These life tables give an estimate of the annual probability of death given a person's age and gender. A starting age of 49 was applied in the model based on the average age reported in Piccart-Gebhart 2005. The other cause mortality estimates were used in conjunction with the overall survival estimates above to estimate the proportion of people that died of disease-specific and other causes.

Costs

The costs considered in the model reflect the perspective of the analysis, thus only costs that are relevant to the UK NHS & PSS were included. Where possible, all costs were estimated in 2015/16 prices.

The majority of costs were sourced from NHS reference costs 2015/16 by applying tariffs associated with the appropriate Healthcare Resource Groups (HRG) code. Drug costs were calculated using unit cost data from the electronic market information tool (eMit) combined with dose information from the British National Formulary (BNF). Where costs were not available from eMit, list prices from the BNF were used. Other resource use and cost information were sourced from the Personal Social Services Research Unit (PSSRU) and the advice of the guideline committee.

Costs were estimated for the adjuvant chemotherapy regimens that are most likely to be used in current clinical practice (based on the opinion of the guideline committee). Costs were estimated for a regimen of docetaxel and cyclophosphamide (TC) and a weekly paclitaxel regimen. Chemotherapy drug costs were sourced from eMit while the cost of delivering chemotherapy was sourced from NHS Reference Costs 2015/16.

The cost of trastuzumab was estimated using drug costs from the BNF (since unit costs were not available from eMit) and delivery costs from NHS Reference costs 2015/16. Note that, since the previous NICE technology appraisal (TA) on trastuzumab was published (NICE TA107), the most common route of administration has changed. Previously trastuzumab was delivered intravenously but it is now most commonly delivered as a subcutaneous injection. The total cost for one year of trastuzumab was estimated to be £25,580.49.

Subsequent treatment costs (following disease recurrence or progression) were estimated based on the average treatment that would be most likely to be used (based on the estimation of the guideline committee). It was assumed that treatment would vary depending upon the type of recurrence with data from the HERA trial used to estimate the proportion of recurrences that were locoregional (18%), regional (5%), contralateral (8%) and distant (69%).

It was assumed that people with locoregional, regional or contralateral recurrence would undergo a mastectomy if they originally had breast conserving surgery (42% from Cameron 2017) or a 'major breast procedure' if they originally had a mastectomy (58% from Cameron 2017). It was also assumed that breast reconstruction would be performed (either delayed or at the time of mastectomy). It was further assumed that lymph node clearance would be performed for people with regional recurrence. It was also assumed that radiotherapy would be given in people that were not previously treated with radiotherapy (24% from Cameron 2017) and that everyone would receive adjuvant chemotherapy, trastuzumab and pertuzumab. In people with distant recurrence, it was assumed that they would receive chemotherapy, trastuzumab and pertuzumab.

Treatment with trastuzumab is associated with a risk of cardiotoxicity and therefore people receiving trastuzumab typically undergo cardiac monitoring. In clinical practice, echocardiograms are typically used for cardiac monitoring but in some cases multi-gated

acquisition (MUGA) scans or cardiac magnetic resonance imaging (MRI) scans may be used. In the model, a weighted average cost per scan was calculated using weightings estimated by the guideline committee. It was assumed that 80% of scans would be echocardiograms, 10% would be MUGA scans and 10% would be cardiac MRI scans. The cost for each scan was sourced from NHS reference costs 2015/16. Reflecting clinical practice, it was assumed that people would undergo five cardiac monitoring scans in the year that they receive trastuzumab.

The cost of post-treatment follow-up to detect disease recurrence was incorporated in the model. It was assumed that people would have clinical follow-up appointments every three to six months in the years one to three, every six to twelve months in years four to five and annually thereafter. The cost for each follow-up appointment was estimated to be £120.98 based on the cost of a 'consultant led, non-admitted face to face attendance, follow-up' from NHS Reference Costs 2015/16.

The cost of palliative care was estimated using estimates from a costing report by the Nuffield Trust (Georghiou 2014, 'Exploring the cost of care at the end of life'). A cost of £7,287 for 3 months was applied based on the average resource use of people with cancer in the last three months of life.

Health-related quality of life

As recommended in the NICE reference case, the model estimates effectiveness in terms of quality adjusted life years (QALYs). These are estimated by combining the life year estimates with utility values (or QoL weights) associated with being in a particular health state.

The QoL values applied in the model were sourced from Essers 2010, which reported utility values for people with HER2-positive breast cancer and was applicable to the UK setting. This study was identified and used by the Evidence Review Group (ERG) in their revised economic analysis as part of the technology appraisal for pertuzumab in neoadjuvant treatment of HER2-positive breast cancer (NICE TA 424). People in the 'disease free' health state would have a QoL value of 0.847 which decreases to 0.810 in people with a recurrence. The QoL value for metastatic disease was applied to people in the last year of life before dying of cancer specific mortality.

Results

Base case results

The base case results of the analysis are shown in Table 5 and Table 6 below for two scenarios. In the first scenario, adjuvant chemotherapy and trastuzumab are compared against observation while in the second scenario the use of adjuvant chemotherapy without trastuzumab is considered as another treatment option.

In the first scenario, it can be seen that adjuvant chemotherapy and trastuzumab was found to be less costly (-£27,881) and more effective than observation (1.09 QALYs) and is therefore dominant.

In the second scenario, it can be seen that observation was found to be more costly and less effective than both adjuvant chemotherapy and adjuvant chemotherapy and trastuzumab and is therefore dominated. When comparing adjuvant chemotherapy and trastuzumab against adjuvant chemotherapy alone, the addition of trastuzumab was found to improve effectiveness but also significantly increase costs. The resulting ICER of £20,170 per QALY was marginally higher than the NICE threshold of £20,000 per QALY. Therefore the strategy was not cost-effective when compared against adjuvant chemotherapy.

Table 5: Base case results for adjuvant chemotherapy and trastuzumab in comparison to observation

Strategy	Cost		QALYs		ICER (cost per QALY
	Total	Incremental	Total	Incremental	
Observation	£111,242	-	13.81	-	**-**
Adjuvant chemotherapy + trastuzumab	£83,361	*-£27,881*	14.90	*1.09*	**Dominant**

ICER; incremental cost-effectiveness ratio; QALYs, quality adjusted life years

Table 6: Base case results for three way comparison

Strategy	Cost		QALYs		ICER (cost per QALY
	Total	Incremental	Total	Incremental	
Adjuvant chemotherapy	£70,758	-	14.28	-	**-**
Adjuvant chemotherapy + trastuzumab	£83,361	*£12,603*	14.90	*0.62*	**£20,170**
Observation	£111,242	*£27,881*	13.81	*-1.09*	**Dominated**

ICER; incremental cost-effectiveness ratio; QALYs, quality adjusted life years

Deterministic sensitivity results

A series of deterministic sensitivity analyses were conducted, whereby an input parameter is changed, the model is re-run and the new cost-effectiveness result is recorded. This analysis (Table 7) is a useful way of estimating uncertainty and determining the key drivers of the model result.

In the 2-way comparison between observation and adjuvant chemotherapy and trastuzumab, it can be seen that the conclusion of the analysis remains unchanged in all scenarios. Notably this includes scenarios where the upper HR estimate is used for both overall survival and disease free survival (thereby reducing the effectiveness of treatment)..

In the 3-way comparison, it can again be seen that the conclusion of the analysis changes in numerous scenarios with adjuvant chemotherapy and trastuzumab found to be cost-effective with ICER values below £20,000 per QALY. This includes scenarios in which baseline OS and DFS risk is lowered (thereby increasing the baseline risk and increasing the scope for treatment to be effective). The addition of trastuzumab was also found to be cost-effective in scenarios where lower HRs are used for mortality and recurrence. This includes scenarios in which the lower estimates for OS and DFS from the 95% CI interval range are applied and scenarios where the HRs from the clinical evidence review were applied (sourced from observational studies of patients with T1 tumours). It is also noteworthy that the addition of trastuzumab was found to be cost-effective in a scenario where the delivery cost is reduced by 60%. There is some uncertainty around the appropriate delivery cost and it is possible that the base case value is an overestimate (a 60% reduction was considered to be a plausible reduction in the cost).

Table 7: Deterministic sensitivity results

Change made	Two way comparison	Three way comparison
Base case	**Adjuvant chemotherapy + trastuzumab**	**Adjuvant chemotherapy**
Baseline DFS = 75%	Adjuvant chemotherapy + trastuzumab	***Adjuvant chemotherapy + trastuzumab***
Baseline DFS = 65%	Adjuvant chemotherapy + trastuzumab	***Adjuvant chemotherapy + trastuzumab***

Change made	Two way comparison	Three way comparison
Baseline OS = 85%	Adjuvant chemotherapy + trastuzumab	***Adjuvant chemotherapy + trastuzumab***
Baseline OS = 75%	Adjuvant chemotherapy + trastuzumab	***Adjuvant chemotherapy + trastuzumab***
OS and DFS upper RR	Adjuvant chemotherapy + trastuzumab	Adjuvant chemotherapy
OS and DFS lower RR	Adjuvant chemotherapy + trastuzumab	***Adjuvant chemotherapy + trastuzumab***
HR for DFS from evidence review (0.13)	Adjuvant chemotherapy + trastuzumab	***Adjuvant chemotherapy + trastuzumab***
HR for OS from evidence review (0.27)	Adjuvant chemotherapy + trastuzumab	***Adjuvant chemotherapy + trastuzumab***
HR for OS and DFS from evidence review	Adjuvant chemotherapy + trastuzumab	***Adjuvant chemotherapy + trastuzumab***
Adjuvant chemotherapy DFS RR = 0.54	Adjuvant chemotherapy + trastuzumab	Adjuvant chemotherapy
Trastuzumab delivery cost 60% lower	Adjuvant chemotherapy + trastuzumab	***Adjuvant chemotherapy + trastuzumab***

DFS, disease-free survival; OS, overall survival; RR, risk ratio

Probabilistic sensitivity results

Probabilistic sensitivity analysis (PSA) was conducted to assess the combined parameter uncertainty in the model. In this analysis, the mean values that were utilised in the base case are replaced with values drawn from distributions around the mean values. The results of 10,000 runs of the PSA are shown using cost-effectiveness acceptability curves (CEAC), which show the probability of each strategy being considered cost-effective at the various cost-effectiveness thresholds on the x axis.

The CEAC for the two-way comparison (Figure 1) between observation and adjuvant chemotherapy and trastuzumab shows that the probability of adjuvant chemotherapy and trastuzumab being cost-effective remains fairly constant but does increase slightly as the cost-effectiveness threshold increases. At the NICE threshold of £20,000 per QALY, adjuvant chemotherapy and trastuzumab was found to have a 98% probability of being cost-effective while observation had a 2% probability of being cost-effective.

The CEAC for the three-way comparison (in which adjuvant chemotherapy is also considered) (Figure 2) shows that the probability of adjuvant chemotherapy and trastuzumab being cost-effective increases as the cost-effectiveness threshold increases. Adjuvant chemotherapy alone starts with a much higher probability of being cost-effective, which decreases as the threshold increases. At the NICE threshold of £20,000 per QALY, adjuvant chemotherapy and trastuzumab was found to have a 58% probability of being cost-effective while adjuvant chemotherapy had a 42% probability of being cost-effective and observation had a 0% probability of being cost-effective.

Figure 1: Cost-effectiveness acceptability curve for adjuvant chemotherapy and trastuzumab in comparison to observation

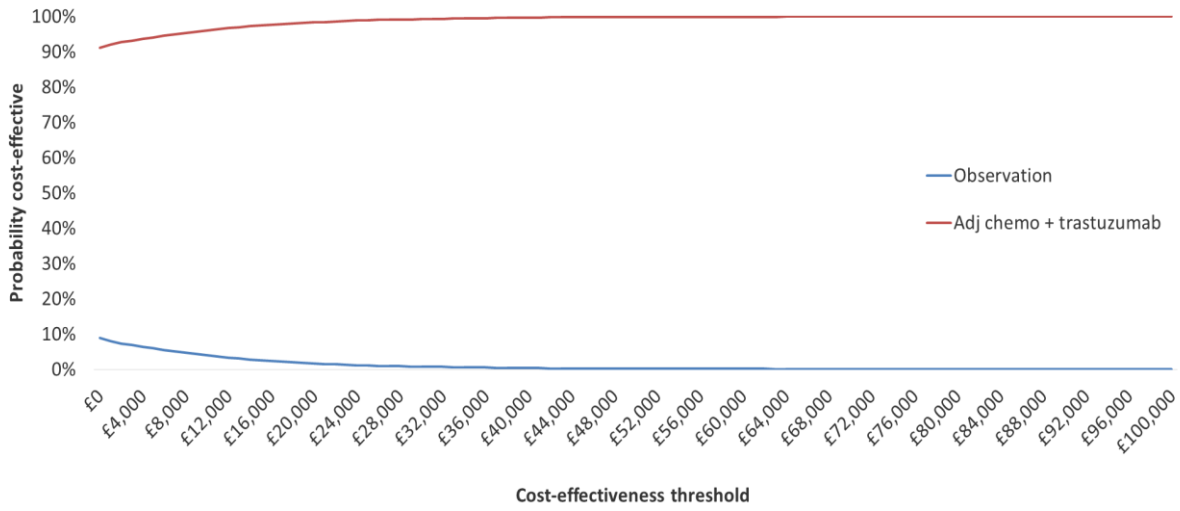
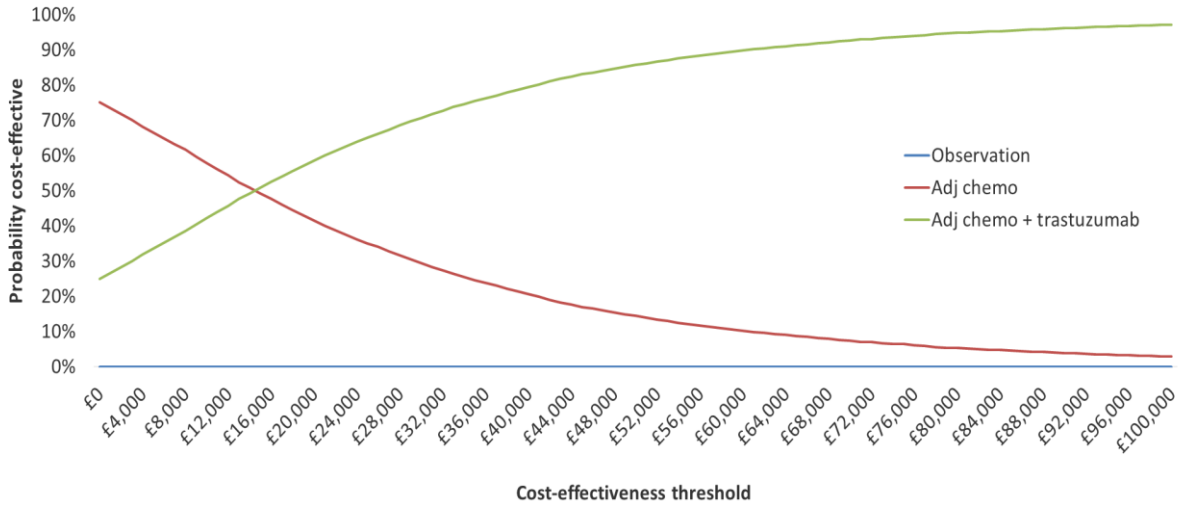


Figure 2: Cost-effectiveness acceptability curve for three way comparison



Conclusion

The results of the analysis suggest that active treatment is superior to observation in people with HER2-positive T1 tumours. When compared against observation adjuvant chemotherapy and trastuzumab is found to be cost-effective with an ICER below the NICE threshold of £20,000 per QALY. However, if adjuvant chemotherapy alone is considered to be an appropriate treatment in this population then adjuvant chemotherapy and trastuzumab may not be cost-effective as its ICER value exceeds the NICE threshold of £20,000 per QALY when compared against adjuvant chemotherapy alone.

Evidence statements

Comparison 1. Adjuvant trastuzumab and chemotherapy versus chemotherapy alone

Critical outcomes

Treatment-related morbidity

- There is very low quality evidence from 1 retrospective cohort study (*N*=244) that adjuvant trastuzumab and chemotherapy produces clinically meaningful increases in congestive heart failure at 4 year follow-up compared with chemotherapy alone for people with T1N0, HER2+ invasive breast cancer. However, this was not statistically significant.
- There is very low quality evidence from 1 retrospective cohort study (*N*=244) that there is no clinically important effect of adjuvant trastuzumab on secondary cancer at 4 year follow-up for people with T1N0, HER2+ invasive breast cancer.

Disease-free survival

- There is very low quality evidence from 1 retrospective cohort study (*N*=261) that adjuvant trastuzumab and chemotherapy produces clinically meaningful increases in disease-free survival compared with chemotherapy alone at 3 year follow-up for people with T1N0, HER2+ invasive breast cancer.
- There is very low quality evidence from 2 retrospective cohort studies (*N*=158) that adjuvant trastuzumab and chemotherapy produces clinically meaningful increases in disease-free survival compared with chemotherapy alone at 3 year follow-up for people with T1a/bN0, HER2+ invasive breast cancer.
- There is very low quality evidence from 1 retrospective cohort study (*N*=224) that adjuvant trastuzumab and chemotherapy produces clinically meaningful increases in disease-free survival compared with chemotherapy alone at 5 year follow-up for people with T1cN0, HER2+ invasive breast cancer.
- There is evidence from 1 systematic review (N=1,092) that adjuvant trastuzumab and chemotherapy produces clinically meaningful increases in disease-free survival compared with chemotherapy alone at 8 year follow-up for people with T1, hormone-receptor positive, HER2+ invasive breast cancer with ≤1 positive lymph node. It was not possible to judge risk of bias, and therefore quality of this evidence, as insufficient information was presented in the systematic review.
- There is evidence from 1 systematic review (N=1,040) that adjuvant trastuzumab and chemotherapy produces clinically meaningful increases in disease-free survival compared with chemotherapy alone at 8 year follow-up for people with T1, hormone-receptor negative, HER2+ invasive breast cancer with ≤1 positive lymph node. It was not possible to judge risk of bias, and therefore quality of this evidence, as insufficient information was presented in the systematic review.

Overall survival

- There is very low quality evidence from 1 retrospective cohort study (*N*=261) that there is no clinically important effect of adjuvant trastuzumab on overall survival at 3 year follow-up for people with T1N0, HER2+ invasive breast cancer.
- There is very low quality evidence from 1 retrospective cohort study (*N*=99) that there is no clinically important effect of adjuvant trastuzumab on overall survival at 3 year follow-up for people with T1a/bN0, HER2+ invasive breast cancer.
- There is very low quality evidence from 1 retrospective cohort study (*N*=224) that adjuvant trastuzumab and chemotherapy produces clinically meaningful increases in overall survival compared with chemotherapy alone at 5 year follow-up for people with T1cN0, HER2+ invasive breast cancer.

- There is evidence from 1 systematic review (N=1,092) that there is no clinically important effect of adjuvant trastuzumab on overall survival at 8 year follow-up for people with T1, hormone-receptor positive, HER2+ invasive breast cancer with ≤1 positive lymph node. It was not possible to judge risk of bias, and therefore quality of this evidence, as insufficient information was presented in the systematic review.
- There is evidence from 1 systematic review (N=1,040) that there is no clinically important effect of adjuvant trastuzumab on overall survival at 8 year follow-up for people with T1, hormone-receptor negative, HER2+ invasive breast cancer with ≤1 positive lymph node. It was not possible to judge risk of bias, and therefore quality of this evidence, as insufficient information was presented in the systematic review.

Important outcomes

Treatment-related mortality

- No evidence was found for this outcome.

HRQoL

- No evidence was found for this outcome.

Comparison 2. Adjuvant trastuzumab and chemotherapy versus no adjuvant therapy

Critical outcomes

Treatment-related morbidity

- No evidence was found for this outcome.

Disease-free survival

- There is moderate quality evidence from 3 retrospective cohort studies (*N*=582) that adjuvant trastuzumab and chemotherapy produces clinically meaningful increases in disease-free survival compared with no adjuvant chemotherapy or trastuzumab at 3 year follow-up for people with T1N0, HER2+ invasive breast cancer.

Overall survival

- There is moderate quality evidence from 2 retrospective cohort studies (*N*=3604) that adjuvant trastuzumab and chemotherapy produces clinically meaningful increases in overall survival compared with no adjuvant chemotherapy or trastuzumab at 3 year follow-up for people with T1N0, HER2+ invasive breast cancer.
- There is moderate quality evidence from 1 retrospective cohort study (*N*=385) that adjuvant trastuzumab and chemotherapy produces clinically meaningful increases in overall survival compared with no adjuvant chemotherapy or trastuzumab at 8 year follow-up for people with T1aN0, HER2+ invasive breast cancer.
- There is moderate quality evidence from 1 retrospective cohort study (*N*=800) that adjuvant trastuzumab and chemotherapy produces clinically meaningful increases in overall survival compared with no adjuvant chemotherapy or trastuzumab at 8 year follow-up for people with T1bN0, HER2+ invasive breast cancer.
- There is low quality evidence from 1 retrospective cohort study (*N*=2327) that adjuvant trastuzumab and chemotherapy produces clinically meaningful increases in overall survival compared with no adjuvant chemotherapy or trastuzumab at 8 year follow-up for people with T1cN0, HER2+ invasive breast cancer.

Important outcomes

Treatment-related mortality

- No evidence was found for this outcome.

HRQoL

- No evidence was found for this outcome

Economic evidence statement

- Evidence from a de novo cost-utility analysis showed that adjuvant chemotherapy and trastuzumab was more effective and less costly than observation and therefore dominant. In comparison to adjuvant chemotherapy, adjuvant chemotherapy and trastuzumab was found to be more effective and more costly but not cost-effective with an ICER of £20,170 per QALY, marginally above the NICE threshold of £20,000 per QALY. The analysis was directly applicable with minor limitations.

Recommendations

F1. Consider trastuzumab as adjuvant treatment for people with T1a/T1b HER2-positive invasive breast cancer, taking into account any comorbidities, prognostic features and possible cardiac toxicity of anthracycline treatment.

Rationale and impact

Why the committee made the recommendations

There was evidence that adjuvant trastuzumab can improve disease-free survival and overall survival in some people with T1a and T1b HER2-positive invasive breast cancer who were treated with adjuvant trastuzumab and chemotherapy. However, only a small number of people will benefit from this treatment and, because trastuzumab can cause heart problems, it is important to avoid offering it to people who do not need it. Because of this, the committee agreed that adjuvant trastuzumab should be an option for women with T1a and T1b tumours rather than a standard treatment.

Chemotherapy alone compared with no treatment was found to be more cost-effective than chemotherapy and trastuzumab combined. However, the committee agreed that it was more appropriate to offer combined chemotherapy and trastuzumab, because it is the HER2-positivity that increases risk of recurrence for people with small (T1a and T1b) tumours sufficiently for chemotherapy to be of benefit. From a clinical perspective, it does not make sense to not treat the component that is increasing risk (that is, trastuzumab treatment for HER2-positivity). Further, the effect of chemotherapy alone in the economic model may be overestimated as the data was taken from the HERA trial, which included larger tumours, as this evidence was considered more robust than the clinical evidence in this review.

Impact of the recommendations on practice

Currently, T1 tumours are not routinely treated with adjuvant trastuzumab, so this recommendation will lead to a change in practice. However, the committee agreed that the number of additional people having treatment would be small and so the impact on current practice would be minor.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

As this review question is considering a treatment used after surgery to ensure there is no disease recurrence, disease-free survival, overall survival and treatment-related morbidities were selected as critical outcomes by the committee. The inclusion of treatment-related morbidities was to allow a balance of the benefits and harms of treatments to be made. Treatment-related mortality and health-related quality of life were identified as important outcomes.

Survival outcomes are prioritised by people with breast cancer; however, treatment-related morbidities, and the impact these have on quality of life, are also important as they affect peoples' acceptance of, and adherence to, treatment.

No evidence was available for treatment-related mortality or health-related quality of life for either comparison. Additionally, there was no evidence regarding treatment-related morbidities for trastuzumab and chemotherapy compared with no treatment.

The quality of the evidence

The quality of evidence for this review was assessed using GRADE, with cohort studies starting off as low quality.

For the comparison of trastuzumab and chemotherapy with chemotherapy alone, the retrospective evidence for all the outcomes (disease-free survival, overall survival, congestive heart failure and secondary cancer) was low quality due to difference in the chemotherapy regimens between arms, small number of events of interest and some indirect evidence. It was not possible to assess the quality of the systematic review evidence due to insufficient information available in the publication.

For the comparison of trastuzumab and chemotherapy with no treatment, the evidence for disease-free survival was low quality. The evidence was downgraded because of uncertainty around the estimate due to the small number of events of interest, but was upgraded due to the large effect size.

For overall survival, the evidence for the mixed population was of moderate quality, and was upgraded to this due to the large effect size. For the T1a subgroup the evidence was also moderate quality due to downgrading because of uncertainty around the estimate due to the small number of events of interest, but upgraded twice due to the very large effect size. For the T1b subgroup the evidence was very low quality due to downgrading for uncertainty around estimate due to small number of events of interest. Although the point estimate for the HR shows a very strong association, the confidence interval is very wide so the quality was not upgraded. For the T1c subgroup the evidence was low quality, downgraded because of uncertainty around the estimate due to the small number of events of interest but upgraded due to the large effect size.

The recommendation made by the committee was mainly driven by the comparison of trastuzumab and chemotherapy versus no treatment, as in clinical practice the committee agreed that people with T1N0 HER2-negative early breast cancer would not usually receive chemotherapy at all. However, the HER2-positive status increased their risk, and so treatment with trastuzumab and chemotherapy was indicated, and there was moderate quality evidence for improved overall survival and low quality evidence for improved disease-free survival when compared against no treatment. Whilst the quality of evidence for other outcomes and subgroups was low or very low, there was a strong association (i.e., a large effect size) for the comparison.

Benefits and harms

The combination of trastuzumab with chemotherapy leads to improved disease-free survival and overall survival compared to no treatment, in people with T1a, T1b and T1c tumours. Specifically, an additional 14% of people would be free from disease at 3 years and an additional 9-15% would be alive at 8 years (T1a 14%, T1b 11%, T1c 15%) with the combination compared to no treatment.

By treating people with early disease and small tumours there is, however, a risk of over-treatment and of people suffering the adverse effects from the trastuzumab and chemotherapy. There was little evidence from this review of harms, except for the increased incidence of congestive heart failure seen in low quality evidence from one retrospective cohort study. However, this is a known adverse effect of trastuzumab and this is reflected in the additional monitoring recommended.

Even without treatment, 84% of people with T1a/T1b tumours would be disease-free at 3 years, and 80 to 89% would be alive at 8 years. Therefore the population who may gain benefit from the combination of trastuzumab and chemotherapy is small, but for these individuals an increase in disease-free and overall survival is important, and survival is usually prioritised by people over side-effects. In addition, due to the large effect sizes favouring trastuzumab and chemotherapy compared with no treatment, the numbers needed to treat are small, and only 7-11 people would need to be treated for one additional person to be free from disease or be alive.

Cost effectiveness and resource use

A systematic review of the economic literature was conducted but no relevant studies were identified which were applicable to this review question. An economic analysis was undertaken for this question assessing the cost-effectiveness of the addition of adjuvant chemotherapy and trastuzumab in people with T1N0 breast cancer.

The base case results of the analysis were presented for 2 scenarios. In the first scenario, a two-way comparison between observation and adjuvant chemotherapy and trastuzumab was considered. In the second scenario, a three way comparison between observation, adjuvant chemotherapy and adjuvant chemotherapy and trastuzumab was considered. The analysis was separated into these sections to reflect the uncertainty around the appropriateness of the use of adjuvant chemotherapy alone in this setting.

In the first scenario, it was found that adjuvant chemotherapy and trastuzumab was less costly and more effective than observation and was therefore dominant. In the second scenario, observation was found to be dominated by both intervention strategies (adjuvant chemotherapy and adjuvant chemotherapy and trastuzumab). When comparing adjuvant chemotherapy and trastuzumab against adjuvant chemotherapy alone, the addition of trastuzumab was found to improve effectiveness but also significantly increase costs. The resulting ICER of £20,170 per QALY was marginally higher than the NICE threshold of £20,000 per QALY. Therefore the strategy was not cost-effective when compared against adjuvant chemotherapy.

The results in the scenario where adjuvant chemotherapy and trastuzumab was compared against observation was found to be very robust in sensitivity analysis. The conclusion remained unchanged in all of the deterministic sensitivity analyses while in probabilistic sensitivity analysis, adjuvant chemotherapy and trastuzumab was found to have a 98% probability of being cost-effective. In the 3-way comparison, the result changed in numerous scenarios with adjuvant chemotherapy and trastuzumab becoming the preferred strategy. In probabilistic sensitivity analysis, adjuvant chemotherapy and trastuzumab was found to have a 58% probability of being cost-effective while adjuvant chemotherapy had a 42% probability of being cost-effective.

Overall, the results indicate that adjuvant chemotherapy and trastuzumab is very likely to be cost-effective in comparison to no treatment. However, there is uncertainty around whether it is cost-effective in comparison to adjuvant chemotherapy alone. The view of the committee was that the use of adjuvant chemotherapy alone was not appropriate in this setting as it would make clinical sense for people shown to have HER2-positive disease to receive a treatment targeted at this subtype (i.e. trastuzumab). Therefore, the committee focused on the results of the 2-way comparison when drafting their recommendations.

In terms of resource impact, the recommendations are likely to require an increase in resources as T1 tumours are not routinely treated with adjuvant trastuzumab. However, the number of additional people having treatment would be relatively small and so the committee did not anticipate that the recommendations would require a significant increase in resources.

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Appendices

Appendix A – Review protocols

Review protocol for 6.1 Which people with T1 N0 human epidermal growth receptor 2 (HER2)-positive breast cancers benefit from adjuvant trastuzumab in combination with chemotherapy?

Field (based on PRISMA-P)	Content
Review question	Which people with T1 N0 human epidermal growth receptor 2 (HER2)-positive breast cancers benefit from adjuvant trastuzumab in combination with chemotherapy?
Type of review question	Intervention review
Objective of the review	The objective of this review is to determine whether the addition of adjuvant trastuzumab to chemotherapy is clinically and cost effective. Recommendations will aim to cover which small, HER2-positive tumours should be considered for chemotherapy and trastuzumab.
Eligibility criteria – population/disease/condition/issue/domain	Adults (18 or over) with invasive human epidermal growth receptor 2 (HER2)-positive breast cancer (T1, N0, M0) who have undergone surgery
Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	Trastuzumab with chemotherapy
Eligibility criteria – comparator(s)/control or reference (gold) standard	No adjuvant Trastuzumab or chemotherapy No RCTs, or controlled non-randomised studies comparing trastuzumab + chemotherapy with no adjuvant chemotherapy or trastuzumab were found so the protocol was amended to include: Chemotherapy alone
Outcomes and prioritisation	Critical (up to 3 outcomes) Disease-free survival (MID: any statistically significant difference) Treatment-related morbidity (e.g., cardiac toxicity [MID: GRADE default values]) Overall survival (MID: any statistically significant difference) Important but not critical

Field (based on PRISMA-P)	Content
	Treatment-related mortality (MID: any statistically significant difference) HRQoL (MID: values from the literature where available, otherwise GRADE default values) 10 year follow-up periods, or the longest follow-up period available, will be prioritised when multiple time points are reported. HRQoL MID values from the literature: FACT-G total: 3-7 points FACT-B total: 7-8 points TOI (trial outcome index) of FACT-B: 5-6 points BCS of FACT-B: 2-3 points WHOQOL-100: 1 point
Eligibility criteria – study design	Systematic reviews/meta-analyses of RCTs RCTs Controlled non-randomised studies (n>100 patients) No RCTs, or controlled non-randomised studies comparing trastuzumab + chemotherapy with no adjuvant chemotherapy or trastuzumab were found so the protocol was amended to include: Cohort studies (N>50)
Other inclusion exclusion criteria	Foreign language studies, conference abstracts, and narrative reviews will not routinely be included.
Proposed sensitivity/sub-group analysis, or meta-regression	Subgroups (for critical outcomes only – excluding treatment-related morbidity): Grade (1/2/3) ER status (+/-) T stage (1a/1b/1c)
Selection process – duplicate screening/selection/analysis	Sifting, data extraction, appraisal of methodological quality and GRADE assessment will be performed by the reviewing team. Quality control will be performed by the senior systematic reviewer. Dual sifting will not be performed for this question as it is a straightforward intervention review limited to RCTs.

Field (based on PRISMA-P)	Content
Data management (software)	Study sifting and data extraction will be undertaken in STAR. Pairwise meta-analyses will be performed using Cochrane Reviewer Manager (RevMan 5). GRADEpro will be used to assess the quality of evidence for each outcome.
Information sources – databases and dates	The following key databases will be searched: Cochrane Library (CDSR, DARE, CENTRAL, HTA) through Wiley, Medline & Medline in Process and Embase through OVID. Additionally Web of Science may be searched and consideration will be given to subject-specific databases and used as appropriate. Searches will be undertaken from 2008 onwards as it is an update from the previous version of this guideline.
Identify if an update	Previous topics/questions: CG80 1: What is the clinical and cost effectiveness of trastuzumab for the treatment of early breast cancer (neoadjuvant or adjuvant)? CG80 2: What is the most clinical and cost effective frequency of treatment and duration of treatment with trastuzumab for early breast cancer? TA107: Trastuzumab for the adjuvant treatment of early-stage HER-2 positive breast cancer Date of update search from previous guideline: 24/07/2008 Date of TA107: 23/08/2006 Relevant recommendation(s) from previous guidelines: CG80 1) Offer trastuzumab, given at 3-week intervals for 1 year or until disease recurrence (whichever is the shorter period), as an adjuvant treatment to women with HER2- positive early invasive breast cancer following surgery, chemotherapy, and radiotherapy when applicable. CG80 2) Assess cardiac function before starting treatment with trastuzumab. Do not offer trastuzumab treatment to women who have any of the following: − a left ventricular ejection fraction (LVEF) of 55% or less − a history of documented congestive heart failure − high-risk uncontrolled arrhythmias − angina pectoris requiring medication − clinically significant valvular disease − evidence of transmural infarction on electrocardiograph (ECG) − poorly controlled hypertension. CG80 3) Repeat cardiac functional assessments every 3 months during trastuzumab treatment. If the LVEF drops by 10

Field (based on PRISMA-P)	Content
	percentage (ejection) points or more from baseline and to below 50% then trastuzumab treatment should be suspended. Restart trastuzumab therapy only after further cardiac assessment and a fully informed discussion of the risks and benefits with the woman.
Author contacts	Please the guideline in development web site.
Highlight if amendment to previous protocol	For details please see Section 4.5 of Developing NICE guidelines: the manual
Search strategy	For details please see appendix B.
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix G (clinical evidence tables) or appendix H (economic evidence tables).
Data items – define all variables to be collected	For details please see evidence tables in appendix D (clinical evidence tables) or appendix H (economic evidence tables).
Methods for assessing bias at outcome/study level	Standard study checklists were used to critically appraise individual studies. For details please see Section 6.2 of Developing NICE guidelines: the manual The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
Criteria for quantitative synthesis	For details please see Section 6.4 of Developing NICE guidelines: the manual
Methods for quantitative analysis – combining studies and exploring (in)consistency	For details please see the methods chapter.
Meta-bias assessment – publication bias, selective reporting bias	For details please see Section 6.2 of Developing NICE guidelines: the manual.
Confidence in cumulative evidence	For details please see Sections 6.4 and 9.1 of Developing NICE guidelines: the manual
Rationale/context – what is known	For details please see the introduction to the evidence review.

Field (based on PRISMA-P)	Content
Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by the NGA and chaired by Dr Jane Barrett in line with section 3 of Developing NICE guidelines: the manual. Staff from NGA undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details please see the methods chapter.
Sources of funding/support	The NGA is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists.
Name of sponsor	The NGA is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists.
Roles of sponsor	NICE funds the NGA to develop guidelines for the NHS in England.
PROSPERO registration number	N/A

BCS, breast cancer subscale; ER, oestrogen receptor; FACT-B, Functional assessment of cancer therapy – Breast cancer; FACT-G, Functional assessment of cancer therapy – General; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HER2, human epidermal growth factor receptor 2; HRQoL, health-related quality of life; MID, minimally important difference; N/A, not applicable; NHS, National Health Service, NICE, National Institute of Health and Care Excellence; NGA, National Guideline Alliance; RCT, randomised controlled trial; TOI, Trial outcome index; WHOQOL, World Health Organization quality of life

Appendix B – Literature search strategies

Review question: Which people with T1 N0 human epidermal growth receptor 2 (HER2)-positive breast cancers benefit from adjuvant trastuzumab in combination with chemotherapy?

Database: Medline & Embase (Multifile)

Last searched on Embase 1974 to 2017 February 06, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present.

Date of last search: 7 February 2017

#	Searches
1	exp breast cancer/ use oemezd
2	exp breast carcinoma/ use oemezd
3	exp medullary carcinoma/ use oemezd
4	exp intraductal carcinoma/ use oemezd
5	exp breast tumor/ use oemezd
6	exp Breast Neoplasms/ use prmz
7	exp "Neoplasms, Ductal, Lobular, and Medullary"/ use prmz
8	Carcinoma, Intraductal, Noninfiltrating/ use prmz
9	Carcinoma, Lobular/ use prmz
10	Carcinoma, Medullary/ use prmz
11	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12	exp breast/ use oemezd
13	exp Breast/ use prmz
14	breast.tw.
15	12 or 13 or 14
16	(breast adj milk).tw.
17	(breast adj tender$).tw.
18	16 or 17
19	15 not 18
20	exp neoplasm/ use oemezd
21	exp Neoplasms/ use prmz
22	20 or 21
23	19 and 22
24	(breast$ adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or leiomyosarcoma$ or dcis or duct$ or infiltrat$ or intraduct$ or lobul$ or medullary or tubular)).tw. use oemezd
25	(mammar$ adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or leiomyosarcoma$ or dcis or duct$ or infiltrat$ or intraduct$ or lobul$ or medullary or tubular)).tw. use oemezd
26	(breast$ adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or leiomyosarcoma$ or dcis or duct$ or infiltrat$ or intraduct$ or lobul$ or medullary or tubular)).mp. use prmz
27	(mammar$ adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or leiomyosarcoma$ or dcis or duct$ or infiltrat$ or intraduct$ or lobul$ or medullary or tubular)).mp. use prmz
28	exp Paget nipple disease/ use oemezd

#	Searches
29	Paget's Disease, Mammary/ use prmz
30	(paget$ and (breast$ or mammary or nipple$)).tw.
31	23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
32	11 or 31
33	Trastuzumab/ use prmz
34	trastuzumab/ use oemezd
35	(trastuzumab or herceptin or haerceptin).tw.
36	33 or 34 or 35
37	32 and 36
38	"stage 1".tw.
39	"stage I".tw.
40	(pT1$ or T1$).tw.
41	(pN0$ or N0$).tw.
42	M0$.tw.
43	(small adj4 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$)).tw.
44	(non-metastatic or nonmetastatic).tw.
45	((node or nodal) adj3 negative).tw.
46	38 or 39 or 40 or 41 or 42 or 43 or 44 or 45
47	37 and 46
48	(adjuvant adj trastuzumab).tw.
49	pT1a-bN0M0.tw.
50	T1N0M0.tw.
51	(infracentimetri$ or centrimetri$).tw.
52	48 or 49 or 50 or 51
53	32 and 52
54	47 or 53
55	limit 54 to yr="2008 -Current"
56	remove duplicates from 55 [Then general exclusions filter applied]

Database: Cochrane Library via Wiley Online

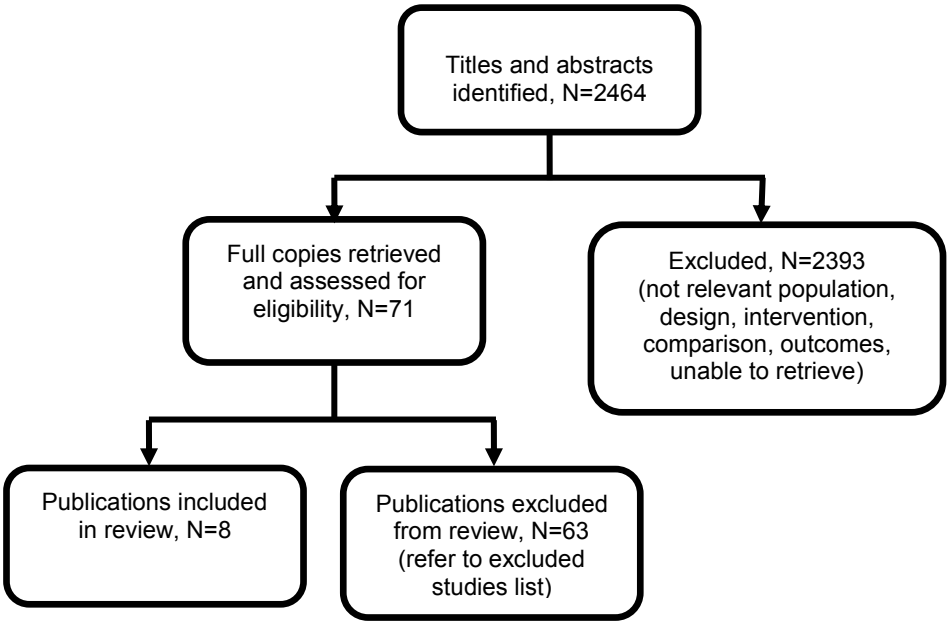
Date of last search: 7 February 2017.

#	Searches
#1	MeSH descriptor: [Breast Neoplasms] explode all trees
#2	MeSH descriptor: [Neoplasms, Ductal, Lobular, and Medullary] explode all trees
#3	MeSH descriptor: [Carcinoma, Intraductal, Noninfiltrating] explode all trees
#4	MeSH descriptor: [Carcinoma, Lobular] this term only
#5	MeSH descriptor: [Carcinoma, Medullary] this term only
#6	#1 or #2 or #3 or #4 or #5
#7	MeSH descriptor: [Breast] explode all trees
#8	breast:ti,ab,kw (Word variations have been searched)
#9	#7 or #8
#10	(breast next milk):ti,ab,kw (Word variations have been searched)
#11	(breast next tender*):ti,ab,kw (Word variations have been searched)
#12	#10 or #11

#	Searches
#13	#9 not #12
#14	MeSH descriptor: [Neoplasms] explode all trees
#15	#13 and #14
#16	(breast* near/5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular)):ti,ab,kw (Word variations have been searched)
#17	(mammar* near/5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular)):ti,ab,kw (Word variations have been searched)
#18	MeSH descriptor: [Paget's Disease, Mammary] this term only
#19	(paget* and (breast* or mammary or nipple*)):ti,ab,kw (Word variations have been searched)
#20	#15 or #16 or #17 or #18 or #19
#21	#6 or #20
#22	MeSH descriptor: [Trastuzumab] explode all trees
#23	(trastuzumab or herceptin or haerceptin):ti,ab,kw (Word variations have been searched)
#24	#22 or #23
#25	#21 and #24 Publication Year from 2008 to 2017

Appendix C – Clinical evidence study selection

Figure 3: Flow diagram of clinical article selection for adjuvant trastuzumab



Appendix D – Clinical evidence tables

Table 8: Studies included in the evidence review for adjuvant trastuzumab

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Full citation Cadoo, K. A., Morris, P. G., Cowell, E. P., Patil, S., Hudis, C. A., McArthur, H. L., Adjuvant Chemotherapy and Trastuzumab Is Safe and Effective in Older Women With Small, Node-Negative, HER2-Positive Early-Stage Breast Cancer, Clinical breast cancer, 16, 487-493, 2016 Ref Id 581572 **Country/ies where the study was carried out** USA **Study type** Retrospective cohort study **Aim of the study** To determine the impact of trastuzumab on breast cancer outcomes and cardiac safety for patients with smaller, node-negative tumours	**Sample size** 244 **Characteristics** Gender: 100% women Age: CT+T median 62; CT-T median 64; range 55-87 Ethnicity: NR **Inclusion criteria** Age ≥ 55 years, pathologically confirmed invasive breast cancer ≤2 cm without lymph node involvement (T1N0), HER2+ disease defined as 3+ by immunohistochemistry and/or gene amplification (≥2) by fluorescence in situ hybridization (FISH). **Exclusion criteria** No additional criteria reported **Reported subgroups** None of interest	**Interventions** **Intervention arm:** adjuvant chemotherapy and trastuzumab **Control arm:** no adjuvant trastuzumab (53 % received chemotherapy)	**Details** **Intervention arm (CT+T):** adjuvant trastuzumab and chemotherapy (50% taxane-based, 34% taxane and anthracycline-based) following breast conserving surgery (63%) or mastectomy (38%) - 54% also received adjuvant hormonal therapy **Control arm (CT-T):** no adjuvant trastuzumab following breast conserving surgery (67%) or mastectomy (33%) - 53% received chemotherapy (75% anthracycline-based) and 66% received adjuvant hormonal therapy	**Results** **Treatment-related morbidity - congestive heart failure:** CT+T 4/128; CT-T 1/116 **Treatment-related morbidity - secondary cancer:** CT+T 2/128; CT-T 3/116	**Selection:** Method of selection appropriate and likely to produce cohort representative of the specific population of interest. Outcomes not present at start of study. **Comparability:** Groups not comparable at baseline for tumour grade, lymphovascular invasion, ER status or receipt of chemotherapy; also significant differences in chemotherapy regimens. However, equivalent for cardiac outcomes and secondary cancer at baseline. **Outcome:** Follow-up adequate. Outcome assessment unclear **Indirectness** Comparison: only 53% of comparison arm received chemotherapy - very serious **Limitations**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Study dates No trastuzumab cohort: diagnosed January 1999 to May 2004; trastuzumab cohort: diagnosed May 2005 to December 2010 **Source of funding** NIH/NCI Cancer Center Support Grant No. P30 CA008748					Follow-up in no-trastuzumab cohort longer than trastuzumab cohort so longer-term toxicity of trastuzumab-based therapy is less well-described here. Differences between arms: higher proportion of tumours with poorer prognostic features in the trastuzumab cohort (higher proportion grade III, with lymphovascular invasion and oestrogen receptor-negative). Chemotherapy administration practices have changed over time, and the majority of patients in the trastuzumab cohort received taxane without anthracycline therapy, whereas the majority of patients in the no-trastuzumab cohort who received chemotherapy had an anthracycline without taxane. **Other information**
Full citation Gori, S., Inno, A., Fiorio, E., Foglietta, J., Ferro, A., Gulisano, M., Pinotti, G., Gubiotti, M., Cavazzini, M. G., Turazza, M., Duranti, S., De Simone, V.,	**Sample size** 303 patient included - only interested in the adjuvant systemic therapy with trastuzumab (n=204) and no adjuvant systemic therapy (n=34) groups	**Interventions** **Intervention arm:** adjuvant systemic therapy (chemotherapy and/or hormone	**Details** **Intervention arm (CT+T):** 93% received chemotherapy + endocrine therapy with trastuzumab, 7% received endocrine therapy only with	**Results** **DFS (median follow-up 38.6 months):** O-	**Selection:** Method of selection appropriate. However excluding those with any in situ component may not be representative

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Iezzi, L., Bisagni, G., Spazzapan, S., Cavanna, L., Saggia, C., Bria, E., Cretella, E., Vici, P., Santini, D., Fabi, A., Garrone, O., Frassoldati, A., Amaducci, L., Saracchini, S., Evangelisti, L., Barni, S., Gamucci, T., Mentuccia, L., Laudadio, L., Zoboli, A., Marchetti, F., Bogina, G., Lunardi, G., Boni, L., The Promher Study: An Observational Italian Study on Adjuvant Therapy for HER2-Positive, pT1a-b pN0 Breast Cancer.[Erratum appears in PLoS One. 2015;10(9):e0139650; PMID: 26406908], PLoS ONE [Electronic Resource]PLoS ONE, 10, e0136731, 2015 **Ref Id** 540538 **Country/ies where the study was carried out** Italy **Study type** Retrospective cohort study **Aim of the study** To identify the clinicopathological features	**Characteristics** Gender: NR Age: Median 57; range 31-84 Ethnicity: NR **Inclusion criteria** Patients were eligible if at the pathology examination of surgical specimen they had ≤1 cm in size breast cancer, negative nodal status assessed with sentinel lymph node biopsy (SLNB) or axillary lymph nodes dissection (ALND), HER2-positive (immunohistochemistry 3+ and/or FISH amplified) disease. **Exclusion criteria** Main exclusion criteria were any neoadjuvant treatment, in situ breast carcinoma or micro-invasive carcinoma (i.e. ≤1 mm of invasive tumour). **Reported subgroups** None of interest	therapy) with trastuzumab **Control arm:** no adjuvant systemic therapy **Control arm 2:** no adjuvant systemic therapy	trastuzumab following BCS (78%) or mastectomy (22%) **Control arm (no treatment):** no adjuvant systemic therapy following BCS (47%) or mastectomy (53%)	E: -3.26; V: 0.98	**Comparability:** Groups not comparable at baseline on a number of characteristics. Hazards ratios are adjusted but unclear what for. **Outcome:** Follow-up period relatively short. Outcome assessment unclear **Indirectness** Intervention: 7% of treatment arm did not receive chemotherapy - unlikely to impact results **Limitations** Tumour size, Ki67 status, age and hormone receptor status were significantly associated with the administration of adjuvant systemic therapy with trastuzumab - therefore these characters differed significantly between groups. Small sample size, particularly in no treatment arm. Short follow-up period (study not specifically designed to detect efficacy of trastuzumab). **Other information**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
influencing Italian medical oncologists in the choice of the adjuvant systemic therapy with or without trastuzumab for patients with HER2-positive, pT1a-b pN0 breast cancer in clinical practice. A secondary objective of the study was to investigate any difference in terms of outcome according to the type of adjuvant systemic therapy. **Study dates** Underwent surgery January 2007 to December 2012 **Source of funding** No specific funding was received for this work					
Full citation McArthur, H. L., Mahoney, K. M., Morris, P. G., Patil, S., Jacks, L. M., Howard, J., Norton, L., Hudis, C. A., Adjuvant trastuzumab with chemotherapy is effective in women with small, node-negative, HER2-positive breast cancer, Cancer, 117, 5461-5468, 2011 **Ref Id**	**Sample size** 261 **Characteristics** Gender: 100% women Age: CT+T median 52; CT-T median 51; range 23-84 Ethnicity: NR **Inclusion criteria**	**Interventions** **Intervention arm:** Adjuvant chemotherapy and trastuzumab **Control arm:** No adjuvant trastuzumab; 66%	**Details** **Intervention arm (CT+T):** adjuvant trastuzumab (mean duration 52 weeks; range 1-68) and chemotherapy (61% anthracycline and taxane; 26% taxane) following breast conserving surgery (54%) or mastectomy (46%) - 61% also received hormone therapy	**Results** **Whole sample:** **DFS (3 year follow-up):** O-E: -7.52; V: 3.74	**Selection:** Method of selection appropriate and likely to produce cohort representative of the specific population of interest. **Comparability:** Groups relatively comparable at baseline but significant differences in chemotherapy regimens.

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
551982 **Country/ies where the study was carried out** USA **Study type** Retrospective cohort study **Aim of the study** To address the potential role of trastuzumab in women with ≤2cm, node negative HER2+ breast cancer **Study dates** No trastuzumab cohort: diagnosed January 2002 to May 2004; trastuzumab cohort: diagnosed May 2005 to December 2008 **Source of funding** Memorial Sloan-Kettering Cancer Center breast cancer fellowship support fund and the Julie Laub Fund	Pathologically confirmed ≤2cm, node negative, HER2+ invasive breast cancer (HER2+ was defined as 3+ by immunohistochemistry (IHC) and/or ≥2 (HER2 to chromosome 17centromere signals) by fluorescence in situ hybridization (FISH)) **Exclusion criteria** Women with bilateral invasive breast cancer; any concurrent, invasive secondary cancer; inadequate locoregional and/or systemic therapy documentation; or treatment with other adjuvant HER2-targeted agents including lapatinib were excluded. Women with a prior history of invasive breast cancer, anthracycline and/or taxane therapy, any metastatic cancer, or mantle irradiation were also excluded. **Reported subgroups** T stage (1a/b)	received chemotherapy	**Control arm (CT-T):** no adjuvant trastuzumab following breast conserving surgery (55%) or mastectomy (45%) - 66% received adjuvant chemotherapy (64% anthracycline; 19% anthracycline and taxane); 59% also received hormone therapy	**OS (3 year follow-up):** O-E: -1.37; V: 1.04 **T1a/1b:** **DFS (3 year follow-up):** O-E: -3.39; V: 2.12 **OS (3 year follow-up):** O-E: -0.22; V: 0.49	**Outcome:** Follow-up relatively short. Outcome assessment adequate. **Indirectness** Comparison: only 66% of the comparison arm received chemotherapy: very serious **Limitations** Change in chemotherapy practice over time - differences between treatment arms: intervention arm primarily received anthracycline and taxanes whereas comparison arm primarily received anthracycline only **Other information**
Full citation	**Sample size**	**Interventions**	**Details**	**Results**	**A priori design**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
O'Sullivan, C. C., Bradbury, I., Campbell, C., Spielmann, M., Perez, E. A., Joensuu, H., Costantino, J. P., Delaloge, S., Rastogi, P., Zardavas, D., Ballman, K. V., Holmes, E., De Azambuja, E., Piccart-Gebhart, M., Zujewski, J. A., Gelber, R. D., Efficacy of adjuvant trastuzumab for patients with human epidermal growth factor receptor 2-positive early breast cancer and tumors < 2 cm: A meta-analysis of the randomized trastuzumab trials, Journal of clinical oncology, 33, 2600-2608, 2015 **Ref Id** 582757 **Country/ies where the study was carried out** Not reported **Study type** Systematic review of RCTs **Aim of the study** To compare the efficacy of adjuvant trastuzumab versus no trastuzumab for patients with HER2-positive breast cancer and tumours ≤2 cm.	4,220 - only interested in patients with 1 or less positive nodes (n=2132) **Characteristics** Gender: NR Age: NR Ethnicity: NR **Inclusion criteria** Patients with resected HER2-positive tumours measuring ≤2cm who either received or did not receive 9 weeks, 1 year, or 2 years of trastuzumab. **Exclusion criteria** No additional criteria reported **Reported subgroups** Hormone-receptor status (+/-)	**Intervention arm:** Adjuvant trastuzumab and chemotherapy **Control arm:** Adjuvant chemotherapy without trastuzumab	**Intervention arm (CT+T):** Adjuvant trastuzumab (duration 9 weeks to 2 years; 73% 1 year) and chemotherapy (96% anthracycline based) **Control arm (CT-T):** no further details reported	**HR+** **DFS (8 year follow-up):** O-E: -21.20; V: 47.51 **OS (8 year follow-up):** O-E: -6.39; V: 16.58 **HR-** **DFS (8 year follow-up):** O-E: -14.43; V: 55.19 **OS (8 year follow-up):** O-E: -8.57; V: 23.09	Unclear **Duplicate selection/extraction** Not reported: Unclear **Comprehensive literature search** PubMed only database used but reference lists of reviews/published trials searched. Key words/MESH terms provided. **Publication status** Unclear if grey literature etc. was considered **List of studies provided** Excluded studies not reported **Characteristics of included studies** Basic study characteristics (age, gender etc.) not reported **Quality assessment** Not reported **Impact of quality assessment on conclusions** Not applicable as quality not reported

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Study dates Articles published between 1995 and 2013 - dates of participant recruitment in individual studies not reported **Source of funding** Not reported					**Appropriate methods for meta-analysis** Appropriate use of mixed-effects models **Publication bias** Not assessed **Conflict of interest** Funding reported for review but not individual studies **Indirectness** Population: included patients with 1 positive lymph node - proportion unclear - very serious **Limitations** **Other information** Individual patient data from HERA, NCCTG N9831, NSABP B31 , PACS-04, FinHER
Full citation Rodrigues, M. J., Peron, J., Frenel, J. S., Vano, Y. A., Wassermann, J., Debled, M., Picaud, F., Albiges, L., Vincent-Salomon, A., Cottu, P. H., Benefit of adjuvant trastuzumab-	**Sample size** 276 - but 5 received trastuzumab alone and 19 received chemotherapy alone so only interested in 252 cases **Characteristics**	**Interventions** **Intervention arm:** adjuvant trastuzumab-based chemotherapy	**Details** **Intervention arm (CT+T):** trastuzumab was given in a 3-weekly schedule after an anthracycline-based regimen (29%), concomitantly with a taxane after an anthracycline-	**Results** **DFS (40 month follow-up):** O-E: -2.51; V: 1.12	**Selection:** Method of selection appropriate and likely to produce cohort representative of the specific population of interest. **Comparability:**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
based chemotherapy in T1ab node-negative HER2-overexpressing breast carcinomas: A multicenter retrospective series, Annals of Oncology, 24, 916-924, 2013 **Ref Id** 552588 **Country/ies where the study was carried out** France **Study type** Retrospective cohort study **Aim of the study** To establish an accurate description of pT1abN0 HER2+ breast cancers and to evaluate the benefit of adjuvant trastuzumab-based chemotherapy (ATBC) in these patients **Study dates** 2001 to 2010 **Source of funding** French National Association of Residents in Oncology (AERIO; Association d'Enseignement et de Recherche des Internes en	Gender: NR Age: Median: 56, range: 30-81 Ethnicity: NR **Inclusion criteria** Inclusion criteria were invasive carcinoma 2–10 mm in size and prospective determination of HER2 status according to French guidelines from 2001 to 2007 and to ASCO/CAP guidelines from 2007 to 2010. **Exclusion criteria** Neoadjuvant chemotherapy, past medical history of invasive breast carcinoma, and multifocal or multicentric foci. **Reported subgroups** None of interest	**Control arm:** no adjuvant chemotherapy or trastuzumab	based regimen (43%), concomitantly with a taxane-only regimen (28%), and after the completion of concomitant anthracycline–taxane (1%). The median duration of trastuzumab therapy was 12 months (range: 2–12). Surgical treatment was BCS (73%) or mastectomy (27%) - 67% has sentinel node procedure and 32% axillary dissection. **Control arm (no treatment):** Surgical treatment was BCS (70%) or mastectomy (30%) - 64% has sentinel node procedure and 35% axillary dissection.		Groups not comparable at baseline but this was controlled for in analysis. **Outcome:** Follow-up relatively short. Outcome assessment unclear. **Indirectness** None **Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Oncologie; www.aerio-oncologie.org)					
Full citation van Ramshorst, M. S., van der Heiden-van der Loo, M., Dackus, G. M. H. E., Linn, S. C., Sonke, G. S., The effect of trastuzumab-based chemotherapy in small node-negative HER2-positive breast cancer [Erratum: 2016; 159(2): 393], Breast Cancer Research and Treatment, 158, 361-371, 2016 **Ref Id** 583295 **Country/ies where the study was carried out** Netherlands **Study type** Retrospective cohort study **Aim of the study** To provide evidence for offering trastuzumab-based adjuvant chemotherapy to patients with stage I HER2-positive breast cancer **Study dates**	**Sample size** 3512 **Characteristics** Gender: NR Age: Median 57, range 19-90 Ethnicity: NR **Inclusion criteria** Aged 18 years or above diagnosed with T1N0M0 HER2-positive invasive breast cancer. HER2-positive tumors were defined as tumors with a 3+ immunohistochemistry score or a positive result by in situ hybridization **Exclusion criteria** No additional criteria reported **Reported subgroups** T stage (1a,1b,1c)	**Interventions** **Intervention arm:** adjuvant chemotherapy and trastuzumab **Control arm:** no adjuvant systemic therapy	**Details** **Intervention arm (CT+T):** 92% received chemotherapy and trastuzumab, 5% received chemotherapy only, 3% trastuzumab only - 55% also received endocrine therapy. No further details reported **Control arm (no treatment):** 24% received endocrine therapy. No further details reported	**Results** **Whole sample:** **OS (8 year follow-up):** O-E: -42.49, V: 34.33 **T1a:** **OS (8 year follow-up):** O-E: -40.11; V: 13.39 **T1b:** **OS (8 year follow-up):** O-E: -1.98; V: 1.01	**Selection:** Method of selection appropriate and likely to produce cohort representative of the specific population of interest. **Comparability:** Groups not comparable at baseline but this was controlled for in analysis. **Outcome:** Follow-up and outcome assessment adequate. **Indirectness** Intervention: only 92% of intervention arm received chemotherapy and trastuzumab - unlikely to significantly impact results **Limitations** Imbalances in baseline characteristics between arms - untreated group older and therefore had shorter life expectancy and significantly more patients in the treatment groups received endocrine therapy. However, effect of

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Diagnosed 2006-2012 **Source of funding** Roche				**T1c:** **OS (8 year follow-up):** O-E: -43.09; V: 29.32	systemic treatment on survival remained significant after correcting for age and endocrine therapy in multivariable analysis **Other information**
Full citation Vici, P., Pizzuti, L., Natoli, C., Moscetti, L., Mentuccia, L., Vaccaro, A., Sergi, D., Di Lauro, L., Trenta, P., Seminara, P., Santini, D., Iezzi, L., Tinari, N., Bertolini, I., Sini, V., Mottolese, M., Giannarelli, D., Giotta, F., Maugeri-Sacca, M., Barba, M., Marchetti, P., Michelotti, A., Sperduti, I., Gamucci, T., Outcomes of HER2-positive early breast cancer patients in the pre-trastuzumab and trastuzumab eras: a real-world multicenter observational analysis. The RETROHER study, Breast Cancer Research and Treatment, 147, 599-607, 2014 **Ref Id** 583328	**Sample size** 925 patient - only interested in T1a/b N0 (n=59) and T1cN0 (224) groups **Characteristics** Gender: NR Age: median 55, range 23-87 (whole sample) Ethnicity: NR **Inclusion criteria** HER2 positive early breast cancer treated with adjuvant chemotherapy ± trastuzumab **Exclusion criteria** None reported **Reported subgroups**	**Interventions** **Intervention arm:** adjuvant chemotherapy with trastuzumab **Control arm:** adjuvant chemotherapy without trastuzumab	**Details** **Intervention arm (CT+T):** adjuvant chemotherapy (16% anthracycline-based, 65% anthraxycline+taxane-based - whole sample) + trastuzumab (58% concurrent with chemotherapy - whole sample) for median of 52 weeks (range 1-104), following BCS (60%) or mastectomy (40%) **Control arm (CT-T):** adjuvant chemotherapy (49% anthracycline-based, 20% anthraxycline+taxane-based - whole sample) following BCS (57%) or mastectomy (43%)	**Results** **T1a/b:** **DFS (3 year follow-up):** O-E: -2.77; V: 1.34 **T1c:** **DFS (5 year follow-up):** O-E: -6.88; V: 5.37 **OS (5 year follow-up):**	**Selection:** Method of selection appropriate and likely to produce cohort representative of the specific population of interest. **Comparability:** Groups largely comparable at baseline but differences in chemotherapy regimens received. **Outcome:** Follow-up not equivalent across arms. Outcome assessment adequate. **Indirectness** None **Limitations**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Country/ies where the study was carried out Italy **Study type** Retrospective cohort study **Aim of the study** To determine outcomes in terms of 3 year relapse rate, relapse free survival, breast cancer specific survival and overall survival for HER2 positive early breast cancer patients treated with adjuvant chemotherapy alone or with chemotherapy and trastuzumab. **Study dates** Treated January 1998 to December 2011: trastuzumab cohort 2006 onwards, non-trastuzumab cohort mostly pre-2006 **Source of funding** None reported	T stage (1a/b,1c)			O-E: -5.91; V: 3.65	Differences in type of chemotherapy received between arms. Small sample sizes, particularly for T1a/b tumours. Differences in timing of treatment may mean that treatment (excluding trastuzumab) was not equivalent across arms. Differences in follow-up periods - some late recurrences may have been missed in the latter cohort (trastuzumab arm) **Other information**
Full citation	**Sample size**	**Interventions**	**Details**	**Results**	**Selection:**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Webster, R. M., Abraham, J., Palaniappan, N., Caley, A., Jasani, B., Barrett-Lee, P., Exploring the use and impact of adjuvant trastuzumab for HER2-positive breast cancer patients in a large UK cancer network. Do the results of international clinical trials translate into a similar benefit for patients in South East Wales?, British journal of cancer, 106, 32-8, 2012 **Ref Id** 583377 **Country/ies where the study was carried out** Wales **Study type** Retrospective cohort study **Aim of the study** To demonstrate a benefit, if any, of adjuvant Trastuzumab in HER2+ patients with node-negative T1a or T1b tumours **Study dates** 2005-2008 **Source of funding**	338 but just interested in stage I cancer (n=92) **Characteristics** Gender: NR Age: Median 56, range 27-85 Ethnicity: NR **Inclusion criteria** HER2+ breast cancer - defined as grade 3 on immunohistochemical (IHC) criteria, or as grade 2 on IHC but with HER2-positive status on FISH analysis **Exclusion criteria** No additional criteria reported **Reported subgroups** None of interest	**Intervention arm:** adjuvant chemotherapy and trastuzumab **Control arm:** no adjuvant trastuzumab (13% of stage I patients received chemotherapy)	**Intervention arm (CT+T):** No details reported specifically for stage I patients - 24% of whole sample received taxane containing chemotherapy regimen; 81% completed full course (18 cycles, administered once every 21 days) of trastuzumab **Control arm (no treatment):** No further details reported	**DFS (3 year follow-up):** O-E: -2.52; V: 1.79 **OS (3 year follow-up):** O-E: -1.20; V: 0.50	Method of selection appropriate and likely to produce cohort representative of the specific population of interest. **Comparability:** Unclear whether groups were comparable at baseline. **Outcome:** Follow-up relatively short. Outcome assessment adequate. **Indirectness** Comparison: 13% of control arm received chemotherapy - serious **Limitations** Relatively small sample size **Other information**

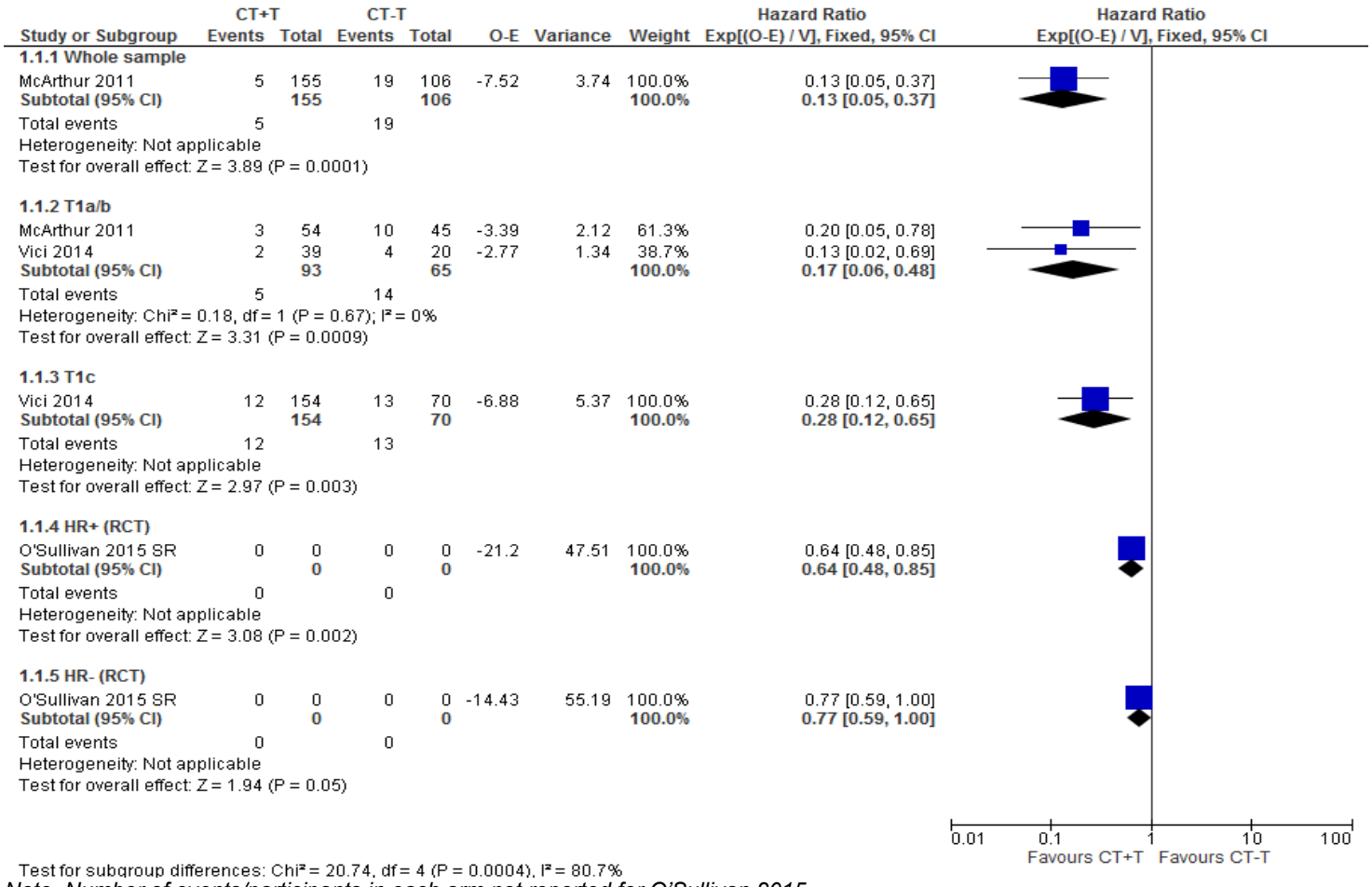
Study details	Participants	Interventions	Methods	Outcomes and results	Comments
None reported					

ALND, axillary lymph node dissection; ASCO, American Society of Clinical Oncology; CAP, College of American Pathologists; CT, chemotherapy; DFS, disease-free survival; ER, oestrogen receptor; FISH, fluorescence in situ hybridization; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; NR, not reported; OS, overall survival; SLNB, sentinel lymph node biopsy; T, trastuzumab

Appendix E – Forest plots

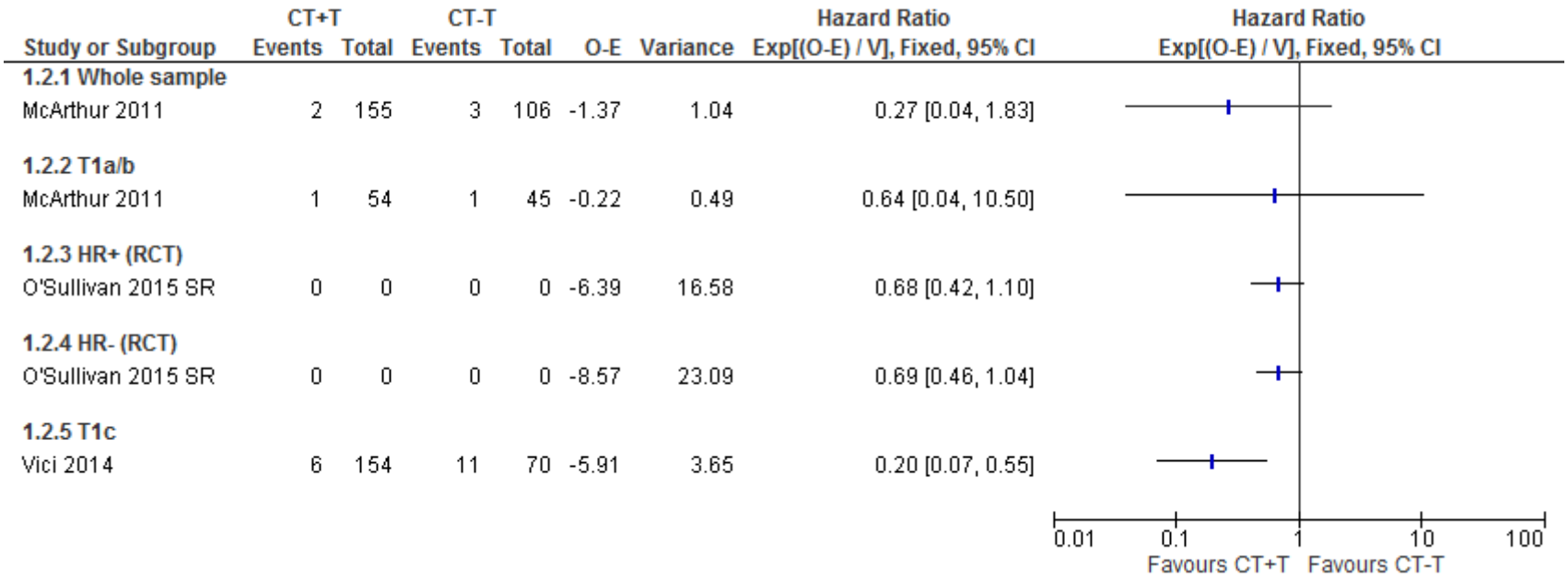
Comparison 1: Adjuvant trastuzumab and chemotherapy versus chemotherapy alone

Figure 4: Disease-free survival at 3 to 8 year follow-up



Note. Number of events/participants in each arm not reported for O'Sullivan 2015

Figure 5: Overall survival at 3 to 8 year follow-up



Number of events/participants in each arm not reported for O'Sullivan 2015

Figure 6: Treatment-related morbidity: congestive heart failure at 4 year follow-up

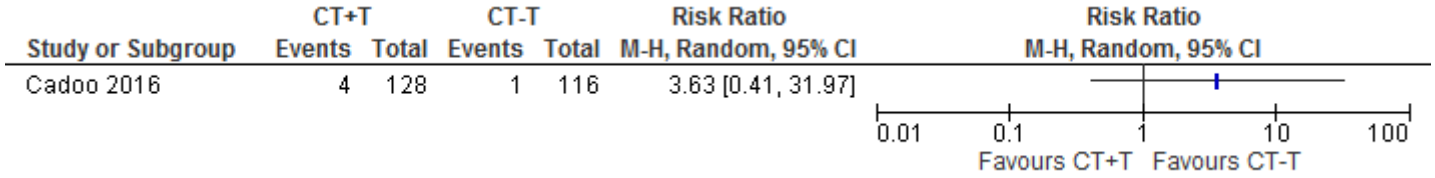
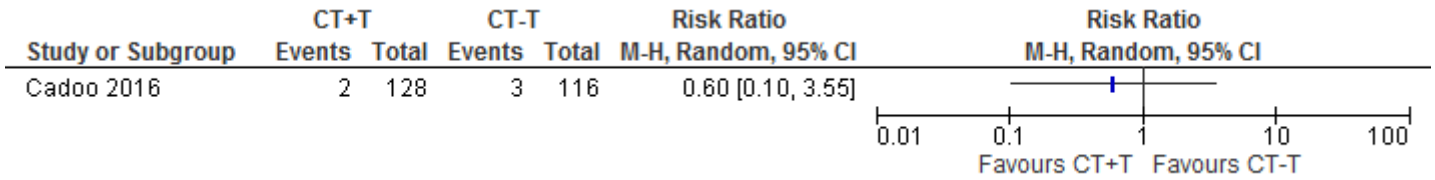


Figure 7: Treatment-related morbidity: secondary cancer at 4 year follow-up



Comparison 2. Adjuvant trastuzumab and chemotherapy versus no adjuvant therapy

Figure 8: Disease-free survival at ~3 year follow-up

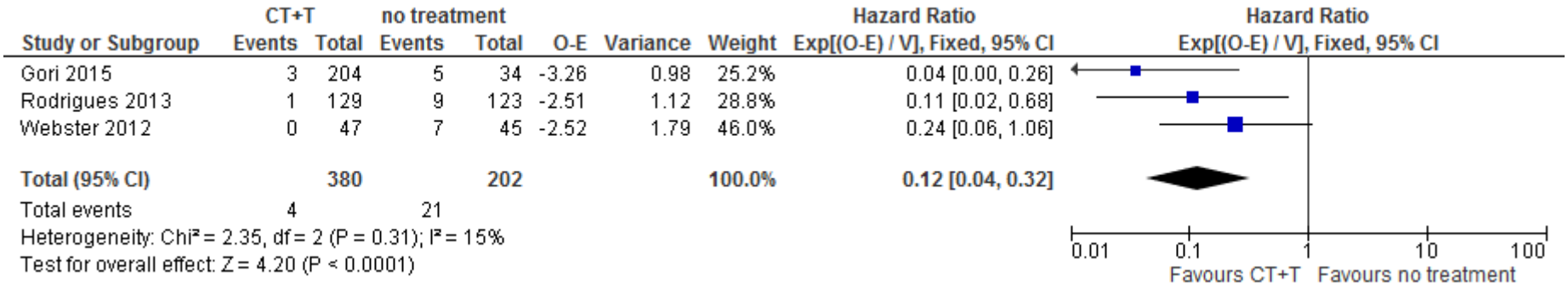
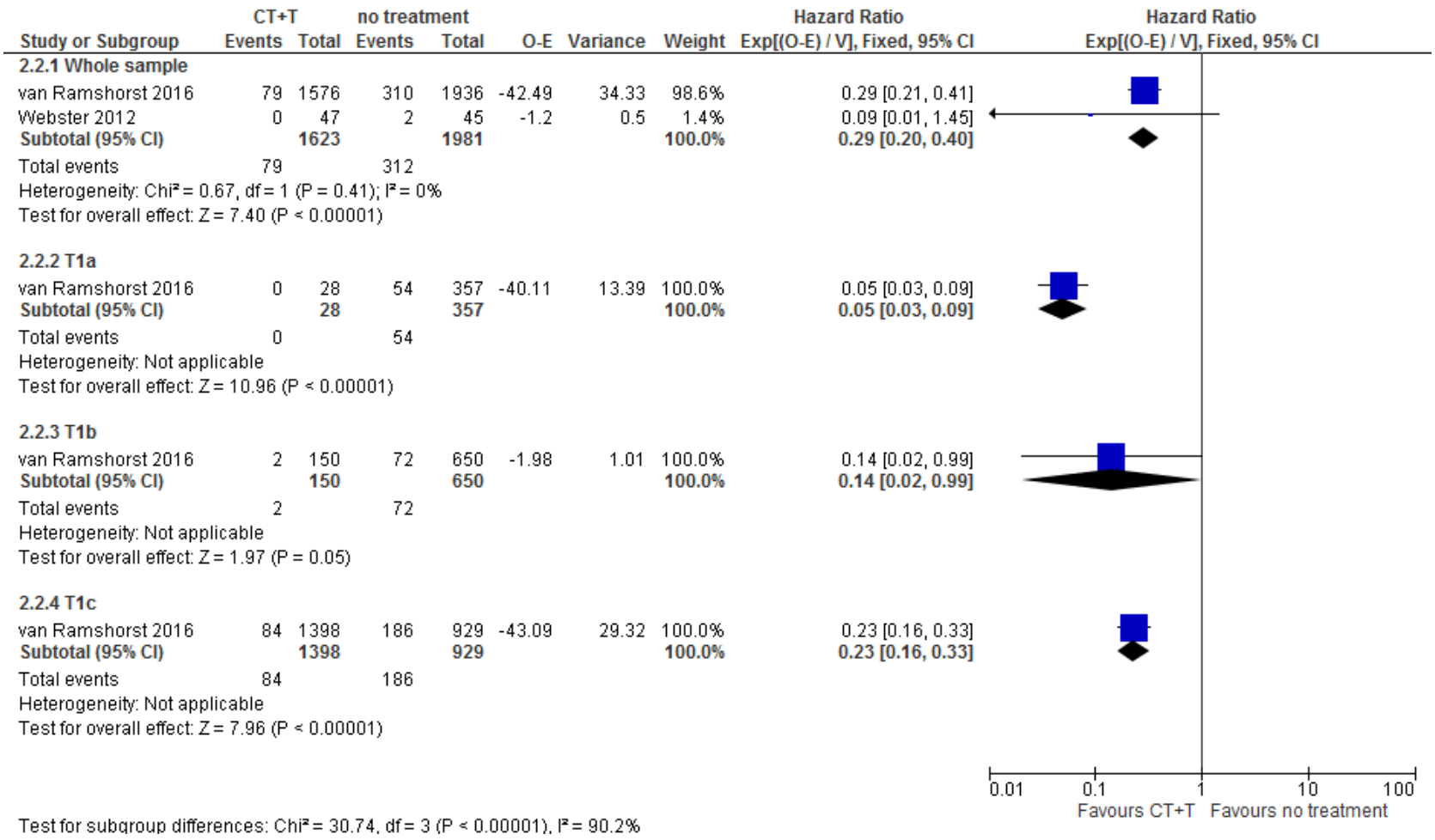


Figure 9: Overall survival at 3 to 8 year follow-up



Appendix F – GRADE tables

Table 9: Clinical evidence profile: Comparison 1. Adjuvant trastuzumab and chemotherapy versus adjuvant chemotherapy only

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CT+T	CT-T	Relative (95% CI)	Absolute	Quality	Importance
Disease-free survival - Whole sample (3 year follow-up)												
1	Observational studies	Serious[10]	No serious inconsistency	Very serious[1]	Serious[2]	None	5/155 (3.2%)	19/106 (17.9%)	HR 0.13 (0.05 to 0.37)	154 fewer per 1000 (from 109 fewer to 169 fewer)	VERY LOW	CRITICAL
Disease-free survival - t1a/b (3 year follow-up)												
2	Observational studies	Serious[10]	No serious inconsistency	Serious[3]	Serious[2]	None	5/93 (5.4%)	14/65 (21.5%)	HR 0.19 (0.07 to 0.51)	174 fewer per 1000 (from 106 fewer to 200 fewer)	VERY LOW	CRITICAL
Disease-free survival - T1c (5 year follow-up)												
1	Observational studies	Serious[10]	No serious inconsistency	No serious indirectness	Serious[2]	None	12/154 (7.8%)	13/70 (18.6%)	HR 0.28 (0.12 to 0.65)	130 fewer per 1000 (from 61 fewer to 161 fewer)	VERY LOW	CRITICAL
Disease-free survival - HR+ (RCT; 8 year follow-up)												
1	Randomised trials	[4]	No serious inconsistency	Very serious[5]	[6]	None	-	-	HR 0.64 (0.48 to 0.85)	-	CANNOT BE ASSESSED	CRITICAL
Disease-free survival - HR- (RCT; 8 year follow-up)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CT+T	CT-T	Relative (95% CI)	Absolute		
1	Randomised trials	[4]	No serious inconsistency	Very serious[5]	[6]	None	-	-	HR 0.77 (0.59 to 1)	-	CANNOT BE ASSESSED	CRITICAL
Overall survival - Whole sample (3 year follow-up)												
1	Observational studies	Serious[10]	No serious inconsistency	Very serious[1]	Serious[2]	None	2/155 (1.3%)	3/106 (2.8%)	HR 0.27 (0.04 to 1.83)	21 fewer per 1000 (from 27 fewer to 23 more)	VERY LOW	CRITICAL
Overall survival - t1a/b (3 year follow-up)												
1	Observational studies	Serious[10]	No serious inconsistency	Very serious[1]	Serious[2]	None	1/54 (1.9%)	1/45 (2.2%)	HR 0.64 (0.04 to 10.5)	8 fewer per 1000 (from 21 fewer to 188 more)	VERY LOW	CRITICAL
Overall survival - HR+ (RCT; 8 year follow-up)												
1	Randomised trials	[4]	No serious inconsistency	Very serious[5]	[6]	None	-	-	HR 0.68 (0.42 to 1.1)	-	CANNOT BE ASSESSED	CRITICAL
Overall survival - HR- (RCT; 8 year follow-up)												
1	Randomised trials	[4]	No serious inconsistency	Very serious[5]	[6]	None	-	-	HR 0.69 (0.46 to 1.04)	-	CANNOT BE ASSESSED	CRITICAL
Overall survival - T1c (5 year follow-up)												
1	Observational studies	Serious[10]	No serious inconsistency	No serious indirectness	Serious[2]	None	6/154 (3.9%)	11/70 (15.7%)	HR 0.2 (0.07 to 0.55)	124 fewer per 1000 (from 67 fewer to 145 fewer)	VERY LOW	CRITICAL
Treatment-related morbidity: congestive heart failure (4 year follow-up)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CT+T	CT-T	Relative (95% CI)	Absolute		
1	Observational studies	Serious[10]	No serious inconsistency	Very serious[8]	Very serious[9]	None	4/128 (3.1%)	1/116 (0.86%)	RR 3.62 (0.41 to 31.97)	23 more per 1000 (from 5 fewer to 267 more)	VERY LOW	CRITICAL
Treatment-related morbidity: secondary cancer (4 year follow-up)												
1	Observational studies	Serious[10]	No serious inconsistency	No serious indirectness	Serious[2]	None	2/128 (1.6%)	3/116 (2.6%)	RR 0.6 (0.1 to 3.55)	10 fewer per 1000 (from 23 fewer to 66 more)	VERY LOW	CRITICAL

CI: Confidence interval; CT: chemotherapy; HR: Hazard ratio; HR+: hormone receptor positive; HR-: hormone receptor negative; RR: Risk ratio; T: trastuzumab
[1] Comparison: only 66% of comparison arm received chemotherapy
[2] <300 events
[3] Comparison: study with greatest weight only 66% of comparison arm received chemotherapy
[4] Cannot be determined - quality of included studies not reported
[5] Population: included patients with 1 positive lymph node - proportion unclear
[6] Cannot be determined - number of events not reported
[8] Comparison: only 53% of comparison arm received chemotherapy
[9] events <300 and 95%CI crosses boundaries for no effect (1) and minimally important differences (0.80 and 1.25) based on GRADE default values
[10] Groups not comparable due to differences in chemotherapy regimens

Table 10: Clinical evidence profile: Comparison 2. Adjuvant trastuzumab and chemotherapy versus no adjuvant chemotherapy or trastuzumab

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CT+T	no treatment	Relative (95% CI)	Absolute		
Disease-free survival (3 year follow-up)												
3	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	Strong association[2]	4/380 (1.1%)	21/202 (10.4%)	HR 0.12 (0.04 to 0.32)	91 fewer per 1000 (from 69 fewer to 100 fewer)	LOW	CRITICAL
Overall survival - Whole sample (3 year follow-up)												
2	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Strong association[3]	79/1623 (4.9%)	312/1981 (15.7%)	HR 0.29 (0.2 to 0.4)	109 fewer per 1000 (from 91 fewer to 124 fewer)	MODERATE	CRITICAL
Overall survival - T1a (8 year follow-up)												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	Very strong association[2]	0/28 (0%)	54/357 (15.1%)	HR 0.05 (0.03 to 0.09)	143 fewer per 1000 (from 137 fewer to 146 fewer)	MODERATE	CRITICAL
Overall survival - T1b (8 year follow-up)												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	2/150 (1.3%)	72/650 (11.1%)	HR 0.14 (0.02 to 0.99)	94 fewer per 1000 (from 1 fewer to 108 fewer)	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CT+T	no treatment	Relative (95% CI)	Absolute		
Overall survival - T1c (8 year follow-up)												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	Strong association[3]	84/1398 (6%)	186/929 (20%)	HR 0.23 (0.16 to 0.33)	150 fewer per 1000 (from 129 fewer to 165 fewer)	LOW	CRITICAL

CI: Confidence interval; CT: chemotherapy; HR: Hazard ratio; T: trastuzumab
[1] <300 events
[2] Estimated HR <0.20
[3] Estimated HR <0.50

Appendix G – Economic evidence study selection

See Supplement 1: Health economics literature review for details of economic study selection.

Appendix H – Economic evidence tables

No economic evidence was identified for this review question.

Appendix I – Health economic evidence profiles

No economic evidence was identified for this review question.

Appendix J – Health economic analysis: The cost-effectiveness of adjuvant trastuzumab in combination with chemotherapy in people with T1N0 HER2 positive breast cancer

Background

The standard of care for the adjuvant treatment of HER2-positive breast cancer is chemotherapy and trastuzumab. This was based on large adjuvant trials, which demonstrated that the addition of trastuzumab to chemotherapy reduced the risk of recurrence by around 50%. However, the trials only included people who had cancers that were at least 1cm in diameter and therefore people with T1 cancers are not routinely treated with trastuzumab. More recent data from cohort studies has shown that T1 HER2-positive cancers have a much higher risk of recurrence than equivalently sized HER2- cancers and therefore people with T1 HER2-positive cancers are likely to gain reasonable benefit from trastuzumab.

Aim

To estimate the cost-effectiveness of adjuvant trastuzumab in combination with chemotherapy in people with T1N0 HER2 positive breast cancer.

Methods

Existing economic evidence

A systematic literature review was conducted to identify economic evaluations that may be applicable to the current decision problem. No relevant economic studies were identified that were directly applicable.

De novo economic evaluation

Since the current economic literature didn't adequately address the decision problem, a de novo economic evaluation was undertaken to assess cost-effectiveness. The analysis was developed in Microsoft Excel® and was conducted from the perspective of the NHS and Personal Social Services (PSS) as outlined in the NICE Reference Case (see Developing NICE guidelines: the manual). The model considered a fifty year time horizon with future costs and benefits discounted at a rate of 3.5% (as recommended in the NICE reference case).

Clinical data and model approach

The economic analysis was based on overall survival and progression free survival estimates for each of the treatments included in the analysis. The analysis essentially took the form of a simple partitioned survival analysis (as illustrated in the diagram below), in which 3 mutually exclusive health states were derived from the overall survival and progression free survival estimates:

- alive without progressed disease
- alive with progressed disease

- dead.

Figure 10: Illustrative example of partitioned survival analysis

Overall and disease free survival

Overall and disease free survival for each of the interventions was estimated using data on absolute risk combined with data on treatment effects from the HERA trial (Cameron 2017 and Piccart-Gebhart 2005). Note that data identified in the accompanying clinical evidence review conducted for this topic has not been used to inform the model. This reflects the view of the committee that the best evidence on relative effectiveness comes from the long term results of the HERA trial (Cameron 2017) despite it being in a broader and higher risk population. While the data in clinical evidence review considered the specific population of interest (T1 tumours), the data was considered to be of poorer quality (this view is reflected somewhat in the low quality GRADE rating of the data in the clinical evidence review). Furthermore, in the opinion of the committee, the relative effect of trastuzumab would be consistent across all populations with HER2-positive disease. The difference in the effectiveness of treatment instead comes from differences in the absolute risk of the population.

Absolute overall and disease free survival for people with HER2-positive T1 tumours was sourced from Vas-Luiz 2014. The study included 257 HER2-positive people with T1a-b tumours that had not received chemotherapy or trastuzumab. The study reported an average overall survival of 94.9% and disease free survival of 84.4% at five years. However, it should be noted that there is some uncertainty around these estimates as there are few retrospective studies which have estimated absolute risk in people with HER2-positive T1 tumours. There is also some variation in the estimates available, which are sometimes shown to be close to higher risk populations and sometimes close to the risk in people without HER2-positive disease. Alternative estimates were therefore considered in the sensitivity analysis.

In order to estimate baseline risk in people receiving adjuvant chemotherapy, a treatment effect associated with adjuvant chemotherapy was applied to the absolute risks in the observation arm. An EBCTCG review from 2012 estimated ten year relative risks (RRs) of 0.73 for recurrence and 0.84 for overall mortality in people receiving anthracycline based

chemotherapy in comparison to no chemotherapy. This gives an estimated OS of 95.8% and DFS of 88.9% at 5 years (compared to 94.9% and 84.4% in no treatment group)

Overall and disease free survival values for the adjuvant chemotherapy and trastuzumab arm were derived based on treatment effects from the long-term results of the HERA trial (Cameron 2017). Hazard ratios (HRs) of 0.74 and 0.76 for overall survival and disease free survival respectively. Applying these relative effects to the absolute risk estimated in the adjuvant chemotherapy arm results in an overall survival estimate of 96.9% and a disease free survival estimate of 91.5% at five years.

Mortality from other causes was captured using 2013-2015 life tables for England and Wales from the office of national statistics (ONS). These life tables give an estimate of the annual probability of death given a person's age and gender. A starting age of 49 was applied in the model based on the average age reported in Piccart-Gebhart 2005. The other cause mortality estimates were used in conjunction with the overall survival estimates above to estimate the proportion of people that died of disease-specific and other causes.

Costs

The costs considered in the model reflect the perspective of the analysis, thus only costs that are relevant to the UK NHS & PSS were included. Where possible, all costs were estimated in 2015/16 prices.

The majority of costs were sourced from NHS reference costs 2015/16 by applying tariffs associated with the appropriate HRG code. Drug costs were calculated using unit cost data from the electronic market information tool (eMit) combined with dose information from the British National Formulary (BNF). Where costs were not available from eMit, list prices from the BNF were used. Other resource use and cost information were sourced from the Personal Social Services Research Unit (PSSRU) and the advice of the guideline committee.

Adjuvant chemotherapy and trastuzumab costs

Costs were estimated for the adjuvant chemotherapy regimens that are most likely to be used in current clinical practice (based on the opinion of the guideline committee). Costs were estimated for a regimen of docetaxel and cyclophosphamide (TC) and a weekly paclitaxel regimen. Chemotherapy drug costs were sourced from eMit while the cost of delivering chemotherapy was sourced from NHS Reference Costs 2015/16. Table 11 details the cost of each chemotherapy regimen.

Table 11: Adjuvant chemotherapy costs

Treatment	Cost	Source
Paclitaxel		
Deliver simple parenteral chemotherapy	£253.32	NHS Reference costs 2015/16 – day case
Deliver subsequent elements of a chemotherapy cycle	£361.04	NHS Reference costs 2015/16 – day case
Paclitaxel 80mg/m^2 on day one, eight and fifteen	£37.65	eMit
Cost per cycle	£652.01	
Total cost for four cycles	£2,608.04	
Docetaxel and cyclophosphamide (TC)		

Treatment	Cost	Source
Deliver more complex parenteral chemotherapy	£336.57	NHS Reference costs 2015/16 – day case
Docetaxel 75mg/m^2 on day one	£20.62	eMit
Cyclophosphamide 600mg/m^2 on day one	£16.71	eMit
Cost per cycle	**£1,495.61**	
Total cost for four cycles	**£1,635.48**	

eMit, electronic market information tool; NHS, National Health Service

The cost of trastuzumab was estimated using drug costs from the BNF (since unit costs were not available from eMit) and delivery costs from NHS Reference costs 2015/16. Note that, since the previous NICE technology appraisal guidance on trastuzumab was published (TA107; NICE 2006), the most common route of administration has changed. Previously trastuzumab was delivered intravenously but it is now most commonly delivered as a subcutaneous injection. The cost of trastuzumab applied in the model is shown in Table 12. It can be seen that the total cost for one year of trastuzumab was estimated to be £25,580.49.

Table 12: Trastuzumab costs

Treatment	Cost	Source
Deliver simple parenteral chemotherapy	£198.94	NHS Reference costs 2015/16 – outpatient
Cost per trastuzumab dose (subcutaneous injection)	£1,222.20	BNF
Total cost for one year of trastuzumab	**£25,580.49**	

BNF, British National Formulary; NHS, National Health Service

Subsequent treatment costs

Subsequent treatment costs (following disease recurrence or progression) were estimated based on the average treatment that would be most likely to be used (based on the estimation of the guideline committee). It was assumed that treatment would vary depending upon the type of recurrence with data from the HERA trial used to estimate the proportion of recurrences that were locoregional (18%), regional (5%), contralateral (8%) and distant (69%).

It was assumed that people with locoregional, regional or contralateral recurrence would undergo a mastectomy if they originally had breast conserving surgery (42% from Cameron 2017) or a 'major breast procedure' if they originally had a mastectomy (58% from Cameron 2017). It was also assumed that breast reconstruction would be performed (either delayed or at the time of mastectomy). It was further assumed that lymph node clearance would be performed for people with regional recurrence. It was also assumed that radiotherapy would be given in people that were not previously treated with radiotherapy (24% from Cameron 2017) and that all people would receive adjuvant chemotherapy, trastuzumab and pertuzumab. In people with distant recurrence, it was assumed that people would receive chemotherapy, trastuzumab and pertuzumab.

Table 13 to Table 16 detail the costs that were applied for each type of recurrence.

Table 13: Subsequent treatment costs for locoregional recurrence

Treatment	Proportion†	Cost	Source
Major breast procedures (if patients originally had mastectomy)			

Treatment	Proportion†	Cost	Source
Unilateral Major Breast Procedures with CC Score 6+ (JA20D)	4%	£3,797	NHS Reference costs 2015/16 - Elective inpatient
Unilateral Major Breast Procedures with CC Score 3-5 (JA20E)	17%	£3,265	NHS Reference costs 2015/16 - Elective inpatient
Unilateral Major Breast Procedures with CC Score 0-2 (JA20F)	59%	£2,915	NHS Reference costs 2015/16 - Elective inpatient
Bilateral Major Breast Procedures with CC Score 1+ (JA21A)	9%	£4,143	NHS Reference costs 2015/16 - Elective inpatient
Bilateral Major Breast Procedures with CC Score 0 (JA21B)	10%	£3,834	NHS Reference costs 2015/16 - Elective inpatient
Weighted average cost		**£3,219.70**	
Delayed breast reconstruction			
Unilateral Delayed Pedicled Myocutaneous Breast Reconstruction (JA30Z)	41%	£5,825	NHS Reference costs 2015/16 - Elective inpatient
Bilateral Delayed Pedicled Myocutaneous Breast Reconstruction (JA31Z)	11%	£5,799	NHS Reference costs 2015/16 - Elective inpatient
Unilateral Delayed Free Perforator Flap Breast Reconstruction (JA34Z)	39%	£9,393	NHS Reference costs 2015/16 - Elective inpatient
Bilateral Delayed Free Perforator Flap Breast Reconstruction (JA35Z)	10%	£11,145	NHS Reference costs 2015/16 - Elective inpatient
Weighted average cost		**£7,736.86**	
Mastectomy with reconstruction (if patients originally had breast conserving surgery)			
Unilateral Excision of Breast with Immediate Pedicled Myocutaneous Flap Reconstruction (JA32Z)	54%	£5,883	NHS Reference costs 2015/16 - Elective inpatient
Bilateral Excision of Breast with Immediate Pedicled Myocutaneous Flap Reconstruction (JA33Z)	23%	£7,079	NHS Reference costs 2015/16 - Elective inpatient
Unilateral Excision of Breast with Immediate Free Perforator Flap Reconstruction (JA36Z)	16%	£10,627	NHS Reference costs 2015/16 - Elective inpatient
Bilateral Excision of Breast with Immediate Free Perforator Flap Reconstruction (JA37Z)	7%	£13,083	NHS Reference costs 2015/16 - Elective inpatient
Weighted average cost		**£7,451.79**	
Radiotherapy			
Preparation for Complex Conformal Radiotherapy (SC51Z)	-	£654.57	NHS Reference costs 2015/16 - outpatient

Treatment	Proportion†	Cost	Source
Deliver a Fraction of Complex Treatment on a Megavoltage Machine (SC23Z)	-	£126.48	NHS Reference costs 2015/16 - outpatient
Number of fractions	-	20	Assumption
Total radiotherapy cost		**£3,184.15**	
Adjuvant chemotherapy, trastuzumab and pertuzumab			
Cycle 1			**Cycle 1**
Deliver simple parenteral chemotherapy	-	£253.32	NHS Reference costs 2015/16 - Day case
Deliver Subsequent Elements of a Chemotherapy Cycle	-	£361.04	NHS Reference costs 2015/16 - Day case
Chemotherapy (docetaxel or pacliatxel)	-	£37.49	eMit
Trastuzumab cost per subcutaneous injection 600mg	-	£1,222.20	BNF
Pertuzumab cost for two 420mg vials (loading dose)	-	£4,790.00	NICE TA and BNF
Total cost per cycle		***£6,664.05***	
Cycles 2-6			**Cycles 2-6**
Deliver more complex parenteral chemotherapy	-	£336.57	NHS Reference costs 2015/16 - Day case
Chemotherapy (docetaxel or paclitaxel)	-	£34.40	eMit
Trastuzumab cost per subcutaneous injection 600mg	-	£1,222.20	BNF
Pertuzumab cost for 420mg vial	-	£2,395.00	NICE TA and BNF
Total cost per cycle	-	***£3,988.17***	
Subsequent cycles (until disease progression)			
Deliver simple parenteral chemotherapy	-	£253.32	NHS Reference costs 2015/16 - Day case
Trastuzumab cost per subcutaneous injection 600mg	-	£1,222.20	BNF
Pertuzumab cost for 420mg vial	-	£2,395.00	NICE TA and BNF
Total cost per cycle	-	***£3,870.52***	

† Proportions estimated based on the number of procedures recorded in NHS Reference Costs
BNF, British National Formulary; eMit, electronic market information tool; NICE, National Institute of Health and Care Excellence; TA, technology appraisal

Table 14: Subsequent treatment costs for regional recurrences

Treatment	Proportion†	Cost	Source
Major breast procedures with lymph node clearance (for regional recurrences in patients that originally had mastectomy)			
Unilateral Major Breast Procedures with Lymph Node Clearance, with CC Score 5+ (JA38A)	13%	£4,535	NHS Reference costs 2015/16 - Elective inpatient
Unilateral Major Breast Procedures with Lymph Node Clearance, with CC Score 2-4 (JA38B)	38%	£3,814	NHS Reference costs 2015/16 - Elective inpatient
Unilateral Major Breast Procedures with Lymph Node Clearance, with CC Score 0-1 (JA38C)	42%	£3,694	NHS Reference costs 2015/16 - Elective inpatient
Bilateral Major Breast Procedures with Lymph Node Clearance (JA39Z)	7%	£5,522	NHS Reference costs 2015/16 - Elective inpatient
Weighted average cost		**£3,971.97**	
Delayed breast reconstruction			
Unilateral Delayed Pedicled Myocutaneous Breast Reconstruction (JA30Z)	41%	£5,825	NHS Reference costs 2015/16 - Elective inpatient
Bilateral Delayed Pedicled Myocutaneous Breast Reconstruction (JA31Z)	11%	£5,799	NHS Reference costs 2015/16 - Elective inpatient
Unilateral Delayed Free Perforator Flap Breast Reconstruction (JA34Z)	39%	£9,393	NHS Reference costs 2015/16 - Elective inpatient
Bilateral Delayed Free Perforator Flap Breast Reconstruction (JA35Z)	10%	£11,145	NHS Reference costs 2015/16 - Elective inpatient
Weighted average cost		**£7,736.86**	
Mastectomy with reconstruction (if patients originally had breast conserving surgery)			
Unilateral Excision of Breast with Immediate Pedicled Myocutaneous Flap Reconstruction (JA32Z)	54%	£5,883	NHS Reference costs 2015/16 - Elective inpatient
Bilateral Excision of Breast with Immediate Pedicled Myocutaneous Flap Reconstruction (JA33Z)	23%	£7,079	NHS Reference costs 2015/16 - Elective inpatient
Unilateral Excision of Breast with Immediate Free Perforator Flap Reconstruction (JA36Z)	16%	£10,627	NHS Reference costs 2015/16 - Elective inpatient
Bilateral Excision of Breast with Immediate Free Perforator Flap Reconstruction (JA37Z)	7%	£13,083	NHS Reference costs 2015/16 - Elective inpatient
Weighted average cost		**£7,451.79**	
Radiotherapy			
Preparation for Complex Conformal Radiotherapy (SC51Z)	-	£654.57	NHS Reference costs 2015/16 - outpatient

Treatment	Proportion†	Cost	Source
Deliver a Fraction of Complex Treatment on a Megavoltage Machine (SC23Z)	-	£126.48	NHS Reference costs 2015/16 - outpatient
Number of fractions	-	20	Assumption
Total radiotherapy cost		**£3,184.15**	
Adjuvant chemotherapy, trastuzumab and pertuzumab			
Cycle 1			**Cycle 1**
Deliver simple parenteral chemotherapy	-	£253.32	NHS Reference costs 2015/16 - Day case
Deliver Subsequent Elements of a Chemotherapy Cycle	-	£361.04	NHS Reference costs 2015/16 - Day case
Chemotherapy (docetaxel or paclitaxel)	-	£37.49	eMit
Trastuzumab cost per subcutaneous injection 600mg	-	£1,222.20	BNF
Pertuzumab cost for two 420mg vials (loading dose)	-	£4,790.00	NICE TA and BNF
Total cost per cycle		***£6,664.05***	
Cycles 2-6			**Cycles 2-6**
Deliver more complex parenteral chemotherapy	-	£336.57	NHS Reference costs 2015/16 - Day case
Chemotherapy (docetaxel or paclitaxel)	-	£34.40	eMit
Trastuzumab cost per subcutaneous injection 600mg	-	£1,222.20	BNF
Pertuzumab cost for 420mg vial	-	£2,395.00	NICE TA and BNF
Total cost per cycle	-	***£3,988.17***	
Subsequent cycles (until disease progression)			
Deliver simple parenteral chemotherapy	-	£253.32	NHS Reference costs 2015/16 - Day case
Trastuzumab cost per subcutaneous injection 600mg	-	£1,222.20	BNF
Pertuzumab cost for 420mg vial	-	£2,395.00	NICE TA and BNF
Total cost per cycle	-	***£3,870.52***	

† Proportions estimated based on the number of procedures recorded in NHS Reference Costs
BNF, British National Formulary; CC, complete cytoreduction; eMit, electronic market information tool; NICE, National Institute of Health and Care Excellence; TA, technology appraisal

Table 15: Subsequent treatment costs for contralateral recurrence

Treatment	Proportion†	Cost	Source
Major breast procedures (if patients originally had mastectomy)			
Unilateral Major Breast Procedures with CC Score 6+ (JA20D)	5%	£3,797	NHS Reference costs 2015/16 - Elective inpatient

Treatment	Proportion†	Cost	Source
Unilateral Major Breast Procedures with CC Score 3-5 (JA20E)	21%	£3,265	NHS Reference costs 2015/16 - Elective inpatient
Unilateral Major Breast Procedures with CC Score 0-2 (JA20F)	74%	£2,915	NHS Reference costs 2015/16 - Elective inpatient
Weighted average cost		**£3,036.41**	
Delayed breast reconstruction			
Unilateral Delayed Pedicled Myocutaneous Breast Reconstruction (JA30Z)	51%	£5,825	NHS Reference costs 2015/16 - Elective inpatient
Unilateral Delayed Free Perforator Flap Breast Reconstruction (JA34Z)	49%	£9,393	NHS Reference costs 2015/16 - Elective inpatient
Weighted average cost		**£7,571.91**	
Mastectomy with reconstruction (if patients originally had breast conserving surgery)			
Unilateral Excision of Breast with Immediate Pedicled Myocutaneous Flap Reconstruction (JA32Z)	77%	£5,883	NHS Reference costs 2015/16 - Elective inpatient
Unilateral Excision of Breast with Immediate Free Perforator Flap Reconstruction (JA36Z)	23%	£10,627	NHS Reference costs 2015/16 - Elective inpatient
Weighted average cost		**£6,973.11**	
Radiotherapy			
Preparation for Complex Conformal Radiotherapy (SC51Z)	-	£654.57	NHS Reference costs 2015/16 - outpatient
Deliver a Fraction of Complex Treatment on a Megavoltage Machine (SC23Z)	-	£126.48	NHS Reference costs 2015/16 - outpatient
Number of fractions	-	20	Assumption
Total radiotherapy cost		**£3,184.15**	
Adjuvant chemotherapy, trastuzumab and pertuzumab			
Cycle 1			**Cycle 1**
Deliver simple parenteral chemotherapy	**-**	£253.32	NHS Reference costs 2015/16 - Day case
Deliver Subsequent Elements of a Chemotherapy Cycle	**-**	£361.04	NHS Reference costs 2015/16 - Day case
Chemotherapy (docetaxel or paclitaxel)	**-**	£37.49	eMit
Trastuzumab cost per subcutaneous injection 600mg	**-**	£1,222.20	BNF
Pertuzumab cost for two 420mg vials (loading dose)	**-**	£4,790.00	NICE TA and BNF
Total cost per cycle		***£6,664.05***	
Cycles 2-6			**Cycles 2-6**

Treatment	Proportion†	Cost	Source
Deliver more complex parenteral chemotherapy	-	£336.57	NHS Reference costs 2015/16 - Day case
Chemotherapy (docetaxel or paclitaxel)	-	£34.40	eMit
Trastuzumab cost per subcutaneous injection 600mg	-	£1,222.20	BNF
Pertuzumab cost for 420mg vial	-	£2,395.00	NICE TA and BNF
Total cost per cycle	-	***£3,988.17***	
Subsequent cycles (until disease progression)			
Deliver simple parenteral chemotherapy	-	£253.32	NHS Reference costs 2015/16 - Day case
Trastuzumab cost per subcutaneous injection 600mg	-	£1,222.20	BNF
Pertuzumab cost for 420mg vial	-	£2,395.00	NICE TA and BNF
Total cost per cycle	-	***£3,870.52***	

† Proportions estimated based on the number of procedures recorded in NHS Reference Costs
BNF, British National Formulary; CC, complete cytoreduction; eMit, electronic market information tool; NICE, National Institute of Health and Care Excellence; TA, technology appraisal

Table 16: Subsequent treatment costs for distant recurrence

Treatment	Proportion†	Cost	Source
Adjuvant chemotherapy, trastuzumab and pertuzumab			
Cycle 1			**Cycle 1**
Deliver simple parenteral chemotherapy	-	£253.32	NHS Reference costs 2015/16 - Day case
Deliver Subsequent Elements of a Chemotherapy Cycle	-	£361.04	NHS Reference costs 2015/16 - Day case
Chemotherapy (docetaxel or paclitaxel)	-	£37.49	eMit
Trastuzumab cost per subcutaneous injection 600mg	-	£1,222.20	BNF
Pertuzumab cost for two 420mg vials (loading dose)	-	£4,790.00	NICE TA and BNF
Total cost per cycle		***£6,664.05***	
Cycles 2-6			**Cycles 2-6**
Deliver more complex parenteral chemotherapy	-	£336.57	NHS Reference costs 2015/16 - Day case
Chemotherapy (docetaxel or paclitaxel)	-	£34.40	eMit
Trastuzumab cost per subcutaneous injection 600mg	-	£1,222.20	BNF
Pertuzumab cost for 420mg vial	-	£2,395.00	NICE TA and BNF
Total cost per cycle	-	***£3,988.17***	
Subsequent cycles (until disease progression)			

Treatment	Proportion†	Cost	Source
Deliver simple parenteral chemotherapy	-	£253.32	NHS Reference costs 2015/16 - Day case
Trastuzumab cost per subcutaneous injection 600mg	-	£1,222.20	BNF
Pertuzumab cost for 420mg vial	-	£2,395.00	NICE TA and BNF
Total cost per cycle	-	***£3,870.52***	

† Proportions estimated based on the number of procedures recorded in NHS Reference Costs
BNF, British National Formulary; eMit, electronic market information tool; NICE, National Institute of Health and Care Excellence; TA, technology appraisal

Cardiac event monitoring costs

Treatment with trastuzumab is associated with a risk of cardiotoxicity and therefore people receiving trastuzumab typically undergo cardiac monitoring. In clinical practice, echocardiograms are typically used for cardiac monitoring but in some cases multi gated acquisition (MUGA) scans or cardiac MRI scans may be used.

In the model, a weighted average cost per scan was calculated using weightings estimated by the guideline committee. It was assumed that 80% of scans would be echocardiograms, 10% would be MUGA scans and 10% would be cardiac MRI scans. The cost for each scan was sourced from NHS reference costs 2015/16. Reflecting clinical practice, it was assumed that people would undergo five cardiac monitoring scans in the year that they receive trastuzumab.

Table 17 details the cost of cardiac event monitoring applied in the model.

Table 17: Cardiac event monitoring costs

Treatment	Proportion†	Cost	Source
Simple Echocardiogram, 19 years and over (RD51A)	80%	£72.00	NHS Reference Costs 2015/16 – outpatient
Multi Gated Acquisition (MUGA) Scan (RN22Z)	10%	£204.70	NHS Reference Costs 2015/16 – outpatient
Cardiac Magnetic Resonance Imaging Scan with pre and post contrast (RD10Z)	10%	£329.27	NHS Reference Costs 2015/16 – outpatient
Weighted average cost per scan		**£111.00**	
Average cost for five scans		**£554.99**	

† Proportions estimated based on the number of procedures recorded in NHS Reference Costs
MUGA, Multi Gated Acquisition; NHS, National Health Service; NICE, National Institute of Health and Care Excellence

Follow-up costs

The cost of post-treatment follow-up to detect disease recurrence was incorporated in the model. It was assumed that people would have clinical follow-up appointments every 3 to 6 months in the years 1 to 3, every 6 to 12 months in years 4 to 5 and annually thereafter. The

cost for each follow-up appointment was estimated to be £120.98 based on the cost of a 'consultant led, non-admitted face to face attendance, follow-up' from NHS Reference Costs 2015/16.

Palliative care costs

The cost of palliative care was estimated using estimates from a costing report by the Nuffield Trust (Georghiou 2014, 'Exploring the cost of care at the end of life'). A cost of £7,287 for 3 months was applied based on the average resource use of people with cancer in the last three months of life. Table 18 details the palliative care cost applied in the model.

Table 18: Estimated palliative care cost per person in the last three months of life

Type of care	Average cost per cancer person	Source
Cost of all hospital contacts	£5,890	Exploring the cost of care at the end of life (Nuffield Trust, Georghiou 2014)
Local authority-funded care	£444	
District nursing care	£588	
GP contacts	£365	
Average palliative care cost per person	**£7,287**	

GP, General Practitioner

It should be noted that this cost is generic to all cancers and is not specifically related to breast cancer. However, in the absence of more robust data, it has been assumed that the costs in breast cancer would not differ substantially.

Health-related quality of life

As recommended in the NICE reference case, the model estimates effectiveness in terms of quality adjusted life years (QALYs). These are estimated by combining the life year estimates with utility values (or QoL weights) associated with being in a particular health state.

The QoL values applied in the model were sourced from Essers 2010, which reported utility values for people with HER2-positive breast cancer and was applicable to the UK setting. This study was identified and used by the Evidence Review Group (ERG) in their revised economic analysis as part of the technology appraisal for pertuzumab in neoadjuvant treatment of HER2-positive breast cancer (NICE TA424).

Table 19 details the QoL values applied in the analysis. It can be seen that people in the 'disease free' health state would have a QoL value of 0.847 which decreases to 0.810 in people with a recurrence. The QoL value for metastatic disease was applied to people in the last year of life before dying of cancer specific mortality.

Table 19: Health-related quality of life values

Health state	Value	Source
Event free or remission	0.847	Essers 2010
Recurrence	0.810	Essers 2010
Metastases	0.484	Essers 2010

Results

Base case results

The base case results of the analysis are shown in Table 20 and Table 21 for 2 scenarios. In the first scenario, adjuvant chemotherapy and trastuzumab are compared against observation while in the second scenario the use of adjuvant chemotherapy without trastuzumab is considered as another treatment option.

In the first scenario, it can be seen that adjuvant chemotherapy and trastuzumab was found to be less costly (-£27,881) and more effective than observation (1.09 QALYs) and is therefore considered dominant.

In the second scenario, it can be seen that observation was found to be more costly and less effective than both adjuvant chemotherapy and adjuvant chemotherapy and trastuzumab and is therefore dominated. When comparing adjuvant chemotherapy and trastuzumab against adjuvant chemotherapy alone, the addition of trastuzumab was found to improve effectiveness but also significantly increase costs. The resulting ICER of £20,170 per QALY is marginally higher than the NICE threshold of £20,000 per QALY. Therefore the strategy is not cost-effective when compared against adjuvant chemotherapy.

Table 20: Base case results for adjuvant chemotherapy and trastuzumab in comparison to observation

Strategy	Cost		QALYs		ICER (cost per QALY
	Total	Incremental	Total	Incremental	
Observation	£111,242	-	13.81	-	**-**
Adjuvant chemotherapy + trastuzumab	£83,361	*-£27,881*	14.90	*1.09*	**Dominant**

ICER; incremental cost-effectiveness ratio; QALYs, quality adjusted life years

Table 21: Base case results for three way comparison

Strategy	Cost		QALYs		ICER (cost per QALY
	Total	Incremental	Total	Incremental	
Adjuvant chemotherapy	£70,758	-	14.28	-	**-**
Adjuvant chemotherapy + trastuzumab	£83,361	*£12,603*	14.90	*0.62*	**£20,170**
Observation	£111,242	*£27,881*	13.81	*-1.09*	**Dominated**

ICER; incremental cost-effectiveness ratio; QALYs, quality adjusted life years

Deterministic sensitivity results

A series of deterministic sensitivity analyses were conducted, whereby an input parameter is changed, the model is re-run and the new cost-effectiveness result is recorded. This analysis is a useful way of estimating uncertainty and determining the key drivers of the model result (Table 22).

In the 2-way comparison between observation and adjuvant chemotherapy and trastuzumab, it can be seen that the conclusion of the analysis remains unchanged in all scenarios.

Notably this includes scenarios where the upper HR estimate is used for both overall survival and disease free survival (thereby reducing the effectiveness of treatment).

In the 3-way comparison, it can be seen that the conclusion of the analysis changes in numerous scenarios with adjuvant chemotherapy and trastuzumab found to be cost-effective with ICER values below £20,000 per QALY. This includes scenarios in which baseline OS and DFS risk is lowered (thereby increasing the baseline risk and increasing the scope for treatment to be effective). The addition of trastuzumab was also found to be cost-effective in scenarios where lower HRs are used for mortality and recurrence. This includes scenarios in which the lower estimates for OS and DFS from the 95% CI interval range are applied and scenarios where the HRs from the clinical evidence review were applied (sourced from observational studies of patients with T1 tumours). It's also noteworthy that the addition of trastuzumab was found to be cost-effective in a scenario where the delivery cost is reduced by 60%. There is some uncertainty around the appropriate delivery cost and it's possible that the base case value is an overestimate (a 60% reduction was considered to be a plausible reduction in the cost). .

Table 22: Deterministic sensitivity results

Change made	Two way comparison	Three way comparison
Base case	**Adjuvant chemotherapy + trastuzumab**	**Adjuvant chemotherapy**
Baseline DFS = 75%	Adjuvant chemotherapy + trastuzumab	Adjuvant chemotherapy + trastuzumab
Baseline DFS = 65%	Adjuvant chemotherapy + trastuzumab	Adjuvant chemotherapy + trastuzumab
Baseline OS = 85%	Adjuvant chemotherapy + trastuzumab	***Adjuvant chemotherapy + trastuzumab***
Baseline OS = 75%	Adjuvant chemotherapy + trastuzumab	***Adjuvant chemotherapy + trastuzumab***
OS and DFS upper HR	Adjuvant chemotherapy + trastuzumab	Adjuvant chemotherapy
OS and DFS lower HR	Adjuvant chemotherapy + trastuzumab	Adjuvant chemotherapy + trastuzumab
HR for DFS from evidence review (0.13)	Adjuvant chemotherapy + trastuzumab	Adjuvant chemotherapy + trastuzumab
HR for OS from evidence review (0.27)	Adjuvant chemotherapy + trastuzumab	Adjuvant chemotherapy + trastuzumab
HR for OS and DFS from evidence review	Adjuvant chemotherapy + trastuzumab	Adjuvant chemotherapy + trastuzumab
DFS RR = 0.54	Adjuvant chemotherapy + trastuzumab	Adjuvant chemotherapy
Trastuzumab delivery cost 60% lower	Adjuvant chemotherapy + trastuzumab	Adjuvant chemotherapy + trastuzumab

DFS, disease-free survival; OS, overall survival; RR, risk ratio

Probabilistic sensitivity results

Probabilistic sensitivity analysis (PSA) was conducted to assess the combined parameter uncertainty in the model. In this analysis, the mean values that were utilised in the base case are replaced with values drawn from distributions around the mean values. The results of

10,000 runs of the PSA are shown using ICER scatterplots and cost-effectiveness acceptability curves (CEAC). The ICER scatter plots show the incremental costs and QALYs associated with each of the 10,000 runs of the PSA along with the mean result. The CEAC graphs show the probability of each strategy being considered cost-effective at the various cost-effectiveness thresholds on the x axis.

Figure 11 and Figure 12 show the ICER scatterplot and CEAC for the 2-way comparison between observation and adjuvant chemotherapy and trastuzumab. From the ICER scatterplot, it can be seen that the vast majority of results reside in the South East quadrant of the graph, indicating that adjuvant chemotherapy and trastuzumab is less expensive and more effective than observation in most modelled scenarios. The CEAC shows that the probability of adjuvant chemotherapy and trastuzumab being cost-effective remains fairly constant but does increase slightly as the cost-effectiveness threshold increases. At the NICE threshold of £20,000 per QALY, adjuvant chemotherapy and trastuzumab was found to have a 98% probability of being cost-effective while observation had a 2% probability of being cost-effective.

Figure 11: ICER Scatterplot for adjuvant chemotherapy and trastuzumab in comparison to observation

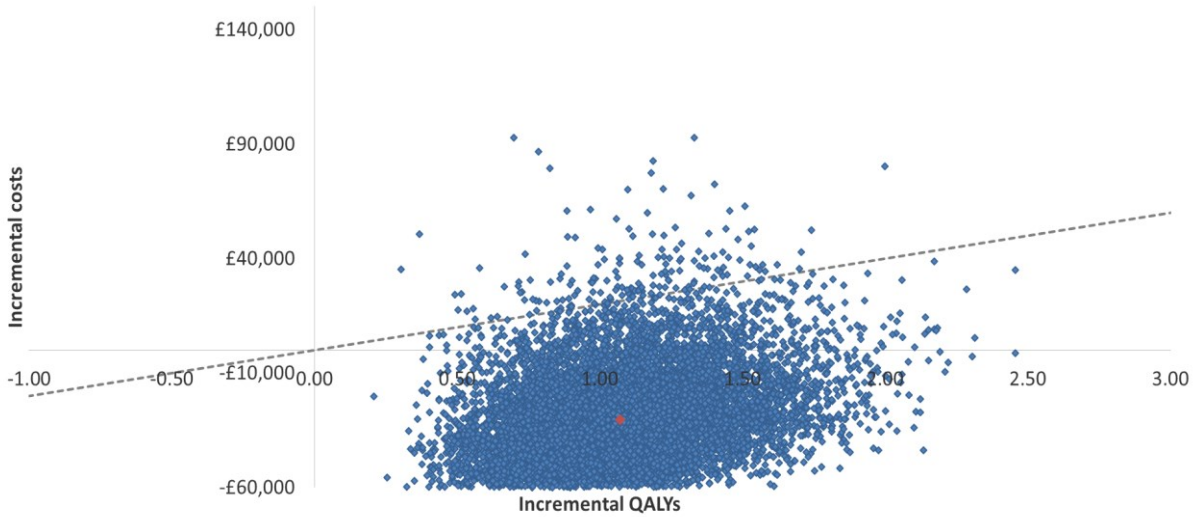


Figure 12: Cost-effectiveness acceptability curve for adjuvant chemotherapy and trastuzumab in comparison to observation

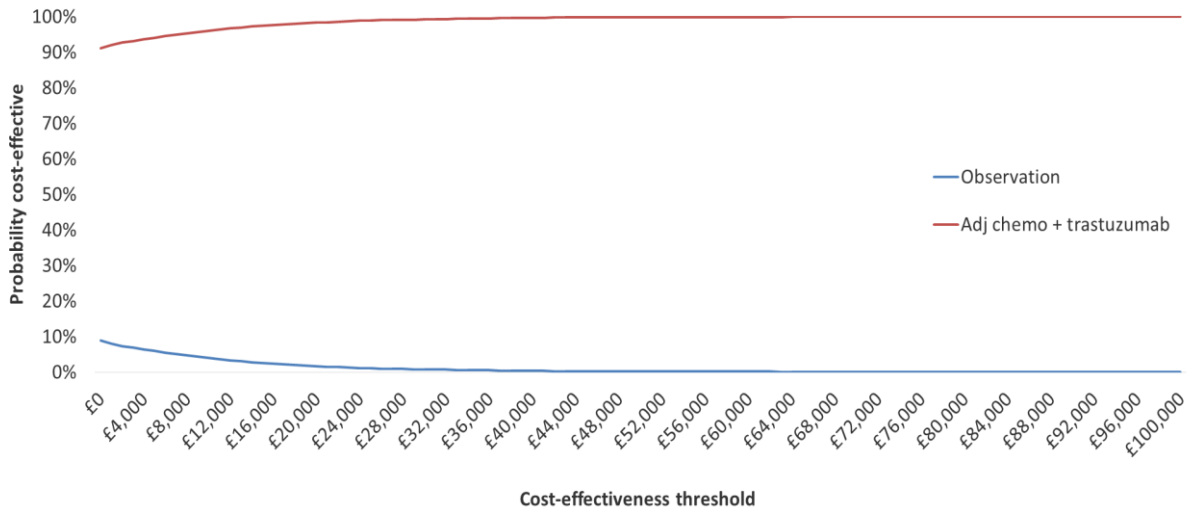
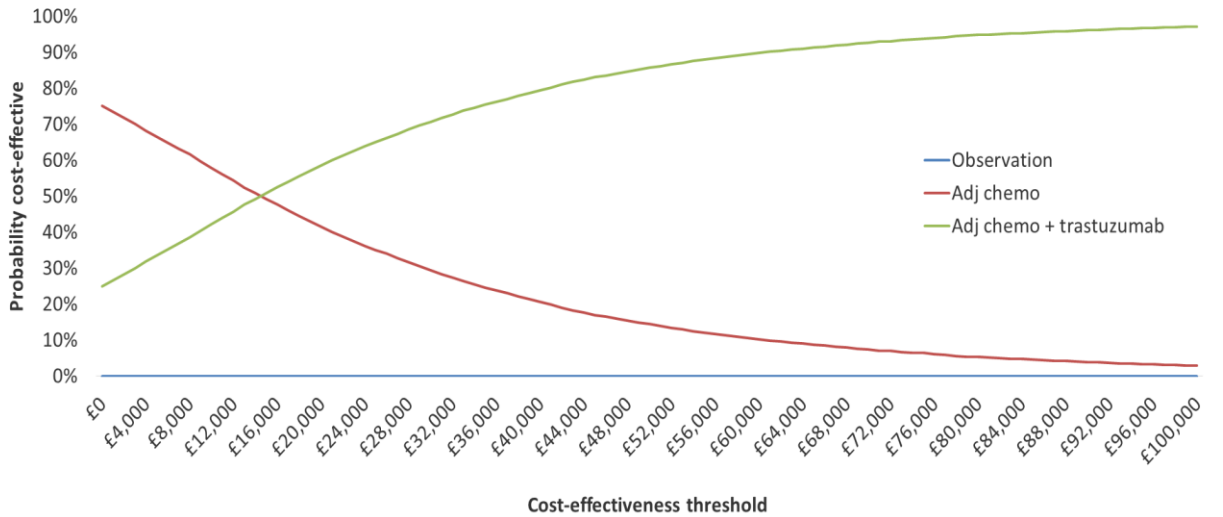


Figure 13 shows the CEAC for the three-way comparison, in which adjuvant chemotherapy is also considered. It can again be seen that the probability of adjuvant chemotherapy and trastuzumab being cost-effective increases as the cost-effectiveness threshold increases while adjuvant chemotherapy alone starts with a much higher probability of being cost-effective, which decreases as the threshold increases. At the NICE threshold of £20,000 per QALY, adjuvant chemotherapy and trastuzumab was found to have a 58% probability of being cost-effective while adjuvant chemotherapy had a 42% probability of being cost-effective and observation had a 0% probability of being cost-effective.

Figure 13: Cost-effectiveness acceptability curve for three way comparison



Probabilistic base case results

In addition to the deterministic results, the base case results were also generated probabilistically. In this analysis the mean total costs and QALYs were recorded after 10,000 probabilistic runs of the analysis. The probabilistic base case results are presented in Table 23 and Table 24.

It can be seen that the results in in the two-way comparison do not differ substantially from the deterministic analysis with adjuvant chemotherapy and trastuzumab found to be less costly and more effective than observation (i.e. dominant). In the three way comparison, observation was again found to be more costly and less effective than adjuvant chemotherapy and adjuvant chemotherapy and trastuzumab and was therefore dominated. When comparing adjuvant chemotherapy and trastuzumab against adjuvant chemotherapy alone, the resulting ICER of £20,170 per QALY is a little higher than in the deterministic analysis and is still higher than the NICE threshold of £20,000 per QALY. Therefore the strategy is not cost-effective when compared against adjuvant chemotherapy.

Table 23: Probabilistic base case results for adjuvant chemotherapy and trastuzumab in comparison to observation

Strategy	Cost		QALYs		ICER (cost per QALY)
	Total	Incremental	Total	Incremental	
Observation	£116,811	-	13.86	-	**-**
Adjuvant chemotherapy + trastuzumab	£86,345	*-£30,466*	14.93	*1.07*	**Dominant**

ICER; incremental cost-effectiveness ratio; QALYs, quality adjusted life years

Table 24: Probabilistic base case results for three way comparison

Strategy	Cost		QALYs		ICER (cost per QALY)
	Total	Incremental	Total	Incremental	
Adjuvant chemotherapy	£74,026	-	14.32	-	-
Adjuvant chemotherapy + trastuzumab	£86,345	*£12,319*	14.93	*0.61*	**£20,277**
Observation	£116,811	*£30,466*	13.86	*-1.07*	**Dominated**

ICER; incremental cost-effectiveness ratio; QALYs, quality adjusted life years

Conclusion

The results of the analysis suggest that active treatment is superior to observation in people with HER2-positive T1 tumours. When compared against observation adjuvant chemotherapy and trastuzumab is found to be cost-effective with an ICER below the NICE threshold of £20,000 per QALY. However, if adjuvant chemotherapy alone is considered to be an appropriate treatment in this population then adjuvant chemotherapy and trastuzumab may not be cost-effective as its ICER value marginally exceeds the NICE threshold of £20,000 per QALY when compared against adjuvant chemotherapy alone. .

Appendix K – Excluded studies

Clinical studies

Excluded studies - RQ6.1 Which people with T1 N0 human epidermal growth receptor 2 (HER2)-positive breast cancers benefit from adjuvant trastuzumab in combination with chemotherapy?	
Study	**Reason for exclusion**
Advani, P. P., Ballman, K. V., Dockter, T. J., Colon-Otero, G., Perez, E. A., Long-Term Cardiac Safety Analysis of NCCTG N9831 (Alliance) Adjuvant Trastuzumab Trial, Journal of clinical oncology, 34, 581-7, 2016	Data cannot be extracted separately for T1N0M0
Akiyoshi, S., Ishida, M., Koga, C., Nakamura, Y., Taguchi, K., Ohno, S., Tokunaga, E., Adjuvant trastuzumab improved the prognosis of HER2-positive early breast cancer: Single institutional cohort study from clinical practice, Cancer Research. Conference: 38th Annual CTRC AACR San Antonio Breast Cancer Symposium. San Antonio, TX United States. Conference Start, 76, 2016	Abstract only - insufficient information
Azambuja, E, Procter, Mj, Veldhuisen, Dj, Agbor-Tarh, D, Metzger-Filho, O, Steinseifer, J, Untch, M, Smith, Ie, Gianni, L, Baselga, J, Jackisch, C, Cameron, Da, Bell, R, Leyland-Jones, B, Dowsett, M, Gelber, Rd, Piccart-Gebhart, Mj, Suter, Tm, Trastuzumab-associated cardiac events at 8 years of median follow-up in the Herceptin Adjuvant trial (BIG 1-01), Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 32, 2159-65, 2014	Data cannot be extracted separately for T1N0M0
Ban, M., Viculin, J., Tomic, S., Capkun, V., Strikic, A., Petric Mise, B., Utrobicic, I., Vrdoljak, E., Retrospective analysis of efficacy of trastuzumab in adjuvant treatment of HER 2 positive early breast cancer - Single institution experience, Neoplasma, 63, 761-767, 2016	Data not presented separately for T1N0
Bates, B., Adjuvant trastuzumab is more effective with concurrent taxane, Oncology Report, 16, 2010	Commentary
Bria, E., Cuppone, F., Fornier, M., Nistico, C., Carlini, P., Milella, M., Sperduti, I., Terzoli, E., Cognetti, F., Giannarelli, D., Cardiotoxicity and incidence of brain metastases after adjuvant trastuzumab for early breast cancer: the dark side of the moon? A meta-analysis of the randomized trials, Breast Cancer Research & Treatment, 109, 231-9, 2008	Populations outside scope/data not presented separately for T1N0M0
Brollo, J., Curigliano, G., Disalvatore, D., Marrone, B. F., Criscitiello, C., Bagnardi, V., Kneubil, M. C., Fumagalli, L., Locatelli, M., Manunta, S., Goldhirsch, A., Adjuvant trastuzumab in elderly with HER-2 positive breast cancer: A systematic review of randomized controlled trials, Cancer Treatment Reviews, 39, 44-50, 2013	Populations outside scope/data not presented separately for T1N0M0
Brown-Glaberman, U., Dayao, Z., Royce, M., HER2-targeted therapy for early-stage breast cancer: A comprehensive review, Oncology, 28, 2014	Narrative review

Excluded studies - RQ6.1 Which people with T1 N0 human epidermal growth receptor 2 (HER2)-positive breast cancers benefit from adjuvant trastuzumab in combination with chemotherapy?	
Study	**Reason for exclusion**
Chavez-MacGregor, M., Zhang, N., Buchholz, T. A., Zhang, Y., Niu, J., Elting, L., Smith, B. D., Hortobagyi, G. N., Giordano, S. H., Trastuzumab-related cardiotoxicity among older patients with breast cancer, Journal of clinical oncology, 31, 4222-4228, 2013	Data cannot be extracted separately for HER2 T1N0M0
Chen, J., Long, J. B., Hurria, A., Owusu, C., Steingart, R. M., Gross, C. P., Incidence of heart failure or cardiomyopathy after adjuvant trastuzumab therapy for breast cancer, Journal of the American College of Cardiology, 60, 2504-2512, 2012	Data cannot be extracted separately for HER2 T1N0M0
Chien, H. C., Yang, Y. H. K., Bai, J. P. F., Cardiotoxicity of adjuvant trastuzumab in Taiwan breast cancer patients: A population-based study, Pharmacoepidemiology and Drug Safety, 24, 390, 2015	Abstract only: insufficient information available
Dall, P., Lenzen, G., Gohler, T., Lerchenmuller, C., Feisel-Schwickardi, G., Koch, T., Eggert, J., Heilmann, V., Schindler, C., Wilke, J., Tesch, H., Selbach, J., Wohlfarth, T., Eustermann, H., Hinke, A., Trastuzumab in the treatment of elderly patients with early breast cancer: Results from an observational study in Germany, Journal of Geriatric Oncology, 6, 462-9, 2015	Data cannot be extracted separately for T1N0M0
De Nonneville, A., Goncalves, A., Zemmour, C., Classe, J. M., Cohen, M., Lambaudie, E., Reyal, F., Giard, S., Rouzier, R., Villet, R., Boher, J. M., Houvenaeghel, G., Benefit of adjuvant chemotherapy and/or trastuzumab in Tlab node-negative human epidermal growth factor receptor 2-positive breast carcinomas: Results of a national multi-institutional study, Journal of Clinical Oncology. Conference, 34, 2016	Abstract only
Fokter Dovnik, N., Dovnik, A., Cas Sikosek, N., Ravnik, M., Arko, D., Takac, I., Prognostic Role of HER2 Status and Adjuvant Trastuzumab Treatment in Lymph Node-Negative Breast Cancer Patients - A Retrospective Single Center Analysis, Breast Care, 11, 406-410, 2016	Data cannot be extracted separately for T1N0M0
Freedman, R. A., Trastuzumab-related cardiotoxicity among older patients with breast cancer: Chavez-MacGregor M, Zhang N, Buchholz TA, et al (Univ of Texas MD Anderson Cancer Ctr, Houston) J Clin Oncol 31:4222-4228, 2013, Breast Diseases, 26, 166-168, 2014	Commentary
Gianni, L., Dafni, U., Gelber, R. D., Azambuja, E., Muehlbauer, S., Goldhirsch, A., Untch, M., Smith, I., Baselga, J., Jackisch, C., Cameron, D., Mano, M., Pedrini, J. L., Veronesi, A., Mendiola, C., Pluzanska, A., Semiglazov, V., Vrdoljak, E., Eckart, M. J., Shen, Z., Skiadopoulos, G., Procter, M., Pritchard, K. I., Piccart-Gebhart, M. J., Bell, R., Treatment with trastuzumab for 1 year after adjuvant chemotherapy in patients with HER2-positive early breast cancer: A 4-year follow-up of a randomised controlled trial, The Lancet Oncology, 12, 236-244, 2011	Data cannot be extracted separately for T1N0M0
Goldhar, H. A., Yan, A. T., Ko, D. T., Earle, C. C., Tomlinson, G. A., Trudeau, M. E., Krahn, M. D., Krzyzanowska, M. K., Pal, R. S., Brezden-Masley, C., Gavura, S., Lien, K., Chan, K. K., The Temporal Risk of Heart Failure Associated With Adjuvant Trastuzumab in Breast Cancer Patients: A Population Study, Journal of the National Cancer Institute, 108, 2016	Data cannot be extracted separately for HER2 T1N0M0

Excluded studies - RQ6.1 Which people with T1 N0 human epidermal growth receptor 2 (HER2)-positive breast cancers benefit from adjuvant trastuzumab in combination with chemotherapy?	
Study	**Reason for exclusion**
Horio, A., Fujita, T., Hayashi, H., Hattori, M., Kondou, N., Yamada, M., Adachi, E., Ushio, A., Gondou, N., Sueta, A., Yatabe, Y., Iwata, H., High recurrence risk and use of adjuvant trastuzumab in patients with small, HER2-positive, node-negative breast cancers, International journal of clinical oncology, 17, 131-136, 2012	Insufficient presentation of results
Jackisch, C., Piccart, M. J., Gelber, R. D., Procter, M., Goldhirsch, A., DeAzambuja, E., Castro Jr, G., Untch, M., Smith, I., Gianni, L., Baselga, J., Al-Sakaff, N., Lauer, S., McFadden, E., Leyland-Jones, B., Bell, R., Dowsett, M., Cameron, D., HERA trial: 10 years follow up of trastuzumab after adjuvant chemotherapy in HER2 positive early breast cancer-final analysis, Cancer Research. Conference: 38th Annual CTRC AACR San Antonio Breast Cancer Symposium. San Antonio, TX United States. Conference Start, 76, 2016	Abstract only: insufficient presentation of results
Joensuu, H., Bono, P., Kataja, V., Alanko, T., Kokko, R., Asola, R., Utriainen, T., Turpeenniemi-Hujanen, T., Jyrkkio, S., Moykkynen, K., Helle, L., Ingalsuo, S., Pajunen, M., Huusko, M., Salminen, T., Auvinen, P., Leinonen, H., Leinonen, M., Isola, J., Kellokumpu-Lehtinen, P. L., Fluorouracil, epirubicin, and cyclophosphamide with either docetaxel or vinorelbine, with or without trastuzumab, as adjuvant treatments of breast cancer: final results of the FinHer Trial, Journal of clinical oncology, 27, 5685-92, 2009	Data not presented separately for HER2 T1N0M0
Joensuu, H., Kellokumpu-Lehtinen, P. L., Huovinen, R., Jukkola-Vuorinen, A., Tanner, M., Kokko, R., Ahlgren, J., Auvinen, P., Saarni, O., Helle, L., Villman, K., Nyandoto, P., Nilsson, G., Leinonen, M., Kataja, V., Bono, P., Lindman, H., Outcome of patients with HER2-positive breast cancer treated with or without adjuvant trastuzumab in the Finland Capecitabine Trial (FinXX), Acta oncologica, 53, 186-94, 2014	T1N0M0 patients not included
Kanjanapan, Y., Thomas, S. N., Yip, D., Dahlstrom, J. E., Pathmanathan, N., Craft, P. S., Effects of adjuvant trastuzumab with chemotherapy (ATWC) in T1N0 HER2 positive (HER2+) breast cancer, Journal of Clinical Oncology. Conference, 33, 2015	Abstract only
Kayahan, M., Kadioglu, H., Muslumanoglu, M., Igci, A., Ozmen, V., Idiz, O., Eralp, Y., Tuzlali, S., Trastuzumab use and survival in HER2 (+) nonmetastatic breast cancer among Turkish women, Journal of clinical oncology, 29, 56, 2011	Abstract >2 years old
Kiess, A. P., McArthur, H. L., Mahoney, K., Patil, S., Morris, P. G., Ho, A., Hudis, C. A., McCormick, B., Adjuvant trastuzumab reduces locoregional recurrence in women who receive breast-conservation therapy for lymph node-negative, human epidermal growth factor receptor 2-positive breast cancer, Cancer, 118, 1982-8, 2012	Data not presented separately for T1N0M0
Lanning, R. M., Morrow, M., Riaz, N., McArthur, H. L., Dang, C., Moo, T. A., El-Tamer, M., Krause, K., Siu, C., Hsu, M., Zhang, Z., Pei, X., McCormick, B., Powell, S. N., Ho, A., The Effect of Adjuvant	Data not presented separately for T1N0M0

Excluded studies - RQ6.1 Which people with T1 N0 human epidermal growth receptor 2 (HER2)-positive breast cancers benefit from adjuvant trastuzumab in combination with chemotherapy?	
Study	**Reason for exclusion**
Trastuzumab on Locoregional Recurrence of Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer Treated with Mastectomy, Annals of surgical oncology, 22, 2517-2525, 2015	
Long, H. D., Lin, Y. E., Zhang, J. J., Zhong, W. Z., Zheng, R. N., Risk of congestive heart failure in early breast cancer patients undergoing adjuvant treatment with trastuzumab: A meta-analysis, Oncologist, 21, 547-554, 2016	Populations outside scope/Data not presented separately for T1N0M0
Madarnas, Y., Trudeau, M., Franek, J. A., McCready, D., Pritchard, K. I., Messersmith, H., Adjuvant/neoadjuvant trastuzumab therapy in women with HER-2/neu-overexpressing breast cancer: A systematic review, Cancer treatment reviews, 34, 539-557, 2008	Populations outside scope/Data not presented separately for T1N0M0
Mantarro, S, Rossi, M, Blandizzi, C, Capogrosso, Sansone A, Convertino, I, Montagnani, S, Marino, A, Saporiti, A, Garibaldi, D, D'Amico, R, Negri, E, Vecchia, C, Moja, L, Tuccori, M, Severe cardiac events following treatment with trastuzumab in women with breast cancer: A meta-analysis of clinical trials and cohort studies, Drug Safety. Conference: 15th ISoP Annual Meeting "Cubism in Pharmacovigilance" Prague Czech Republic. Conference Start: 20151027 Conference End: 20151030. Conference Publication: (var.pagings), 38, 972-3, 2015	Abstract only - insufficient information
Mates, M., Fletcher, G. G., Freedman, O. C., Eisen, A., Gandhi, S., Trudeau, M. E., Dent, S. F., Systemic targeted therapy for HER2-positive early female breast cancer: A systematic review of the evidence for the 2014 cancer care Ontario systemic therapy guideline, Current Oncology, 22, S114-S122, 2015	Populations/Comparisons outside scope
Matos, E., Zakotnik, B., Kuhar, C. G., Effectiveness of adjuvant trastuzumab in daily clinical practice, Radiology and Oncology, 48, 403-407, 2014	No comparison
McGuire, A, Lowery, A, Brown, J, Kerin, M, Effects of trastuzumab treatment on the patterns of survival and metastasis in Her-2 positive breast cancers, European Journal of Surgical Oncology. Conference: Association of Breast Surgery Conference and AGM, ABS 2015 Bournemouth United Kingdom. Conference Start: 20150615 Conference End: 20150616. Conference Publication: (var.pagings), 41, S59, 2015	Abstract only: insufficient presentation of results
Metzger-Filho, O., Procter, M., de Azambuja, E., Leyland-Jones, B., Gelber, R. D., Dowsett, M., Loi, S., Saini, K. S., Cameron, D., Untch, M., Smith, I., Gianni, L., Baselga, J., Jackisch, C., Bell, R., Sotiriou, C., Viale, G., Piccart-Gebhart, M., Magnitude of trastuzumab benefit in patients with HER2-positive, invasive lobular breast carcinoma: results from the HERA trial, Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 31, 1954-1960, 2013	Data not presented separately for T1N0M0
Moja,Lorenzo, Tagliabue,Ludovica, Balduzzi,Sara, Parmelli,Elena, Pistotti,Vanna, Guarneri,Valentina, D'Amico,Roberto, Trastuzumab containing regimens for early breast cancer, Cochrane Database of Systematic Reviews, -, 2012	Populations outside scope/Data not presented separately for T1N0M0

Excluded studies - RQ6.1 Which people with T1 N0 human epidermal growth receptor 2 (HER2)-positive breast cancers benefit from adjuvant trastuzumab in combination with chemotherapy?	
Study	**Reason for exclusion**
Mustacchi, G., Puglisi, F., Molino, A. M., Crivellari, D., Ghiotto, C., Ferro, A., Brunello, A., Saracchini, S., Turazza, M., Cretella, E., Iop, A., Malagoli, M., Stefani, M., Observational study on adjuvant trastuzumab in HER2-positive early breast cancer patients, Future Oncology, 11, 1493-500, 2015	Cannot extract data separately for T1N0M0
Nihr, Hsric, Pertuzumab (Perjeta) with chemotherapy and trastuzumab for HER2-positive early breast cancer? adjuvant therapy (Structured abstract), Health Technology Assessment Database, 2016	Comparison outside scope
Olson, E. M., Abdel-Rasoul, M., Maly, J., Wu, C. S., Lin, N. U., Shapiro, C. L., Incidence and risk of central nervous system metastases as site of first recurrence in patients with HER2-positive breast cancer treated with adjuvant trastuzumab, Annals of Oncology, 24, 1526-1533, 2013	Populations outside scope/Data not presented separately for T1N0M0
Palmieri, C., Shah, D., Krell, J., Gojis, O., Hogben, K., Riddle, P., Ahmad, R., Tat, T., Fox, K., Porter, A., Mahmoud, S., Kirschke, S., Shousha, S., Gudi, M., Charles Coombes, R., Leonard, R., Cleator, S., Management and outcome of HER2-positive early breast cancer treated with or without trastuzumab in the adjuvant trastuzumab era, Clinical breast cancer, 11, 93-102, 2011	Data not presented separately for T1N0M0
Palmieri, F. M., Myatt, C. V., Perez, E. A., Adjuvant trastuzumab for HER2-positive early breast cancer, Clinical journal of oncology nursing, 14, 326-336, 2010	Narrative review
Partridge, Ah, Gelber, S, Piccart-Gebhart, Mj, Focant, F, Scullion, M, Holmes, E, Winer, Ep, Gelber, Rd, Effect of age on breast cancer outcomes in women with human epidermal growth factor receptor 2-positive breast cancer: results from a herceptin adjuvant trial, Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 31, 2692-8, 2013	Data not presented separately for T1N0M0
Perez, E. A., Romond, E. H., Suman, V. J., Jeong, J. H., Davidson, N. E., Geyer Jr, C. E., Martino, S., Mamounas, E. P., Kaufman, P. A., Wolmark, N., Four-year follow-up of trastuzumab plus adjuvant chemotherapy for operable human epidermal growth factor receptor 2-positive breast cancer: Joint analysis of data from NCCTG N9831 and NSABP B-31, Journal of clinical oncology, 29, 3366-3373, 2011	Data not reported separately for T1N0M0
Perez, Ea, Romond, Eh, Suman, Vj, Jeong, Jh, Sledge, G, Geyer, Ce, Martino, S, Rastogi, P, Gralow, J, Swain, Sm, Winer, Ep, Colon-Otero, G, Davidson, Ne, Mamounas, E, Zujewski, Ja, Wolmark, N, Trastuzumab plus adjuvant chemotherapy for human epidermal growth factor receptor 2-positive breast cancer: planned joint analysis of overall survival from NSABP B-31 and NCCTG N9831, Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 32, 3744-52, 2014	Data not reported separately for T1N0M0
Perez, Ea, Suman, Vj, Davidson, Ne, Gralow, Jr, Kaufman, Pa, Visscher, Dw, Chen, B, Ingle, Jn, Dakhil, Sr, Zujewski, J, Moreno-Aspitia, A, Pisansky, Tm, Jenkins, Rb, Sequential versus concurrent trastuzumab in adjuvant chemotherapy for breast cancer, Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 29, 4491-7, 2011	Data cannot be extracted separately for T1N0M0

Excluded studies - RQ6.1 Which people with T1 N0 human epidermal growth receptor 2 (HER2)-positive breast cancers benefit from adjuvant trastuzumab in combination with chemotherapy?	
Study	**Reason for exclusion**
Perez, Ea, Suman, Vj, Davidson, Ne, Sledge, Gw, Kaufman, Pa, Hudis, Ca, Martino, S, Gralow, Jr, Dakhil, Sr, Ingle, Jn, Winer, Ep, Gelmon, Ka, Gersh, Bj, Jaffe, As, Rodeheffer, Rj, Cardiac safety analysis of doxorubicin and cyclophosphamide followed by paclitaxel with or without trastuzumab in the North Central Cancer Treatment Group N9831 adjuvant breast cancer trial, Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 26, 1231-8, 2008	Data cannot be extracted separately for T1N0M0
Pestalozzi, B. C., Holmes, E., de Azambuja, E., Metzger-Filho, O., Hogge, L., Scullion, M., Lang, I., Wardley, A., Lichinitser, M., Sanchez, R. I. L., Muller, V., Dodwell, D., Gelber, R. D., Piccart-Gebhart, M. J., Cameron, D., CNS relapses in patients with HER2-positive early breast cancer who have and have not received adjuvant trastuzumab: A retrospective substudy of the HERA trial (BIG 1-01), The Lancet Oncology, 14, 244-248, 2013	Data not reported separately for T1N0M0
Peterson, D. J., Truong, P. T., Sadek, B. T., Alexander, C. S., Wiksyk, B., Shenouda, M., Raad, R. A., Taghian, A. G., Locoregional Recurrence and Survival Outcomes by Type of Local Therapy and Trastuzumab Use Among Women with Node-Negative, HER2-Positive Breast Cancer, Annals of surgical oncology, 21, 3490-3496, 2014	Unclear what proportion in each arm received chemotherapy so cannot determine the comparison
Procter, M, Suter, Tm, Azambuja, E, Dafni, U, Dooren, V, Muehlbauer, S, Climent, Ma, Rechberger, E, Liu, Wt, Toi, M, Coombes, Rc, Dodwell, D, Pagani, O, Madrid, J, Hall, M, Chen, Sc, Focan, C, Muschol, M, Veldhuisen, Dj, Piccart-Gebhart, Mj, Longer-term assessment of trastuzumab-related cardiac adverse events in the Herceptin Adjuvant (HERA) trial, Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 28, 3422-8, 2010	Data not presented separately for T1N0M0
Rebelo Ferreira, A., Palha, A., Correia, L., Filipe, P., Rodrigues, V., Costa, L., Miranda, A., Andre, R., Fernandes, J., Gouveia, J., Passos Coelho, J. L., Moreira, A., Brito, M., Ribeiro, J., Freedman, R., Metzger- Filho, O., Lin, N. U., Vaz-Luis, I., The use of trastuzumab in patients with early breast cancer: A multi-institutional study, European Journal of Cancer, 51, S320, 2015	Abstract only: insufficient presentation of results
Riaz, N., Morrow, M., Moo, T. A., El-Tamer, M., Krause, K., Chen, Y., Pei, X., Powell, S. N., Ho, A. Y., Effect of adjuvant trastuzumab on locoregional recurrence in human epidermal growth factor receptor 2-positive breast cancer treated with post-mastectomy radiation therapy, Journal of clinical oncology, 31, 61, 2013	Abstract >2 years old
Russell, S. D., Blackwell, K. L., Lawrence, J., Pippen Jr, J. E., Roe, M. T., Wood, F., Paton, V., Holmgren, E., Mahaffey, K. W., Independent adjudication of symptomatic heart failure with the use of doxorubicin and cyclophosphamide followed by trastuzumab adjuvant therapy: A combined review of cardiac data from the National Surgical Adjuvant Breast and Bowel Project B-31 and the North Central Cancer Treatment Group N9831 clinical trials, Journal of clinical oncology, 28, 3416-3421, 2010	Data not reported separately for T1N0M0
Schott, A. F., Adjuvant Trastuzumab Benefit in Patients Diagnosed With Triple-Positive Breast Cancer, JAMA oncology, 2, 1047-8, 2016	Commentary

Excluded studies - RQ6.1 Which people with T1 N0 human epidermal growth receptor 2 (HER2)-positive breast cancers benefit from adjuvant trastuzumab in combination with chemotherapy?	
Study	**Reason for exclusion**
Seal, M. D., Speers, C. H., O'Reilly, S., Gelmon, K. A., Ellard, S. L., Chia, S. K., Outcomes of women with early-stage breast cancer receiving adjuvant trastuzumab, Current Oncology, 19, 197-201, 2012	Data not reported separately for T1N0M0
Seferina, S. C., Lobbezoo, D. J. A., De Boer, M., Dercksen, M. W., Van Den Berkmorte, F., Van Kampen, R. J. W., Van De wouw, A. J., De Vries, B., Joore, M. A., Peer, P. G. M., Voogd, A. C., Tjan-Heijnen, V. C. G., Real-life use and effectiveness of adjuvant trastuzumab in early breast cancer patients: A study of the Southeast Netherlands breast cancer consortium, Oncologist, 20, 856-863, 2015	Data not reported separately for T1N0M0
Shen, S, Sun, Q, Xu, Y, Zhou, Y, Guan, J, Mao, F, Lin, Y, Wang, X, Trastuzumab can be safely administered concurrently with anthracycline for adjuvant treatment of HER2-positive breast cancer, Cancer Research, 75, 2015	Abstract only: insufficient information
Singhal, M. K., Kapoor, A., Narayan, S., Maharia, S., Nirban, R. K., Beniwal, S. K., Kumar, H. S., A phase III randomized study of paclitaxel and trastuzumab versus paclitaxel alone for early stage, ER and PR receptor negative and HER2-positive breast cancer as adjuvant treatment, Annals of Oncology, 26, iii1, 2015	Data not presented separately for T1N0M0
Slamon, D. J., Eiermann, W., Robert, N. J., Giermek, J., Martin, M., Jasiowka, M., Mackey, J. R., Chan, A., Liu, M. C., Pinter, T., Valero, V., Falkson, C., Fornander, T., Shiftan, T. A., Bensfia, S., Hitier, S., Xu, N., Bee-Munteanu, V., Drevot, P., Press, M. F., Crown, J., Ten year follow-up of BCIRG-006 comparing doxorubicin plus cyclophosphamide followed by docetaxel (AC->T) with doxorubicin plus cyclophosphamide followed by docetaxel and trastuzumab (AC->TH) with docetaxel, carboplatin and trastuzumab (TCH) in HER2+ early breast cancer, Cancer Research. Conference: 38th Annual CTRC AACR San Antonio Breast Cancer Symposium. San Antonio, TX United States. Conference Start, 76, 2016	Data not presented separately for T1N0M0
Slamon, D., Eiermann, W., Robert, N., Pienkowski, T., Martin, M., Press, M., Mackey, J., Glaspy, J., Chan, A., Pawlicki, M., Pinter, T., Valero, V., Liu, M. C., Sauter, G., von Minckwitz, G., Visco, F., Bee, V., Buyse, M., Bendahmane, B., Tabah-Fisch, I., Lindsay, M. A., Riva, A., Crown, J., Breast Cancer International Research, Group, Adjuvant trastuzumab in HER2-positive breast cancer, The New England journal of medicine, 365, 1273-1283, 2011	Data not reported separately for T1N0M0
Sun, G., Yang, L., Fan, Z. L., Ma, B., Bin, L. M., Efficacy and prognosis of adjuvant trastuzumab therapy in T1 HER2-over-expressing early primary breast cancer: A single-center retrospective analysis, Journal of Clinical Oncology. Conference, 34, 2016	Abstract only: insufficient presentation of results
Tiwari, S. R., Raska, P., Moore, H. C. F., Emamekhoo, H., Abraham, J., Budd, G. T., Montero, A. J., Improved outcomes in stage I HER2 positive breast cancer patients treated with trastuzumab and chemotherapy, Journal of Clinical Oncology. Conference, 34, 2016	Abstract only: insufficient presentation of results

Excluded studies - RQ6.1 Which people with T1 N0 human epidermal growth receptor 2 (HER2)-positive breast cancers benefit from adjuvant trastuzumab in combination with chemotherapy?	
Study	**Reason for exclusion**
Untch, M., Gelber, R. D., Jackisch, C., Procter, M., Baselga, J., Bell, R., Cameron, D., Bari, M., Smith, I., Leyland-Jones, B., De Azambuja, E., Wermuth, P., Khasanov, R., Feng-Yi, F., Constantin, C., Mayordomo, J. I., Su, C. H., Yu, S. Y., Lluch, A., Senkus-Konefka, E., Price, C., Haslbauer, F., Sahui, S. T., Srimuninnimit, V., Colleoni, M., Coates, A. S., Piccart-Gebhart, M. J., Goldhirsch, A., Estimating the magnitude of trastuzumab effects within patient subgroups in the HERA trial, Annals of Oncology, 19, 1090-1096, 2008	Data not reported separately for T1N0M0
Van Ramshorst, M. S., Van Der Heijden-Van Der Loo, M., Dackus, G. M. H. E., Linn, S. C., Sonke, G. S., The effect of trastuzumab-based therapy on overall survival in small, node-negative HER2-positive breast cancer: To treat or not to treat?, Cancer Research. Conference: 38th Annual CTRC AACR San Antonio Breast Cancer Symposium. San Antonio, TX United States. Conference Start, 76, 2016	Abstract only
Yin, W., Jiang, Y., Shen, Z., Shao, Z., Lu, J., Trastuzumab in the adjuvant treatment of HER2-positive early breast cancer patients: A meta-analysis of published randomized controlled trials, PLoS ONE [Electronic Resource]PLoS ONE, 6 (6) (no pagination), 2011	Populations outside scope/Data not presented separately for T1N0M0
Zhang, N., Niu, J., Zhang, Y., Buchholz, T. A., Elting, L. S., Hortobagyi, G. N., Giordano, S. H., Trastuzumab-related cardiotoxicity among older breast cancer patients, Journal of clinical oncology, 30, 135, 2012	Abstract >2 years old
Zhou, Q., Yin, W., Du, Y., Lu, J., For or against adjuvant trastuzumab for pT1a-bN0M0 breast cancer patients with HER2-positive tumors: a meta-analysis of published literatures, PLoS ONE [Electronic Resource], 9, e83646, 2014	Insufficient presentation of results - No new studies identified

HER2, human epidermal growth factor receptor 2

Economic studies

See Supplement 1: Health economics literature review for list of excluded economic studies.

Appendix L – Research recommendations

No research recommendation was made for this review question.