NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Pertuzumab in combination with trastuzumab and docetaxel for treating HER2-positive metastatic or locally recurrent unresectable breast cancer [ID523]

Committee Papers – Appraisal Committee Meeting 3 (08/02/17)

NICE National Institute for Health and Care Excellence

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SINGLE TECHNOLOGY APPRAISAL

Pertuzumab in combination with trastuzumab and docetaxel for treating HER2-positive metastatic or locally recurrent unresectable breast cancer [ID523]

Contents:

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technology appraisals

Submission template for the re-consideration of current CDF technologies under the new proposed CDF criteria

Perjeta®▼(pertuzumab) for HER2-positive metastatic or locally recurrent unresectable breast cancer [ID523]

Roche Products Ltd

11th November 2016

1 Introduction

1 All cancer drugs that were previously appraised by NICE and are currently funded through the current Cancer Drugs Fund (CDF) will be re-considered by NICE in line with Guide to the methods of technology appraisal (2013) and modifications to incorporate the proposed new CDF criteria outlined in the CDF consultation paper.

2 In order to allow for the transition of drugs currently in the CDF to take place before 31 March 2017, NICE needs to prepare for re-considering those drugs. This preparation is taking place in parallel with the consultation on the new CDF arrangements, without prejudging the outcome of that consultation. This content of this submission template is therefore provisional and may change if the proposed CDF arrangements are amended after the consultation. Companies will have the opportunity to change their evidence submissions to NICE if substantial changes are made to the proposals after the CDF consultation.

3 The scope for re-consideration remains the same as the final scope used for the published technology appraisal guidance.

4 The company evidence submission should focus on cost effectiveness analyses using a new patient access scheme, an amendment to the existing patient access scheme agreed with the Department of Health (see Appendix 5.1) or as a commercial access arrangement with NHS England (for a definition of commercial access arrangement please see the CDF consultation paper).

5 A new patient access scheme, an amendment to an existing patient access scheme, or a commercial access arrangement, must have been formally agreed with the relevant organisation (that is, the Department of Health for a patient access scheme or NHS England for a commercial access arrangement by the time the Appraisal Committee meets for the first Committee meeting.

6 Some details of patient access schemes or commercial access arrangements, submitted through the rapid re-consideration process, can be treated by NICE as commercial in confidence if the company requests this.

7 The cost-effectiveness analyses included in the company evidence submission must use the assumptions that determined the most plausible incremental cost-effectiveness ratio(s) as identified in the published guidance. If the published guidance refers to more than one plausible ICER, analyses relating to all plausible ICERs should be included in the submission.

8 Only in exceptional circumstances and with prior written agreement from NICE should new clinical evidence be included. New clinical evidence is acceptable only when it addresses uncertainties identified previously by the Appraisal Committee. Submission of new clinical evidence must not lead to structural changes in the company's cost-effectiveness model.

9 The submission should take account of the proposed changes to NICE's methods of technology appraisal set out in the CDF consultation paper, in particular those concerning the appraisal of life-extending products at the end of life.

2 Instructions for companies

If companies want the National Institute for Health and Care Excellence (NICE) to re-consider a NICE recommendation for a drug currently funded through the CDF, they should use this template.

The template contains the information NICE requires to assess the impact of a patient access scheme or commercial access agreement on the clinical and cost effectiveness of a technology, in the context of this re-consideration, and explains the way in the evidence should be presented. If you are unable to follow this format, you must state your reasons clearly. You should insert 'N/A' against sections that you do not consider relevant, and give a reason for this response.

In addition to the CDF consultation paper, please refer to the following documents when completing the template:

- 'Guide to the methods of technology appraisal'
- 'Specification for company submission of evidence' and
- Pharmaceutical Price Regulation Scheme 2014.

For further details on the technology appraisal process, please see NICE's 'Guide to the processes of technology appraisal'. The 'Specification for company submission of evidence' provides details on disclosure of information and equality issues.

Make the submission as brief and informative as possible. Only mark information as confidential when absolutely necessary. Sufficient information must be publicly available for stakeholders to comment on the full content of the technology appraisal, including details of the proposed patient access scheme or commercial access agreement. Send submissions electronically via NICE docs: https://appraisals.nice.org.uk.

Appendices may be used to include additional information that is considered relevant to the submission. Do not include information in the appendices that

has been requested in the template. Appendices should be clearly referenced in the main submission.

When making a submission, include:

- an updated version of the checklist of confidential information, if necessary
- an economic model with the patient access scheme or commercial access agreement incorporated, in accordance with the 'Guide to the methods of technology appraisal'.

3 Details of the patient access scheme/ commercial access agreement

3.1 Please give the name of the technology and the disease area to which the patient access scheme agreement applies.

Pertuzumab (brand name Perjeta)

The patient access scheme applies to the use of the medicine within its licensed indications for HER2 positive breast cancer ("use in combination with trastuzumab and docetaxel in adults with HER2-positive metastatic or locally recurrent unresectable breast cancer, who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease" or "use in combination with trastuzumab and chemotherapy for the neoadjuvant treatment of adult patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer at high risk of recurrence")

3.2 Please outline the rationale for developing the patient access scheme/ commercial access agreement.

NICE originally reviewed this product in its metastatic breast cancer indication in 2013, but were unable to release a Final Appraisal Determination due to the finding that it was not possible to set a price at which Perjeta would meet the acceptability criteria for cost effectiveness in the ERG's economic modelling. A discussion paper on this issue was subsequently published by the NICE Decision Support Unit (DSU).

The DSU report suggested that:

"…if the background care costs in the population defined in the scope were found to be too high to allow a life-extending treatment to be cost-effective despite being delivered for zero cost, the Committee may still wish to consider whether there are any legal or ethical reasons for recommending the

treatment despite the high ICER. This would be in line with NICE existing Social Value Judgement policy which describes the need to 'distribute health resources in the fairest way within society as a whole."

Given this Roche has been developing a pricing solution that would enable this technology to be judged cost effective by the NICE committee under the current appraisal. Currently Roche is able to offer a simple patient access scheme. The simple scheme was approved by the Department of Health on 21 October 2016 during the course of the appraisal of Pertuzumab for the neoadjuvant treatment of HER2-positive breast cancer [ID767]. The simple scheme becomes effective upon publication of positive NICE guidance. The FAD for ID767 was issued on 10th November and is positive, however remains confidential through to 17th November.

In our updated economic model the magnitude of the simple discount required to reach a £30,000 per QALY threshold makes this a commercially unstainable option. [redacted]

As such Roche had hoped to be able to combine this simple PAS with a (complex) commercial access agreement (CAA), but unfortunately at the time of this submission NHS England have not been able to approve this commercial scheme. We have however included the cost effectiveness results of this scheme in a separate document (Appendix 1).

3.3 Please describe the type of patient access scheme (as defined by the PPRS)/ commercial access agreement.

The currently approved patient access scheme is a simple discount scheme of [redacted]

The complex CAA offered to NHS England for Perjeta in this indication to NHS England comprises of the following:

[redacted]

- [redacted]

[redacted]

We would be happy to provide full details of the complex scheme if required.

3.4 Please provide specific details of the patient population to which the patient access scheme/ commercial access agreement applies. Does the scheme apply to the whole licensed population or only to a specific subgroup (for example, type of tumour, location of tumour)? In case of the latter, please state:

How is the subgroup defined?
If certain criteria have been used to select patients, why have these have been chosen?
How are the criteria measured and why have the measures been chosen?

The proposed patient access scheme will apply to the whole licensed population as defined in section 3.1

3.5 Please provide details of when the scheme/ commercial access agreement will apply to the population specified in 3.4. Is the scheme dependent on certain criteria, for example, degree of response, response by a certain time point, number of injections? If so:

Why have the criteria been chosen?
How are the criteria measured and why have the measures been chosen.

The simple patient access scheme will apply upon publication of positive NICE guidance for ID767. [redacted]

3.6 What proportion of the patient population (specified in 3.4) is expected to meet the patient access scheme/

commercial access agreement criteria (specified in 3.5)?

As a simple discount there are no criteria to be met, so the patient access scheme applies to the entire patient population.

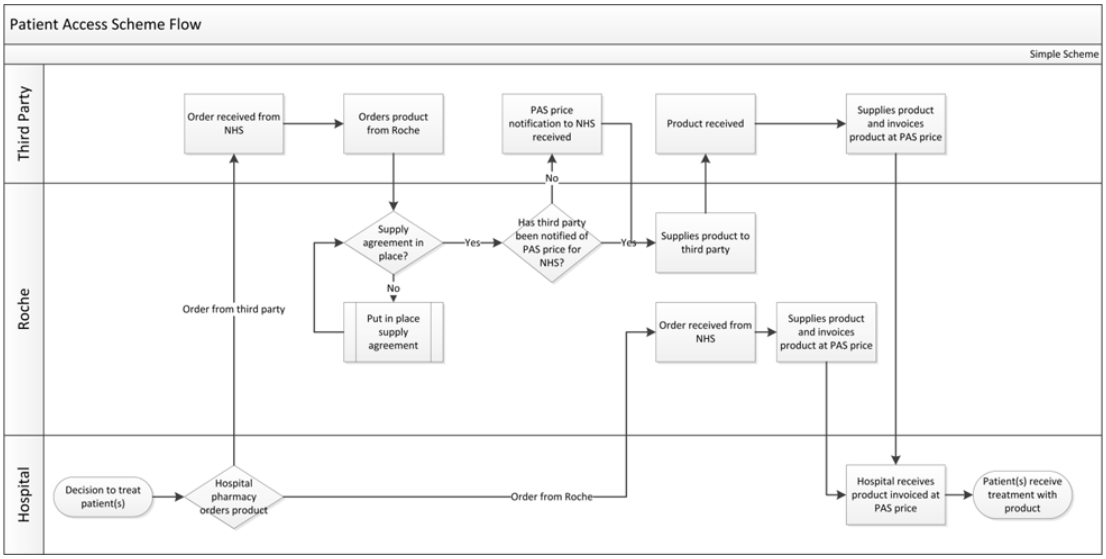
3.7 Please explain in detail the financial aspects of the patient access scheme/ commercial access agreement. How will any rebates be calculated and paid?

[redacted] *will be applied at the point of sale, with the NHS being invoiced at the discount price.*

3.8 Please provide details of how the patient access scheme/ commercial access agreement will be administered. Please specify whether any additional information will need to be collected, explaining when this will be done and by whom.

As a simple discount no additional information will be need to be collected.

3.9 Please provide a flow diagram that clearly shows how the patient access scheme/ commercial access agreement will operate. Any funding flows must be clearly demonstrated.



3.10 Please provide details of the duration of the patient access scheme/ commercial access agreement.

The scheme may be withdrawn or modified following a future NICE appraisal of Perjeta. Six months' notice would be given prior to withdrawal or amendment. We would contact the Department of Health prior to this and work with them in order to make the required changes to the scheme.

3.11 Are there any equity or equalities issues relating to the patient access scheme/ commercial access agreement, taking into account current legislation and, if applicable, any concerns identified during the course of the appraisal? If so, how have these been addressed?

An equalities assessment has been undertaken and no issues were identified.

3.12 If available, please list any patient access scheme/ commercial access agreement forms, patient registration forms, pharmacy claim forms/rebate forms,

guides for pharmacists and physicians and patient information documents. Please include copies in the appendices.

As a simple scheme there are no associated forms. Additionally the simple PAS has been approved by the Department of Health on 21st October 2016.

3.13 In the exceptional case that you are submitting an outcome-based scheme, as defined by the PPRS, please also refer to appendix 5.2.

Roche are not submitting an outcome based scheme and therefore this is not applicable.

4 Cost effectiveness

4.1 Please show the changes made to the original company base case to align with the assumptions that determined the most plausible incremental cost effectiveness ratio(s) as determined by the Appraisal Committee and presented in the published guidance. A suggested format is presented in table 1. **Error! Hyperlink reference not valid.**Provide sufficient detail about how the Appraisal Committee's preferred assumptions have been implemented in the economic model. Provide sufficient detail to allow the replication of the changes made to the original base case. For example, include sheet and cell references and state the old and new cell values. No other changes should be made to the model.

The ACD commented on two ICERs, the Roche ICER of [redacted] and the ERG ICER of [redacted]. It was noted that both ICERs are above the range normally considered cost effective. The Roche ICER was considered to be optimistic and the ERG ICER to be pessimistic. The most plausible ICER is not specified within the ACD.

It has been determined that under the NICE willingness to pay threshold of £30,000 per incremental QALY, Perjeta plus Herceptin and docetaxel is not cost effective at zero price, in the scenario favoured by the ERG. In the Roche analysis the level of discount required to achieve the £30,000 threshold is commercially unsustainable. The NICE Decision Support Unit was commissioned to investigate how this issue could be resolved; however the resulting report (July 2014) was unable to identify a solution. Since this time Roche has continued to engage with NICE, however a solution has not been forthcoming.

In the absence of a clear definition of the most plausible ICER, the following analyses are based on the Roche ICER of [redacted]

A summary of the adaptions made to the base case are summarised in the box below:

Please see below a summary of the updates that have been made to the original company base case:

Survival Modelling

- ***Updated clinical data has been used to model survival***

  Longer follow-up data for the addition of Perjeta to Herceptin + docetaxel in the first-line treatment of HER2-positive mBC are now available from the final analysis of the CLEOPATRA study.
  The main change is the use of clinical data from the most recent data cut-off of the CLEOPATRA study (11 February 2014; maximum follow-up duration 70 months) as opposed to the interim analysis (data cut-off 14 May 2012) that was used in the original submission.

- ***Parametric modelling of survival curves***

  As a result of longer-term survival data from CLEOPATRA, the extrapolations used in the new model are better-informed, giving more confidence in the resultant ICERs. The availability of longer-term PFS and OS estimates in particular have led to a change in the parametric functions used to extrapolate PFS and OS; the log-logistic and gamma functions, respectively, were found to fit the data best.

Costs

- ***Input costs***

  The following costs have been updated to reflect current costs: acquisition cost of docetaxel, the administration costs, supportive care costs and adverse event costs.

- ***Cost of Herceptin sub-cutaneous administration***

  In addition the cost of Herceptin when administered sub-cutaneously is now included in the analysis for the comparator arm.

- ***Adverse event (AE)***

  The way in which the frequency of AEs is calculated in the model has been amended

Utility values

- ***Utility values have been updated since the original submission***

Patient Access Scheme (PAS)

- ***The cost-effectiveness analysis has been updated to include a patient access scheme***

Guidance from NICE up until October 2016 was for Roche not make changes or introduce new data into the CDF transition appraisal, which we were happy to comply with. Communication from NICE in late October relaxed this requirement and therefore we are taking the opportunity to update the economic model with the latest data cut within this submission. Given the short timeframe within which to update our submission some aspects are aligned to a submission made to the SMC. Where this is the case it is discussed in the relevant section.

Details of the above changes are explained more fully below.

Clinical data

Longer-term data from the CLEOPATRA study to 11 February 2014 (maximum follow-up duration 70 months in the Perjeta arm and 69 months in the placebo arm) has been incorporated in the new economic model which provides further evidence for the sustained OS and PFS benefits of Perjeta (Swain et al.2015).

As highlighted in the clinical appendix, the addition of Perjeta to Herceptin + docetaxel significantly improved median OS by 15.7 months as compared to placebo + Herceptin + docetaxel (56.5 months versus 40.8 months; HR=0.68; 95% CI: 0.56–0.84; P<0.001).

Median PFS as assessed by investigators improved by 6.3 months in the Perjeta + Herceptin + docetaxel group compared to the placebo + Herceptin + docetaxel group (18.7 months versus 12.4 months; HR=0.68; 95% CI: 0.58–0.80; P<0.001).12

These longer follow-up data extend the results of previous analyses and confirm the efficacy of this drug combination. Please see the clinical appendix for more detail on the 11 February 2014 data cut.

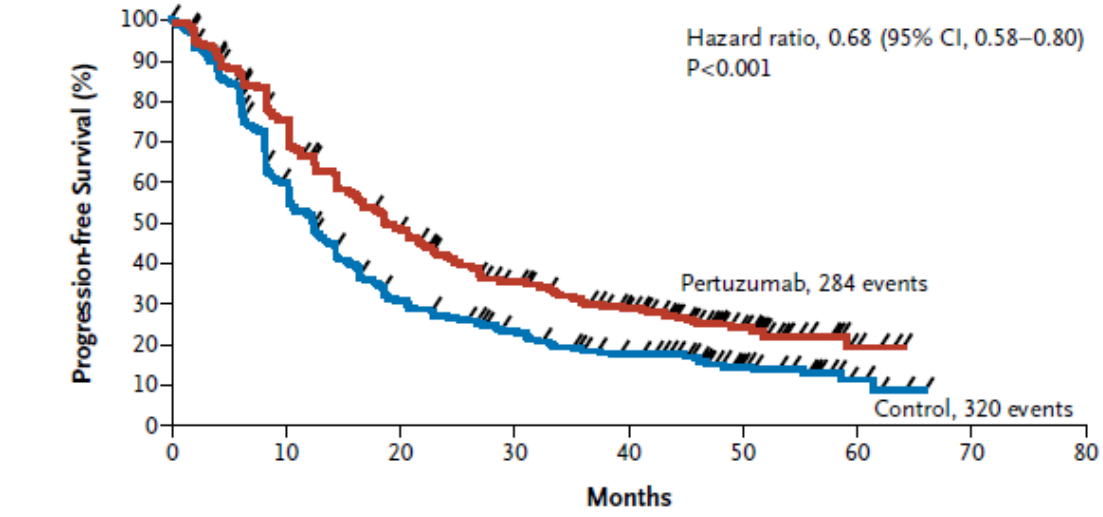
Progression-free Survival

The proportion of patients in the PFS health state was derived using the hazard rates observed in the Perjeta + Herceptin + docetaxel and placebo + Herceptin + docetaxel arms of the CLEOPATRA trial. The model was developed using the 11 February 2014 cut-off of the CLEOPATRA data (maximum follow-up duration 70 months in the Perjeta + Herceptin + docetaxel arm and 69 months in the placebo + Herceptin + docetaxel arm). This data cut-off features investigator-assessed PFS.

As shown in Section 3 (Figure 1), the addition of Perjeta to a regimen of Herceptin + docetaxel resulted in an increase of median PFS of 6.3 months

(18.7 versus 12.4) in previously untreated HER2-positive mBC patients, which was a statistically significant improvement (HR=0.68; 95% CI: 0.58–0.80; P<0.001) compared to placebo + Herceptin + docetaxel (Swain et al. 2015). The data used to inform the model were ***not adjusted*** *for crossover.*

Figure 1: Investigator-assessed PFS in the CLEOPATRA study – final analysis (cut-off 11 February 2014)



No. at Risk									
Pertuzumab	402	284	179	121	87	37	6	0	0
Control	406	223	110	75	51	21	6	0	0

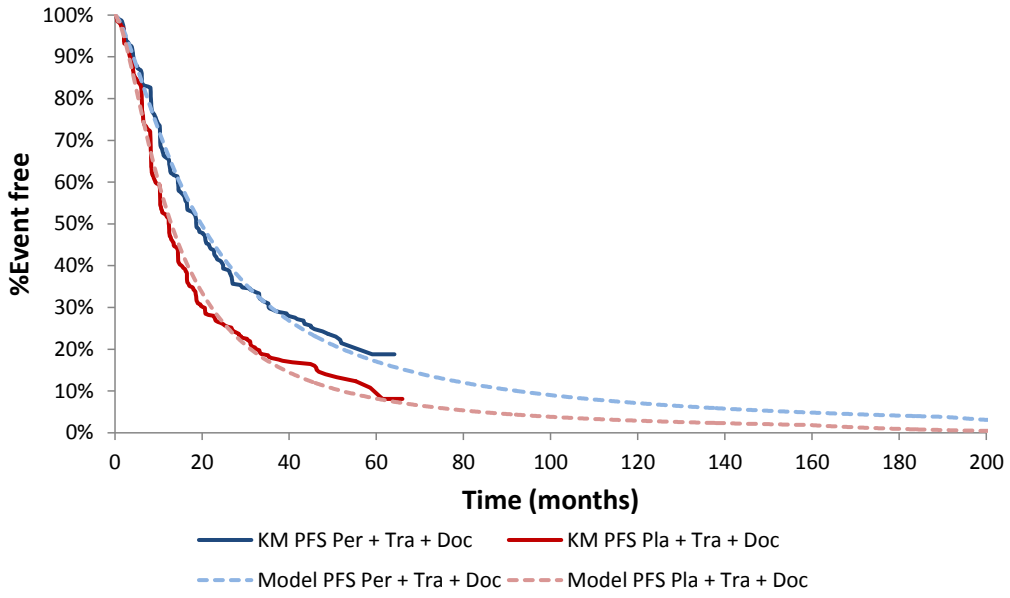
Extrapolation beyond the clinical follow-up period was performed by fitting a parametric distribution to the observed PFS times from the study period of the CLEOPATRA trial. This was done independently for each treatment arm (assuming independent shape). The Akaike information criterion (AIC) was used to assess the goodness of fit of each of the functions tested to model PFS.

Table 1 provides the AIC results for each of the functions used to model PFS. Based on visual examination and the AIC statistics, the log-logistic function was determined to be the best fit to the data for both treatment arms independently. Figure 2 shows the graphical assessment of the best fit parametric distribution (log-logistic) by treatment arm. Alternative parametric fits were tested in sensitivity analyses.

Table 1: Goodness of fit (AIC) for parametric functions of PFS

Parametric Model (PFS)	***AIC Perjeta + Herceptin + docetaxel arm***	***AIC placebo + Herceptin + docetaxel arm***
Weibull	*1,137.4*	*1,168.9*
Exponential	*1,136.0*	*1,167.3*
Log-logistic	***1,112.7***	***1,118.9***
LogNormal	*1,115.9*	*1,130.3*
Gamma	*1,117.3*	*1,132.0*
Gompertz	*1,138.0*	*1,169.3*
Abbreviations: AIC, Akaike information criterion; PFS, progression-free survival.		

Figure 2: Investigator-assessed PFS from CLEOPATRA modelled with log-logistic distribution



Abbreviations: Doc, docetaxel; KM, Kaplan-Meier; Per, Perjeta; Pla, placebo; Tra, Trastuzumab (Herceptin).

Overall Survival

The model used OS data from the final data cut-off of 11 February 2014 of the CLEOPATRA trial, in which median OS was reached in both arms. This final analysis of OS was ***not adjusted*** *for crossover of patients from the control to the Perjeta group and is therefore conservative. As shown in Table 1 in the clinical appendix, at the final data cut-off 41.8% of the patients in the Perjeta + Herceptin + docetaxel arm and 54.4% of patients in the placebo + Herceptin + docetaxel arm had died (Swain et al. 2015).*

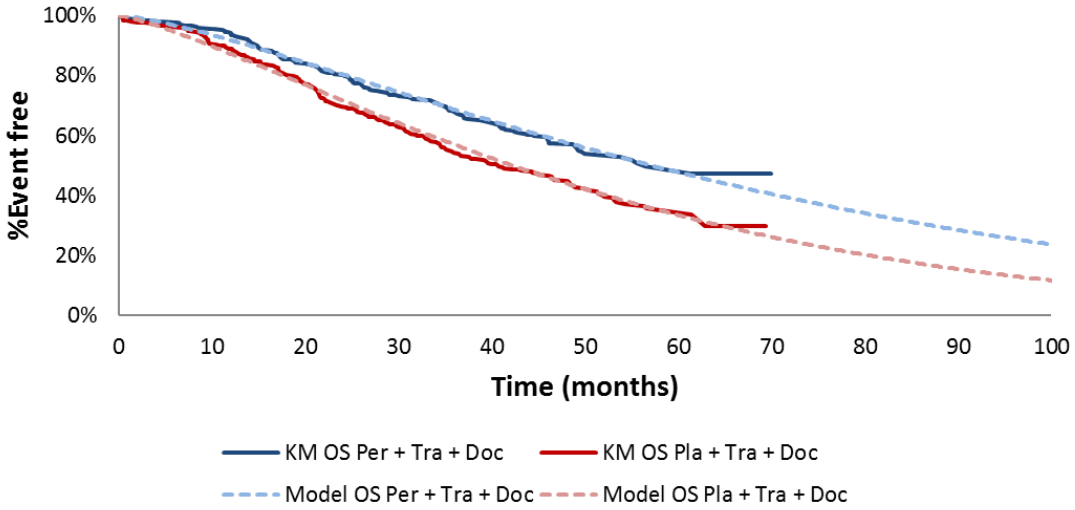
Regarding PFS, parametric functions for OS were assessed for their goodness of fit to the data using AIC, graphical assessment of each parametric function and knowledge of the expected extrapolation of the PFS times. This was done independently for each treatment arm. Based on assessment via visual examination and the AIC statistics (Table 2), the gamma function was determined to be the best fit to the data for both treatment arms, under the assumption of independent shape. Figure 3 displays the graphical assessment of the best fit parametric distribution by treatment arm. Alternative parametric fits were tested in sensitivity analyses.

Table 2: Goodness of fit (AIC) for parametric functions of OS

Parametric Model (OS)	***AIC Perjeta + Herceptin + docetaxel arm***	***AIC placebo + Herceptin + docetaxel arm***
Weibull	*809.01*	*939.01*
Exponential	*822.74*	*953.79*
Log-logistic	*808.54*	*941.51*
LogNormal	*827.91*	*973.04*
Gamma	***810.95***	***940.98***
Gompertz	*814.15*	*943.58*

Abbreviations: AIC, Akaike information criterion; OS, overall survival

Figure 3: OS from CLEOPATRA modelled with gamma distribution



Abbreviations: Doc, docetaxel; KM, Kaplan-Meier; OS, overall survival; Per, Perjeta; Pla, placebo; Tra, Trastuzumab (Herceptin).

Summary of costs used in the model

Perjeta

Perjeta can be purchased in a 420 mg vial for £2,395. This equates to a cost of £4,790 for the initial dose, followed by £2,395 for subsequent doses (BNF 2016).

When the patient access scheme is applied ([redacted] discount on invoice for Perjeta) is taken into account the cost of a 420mg vial is [redacted]. This equates to a [redacted] for the initial dose, followed by [redacted] for the subsequent doses.

Herceptin

Herceptin can be purchased as a powder for solution for infusion (150 mg vial = £407.40) (BNF 2016). The cost of Herceptin IV in the model was based on the distribution of body weight of participants in the CLEOPATRA trial (instead

of using an average body weight of participants in the trial). Based on the distribution of body weights (mean patient weight 66.59 kg), the mean initial dose of Herceptin was 532.75 mg, and the mean maintenance dose of Herceptin was 399.56 mg. Thus, the mean number of vials was 4.02 x 150 mg for the initial dose, and 3.15 x 150 mg for subsequent doses (if assumed that no vial sharing took place). The mean per protocol per cycle cost of treatment with Herceptin, including consideration of wastage and based on the distribution of patient weight, was £1,638.17 for the initial dose and £1,284.72 for the maintenance dose.

Alternatively, Herceptin is available as a solution for injection (600 mg vial = £1,222.20) (BNF 2016). Herceptin SC cannot be used in combination with Perjeta, therefore is only relevant to the comparator arms of the model (ie. Herceptin + docetaxel or paclitaxel). In the mBC setting, the market share for Herceptin SC is approximately [redacted] and a discount applied on invoice reduces the price per 600 mg vial to [redacted] (Roche DoF Sept 2016).

Docetaxel

As docetaxel is a generic drug, the base case applies acquisition costs of docetaxel obtained from the Commercial Medicines Unit electronic market information tool (CMU eMIT) (DoH eMIT 2016). The CMU eMIT is an online source of information on the historical average price paid for a product. The estimates provided are derived from data collected via a system covering approximately 95% of English NHS Trusts.

The average cost of the 80 mg vial size of docetaxel obtained from CMU eMIT was £12.47 (National Product Code – DHC029) and the average cost of the 20 mg vial size was £4.92 (National Product Code – DHC025) (DoH eMIT 2016). Thus, the mean per protocol per cycle cost of treatment with docetaxel, based on the distribution of patient body surface area, was £25.09.

The impact on the ICER of applying acquisition costs of docetaxel obtained from the Joint Formulary Committee was explored in the sensitivity analysis.

Administration and Pharmacy Costs

There is a cost associated with both the pharmacy preparation of the infusion and the administration of the technologies (typically within a hospital setting). The administration cost of the first cycle for each technology was based on English NHS Reference Costs (Chemotherapy [SB13Z]: Deliver more complex parenteral chemotherapy at first attendance, day case and regular day / night; £329) (DoH reference costs 2016). It was assumed that all technologies were administered under the same English NHS Reference cost code for subsequent cycles. The administration cost of subsequent cycles was obtained from English NHS Reference Costs (Chemotherapy [SB15Z]: Deliver subsequent elements of a chemotherapy cycle, day case and regular day / night; £362) (DoH reference costs 2016).

One hour of pharmacist time performing patient-related activities (accounting for overheads, qualifications, and salary on costs) costs £72 (PSSRU 2016). The cost of dispensing treatments in the economic model was estimated to be £18 (£72 x 15 / 60) per IV administration, based on 15 minutes of pharmacist preparation time. A discount of 60% was assumed for subcutaneous administration costs compared to IV administration costs.

Post-progression Treatments

Due to the short timeframe to update the economic model the post progression costs included in the model are based on Scottish treatment pathway. We believe that in England second line treatment are the same as included in the submission for Perjeta for the neoadjuvant treatment of HER2-positive breast cancer [ID767]. That is 7% would receive Herceptin in combination with Capecitabine, 27% PHD, 50% Kadcyla and 4% Lapatinib in combination with Capecitabine. Sensitivity analysis is provided in section 4.8 to see the impact of changing the cost of post-progressions treatment costs.

Given that the treatments above are more expensive than vinorelbine or Capecitabine monotherapy the current costs in the economic model are an underestimate. This means that the overall cost effectiveness estimates are

slightly conservative as people in the control arm progress to second line treatments earlier.

As shown in the sensitivity analysis and the fact that excluding treatments such as Herceptin and Kadcyla makes estimates slightly more conservative we feel that this is a second order issue.

The NICE guidance document "Handling of products on Cancer Drugs Fund as of 1 April 2016 as comparator, or in a treatment sequence, in the appraisal of a new cancer product" issued on 2nd June 2016, stipulates that "Companies are encouraged to present a case for cost effectiveness that mitigates the risk of recommendations for their new cancer product being reviewed if CDF products are no longer widely available after the CDF reviews have concluded". Given this guidance and that Kadcyla (trastuzumab emtansine) is currently undergoing re-evaluation by NICE as part of the CDF transition process it is thought that including this in the model may be of concern to the committee. Additionally any improvement in the ICER from including Kadcyla would need to be mitigated with a risk mitigation scheme (PAS), we therefore took the decision to not include it in the economic model.

Post-progression treatments applied in the model were vinorelbine and capecitabine, based on clinical opinion of Scottish clinicians. As vinorelbine is a generic drug, acquisition costs of vinorelbine were obtained from the CMU eMIT: the average price per mg of vinorelbine, weighted by use, was £0.39 per mg (National Product Codes – DHA220, DHA221, DHA288, DHA289) (DoH eMIT 2016).

The model estimated the cost of vinorelbine by applying a weekly dose of 25 mg/m^2 body surface area. The price per mg of vinorelbine was then multiplied by the average body surface area (calculated using the Du Bois formula) of participants in the CLEOPATRA trial. As vinorelbine is intravenously administered, administration costs were the same as those for intravenously-administered first line treatments in the model.

The model applied a three-week treatment cycle for capecitabine: 1,250 mg/m^2 body surface area given twice daily for 14 days, followed by a 7-day

treatment gap. Capecitabine was included in the model as 150 mg tablets, priced at £7.73 for a 60 tab pack (National Product Code – DHA224) (DoH eMIT 2016). Thus, the average cost per 150 mg tablet was £0.13 (£7.73 / 60). Administration costs for capecitabine were £6 (£72 x 5 / 60), based on 5 minutes of pharmacist preparation time for an oral administration, and the same hourly pharmacist cost as first line treatments (PSSRU 2016).

Health State Costs

As the model had a weekly cycle length, monthly costs were split into weekly costs prior to being applied in the model (Table). Best supportive care costs were based on a package of care described in NICE CG81 (NICE CG81).

Table 3: List of health states and associated costs

Health state	**Item**	**Frequency**	**Unit cost**	**Total weekly cost**
PFS best supportive care	*Community Nurse (home visit)*	*20 mins every 2 weeks*	*£67 / hour*[i]	*£11.17*
	GP contact (surgery visit)	*1 every month*	*£44 / patient contact (11.7 mins)* [i]	*£10.12*
	Clinical Nurse specialist	*1 hr every month*	*£91 / hour of client contact*[i]	*£20.93*
	Total cost	***-***	***-***	***£42.21***
	Social Worker	*1 hour once*	*£95 (client-related work)* [i]	*-*
	Cardiac assessment	*1 every 3 months*	*192.12 / 81.48*[ii] *(30%/70%)=£114.69*	*-*

	(MUGA/ECHO)			
	Outpatient CT scan	*1 scan once*	*£120.92* [ii]	*-*
	Consultant outpatient visit	*1 visit once*	*£138.37* [ii]	*-*
Post-progression survival best supportive care	*Community Nurse (home visit)*	*20 mins every 2 weeks*	*£67 / hour* [i]	*£11.17*
	GP contact (surgery visit)	*1 every month*	*£44 / patient contact (11.7 minutes)* [i]	*£10.12*
	Clinical Nurse specialist	*1 hour every month*	*£91 / hour of client contact* [i]	*£20.93*
	Total cost	***-***	***-***	***£42.21***
End of life care cost	*£3,702.16*			

Abbreviations: CT, computerised tomography; ECHO, echocardiography; GP, general practitioner; MUGA, multigated acquisition; PFS, progression-free survival.

Reference

[i] PSSRU 2016

[ii] DoH reference cost 2016

In order to assess response to treatment, outpatient visits and CT scans were applied in the model. In clinical trials a CT scan is typically conducted every three months to assess whether a patient's disease has progressed. Clinical advice from clinicians at the time of the original submission in 2014 confirms that frequency of assessing treatment with a CT scan (and an associated outpatient visit) varies across England and Wales. In light of this and the

assumptions made in previous NICE appraisals, the model applies a conservative estimate of a CT scan and outpatient visit every three months during treatment.

A CT scan in the model was associated with a cost of £120.92 (All NHS trusts and NHS foundation trusts - HRG Data [RD24Z]: Computerised Tomography scan of two areas with contrast) and the cost of an outpatient visit was £138.37 (All NHS trusts and NHS foundation trusts - Outpatient Attendances Data [service code 800]: Clinical Oncology (Previously Radiotherapy) Consultant Led) (DoH reference cost 2016). The impact on the ICER of applying alternative frequencies of CT scan and outpatient visits was explored in sensitivity analyses.

An additional cost of cardiac assessment was applied during the progression-free health state. These assessments were applied every nine months in the Perjeta + Herceptin + docetaxel arm and every 12 months in the Herceptin + docetaxel arm, as specified in the licensed indications for these technologies. The cost of cardiac assessments were applied as a weighted average of 30% MUGA scan (NHS trusts and NHS foundation trusts - Diagnostic Imaging [RN22Z]: Outpatient MUGA scan, £192.12) and 70% ECHO scan (NHS trusts and NHS foundation trusts - HRG Data [RD51A]: Simple Echocardiogram, 19 years and over, £81.48) (DoH reference cost 2016). This was based on clinical specialist advice to the Evidence Review Group in NICE MTA TA257 (NICE TA257). The impact on the ICER of applying alternative frequencies of cardiac assessments, and of alternative proportions of MUGA and ECHO scans, was explored in sensitivity analyses.

The cost of palliative care was included within the model through application of costs from Guest et al (2006). Guest et al. examined the treatment patterns and corresponding costs of healthcare resource use associated with palliative care for patients with different types of advanced cancer; from initiation of strong opioid treatment until death. Resource utilisation data associated with palliative care were obtained from the DIN-LINK database, an anonymised database of individual primary care records in the UK, from general practices

that use a health information systems software program (iSOFT, formerly Torex; iSOFT Group, plc, Manchester, UK). Palliative care costs for breast cancer were estimated to be £2,482 per patient using costs from 2000–2001 (Guest 2006). This cost was inflated to current prices (£3,702.16) using inflation indices for Hospital and Community Health Services (PSSRU 2016). The cost of palliative care cost was applied as one lump sum upon death in the model.

Adverse Event Costs

Only AEs occurring in 2% or more patients in either arm of the CLEOPATRA trial at grade 3, 4 or 5 severity were incorporated into the model. The occurrence of the relevant AEs was modelled as follows: the frequency of treatment-related AEs that occurred between the start of study drug and 28 days following the last first-line dose inclusively, and the number of patients experiencing the AEs, were obtained from the CLEOPATRA study at the time of the last data cut-off (11 February 2014). However, as AEs are likely to occur for the entire time patients are exposed to the study medications, to more accurately account for the continual occurrence of these events, the associated costs were applied for the duration of time in which patients were considered to be on treatment (as determined by the TTOT scenario). The total number of events for each specific AE was divided by the total amount of follow-up for all patients for the period of time in which treatment-related AEs could occur. This probability was then multiplied by the average cost per event to derive a total cost per patient week.

In all instances the most recent English NHS reference costs were used in the model (DoH reference costs). Given that AEs typically occur during the beginning of treatment, the costs of AEs were applied in week one in the model and so were not discounted. It was assumed that treatment regimens of Herceptin + docetaxel and Herceptin + paclitaxel had the same toxicity profile. This likely overestimates the AE incidence and costs associated with paclitaxel, given that clinical specialist opinion indicates that weekly paclitaxel is slightly better tolerated than three-weekly docetaxel, as discussed in Section 5. The impact on the ICER of assuming a lower incidence of AEs for

treatment with paclitaxel was explored in the sensitivity analysis by reducing the incidence of AEs by 50%. The costs associated with AEs that occur in 2% or more patients in either arm of the CLEOPATRA trial at grade 3, 4 or 5 severity that have been incorporated into the model and are outlined in Table 4.

Table 4: AEs and costs included in the economic model

AEs	*% patients in Perjeta + Herceptin + docetaxel arm*	*% patients in placebo + Herceptin + docetaxel arm*	*Most likely cost per episode (£)*	*Source (English NHS reference cost 2014/15 unless stated otherwise)*
Anaemia (Grade 3)	*1.99*	*2.22*	*405.47*	*All NHS trusts and NHS foundation trusts - HRG Data [SA04L]: Iron Deficiency Anaemia with CC score 0–1 (total)*[i]
Diarrhoea (Grade 3)	*6.72*	*3.45*	*431.07*	*All NHS trusts and NHS foundation trusts - HRG Data [JA12L]: Malignant Breast Disorders [without interventions], with CC score 0–1 (total)*[i]
Fatigue (Grade 3)	*1.49*	*2.71*	*431.07*	*All NHS trusts and NHS foundation trusts - HRG Data [JA12L]: Malignant Breast Disorders [without interventions], with CC score 0–1 (total)*[i]
Febrile Neutropenia (Grade 3 and 4)	*13.43*	*7.14*	*8,836.87*	*All NHS trusts and NHS foundation trusts - HRG Data [PA45Z]: Febrile Neutropenia with Malignancy (Elective Inpatient) (2012-13; £8,662 inflated to current prices using inflation indices for PSSRU)*[ii, iii]
Neutropenia (Grade 3 and 4)	*62.19*	*58.13*	*124.57*	*All NHS trusts and NHS foundation trusts - High Cost Drugs [XD25Z]: Neutropenia Drugs, Band 1 (outpatients)*[i]
Peripheral Neuropathy (Grade 3)	*2.49*	*1.72*	*431.07*	*All NHS trusts and NHS foundation trusts - HRG Data [JA12L]: Malignant Breast Disorders [without interventions], with CC score 0–1 (total)*[i]
Leukopenia (Grade 3)	*10.20*	*12.56*	*124.57*	*NHS trusts and NHS foundation trusts - High Cost Drugs [XD25Z]: Neutropenia Drugs, Band 1 (outpatients)*[i]

References
[i] DoH reference costs 2014-2016
[ii] PSSRU 2016
[iii] DoH reference costs 2012-2013

Utility Values

The utility values have been changed since the original submission. While the source remains the same, Lloyd (2006), the values themselves have changed. In the original submission the ERG highlighted some errors in the method of calculation which may have biased the utility results in favour of Perjeta.

Specifically, the ERG states "patient frequencies (proportions) for AEs have been used in the calculation of utility values instead of binary figures (0 or 1). This is inaccurate in a logistic model where estimates should be obtained separately for the states with and without each AE, and the results subjected to weighted averaging outside of the mixed model". This error has been corrected in the new economic model.

The Utility values used in the new model are show in table 5 below.

***Table 5:** Utility values in model*

Health state	*Utility value*
PFS PTD (under docetaxel)	*0.792*
PFS TD (under docetaxel)	*0.793*
PFS PTD (after docetaxel)	*0.810*
PFS TD (after docetaxel)	*0.802*
Progression health state	*0.535*
Abbreviations: PFS, progression-free survival; PTD, Perjeta + Herceptin + docetaxel; TD, Herceptin + docetaxel; TP, Herceptin + paclitaxel.	

'End-of-Life' Criteria

In addition to the changes highlighted above we would like the committee to consider Perjeta under the end of life criteria. The rationale for this is provided below.

Key points

- *The combination of Perjeta and Herceptin offers a dramatic median extension to life of >15 months compared to Herceptin and docetaxel, which far exceeds the extension to life of 3 months specified by the end-of-life criteria.*
- *As such, assessment of Perjeta according to the end-of-life criteria should be considered in light of such a dramatic improvement in OS in a condition with a comparatively poor prognosis.*
- *The life expectancy of HER2+ mBC patients treated with chemotherapy alone in the first line is less than 2 years.*

Given the poor prognosis and clinical and patient burden of HER2-positive mBC and the unprecedented survival benefit above the existing 3 month end-of-life threshold that is offered by Perjeta in this indication, as compared to the SOC, we feel there is sufficient evidence for the Committee to consider Perjeta in its licenced indication as meeting the end-of-life criteria.

The first randomised controlled trial assessing Herceptin in combination with chemotherapy reported a median overall survival of 25.1 months (Slamon et al. 2001, Mendes et al. 2015). Subsequently systematic review has reported OS ranging from 28.9 (95% CI [NR]) to 37.1(95% CI [32.6, 43.6]) months for patients receiving first-line treatment with Herceptin plus paclitaxel or docetaxel respectively (Valero et al. 2011, Baselga et al. 2014, Mendes et al. 2015).

In addition, a retrospective analysis of patients who had received first-line Herceptin-containing therapy at a single centre in the UK found the median OS to be 2.6 years (95% CI [2.2, 3.3]) (Yeo et al. 2015).

It should be noted, however, that despite the significant improvements in life expectancy that have resulted from the introduction of Herceptin, ~50% of patients will have died at 3 years following diagnosis with metastatic disease (Clarke et al. 2014). Therefore, despite treatment advances including the introduction of Perjeta, the clinical and patient burden of HER2-positive mBC is significant; the removal of access to Perjeta would further exacerbate this burden, not only for patients but society as a whole.

Recently a published systematic review of Phase III studies reported median OS ranging from 20.3 (95% CI [NR]) to 20.5 months (95% CI [NR]) for HER2+ first-line mBC patients treated with chemotherapy alone (Mendes et al. 2015). This clearly indicates that HER2+ mBC has the life expectancy of an end-of-life condition in the first-line when treated with chemotherapy alone.

The total median OS observed in first-line HER2+ mBC patients receiving Perjeta in addition to Herceptin and Docetaxel was 56.5 months (Swain et al. 2015). These results demonstrate that adding the combination of Perjeta and Herceptin to chemotherapy represents a survival benefit of 15.7 months over Herceptin and docetaxel and suggest a benefit over 2 years compared to chemotherapy alone.

Considering all these data it is clear that the most efficacious option for the treatment of HER2+ mBC in the first-line is the combination Perjeta, Herceptin and docetaxel, which offer the significant benefit in a condition where the life-expectancy is poor.

We acknowledge that the life expectancy of patients receiving a first-line treatment for mBC now exceeds 24 months when treated with the most relevant comparator for Perjeta, Herceptin plus taxane which currently precludes Perjeta being considered under the strict end-of-life criteria.

However the extension to survival of over 15 months that PHD offers compared to HD, which significantly exceeds the required 3 months, has substantial impact on patients and is of prime importance to patients, their families and wider-society. Therefore, an appropriate weighting to the end-of-

life criteria should be considered when assessing such a dramatic increase in life expectancy.

4.2 If the population to whom the patient access scheme/ commercial access agreement applies (as described in sections 3.4 and 3.5) is not the same as that in the published technology appraisal (for example, the population is different as there has been a change in clinical outcomes or a new continuation rule), please (re-)submit the relevant sections from the 'Specification for company submission of evidence' (particularly sections 5.5, 6.7 and 6.9). You should complete those sections both with and without the patient access scheme/ commercial access agreement. You must also complete the rest of this template.

The population that the approved simple patient access scheme relates to is as defined in section 3.1 and is the same as considered by NICE in the ACD.

4.3 Please provide a summary of the clinical effectiveness parameters (resulting from the Committee's preferred evidence synthesis) which are used in the economic model which includes the patient access scheme/ commercial access agreement.

Changes to clinical parameters are highlighted in section 4.1.

4.4 Please list any costs associated with the implementation and operation of the patient access scheme/ commercial access agreement (for example, additional pharmacy time for stock management or rebate calculations). A suggested format is presented in table 2. Please give the reference source of these costs. Please provide sufficient detail to allow the replication of changes made to the original base case.

For example, include sheet and cell references and state the old and new cell values. Please refer to section 6.5 of the 'Specification for company submission of evidence'

As a simple patient access scheme there are no costs associated with the implementation or operation of the scheme.

4.5 Please provide details of any additional treatment-related costs incurred by implementing the patient access scheme/ commercial access agreement. A suggested format is presented in table 3. The costs should be provided for the intervention both with and without the patient access scheme. Please give the reference source of these costs.

There are no additional treatment related costs associated with implementing the commercial access agreement. Table 3 is therefore not completed.

***Table 3** Additional treatment-related costs for the intervention both with and without the patient access scheme (PAS)/ commercial access agreement (CAA)*

	Intervention without PAS/ CAA		*Intervention with PAS/ CAA*		*Reference source*
	Unit cost (£)	*Total cost e.g. per cycle, per patient (£)*	*Unit cost (£)*	*Total cost e.g. per cycle, per patient (£)*	
Interventions	-	-	-	-	-
Monitoring tests	-	-	-	-	-
Diagnostic tests	-	-	-	-	-
Appointments	-	-	-	-	-
Other costs…	-	-	-	-	-
Total treatment-related costs	-	-	-	-	-

Summary results

New base-case analysis

4.6 Please present in separate tables the cost-effectiveness results as follows.[1]

the results for the intervention without any (new) patient access scheme/ commercial access agreement; that is with the price for the technology considered in the published guidance.
the results for the intervention with the patient access scheme/ commercial access agreement.

A suggested format is shown below (table 4).

[1] For outcome-based schemes, please see section 5.2.8 in appendix B.

The results below show the cost-effectiveness at list price and the price accounting for the simple PAS. Please be advised that improved cost-effectiveness results which include the CAA are provided in a separate document (appendix 1).

***Table 4a** New base-case cost-effectiveness results using the price as in the published technology appraisal*

	Perjeta, Herceptin and docetaxel	**Herceptin and docetaxel**
Intervention cost (£)	[redacted]	[redacted]
Other costs (£)	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]
Difference in total costs (£)	[redacted]	[redacted]
LYG	[redacted]	[redacted]
LYG difference	[redacted]	[redacted]
QALYs	[redacted]	[redacted]
QALY difference	[redacted]	[redacted]
ICER (£)	[redacted]	[redacted]

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

Table 4b *New base-case cost-effectiveness results using the patient access scheme*

	Perjeta, Herceptin and docetaxel	*Herceptin and docetaxel*
Intervention cost (£)	[redacted]	[redacted]
Other costs (£)	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]
Difference in total costs (£)	[redacted]	[redacted]
LYG	[redacted]	[redacted]
LYG difference	[redacted]	[redacted]
QALYs	[redacted]	[redacted]
QALY difference	[redacted]	[redacted]
ICER (£)	[redacted]	[redacted]

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

4.7 Please present in separate tables the incremental results as follows. [2]

The results for the intervention without the (new) patient access scheme/ commercial access agreement, that is with the price for the technology considered in the published appraisal.
the results for the intervention with the patient access scheme/ commercial access agreement.

List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental analysis ranking technologies in terms of

[2] For outcome-based schemes, please see section 5.3.9 in appendix 5.3.

dominance and extended dominance. A suggested format is presented in table 5.

Table 5a *New base-case incremental results using the price as in the published technology appraisal*

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Herceptin and docetaxel	[redacted]							
Perjeta, Herceptin and docetaxel	[redacted]							

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

Table 5b *New base-case incremental results using the patient access scheme*

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Herceptin and docetaxel	[redacted]							
Perjeta, Herceptin and docetaxel	[redacted]							

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

Sensitivity analyses with the relevant PAS/CAA

4.8 Please refer to the published guidance to identify the key sensitivity and scenario analyses (that is, analyses that were discussed in the 'considerations' section and which alter the ICER). Present the results of these sensitivity and scenario analyses **with** the patient access scheme/ commercial access agreement.

The ACD notes that the economic analysis is sensitive to the long term projection of overall survival. The results of re-running the sensitivity analysis with the patient access scheme are shown below.

The extrapolation of OS provides the widest range of ICERS, ranging from [redacted].

***Table 6a**: Sensitivity analysis for projection of overall survival*

Parametric functions			
Progression Free Survival	*Log logistic*	*Weibull*	[redacted]
		Exponential	[redacted]
		Log normal	[redacted]
		Gamma	[redacted]
		Kaplan-Meier with (non-piecewise) tail	
		Weibull	[redacted]
		Exponential	[redacted]
		Log normal	[redacted]
		Gamma	[redacted]
		Log logistic	[redacted]
Overall survival	*Gamma*	*Weibull*	[redacted]
		Exponential	[redacted]
		Log normal	[redacted]
		Log Logistic	[redacted]
		Gompertz	[redacted]
		Kaplan-Meier with (non-piecewise) tail	
		Weibull	[redacted]
		Exponential	[redacted]
		Log-logistic	[redacted]
		Log normal	[redacted]
		Gamma	[redacted]
		Gompertz	[redacted]

As described in section 4.1 sensitivity analysis has been undertaken to assess the impact of including more expensive post progression treatment costs. Currently the total costs for second line treatment, which consists of drug and administration costs is £9,012. If this total cost is increased to £50,000 the ICER falls from [redacted] to [redacted]

4.9 Please present any probabilistic sensitivity analysis results, and include scatter plots and cost-effectiveness acceptability curves.

A 1000 iteration simulation was run. The results are shown below.

At a £30,000 willingness to pay threshold, there is [redacted] chance that Perjeta is cost effective.

At a £50,000 willingness to pay threshold, there is [redacted] chance that Perjeta is cost effective.

***Figure 1**: Incremental Cost-effectiveness plane*
GRAPH REDACTED

***Figure 2:** Cost -effectiveness acceptability curve*
GRAPH REDACTED

4.10 If any of the criteria on which the patient access scheme/ commercial access agreement depends is a clinical variable (for example, choice of response measure, level of response, duration of treatment), sensitivity analyses around the individual criteria should be provided, so that the Appraisal Committee can determine which criteria are the most appropriate to use.

As a simple discount there are no criteria (clinical or otherwise) upon which it depends.

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5 Appendices

5.1 Information about patient access schemes

5.1.1 The 2014 Pharmaceutical Price Regulation Scheme (PPRS) is a non-contractual scheme between the Department of Health and the Association of the British Pharmaceutical Industry. The purpose of the 2014 PPRS is to ensure that safe and cost-effective medicines are available on reasonable terms to the NHS in England and Wales. One of the features of the 2014 PPRS is to improve patients' access to medicines at prices that better reflect their value through patient access schemes.

5.1.2 Patient access schemes are arrangements which may be used on an exceptional basis for the acquisition of medicines for the NHS in England and Wales. Patient access schemes propose either a discount or rebate that may be linked to the number, type or response of patients, or a change in the list price of a medicine linked to the collection of new evidence (outcomes). These schemes help to improve the cost effectiveness of a medicine and therefore allow the National Institute for Health and Care Excellence (NICE) to recommend treatments which it would otherwise not have found to be cost effective. More information on the framework for patient access schemes is provided in the 2014 PPRS.

5.1.3 Patient access schemes are proposed by a pharmaceutical company and agreed with the Department of Health, with input from the Patient Access Schemes Liaison Unit (PASLU) within the Centre for Health Technology Evaluation at NICE.

5.2 Additional documents

5.2.1 If available, please include copies of patient access scheme agreement forms/ commercial access agreement, patient registration forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians, patient information documents.

5.3 Details of outcome-based schemes

5.3.1 If you are submitting a proven value: price increase scheme, as defined in the PPRS, please provide the following information:

the current price of the intervention
the proposed higher price of the intervention, which will be supported by the collection of new evidence

- a suggested date for when NICE should consider the additional evidence.

Not applicable

5.3.2 If you are submitting an expected value: rebate scheme, as defined in the PPRS, please provide the following details:

the current price of the intervention (the price that will be supported by the collection of new evidence)
the planned lower price of the intervention in the event that the additional evidence does not support the current price

- a suggested date for when NICE should consider the additional evidence.

Not applicable

5.3.3 If you are submitting a risk-sharing scheme, as defined in the PPRS, please provide the following details:

the current price of the intervention (the price that will be supported by the collection of new evidence)
the proposed relationship between future price changes and the evidence to be collected.

Not applicable

5.3.4 For outcome-based schemes, as defined in the PPRS, please provide the full details of the new information (evidence) planned to be collected, who will collect it and who will carry the cost associated with this planned data collection. Details of the new information (evidence) may include:

- design of the new study
- patient population of the new study
- outcomes of the new study
- expected duration of data collection
- planned statistical analysis, definition of study groups and reporting (including uncertainty)
- expected results of the new study
- planned evidence synthesis/pooling of data (if applicable)
    - expected results of the evidence synthesis/pooling of data (if applicable).

Not applicable

5.3.5 If you are submitting a risk-sharing scheme, please specify the period between the time points when the additional evidence will be considered.

Not applicable

5.3.6 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic modelling of the patient access scheme at the different time points when the additional evidence is to be considered.

Not applicable

5.3.7 Please provide the other data used in the economic modelling of the patient access scheme at the different

time points when the additional evidence is to be considered. These data could include cost/resource use, health-related quality of life and utilities.

Not applicable

5.3.8 Please present the cost-effectiveness results as follows.

For proven value: price increase schemes, please summarise in separate tables:

- the results based on current evidence and current price
- the anticipated results based on the expected new evidence and the proposed higher price.

For expected value: rebate schemes, please summarise in separate tables:

- the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)
- the results based on the current evidence and the lower price (if the new evidence is not forthcoming).

For risk-sharing schemes, please summarise in separate tables:

- the results based on current evidence and current price
- the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)
- the results based on the current evidence and the lower price (if the new evidence is not forthcoming)
- the anticipated results based on the expected new evidence and the proposed higher price.

A suggested format is shown in table 3, section 4.7.

Not applicable

5.3.9 Please present in separate tables the incremental results for the different scenarios as described above in section 5.2.8 for the type of outcome-based scheme being submitted.

List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental analysis ranking technologies in terms of dominance and extended dominance. A suggested format is presented in table 4, section 4.8.

Not applicable

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appendix

CDF rapid reconsideration process: Breast cancer (HER2 positive, metastatic) – pertuzumab (Perjeta®▼) (with trastuzumab and docetaxel) [ID523]

26th February 2016

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1. Executive Summary

Human epidermal growth factor receptor 2 (HER2) positive disease accounts for 15–20% of all breast cancers and has a poorer prognosis compared to other breast cancers when diagnosed (Wolff et al. 2013). HER2-targeted treatments, such as pertuzumab (Perjeta®▼), have revolutionised outcomes for these patients, with prognosis now similar between patients with HER2-positive and HER2-negative disease (Dawood et al. 2010, Clarke et al. 2014). Since becoming available through the Cancer Drugs Fund (CDF) in April 2013, Perjeta in combination with trastuzumab (Herceptin®) and chemotherapy has become the standard-of-care (SOC) for the first-line treatment of patients with HER2-positive metastatic breast cancer (mBC) (Cancer Drugs Fund 2013, Cardoso et al. 2014, Giordano et al. 2014). Consistent with this, market share data confirms that the majority of patients receiving first-line therapy for mBC are on a Perjeta-based regimen, and therefore currently experiencing the benefit of this development in the treatment of HER2-positive metastatic disease (Roche Data on File 2015).

The addition of Perjeta to Herceptin and docetaxel in the first-line treatment of HER2-positive mBC has been studied in the large, multinational, Phase III, randomised controlled trial, the CLEOPATRA study (Baselga et al. 2012). The benefit of the addition of Perjeta was reported in the primary analysis of the study with a clinical data cut-off of 13th May 2011 and the second interim analysis with a data cut-off of 14th May 2012 (Baselga et al. 2012, Swain et al. 2013). These data formed the basis of the NICE STA submission for Perjeta (April 2013 [ID523]) (NICE 2013). Subsequently, Perjeta in combination with Herceptin and chemotherapy has become the recommended treatment strategy for the first-line treatment of HER2-positive mBC (Cardoso et al. 2014, Giordano et al. 2014).

Longer-term data on the efficacy and tolerability of the addition of Perjeta to Herceptin and docetaxel in the first-line treatment of HER2-positive mBC is now available from the final analysis of the CLEOPATRA study, with a clinical data cut-off of 11th February 2014 (Swain et al. 2015). This final data cut extends the median follow-up of patients to over 4 years (49.5 months in the Perjeta group and 50.6 months in the control group), an increase from 19.3 months in both groups in the primary analysis and 30 months in both groups in the interim secondary analysis (Baselga et al. 2012, Swain et al. 2013, Swain et al. 2015).

The final analysis shows that the addition of Perjeta to Herceptin and docetaxel significantly increased median overall survival (OS) by 15.7 months (56.5 months in the Perjeta group compared to 40.8 months in the control group; (hazard ratio [HR]=0.68 95% CI [0.56, 0.84]; P<0.001) (Swain et al. 2015). Furthermore, the median progression-free survival (PFS), as assessed by investigators, improved by 6.3 months in the Perjeta group compared to the control group (18.7 months vs 12.4 months; HR=0.68; 95% CI [0.58, 0.80]). These data extend the results of previous analyses and confirm the efficacy of this drug combination.

The longer-term data from the CLEOPATRA study continues to show that Perjeta when added to Herceptin and docetaxel is well-tolerated with a safety profile that is consistent with earlier analyses. No new safety signals were observed at the final data analysis.

Perjeta is currently precluded from being considered as an end-of-life medicine due to the strict nature of the criterion on current survival. However, this submission, and the end-of-life criteria, should be considered in light of the dramatic extent to which Perjeta extends OS for patients with HER2-positive mBC.

In conclusion, Perjeta has made an unprecedented impact on survival outcomes for patients with HER2-positive mBC and as a result, is now considered the SOC at first-line. Therefore, removal of access to Perjeta would be a major regression in treatment, resulting in significantly shorter life expectancy for a substantial group of women, who despite treatment advances still face a life-limiting disease and an extremely poor prognosis.

2. Context

- Perjeta in combination with Herceptin and chemotherapy has become the SOC for the first-line treatment of HER2-positive mBC.
- Perjeta offers a substantial benefit to patients in terms of OS and PFS, as well as improved quality-of-life (QoL).
- The majority of patients receiving first-line therapy for mBC are on a Perjeta-based regimen, with 412 applications for Perjeta received by the CDF between April and September 2015.
- These patients are therefore currently experiencing the substantial benefit of this important development in the treatment of mBC.

2.1 Burden of HER2-positive Breast Cancer

Breast cancer is the second most common cause of cancer-related death in women, with 11,716 deaths from breast cancer in the UK in 2012 (Cancer Research UK 2016). Between 15–20% of all breast cancers have gene amplification and/or overexpression of HER2, which is associated with a more aggressive phenotype and a poorer prognosis (Dawood et al. 2010, Wolff et al. 2013). The introduction of HER2-targeted therapies has dramatically improved clinical outcomes for patients with HER2-positive disease, with survival outcomes now similar to those with HER2-negative disease (Dawood et al. 2010, Clarke et al. 2014). However, despite these improvements, ~50% of patients will have died at 3 years following diagnosis with metastatic disease (Clarke et al. 2014).

2.2 Treatment Pathway and Existing Guidelines

Perjeta acts by inhibiting HER2 dimerisation, offering a complementary mechanism to the action of Herceptin (Moya-Horno et al. 2015). As described in Section 3.1, results from the Phase III trial CLEOPATRA have demonstrated that Perjeta in combination with Herceptin and docetaxel dramatically improve PFS, OS and objective response rate (RR) when used in the first-line treatment of HER2-positive mBC (Baselga et al. 2012, Swain et al. 2013, Swain et al. 2015). As such, Perjeta has provided a further step-change in the treatment of patients with mBC, offering a substantial gain in survival for patients facing the aggressive phenotype and poor prognosis of HER2-positive disease.

Following the introduction of Perjeta, international consensus guidelines such as the Advanced Breast Cancer 2 (ABC2) and the American Society of Clinical Oncology (ASCO) Clinical Practice Guideline have recognised the superiority of Perjeta in combination with Herceptin and chemotherapy as compared to Herceptin and chemotherapy alone, recommending the Perjeta regimen as the SOC at first-line for patients with HER2-positive metastatic

disease (Cardoso et al. 2014, Giordano et al. 2014, Hurvitz 2015). Furthermore, the updated ABC3 presented at the San Antonio Breast Cancer Symposium 2015 confirmed that the standard first-line therapy for patients previously untreated with anti-HER2 therapy is Perjeta in combination with Herceptin and chemotherapy (Hurvitz 2015).

Perjeta was submitted to NICE for a single technology appraisal (STA) on 3rd April 2013 [ID523] (NICE 2013). Since becoming available via the CDF in April 2013, the combination of Perjeta, Herceptin and chemotherapy has become the SOC first-line treatment in the UK (Cancer Drugs Fund 2013, Roche Data on File 2015).

2.3 Standard-of-care

Perjeta is widely used as the first-line treatment option for patients with HER2-positive mBC both within the UK and internationally. Consistent with the international consensus guidelines, UK market research data confirms that Perjeta in combination with Herceptin and chemotherapy has become the SOC for first-line therapy, with [redacted] of patients on a Perjeta-based regimen in Q3 2015 (Roche Data on File 2015). Furthermore, this is likely to be an underestimate due to some charts respondents not specifying the patient segment, leading to exclusion of these charts from the weighted share. In addition, 412 applications for Perjeta were received by the CDF between April 2015 and September 2015, highlighting the importance of Perjeta in current treatment regimens (Cancer Drugs Fund 2016).

The next most frequently used treatment regimen according to the market share estimates is Herceptin and taxane; [redacted] of patients received this treatment regimen at first-line. The comparator for Perjeta in combination with Herceptin and docetaxel therefore remains Herceptin in combination with a taxane (docetaxel or paclitaxel), consistent with the NICE STA for Perjeta [ID523] (NICE 2013). As such, should Perjeta be made unavailable to patients in England, patients would likely receive a Herceptin and taxane regimen. The recent CLEOPATRA data presented in Section 3.1 shows that the median OS of patients receiving Herceptin and docetaxel is 40.8 months, which is 15.7 months less than patients receiving Perjeta in combination with Herceptin and docetaxel (median OS 56.5 months) (Swain et al. 2015). As such, removal of Perjeta from the CDF would result in a dramatic reduction in the OS of patients with HER2-positive mBC.

Beyond the UK, Perjeta has become widely adopted as the SOC for the first-line treatment of mBC. Market share data from the European Union (EU) 5 demonstrates that Perjeta is the most widely used treatment regimen at first-line across France, Germany, Italy and Spain as well as the UK (Roche Data on File 2015). Furthermore, preliminary analysis from the Systemic Therapies for HER2-positive Metastatic Breast Cancer Registry (SystHERs) in the United States found 494/699 (71%) of patients were receiving Perjeta, Herceptin and chemotherapy as their first-line HER2-targeted therapy, of which 478/494 (97%) were receiving Perjeta, Herceptin and any taxane (Hurvitz et al. 2015).

In conclusion, Perjeta has made a dramatic impact on treatment outcomes for patients with HER2-positive mBC, significantly improving PFS, OS and RR (Moya-Horno et al. 2015, Swain et al. 2015). The wide uptake of Perjeta in the UK confirms its place as the SOC at first-line, and highlights the large number of patients currently benefiting from this advance in treatment (Roche Data on File 2015). Therefore, removal of access to Perjeta would be a major regression in treatment resulting in significantly shorter life expectancy for a substantial group of women, who despite treatment advances still face a life-limiting disease and an extremely poor prognosis.

3. Clinical Evidence

- Longer follow-up data for the addition of Perjeta to Herceptin and docetaxel in the first-line treatment of HER2-positive mBC is available from the final analysis of the CLEOPATRA study.
    - The addition of Perjeta to Herceptin and docetaxel significantly improved the median OS by 15.7 months as compared to Herceptin and docetaxel alone (56.5 months vs 40.8 months; HR=0.68; 95% CI [0.56, 0.84]; P<0.001).
    - The median PFS as assessed by investigators improved by 6.3 months in the Perjeta group compared to the control group (18.7 months vs 12.4 months; HR=0.68; 95% CI [0.58, 0.80]).
    - This longer follow-up data extends the results of previous analyses and confirms the efficacy of this drug combination.
- Longer follow-up data from the CLEOPATRA study continues to show that Perjeta is well-tolerated when added to Herceptin and docetaxel, with a safety profile that is consistent with earlier analyses; no new safety signals have been observed.

3.1 CLEOPATRA Study

The addition of Perjeta to Herceptin and docetaxel in the first-line treatment of HER2-positive mBC has been studied in a large, multinational, Phase III, randomised controlled trial, CLEOPATRA (Baselga et al. 2012). The full methodology of the CLEOPATRA study is described in Section 6.3 of the NICE STA submission for Perjeta (April 2013 [ID523]) (NICE 2013).

The study enrolled 808 patients with HER2-positive mBC, randomising patients in a 1:1 ratio to one of two treatment arms (Baselga et al. 2012). In the Perjeta group (n=402) patients received Perjeta plus Herceptin plus docetaxel at the following doses:

- Perjeta: loading dose of 840 mg intravenous (IV) infusion, followed by 420 mg IV infusion every 3 weeks (q3w)
- Herceptin: loading dose of 8 mg/kg IV infusion, followed by 6 mg/kg IV infusion q3w
- Docetaxel: 75 mg/m^2 IV infusion q3w for at least 6 cycles (may be increased to 100 mg/m^2 at the investigator's discretion)

In the control group (n=406) patients received placebo plus Herceptin plus docetaxel at the following doses:

- Perjeta placebo: IV infusion q3w
- Herceptin: loading dose of 8 mg/kg IV infusion, followed by 6 mg/kg IV infusion q3w

- Docetaxel: 75 mg/m^2 IV infusion q3w for at least 6 cycles (may be increased to 100 mg/m^2 at the investigator's discretion)

Patients could have received one hormonal treatment for metastatic disease before randomisation. Adjuvant or neoadjuvant chemotherapy with or without Herceptin was allowed provided that the disease-free interval was at least 12 months from completion of the neoadjuvant or adjuvant treatment to diagnosis of mBC (Baselga et al. 2012).

The treatment groups were generally comparable with regard to baseline characteristics (see Section 6.3.4. of the NICE STA submission for Perjeta (April 2013 [ID523) (NICE 2013). Forty seven patients (11.7%) in the Perjeta group and 41 patients (10.1%) in the control group had received prior adjuvant or neoadjuvant chemotherapy with Herceptin (Baselga et al. 2012).

The primary outcome of the CLEOPATRA study was PFS based on tumour assessments by independent review. Secondary outcomes were OS, PFS based on investigator assessments, overall RR, duration of objective response and health-related QoL.

Primary Analysis: Clinical Data Cut-Off 13th May 2011

The primary efficacy analysis was performed from a clinical data cut-off on 13th May 2011 (a median follow-up of 19.3 months) (Baselga et al. 2012). This analysis was presented in the NICE STA submission for Perjeta (April 2013 [ID523]) (NICE 2013).

The study met its primary endpoint, PFS, at the first data cut-off (Baselga et al. 2012). Treatment with Perjeta plus Herceptin plus docetaxel resulted in a statistically significant increase of 6.1 months in independent review facility-assessed median PFS as compared to the Herceptin plus docetaxel arm (18.5 months vs 12.4 months; HR=0.62; 95% CI [0.51, 0.75]; P<0.001) (Baselga et al. 2012). The independent review of PFS was stopped after the first analysis. Therefore, only investigator-assessed PFS is presented for the subsequent analyses.

There was a trend towards an OS benefit with Perjeta, Herceptin and docetaxel (HR=0.64; 95% CI [0.47, 0.88]; P=0.005) at the first clinical data cut (Baselga et al. 2012). However, the estimated HR did not meet the O'Brien-Fleming stopping boundary (HR≤0.603; P≤0.0012) for this primary analysis of survival and was therefore not deemed statistically significant.

Second Interim Analysis: Clinical Data Cut-Off 14th May 2012

During the review process the regulatory authorities requested a further analysis for OS. This was carried out with an additional year of data from a clinical cut-off of 14th May 2012 (median follow-up of 30 months in both arms) (Swain et al. 2013). This analysis was presented in the NICE STA submission for Perjeta (April 2013 [ID523) (NICE 2013).

At this second interim analysis of OS the HR crossed the pre-defined O'Brien-Fleming stopping boundary (HR≤0.739; P≤0.0138): HR=0.66; 95% CI [0.52, 0.84]; P=0.0008; stratified by prior treatment and region). This

demonstrated that there was a statistically significant survival benefit for Perjeta, Herceptin and docetaxel (Swain et al. 2013).

This second interim analysis also provided updated investigator-assessed PFS and safety data.

Per protocol, after the second analysis the study was fully unblinded and crossover was permitted for those patients in the control arm whose disease had not yet progressed and who were still receiving treatment with Herceptin.

Final Analysis: Clinical Data Cut-Off 11th February 2014

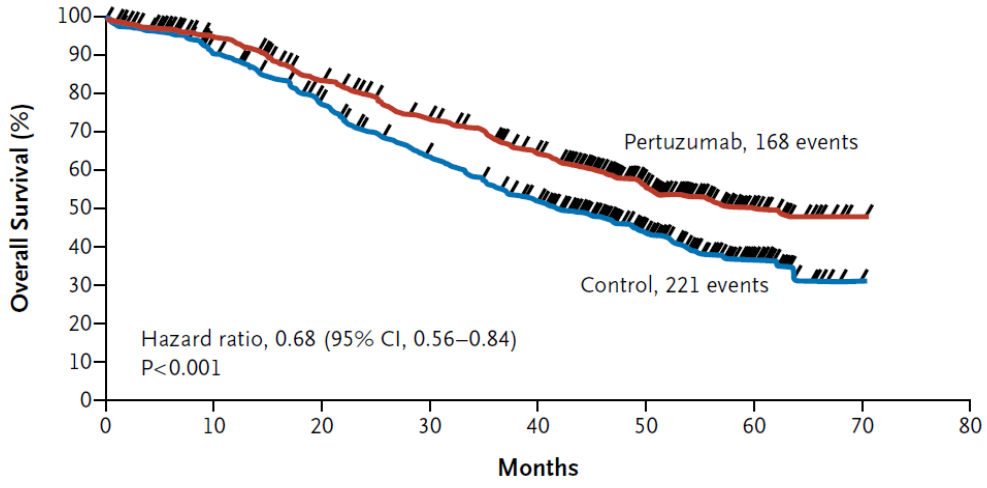
The final analysis was conducted from a clinical cut-off on 11th February 2014 (median follow-up of 49.5 months in the Perjeta group and 50.6 months in the control group) (Swain et al. 2015). The efficacy and tolerability data from this final cut-off is presented in Section 3.1.1 and Section 3.1.2 below.

3.1.1 Efficacy

3.1.1.1 Overall Survival

At the final analysis (clinical data cut 11th February 2014) the median OS was 56.5 months in the Perjeta group and 40.8 months in the control group, a difference of 15.7 months (HR=0.68; 95% CI [0.56, 0.84]; P<0.001) (Figure 1) (Swain et al. 2015).

Figure 1: OS in the CLEOPATRA study - final analysis (clinical data cut 11th February 2014)



No. at Risk									
Pertuzumab	402	371	318	268	226	104	28	1	0
Control	406	350	289	230	179	91	23	0	0

Abbreviations: CI, confidence interval; OS, overall survival.
Source: Swain et al. 2015

The results of this analysis were consistent with those of the previous data cut-offs (Table 1) (Baselga et al. 2012, Swain et al. 2013).

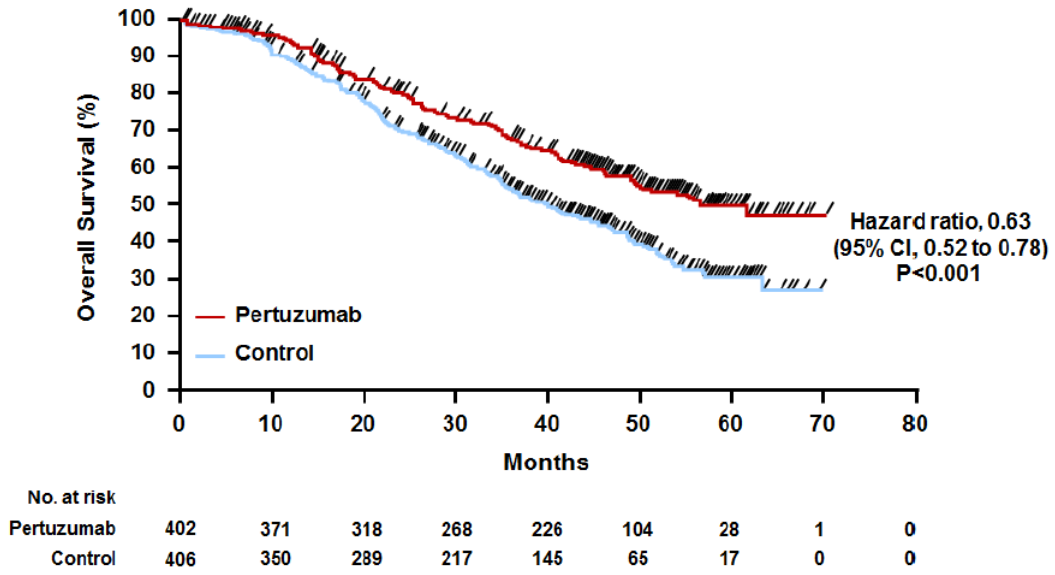
Table 1: OS analysis of the CLEOPATRA study

OS analysis	Date [median follow-up]		Perjeta group (Perjeta + Herceptin + docetaxel)	Control group (placebo + Herceptin + docetaxel)	HR [95% CI]	P-value
Primary analysis (Baselga et al. 2012)	13th May 2011 [19.3 months in both groups]	n (% OS events)	69 (17.2)	96 (23.6)	0.64 [0.47, 0.88]	0.005
		Median OS (months)	NE	NE		
Second interim analysis (Swain et al. 2013)	14th May 2012 [30 months in both groups]	n (% OS events)	113 (28.1)	154 (37.9)	0.66 [0.52, 0.84]	0.0008
		Median OS (months)	NE	37.6		
Final analysis* (Swain et al. 2015)	11th February 2014 [49.5 months in the Perjeta group; 50.6 months in the control group]	n (% OS events)	168 (41.8)	221 (54.4)	0.68 [0.56, 0.84]	<0.001
		Median OS (months)	56.5	40.8		

*Results presented at this data cut are from the intention-to-treat population; therefore data from crossover patients were analysed in the control group
Abbreviations: CI, confidence interval; HR, hazard ratio; NE, not evaluable; OS, overall survival.
Source: as indicated.

This final analysis of OS was not adjusted for crossover of patients from the control to the Perjeta group and is therefore conservative (Swain et al. 2015). There were 48 patients without disease progression who opted to cross over from the control group to receive Perjeta, further highlighting the confidence of patients and physicians in the Perjeta treatment regimen. All patients who crossed over had been receiving treatment for at least 2 years. When their data was censored at the time of the first Perjeta dose the median OS was increased by 16.9 months in the Perjeta group (56.5 months vs 39.6 months in the control group, HR=0.63; 95% CI [0.52, 0.78]; P<0.001) (Figure 2).

Figure 2: OS in the CLEOPATRA study when crossover patients were censored, stratified according to prior treatment and region - final analysis (clinical data cut 11th February 2014)



Abbreviations: CI, confidence interval; OS, overall survival.
Source: Swain et al. 2015.

The median OS among patients who had previously been treated with Herceptin (47 patients in the Perjeta group and 41 patients in the control group) was *XXXXXXX* months in the Perjeta group compared to *XXXXXXX* months in the control group (HR=0.80; 95% CI [0.44, 1.47]) (Roche Clinical Study Report 2014).

Kaplan-Meier OS estimates are presented in Figure 3 below. Estimates were obtained directly from the statistical model based on the final analysis of OS (Roche Data on File 2016).

Figure 3: Kaplan-Meier OS estimates at 12, 18 and 24 months in the CLEOPATRA study

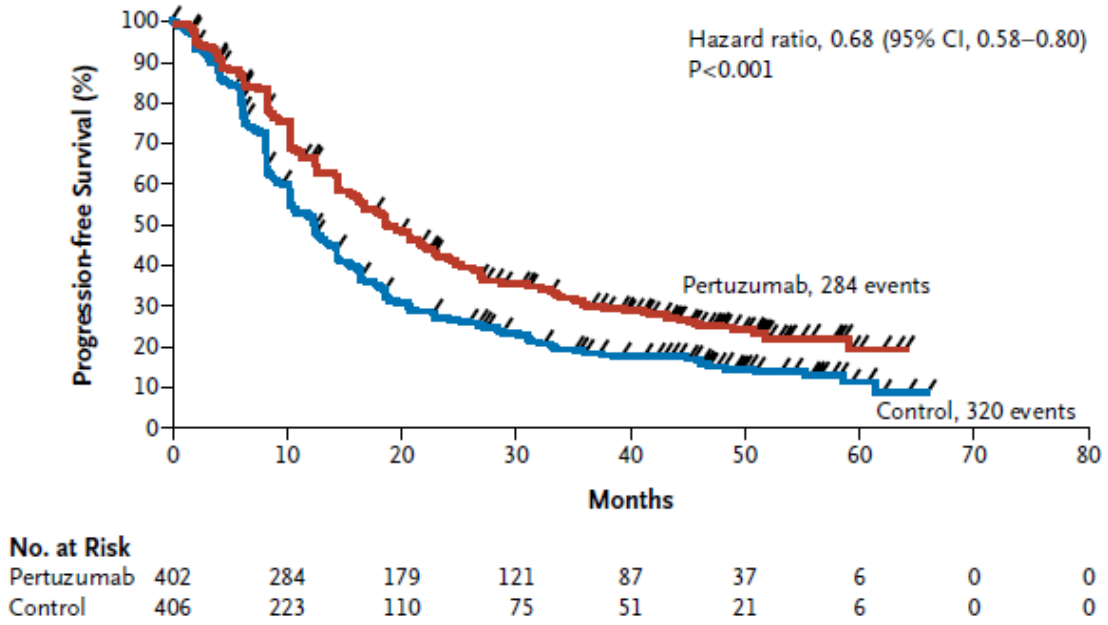
GRAPH REDACTED

Abbreviations: OS, overall survival.
Source: Roche Data on File 2016 (RXUKPERT00260)

3.1.1.2 Progression-free Survival

At the final analysis (clinical data cut 11th February 2014) the median PFS as assessed by investigators was 6.3 months longer in the Perjeta group compared to the control group (18.7 months vs 12.4 months; HR=0.68; 95% CI [0.58, 0.80]) (Figure 4) (Swain et al. 2015).

Figure 4: Investigator-assessed PFS analysis of the CLEOPATRA study - final analysis (clinical data cut 11th February 2014)



Abbreviations: CI, confidence interval; PFS, progression-free survival.
Source: Swain et al. 2015

This was consistent with the primary analysis and the second interim analysis (Table 2) (Baselga et al. 2012, Swain et al. 2013).

Table 2: PFS analysis of the CLEOPATRA study

PFS analysis	Date [median follow-up]		Perjeta group (Perjeta + Herceptin + docetaxel)	Control group (placebo + Herceptin + docetaxel)	HR [95% CI]	P-value
Primary analysis (independently assessed) (Baselga et al. 2012)	13th May 2011 [19.3 months in both groups]	n (% PFS events)	NR	NR	0.62 [0.51, 0.75]	<0.001
		Median PFS (months)	18.5	12.4		
Primary analysis (investigator-assessed) (Baselga et al. 2012)	13th May 2011 [19.3 months in both groups]	n (% PFS events)	NR	NR	0.65 [0.54, 0.78]	<0.0001
		Median PFS (months)	18.5	12.4		
Second interim analysis (investigator-assessed) (Swain et al. 2013)	14th May 2012 [30 months in both groups]	n (% PFS events)	257 (63.9)	296 (72.9)	0.69 [0.58, 0.81]	NR
		Median PFS (months)	18.7	12.4		
Final analysis (investigator-	11th February 2014	n (% PFS events)	284 (70.6)	320 (78.8)	0.68 [0.58,	<0.001

assessed) (Swain et al. 2015)	[49.5 months in the Perjeta group; 50.6 months in the control group]	Median PFS (months)	18.7	12.4	0.80]	

Abbreviations: CI, confidence interval; HR, hazard ratio; NR, not reported; PFS, progression-free survival.
Source: as indicated.

Kaplan-Meier survival estimates of independently-assessed and investigator-assessed PFS are presented in Figure 5. Estimates were obtained directly from the statistical model based on independently-assessed PFS data acquired during the primary analysis, and investigator-assessed PFS data from the final analysis (Roche Data on File 2016).

The investigator-assessed PFS in the Perjeta group was *XX* at 12 months, *XX* at 18 months and *XX* at 24 months. In the control group PFS declined from *XX* at 12 months to *XX* at 18 months and *XX* at 24 months. Whether assessed independently or by the investigator, a higher proportion of patients in the Perjeta group were estimated to be progression-free at 12, 18 and 24 months of treatment compared to the control group.

Figure 5: Kaplan-Meier survival estimates of patients who were progression-free at 12, 18 and 24 months in the CLEOPATRA study

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Abbreviations: Inv, investigator-assessed; Irf, independent review facility; PFS, progression-free survival.
Source: Roche Data on File 2016 (RXUKPERT00260)

3.1.2 Tolerability

The median number of study-treatment cycles received by patients in the safety population was 24 in the Perjeta group (range [1, 96]; 197 patients received more than the median number) and 15 in the control group (range [1, 67]) (Swain et al. 2015). Patients who crossed over from the control group to the Perjeta group received a median of 22.5 cycles of Perjeta (range [1, 28]), which was similar to the median number of cycles received by patients in the Perjeta safety population (all patients who received at least one dose of a study drug). Docetaxel exposure did not change between data cuts (median was 8 cycles in each group).

At the final analysis the rate of adverse events (AEs) remained consistent with the primary analysis (Baselga et al. 2012, Swain et al. 2015). Headache, upper respiratory tract infection, and muscle spasm were reported as new AEs with a difference of at least 5 percentage points between groups (Table 3) (Swain et al. 2015).

Most AEs were grade 1 or 2 and occurred during docetaxel administration and declined after docetaxel was discontinued (Table 3).

Table 3: AEs in the CLEOPATRA study (safety population*) - final analysis (clinical data cut 11th February 2014)

Adverse event	Perjeta group (Perjeta + Herceptin + docetaxel)	Control group (placebo + Herceptin + docetaxel)
	Number (percent)	
Most common AEs (all grades) †	**n=408**	**n=396**
Alopecia	248 (60.8)	240 (60.6)
Diarrhoea	279 (68.4)	193 (48.7)
Neutropenia	218 (53.4)	198 (50.0)
Nausea	183 (44.9)	168 (42.2)
Fatigue	155 (38.0)	148 (37.4)
Rash	153 (37.5)	95 (24.0)
Asthenia	113 (27.7)	122 (30.8)
Decreased appetite	121 (29.7)	106 (26.8)
Peripheral oedema	98 (24.0)	111 (28.0)
Vomiting	106 (26.0)	97 (24.5)
Myalgia	99 (24.3)	99 (25.0)
Mucosal inflammation	111 (27.2)	79 (19.9)
Headache	105 (25.7)	76 (19.2)
Constipation	65 (15.9)	101 (25.5)
Upper respiratory tract infection	85 (20.8)	57 (14.4)
Pruritus	72 (17.6)	40 (10.1)
Febrile neutropenia	56 (13.7)	30 (7.6)
Dry skin	46 (11.3)	24 (6.1)
Muscle spasms	42 (10.3)	20 (5.1)
Most common AEs post-docetaxel (all grades)	**n=306**	**n=261**
Alopecia	5 (1.6)	6 (2.3)
Diarrhoea	86 (28.1)	37 (14.2)
Neutropenia	10 (3.3)	13 (5.0)
Nausea	39 (12.7)	30 (11.5)
Fatigue	41 (13.4)	25 (9.6)
Rash	56 (18.3)	21 (8.0)
Asthenia	41 (13.4)	23 (8.8)
Decreased appetite	22 (7.2)	14 (5.4)

Peripheral oedema	28 (9.2)	32 (12.3)
Vomiting	30 (9.8)	17 (6.5)
Myalgia	25 (8.2)	19 (7.3)
Mucosal inflammation	11 (3.6)	4 (1.5)
Headache	52 (17.0)	32 (12.3)
Constipation	17 (5.6)	18 (6.9)
Upper respiratory tract infection	56 (18.3)	32 (12.3)
Pruritus	42 (13.7)	15 (5.7)
Febrile neutropenia	0	0
Dry skin	10 (3.3)	10 (3.8)
Muscle spasms	24 (7.8)	6 (2.3)
Grade 3 or higher events‡	**n=408**	**n=396**
Neutropenia	200 (49.0)	183 (46.2)
Leukopenia	50 (12.3)	59 (14.9)
Febrile neutropenia	56 (13.7)	30 (7.6)
Diarrhoea	38 (9.3)	20 (5.1)
Anaemia	10 (2.5)	14 (3.5)
Fatigue	9 (2.2)	13 (3.3)
Left ventricular dysfunction	6 (1.5)	13 (3.3)
Asthenia	11 (2.7)	7 (1.8)
Peripheral neuropathy	11 (2.7)	7 (1.8)
Granulocytopenia	6 (1.5)	9 (2.3)
Dyspnoea	4 (1.0)	8 (2.0)
Hypertension	8 (2.0)	7 (1.8)
Pneumonia	4 (1.0)	8 (2.0)
Serious events‡§	**n=408**	**n=396**
Febrile neutropenia	46 (11.3)	20 (5.1)
Neutropenia	18 (4.4)	19 (4.8)
Pneumonia	5 (1.2)	9 (2.3)
Cellulitis	10 (2.5)	2 (0.5)
Pneumonia	13 (3.2)	5 (1.3)

*All patients who received at least one dose of study drug
† Frequency of 25% or higher or at least 5% difference between treatment groups
‡ Frequency of 2% or higher
§ According to International Conference on Harmonisation Guidelines for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Topic E2.

Source: Swain et al. 2015.

The rate of left ventricular dysfunction, as defined by the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0, and the New York Heart Association, was lower in the Perjeta group than in the control group (6.6% [27 of 408 patients] vs 8.6% [34 of 396 patients]). There was one new event of symptomatic left ventricular dysfunction in the Perjeta group after 40 months; this event resolved after 3 months with both antibodies discontinued. Reductions in the left ventricular ejection fraction of 10% or more from baseline to an absolute value of less than 50% occurred in 6.1% of patients (24/394) in the Perjeta group and 7.4% of patients (28/378) in the control group. Declines were reversed in 21 of 24 patients (87.5%) in the Perjeta group and 22 of 28 patients (78.6%) in the control group.

Most deaths were due to disease progression (150 of 408 patients [36.8%] in the Perjeta group and 196 of 396 patients [49.5%] in the control group). Other causes of death were febrile neutropenia or infection (7 of 408 patients [1.7%] in the Perjeta group and 6 of 396 patients [1.5%] in the control group) and causes that were classified as “other” or “unknown” (12 of 408 patients [2.9%] in the Perjeta group and 15 of 396 patients [3.8%] in the control group).

3.1.2.1 Tolerability in Crossover Population

There were no new safety signals identified among patients in the control group who crossed over to receive Perjeta (Swain et al. 2015). Most adverse events in these patients were of grade 1 or 2. Of the 221 adverse events in the crossover group, 7 were grade 3 events, and 2 were grade 4 events (diarrhoea and dehydration in the same patient). There was one death from an unknown cause. No symptomatic left ventricular dysfunction was reported after crossover. Two patients had asymptomatic reductions in the left ventricular ejection fraction.

3.2 Ongoing Studies

3.2.1 Clinical Trials

Of relevance to this submission is the ongoing multicentre, open-label, single-arm, Phase IIIb trial PERUSE (MO28047) (ClinicalTrials.gov NCT01572038). PERUSE investigates Perjeta in combination with Herceptin and taxane for the first-line treatment of patients with HER2-positive advanced breast cancer. The primary endpoint is safety and secondary endpoints include PFS, OS, objective RR and QoL. The estimated completion date of the study is 2019.

As noted in the previous NICE STA submission, interim safety results of PERUSE have now become available (NICE 2013) (Bachelot et al. 2014). These results show a safety profile consistent with previous clinical experience of Perjeta, Herceptin and docetaxel.

3.2.2 Real-world Evidence

Since the NICE STA submission for Perjeta in April 2013 (ID523), Roche has initiated recruitment into the ESTHER study, which is a UK-based observational cohort study of patients with HER2-positive, unresectable,

locally advanced/metastatic breast cancer who have been diagnosed with advanced disease within the previous 6 months (ClinicalTrials.gov NCT02393924). The ESTHER study will ultimately form part of a larger international study.

The aim of the ESTHER study is to observe the different anti-cancer treatment regimens, including Perjeta, and their sequencing throughout the course of the disease and as such will provide further data on the use of Perjeta in the UK. The primary analysis will be PFS for each treatment regimen, and a range of other endpoints will be assessed as secondary outcomes, including OS, objective RR, serious AEs, and patient-reported outcomes to assess QoL.

The ESTHER study started enrolling patients in 2015 and it is estimated that recruitment of the target enrolment of 390 patients will be complete in 2018. Reporting of PFS is estimated for 2019 and beyond, with study completion estimated for 2023.

In addition to the ESTHER study, Roche is also undertaking the SystHERs observational study of patients with HER2-positive mBC in the United States (Tripathy et al. 2014). Enrolment is ongoing and study completion is estimated for 2020 (ClinicalTrials.gov NCT01615068). As discussed in Section 2.3, initial analysis has confirmed the widespread use of Perjeta as a first-line HER2-targeted therapy (Hurvitz et al. 2015).

4. ‘End-of-Life’ Criteria

- Perjeta offers a dramatic median extension to life of >15 months, which far exceeds the extension to life of 3 months specified by the end-of-life criteria.
- As such, assessment of Perjeta according to the end-of-life criteria should be considered in light of such a dramatic improvement in OS.

The life expectancy of patients receiving a first-line treatment for mBC now exceeds 24 months when treated with the most relevant comparator for Perjeta, Herceptin plus taxane; this currently precludes Perjeta being considered under the strict end-of-life criteria. The first randomised controlled trial assessing Herceptin in combination with chemotherapy reported a median overall survival of 25.1 months (Slamon et al. 2001, Mendes et al. 2015). More recently a published systematic review of Phase III studies reported median OS ranging from 28.9 (95% CI [NR]) to 37.1(95% CI [32.6, 43.6]) months in the BCIRG 007 study for patients receiving first-line treatment with Herceptin plus paclitaxel or docetaxel respectively (Valero et al. 2011, Baselga et al. 2014, Mendes et al. 2015). In addition, a retrospective analysis of patients who had received first-line Herceptin-containing therapy at a single centre in the UK found the median OS to be 2.6 years (95% CI [2.2, 3.3]) (Yeo et al. 2015).

It should be noted, however, that despite the significant improvements in life expectancy that have resulted from the introduction of Herceptin, ~50% of patients will have died at 3 years following diagnosis with metastatic disease (Clarke et al. 2014). Therefore, despite treatment advances including the introduction of Perjeta, the clinical and patient burden of HER2-positive mBC is significant; the removal of Perjeta from the CDF would further exacerbate this burden, not only for patients but society as a whole.

The addition of Perjeta to Herceptin and docetaxel results in a dramatic median extension of life of 15.7 months, five times greater than the 3 month threshold for the end-of-life criteria (Swain et al. 2015). This extension has substantial impact on patients and is of prime importance to patients, their families and wider-society. Therefore, an appropriate weighting to the end-of-life criteria should be considered when assessing such a dramatic increase in life expectancy.

Given the poor prognosis and clinical and patient burden of HER2-positive mBC, the unprecedented survival benefit above the existing 3 month end-of-life threshold that is offered by Perjeta in this indication, as compared to the SOC, is sufficient evidence to accept Perjeta in its licenced indication as meeting the end-of-life criteria.

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Appendix G – Patient/carer organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Pertuzumab in combination with trastuzumab and docetaxel for the treatment of HER2 positive metastatic or locally recurrent unresectable breast cancer

Thank you for agreeing to give us your views on the technology and the way it should be used in the NHS.

Patients and patient advocates can provide a unique perspective on the technology, which is not typically available from the published literature.

To help you give your views, we have provided a template. The questions are there as prompts to guide you. You do not have to answer every question. Please do not exceed the 8-page limit.

About you

Your name:

Name of your organisation: Breakthrough Breast Cancer

Are you (tick all that apply):

- a patient with the condition for which NICE is considering this technology?
- a carer of a patient with the condition for which NICE is considering this technology?
- **an employee of a patient organisation that represents patients with the condition for which NICE is considering the technology? If so, give your position in the organisation where appropriate (e.g. policy officer, trustee, member, etc)**
- other? (please specify)

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NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

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What do patients and/or carers consider to be the advantages and disadvantages of the technology for the condition?

1. Advantages

(a) Please list the specific aspect(s) of the condition that you expect the technology to help with. For each aspect you list please describe, if possible, what difference you expect the technology to make.

This review considers the use of pertuzumab in combination with trastuzumab and docetaxel for the treatment of patients with HER2 positive breast cancer that has advanced or locally recurred. This is a first line indication. Typical treatment for these women would be trastuzumab and docetaxel.

HER2 positive breast cancer is so called due to the presence of the HER2 receptor on the surface of the cancer cells. It is these receptors that are targeted by trastuzumab. However, it is possible for HER2 positive cancer cells to evade destruction by trastuzumab. They do this by forming pairs with other receptors that are members of the HER family and it is these resulting dimers which can ultimately lead to tumour growth and survival. Pertuzumab is able to limit tumour growth and promote cancer cell destruction by blocking the pairing of HER2 family proteins.

The CLEOPATRA trial, that compares trastuzumab plus docetaxel with or without the addition of pertuzumab, demonstrates the latter is effective at limiting tumour progression to a greater extent than is observed for trastuzumab and docetaxel alone. Specifically, it was found that patients who received pertuzumab had a 6.1 month progression free survival benefit compared to patients who received only trastuzumab and docetaxel (18.5 months vs 12.4 months).[1]

It's also expected that treatment with pertuzumab will lead patients to have longer overall survival. Currently, precise data on survival is not available. However, survival findings presented thus far have been positive and it's been reported that pertuzumab reduces risk of death by 34%.[2] When considering patients who received pertuzumab versus patients who did not the following survival data has been reported:[2]
Patients alive after 1 year: 94% vs 89%
Patients alive after 2 years: 81% vs 69%
Patients alive after 3 years: 66% vs 50%

(b) Please list any short-term and/or long-term benefits that patients expect to gain from using the technology. These might include the effect of the technology on:

[1] Baselga *et al*., New England Journal of Medicine. 2012
[2] Swain *et al*. San Antonio Breast Cancer Symposium 2012. Poster P5-18-26

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (lifestyle, work, social functioning etc.)
- other quality of life issues not listed above
- other people (for example family, friends, employers)
- other issues not listed above

As described above pertuzumab in combination with trastuzumab and docetaxel can offer patients enhanced progression-free survival compared to treatment with trastuzumab and docetaxel alone. We know patients who have locally recurrent or metastatic breast cancer, for which there is no cure, value treatments that can help them control their cancer and stop it progressing. This can give them a more positive outlook on their treatment regimen and the course of their illness.

Certainly delayed time to disease progression, if associated with few severe side effects of treatment, allows patients with metastatic breast cancer to continue with some aspects of their normal daily life and delays the associated debilitating symptoms and emotional distress that progression may bring.

Specifically, recent data from the CLEOPATRA study showed patients who received pertuzumab had less incidence of constipation and peripheral oedema than those who received trastuzumab and docetaxel alone. The number of patients who experienced these events are as follows (patients who received pertuzumab vs patients who did not):[2]
constipation -101 patients (24.8%) vs 122 patients (30.8%)
peripheral oedema - 63 patients (15.4%) vs 101 patients (25.5%)

2. Disadvantages

Please list any problems with or concerns you have about the technology. Disadvantages might include:

- aspects of the condition that the technology cannot help with or might make worse
- difficulties in taking or using the technology
- side effects (please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- impact on others (for example family, friends, employers)
- financial impact on the patient and/or thier family (for example cost of travel needed to access the technology, or the cost of paying a carer)

In the CLEOPATRA study there were some treatment-related side effects that are more prevalent for patients who received pertuzumab than those who did not. These included febrile neutropenia, diarrhoea, rash and mucosal inflammation. The number of patients on

the CLEOPATRA study who experienced these events are as follows (patients who received pertuzumab vs patients who did not):[2]
febrile neutropenia – 56 patients (13.7%) vs 30 patients (7.6%)
diarrhoea – 278 patients (68.1%) vs 191 patients (48.2%)
rash – 149 (36.5%) vs 95 (24%)
mucosal inflammation - 112 patients (27.5) vs 79 patients (19.9)

What is important to note is that in the CLEOPATRA study most events of febrile neutropenia, diarrhoea and rash occurred only during the period when treatment involved docetaxel. Furthermore, the longer treatment progressed the less likely these adverse events were to occur.

Patients are often willing to accept negative side-effects as part of their treatment so long as they know what to expect and have been given all the necessary information before they begin treatment.[3] Certainly, when negative side-effects are associated with gains in progression-free survival or overall survival many patients are willing to accept these adverse effects.

3. Are there differences in opinion between patients about the usefulness or otherwise of this technology? If so, please describe them.

As highlighted above patients will differ in their willingness to accept risks associated with different treatment regimens. It is therefore very important that all patients are made aware and fully understand the possible risks and benefits of a treatment before making a decision about their treatment options.

4. Are there any groups of patients who might benefit **more** from the technology than others? Are there any groups of patients who might benefit **less** from the technology than others?

Not all breast cancer patients will benefit from this treatment because, as described above, it is only appropriate for the treatment of patients with HER2 positive category of the disease.

[3] Baselga *et al*. ASCO. Abstract 597

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Single Technology Appraisal (STA)

Pertuzumab in combination with trastuzumab and docetaxel for the treatment of HER2 positive metastatic or locally recurrent unresectable breast cancer

This appraisal considers pertuzumab use as a first line treatment for metastatic disease. Studies on the efficacy of this drug in the adjuvant and neoadjuvant setting are currently ongoing.

Comparing the technology with alternative available treatments or technologies

NICE is interested in your views on how the technology compares with existing treatments for this condition in the UK.

(i) Please list any current standard practice (alternatives if any) used in the UK.

There is only one drug that specifically targets HER2 positive breast cancer and that is trastuzumab (Herceptin). This is given with chemotherapy, typically docetaxel.

(ii) If you think that the new technology has any **advantages** for patients over other current standard practice, please describe them. Advantages might include:
- improvement of the condition overall
- improvement in certain aspects of the condition
- ease of use (for example tablets rather than injection)
- where the technology has to be used (for example at home rather than in hospital)
- side effects (please describe nature and number of problems, frequency, duration, severity etc)

As described above, pertuzumab in combination with trastuzumab and docetaxel gives patients longer progression free survival.

(iii) If you think that the new technology has any **disadvantages** for patients compared with current standard practice, please describe them. Disadvantages might include:
- worsening of the condition overall

- worsening of specific aspects of the condition
- difficulty in use (for example injection rather than tablets)
- where the technology has to be used (for example in hospital rather than at home)
- side effects (for example nature or number of problems, how often, for how long, how severe).

Some adverse events are higher in patients who receive pertuzumab than those who do not. However, these are short-lived. These are described in more detail above.

Research evidence on patient or carer views of the technology

If you are familiar with the evidence base for the technology, please comment on whether patients' experience of using the technology as part of their routine NHS care reflects that observed under clinical trial conditions.

We are unaware of patients first-hand views and experiences of this technology.

Are there any adverse effects that were not apparent in the clinical trials but have come to light since, during routine NHS care?

Not that we are aware.

Are you aware of any research carried out on patient or carer views of the condition or existing treatments that is relevant to an appraisal of this technology? If yes, please provide references to the relevant studies.

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None that we are aware of.

Availability of this technology to patients in the NHS

What key differences, if any, would it make to patients and/or carers if this technology was made available on the NHS?

There is no cure for metastatic breast cancer. It is therefore vital a range of treatment options are made available that can allow patients to control or halt the progression of their disease and enhance survival.

It has been shown pertuzumab in combination with trastuzumab and docetaxel can enhance progression free survival by just over 6 months. This is a convincing and important finding as there is no other comparative treatment regimen that would elicit such a positive response. It would make a huge difference for patients to have access to this drug as we know the ability to control their disease is something of key importance to breast cancer patients and their loved ones. Furthermore, survival data for this drug has so far been positive. If it is shown this drug gives significant benefits in overall survival it is essential NHS patients have access this treatment option.

What implications would it have for patients and/or carers if the technology was **not** made available to patients on the NHS?

Given the high level of efficacy and relatively low toxicity of this treatment regimen we would be very disappointed if pertuzumab was not made available to NHS patients.

This drug represents one of the most positive advancements in the treatment of advanced HER2 positive breast cancer in recent years. If NICE fail to approve this drug it will deny patients access to a treatment with proven benefits. It would be deeply concerning if this were to be the case as it would indicate an uncertain future for the access patients have to breast cancer drugs.

Guidance for this drug is likely to be made available at the end of the year. If the committee decide against the approval of this technology it will most likely be too late for many patients to able to access it via the Cancer Drugs Fund (given that the Cancer Drugs Fund is

due to end at the end of March 2014). This could result in many patients, who are already in the end stages of their lives, being denied a treatment that has the potential to keep them alive for a significant extra number of months. We strongly hope the Committee is able to work with manufacturer and other stakeholders to approve this technology which could give patients extra time to spend with their families and loved ones, something of great importance to all concerned.

Are there groups of patients that have difficulties using the technology?

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

N/A

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Other Issues
Please consider here any other issues you would like the Appraisal Committee to consider when appraising this technology.

N/A

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NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Pertuzumab in combination with trastuzumab and docetaxel for the treatment of HER2 positive metastatic or locally recurrent unresectable breast cancer

Thank you for agreeing to give us your views on the technology and the way it should be used in the NHS.

Patients and patient advocates can provide a unique perspective on the technology, which is not typically available from the published literature.

To help you give your views, we have provided a template. The questions are there as prompts to guide you. You do not have to answer every question. Please do not exceed the 8-page limit.

About you

Your name: Tara Beaumont

Name of your organisation: Breast Cancer Care

Are you (tick all that apply):

- a patient with the condition for which NICE is considering this technology?
- a carer of a patient with the condition for which NICE is considering this technology?
- X an employee of a patient organisation that represents patients with the condition for which NICE is considering the technology? If so, give your position in the organisation where appropriate (e.g. policy officer, trustee, member, etc) Clinical Nurse Specialist- metastatic breast cancer
- other? (please specify)

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What do patients and/or carers consider to be the advantages and disadvantages of the technology for the condition?

1. Advantages

(a) Please list the specific aspect(s) of the condition that you expect the technology to help with. For each aspect you list please describe, if possible, what difference you expect the technology to make.

The data from the CLEOPATRA study demonstrated progression free survival (PFS) was significantly better in the pertuzumab arm of the study, with an approximate increase of 6 months PFS. Data also showed possible increase in overall survival, but data was not mature at time of article publication (Baselga 2012).

Metastatic breast cancer is a life limiting disease; average survival data suggests one-year survival rates of 55%, two-years 35% and five-year survival rates of just 20% (Glare and Christakis 2008). Patients frequently experience ongoing symptoms due to the disease, control of the disease progression is therefore important to maintaining a good quality of life for as long as possible. For patients with metastatic breast cancer the importance of quality of life must not be underestimated. Patients frequently talk with us at Breast Cancer Care, telling us they want access to treatments that will give them improved quality of life to spend more quality time with their friends and families.

(b) Please list any short-term and/or long-term benefits that patients expect to gain from using the technology. These might include the effect of the technology on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (lifestyle, work, social functioning etc.)
- other quality of life issues not listed above
- other people (for example family, friends, employers)
- other issues not listed above

Benefits to patients may include control of physical symptoms; maintain a good quality of life, including time spent with family and friends. Early data suggest a possible overall survival benefit of even a few months or weeks is extremely

important to this client group, where life expectancy is significantly reduced due to the disease progression.

2. Disadvantages
Please list any problems with or concerns you have about the technology.
Disadvantages might include:
- aspects of the condition that the technology cannot help with or might make worse
- difficulties in taking or using the technology
- side effects (please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- impact on others (for example family, friends, employers)
- financial impact on the patient and/or thier family (for example cost of travel needed to access the technology, or the cost of paying a carer)

Side-effects experienced by patients in the study were considered tolerable. Patients often tell us they are willing to experience significant side-effects to gain control of the disease and hope for a potential survival benefit, even of a few weeks or months.

3. Are there differences in opinion between patients about the usefulness or otherwise of this technology? If so, please describe them.

None known

4. Are there any groups of patients who might benefit **more** from the technology than others? Are there any groups of patients who might benefit **less** from the technology than others?
This technology is only suitable for patients with HER2 positive breast cancer

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Pertuzumab in combination with trastuzumab and docetaxel for the treatment of HER2 positive metastatic or locally recurrent unresectable breast cancer

Comparing the technology with alternative available treatments or technologies

NICE is interested in your views on how the technology compares with existing treatments for this condition in the UK.

(i) Please list any current standard practice (alternatives if any) used in the UK.

IV Herceptin in combination with chemotherapy, usually a Taxane

(ii) If you think that the new technology has any **advantages** for patients over other current standard practice, please describe them. Advantages might include:
- improvement of the condition overall
- improvement in certain aspects of the condition
- ease of use (for example tablets rather than injection)
- where the technology has to be used (for example at home rather than in hospital)
- side effects (please describe nature and number of problems, frequency, duration, severity etc)

The data from the CLEOPATRA study demonstrated progression free survival (PFS) was significantly better in the pertuzumab arm of the study, with an approximate increase of 6 months PFS. Data also showed possible increase in overall survival, but data is not mature at time of article publication (Baselga 2012).

This technology is a new drug, the advantage being it is given at the same time as current standard therapy, therefore additional visits to the hospital are not required by the patient, nor additional venous access.

The side-effects experienced in the pertuzumab arm of the study were within tolerable levels. Patients in contact with Breast Cancer Care, who have been receiving pertuzumab, have not reported unacceptable side-effects.

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(iii) If you think that the new technology has any **disadvantages** for patients compared with current standard practice, please describe them. Disadvantages might include:
- worsening of the condition overall
- worsening of specific aspects of the condition
- difficulty in use (for example injection rather than tablets)
- where the technology has to be used (for example in hospital rather than at home)
- side effects (for example nature or number of problems, how often, for how long, how severe).

None known

Research evidence on patient or carer views of the technology
If you are familiar with the evidence base for the technology, please comment on whether patients' experience of using the technology as part of their routine NHS care reflects that observed under clinical trial conditions.

Patients in contact with Breast Cancer Care, who have received pertuzumab, have reported tolerable side-effects.

Are there any adverse effects that were not apparent in the clinical trials but have come to light since, during routine NHS care?
None known

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Pertuzumab in combination with trastuzumab and docetaxel for the treatment of HER2 positive metastatic or locally recurrent unresectable breast cancer

Are you aware of any research carried out on patient or carer views of the condition or existing treatments that is relevant to an appraisal of this technology? If yes, please provide references to the relevant studies.

Availability of this technology to patients in the NHS
What key differences, if any, would it make to patients and/or carers if this technology was made available on the NHS?

The data from the CLEOPATRA study demonstrated progression free survival (PFS) was significantly better in the pertuzumab arm of the study, with an approximate increase of 6 months PFS. Data also showed possible increase in overall survival, but data is not mature at time of article publication (Baselga 2012).

Patients frequently talk with us at Breast Cancer Care, telling us they want access to treatments that will give them improved quality of life to spend more quality time with their friends and families.

What implications would it have for patients and/or carers if the technology was **not** made available to patients on the NHS?

To not have access to this new drug via the NHS would potentially mean patients are denied the opportunity to gain control of their disease for a significant amount of time,

and potentially be denied the possibility of extending their life, even by a few months, which patients report to us as being extremely important.

Are there groups of patients that have difficulties using the technology?

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

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Other Issues
Please consider here any other issues you would like the Appraisal Committee to consider when appraising this technology.

References cited;
Baselga J (2012) Pertuzumab plus Trastuzumab plus Docetaxel for Metastatic breast cancer *The New England Journal of Medicine*

Glare P Christakis NA (Eds) (2008) Prognosis in Advanced Cancer Oxford Oxford University Press

Dear Bijal

Nurses working in this area of health were invited to submit a professional organisation statement to inform the above health technology appraisal.

Feedback from them suggests that there are no comments to submit at this stage on behalf of the Royal College of Nursing.

Thank you for the invitation to submit a statement and we look forward to participating in the next stage of the appraisal.

Please acknowledge receipt.

Kind Regards

Appendix G -Professional organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Pertuzumab in combination with trastuzumab and docetaxel for the treatment of HER2 positive metastatic or locally recurrent unresectable breast cancer [ID523]

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation: NCRI/RCP/RCR/ACP/JCCO
Comments coordinated by Dr Helena Earl

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology?

- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)?

- other? (please specify)

Appendix G -Professional organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Pertuzumab in combination with trastuzumab and docetaxel for the treatment of HER2 positive metastatic or locally recurrent unresectable breast cancer [ID523]

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS?
First-line HER2+ve metastatic breast cancer at present is treated in the NHS with trastuzumab concomitantly with chemotherapy (often docetaxel). The CLEOPATRA trial ran from 2008 to 2010, and it is of interest that in the publication (Baselga J, Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. NEJM 2012;366:109-19) only 10-11% of patients had received trastuzumab in the neo/adjuvant setting. Today this percentage would be much higher, and in the UK over 90% of HER2+ve patients under the age of 75yrs would receive trastuzumab in the neo/adjuvant setting. The trial eligibility criteria included a 12 month treatment free interval. Currently in the NHS, even with neo/adjuvant trastuzumab, after 12 months standard treatment would be trastuzumab and docetaxel.

Is there significant geographical variation in current practice?
No significant geographical variation.

Are there differences of opinion between professionals as to what current practice should be?
No substantial disagreements amongst professionals about current practice for firstline relapse without CNS disease.

What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?
Pertuzumab represents an addition to the current technology. There is no alternative at present.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient?
In the era before the availability of neo/adjuvant trastuzumab, the HER2 subgroup of breast cancer patients had the worse prognosis (Curtis et al. The genomic and transcriptomic architecture of 2,000 breast tumours reveals novel subgroups. Nature. 2012 Apr 18;486(7403):346-52). This work led by Caldas, shows that integrative cluster 5 which is predominantly HER2+ve, shows the fastest rate of relapse within the first 5 years. This is shown in all other trial databases in the pre-trastuzumab era. The subgroup eligible for the CLEOPATRA trial, is probably a prognostically more favourable sub group of the HER2 breast cancer population. In particular, most had not received neo/adjuvant trastuzumab, and 12 months had passed since the end of adjuvant treatment. Patients excluded from this trial are those who (not having received trastuzumab), relapsed within the first 12 months. TH majority of the population is trastuzumab naïve, and therefore there is no chance of resistance to HER2 antibodies having developed.

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Pertuzumab in combination with trastuzumab and docetaxel for the treatment of HER2 positive metastatic or locally recurrent unresectable breast cancer [ID523]

Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?
So far our experts have looked at how the patients got onto the trial, rather than examining the characteristics of those who were eligible. No particular subgroup seem more at risk from the new technology. The new technology may cause more heart damage, and therefore patients had an upper limit of previous doxorubicin exposure of 360mg/m2. This represents a quite low level of previous exposure which is usually at 450-500mg/m2. The risk of previous anthracycline cardiac damage is going to be very low in this group. Pertuzumab is possibly more active in patients with visceral rather than non-visceral (bone) metastatic disease.

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics?
Pertuzumab would be prescribed in secondary care, but can be delivered in primary care, or in the patients own home. Trastuzumab is at present successfully delivered in this way.

Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?
See above.

If the technology is already available, is there variation in how it is being used in the NHS?
We are not aware that it is yet available in the NHS.

Is it always used within its licensed indications? If not, under what circumstances does this occur? N/A

Please tell us about any relevant clinical guidelines and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.
We are not aware of any clinical guidelines that have been developed for pertuzumab.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?
The technology is very similar to using trastuzumab, and will be given concomitantly with it. All the mechanisms for delivery of IV monoclonal antibodies are well worked out, the only issue will be that delivery will take longer adding at least one hour to each delivery time.

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Pertuzumab in combination with trastuzumab and docetaxel for the treatment of HER2 positive metastatic or locally recurrent unresectable breast cancer [ID523]

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.
Except for apply the same criteria as in the trial, we are not aware of the development of informal or formal starting or stopping rules.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice.
Yes, in broad terms. Increasingly the majority of patients will have received neo/adjuvant trastuzumab, rather than in the trial where it was the minority. Although the trial presents results broken down into the subgroup who had received previous trastuzumab, this subgroup is only 88 patients, and represents only 10-11% of the trial population.

Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting?
The eligibility criteria of a 12 month DFI should probably be maintained in clinical practice if pertuzumab use is accepted in this NICE appraisal.

What, in your view, are the most important outcomes, and were they measured in the trials?
It is the view of our experts that disease-free survival is an important outcome in metastatic breast cancer trials. In a disease for which there is available many subsequent lines of treatment, overall survival without control of crossover to active treatment, becomes a somewhat meaningless outcome measure. The primary endpoint was independently assessed disease-free survival, which we believe is the most appropriate in metastatic breast cancer.

If surrogate measures of outcome were used, do they adequately predict long-term outcomes?
This trial restricted the use of cross-over, and it was not allowed until the primary endpoint analysis had been published. In that situation when the cross-over to pertuzumab of the control arm is likely to be minimal, the disease-free survival should predict overall survival. This information may be available to the committee before the appraisal takes place.

What is the relative significance of any side effects or adverse reactions?
No increase in cardiac problems was found. Some increase in non-life-threatening and temporary side effects. Relatively insignificant.

In what ways do these affect the management of the condition and the patient's quality of life?
Very little in the opinion of our experts.

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Pertuzumab in combination with trastuzumab and docetaxel for the treatment of HER2 positive metastatic or locally recurrent unresectable breast cancer [ID523]

Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?
No

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

We are aware that a manuscript describing overall survival in the CLEOPATRA study has been prepared and the contents may be made available to NICE appraisals committee. The manuscript may be published before the July appraisal date.

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition?
Patients would benefit in terms of disease-free and probably overall survival from pertuzumab.

Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?
No significant increase in training. Only resources would increase pharmacy and delivery in chemotherapy day unit facilities.

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Pertuzumab in combination with trastuzumab and docetaxel for the treatment of HER2 positive metastatic or locally recurrent unresectable breast cancer [ID523]

Equality
NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed; No exclusions on these grounds
- **could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;** No
- **could lead to recommendations that have any adverse impact on people with a particular disability or disabilities**. No

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.
N/A

NHS England submission into the NICE appraisal of pertuzumab February 2017

1. Pertuzumab has a licensed indication when used in combination with intravenous trastuzumab and docetaxel for the treatment of HER-2 positive patients with unresectable locally recurrent or metastatic breast cancer who have not previously received anti-HER-2 therapy or chemotherapy for their advanced/metastatic disease. The license and clinical practice concur with patients being treated until disease progression or the development of unmanageable toxicity, the latter being rare. Once the docetaxel part of the combination treatment has been completed (the usual maximum is 6 cycles), pertuzumab and intravenous trastuzumab are continued. No dose reductions of pertuzumab are recommended in the SPC but if trastuzumab is discontinued for whatever reason, then pertuzumab should also be stopped.

2. There is 1 main trial which shows the benefit of pertuzumab in advanced breast cancer.

3. This trial is the CLEOPATRA study which enrolled 808 HER-2 positive patients who had not been previously treated with anti-HER-2 therapy or chemotherapy for their locally recurrent/metastatic breast cancer. All patients received the combination of docetaxel and trastuzumab and patients were randomised to the addition of pertuzumab or placebo in a double blind fashion. Patients with brain metastases were excluded. Patients were stratified according to geographical region, previous adjuvant/neoadjuvant treatment and whether treatment in the trial represented de novo treatment of their HER-2 breast cancer. Patients with previous adjuvant or neoadjuvant treatment had to have completed treatment at least 12 months before entry into the study. The primary efficacy endpoint of the study was progression free survival (as assessed by independent review). Only patients of ECOG performance score of 0-1 were enrolled. Crossover was allowed in this study after the benefit in overall survival was first reported. The amount of crossover was small.

4. 48% of the patients had oestrogen/progesterone receptor positive disease and 47% had previously had adjuvant/neoadjuvant chemotherapy. Only 11% had previously been treated with adjuvant/neoadjuvant trastuzumab. The great majority of those treated with adjuvant/neoadjuvant chemotherapy received anthracycline chemotherapy and about half received a taxane. 78% of patients had visceral disease.

5. The median duration of follow-up was 50 months. The median progression free survival (PFS) was significantly greater with pertuzumab than with placebo (18.5 vs 12.5 mo, Δ 6.0 mo, hazard ratio 0.62, 95% confidence interval 0.51-0.75, $p<0.0001$). Overall survival (OS) was significantly greater with pertuzumab at the time of the 2nd interim analysis (56.5 vs 40.8 mo, Δ 15.7 mo, HR 0.68, 95% CI 0.56-0.84, $p=0.0002$).

6. A post hoc exploratory analysis of the 88 patients who previously had received trastuzumab showed a HR for PFS of 0.62 (95% CI 0.35-1.07). A further post hoc exploratory analysis of the 288 patients who previously had

received just chemotherapy (ie without trastuzumab) showed a HR for PFS of 0.60 (95% CI 0.43-0.83).

7. Toxicity was similar in both treatment arms, most of this being during the chemotherapy part of the treatment program. The key point is that the additional toxicity of pertuzumab was very minor.

8. Quality of life (QOL) was assessed in this trial using the FACT-B questionnaire and there was no significant difference between treatment arms in the FACT-B Treatment Outcome Index.

9. Treatments given after progression on pertuzumab or placebo and trastuzumab were similar in both arms: 43% received HER-2 targeted treatment (ie further trastuzumab), 48% were treated with lapatinib plus capecitabine and 12 % received trastuzumab emtansine. Capecitabine chemotherapy was used in 56%, vinorelbine in 28%, doxorubicin in 18% and a taxane in 17%. Further hormone treatment was used in 23% of patients.

Comment on the CLEOPATRA study and its implications

10. The 16 month survival gain with the addition of pertuzumab to standard therapy is very impressive for a population of patients with locally recurrent or metastatic HER-2 positive breast cancer. The OS data is much more mature than it was when first appraised by NICE, now with a reported median duration of follow-up of 50 months in the last clinical trial publication.

11. It has been argued that the CLEOPATRA population had favourable prognostic features in that patients treated with adjuvant/neoadjuvant treatment had to have completed chemotherapy at least 12 months prior to entry into the study. In addition, only about one quarter of the patients in the trial having previous adjuvant or neoadjuvant chemotherapies received such treatment with trastuzumab (whereas virtually all HER-2 patients having such adjuvant/neoadjuvant chemotherapy in 2017 in England would receive chemotherapy with trastuzumab). As a possible indication of this favourable population in the CLEOPATRA trial is the median OS of between 25 and 38 mo for advanced breast cancer patients in other studies treated with a taxane and trastuzumab though these studies are older and in differing populations than in CLEOPATRA. However, the evidence is mixed as to whether patients with metastatic HER-2 positive breast cancer do worse if patients have been previously treated with trastuzumab as part of adjuvant/neoadjuvant therapy. NHS England therefore regards the CLEOPATRA population as being only modestly more favourable than in the previous docetaxel/trastuzumab studies and still regards the OS advantage of the addition of pertuzumab as being great in breast cancer (and also in oncology).

12. The addition of 16 months to median OS is unprecedented in the treatment and palliation of advanced breast cancer, especially with a drug that in effect does not add any significant toxicity to treatment. The addition of pertuzumab to standard treatment does represent a step change in the treatment of advanced HER-2 breast cancer. As subsequent treatments after

pertuzumab/placebo in CLEOPATRA were identical, the gain in OS seen in the pertuzumab arm can be safely attributed to the impact of pertuzumab.

13. NHS England does not place any undue significance in the degree of difference in PFS (6 mo) and OS (16 mo) in the CLEOPATRA trial. The interplay between radiologically assessed PFS and OS in advanced breast cancer is a complex one but a greater difference in OS vs PFS is now more commonly seen than before, partly because of ever greater radiological sophistication in assessment of disease progression. In addition, RECIST-derived durations of PFS frequently reflect differences in dimensions of disease which although satisfying RECIST criteria for disease progression represent changes in the amount of disease which are small in comparison to what the disease may have been at diagnosis and also small in terms of signifying the imminent onset of symptomatic deterioration.

14. There are currently no known biomarker tests which can predict those patients who derive much greater benefit from pertuzumab.

15. Should pertuzumab be recommended for this indication by NICE, NHSE would wish pertuzumab and intravenous trastuzumab to be given in combination with docetaxel. The evidence for the combination of paclitaxel, pertuzumab and trastuzumab is much less robust as currently there is only phase 2 evidence which for the 51 patients having this combination as first line treatment, the median OS was 44 mo.

16. The survival benefit of pertuzumab is such, together with the lack of any significant additional toxicity, that some patients with advanced breast cancer receiving pertuzumab do have the opportunity of resuming active and independent life styles for much longer than traditionally seen in patients receiving systemic therapy for advanced breast cancer. NHS England would therefore wish to observe that this health benefit to patients and their carers in respect of all the care within the NHS and personal social services budgets has been adequately captured in the cost effectiveness analysis.

17. NHS England also wishes to emphasize the high QOL for patients receiving pertuzumab during the PFS state. Given the degree of response to pertuzumab, it is likely that this good QOL will be preserved for a significant time during the post-progression disease state. The clinical benefit of pertuzumab is thus not just in the PFS state (as the PFS duration indicates versus that of the OS duration) but also in terms of the QOL experienced by patients in the earlier part of the post progression state.

18. Wastage of pertuzumab is likely to be low in NHS practice. NHS England places great emphasis on oncology pharmacies minimising waste of any product that needs reconstitution for parenteral use. Batching of reconstitution of pertuzumab is now normal practice and hence wastage is kept to a minimum. In many treating units/centres, patients on pertuzumab and in the chemotherapy phase of their treatment are checked the day before as to their fitness for treatment. Once the pertuzumab plus trastuzumab phase

commences, it is rare for patients not to receive the drugs when scheduled to do so as the combination is so well tolerated.

19. NHS England recognises the challenge imposed when one drug works very well (pertuzumab) but part of that efficacy translates into a greater period of treatment of another drug (intravenous trastuzumab). This challenge is increased by the presence of a low but significant percentage of patients who are 'super responders' ie have many years of treatment of the combination and thus this consequence significantly increases the mean treatment cost over that of the median.

20. 2017 will see the availability of biosimilar intravenous trastuzumabs and hence NHS England expects to see the cost paid by the NHS for intravenous trastuzumab to fall significantly. This therefore means that the incremental cost of docetaxel/pertuzumab/trastuzumab over docetaxel/trastuzumab will fall. As yet, NHS England does not know the prices of such biosimilar intravenous trastuzumabs but intends to maximise the opportunity of such savings by offering appropriate incentives to NHS Trusts.

Chair NHS England Chemotherapy Clinical Reference Group and National Clinical Lead for the Cancer Drug Fund.

February 2017

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Pertuzumab in combination with trastuzumab and docetaxel for the treatment of HER2 positive metastatic or locally recurrent unresectable breast cancer

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Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: Dr Helena Earl

Name of your organisation: NCRI/RCP/RCR/ACP/JCCO

Are you (tick all that apply):

√ a specialist in the treatment of people with the condition for which NICE is considering this technology?

√ a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?

- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)?
- other? (please specify)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS?
First-line HER2+ve metastatic breast cancer at present is treated in the NHS with trastuzumab concomitantly with chemotherapy (often docetaxel). The CLEOPATRA trial ran from 2008 to 2010, and it is of interest that in the publication (Baselga J, Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. NEJM 2012;366:109-19) only 10-11% of patients had received trastuzumab in the neo/adjuvant setting. Today the percentage of patients relapsing with metastatic HER2+ve breast cancer would be much higher, and in the UK over 90% of HER2+ve patients under the age of 75yrs would receive trastuzumab in the neo/adjuvant setting. The trial eligibility criteria included a 12 month treatment free interval. Currently in the NHS, even with neo/adjuvant trastuzumab, after 12 months standard treatment would be trastuzumab and docetaxel. Therefore the treatment for this condition currently is the control / standard arm of the Cleopatra study.

Is there significant geographical variation in current practice?
No significant geographical variation.

Are there differences of opinion between professionals as to what current practice should be?
No substantial disagreements amongst professionals about current practice for firstline relapse without CNS disease.

What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?
Pertuzumab represents an addition to the current technology. There is no alternative at present.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient?
In the era before the availability of neo/adjuvant trastuzumab, the HER2 subgroup of breast cancer patients had the worse prognosis (Curtis et al. The genomic and transcriptomic architecture of 2,000 breast tumours reveals novel subgroups. Nature. 2012 Apr 18;486(7403):346-52). This work led by Caldas, shows that integrative cluster 5 which is predominantly HER2+ve, shows the fastest rate of relapse within the first 5 years. This is shown in all other trial databases in the pre-trastuzumab era. The subgroup eligible for the CLEOPATRA trial, is probably a prognostically more favourable sub group of the HER2 breast cancer population. In particular, most had not received neo/adjuvant trastuzumab, and 12 months had passed since the end of adjuvant treatment. Patients excluded from this trial are those who (not having received trastuzumab), relapsed within the first 12 months. The majority of the population treated in the CLEOPATRA trials is trastuzumab naïve, and therefore there is no chance of resistance to anti-HER2 treatment having developed.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?
So far our experts have looked at how the patients got onto the trial, rather than examining the characteristics of those who were eligible. No particular subgroup seem more at risk from the new technology. The new technology may cause more heart damage, and therefore patients had an upper limit of previous doxorubicin exposure of 360mg/m2. This represents a quite low level of previous exposure which is usually at 450-500mg/m2. The risk of previous anthracycline cardiac damage is going to be very low in this group. Pertuzumab is possibly more active in patients with visceral rather than non-visceral (bone) metastatic disease.

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics?
Pertuzumab would be prescribed in secondary care, but can be delivered either in primary or secondary care, or in the patients own home. Trastuzumab is at present successfully delivered in this way.

Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?
See above.

If the technology is already available, is there variation in how it is being used in the NHS?
The technology has been made available in 2 ways. The PERUSE trial (a phase IV trial) has made Pertuzumab available in the NHS, and the National CDF has agreed its use in first relapse (12 months post adjuvant trastuzumab) for HER2+ve breast cancer pending the NICE single technology appraisal.
The introduction of National CDF Approved lists on April 1st, should mean there is no variation in the take-up of new technology.

Is it always used within its licensed indications? If not, under what circumstances does this occur? N/A

Please tell us about any relevant clinical guidelines and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.
The National CDF has agreed its use in first relapse (12 months post adjuvant trastuzumab) for HER2+ve breast cancer pending the NICE single technology appraisal. The CDF agrees first line metastatic use with docetaxel and trastuzumab, in patients who have a 12 month treatment-free interval from all adjuvant treatment.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

The technology is very similar to using trastuzumab, and will be given concomitantly with it. All the mechanisms for delivery of IV monoclonal antibodies are well worked out; the only issue will be that delivery will take longer adding at least one hour to each delivery time.

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

Except for apply the same criteria as in the trial, we are not aware of the development of informal or formal starting or stopping rules.

In view of the fact that the majority of the patients in the CLEOPATRA Trial had NOT received trastuzumab or any other anti-HER2 directed therapy in adjuvant setting before relapsing and going into the trial. The 12 month treatment-free interval is likely to mean that (even in those patients who do receive trastuzumab in the adjuvant setting) patients remain sensitive to HER2 directed therapy. It is likely that patients who are *a priori* resistant to trastuzumab, and those who develop resistance during their adjuvant treatment, would relapse within the 12 months after completion of therapy, and therefore would not fulfil the criteria for Pertuzumab treatment.

The unanswered question is whether metastatic disease in patients who have received adjuvant HER2-directed therapy (mostly trastuzumab), has changed its biological nature and become HER2-ve. In the trial, since over 85% of patients had not received previous HER2-directed therapy, this is unlikely to be the case. However in the environment in which the technology will be delivered in 2013 onwards, the majority of patients will have received HER2-directed therapy as an adjuvant treatment.

The possibility of a biological change in the nature of HER2+ve breast cancer at relapse is evidenced by the change in the shape of the survival curves (progression-free and overall survival) from the 8 year FU of the HERA trial reported recently. The original HERA reports demonstrated an early and dramatic improvement in DFS and OS. This report gives longer term FU and also examines 12 versus 24 months (12 months shows no additional benefit). The survival curves for treated patients shows a small but gradual year-on-year increase in relapses. However the shape of the curve has a very gradual slope, much more similar to hormone receptor positive breast cancer.

The biological question is – Has all HER2+ve disease been eradicated leaving a more indolent breast cancer population subgroup? The effectiveness of dual HER2-directed therapy will be significantly dependent on the answer to this question.

Pertuzumab added to trastuzumab and docetaxel, as evidenced by the CLEOPATRA study, provides a significant improvement in firstline metastatic therapy for HER2+ve breast cancer, previously untreated with HER-directed therapy.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

However in 2013, the majority of our patients in this category will have received previous trastuzumab.
Should we consider biopsy of metastatic disease to confirm persisting HER2+ve status?

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice.
Yes, in broad terms. Increasingly the majority of patients will have received neo/adjuvant trastuzumab, rather than in the trial where it was the minority. Although the trial presents results broken down into the subgroup who had received previous trastuzumab, this subgroup is only 88 patients, and represents only 10-11% of the trial population.

Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting?
The eligibility criteria of a 12 month DFI should probably be maintained in clinical practice if pertuzumab use is accepted in this NICE appraisal.

What, in your view, are the most important outcomes, and were they measured in the trials?
Disease-free survival is an important outcome in metastatic breast cancer trials. In a disease for which there is available many subsequent lines of treatment, overall survival without control of crossover to active treatment, becomes a somewhat meaningless outcome measure. The primary endpoint was independently assessed disease-free survival, which we believe is the most appropriate in metastatic breast cancer.

If surrogate measures of outcome were used, do they adequately predict long-term outcomes?
This trial restricted the use of cross-over, and it was not allowed until the primary endpoint analysis had been published. In that situation when the cross-over to pertuzumab of the control arm is likely to be minimal, the disease-free survival should predict overall survival. This information is now available and a six month DFS advantage, translates into a six month overall survival advantage...

What is the relative significance of any side effects or adverse reactions?
No increase in cardiac problems was found. Some increase in non-life-threatening and temporary side effects. Relatively insignificant.

In what ways do these affect the management of the condition and the patient's quality of life?
Not significantly.

Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?
No

Any additional sources of evidence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

A manuscript describing overall survival in the CLEOPATRA study has been prepared and the contents may be made available to NICE appraisals committee. The manuscript has been published – Swain SM et al. Pertzumab, trastuzumab and docetaxel for HER2-positive breast cancer (CLEOPATRA Study): overall survival results from a randomised double-blind, placebo-controlled phase 3 study Lancet Oncology 2013 May;14(6):461-71

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within
3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition?
Patients would benefit in terms of disease-free and probably overall survival from pertuzumab.

Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?
No significant increase in training. Only resources would increase pharmacy and delivery in chemotherapy day unit facilities.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed; No exclusions on these grounds
- **could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;** No
- **could lead to recommendations that have any adverse impact on people with a particular disability or disabilities**. No

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.
N/A
Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

No additional information

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Pertuzumab in combination with trastuzumab and docetaxel for the treatment of HER2 positive metastatic or locally recurrent unresectable breast cancer, which has not been previously treated, or has relapsed after adjuvant therapy

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: David Miles

Name of your organisation: UK Breast Cancer Group

Are you (tick all that apply):

- ✓ a specialist in the treatment of people with the condition for which NICE is considering this technology?
- ✓ a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- ✓ an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate ~~(e.g. policy officer, trustee~~, member etc.)?
- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

None

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

In people with HER2-positive breast cancer, a subtype of breast cancer normally associated with a relatively poor prognosis, the use of the humanised monoclonal antibody to HER2, trastuzumab, in combination with chemotherapy demonstrated improved survival compared to chemotherapy alone. As a consequence, NICE guidelines for the treatment of HER2-positive metastatic breast cancer published in 2009, recommended the use of trastuzumab and the combination has become the standard of care since.

Resistance to trastuzumab was demonstrably reversed by the addition of a second antibody, pertuzumab in a phase II study. In a subsequent randomised, placebo controlled phase III study involving over 800 patients with HER2-positive metastatic breast cancer (the CLEOPATRA study), the addition of pertuzumab to trastuzumab and docetaxel chemotherapy, lead to improvements in response rates, progression-free survival and demonstrated an improvement in survival of 15.7 months. This survival benefit is unprecedented in metastatic breast cancer and indeed most common epithelial malignancies. While increased occurrence of some side-effects was observed, these were predominantly during the concurrent chemotherapy administration, with patients tolerating antibodies alone with relatively little toxicity. The quality of life during this improved survival was therefore maintained.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

The data from the CLEOPATRA study are a logical extension of clinical practice in the UK by addition of the second antibody, pertuzumab, to an established regimen leading to a large improvement in survival, with little incremental toxicity. For people with metastatic breast cancer, good quality survival is the most relevant objective and was clearly demonstrated in this study.

The applicability of the data have been demonstrated more recently at the San Antonio Breast Cancer Symposium (SABCS). Bachelot & Miles et al demonstrated progression-free survival similar to that observed in the randomised study, in a phase IIIb setting of nearly 1500 patients with HER2-positive metastatic breast cancer,

The clinical data are well known to the oncology community and more importantly, in the last couple of years UK clinicians have considerable experience with the use of pertuzumab in addition of trastuzumab and chemotherapy. In a recent survey of breast cancer clinicians (UK Breast Cancer Group), when considering medicines on the Cancer Drug Fund list, pertuzumab was identified as the agent that they would most like to retain access to, with pertuzumab and trastuzmab-emtansine being the only medicines deemed essential to retain.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Equality and Diversity

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- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

The applicability of the data have been demonstrated more recently at the San Antonio Breast Cancer Symposium (SABCS). Bachelot & Miles et al demonstrated progression-free survival similar to that observed in the randomised study, in a phase IIIb setting of nearly 1500 patients with HER2-positive metastatic breast cancer.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Pertuzumab in combination with trastuzumab and docetaxel for the treatment of HER2 positive metastatic or locally recurrent unresectable breast cancer

Please sign and return to:

Marcia Miller, Technology Appraisal Administrator
Email: TACommA@nice.org.uk
Fax: +44 (0)20 7061 9721
Post: NICE, 10 Spring Gardens, London, SW1A 2BU

I confirm that:

- I agree with the content of the statement submitted by **Breast Cancer Care** and consequently I will not be submitting a personal statement.

Name: .....Tara Beaumont.....

Signed: .....

.....

Date: .....30.05.13.....

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Pertuzumab in combination with trastuzumab and docetaxel for the treatment of HER2 positive metastatic or locally recurrent unresectable breast cancer

I confirm that:

- I agree with the content of the statement submitted by **Breakthrough Breast cancer** and consequently I will not be submitting a personal statement.

Name: Dr Caroline Dalton.....

Signed: .....

Date: 03/07/2013.....

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Pertuzumab in combination with trastuzumab and docetaxel for the treatment of HER2 positive metastatic or locally recurrent unresectable breast cancer

Thank you for agreeing to give us your views on the technology and the way it should be used in the NHS.

Patients and patient advocates can provide a unique perspective on the technology, which is not typically available from the published literature.

To help you give your views, we have provided a template. The questions are there as prompts to guide you. You do not have to answer every question. Please do not exceed the 8-page limit.

About you

Your name:
Melanie Sturtevant

Name of your organisation:
Breast Cancer Now

Are you (tick all that apply):

- a patient with the condition for which NICE is considering this technology?
- a carer of a patient with the condition for which NICE is considering this technology?
- **an employee of a patient organisation that represents patients with the condition for which NICE is considering the technology? If so, give your position in the organisation where appropriate (e.g. policy officer, trustee, member, etc)**

  Policy Manager

- other? (please specify)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

What do patients and/or carers consider to be the advantages and disadvantages of the technology for the condition?

1. **Advantages**
(a) Please list the specific aspect(s) of the condition that you expect the technology to help with. For each aspect you list please describe, if possible, what difference you expect the technology to make.

This review considers the use of pertuzumab in combination with trastuzumab and docetaxel for the treatment of patients with HER2 positive breast cancer that has advanced or locally recurred. This is a first line indication. The alternative treatment for these women would be trastuzumab and docetaxel.

HER2 positive breast cancer is so called due to the presence of the HER2 receptor on the surface of the cancer cells. It is these receptors that are targeted by trastuzumab. However, it is possible for HER2 positive cancer cells to evade destruction by trastuzumab. They do this by forming pairs with other receptors that are members of the HER family and it is these resulting dimers which can ultimately lead to tumour growth and survival. Pertuzumab is able to limit tumour growth and promote cancer cell destruction by blocking the pairing of HER2 family proteins.

The CLEOPATRA trial demonstrated that pertuzumab in combination with trastuzumab and docetaxel extended both progression free survival, and overall survival compared to trastuzumab and docetaxel alone. Specifically, patients who received pertuzumab had an additional 6.3 months progression free survival compared to patients who received only trastuzumab and docetaxel; and an additional 15.7 months overall survival.

(b) Please list any short-term and/or long-term benefits that patients expect to gain from using the technology. These might include the effect of the technology on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (lifestyle, work, social functioning etc.)
- other quality of life issues not listed above
- other people (for example family, friends, employers)
- other issues not listed above.

As described above, pertuzumab in combination with trastuzumab and docetaxel can offer patients enhanced progression free survival and overall survival, compared to treatment with trastuzumab and docetaxel alone. We know that patients who have

locally recurrent or metastatic breast cancer, for which there is no cure, value treatments that can help them control their cancer and stop it progressing, as well as extending the time they have with their loved ones. This can give them a more positive outlook on their treatment regime and the course of their illness.

Delaying the progression of their condition, as well as extending the time they have left with their loved ones, especially when associated with few severe side effects, enable patients with metastatic breast cancer to continue with many aspects of their normal daily life.

2. **Disadvantages**
Please list any problems with or concerns you have about the technology.
Disadvantages might include:

- aspects of the condition that the technology cannot help with or might make worse.
- difficulties in taking or using the technology
- side effects (please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- impact on others (for example family, friends, employers)
- financial impact on the patient and/or their family (for example cost of travel needed to access the technology, or the cost of paying a carer).

In the interim analysis of the CLEOPATRA trial the side effects that were at least 5% more common in pertuzumab in combination with trastuzumab and docetaxel, than trastuzumab and docetaxel alone were diarrhoea, rash, mucosal inflammation, febrile neutropenia and dry skin. Most were seen during administration of docetaxel and declined after this was discontinued. Additional side effects that were at least 5% more common in the final analysis were headache, upper respiratory tract infection and muscle spasm.

In terms of side effects that were grade 3 or above, neutropenia, febrile neutropenia, and diarrhoea occurred more often in those taking pertuzumab in combination with trastuzumab and docetaxel:
-neutrophenia - 48.9% with pertuzumab, 45.8% without
-febrile neutrophenia - 13.8% with pertuzumab, 7.6% without
-diarrhoea – 7.9% with pertuzumab, 5% without.

Patients are often willing to accept side effects as part of their treatment so long as they know what to expect and have been given all the necessary information before they begin treatment. Certainly, when side-effects are associated with gains in progression free survival and/or overall survival many patients are willing to accept these side effects.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

3. Are there differences in opinion between patients about the usefulness or otherwise of this technology? If so, please describe them.

As highlighted above patients will differ in their willingness to accept risks associated with different treatment regimes. It is therefore very important that all patients are made aware and fully understand the possible risks and benefits of a treatment before making a decision about their treatment options.

4. Are there any groups of patients who might benefit **more** from the technology than others? Are there any groups of patients who might benefit **less** from the technology than others?

Not all breast cancer patients will benefit from this treatment because, as described above, it is only appropriate for the treatment of patients with the HER2 positive category of the disease. This appraisal considers pertuzumab use as a first line treatment for metastatic disease. NICE has approved pertuzumab for primary breast cancer for use in a neoadjuvant setting.

Comparing the technology with alternative available treatments or technologies

NICE is interested in your views on how the technology compares with existing treatments for this condition in the UK.

(i) Please list any current standard practice (alternatives if any) used in the UK.

Pertuzumab in combination with trastuzumab and docetaxel is currently available through the Cancer Drugs Fund. The alternative would be treatment with trastuzumab and docetaxel alone.

(ii) If you think that the new technology has any **advantages** for patients over other current standard practice, please describe them. Advantages might include:

- improvement in the condition overall
- improvement in certain aspects of the condition
- ease of use (for example tablets rather than injection)
- where the technology has to be used (for example at home rather than in hospital)
- side effects (please describe nature and number of problems, frequency, duration, severity etc.)

As described above, pertuzumab in combination with trastuzumab and docetaxel gives patients an additional 6.3 months of progression free survival and 15.7 months of overall survival compared to trastuzumab and docetaxel alone.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

(iii) If you think that the new technology has any **disadvantages** for patients compared with current standard practice, please describe them. Disadvantages might include:

- worsening of the condition overall
- worsening of specific aspects of the condition
- difficulty in use (for example injection rather than tablets)
- where the technology has to be used (for example in hospital rather than at home)
- side effects (for example nature or number of problems, how often, for how long, how severe).

Some side effects are more likely in patients who receive pertuzumab in combination with trastuzumab and docetaxel, than those who receive trastuzumab and docetaxel alone. These are described in more detail in section 2 above.

Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

Not applicable.

Research evidence on patient or carer views of the technology

If you are familiar with the evidence base for the technology, please comment on whether patients' experience of using the technology as part of their routine NHS care reflects that observed under clinical trial conditions.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Insofar as we are aware, patients experience of using pertuzumab as part of their routine NHS care reflects that observed under clinical trial conditions.

Are there any adverse effects that were not apparent in the clinical trials but have come to light since, during routine NHS care?

None that we are aware of.

Are you aware of any research carried out on patient or carer views of the condition or existing treatments that is relevant to an appraisal of this technology? If yes, please provide references to the relevant studies.

None that we are aware of.

Availability of this technology to patients in the NHS

What key differences, if any, would it make to patients and/or carers if this technology was made available on the NHS?

Patients are currently accessing pertuzumab in combination with trastuzumab and docetaxel on the NHS through the Cancer Drugs Fund. A positive recommendation from NICE would ensure this treatment remains available on the NHS and enable patients to continue to access to a treatment which is both generally well tolerated, and provides significant progression free survival and overall survival benefits.

What implications would it have for patients and/or carers if the technology was **not** made available to patients on the NHS?

As patients are currently accessing pertuzumab in combination with trastuzumab and docetaxel on the NHS through the Cancer Drugs Fund, it is more a case of the treatment being withdrawn from patients on the NHS than it not being made available to them.

Pertuzumab represents one of the most positive advances in the treatment of HER2 positive metastatic breast cancer in recent years. The prospect of a treatment that provides significant progression free survival and overall survival benefits for patients, and which is generally well tolerated, not being available on the NHS will likely cause a huge amount of distress and concern for patients and their loved ones. This distress is only likely to be heightened by the fact that this treatment is currently available to patients on the NHS through the Cancer Drugs Fund.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Are there groups of patients that have difficulties using the technology?

None that we are aware of.

Other Issues

Please include here any other issues you would like the Appraisal Committee to consider when appraising this technology.

ERG REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Pertuzumab for HER2-positive metastatic or locally recurrent unresectable breast cancer [ID523]

CDF rapid reconsideration

Confidential until published

This report was commissioned by the NIHR HTA Programme as project number 08/206/01

Completed 22 December, 2016

Redacted

UNIVERSITY OF LIVERPOOL | LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

1 INTRODUCTION

The National Institute for Health and Care Excellence (NICE) is in the process of assuming responsibility for the Cancer Drugs Fund (CDF). The CDF provided a mechanism for some cancer treatments which failed to receive a positive recommendation when originally appraised for clinical and cost effectiveness for general use in the NHS, to be provided, on a case-by-case basis to selected patients referred to the CDF by their clinician. As part of the transition, a number of historic technology appraisal decisions are being rapidly reconsidered to determine the future status of treatments currently provided only through the CDF, i.e. whether they may now be recommended for general use, continue within the scope of the revised CDF scheme, or not be provided at all through the NHS. The Liverpool Reviews and Implementation Group (LR*i*G) at the University of Liverpool has been commissioned to review the company submission (CS) to assist a NICE Appraisal Committee (AC) in reconsideration of the use of pertuzumab (Perjeta®) in combination with trastuzumab and docetaxel for the treatment of HER2-positive metastatic or locally recurrent unresectable breast cancer who have not previously received chemotherapy or HER2 directed treatment for metastatic disease or whose disease has recurred after adjuvant therapy. The original Single Technology Appraisal (STA) was conducted in 2013, but final NICE guidance was never issued due to uncertainty concerning the initial finding that pertuzumab could not be considered cost-effective even at zero cost to the NHS.

1.1 Context and approach to rapid reconsideration

To allow these rapid reconsideration exercises to proceed with the minimum risk of delay, the procedures have been restricted in scope for the company making a resubmission and for the Evidence Review Group (ERG) who is tasked with providing an independent assessment of the Company Submission (CS). In the case of this appraisal the CS included updated clinical follow-up data and consideration of some of the areas considered by the previous Appraisal Committee (AC).

2 SPECIFIC DETAILS OF THIS RAPID RECONSIDERATION

2.1 Considerations from initial consideration and new CS

As with the original submission the primary data considered in the CS comes from the CLEOPATRA trial.[1] Details of the trial characteristics are presented in **Error! Reference source not found.**

Table 1 CLEOPATRA[1] trial characteristics

Characteristic	Description
Size	808 patients were enrolled
Location	International (204 centres in 25 countries)
Design	Randomised, double-blind, placebo-controlled, phase III trial
Intervention	Pertuzumab + trastuzumab + docetaxel (n=402) • Pertuzumab: loading dose of 840mg/kg IV infusion, followed by 420mg/kg IV every 3 weeks (q3w) • Trastuzumab: loading dose of 8mg/kg IV infusion, followed by 6mg/kg IV q3w • Docetaxel dose of 75mg/m^2 IV infusion q3w for at least six cycles[a]
Comparator	Placebo + trastuzumab + docetaxel (n=406) • Pertuzumab placebo: IV infusion (q3w) • Trastuzumab: loading dose of 8mg/kg IV infusion, followed by 6mg/kg IV infusion q3w • Docetaxel dose of 75mg/m^2 IV infusion q3w for at least six cycles[a]
Duration	Treatment was given until investigator assessed radiographic or clinical progressive disease (or unacceptable toxicity or withdrawal of patient consent) Participants were withdrawn from the study if pertuzumab or placebo and/or trastuzumab were permanently discontinued or withheld for more than two cycles of treatment. If docetaxel was permanently discontinued for unacceptable toxicity, withdrawal from the study was not required. Dose reductions were not permitted for placebo, pertuzumab, or trastuzumab
Method of randomisation	Randomisation in a 1:1 ratio and stratified with the following baseline factors: • Geographic region (Asia, Europe, North America, or South America) • Prior treatment status (prior adjuvant or neoadjuvant chemotherapy vs none)
Method of blinding (care provider, patient and outcome assessor)	Investigators, site staff, and monitors remain blinded until the end of the study, except in cases of suspected, unexpected, serious adverse events considered related to study medication
Method of allocation	Patient identification numbers were allocated sequentially in the order in which the participants were enrolled using an Interactive Voice Response System
Primary endpoint	Progression-free survival (IRF, first data-cut)[b]
Secondary endpoints	Progression-free survival (local investigator- assessed, first data-cut and second data-cut)[b] Overall survival (first data-cut, second data-cut) Objective response rate (first data-cut)[b] Duration of objective response (first data-cut) Health related quality of life – time to symptom progression (first data-cut and second data-cut) Safety parameters (first data-cut and second data-cut): • Incidence of CHF and asymptomatic LVEF events • LVEF measurements over the course of the study • Incidence and severity of AEs and serious adverse events (SAEs) • Laboratory test abnormalities
Duration of follow-up	First data-cut (May 2011) – median follow-up of 19 months Second data-cut (May 2012) – median follow-up of 30 months

CHF-Congestive Heart Failure; IRF=independent review facility; LVEF-Left ventricular ejection fraction
[a] may be increased to 100mg/m^2 at the investigators discretion
[b] Using RECIST criteria

Pertuzumab drug costs

The company has proposed a new pertuzumab price of [redacted], which incorporates a patient access scheme (PAS). The company states that this new price represents a [redacted] from the list price (£2,395).

It is worth noting that the CS also contained details of a complex commercial access agreement (CAA) that had been submitted, was not approved and therefore is not considered in this report.

3 MODEL ALTERATIONS

The CS is based on a modified version of the decision model used in the original technology appraisal (ID523), with amendments to address some of the issues highlighted by the ERG in their 2013 report and specifically considered by the Appraisal Committee[2] In addition the company received agreement from NICE to submit additional published evidence of the final results of the CLEOPATRA trial [3] as part of this rapid reconsideration. In particular the company's revised decision model incorporates new data relating to overall survival (OS), progression-free survival (PFS) and time-to-off-treatment (TTOT). The ERG has used digitized values from the Swain paper in order to validate the OS and PFS trends used in the updated company model, and Kaplan-Meier TTOT data incorporated in the company model to validate TTOT trends.

3.1 Updated Time to Event data

3.1.1 Updated PFS analysis

Figure 1reveals clearly a distinct change in hazard trend in both trial arms, from 21 months in the pertuzumab arm, and from 27 months in the comparator arm. The ERG has calibrated revised PFS data for the updated model using the trial Kaplan-Meier values for both arms as far as possible, followed by the estimated long-term exponential projective models thereafter (a linear trend in cumulative hazard is equivalent to an exponential trend in PFS). The estimated mean time in PFS is 37.1 months for those treated with pertuzumab, and 24.7 months for control patients, indicating a net mean PFS gain of 12.4 months attributable to treatment with pertuzumab.

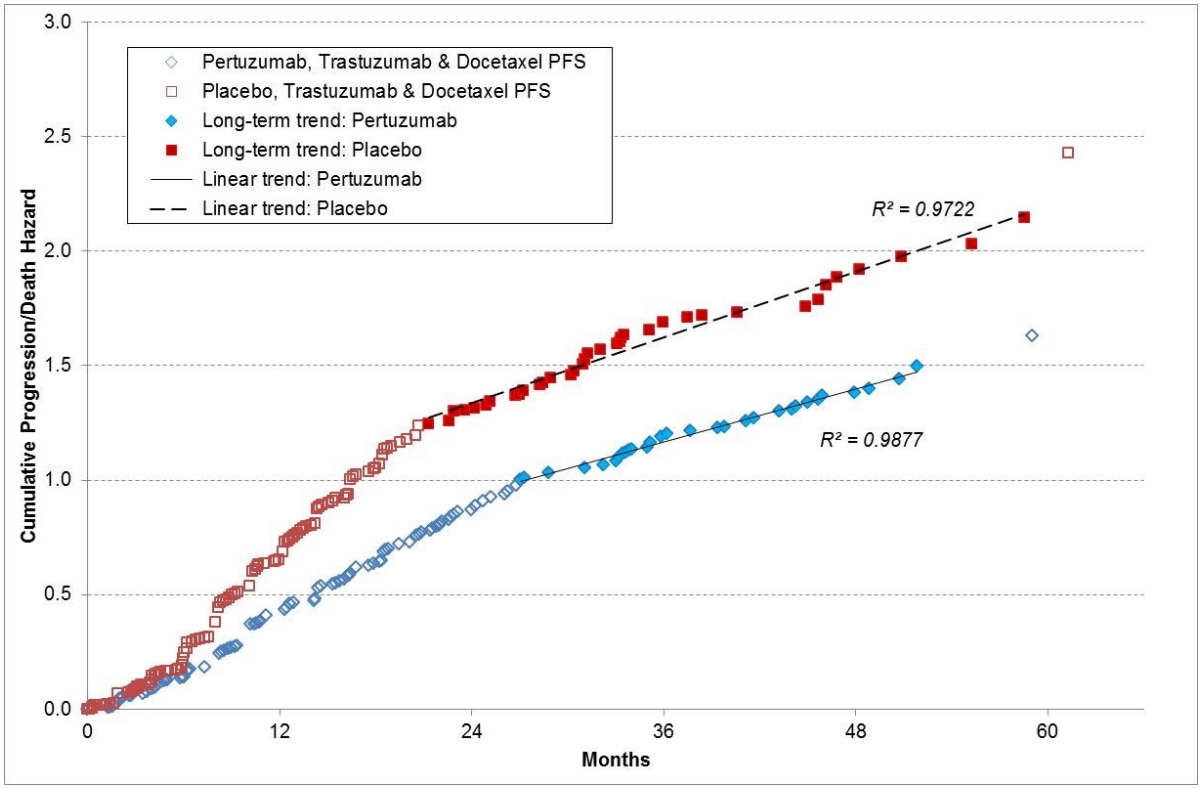

Figure 1: Updated PFS cumulative hazard trends using digitized data from CLEOPATRA trial[3] (mean PFS is estimated by the area under curve (AUC) from time zero to the last event used for trend calibration, followed by fitted long-term exponential projection to end of life)

3.1.2 Updated OS analysis

The OS updated data (Figure 2) show very clear 2-phase trends with low mortality rates in the first 11 months, followed by higher steady mortality rates thereafter. Using the trial Kaplan-Meier values for both arms as far as possible, followed by the estimated long-term exponential projective OS models thereafter, the estimated mean OS is 82.1 months for those treated with pertuzumab, and 58.2 months for control patients, indicating a net mean OS gain of 23.9 months attributable to treatment with pertuzumab.

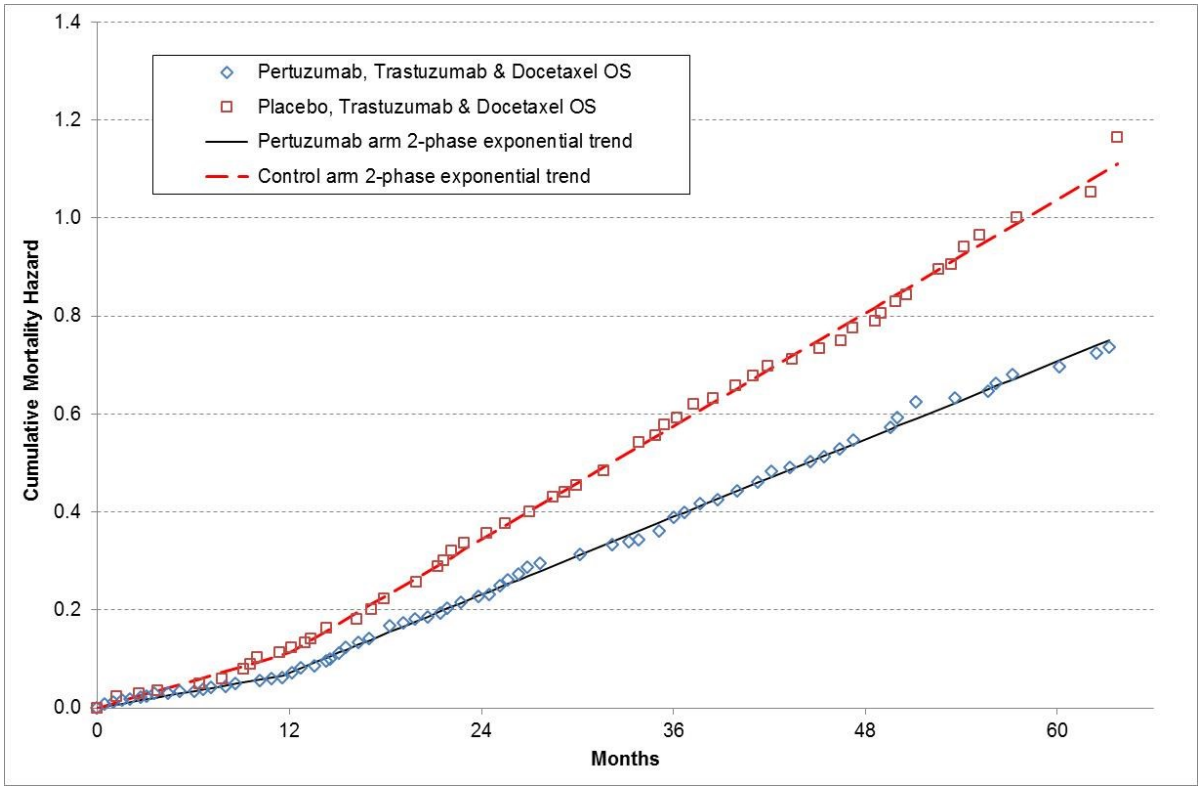

Figure 2: Updated OS cumulative hazard trends using digitized data from CLEOPATRA trial[3] (mean OS is estimated by the area under curve (AUC) from time zero to the last event recorded, followed by the fitted long-term exponential projection to end of life)

3.1.3 Update TTOT analysis

[redacted]Figure 3[redacted]

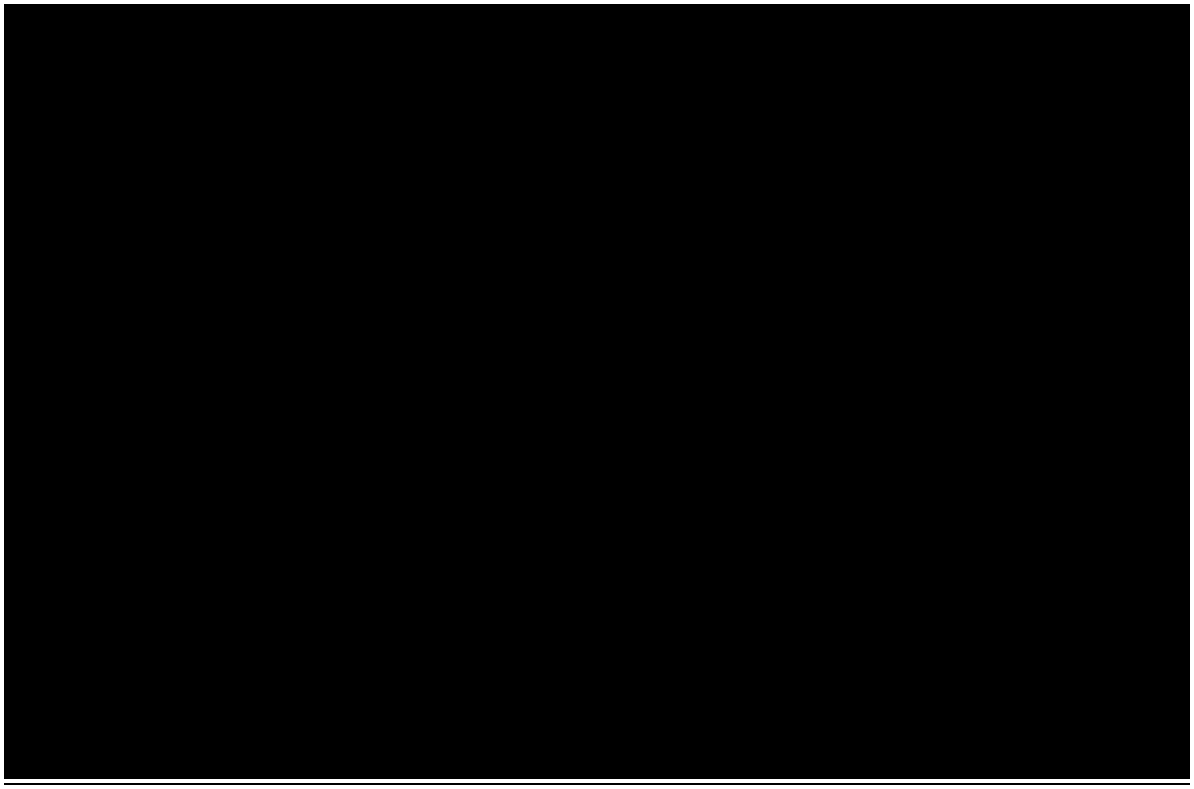

Figure 3 (mean TTOT is estimated by the area under curve (AUC) from time zero to the last event recorded, followed by the fitted long-term exponential projection to end of life)

3.1.4 Estimated drug acquisition costs per dose

In the original ERG report on the company submission for pertuzumab in combination with trastuzumab and docetaxel for the treatment of HER2 positive metastatic or locally recurrent unresectable breast cancer, the ERG commented on the approach taken to estimating the acquisition cost per dose of three drugs (trastuzumab, docetaxel and paclitaxel) as follows:

"*Treatments with doses calculated according to individual body weight (trastuzumab) or according to BSA (docetaxel and paclitaxel) were calculated using the body measurements of all patients in the CLEOPATRA[1] trial, and an average cost calculated for each drug. However, CLEOPATRA18 is a multi-national clinical trial with patients entered from centres in four continents. An analysis of patient characteristics by region indicates wide differences in body weight and size, ranging from Asians with an average weight of 57.0 kg and BSA of 1.55m^2 to North Americans with mean weight of 74.0 kg and BSA of 1.77m^2. The ERG considers that using the average characteristics of the whole CLEOPATRA18 trial is likely to underestimate the doses that would be required for UK patients. The ERG has re-estimated chemotherapy acquisition costs using published survey estimates for England and Wales*"

The revised company model submitted for reconsideration does not take account of this important ERG amendment. In addition, no account is taken of the cost of concomitant medications required with paclitaxel treatment. The ERG has re-estimated the cost per dose for the three treatments. The results are compared with the costs used in the revised company model in Table 1.

Table 2 Comparison of the mean acquisition costs per dose of model treatments, between the revised company model and the ERG.

Treatment	Revised company model	Updated ERG estimates
Trastuzumab 1st dose	£1,638.17	£1,745.09
Trastuzumab later doses	£1,284.72	£1,360.81
Docetaxel all doses	£25.09	£25.61
Paclitaxel all doses	£15.94	£24.00*

Prices from 'Drugs and pharmaceutical electronic market information (eMit)' 4 May 2016
* Including dexamethasone, chlorphenamine and ranitidine

3.1.5 Cost of drug administration

The revised company model features alterations to the calculation of drug administration, which have the effect of reducing the cost of the first cycle of treatment whilst increasing the cost for all subsequent cycles. An additional amendment has been introduced to account for subcutaneous administration of trastuzumab for some patients. No clear justification for these changes is given, and the logic of the model in this regard is too complex to allow their net impact on the estimated ICER to be readily estimated.

3.1.6 Cost of Adverse Events

The method of calculating the estimated cost of adverse events has been changed in the revised version of the company model, but the incremental cost of adverse events is virtually unchanged.

3.1.7 Health State Utility Values

The revised company model includes revised estimates of health state utilities derived from the Lloyd mixed-methods model,[4] correcting an error identified by the ERG in 2013. However, there remains an important uncorrected error in the method used to estimate utilities: the age variable in the Lloyd algorithm has been assumed to reflect the average age of patients in the clinical trial. This is incorrect; it relates to the age of respondents to the Standard Gamble exercise and should be amended to ensure compatibility with the general calibration of utility values. The results were exemplified in Lloyd's Table 3 using and age of 38.2 years (equivalent to the whole UK population), but to achieve compatibility with UK EQ-

5D utility values, the age parameter should be set to 47.055, the mean age of respondents in the original MVH calibration survey.[6]

Table 3provides a comparison between utility values included in the company's revised model, and those calculated by the ERG, consistent with the UK EQ-5D standard tariff.

Table 3: Comparison of the mean health state utility values as estimated in the revised company model and by the ERG.

Health state	Revised company model	ERG estimate
PFS: Pertuzumab + Trastuzumab + Docetaxel (on Docetaxel treatment)	0.7922	0.7827
PFS: Pertuzumab + Trastuzumab + Docetaxel (post-Docetaxel treatment)	0.8099	0.7989
PFS: Placebo + Trastuzumab + Docetaxel (on Docetaxel treatment)	0.7927	0.7864
PFS: Placebo+ Trastuzumab + Docetaxel (post-Docetaxel treatment)	0.8022	0.7952
Progressive disease	0.5349	0.4964

4 RESULTS

Table 4 summarises the cost effectiveness results obtained using the revised decision model submitted by the company, together with results using the various ERG corrections and revisions described above. The ERG's preferred options result in an estimated ICER of £127,268 per QALY gained for pertuzumab in combination with trastuzumab and docetaxel compared with trastuzumab and docetaxel for patients with metastatic or recurrent unresectable HER-2 positive breast cancer without the PAS, an increase of more than £6,600 per QALY gain relative to the base case ICER in the company submission.

5 END OF LIFE

In the original submission there is no case put forward to consider this treatment within the NICE End of Life criteria.

However, the resubmission includes a case to be considered under the following criteria

- The combination of Perjeta and Herceptin offers a dramatic median extension to life of >15 months compared to Herceptin and docetaxel, which far exceeds the extension to life of 3 months specified by the end-of-life criteria.

- As such, assessment of Perjeta according to the end-of-life criteria should be considered in light of such a dramatic improvement in OS in a condition with a comparatively poor prognosis.
- The life expectancy of HER2+ mBC patients treated with chemotherapy alone in the first line is less than 2 years.[5]

6 CONCLUSION

The revised decision model submitted by the company includes the results of additional follow-up data from the CLEOPATRA clinical trial. This has obliged the ERG to revisit its previous analysis relating to OS and PFS, as well as the trial Kaplan-Meier data incorporated into the revised model for TTOT. The ERG has identified a number of other issues involving errors which impact on the estimated ICER, some previously described and some new to the revised model.

The combined result of the various recommended model amendments is that the estimated deterministic ICER increases by about £6,000 per QALY gained. Assuming the current PAS price for pertuzumab reduces the ICER to less than [redacted] per QALY gained. The company have requested that the AC consider this treatment in light of the NICE 'End of Life' criteria.

Table 4 Deterministic cost effectiveness (pertuzumab + trastuzumab + docetaxel versus trastuzumab): ERG revisions to company base case

Model scenario A, B, C ERG revision R1, R2, R3, R4, R5	Pertuzumab+Trastuzumab +Docetaxel			Trastuzumab+Docetaxel			Incremental			ICER	ICER
	Cost	QALYs	Life years	Cost	QALYs	Life years	Cost	QALYs	Life years	Per QALY gained	Change
A. Company updated base case	***£174,978***	***3.503***	***5.852***	***£62,495***	***2.570***	***4.292***	***£112,483***	***0.933***	***1.559***	***£120,586***	**-**
R1) ERG revised PFS estimates	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**-£11,001**
R2) ERG revised OS estimates	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**+£4,063**
R3) ERG revised TTOT estimates	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**+£7,484**
R4) ERG drug cost estimates	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**+£1,910**
R5) ERG health state utility value estimates	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**+£3,507**
B. ERG revised base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**+£6,682**
C. ERG revised base case with PAS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

7 REFERENCES

1. Baselga J, Cortes J, Kim SB, Im SA, Hegg R, Im YH*, et al.* Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. New Engl J Med. 2012; 366:109-19.

2. National Institute for Health and Care Excellence. Breast cancer (HER2 positive, metastatic) - pertuzumab (with trastuzumab and docetaxel) [ID523] London: NICE; 2013; Available from: http://guidance.nice.org.uk/index.jsp?action=byId&o=13815 (Accessed: 25 October 2013).

3. Swain SM, Baselga J, Kim SB, Ro J, Semiglazov V, Campone M*, et al.* Pertuzumab, trastuzumab, and docetaxel in HER2 positive metastatic breast cancer. New Engl J Med. 2015; 372:724-34.

4. Lloyd A, Nafees B, Narewska J, Dewilde S, Watkins J. Health state utilities for metastatic breast cancer. Br J Cancer. 2006; 95:683-90.

5. Roche Products Limited. Perjeta®(pertuzumab) for HER2-positive metastatic or locally recurrent unresectable breast cancer [ID523] company submission to NICE November, 2016: Roche Products Limited 2016.

6. Kind P, Hardman G, Macran S. UK population norms for EQ-5D. CHE Discussion Paper 172 Centre for Health Economics, University of York.

APPENDIX: ERG AMENDMENTS MADE TO COMPANY MODEL

Most revisions are activated by a logic switch with 0 = unchanged, 1 = apply ERG specified modification.

Relevant logic switches are indicated by range variables created in the 'Results' worksheet Mod_*n* where n = 1 – 6.

Summary results as used to transfer to the ERG report are shown in range 'Results'!D70:N70.

ERG Revision	Associated detail	Implementation details
R1. ERG OS estimates (Binary switch Mod_1)	ERG OS/PFS/TTOT estimates are included in the modified model worksheet "Pertuzumab" columns BO/BP/BQ and worksheet "Comparator"	In Sheet 'Pertuzumab' **Replace** formula in cell AK9 by =IF(Mod_1=1,BQ9,IF(dist_os_munich_num = "Yes", AG9, CHOOSE(MATCH(dist_os,options_OS,0),Y9,Z9,AA9,AB9,AC9,AD9,AJ9,AJ9,AJ9,AJ9,AJ9,AJ9,AE9))) **Copy** formula in cell AK9 and paste into range AK10:AK1626 In Sheet 'Comparator' **Replace** formula in cell AK9 by =IF(Mod_1=1,BR9,IF(dist_os_munich_num = "Yes", AG9, CHOOSE(MATCH(dist_os,options_OS,0),Y9,Z9,AA9,AB9,AC9,AD9,AJ9,AJ9,AJ9,AJ9,AJ9,AJ9,AE9))) **Copy** formula in cell AK9 and paste into range AK10:AK1626
R2. ERG PFS estimates (Binary switch Mod_2)	ERG OS/PFS/TTOT estimates are included in the modified model worksheet "Pertuzumab" columns BO/BP/BQ and worksheet "Comparator"	In Sheet 'Pertuzumab' **Replace** formula in cell W9 by =IF(Mod_2=1,BP9,IF(CHOOSE(MATCH(dist_pfs,options_PFS,0),N9,O9,P9,Q9,R9,V9,V9,V9,V9,V9, S9) < AK9, CHOOSE(MATCH(dist_pfs,options_PFS,0),N9,O9,P9,Q9,R9,V9,V9,V9,V9,V9, S9), AK9)) **Copy** formula in cell WK9 and paste into range W10:W1626 In Sheet 'Comparator',

ERG Revision	Associated detail	Implementation details
		Replace formula in cell W9 by =IF(Mod_2=1,BQ9,IF(CHOOSE(MATCH(dist_pfs,options_PFS,0),N9,O9,P9,Q9,R9,V9,V9,V9,V9,V9, S9) < AK9, CHOOSE(MATCH(dist_pfs,options_PFS,0),N9,O9,P9,Q9,R9,V9,V9,V9,V9,V9, S9), AK9)) **Copy** formula in cell W9 and paste to range W10:W1626
R3. ERG TTOT estimates (Binary switch Mod_3)	ERG OS/PFS/TTOT estimates are included in the modified model worksheet "Pertuzumab" columns BO/BP/BQ and worksheet "Comparator"	In Sheet 'Pertuzumab' **Replace** formula in cell AU9 by =IF(Mod_3=1,BO9,MIN(IF(tx_dur="Actual treatment duration",CHOOSE(MATCH(dist_ttot,options_TTOT,0),E9,F9,G9,H9,I9,M9,M9,M9,M9,M9,J9),W9),W9)) **Copy** formula in cell AU9 and paste to range AU10:AU1626 In Sheet 'Comparator', **Replace** formula in cell AU9 by =IF(Mod_3=1,BP9,MIN(IF(tx_dur="Actual treatment duration",CHOOSE(MATCH(dist_ttot,options_TTOT,0),E9,F9,G9,H9,I9,M9,M9,M9,M9,M9,J9),W9))) **Copy** formula in cell AU9 and paste to range AU10:AU1626
R4. ERG estimates of drug per cycle (Binary switch Mod_4)	None	In Sheet 'Model Inputs', **Enter** Cell N12 ='ERG estimates **Enter** Cell N13 = '1st cycle **Enter** Cell O13 = 'subsequent cycles **Enter** Cell N15 = 1745.09 **Enter** Cell N16 = 25.61 **Enter** Cell N17 = 24 **Enter** Cell O15 = 1360.81 **Enter** Cell O16 = 25.61 **Enter** Cell O17 = 24 **Replace** Cell H277 by =IF(Mod_4=1,18.3872,H275*25*dm_bsa) **Replace** Cell H279 by =IF(Mod_4=1,21.5661,H275*30*dm_bsa) **Replace** Cell H291 by =IF(Mod_4=1,1.936,H287*H289)
	None	In Sheet 'Model Inputs',

ERG Revision	Associated detail	Implementation details
R5. ERG health state utility estimates (Binary switch Mod_5)		Replace Cell K202 by =IF(Mod_5=1,M202,Utilities!E31)*P202 Replace Cell K203 by =IF(Mod_5=1,M203,Utilities!E32*P203) Replace Cell K204 by =IF(Mod_5=1,M204,Utilities!D31)*P202 Replace Cell K205 by =IF(Mod_5=1,M205,Utilities!D32)*P203 Replace Cell K206 by =IF(Mod_5=1,M206,Utilities!V21)*P204 Set Cell M202= 0.788424849097162 Set Cell M203= 0.804337153390536 Set Cell M204= 0.79208071943801 Set Cell M205= 0.800698795519705 Set Cell M206= 0.505217457431789
R6. Apply PAS discount	None	Replace “Model Inputs”!G14 by =2395*IF(Mod_6=1,0.85,1)

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Pertuzumab in combination with trastuzumab and docetaxel for the treatment of HER2 positive metastatic or locally recurrent unresectable breast cancer, which has not been previously treated, or has relapsed after adjuvant therapy [ID523]

You are asked to check the ERG report from Warwick Evidence to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm, 18 January 2017** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 3.1 Updated time to event data

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Sub-sections 3.1.1-3.1.3: The is no description until which point the Kaplan-Meier is used in the model arms, and from which point the parametric function is fitted to the Kaplan-Meier data	State the time point used and the justification for the selection rather than 'as far as possible'.	Allows discussion on whether this time point is appropriate and allows replication of analysis	The method used for long-term projection is described in detail in the extended titles for Figures 1, 2 and 3

Issue 2 3.1.7 Cost of drug administration

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
No reference is cited in the following statement. *The results were exemplified in Lloyd's Table 3 using and age of 38.2 years (equivalent to the whole UK population), but to achieve compatibility with UK EQ-5D utility values, the age parameter should be set to 47.055, the mean age of respondents in the original MVH calibration survey.(Ref)*	Provide details of reference where it currently states '(*Ref*)'	For completeness of report	The correct reference is: "CHE Discussion Paper 172 Centre for Health Economics, University of York UK population norms for EQ-5D by Paul Kind, Geoffrey Hardman and Susan Macran" This has been added to the ERG report

Issue 3 Section 4

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
It is not clear that the ICER value quoted from the ERG's analysis is at list price	The ERG's preferred options result in an estimated ICER of £127,268 per QALY gained for pertuzumab in combination with trastuzumab and docetaxel compared with trastuzumab and docetaxel for patients with metastatic or recurrent unresectable HER-2 positive breast cancer *without the PAS*, an increase of more than £6,600 per QALY gain relative to the base case	For completeness of report	Amendment accepted

Issue 4 Table 4

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Name of table 4 is incorrect as it states '(*Cetuximab + CTX versus CTX)*'.	Heading should be corrected to pertuzumab	-	Title has been amended

Issue 5 Table 4

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Sub-section 3.1.2 states that the ERG's estimate of incremental net mean OS is	Sub-section 3.1.2 and table 4 should be reviewed as we would expect that the	-	The titles of rows R1 and R2 were accidentally transposed.

23.9 months. This is greater than in our submission where the incremental OS gain is 14.6 months. However in the R2 results in table 4 show the incremental QALYS in the ERG's results are lower than in the company's updated base case.	incremental QALYS should be higher and corresponding ICER to be lower in R2.		These have been corrected with R1 as 'ERG revised OS estimates' and R2 as 'ERG revised PFS estimates'

Issue 6 Table 4/Appendix

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The appendix does not seem to be correct. As such and in the absence of the ERG's model it has not been possible to validate Table 4.	We believe that the appendix: *ERG amendments made to the company model* may relate to the Cetuximab appraisal. We would appreciate either a corrected version of the appendix and the ERG's model in order to validate table 4.	We would like the opportunity to check these values are correct	You are correct. Unfortunately in our haste to meet our submission deadline we did not notice that the correct details of model amendments had not been entered in the Appendix. This has now been corrected.

ASSESSING TECHNOLOGIES THAT ARE NOT COST-EFFECTIVE AT A ZERO PRICE

REPORT BY THE DECISION SUPPORT UNIT

July 2014

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ABOUT THE DECISION SUPPORT UNIT

The Decision Support Unit (DSU) is a collaboration between the Universities of Sheffield, York and Leicester. We also have members at the University of Bristol, London School of Hygiene and Tropical Medicine and Brunel University. The DSU is commissioned by The National Institute for Health and Care Excellence (NICE) to provide a research and training resource to support the Institute's Technology Appraisal Programme. Please see our website for further information www.nicedsu.org.uk

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Acknowledgements

I wish to thank Allan Wailoo who acted as the DSU peer reviewer on this report and Mark Sculpher and Karl Claxton for sharing with me their perspectives on the issues discussed.

EXECUTIVE SUMMARY

There are several scenarios under which clinically effective technologies may be found not to be cost-effective even if they are zero priced. There may be costs associated with delivering the technology which remain even when the price is reduced to zero and these costs alone may outweigh the health benefits achieved. But even in the situation where a clinically effective technology can be acquired and delivered for zero cost, there are scenarios in which that technology may fail to demonstrate cost-effectiveness because it increases other aspects of resource use. We have described four related but different scenarios in which clinically effective treatments result in additional time being spent in health states with high resource use and / or low health-related quality of life either during or after the treatment period. We have also examined case studies identified from the National Institute for Health and Care Excellence's (NICE's) previous appraisals to determine if the factors illustrated in these scenarios are present and whether they contributed to the conclusion that a technology was not cost-effective even when it was zero priced. We found examples of three of the four scenarios within the case studies we examined and in some cases these factors contributed to the conclusions that the technology being appraised would not be cost-effective even if it were zero priced.

The NICE methods guide states that costs which are considered to be unrelated to the technology or condition of interest may be excluded from the cost-effectiveness analysis. We have reviewed the methodological literature around the exclusion of unrelated costs from cost-effectiveness analyses to determine whether there is a case for excluding some of the costs incurred in periods of additional survival in the case studies we identified. In the majority of the case studies, the costs incurred during periods of additional survival were related to either the technology being appraised or the condition the technology was intending to treat. These cannot therefore be considered to be unrelated costs. In one case study which examined a treatment in patients with end-stage renal disease requiring dialysis, the decision about whether to consider the dialysis costs to be related or unrelated seemed to be dependent on whether the condition of interest was end-stage renal disease or the particular complication of end-stage renal disease that the technology is indicated to treat. Given the fairly arbitrary judgement this requires and the fact that there is still a real opportunity cost to patients elsewhere within the NHS of extending dialysis treatment, an alternative would be to include all related and unrelated costs within the cost-effectiveness analysis. This would

allow an ICER to be constructed which is both internally consistent, in its approach to costs and benefits, and externally consistent with the decision makers remit of allocating healthcare budgets to increase population health gain, as described in the methodological literature we reviewed.

We acknowledge that new technologies that are administered in combination with existing treatments may struggle to demonstrate cost-effectiveness if those existing treatments are themselves not cost-effective or if their cost-effectiveness falls very close to NICE's threshold. In some cases a new technology may only be cost-effective at a positive price if discounts are offered on other technologies which are given alongside the new technology. Whilst this may be perceived as a disincentive for investment in new technologies in diseases where there are existing high cost therapies, the cost-effectiveness of the new technology will improve when lower cost generic / biosimilar formulations of existing therapies become available. It might also increase the incentive to develop technologies which provide a more effective alternative to existing therapies instead of technologies which further add to the treatment burden by being administered alongside existing therapies. There is also an incentive here for NICE to ensure that it does not recommend technologies with poor or marginal cost-effectiveness since if these are incorporated into standard care any future technology which prolongs the duration of standard care may fail to demonstrate cost-effectiveness. In some situations it may also be worth exploring whether there is a case for disinvesting from existing treatments that form part of standard care particularly if those existing treatments have not been previously appraised by NICE or if the benefits estimated at the time of appraisal have not been realised.

Whilst we have mainly focused on the issues related to costs incurred in added life years it is also important to consider if the benefits have been properly accounted for in the cost-effectiveness model. Consideration should be given to whether all of the health benefits occurring during periods of high resource usage have been properly accounted for, particularly for interventions such as palliative care where there may be benefits falling on carers in addition to patients or where benefits which may not properly captured by generic quality of life measures. It is also worth considering whether there may be some treatments, such as dialysis and palliative care, which society may consider worthwhile despite their poor cost-effectiveness and whether the value placed on these treatments by society may not be fully captured by the health benefits accrued by either the patients themselves or their carers.

If those wider societal benefits cannot be quantified, then excluding the cost of treatment, whilst including any health gains would provide a lower bound on the incremental cost-effectiveness ratio (ICER).

In addition we discuss how treatments which are cost-effective in the general population may not be cost-effective in particular groups of patients with high background care costs. The Institute's existing 'Social Value Judgements' policy would preclude separate recommendations being made for patients with different characteristics if the differences in the recommendations are based solely on differences in the background care costs. Even in cases where there are high background care costs across the whole population specified in the scope of the appraisal, it may still be important for the Committee to consider whether there are any legal or ethical reasons for recommending the treatment, including the need to distribute health resources in the fairest way in society as a whole.

CONTENTS

FIGURES

ABBREVIATIONS AND DEFINITIONS

ACD	Appraisal consultation document
BSC	Best supportive care
DSU	Decision Support Unit
EDT	Early disease time
ERG	Evidence Review Group
ESRD	End-stage renal disease
FAD	Final appraisal document
FOLFOX	Oxaliplatin plus Fluorouracil plus folic acid
HER2+	Human epidermal growth factor 2 positive
HPV	Human papillomavirus
HR	Hazard ratio
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
LYs	Life-years
MS	Manufacturer submission
MTA	Multiple technology appraisal
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
PC	Palliative care
PFS	Progression-free survival
PPS	Post-progression survival
QALY	Quality-adjusted life-year
SHPT	Secondary hyperparathyroidism
SPC	Summary of product characteristics
STA	Single technology appraisal
TA	Technology appraisal
TAG	Technology assessment group
XELOX	Oxaliplatin plus capecitabine

1. INTRODUCTION

In a recent National Institute for Health and Care Excellence (NICE) appraisal of a new drug (pertuzumab) in metastatic breast cancer the appraisal consultation document (ACD) concluded that pertuzumab, when used in accordance with its licensed indication, did not represent a cost-effective use of NHS resources.[1] The manufacturer had indicated in their comments on the ACD that when using plausible assumptions (those preferred by the evidence review group) there was no price at which pertuzumab would be cost-effective (it was not cost-effective at zero price).[2] The issue driving this relatively high incremental cost-effectiveness ratio (ICER) appeared to be that the drug was given in combination with another drug (also the comparator) and any additional progression-free survival (PFS) was accompanied by the costs of both pertuzumab and the comparator drug. In view of the fact that the technology was associated with substantial benefits in terms of both progression-free and overall survival, the Institute's Guidance Executive decided not to issue the Final Appraisal Documents (FAD) pending further exploration of the issue.

The Decision Support Unit (DSU) was asked to explore the circumstances in which clinically effective technologies are not cost-effective even at a zero price. In the light of this exploration, the DSU was asked to consider the usual rules for assessing cost-effectiveness and their appropriateness or otherwise in these circumstances.

This review

The DSU was asked to consider real and/or hypothetical examples in which a technology is not cost-effective at zero price and to describe the factors that contribute to this. The DSU was also asked to consider whether, in relation to these situations, there are circumstances in which it might be justifiable to depart from the usual range of acceptable ICERs, or otherwise adapt the methods of assessing cost-effectiveness. The DSU was asked to address these issues through;

1. A review of previous NICE appraisals where technologies have been found to be not cost-effective at zero price and consideration of the factors that contributed to this.
2. A consideration of those situations where similar factors are likely to also occur.
3. A literature search for any previous discussion of this issue in the health economic literature.

4. A discussion of any alternative approaches to assessing the cost-effectiveness of clinically effective technologies that are not cost-effective at any positive price.

2. DESCRIPTION OF GENERALISED SCENARIOS

There are several ways in which a new technology which is clinically effective may fail to demonstrate cost-effectiveness even when it is zero priced. Firstly whilst the technology itself may be acquired at zero cost, there may be costs incurred for administering the intervention, such as outpatient or day case procedure costs. There may also be specific investigations required to assess eligibility for treatment or to monitor the patient following treatment. These additional costs associated with delivering the technology must be offset by sufficient quality-adjusted life-year (QALY) gains if the technology is to be deemed cost-effective.

Secondly, for a drug to be clinically effective, it must result in additional QALYS being gained either by improving overall survival and / or by allowing a greater proportion of the patient's life-expectancy to be spent in a health state with better health-related quality of life (HRQoL). Whilst both of these will improve the patient's life-time QALY profile, they may also have an impact on health resource use. We illustrate four such scenarios below.

Scenario 1

For patients with on-going healthcare needs, additional survival may be associated with additional resource use. In patients with high resource use and / or low HRQoL, the cost of additional resource incurred during the additional life-years gained may outweigh the QALYs gained during the period of additional survival. In these circumstances, clinically effective treatments which increase survival may not be cost-effective.

Figure 1: Additional survival results in the existing standard of care being provided for longer

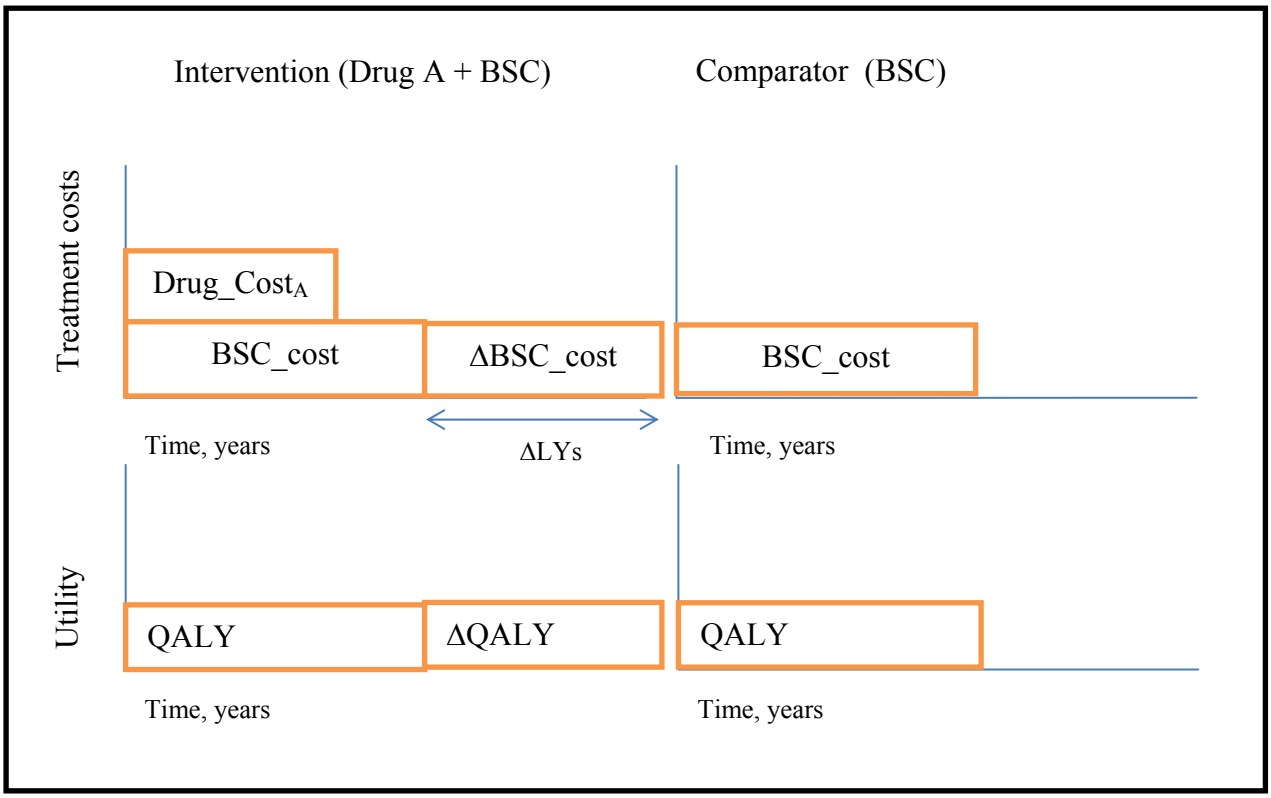


Figure 1 illustrates this for the case where Drug A is given in addition to best supportive care (BSC) resulting in an increase of life expectancy (ΔLYs) and a QALY gain (ΔQALY).

In the general case Drug A will <u>not</u> be cost-effective if;

$$\lambda \times \Delta QALY - (Drug\_Cost_A + \Delta BSC\_cost) < 0$$

where λ is the cost-effectiveness threshold being applied by the decision maker.

However, in the case where Drug A can be purchased (and administered) for no additional cost, it is still possible that Drug A will <u>not</u> be cost-effective if;

$$\lambda \times \Delta QALY < \Delta BSC\_cost$$

or alternatively if we prefer to think in terms of annualized costs and utility values which are constant during the period of additional survival then this expression reduces to;

$\lambda \times \Delta QALY/\Delta LYs < \Delta BSC\_cost/\Delta LYs$

$\lambda \times$ Utility < Annualized BSC cost

We can conclude from this that drugs which increase survival in patients with high ongoing care costs and / or a low HRQoL may fail to demonstrate cost-effectiveness even if they can be acquired and administered at zero cost.

Scenario 2

It is often the case that health states with better HRQoL are associated with lower healthcare costs and therefore clinically effective treatments which delay the onset of more severe health states are often cost saving. However, if transition to a worse disease state results in the patient discontinuing high cost treatments then delaying the on-set of more severe disease may increase the patient's life-time resource use. In this case, then the QALY gains of delaying progression to the more severe health state may not outweigh the additional resource use of increased stay in the less severe state.

Figure 2: Increased time spent in early disease state results in additional time on intensive treatment regimen

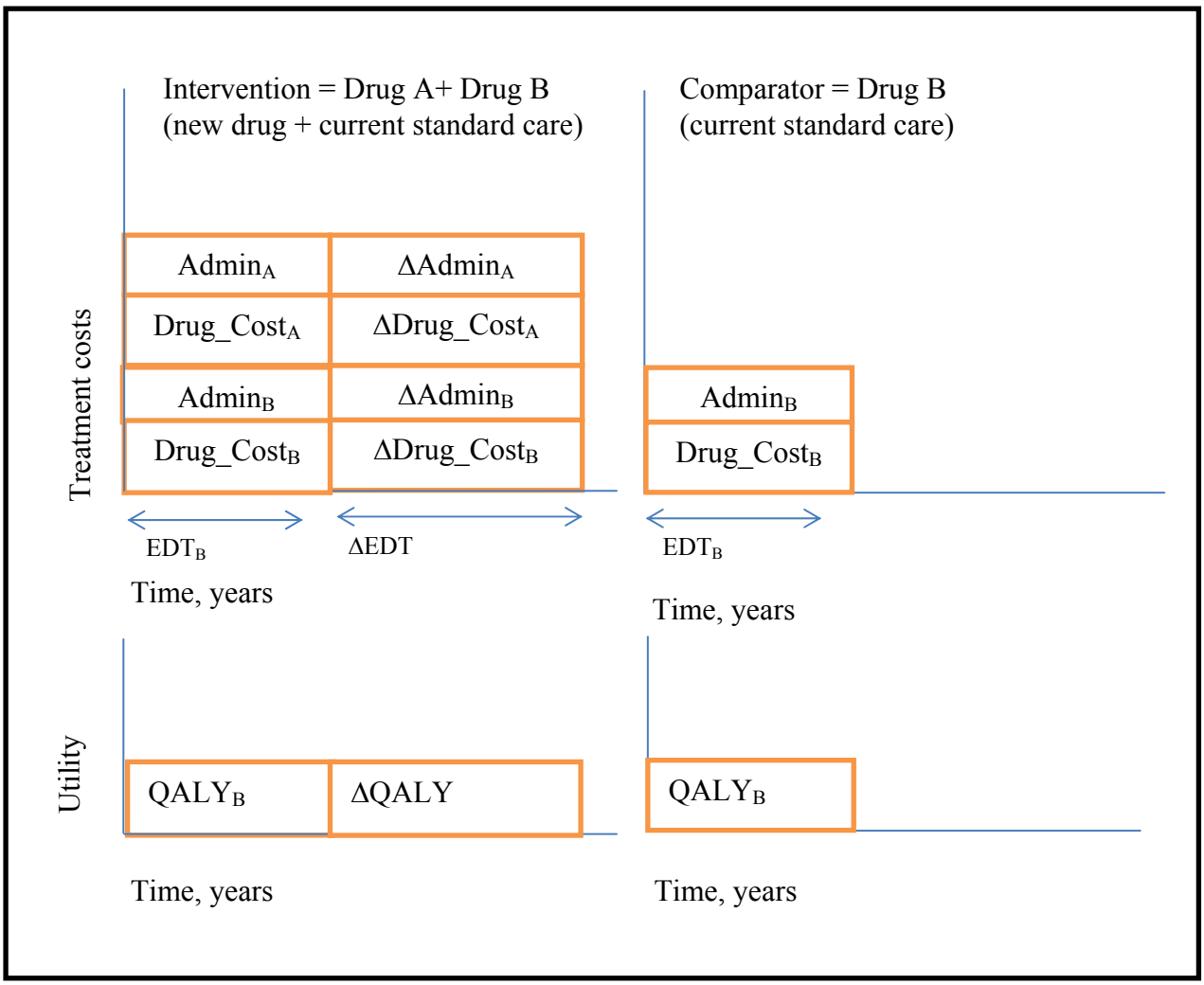


Figure 2 illustrates a situation where a new technology, Drug A, is given alongside the current standard of care, Drug B, for the duration of the early disease state with the comparator being current standard care (Drug B) alone. The new technology results in additional time (ΔEDT) being spent in the early disease health state and treatment with Drug A and Drug B is continued for the duration of early disease. All costs and QALYs accrued after progression to the late disease state are assumed equal between the new technology and the current standard of care and therefore are not included in Figure 2. We can see from Figure 2 that there are two types of additional costs for the new technology; those that relate directly to the drug and administration costs for technology A, and those that relate to the increased usage of B. Even if Drug A can be acquired and administered at zero cost, the net benefit (NB) for intervention compared to comparator would be;

$$NB = (\lambda \times \Delta QALY) - (\Delta Admin_{B+} \Delta Drug\_Cost_{B})$$

Therefore it may not cost-effective to add Drug A to standard care even if it can be acquired and administered at zero cost, if the costs of delivering standard care outweigh the benefits of adding A to standard care.

Scenario 3

Figure 3 Increased time spent in a later disease state with additional healthcare needs

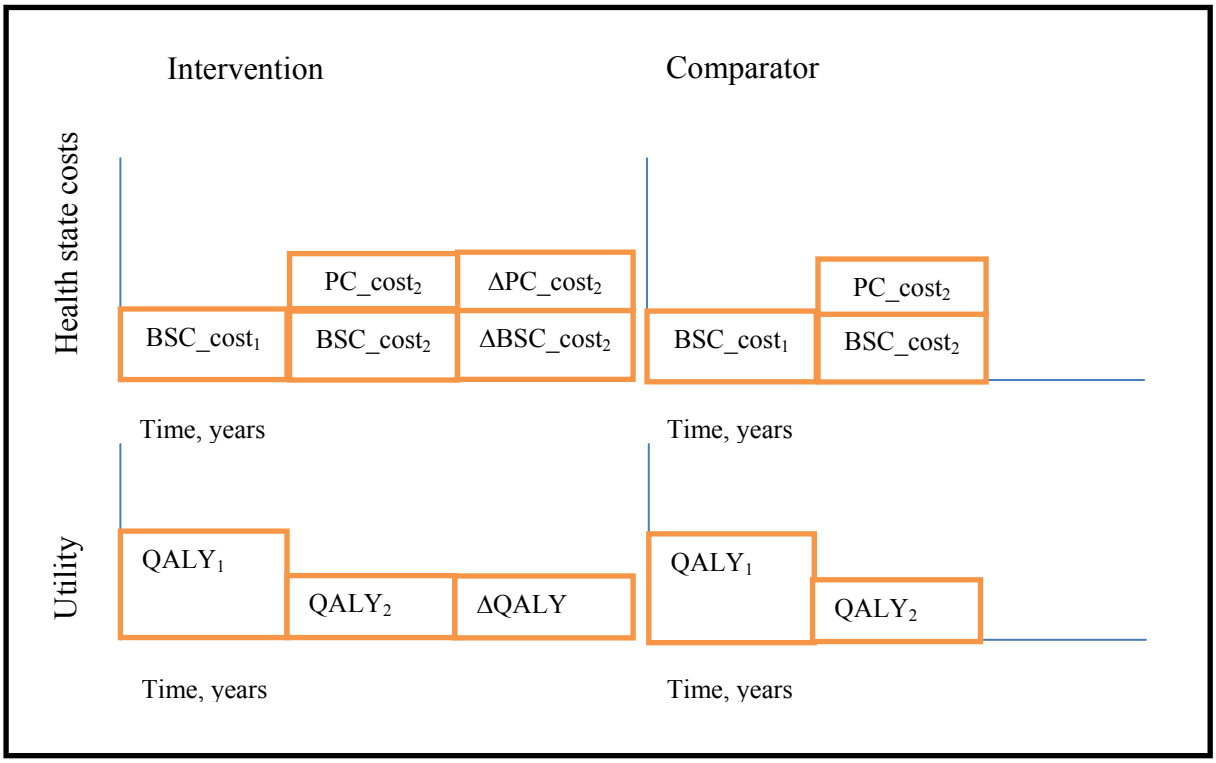


Figure 3 illustrates a third scenario where a new technology may not be cost-effective even when it can be acquired and administered at zero cost. In this scenario the intervention results in additional survival but that increased time is being spent in a late disease health state which has high costs and low HRQoL. The costs have been separated here into best supportive care (BSC), and palliative care (PC). We have assumed that the level of resource use for best supportive care is not increased after moving to the late disease state (i.e $BSC\_cost_1 = BSC\_cost_2$) and all additional costs are captured under palliative care (PC_cost_2) which only occurs in the late disease state. If all other costs (i.e drug and administrative costs) are assumed equal between the intervention and comparator strategies, then the cost-effectiveness is determined by comparing the net benefit realized from the additional QALY gain against the additional best supportive care and palliative care cost, ie.

$$NB = \lambda \times \Delta QALY - (\Delta BSC\_cost_2 + \Delta PC\_cost_2)$$

From this we can see that if either category of cost is sufficiently high relative to the utility of the late disease state it will result in a negative net benefit. If the palliative care costs are set to zero then we have a scenario which is similar to that illustrated in Figure 1, where it is the continuation of current treatments within the period of additional survival which adversely affect the cost-effectiveness of a life-prolonging intervention. However, if the best supportive care costs are set to zero then we have a new situation where it is the addition of new treatments during the period of additional survival which adversely affect the cost-effectiveness of the life-prolonging intervention.

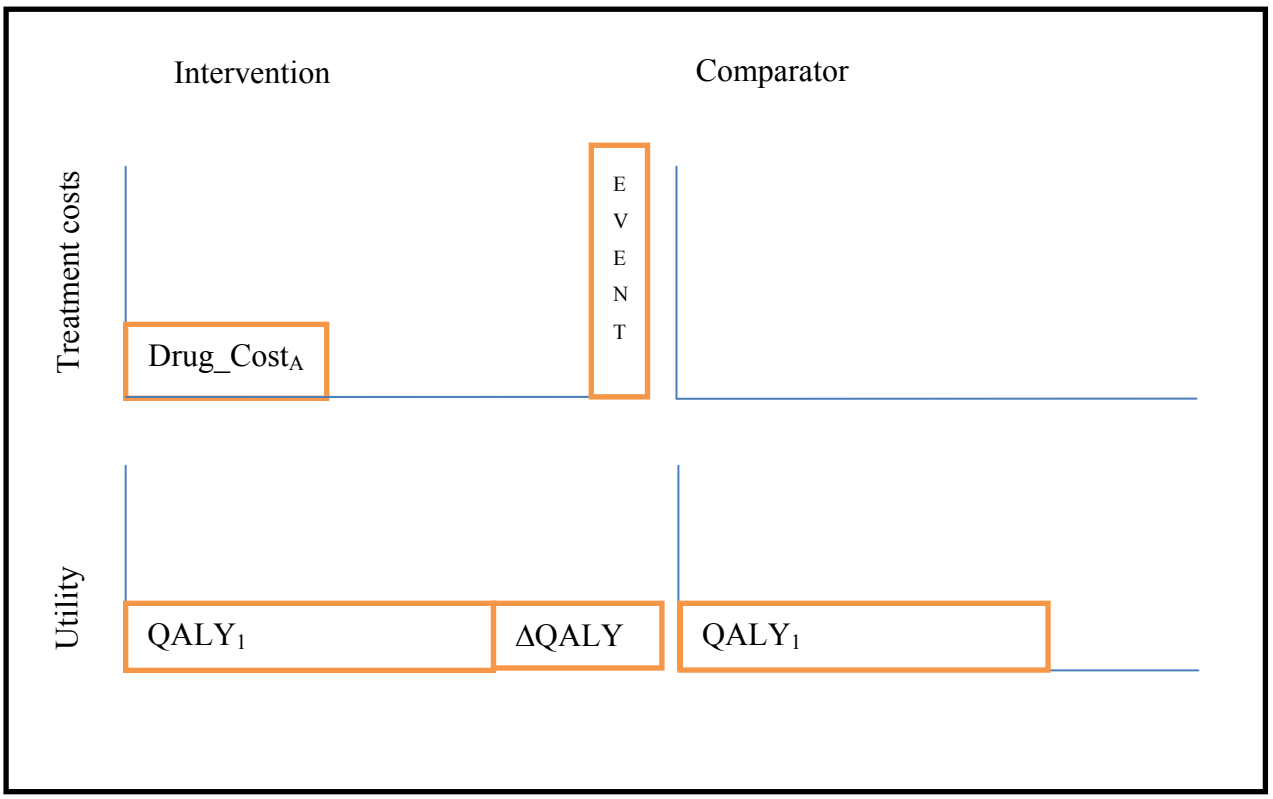
Summary of Scenarios 1 to 3

In all of the scenarios illustrated above, it is the balance between the costs incurred and QALYs gained for the health state in which the additional survival is being spent that determines whether the additional survival has a positive or negative net benefit. If new technologies are given alongside existing technologies which are not themselves cost-effective, or if the benefits of healthcare given later in the disease care pathway do not outweigh the costs of that later care, then this may mean that the new technology may fail to demonstrate cost-effectiveness even if it can be acquired and administered at zero cost.

Scenario 4

A final scenario is illustrated in Figure 4. Here the drug under appraisal (Drug A) increases life-expectancy, but in the period of additional survival the patient goes on to have a high cost event which is not experienced in the comparator arm. Even if Drug A can be obtained at zero cost, it may fail to demonstrate cost-effectiveness if the cost of treating the later event is sufficiently high and outweighs the additional QALYs gained in the years of additional survival. The distinction being drawn between this scenario and the ones illustrated above is that the event may be related to the disease being treated by Drug A or it may be due to a completely unrelated disease. In the latter case, the only relationship between the administration of Drug A and the high cost event is that Drug A increases the duration of survival thereby increasing the patient's chance of experiencing the high cost event during their lifetime.

Figure 4: Patient survives longer but experiences a high cost event later in life



3. CASE STUDIES FROM PREVIOUS NICE APPRAISALS

Section 3 examines case studies identified from previous NICE appraisals which have been selected because they share some characteristics with the general scenarios described in Section 2. These examples were identified using the authors' knowledge of previous NICE appraisals and on advice from the NICE Technical Team. A systematic search through previous TAs to identify all relevant case studies was not conducted. In some cases, such as in the pertuzumab example mentioned in the introduction, explicit statements were made during the appraisal regarding the likely cost-effectiveness when assuming a zero price, whilst in other cases this issue was not explicitly raised during the appraisal.

The descriptions of the case studies provided below are based on the relevant evidence review group (ERG) reports and manufacturer submissions (MS) for those appraisals without access to any of the executable models described within those documents.

3.1. Cinacalcet in end-stage renal disease

Cinacalcet is licensed for the treatment of secondary hyperparathyroidism (SHPT) in patients with end-stage renal disease (ESRD) on maintenance dialysis therapy.[3] Almost all people with ESRD have SHPT.[3] Dialysis therapy is a high cost medical intervention. The technology assessment group (TAG) for the TA of cinacalcet (TA117) estimated the average cost of dialysis to be £15,643 (Table 105 of HTA report).[4] The highest utility value applied to patients in the TAG cost-effectiveness model was 0.6735 (Table 76 of the HTA report).[4] The ratio of costs and benefits for additional time spent on dialysis would therefore be in excess of £20,000 per QALY when excluding all other healthcare costs associated with the management of ESRD. Therefore a life-extending treatment in this patient population may fail to demonstrate cost-effectiveness, at a £20,000 per QALY threshold, unless it also demonstrates a substantial improvement in quality of life or results in substantial cost savings compared to the current standard care of care. This is an example of the scenario illustrated in Figure 1, where the dialysis costs represent the costs of best supportive care in this population.

3.2. Pertuzumab

Pertuzumab is indicated for use in combination with trastuzumab and docetaxel in adult patients with Human epidermal growth factor 2 (HER2)-positive metastatic or locally recurrent unresectable breast cancer, who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease.[5] The ERG report for the NICE appraisal of pertuzumab states that the addition of pertuzumab to the treatment regimen of trastuzumab and docetaxel in this patient population provides improved PFS.[6] At the first data cut (median follow-up of 19 months) there was a difference of 6.1 months in median PFS between the arms as measured by the independent review facility (18.5 months vs 12.4 months, hazard ratio [HR] 0.62, 95% CI: 0.51 to 0.75), with similar findings at the first and second data cut (median follow-up of 30 months) for local investigator assessed PFS.[6] Although a significant difference in overall survival was reported at the second data cut, the ERG and Committee considered there to be uncertainty in the magnitude of the overall survival gain due to immaturity of the data.[1,6] The Summary of Product Characteristics (SPC) states that treatment with pertuzumab should continue until disease progression or unmanageable toxicity and that if trastuzumab treatment is discontinued, treatment with pertuzumab should also be discontinued.[5] Therefore, any gain in PFS would result in additional costs for ongoing treatment with both pertuzumab and trastuzumab.

The MS gives the mean cost per 3 week cycle for trastuzumab as £1,629.60 for the initial dose and £1,222.20 for the maintenance dose (page 143 of the MS).[7] The cost of acquiring docetaxel is substantially lower at £35 per cycle (page 144 of the MS).[7] The cost of administering all three drugs on day 1 of each 21 day cycle is given as £248 for the first dose and £197 for each subsequent cycle with an additional pharmacy dispensing cost of £9.40 per cycle (Table 27 of the MS).[7] In addition to these costs, the economic model described in the MS includes a cost for best supportive care of £157 per month (Table 29 of the MS).[7] Therefore, we calculate the annualized cost of remaining in the progression-free health state to be £27,253 even when assuming a zero price for pertuzumab. These costs would also be incurred by any patient receiving the comparator intervention of trastuzumab combined with docetaxel. These costs associated with the progression-free state act to increase the ICER because treatment with pertuzumab results in an increased duration of PFS.

If we ignore any other factors influencing overall costs (i.e assume that the cost of monitoring, treatment of adverse events and second-line cancer therapies are similar between the pertuzumab and comparator arm), and assume no difference in post-progression survival (PPS), then the cost-effectiveness model simplifies to a trade-off between the QALY gains associated with additional PFS and the acquisition cost of pertuzumab. This is similar to the scenario illustrated in Figure 2 above. To determine whether this additional survival will increase or decrease the ICER, it is necessary to determine whether the additional survival results in a positive or negative change in net benefit. Given the costs described above, the utility value for the progression-free health state for advanced breast cancer would have to be over 0.90 to give a positive net benefit event when applying a willingness to pay threshold of £30,000 per QALY and assuming a zero price for pertuzumab. Given that none of the utility values applied in the manufacturer's model were above 0.785 (Table 25 of the MS),[7] we can say that it is unlikely that pertuzumab would be cost-effective even at zero price in this population if its clinical benefits are limited to extending survival in the progression free state.

3.3. Vinflunine

In the NICE guidance for vinflunine for the treatment of advanced or metastatic transitional cell carcinoma of the urothelial tract (TA272) it is stated, "When a vial price of £0 was used, the ICER was £27,478 per QALY gained."[8] According to Table B42 of the MS, vinflunine in addition to best supportive care (BSC) resulted in additional PFS, PPS and overall survival (OS) compared to BSC.[9] A substantial (41%) proportion of the additional life-years (LYs) gained are accrued due to additional time spent in the post-progression health state even though treatment with vinflunine was ceased after disease progression. According to Table B42 of the MS there is an overall gain of 0.268 in discounted LYs with 0.158 of this relating to gains in PFS and 0.110 of this relating to gains in PPS.[9]

In this appraisal, the costs per month of providing best supportive care were high at £585 and £1340 in the vinflunine arm for the pre- and post- progression states respectively (Table B39 of the MS).[9] The utility values applied to these states were 0.65 and 0.25 respectively (Table B35 of the MS).[9] Therefore, there is a negative net benefit associated with increased PPS when applying a £30,000 per QALY threshold. This is similar to the scenario described in Figure 3 above.

In the case of vinflunine, the ICER is under the upper range of ICERs that are considered to be cost-effective when applying a vial price of £0 and therefore based on the manufacturer's estimates of cost-effectiveness it would be possible to set a positive price at which this clinically effective treatment would be reimbursed providing the Committee were willing to apply a threshold of £30,000 per QALY in this case. However, the high cost and low utility value for time spent in the PPS state for this health condition means that treatments which have a positive effect on PPS would be less cost-effective than those which have a negative effect on PPS for this population.

3.4. Cetuximab for head and neck cancer

Cetuximab is licensed for the treatment of patients with recurrent and/or metastatic squamous cell cancer of the head and neck in combination with platinum-based chemotherapy.[10] In the ERG report for the TA of cetuximab for this indication (TA172), a threshold analysis was presented (on page 69) which showed that the ICER compared to platinum-based chemotherapy was £37,403 when assuming that cetuximab was zero priced.[11] The ERG report cites three reasons for this high ICER. Firstly cetuximab requires more frequent administration than the platinum-based chemotherapy. Secondly, cetuximab is indicated for use until disease progression meaning that any increase in progression free survival also increases the cost of administering cetuximab. Finally, "because cetuximab is associated with better survival, patients experience a longer period during which they are eligible to gain benefit from other follow-on treatments and palliative care, all of which involve additional NHS cost."

However, it can be seen from the figures presented by the ERG that 95% (4480/4709) of the incremental cost (when assuming a zero price) is related to drug administration, suggesting that the provision of follow-on treatments and palliative care during the period of additional survival are not the main drivers of incremental cost in this case.[11] So whilst the scenario illustrated in Figure 3 may have a small negative impact on the ICER, it is not the main driver of the high ICER when assuming a zero drug price.

The drug administration costs presented by the ERG are not broken down into those related to cetuximab administration and those related to the provision of platinum-based

chemotherapy. However the low incremental cost attributable to drug acquisition for other treatments (as presented on page 69 of the ERG report) suggests that the additional administration costs are largely attributable to cetuximab.[11]

In the first 18 weeks of cetuximab administration, it is given along-side platinum-based chemotherapy.[12] We can calculate the cost of extending treatment on this platinum-based chemotherapy using the drug costs and administration costs per cycle using the data presented in the MS.[12] Using the proportions receiving cisplatin (62.8%) and carboplatin (37.2%) based chemotherapy from Table H8, and the drug costs per cycle presented in Table H10 (£712 and £292.44), we can see that the mean drug cost per cycle in the comparator arm was £448.52 per 3 week cycle. The cost of administration for platinum-based chemotherapy are £1184 per cycle based on the unit costs presented in Table H11 (£296) and the duration of inpatient stay (4 days per 3 week cycle) presented in Table H3 of the MS. Therefore the background costs of platinum-based chemotherapy are equivalent to £41,045 per annum. So, even if this health state were associated with full utility, it would not be cost-effective to prolong survival in this state. This suggests that the scenario illustrated in Figure 2 may have a role to play in this example. However, in this case, the impact on the ICER of prolonged survival on the platinum-based chemotherapy regimen is limited due to the fact that the platinum-based chemotherapy was stopped at 18 weeks with only the cetuximab treatment being continued until disease progression. Therefore, any increase in PFS that occurred after this 18 week time-point would not incur additional costs for providing background platinum-based chemotherapy.

It appears that in this case study, the ERG's conclusions that the ICER exceeded £30,000 per QALY when assuming a zero price for cetuximab are being driven by the high costs associated with administering chemotherapy during the period of PFS, and the vast majority of these appear to be related to the administration of cetuximab due to its more frequent administration and the fact that it is continued beyond the 18 weeks limit for administration of platinum-based chemotherapy. So, whilst the scenarios illustrated in Figure 2 and 3 may play some role in increasing the ICER for cetuximab, it is the fact that cetuximab cannot be administered for zero cost that is driving the conclusion that it would not be cost-effective even if it were zero priced.

3.5. Bevacizumab for metastatic colorectal cancer

TA 212 considered the use of bevacizumab in combination with oxaliplatin and either fluorouracil plus folic acid (FOLFOX) or capecitabine (XELOX) for the treatment of metastatic breast cancer.[13] This case study was considered to have similar characteristics to the scenario illustrated in Figure 2 as it involves the addition of a new technology to one of two existing high cost treatment regimens (FOLFOX or XELOX) and compares the cost-effectiveness of combined treatment with the new technology (B+FOLFOX or B+XELOX) against these existing treatment regimens. Treatment is indicated until progression of the underlying disease,[13] therefore, as in the pertuzumab example described above, we have a situation where an increase in PFS would result in additional time being spent on both the new technology (bevacizumab) and the background existing treatment regimen (FOLFOX or XELOX). Table 23 of the MS gives the administration costs applied in the manufacturer's cost-effectiveness model.[14] In the comparator arms these were £526 per month for XELOX and ranged from £1024 to £1735 per month for FOLFOX depending on the exact administration method. The costs of administering these regimens in combination with bevacizumab were similar. It can be seen that for the FOLFOX regimen, the administration costs alone may exceed £20,000 per annum making it difficult for this regimen to be combined in a cost-effective manner with any technology which increases the duration of treatment with FOLFOX. Therefore this is another example of the scenario illustrated in Figure 2.

3.6. Summary of case studies

Several examples have been found within previous NICE TAs in which a clinically effective treatment has extended the period spent by a patient within a high cost health state. Where the costs accrued during this additional survival are not offset by the QALYs gained from additional time spent in this health state, this additional survival has the effect of pushing up the ICER for the clinically effective treatment. In some cases, the balance of costs and benefits associated with prolonged survival may mean that a technology whose only clinical benefit is to increase survival in that health state will fail to demonstrate cost-effectiveness even when it is zero priced.

Sometimes the high costs associated with additional survival are attributable to the ongoing administration of high cost drug therapies which are administered along-side the treatment

being appraised, but are also considered to represent current best practice in patients not receiving the treatment being appraised. In other cases, it is the cost of providing best supportive care to a population with high healthcare needs and low quality of life which is driving the ICER upwards. Finally, in one example, it appears that the main factor driving the ICER above commonly accepted thresholds, when assuming a zero price, is the cost of administering the technology being appraised rather than the cost of treatments given alongside that technology, although, the costs of administering concomitant chemotherapy treatments were also high in this example. No examples were identified which matched the characteristics of scenario 4 in which the increased duration of life-expectancy places patients at risk of requiring high cost future interventions.

4. LITERATURE REVIEW

In Section 2 we identified that a clinically effective technology may be found not to be cost-effective, even when assuming a zero price, if it results in an increased amount of time being spent in a health state associated with a high level of NHS resource use. This situation runs counter to the usual expectation that treatments which improve survival will be cost-effective if they are provided at a reasonable cost, and it is being driven by the high costs accrued during periods of additional survival. There is a reasonable amount of existing literature on the methodological issue of which costs incurred during added life-years should be included in cost-effectiveness analyses.[15-38] We decided to examine this literature to identify whether there could be a case for excluding certain types of costs accrued during periods of additional survival. In Section 5 we go on to examine how any principles for excluding certain types of costs identified in the literature might be applied in practice within the case studies we examined and within the TA programme as whole.

Some of the literature regarding the inclusion of costs incurred during periods of additional survival focuses on the distinction between medical costs accrued during added life-years and the broader costs to society, such as changes in consumption and production.[16,27,28,33] This issue is not relevant within the context of NICE TAs as the perspective for the reference case is limited to costs related to NHS and personal social services (PSS) resources.[39]

However, even for those costs falling within the reference case perspective, a distinction has been drawn in the literature between those costs that are related and unrelated to the technology of interest.[32,35] The NICE methods guide states in section 5.5.7, "Costs related to the condition of interest and incurred in additional years of life gained as a result of treatment should be included in the reference-case analysis. Costs that are considered to be unrelated to the condition or technology of interest should be excluded."[39] Therefore, under the existing NICE methods for TA, it would be acceptable to exclude costs which are considered to be unrelated to the condition or technology of interest.

The example of life-extending treatment in patients with ESRD requiring maintenance dialysis therapy has been used in the literature to illustrate the case for excluding such unrelated costs.[21] Grima *et al.* argue that dialysis costs can be considered to be unrelated and excluded if, "the need for or intensity of dialysis is not impacted by the therapy of interest and incremental dialysis costs are due exclusively to extension of life". They argue that this definition of unrelated costs may apply not only to therapies for unrelated conditions, such as statins, but also to therapies for conditions that are a consequence of renal failure or the use of dialysis. They also argue that the decision to provide dialysis, despite its poor cost-effectiveness, has already been taken and therefore dialysis patients should not be denied subsequent treatments for co-morbid conditions due to the high background costs of providing dialysis.

van Baal *et al.* disagree that unrelated costs should be excluded.[34] They argue that Grima *et al.* have ignored the real opportunity costs of life prolonging treatments in patients with ESRD and that the resources spent on additional dialysis for these patients could generate more health gains by being allocated to other patient groups. They argue that it is better to ignore the distinction between unrelated and related costs, and to include in the analysis all medical costs as these represent real opportunity costs within the healthcare sector. They suggest that if treatments which are cost-effective in other populations are found not to be cost-effective in patients with high background care costs, then the ethical and equity concerns that this finding raises should be dealt with in a process separate from the estimation of cost-effectiveness.

Several authors have attempted to define more specifically what is meant by 'related' and 'unrelated' costs in order to determine what can be excluded from the analysis on this basis.

Nyman tried to approach the definition by requiring that a consistent approach be taken between the estimation of incremental costs and incremental benefits in the ICER.[27] In his definition any resource use which influences the incremental QALYs gained should be included in the incremental cost. Using Nyman's rationale, van Baal *et al.*[35] define a disease as being related to an intervention if the intervention influences its prognosis and/or its age and sex specific incidence rate. Under this definition they claim that the gain in QALYs during life years that would also have been lived without the interventions cannot be attributed to medical care for unrelated diseases and that differences in healthcare costs of unrelated disease occur only if an intervention increases life expectancy. In the scenario illustrated by Figure 4, the high cost future event may be considered to be unrelated under this definition if the intervention being appraised is an intervention to prevent early death such as childhood vaccinations and the high cost future event is something like stroke whose incidence increases with age but whose incidence or prognosis is not influenced by childhood vaccinations. Conversely, the cost incurred in the additional life years gained would be considered to be related if the intervention was smoking cessation in teenagers and the high cost future event was lung cancer treatment.

In a later paper,[37] van Baal *et al.* go back to the theoretical definition first proposed by Garber and Phelps that unrelated costs are conditionally independent of prior expenditures in order to address the issues around postponement of the high costs incurred in the last year of life.[17]. If a treatment postpones death by avoiding death from a particularly cause, for example cervical cancer prevention through human papillomavirus (HPV) vaccination, it is important to consider whether the costs of end of life care for that individual are really avoided or whether they are simply postponed until a later point when death occurs due to a disease unrelated to cervical cancer, such as stroke. Gandjour *et al.* showed that ignoring the costs incurred in the last year of life from unrelated diseases would overestimate the cost-effectiveness of interventions which prevent early death from a particular disease.[40] van Baal *et al.* discuss how costs that are related to time to death can be considered to be related to life-extending treatments, as they are end of life costs which are postponed by the treatment, whereas costs which are related only to age can be considered not to be related.[37] They point out that this definition is not based on defining related and unrelated diseases, but on defining related and unrelated costs as some costs falling within a particular disease area may be conditionally dependent whilst others falling in the same disease area may not be. However, they argue that

separating costs into related and unrelated components is an unnecessary complication which can be avoided if all life-time healthcare costs are included in the analysis.

Rappange *et al.* argue that the ICER should incorporate both unrelated and related medical costs and the health benefits resulting from both these types of costs as this allows an ICER to be constructed which is internally consistent as suggested by Nyman *et al.* and externally consistent with the decision makers remit of allocating healthcare budgets to increase population health gain.[32]

5. ALTERNATIVE APPROACHES TO APPRAISING TREATMENTS WHICH ARE NOT COST-EFFECTIVE AT ZERO PRICE

5.1. Defining costs incurred during added life-years as being unrelated

If one accepts the position put forward by Grima et al.,[21] that costs unrelated to the technology being appraised can be excluded from the ICER, and that costs incurred solely due to increased survival can be classified as unrelated, then it may be possible to argue that some of the costs identified in the examples described in Section 3, could be excluded from the ICER. This could be argued for populations where the costs of providing best supportive care in addition to the technology being appraised are high and not affected by the technology being appraised except through its impact on survival. The most obvious example of where this definition of unrelated costs could be applied is the dialysis example described by Grima *et al.*,[21] but it could be argued that it also applies in cases where the best supportive care costs are high such as in the vinflunine example.[8]

In the cinacalcet case study described above, both the TAG and the manufacturer excluded dialysis costs from their base-case cost-effectiveness analysis, although dialysis costs were included in a sensitivity analysis for the TAG model.[4] Whilst the TAG stated that it was arguable that SHPT is so closely associated with ESRD that the costs of dialysis should be included, it also stated that dialysis is a very expensive treatment that has already been accepted as standard for this population, although it may not be deemed cost-effective. The TAG also acknowledged that this is a, "methodological issue of considerable controversy". The FAD for this appraisal does not describe whether the TA Committee considered the

exclusion of dialysis costs to be appropriate or not in this case. [3] Based on NICE's current methods guidance, the decision to include or exclude dialysis costs would depend on whether those costs are 'related to the condition of interest' or not. The position could be taken that cinacalcet is indicated for SHPT which happens to occur in patients with ESRD but that the ESRD is an unrelated pre-existing condition in this population and therefore the costs of dialysis could be excluded. The rationale for exclusion then comes down to a fairly arbitrary decision as to whether SHPT or ESRD is the 'condition of interest' for that appraisal. For this reason, van Baal *et al*. argue that it is better to include all costs rather than trying to draw distinctions between related and unrelated costs.[34]

It could also be argued that the costs in the last weeks before death are high regardless of the cause of death and therefore the costs for end of life care should be excluded as unrelated for the appraisal of a specific technology because similar costs would be experienced later in life if that individual died of another cause. However, this approach would contradict the definition of related costs put forward by van Baal *et al.* in which costs which are related to proximity to death are considered to be related to life-extending treatments.[37] Furthermore, in the case studies we have examined, the postponement of end of life costs beyond the model horizon has not been an issue as the models have generally taken a life-time approach in accordance with NICE methods guidance.[4,7,9,12,14,39]

It may also be argued that technologies which constitute the current standard of care or best practice in the NHS and whose delivery or effectiveness is not affected by the addition of the technology being appraised, except through its impact on survival, could also be considered to be unrelated. This logic might also be applied to the costs of treatment with FOLFOX or XELOX alongside bevacizumab for colorectal cancer in TA212 or the treatment with trastuzumab alongside pertuzumab for advanced breast cancer.[1,13] However, it would be difficult to argue that the benefits of these technologies are in no way affected by the concomitant administration of the technology being appraised given that they are administered at the same time and with the same treatment intent. Furthermore, without trials examining the separate and combined effects of these treatments (e.g pertuzumab versus trastuzumab versus both combined) it is impossible to say whether they have independent effects on outcomes.

The disadvantages of trying to exclude some of the costs attributable to prolonged survival are those outlined in the literature described in Section 4. The most relevant of these within the context of NICE is the opportunity cost, in terms of health gains forgone in other patient populations, of ignoring costs which differ between the treatment and comparators outlined in the decision problem. These opportunity costs are in no-way diminished by the fact that the costs accrued in the added life-years have been defined as being unrelated to the technology being appraised.

There are also practical difficulties in separating related and unrelated costs. One way to think about the distinction between related and unrelated costs is to consider which future costs the decision maker is committing to by making a recommendation for or against the technology being appraised and whether the estimate of benefit assumes that those future resources will be available. If there are treatments available now which may or may not be available in future, then it may be better to exclude both the costs and the effects of those treatments from the analysis. However, estimating the future health gains in the absence of future care may be difficult as we may only have data on the health gains given current care provision. For example, estimates of general population life-expectancy are often utilised within cost-effectiveness models but these estimates may be dependent on maintaining the current provision of healthcare. Furthermore, excluding all costs and benefits of unrelated future care will only yield an unbiased estimate of the ICER if it can be assumed that all future care will be provided at the cost-effectiveness threshold. If unrelated future care yields a negative net benefit due to higher costs than can be justified by the QALY gains, then excluding future costs and benefits will produce an overly optimistic estimate of the cost-effectiveness of the technology being appraised. If the converse is true, and future benefits can be achieved at below the cost-effectiveness threshold, then excluding future costs and benefits will result in an ICER estimate that is overly pessimistic.

It is hard to see how the definitions of ‘unrelated’ medical costs can be applied to many of the examples described in Section 3. In particular, it is hard to see how the health gains associated with care provided alongside the technology of interest with the same treatment intent can be considered to be unrelated to the health gains attributable to the technology of interest. The examples of unrelated costs given in the literature are often much more clearly unrelated than those considered here and look more like the scenario illustrated in Figure 4. It might be possible to argue convincingly that the health benefits of stroke treatments provided

in later life are unrelated to the effectiveness of childhood vaccinations which allow the patient to survive long enough to be at risk of stroke. However, in the examples considered in Section 3, the costs incurred in the added life-years are actually incurred during or soon after treatment with the technology of interest and are related to treatment of the same condition. It is therefore likely that their ability to produce health benefit will interact in some way with the health gains attributable to the technology being appraised. None of the examples we identified were similar to scenario 4 in which a healthcare cost is incurred during the period of additional survival which may be completely unrelated to the disease being treated by the technology under appraisal.

The exclusion of certain costs from cost-effectiveness analyses on the basis that they are unrelated might lead to inconsistencies being introduced between sequential appraisals of drugs for similar indications. For example, in the appraisal of vinflunine described above, the high costs of best supportive care in the post-progression state meant that any increase in PPS would drive the ICER upwards. It could be argued that the care provided after progression is an unrelated cost as the increased need for such care in patients receiving vinflunine is purely drive by their increased survival. These costs could then be excluded from the ICER on this basis. However, one could conceive that another drug for the same indication may be developed in the future which has the effect of reducing PPS by increasing PFS. For this second drug, accounting for the costs of best supportive care incurred during PPS within the ICER would serve to reduce the ICER and it would seem perverse not to account for the real cost savings that are attributable to this second drug when determining whether it is a cost-effective use of NHS resources. In practice, this problem could be solved by conducting an incremental analysis comparing both drugs within an MTA and applying a consistent approach to defining costs as being related or unrelated within that incremental analysis. However, there is a risk that an inconsistent approach may be taken across different TAs if sequential STAs are used to evaluate multiple drugs within a disease area and each draws a different line between related and unrelated costs.

Rappange *et al.*[32] point out that excluding unrelated costs incurred during added life-years will have distributional consequences if the approach is applied consistently across many TAs and cost-effectiveness in each case is determined by comparison to a single threshold. Under these conditions, the exclusion of future unrelated costs favours treatments which result in additional survival other those that result in quality of life gains. They also states that it

favours preventative treatments aimed at older populations over those aimed at younger population as the costs incurred in future life-years are discounted more in younger populations. However, this bias towards favouring treatments aimed at older populations is unlikely to play out in many of the examples identified above, where life-expectancy is low and therefore discounting has a minimal impact on the ICER.

In those cases where the new technology being appraised is being given alongside a very high cost existing intervention, it may be better to re-examine whether the current standard of care represents good value for the NHS. In the pertuzumab example, a previous NICE appraisal (TA34) considered the cost-effectiveness of trastuzumab in combination with taxane therapy (combination trastuzumab was only licensed for use with paclitaxel at the time of TA34) and the committee concluded that the true ICER for combination therapy compared to taxane therapy was likely to be under the £37,500 per QALY gained estimated by the manufacturer. However, the figures used to populate the economic model submitted for the appraisal of pertuzumab suggest that even if the cost per QALY for trastuzumab in combination with docetaxel is under £30,000 per QALY, as believed by the Committee in TA34, there is probably little room left under the NICE threshold to allow additional life-extending therapies to be added cost-effectively.

As more and more technologies pass through the NICE process it may be that it becomes commonplace for new technologies which are given in addition to existing therapies to struggle to demonstrate cost-effectiveness if those existing therapies have been priced at a level that achieves an ICER just under NICE's threshold. Disinvestment from existing high cost technologies may be warranted in some cases, although this is not an option where the new technology is licensed for use in addition to the existing technology. In these cases it may be that a positive price for the new technology which represents good value to the NHS can only be achieved by obtaining a discounted price on both new and existing technologies. There is precedent for manufacturers proposing cost reductions on drugs given alongside the technology being appraised as the manufacturers of bevacizumab proposed a patient access scheme which involved cost reductions for both bevacizumab and oxaliplatin in TA 212. The need to offer discounts on existing technologies to achieve a positive price on new technologies may be perceived by manufacturers as producing a disincentive to develop drugs in areas where there are existing high cost therapies. However, any disincentive is time-limited by the patent duration on existing therapies as the expectation is that generic and

biosilimar products will emerge allowing existing therapies to be acquired at lower cost. In the case of TA212, where a cost reduction was offered on oxaliplatin when given alongside bevacizumab, the Committee concluded that oxaliplatin was already available at a substantially discounted price though NHS procurement contracts. A difficulty in demonstrating cost-effectiveness for technologies which add-on to existing high cost treatment may also increase the incentive for industry to develop technologies which provide a more effective alternative to existing therapies instead of technologies which further add to the treatment burden by being administered alongside existing therapies.

5.2. Properly accounting for benefits

We have focused here on which costs should be incorporated within the analysis, but it is also important to consider whether the benefits have also been properly accounted for. In the case of vinflunine described above, one of the factors contributing to the high ICER for vinflunine was the low utility of the post-progression state. There are several issues which may be relevant when trying to properly account for benefits within the model. Firstly there may be a lack of evidence meeting the NICE reference case for health state utility valuations on which to base utility estimates leading to an underestimation of the direct health benefits to patients. Secondly, generic measures of health utility may fail to detect differences in quality of life that are important to patients particularly at the end of life. Thirdly, the reference case allows for all health benefits to be included whether they fall to patients or to others such as carers. In some of the case studies, the costs of palliative care, provided as part of best supportive care, were substantial. In the vinflunine case study, 14% of the incremental cost was attributable to palliative care costs incurred post progression. It could be argued that good quality palliative care provides benefits to carers, who avoid the psychological distress of seeing their loved one suffer, and these benefits have not been captured within the manufacturer's analysis.

Finally, there may be some treatments, such as dialysis and palliative care, which society may consider worthwhile despite their poor cost-effectiveness. The value placed on these treatments by society may not be captured by the health benefits accrued by either the patients themselves or their carers. NICE already accepts analyses which explore the additional value placed on 'life-extending treatment at the end of life' through the application of end of life QALY weights.[39] There may be other situations where a QALY weight could

be applied to reflect societal preferences that are not captured within the health benefits already included in the QALY, although this would require a change to the current NICE methods guide. Calculating the ICER including the benefits of the treatment of the high cost background treatment, but excluding the cost, as was done for dialysis within the cinacalcet appraisal, provides a lower bound on the ICER as it assumes that all of the excluded costs are justified by the value of the non-QALY benefits.

5.3. Ethical or legal reasons for accepting a higher ICER

There may be situations, as for the dialysis example described by Grima *et al.*,[21] where a new technology is cost-effective in the general population, where average healthcare costs are low, but not cost-effective in a specific population who are already receiving a high cost maintenance treatment which would not itself be considered cost-effective but is part of the NHS standard of care none the less. As described earlier, in such populations any life-extending treatment is likely to be found not to be cost-effective unless it generates substantial quality of life gains or cost savings in addition to extending survival.

NICE's existing 'Social Value Judgements: Principles for the development of NICE guidance, (2nd Edition)' policy states, "NICE can recommend that use of an intervention is restricted to a particular group of people within the population (for example, people under or over a certain age, or women only), but only in certain circumstances. There must be clear evidence about the increased effectiveness of the intervention in this subgroup, or other reasons relating to fairness for society as a whole, or a legal requirement to act in this way."[41] Under this policy it would not be possible for NICE to make different recommendations for people with high background care costs than for the general population as a whole if the difference in those recommendations was driven solely by a difference in the background costs of care in the two populations.

In the case studies we have identified, the high background care costs, such as dialysis for patients with SHPT in the appraisal of cinacalcet, were incurred by the whole population included within the scope of the appraisal. It may therefore not be relevant to consider whether the intervention would be cost-effective in other populations who have lower background care costs, particularly if the intervention would not be indicated in those populations. However, if the background care costs in the population defined in the scope

were found to be too high to allow a life-extending treatment to be cost-effective despite being delivered for zero cost, the Committee may still wish to consider whether there are any legal or ethical reasons for recommending the treatment despite the high ICER. This would be in line with NICE existing Social Value Judgement policy which describes the need to 'distribute health resources in the fairest way within society as a whole'.[41]

6. CONCLUSIONS

Having considered the examples identified within the NICE TA programme and the methodological literature on this issue, we would argue that all costs which differ between the technology being appraised and the comparator technologies identified in the decision problem should be included within the ICER, provided they fall within the NHS and PSS perspective, as this provides an ICER which reflects the real opportunity cost of recommending the technology being appraised and is consistent with the objective of the NICE TA programme.[39] Whilst this would result in a slightly broader inclusion of costs than included within the current NICE methods guide,[39] in practice none of the costs included in the case studies examined here would have been excluded under the current NICE methods, with the possible exception of dialysis costs in the appraisal of cinacalcet. The rationale for exclusion in this case comes down to a fairly arbitrary decision as to whether SHPT or ESRD is the 'condition of interest' for that appraisal. For this reason, we would agree with van Baal *et al.* that it is better to consider all costs which differ regardless of whether they fall within the 'condition of interest'.[34]

The TA Committee may also wish to consider whether the health benefits to both the patients and their carers of all the care falling within the NHS and PSS budget has been adequately captured in the cost-effectiveness analysis, as including the costs of all NHS and PSS resource use without capturing the full health benefits may under estimate the value of the technology and the value of the care provided alongside it.

The TA Committee may wish to consider whether the population is currently receiving a high cost intervention which does not meet commonly accepted thresholds for cost-effectiveness but which is deemed to be an acceptable use of NHS resources for other reasons and whether the only impact of the technology being appraised on the requirement for this high cost

background intervention is through its effect on survival. The Committee may wish to consider whether there are some additional benefits to society of providing that existing high cost intervention which are not captured in the health benefits accrued by patients or other people. If those additional benefits cannot be quantified, then calculating the ICER including the health benefits of the background intervention, but not its costs would provide a lower bound on the ICER. If there are no additional benefits to society outside of those already captured within the ICER, then the Committee may wish to recommend that existing intervention for appraisal to determine whether the NHS should disinvest from that technology.

Finally, in accordance with their existing policies, the Committee may also wish to consider whether there are any legal or ethical reasons for recommending the treatment when the ICER is in excess of the range usually considered to represent good value for the NHS.

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PMG19 Addendum A - Final amendments to the NICE technology appraisal processes and methods guides to support the proposed new Cancer Drugs Fund arrangements

Technology Appraisal Processes - CDF

This document sets out the proposed changes to the Guide to the Processes of Technology Appraisal necessary to support the joint NHS England and NICE proposals for the management of the Cancer Drugs Fund from April 2016.

Only relevant sections of the Guide are shown. Therefore the sections below need to be read in conjunction with the Guide to the Processes of Technology Appraisal.

New text proposed to be inserted into the guide is shown below in *italics.*

2. Selection of technologies

2.3 Prioritisation

2.3.3 All new cancer drugs and significant new licensed indications for cancer drugs will be referred to NICE for appraisal.

The Appraisal Process for Cancer Drugs

In order to be able to publish guidance on cancer drugs within 90 days of the marketing authorisation, NICE will hold the first Appraisal Committee meeting for a cancer drug before the CHMP opinion is published, ideally at or about the 180 day point in the regulatory process. Because the drug will not, at this stage, have received a regulatory opinion, this Appraisal Committee meeting will be held in private, in order to preserve the confidentiality of the data submitted by the company. Patient, clinical and commissioning experts, and company representatives will be invited to participate in the meeting under normal confidentiality arrangements.

After this Appraisal Committee meeting, an Appraisal Consultation Document (ACD) with a preliminary recommendation, or a Final Appraisal Determination (FAD) will be developed. As soon as the CHMP opinion has been published, NICE will establish whether the CHMP opinion is the same as, or similar to, the indication provided in the company submission. If it is, the ACD and the committee papers will be sent to consultees, commentators, the clinical

experts, NHS commissioning experts and patient experts for consultation (or consideration of appeal where a FAD is produced). In cases where the CHMP opinion is substantially different from the indication provided in the company submission, a further Appraisal Committee discussion may be necessary. An ACD or FAD is confidential until NICE publishes it on its website, normally 5 working days after it has been sent to consultees.

Where an ACD has been produced, the subsequent Appraisal Committee meeting will be held in public shortly after the publication of the Marketing Authorisation.

Consultation on the Appraisal Consultation Document (ACD) (if produced)

3.7.26 When a cancer drug is recommended for use within the Cancer Drugs Fund (CDF), the Appraisal Committee will state the conditions for its use in the Appraisal Consultation Document (ACD) and will identify the nature of the clinical uncertainty which should be addressed through data collection. Details of data collection, including the protocol and the analysis plan, will be set out in a 'managed access agreement'.

3.7.27 *The data collection arrangements will be developed, during the consultation period, by the company, NHS England, and NICE with input from clinicians and patients, and on advice from NHS England's Chemotherapy Clinical Reference Group and NICEs Observational Data Unit (ODU). It will be completed before the final guidance is published. Funding for data collection and analysis will be provided by the company holding the marketing authorisation for the product.*

5 Patient access schemes, flexible pricing and commercial access arrangements

5.2 *In the context of the Cancer Drugs Fund, companies agree 'commercial access arrangements' with NHS England. Such arrangements will be considered in the NICE technology appraisal.*

Definitions

5.5 *A commercial access arrangement is a proposal from a company to NHS England to manage the cost of a drug to the NHS. Commercial access agreements support the inclusion of cancer drugs in the CDF and facilitate patient access to a medicine through the CDF where NICE technology appraisal, on the current evidence base, is unlikely to support a recommendation for routine use.*

5.6 NICE can only consider patient access schemes (see figure 5) and flexible pricing proposals (see figure 6) after these have been formally approved by the Department of Health.

Commercial access arrangements

5.31 When the Appraisal Committee decides to recommend a technology for use within the CDF, the company will be invited to propose a commercial access arrangement, or amend an arrangement that has already been proposed.

5.32 In order for a cancer drug to be recommended for use through the Fund, it must display plausible potential for satisfying the criteria for routine use, taking into account the application of the End of Life criteria where appropriate.

5.33 Companies should work with NICE and ask for advice about the assumptions used in the consideration of clinical and cost effectiveness by the Appraisal Committee, which must form the basis of their proposal for a commercial access arrangement.

6 Reviews

Updating technology appraisals after inclusion in the Cancer Drugs Fund

6.22 NICE will normally review its guidance for a cancer drug funded through the CDF within 24 months of publishing it. The aim of the CDF guidance review is to decide whether or not the cancer drug can be recommended for routine use. The drug (or indication) may not remain in the CDF once the guidance review has been completed

6.23 Progress with data collection will be reviewed regularly. An annual report, provided by the company or the organisation collecting the data, will be submitted to NICE to check whether the data collection is on track, and to establish whether any additional action is needed. This will be coordinated through the NICE Observational Data Unit. Guidance may be considered for review before the published review time when there is significant new evidence that either supports the original case for clinical and cost effectiveness, or when the evidence points to the likelihood that the original recommendations are not valid. The steps involved are shown in table 8, 9 and figure a.

6.24 The published guidance will be withdrawn, and the drug removed from the CDF, if the company stops data collection for reasons other than an early guidance review.

6.25 Review of guidance for cancer drugs funded by the CDF will be scheduled into the technology appraisal work programme to coincide with the end of the data collection period determined at the point of entry of the drug into the fund. This will normally not be longer than 24 months. If NICE considers it reasonable to review the published guidance earlier than at the designated data collection period, the decision to do so will be subject to consultation.

6.26 The guidance review will be undertaken through a shortened technology appraisal process, which will normally take a maximum of 6 months. The company will have 4 weeks to submit the new evidence from data collection, and the ERG will have 4 weeks to critique the new evidence (see table 8).

6.27 The CDF guidance review will take into account the data that have become available since the original appraisal, together with any change to the patient access scheme or commercial access arrangement proposed by the company. No changes to the scope of the appraisal will be considered.

6.28 Companies must provide an evidence submission to support the CDF guidance review. The managed access agreement signed at the time of the original appraisal will include this obligation.

6.29 After the first committee meeting for the guidance review, a Final Appraisal Determination (FAD) will be produced if its recommendations are consistent with the original conditions for use in the Cancer Drugs Fund. In all other circumstances, an ACD will be produced.

Table 8 Expected timelines for the Cancer Drugs Fund guidance review - shortened technology appraisal process

		Weeks (approx.)
Step 1	*NICE invites organisations to participate in the guidance review as consultees or commentators*	*0*

Step 2	*NICE receives evidence submission from company holding the marketing authorisation*	*4*
Step 3	*NICE requests clarification from the company on the evidence submission*	*5*
Step 4	*NICE invites selected clinical experts, NHS commissioning experts and patient experts to attend the Appraisal Committee meeting*	*7*
Step 5	*NICE sends the ERG report to the company for fact checking*	*8*
Step 6	*NICE compiles a review summary report and sends it to the Appraisal Committee*	*10*

**Timelines may change in response to individual appraisal requirements.*

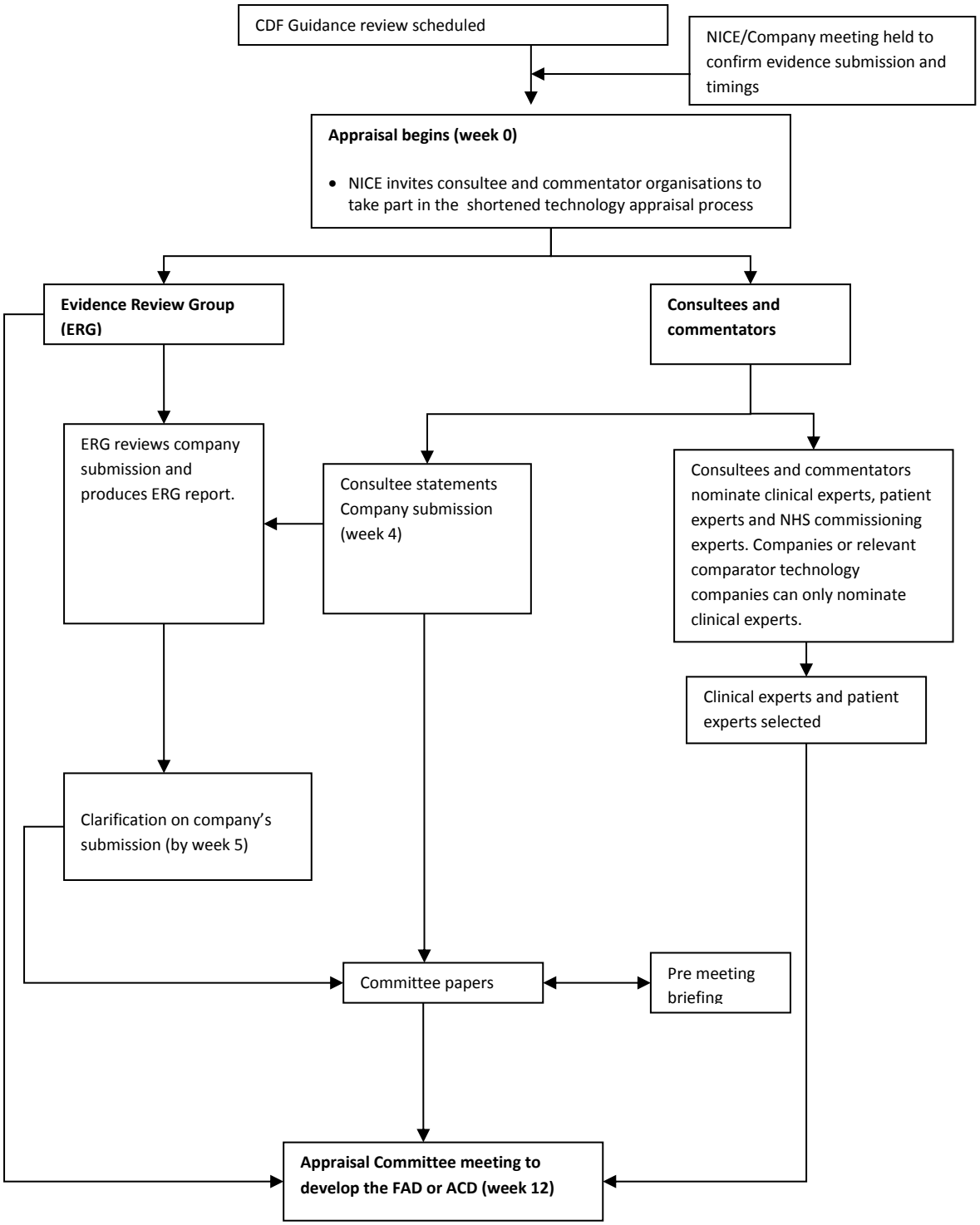
Table 9 Expected timelines for the Cancer Drugs Fund guidance review using the shortened appraisal process if an ACD is produced*

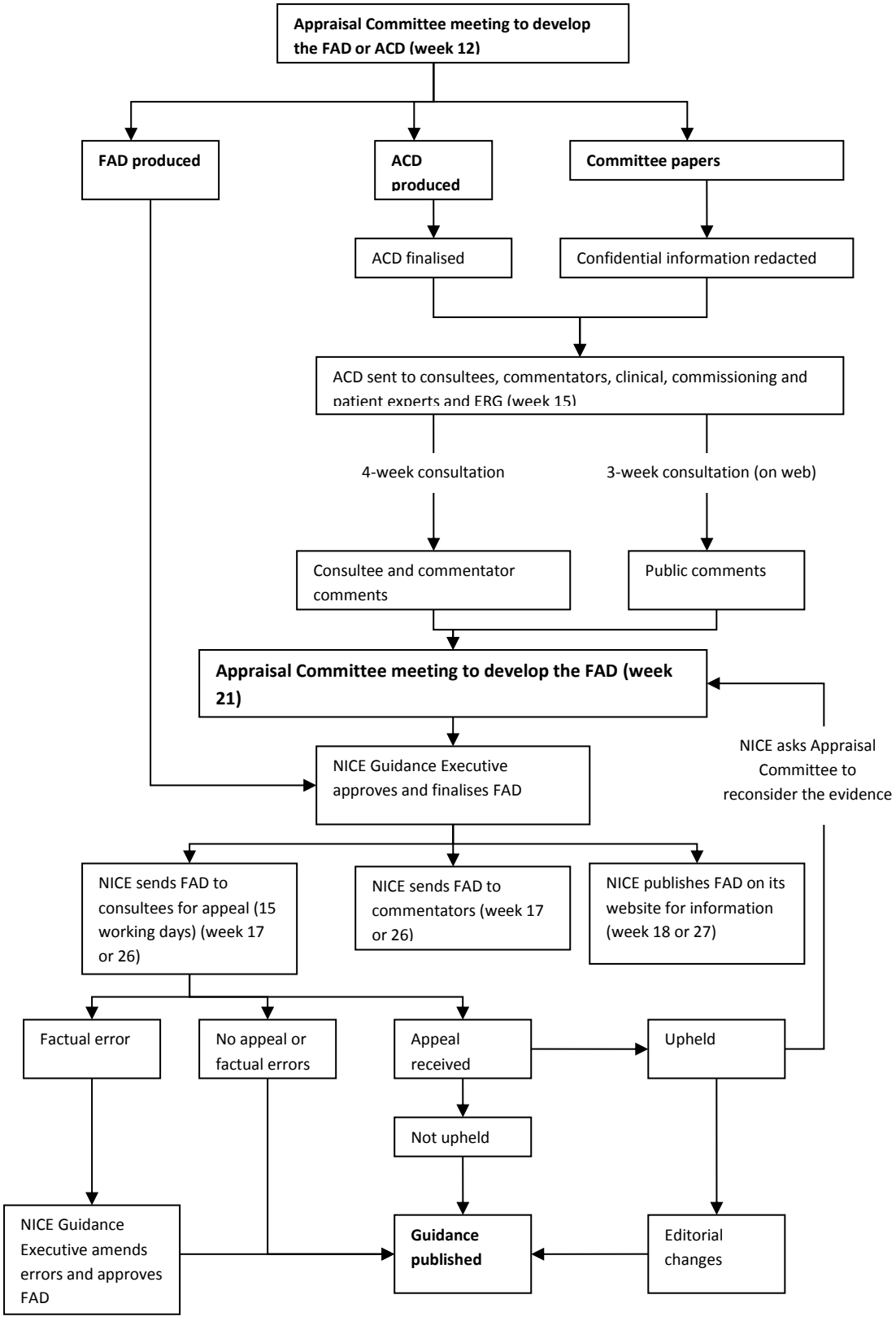
		Weeks
Step 7	*Appraisal Committee meeting*	*12*
Step 8	*The ACD is produced. NICE distributes the ACD and publishes it on the website 5 working days later*	*15*
Step 9	*Fixed 4-week consultation period on the ACD*	*15-19*
Step 10	*Appraisal Committee meeting to consider comments on the ACD from consultees and commentators, and comments received through the consultation on the NICE website. Appraisal Committee agrees the content of the FAD*	*20/21*
Step 11	*The FAD is produced. NICE distributes the FAD and publishes it on the website 5 working days later*	*26*
**Timelines may change in response to individual appraisal requirements.*		

Table 10 Expected timelines for the Cancer Drugs Fund guidance review using the shortened appraisal process if an ACD is not produced*

		Weeks
Step 7	*Appraisal Committee meeting to develop a FAD*	*12*
Step 8	*The FAD is produced. NICE distributes the FAD and publishes it on the website 5 working days later*	*17*
**Timelines may change in response to individual appraisal requirements.*		

Figure a Summary of the Cancer Drugs Fund guidance review using the shortened technology appraisal process




Appraisal Committee meeting to develop the FAD or ACD (week 12)
FAD produced
ACD produced
Committee papers
ACD finalised
Confidential information redacted
ACD sent to consultees, commentators, clinical, commissioning and patient experts and ERG (week 15)
4-week consultation
3-week consultation (on web)
Consultee and commentator comments
Public comments
Appraisal Committee meeting to develop the FAD (week 21)
NICE asks Appraisal Committee to reconsider the evidence
NICE Guidance Executive approves and finalises FAD
NICE sends FAD to consultees for appeal (15 working days) (week 17 or 26)
NICE sends FAD to commentators (week 17 or 26)
NICE publishes FAD on its website for information (week 18 or 27)
Factual error
No appeal or factual errors
Appeal received
Upheld
Not upheld
NICE Guidance Executive amends errors and approves FAD
Guidance published
Editorial changes

Technology Appraisal Methods

This document shows all proposed changes to the Guide to the Methods of Technology Appraisal 2013.

Only relevant sections of the Guide are shown. Therefore the sections below need to be read in conjunction with the Guide to the Methods of Technology Appraisal

New text proposed to be inserted into the guide is shown below in *italics.*

The text ~~scored out~~ is proposed to be deleted from the current Guide.

6 The appraisal of the evidence and structured decision-making

Structured decision-making: clinical effectiveness and health-related factors

6.2.10 In the case of a 'life-extending treatment at the end of life', the Appraisal Committee will satisfy itself that all of the following criteria have been met:

- the treatment is indicated for patients with a short life expectancy, normally less than 24 months and
- there is sufficient evidence to indicate that the treatment has the prospect of offering an extension to life, **normally** of a mean value of at least an additional 3 months, compared with current NHS treatment.

~~and~~

~~the technology is licensed or otherwise indicated, for small patient populations normally not exceeding a cumulative total of 7000 for all licensed indications in England.~~

In addition, the Appraisal Committees will need to be satisfied that:

- the estimates of the extension to life are *sufficiently r*obust and can be shown or reasonably inferred from either progression-free survival or overall survival (taking account of trials in which crossover has occurred and been accounted for in the effectiveness review) and
- the assumptions used in the reference case economic modelling are plausible, objective and robust.

6.2.11 When the conditions described in section 6.2.10 are met, the Appraisal Committee will consider:

- the impact of giving greater weight to QALYs achieved in the later stages of terminal diseases, using the assumption that the extended survival period is experienced at the full quality of life anticipated for a healthy individual of the same age and
- the magnitude of the additional weight that would need to be assigned to the QALY benefits in this patient group for the cost effectiveness of the technology to fall within the normal range of maximum acceptable ICERs, with a maximum weight of 1.7.

6.2.12 Treatments recommended following the application of the 'end-of-life' criteria listed in section 6.2.10 will not necessarily be regarded or accepted as standard comparators for future appraisals of new treatments introduced for the same condition. Second and subsequent extensions to the marketing authorisations for the same product will be considered on their individual merits.

6.5 Making recommendations for use through the Cancer Drugs Fund

6.5.1 *When the evidence for the clinical and cost effectiveness of a drug has been assessed, including, when appropriate, the factors described in 6.2.10–17, the Appraisal Committee will decide whether the drug can be recommended for routine use.*

6.5.2 The Appraisal Committee will determine whether the estimates of the extension to life are sufficiently robust.

6.5.3 If the Appraisal Committee concludes that estimates of the extension to life are not sufficiently robust, such that the uncertainty in the clinical and cost effectiveness data is too great to recommend the drug for routine use, the Committee can consider a recommendation for use within the Cancer Drugs Fund if the following criteria are met:

- *The incremental cost-effectiveness ratios (ICERs) presented have the plausible potential for satisfying the criteria for routine use, taking into account the application of the End of Life criteria where appropriate. (see sections 5.8.10 and 6.3.2–5 of the guide to the methods of technology appraisal).*

- *It is possible that the clinical uncertainty can be addressed through collection of outcome data from patients treated in the NHS.*
- *It is possible that the data collected (including from research already underway) will be able to inform a subsequent update of the guidance. This will normally happen within 24 months.*

6.5.4 *The arrangements for data collection will be part of the managed access arrangement to be drawn up between the company, NHS England, and NICE with input from clinicians and patients, and with advice from NHS England's Chemotherapy Clinical Reference Group and NICE's Observational Data Unit (see the guide to the processes of technology appraisal section 3.7.27) before final guidance is published.*