NICE National Institute for Health and Care Excellence

CDF Rapid Reconsideration

Everolimus in combination with exemestane for treating advanced HER2-negative hormone-receptor-positive breast cancer after endocrine therapy (Cancer Drugs Fund reconsideration of TA295)

Committee Papers

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Contents:

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

Slides for public

Everolimus in combination with exemestane for treating advanced HER2 negative hormone-receptor-positive breast cancer after endocrine therapy

Cancer Drug Fund Rapid Reconsideration Meeting, 26 July 2016

Single Technology Appraisal

Cancer Drug Fund Committee (previously Committee B)

Lead Team: Daniel Hochhauser, Marta Soares, Cliff Snelling

Evidence Review Group: LRiG Liverpool Reviews and Implementation Group

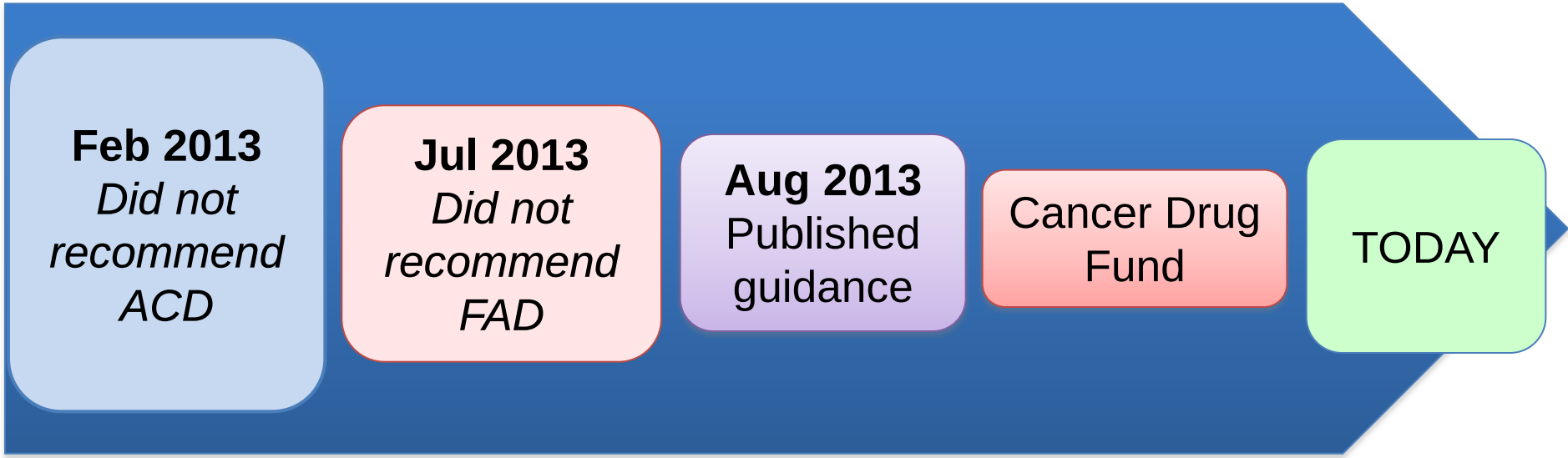
NICE Technical Team: Martyn Burke, Zoe Garrett for ACD, Elisabeth George, Janet Robertson

Company: Novartis

General issues for consideration

- Has the company addressed all the committee's preferred assumptions stated in FAD?
- Are the company's and ERG's estimates of the ICER plausible?
- Does everolimus meet the criteria for a 'life-extending treatment at the end of life'?
- Taking into account the patient access scheme, can everolimus be recommended for use in the NHS?
- Should everolimus be considered for the Cancer Drug Fund?

History of appraisal Committee B



Main question today: Is everolimus clinically and cost-effective against the same comparators in the same population but with more mature data and a new patient access scheme?

Everolimus
Mechanism and Marketing Authorisation

- Inhibitor of mammalian target of rapamycin (mTOR)
- Marketing authorisation for breast cancer when:
  - Advanced, but no symptomatic visceral, disease
  - Hormone-receptor-positive
  - HER-2* negative
  - Previously treated with a non-steroidal aromatase inhibitor
  - Co-administered with exemestane, a steroidal aromatase inhibitor
- Oral – dose 10 mg once daily

**Human Epidermal Growth Factor Receptor 2*

Comparators and evidence

Advanced Hormone receptor+/HER2- post-menopausal women **without symptomatic visceral disease** after nonsteroidal aromatase inhibitor

Everolimus + Exemestane	Exemestane alone	Tamoxifen	Fulvestrant TA239 Not recommended	Chemotherapy Doxorubicin Docetaxel Capecitabine
	‘BOLERO-2’	‘TAMRAD’	Indirect comparison	Naïve chained indirect analysis

BOLERO-2

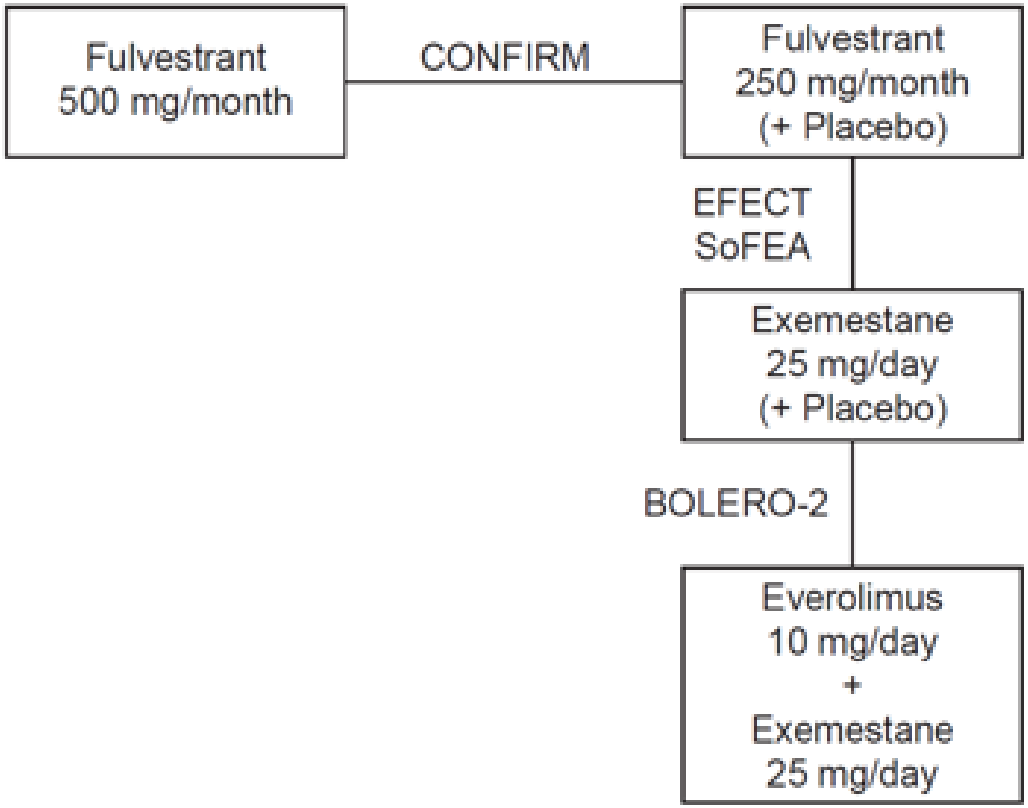
Everolimus +Exemestane

Exemestane

1° outcome
PFS assessed by local investigators (‘locally’)

Company uses SoFEA in its case for end-of-life in this rapid reconsideration

Used by company originally for fulvestrant comparison – Indirect



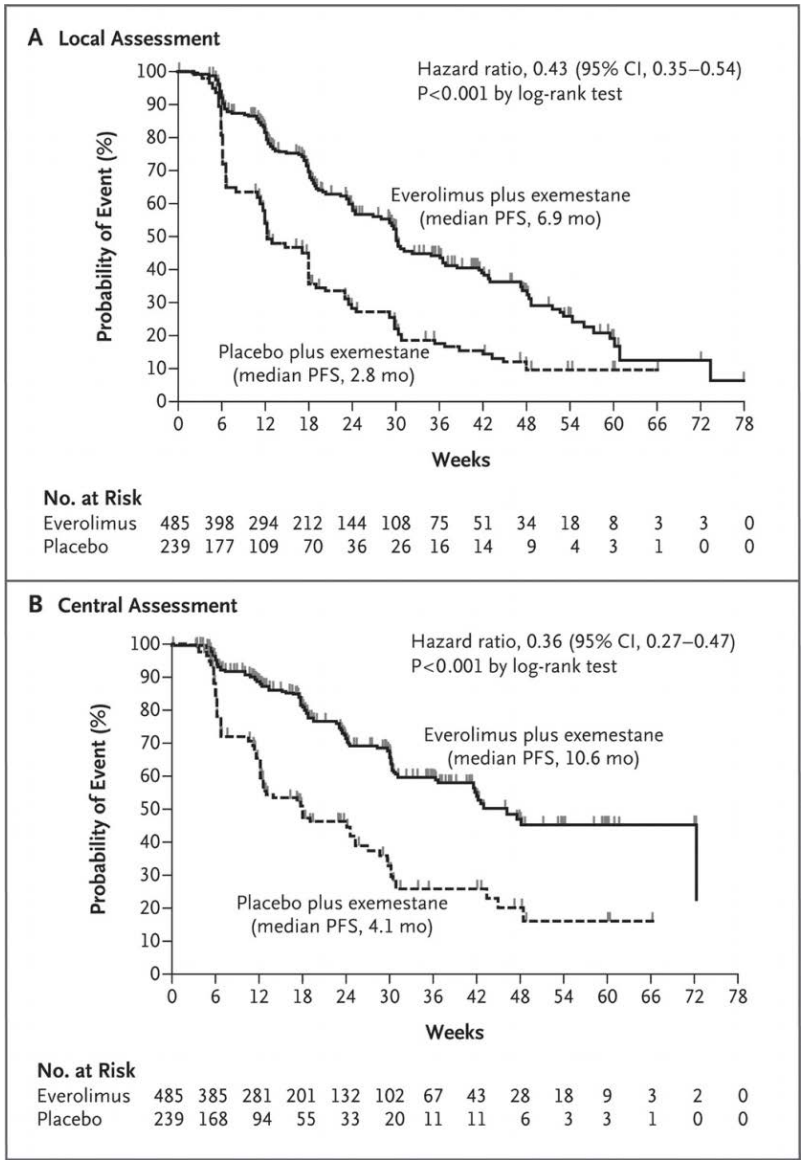
SoFEA population:

1. estrogen receptor + and/or
2. progesterone receptor + ; **but**,
3. not limited to HER2 negative

Progression-free survival : BOLERO-2
Impact of assessing PFS locally vs. centrally

Local Assessment
1 ° endpoint BOLERO-2

Central Assessment
Used previously in economic analyses



N Engl J Med 2012;366:520-9.

Company's original Markov Model

stable disease, progressed disease, death

Horizon	Lifetime = 10 years
Treatment	Until disease progresses
Effectiveness everolimus	BOLERO-2 PFS assessed central assessment. Effect persists over time.
Extrapolating PFS to estimate mean	Company: Best fitting log-logistic; chose Weibull ERG: chose 'piecewise'
Number of patients progressed disease	Patients alive minus estimated number in stable disease state - resulted in negative number
Mean OS	To fix above problem, company lengthened overall survival with 'Beauchemin factor' applied only to everolimus
Adverse events	Not included in base case versus endocrine therapies
Utility	BOLERO-2 collected quality of life but company did not use it; used Lloyd

Committee's considerations in FAD

Comparator	Exemestane alone most relevant comparator
Progression free survival	More appropriate to use data from local not central assessment
Overall survival	Immature data led to considerable uncertainty
	Not appropriate to lengthen with Beauchemin et al 2012 factor
	Mean benefit uncertain but probably lies between: ERG's 'parallel' 1.4 months and company's 10.5 months ERG's 'non-parallel' estimate is 4.6 months reflecting longer time in progression-free survival for everolimus + exemestane
Cost effectiveness – key driver	ICERs most sensitive to: • local vs. central PFS • modelling of overall survival
	Most plausible ICER of £68,000 per QALY gained
End-of-life	Not met, unconvinced life expectancy <24 months; Company model estimates mean overall survival of 28.9 months for exemestane alone. Company did not make a case originally, then provided evidence different population.

Committee's preferences, company response

Preferred assumptions	Addressed?
Use functions to estimate progression-free survival and non-parallel model of overall survival	New, longer data
Remove overall survival adjustment factor (Beauchemin)	Done
Use locally assessed ° endpoint trial data	Done
Include adverse reactions costs and disutility	Done
Use rates of adverse reactions from EPAR	Done
Recalculate time on treatment; include costs of monitoring disease that has not yet progressed	Done; reflects longer follow-up
Correct discounting and utility values for stable disease	Done
Use utility for 'progressed disease' from Lloyd et al.	Done
Omit double counting mortality from non-cancer causes	Done

What is new?

More mature data for overall survival from BOLERO -2 company chooses log logistic; no new data for PFS but now modelled with log logistic instead of Weibull

Revised simple discount patient access scheme; updated unit costs

BOLERO-2 overall survival data
Original and updated

N=724	Original data	Updated data
Number of deaths	182	410
Percentage died	25.1%	56.6%
Median follow-up	16.0 months	39.3 months
Median time to death everolimus	Not reached	31.0 months
Median time to death exemestane	Not reached	26.6 months*
Hazard ratio	0.77	0.89
Confidence interval	0.57 to 1.04	0.73 to 1.10

n.b. no new data cut for progression free survival

** Committee to bear in mind for end of life discussion*

ERG's critique
General comments

- Company applied all committee's preferred assumptions
- ERG identified that company had changed horizon from 10 to 15 years; ERG prefers 20 years
- ERG identified and fixed an error relating to the time horizon in the company's model
- ERG requested of company Kaplan-Meier analysis results for: overall survival, progression-free survival and post-progression survival using an alternative censoring rule to avoid a type of right-censoring bias that can occur in trials with a substantial proportion of patients who are censored at data cut-off
- Received Kaplan-Meier analysis results only for progression-free survival and overall survival with alternative censoring method
  - However, the company had difficulties in applying it because of the way BOLERO-2 data was captured and recorded
- No results provided by company for post progression survival

Progression free survival
summary company and ERG approach

Company

- No new follow-up has been carried out for PFS in the BOLERO-2 trial
- Original censoring rule
- Log logistic function
- Assessing PFS using local investigators

ERG

- Assessing PFS using local investigators
- Exponential model fit both arms
- So, used Kaplan-Meier data directly until few patients at risk then extrapolated with exponential model after
  - 12 months for everolimus
  - 11 months for exemestane

Progression free survival
company's curve-fitting from original appraisal

Best fitting log-logistic, but manufacturer used Weibull– plausibility (experts)

Log logistic is orange (top); Weibull is purple

Figure B22 Progression free survival, all parametric functions fitted: exemestane arm

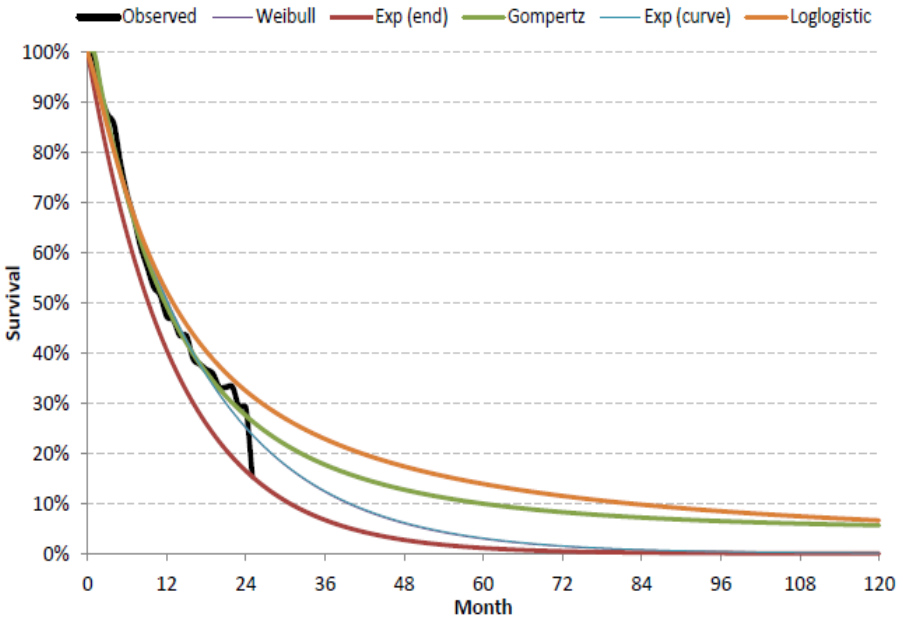


Figure B21 Progression free survival, all parametric functions fitted: exemestane arm

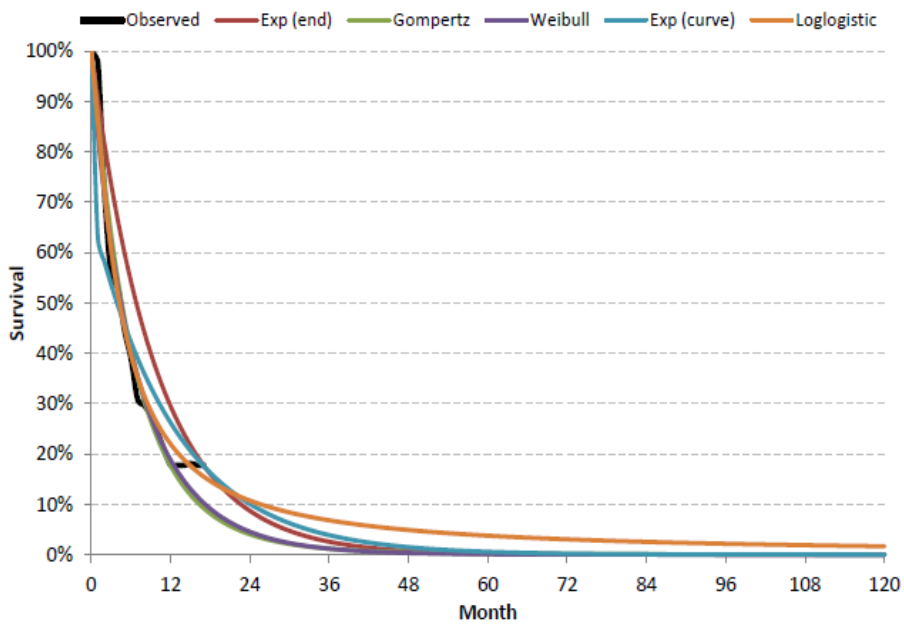


Table B22 appears to be labelled incorrectly in the original submission - observed data match the curve for the everolimus + exemestane arm

Company's statistical tests for choosing curves in CDF reconsideration

Table 2 - AIC and BIC values for each survival model

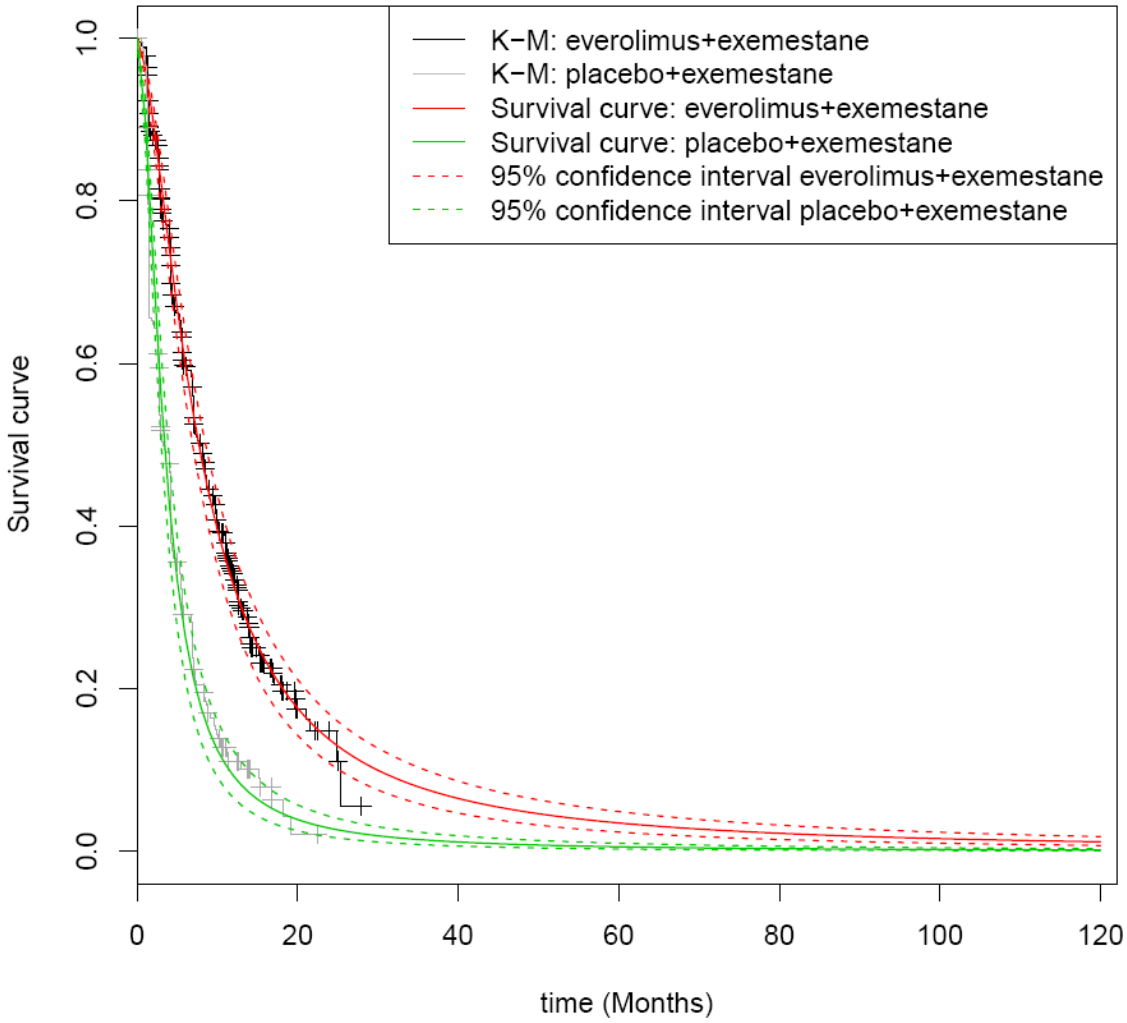
Survival distribution	OS		PFS Central		PFS Local	
	AIC	BIC	AIC	BIC	AIC	BIC
Exponential	3,913.88	3,923.05	2,249.15	2,258.32	3,215.17	3,224.34
Weibull	**3,878.09**	**3,896.43**	2,238.41	2,256.75	3,197.80	3,216.14
Loglogistic	**3,878.29**	**3,896.63**	**2,200.30**	**2,218.64**	**3,149.86**	**3,168.20**
Gompertz	3,891.17	3,909.51	2,250.24	2,268.58	3,216.07	3,234.41

⊙ Is the company justified in changing PFS (local) to log logistic in absence of new data? n.b. in original appraisal Weibull clinically best, log logistic statistically best

⊙ Is company justified on statistical grounds of choosing log-logistic for new more mature overall survival data?

Table 2 Novartis survival analyses

Company extrapolation of progression free disease (local assessment): Log-logistic

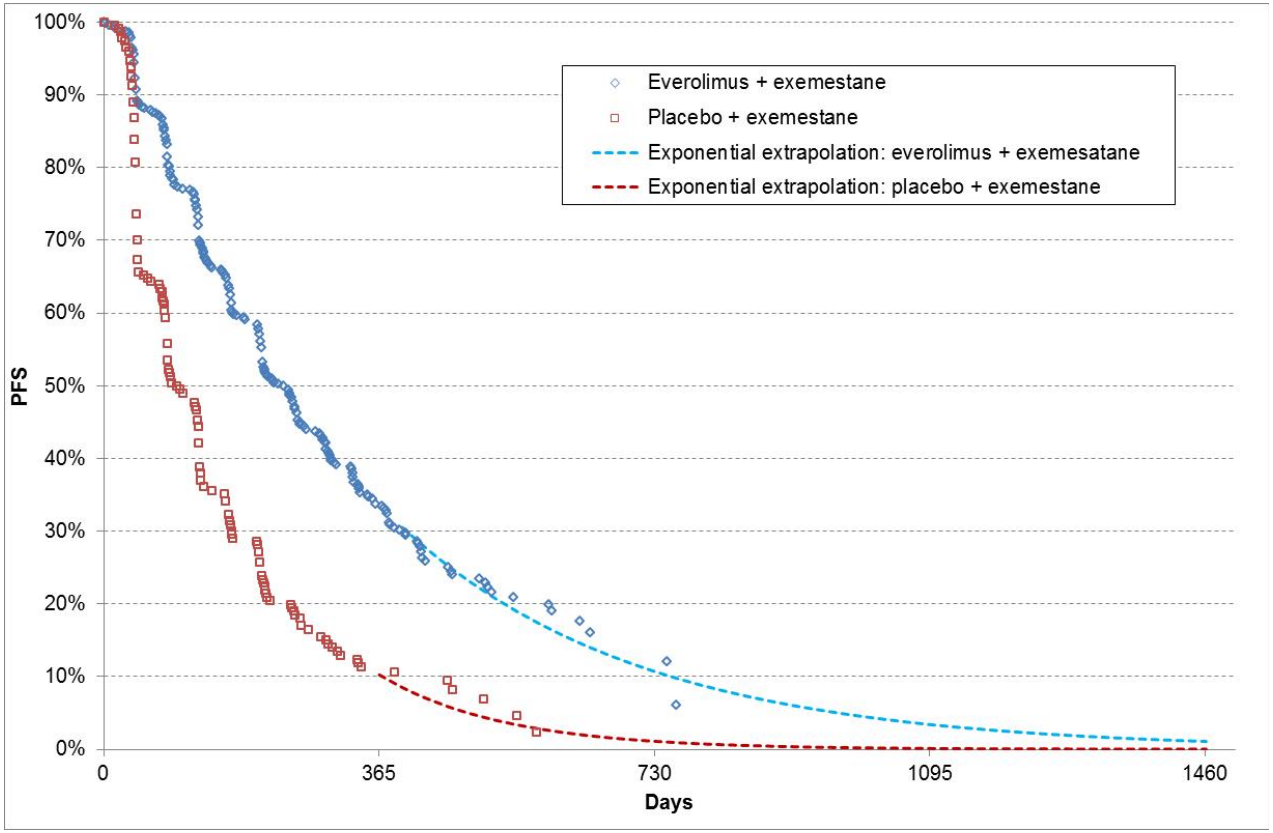


⊙ How does the 'right censoring bias' affect this model? Is the log-logistic curve the best?

Source: Figure 5, company's survival analysis document (individual patient data).

ERG's exploratory analysis of progression free survival 'bolt on'

Progression-free survival K-M estimates (BOLERO-2 clinical trial) with exponential extrapolation curves applied in the decision model after 12 months (everolimus) and 11 months (exemestane)



⊙ How did the ERG pick the point from which to extrapolate?

Which approach does the Committee prefer?

Source: Figure 1, ERG report

Post progression survival company and ERG approach

Company

- ?

ERG

- ERG requested from company but did not receive data for post progression survival

⊙ How did the company and ERG account for the previous problems with time in progressed disease?

Overall survival company and ERG approach

Company

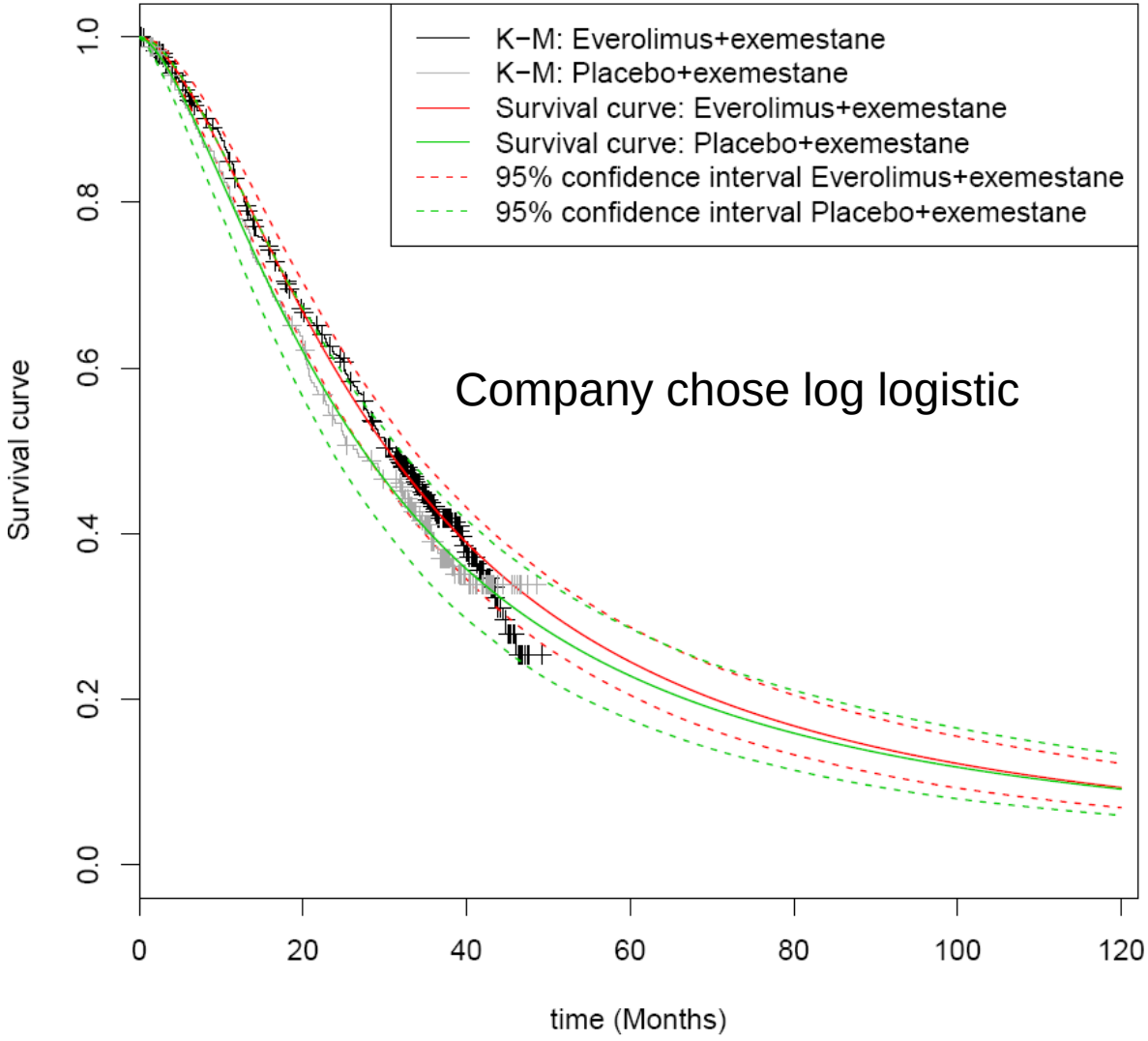
- New more mature data
- New data uses log logistic
- (Company chose Weibull for old data)
- Replaced data with model

ERG

- Assumes that drug extends life until disease progression but not thereafter
- i.e. mortality would be ‘parallel’ after progression
- No modelling
- Difference in survival reflected by area between curves (‘landmark’ analysis’)
- [CIC] months

Company's modelling of overall survival

explored exponential, Gompertz, Weibull and log-logistic

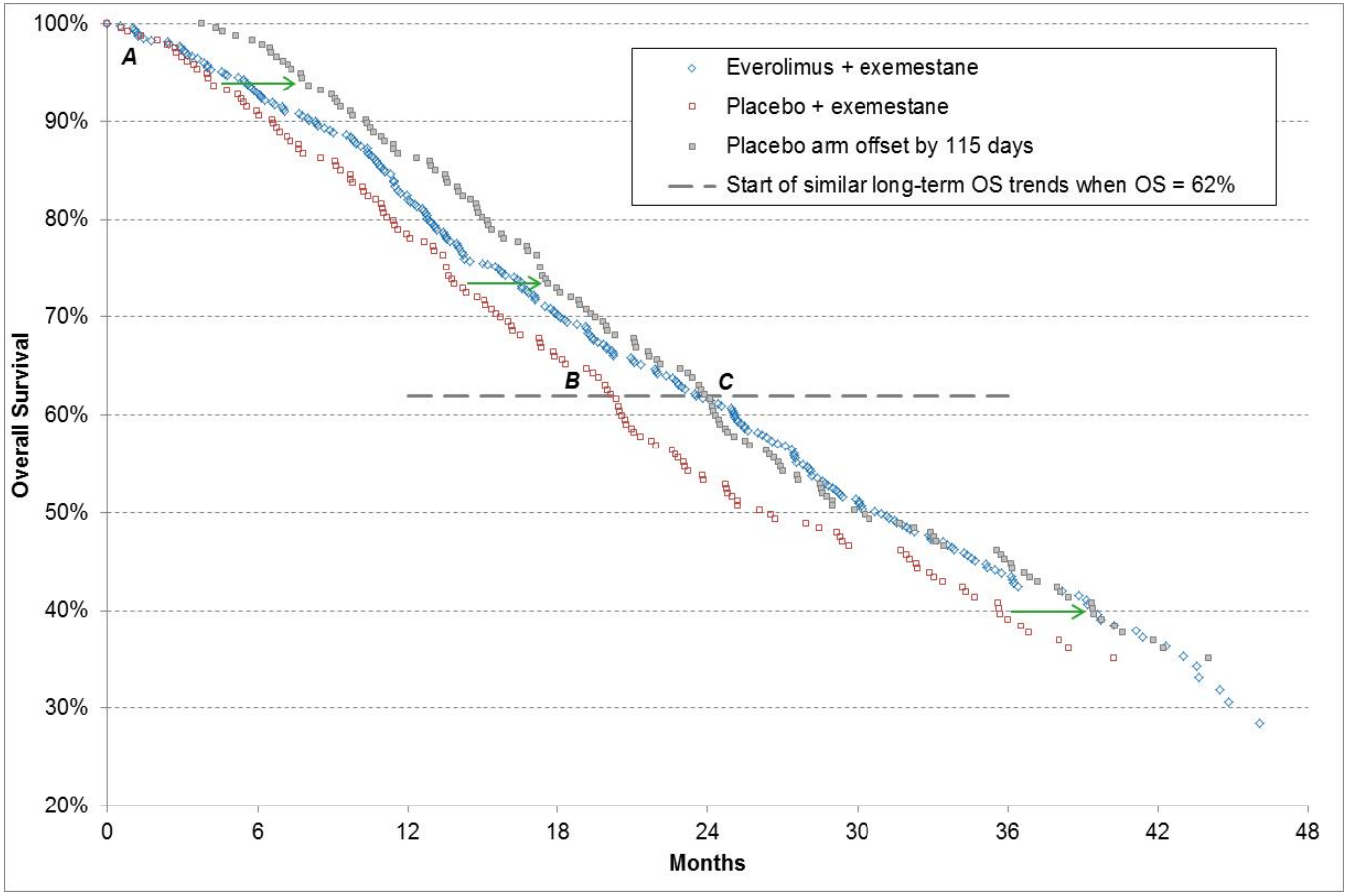


Source: Figures 1 & 2, company's survival analysis document (individual patient data)

Company: "The presence of large censoring in the later part of the data is a limitation of this analysis, causing considerable uncertainty in the estimation of the survival curve."

Source: page 6 company's survival analysis document (individual patient data).

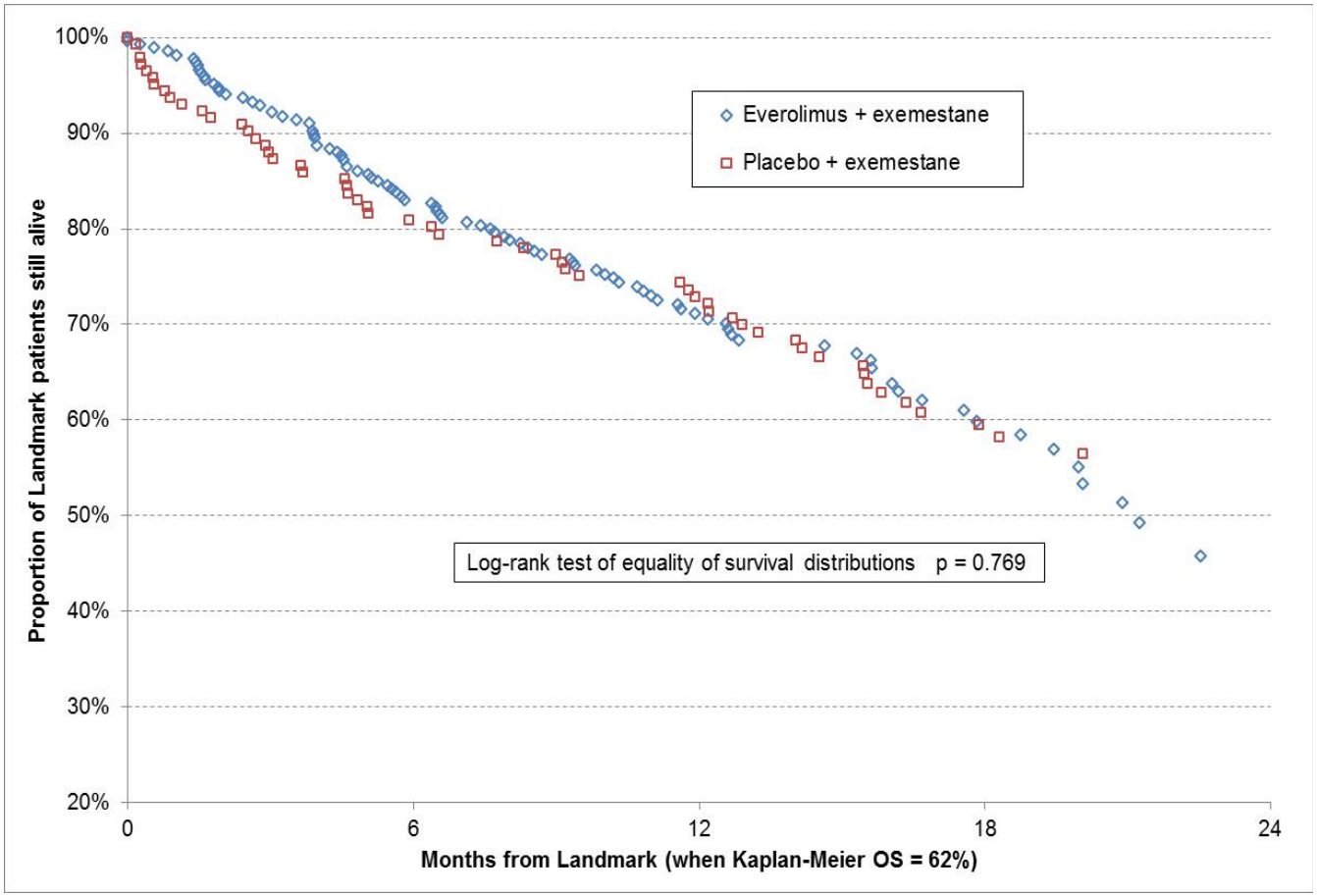
ERG approach to overall survival in BOLERO-2, with 'offset' placebo arm to compare long-term survival patterns



Suggests close correspondence of long-term survival trends in both treatment arms beyond the point at which estimated overall survival is 62% (point C).

Source: Figure 2 ERG report

ERG's exploratory 'landmark' analysis



Source: Figures 3 and 4 of ERG report

⊙ Which approach does the Committee prefer?

Common survival trend applied to all patients beyond the 'landmark' point.

Therefore, difference in overall survival is simply based any differences before this time point – calculated to be [CIC] months (directly estimated from KM data / trial results).

After 62% of patients have died, ERG applied simple exponential extrapolation model.

Company's revised base case with revised PAS

	Everolimus	Exemestane	Incremental
Total costs (£)	[CIC]	£36,677	[CIC]
Life years gained	2.67	2.52	0.15
QALYs	1.59	1.36	0.23
ICER (£/QALY)			**[CIC]**

Abbreviations: ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality-adjusted life years.

Source: Table 4b, page 18 of the company submission.

Company's probabilistic sensitivity analysis with PAS

Base case ICER = [CIC]

At a threshold of £30,000 everolimus + exemestane has a [CIC]% probability of being cost-effective.

Source: pages 19–20 of the company's submission

Company and ERG
Cost effectiveness results with PAS

Model Scenario (table 4b, p18 company submission & table 1, p11 ERG report)	Company revised model (15 year horizon)	ERG corrected model (20 year horizon)	Revised PFS	Revised OS	Both revised
Everolimus cost	[CIC]	[CIC]	[CIC]	[CIC]	[CIC]
Everolimus QALYs	1.59	2.082	2.017	1.850	1.786
Everolimus life years	2.67	4.090	4.090	3.409	3.409
Exemestane cost	£36,677	£51,177	£51,728	£43,742	£44,293
Exemestane QALYs	1.36	1.83	1.81	1.59	1.57
Exemestane life-yrs	2.52	3.90	3.90	3.18	3.18
Incremental cost	[CIC]	[CIC]	[CIC]	[CIC]	[CIC]
Incremental QALYs	+0.23	+0.256	+0.204	+0.268	+0.217
Incremental life years	+0.15	+0.191	+0.191	+0.227	+0.227
Estimated ICER	[CIC]	[CIC]	[CIC]	[CIC]	[CIC]

ERG's values rounded

Company: End-of-life criteria

Life expectancy less than 24 month

From company: SoFEA trial: median overall survival in subgroup of HER2-negative population receiving exemestane alone [CIC] months

n.b.

- SoFEA trial not same population as this appraisal (includes HER2-positive)
- BOLERO analyses exemestane median 26.6 months
- Company revised model exemestane survival 2.52 yrs (30.2 months)

Extension-to-life of normally at least 3 additional months

BOLERO-2	Everolimus	Exemestane	Incremental
Median overall survival (months) and 95% CI	31.0 (28.0 to 34.6)	26.6 (22.6 to 33.1)	4.4

Abbreviations: CI, confidence interval. *Source: Table 1, pages 27–30 of the company submission.*

ERG: End-of-life criteria

- Cost-effectiveness relies on mean costs and outcomes
- Median values based on subset of trial data
- Median arbitrary reference point and any other percentile could be used and may give different results
- Company relies on SoFEA trial for asserting life expectancy less than 24 months, but ignores BOLERO-2
- Mean overall survival in exemestane alone estimated to be [CIC] months in ERG's exploratory analysis
- Therefore, substantial uncertainty in available evidence
- ERG agree with committee's original conclusion

⊙ Has the committee seen evidence to change its decision on life-expectancy?

Issues for consideration

- Has the company addressed the committee's considerations?
- Is the company justified in changing PFS to log logistic?
- For PFS: which approach does committee prefer:
  - log-logistic through out – company
  - data-then-exponential - ERG?
  - Neither?
- For overall survival: which approach does committee prefer:
  - Log-logistic company
  - 'landmark' analysis ERG
  - Neither?
- Has the Committee seen evidence to change its decision on end of life criteria?

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

January 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/ commercial access agreement applies.

Name of the technology: Afinitor® (everolimus)

The proposed scheme will apply to all current and future indications:

- Current indications with marketing authorisations :
    - Hormone receptor-positive advanced breast cancer : Afinitor is indicated for the treatment of hormone receptor-positive, HER2/neu negative advanced breast cancer, in combination with exemestane, in postmenopausal women without symptomatic visceral disease after recurrence or progression following a non-steroidal aromatase inhibitor
    - Neuroendocrine tumours of pancreatic origin : Afinitor is indicated for the treatment of unresectable or metastatic, well- or moderately-differentiated neuroendocrine tumours of pancreatic origin in adults with progressive disease
    - Renal cell carcinoma: Afinitor is indicated for the treatment of patients with advanced renal cell carcinoma, whose disease has progressed on or after treatment with VEGF-targeted therapy.

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

To provide a cost-effective therapy to the NHS, thereby facilitating access for patients treated with Afinitor.

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

xxx

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?

xxx

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 PAS will apply following positive NICE guidance for Afinitor. It will apply when patients commence treatment. It is not dependent on any criteria.

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)?

xxx

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?

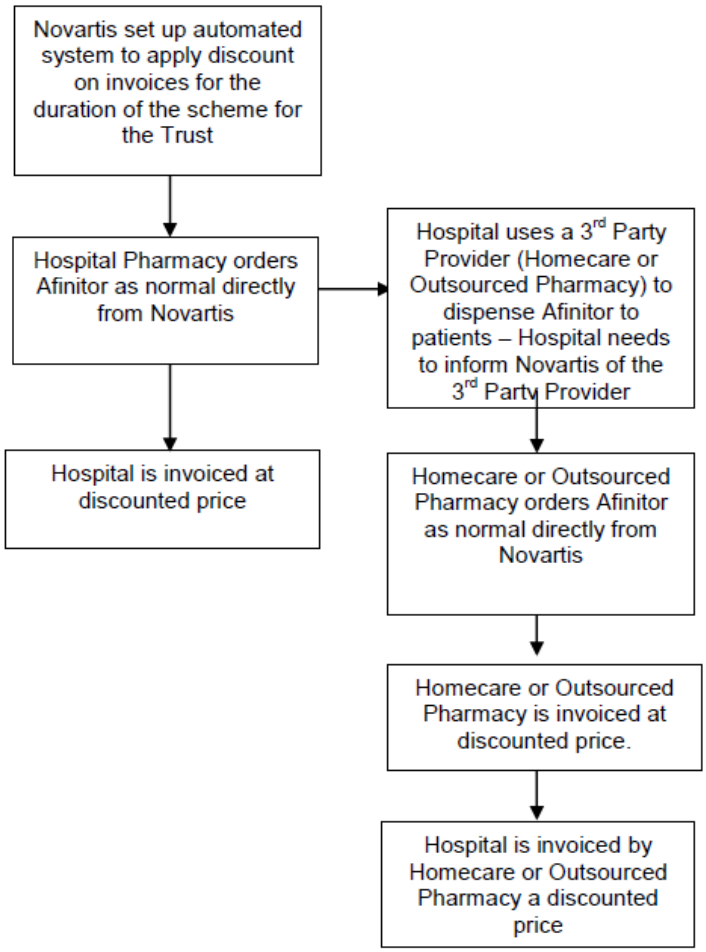
xxx

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.

No additional information, further to the standard NHS pharmacy procurement procedure, needs to be collected routinely.

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.

Afinitor PAS Process Flow



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

xxx

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?

No

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.

No registration or claim forms are required for this scheme.
Novartis would communicate to Hospital trusts using the attached PAS letter.

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.

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. 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.

Table 1 Assumptions in the economic model

Assumption	Original company model	Appraisal Committee's preferred assumption
ERG change from TA295: An arbitrary hazard ratio adjustment to modelled OS was applied	Original model used an adjusted HR.	This is no longer the basis of survival modelling or extrapolation.
ERG change from TA295: Cost of 3-monthly response assessment in PFS	Original model does not include any costs for regular assessment of response to treatment / disease progression whilst patients remain in the stable health state	The model includes 3 monthly monitoring costs in the stable disease health state costs (sheets "Resource Use CG81 Tx" and "Resource Use CG81 Cx").
ERG change from TA295: Discounting	Costs and outcome were discounted in the submitted	Costs and outcomes are discounted on an annual basis.

<table>
<tr><td></td><td>model on a continuous monthly basis from the time of randomisation</td><td></td></tr>
<tr><td>ERG change from TA295: Mortality after 4 years</td><td>In the original model after 4 years an additional multiplier is introduced based on the average monthly mortality rate in the overall female population of the same age.</td><td>This is implemented on the sheet “Effectiveness”, in cells P20-P23, and then carried forwards into an array below that applies the multiplier to the survival probabilities.</td></tr>
<tr><td>ERG change from TA295: Adverse event costs and disutilities</td><td>The original model only presented data on Grade 3/4 AEs, and both the costs and disutilities of AEs are excluded</td><td>EPAR based rates of AEs included, along with costs and disutilities:
<table>
<tr><th>Row</th><th>Column V
Everolimus + exemestane</th><th>Column W
Exemestane</th></tr>
<tr><td>13</td><td>38/482</td><td>2/238</td></tr>
<tr><td>14</td><td>4/482</td><td>0/238</td></tr>
<tr><td>15</td><td>22/482</td><td>3/238</td></tr>
<tr><td>16</td><td>12/482</td><td>2/238</td></tr>
<tr><td>17</td><td>2/482</td><td>0/238</td></tr>
<tr><td>18</td><td>2/482</td><td>0/238</td></tr>
<tr><td>19</td><td>2/482</td><td>0/238</td></tr>
<tr><td>20</td><td>2/482</td><td>0/238</td></tr>
<tr><td>21</td><td>0/482</td><td>0/238</td></tr>
<tr><td>22</td><td>0/482</td><td>0/238</td></tr>
<tr><td>24</td><td>3/482</td><td>0/238</td></tr>
<tr><td>27</td><td>11/482</td><td>3/238</td></tr>
<tr><td>28</td><td>14/482</td><td>1/238</td></tr>
<tr><td>29</td><td>12/482</td><td>1/238</td></tr>
<tr><td>31</td><td>10/482</td><td>1/238</td></tr>
<tr><td>33</td><td>27/482</td><td>1/238</td></tr>
<tr><td>34</td><td>16/482</td><td>3/238</td></tr>
<tr><td>35</td><td>17/482</td><td>3/238</td></tr>
</table>
AE rates, disutilities, and costs, correspond to these figures on the sheet “Safety”.</td></tr>
</table>

<table>
<tr>
<td>ERG change from TA295: On-treatment time and treatment costs</td>
<td>A multiplication factor is applied to the cost of systemic treatment within the original model.</td>
<td>Time on treatment using data from the BOLERO-2 trial has been implemented on sheet “Cost inputs”, cells AD35:AE96

<table>
<tr><th>EVE+EXE %</th><th>EXE %</th></tr>
<tr><td>xxx</td><td>xxx</td></tr>
<tr><td>xxx</td><td>xxx</td></tr>
<tr><td>xxx</td><td>xxx</td></tr>
</table>
</td>
</tr>
<tr>
<td>Unit costs</td>
<td>Original model used unit cost data that is now out of date</td>
<td>Updates to unit costs on sheets “Cost Inputs”, “Resource Use CG81 Tx”, and “Resource Use CG81 Cx”.</td>
</tr>
<tr>
<td>PFS and OS extrapolation</td>
<td></td>
<td>Sheets “Survival” and “Survival parameters” have been added; independent regression-based extrapolation for PFS and OS, for everolimus+exemestane and exemestane regimens, is the basis for survival modeling.

Individual patient level data (IPD) for everolimus+exemestane and exemestane from the Bolero-2 study was used to fit survival models to PFS and OS data.
Survival data were then analyzed using regression based analysis for Exponential, Gompertz, Weibull, Log-normal, and Log-logistic models.
Log-logistic functions are the basis of extrapolation based on the mature PFS and OS IPD. Formerly this was Weibull.</td>
</tr>
<tr>
<td>Only a comparison of everolimus with exemestane was considered by the Committee</td>
<td>Original submission included other comparators as listed in the scope</td>
<td>The current model only has exemestane as a comparator. This is in recognition of the Committee’s conclusions: “The Committee concluded that exemestane alone was the most relevant endocrine comparator for everolimus plus exemestane” – TA 295 considerations section. The other comparators listed in the scope were dismissed by the Committee for various reasons. Although capecitabine and vinorelbine were considered appropriate comparators, there is no robust evidence to indirectly compare them with everolimus.</td>
</tr>
</table>

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 to whom the patient access scheme/ commercial access agreement applies is the same as that in the published technology appraisal

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.

xxx

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'.

xxx

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.

Table 32 Additional treatment-related costs for the intervention both with and without the patient access scheme (PAS)/ commercial access agreement (CAA)

	Everolimis without PAS/ CAA		Everolimus with PAS/ CAA		Reference source
	Unit cost (£)	**Total cost per patient (£)**	**Unit cost (£)**	**Total cost e.g. per patient (£)**	
Treatment and administration costs	2,673*	17,745	xxx	xxx	Economic model
AE costs (grade 3/4)	Model Safety sheet	181	Model Safety sheet	xxx	Economic model
Background costs: Stable	Model Resource Use sheet	3,623	Model Resource Use sheet	xxx	Economic model
Background costs: Progressed	Model Resource Use sheet	25,353	Model Resource Use sheet	xxx	Economic model
Terminal care costs	Model Resource Use sheet	2,863	Model Resource Use sheet	xxx	Economic model
Total treatment-related costs	n/a	49,765	n/a	xxx	Economic model

Note that the Afinitor list price has decreased from £2,970 to £2,673 since the original submission.

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).

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

	Everolimus	**Exemestane**
Everolimus cost (£)	£17,745	£486
Other costs (£)	£32,003	£36,191
Total costs (£)	£49,748	£36,677
Difference in total costs (£)		£13,070
LYG	2.67	2.52
LYG difference		0.15
QALYs	1.58	1.37
QALY difference		0.21
ICER (£)		£61,046

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

Note that the Afinitor list price has decreased from £2,970 to £2,673 since the original submission. The table above uses the new list price. The following table therefore includes both the reduction in list price and the PAS. Due to this price change and the updated approach to survival modelling the base case ICER is different to that in TA295. This ICER also incorporates the key assumptions preferred by the Committee (listed in section 4.8)

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

Table 4b New base-case cost-effectiveness results using the patient access scheme/ commercial access agreement

	Everolimus	Comparator 1
Everolimus cost (£)	£xxx	£xxx
Other costs (£)	£xxx	£xxx
Total costs (£)	£xxx	£xxx
Difference in total costs (£)		£xxx
LYG	xxx	xxx
LYG difference		xxx
QALYs	xxx	xxx
QALY difference		xxx
ICER (£)		xxx

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

The table above contains the only results, as the comparison is Afinitor versus exemestane only and therefore no incremental analysis is required.

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

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 key sensitivity analysis scenarios that were discussed in TA295 have all been incorporated into the updated CEA. This is in line with the approach taken by the ERG where all these scenarios were included in the model cumulatively. These scenarios were as follows:

- Progression-free survival measured locally
- Time on treatment: Used TTD from BOLERO 2 trial
- Age adjusted utility values from Lloyd et al. 2006
- Include 3 monthly monitoring costs
- No mortality from non-cancer causes
- Include Adverse Events from EPAR

There is therefore no need to run these scenarios separately here.

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

	Everolimus vs Exemestane
Incremental costs (£)	£xxx
Incremental QALYs	xxx
Probabilistic ICER (£)	£xxx

xxx

Treatment	Everolimus + exemestane	Incremental costs	£xxx
Comparator	Exemestane	Incremental QALYs	xxx
Time horizon	15 years	Probabilistic ICER	£xxx
		% cost-effective	xx%

xxx

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.

xxx

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.

N/A

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.

N/A

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.

N/A

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.

N/A

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).

N/A

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.

N/A

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.

N/A

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.

N/A

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.

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.

6 Additional consideration : end of life

As described in Table 1 and subsequent sections**,** Afinitor meets the end of life criteria for this indication.

Table 1: End-of-life criteria

<table>
<tr><th>Criterion</th><th>Data available</th><th>Source of evidence</th></tr>
<tr><td>The treatment is indicated for patients with a short life expectancy, normally less than 24 months</td><td>SOFEA OS analysis :
Median OS of exemestane only treated patients is xxx months
<table><tr><th colspan="2">Number of events</th><th colspan="2">Median survival</th></tr><tr><th>Faslodex alone</th><th>Exemestane</th><th>Faslodex alone</th><th>Exemestane</th></tr><tr><td>xxx</td><td>xxx</td><td>xxx</td><td>xxx</td></tr></table></td><td>SOFEA phase 3 clinical study. This overall survival analysis is based on the trial patient population with HER2- positive cases removed.</td></tr>
<tr><td>There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment</td><td>Final OS analysis of Bolero-2: At the time of data cutoff (3 October 2013), median OS in patients receiving EVE + EXE was 31.0 months [95% confidence interval (CI) 28.0–34.6 months] compared with 26.6 months (95% CI 22.6–33.1 months) in patients receiving PBO + EXE (hazard ratio = 0.89; 95% CI 0.73–1.10; log-rank P = 0.14).</td><td>Piccart et al. Annals of oncology. 17 September 2014</td></tr>
</table>

1. The treatment is indicated for patients with a short life expectancy, normally less than 24 months

In the previous NICE submission, Novartis submitted the SoFEA and EFECT trials with a median survival of 22.6 months in patients with advanced breast cancer treated with exemestane alone to support fulfilling end of life criteria. The Committee noted in its previous guidance (TA 295) that a proportion of patients in the SoFEA trial had HER2-positive tumours whilst the EFECT trial did not report the proportion of patients with HER2-negative tumours. As a consequence the Committee concluded that these 2 trials were not relevant in determining life expectancy in women with HR-positive tumours because the trials contained mixed breast cancer populations with different survival patterns. As a consequence, the HTA for everolimus plus exemestane did not convincingly fulfil this criterion for an end-of-life therapy as defined.

xxx

Novartis proposes that the data set from SoFEA provides the more robust analysis of survival specific to the UK for the following reasons.

- Firstly we know that international comparison of survival trends reveals wide differences that are likely to be attributable to differences in access to early diagnosis and varying treatment patterns. The CONCORD-2 Global surveillance study collected data for breast cancer for 5 486 928 women. Most survival estimates were judged as reliable. Global distribution of age-standardised 5-year net survival for women diagnosed with breast cancer during 1995–99, 2000–04, and 2005–09, by continent and country are reported in table below.
- The 5 year survival rates for these countries as well as the UK and Korea have been highlighted.

Figure 2: **Global distribution of age-standardised 5-year net survival for women diagnosed with breast cancer during 1995–99, 2000–04, and 2005–09, by continent and country**
Age-standardised 5-year net survival estimates for other cancers are presented in the appendix (pp 141–51). Survival estimates for every country are ranked from highest to lowest within every continent; for ease of reference, the ranking for 2005–09 is used for 1995–99 and 2000–04. Error bars represent 95% CIs. Grey bars represent African countries; red bars represent America (Central and South); light green bars represent America (North); purple bars represent Asian countries; blue bars represent European countries; and dark green bars represent Oceania. *100% coverage of the national population. †National estimate not age-standardised. §National estimate flagged as less reliable because the only estimate or estimates available are from a registry or registries in this category.

(source : Allemani et al. Lancet 2015)

- Of the 724 patients randomised into BOLERO-2, the largest country enrolments were for the United States (223 patients [30.8%]), Japan (106 patients [14.6%]), Canada (51 patients [7.0%]), France (51 patients [7.0%]), and Belgium (43 patients [5.9%]). The UK enrolled 13 patients. Global distribution of age-standardised 5-year net survival for women diagnosed with breast cancer during 1995–99, 2000–04, and 2005–09 in the USA, Japan, Canada, France and Belgium all exceed that of the UK. It is therefore logical to assume that this improved survival will be reflected in BOLERO-2 when compared to SoFEA which was mainly a UK specific study. Please note a cohort of Korean

patients was also enrolled into SoFEA from a single centre. The 5 year survival survival figures for Korea exceed those of the UK. The median OS from SoFEA for the HER2 –ve subset may therefore be over estimated at xx months as a consequence.

2. There is sufficient evidence to indicate that the treatment offers an extension to life, of at least an additional 3 months, compared with current NHS treatment

At the time of data cut-off for overall survival analysis, 410 deaths had occurred and 13 patients remained on treatment. The median OS in patients receiving EVE + EXE was 31.0 months [95% confidence interval (CI) 28.0–34.6 months] compared with 26.6 months (95% CI 22.6–33.1 months) in patients receiving PBO + EXE (hazard ratio = 0.89; 95% CI 0.73–1.10; log-rank P = 0.14). This represents an absolute difference of 4.4 months. The lack of a statistically significant survival benefit may be due to one or more factors: (1) the sample size being too small; (2) an imbalance in post-study salvage chemotherapy; or (3) the effect of EVE on cell-signalling mechanisms that could theoretically limit the usefulness of post-study chemotherapy.

Due to these confounding factors a case can be made for using PFS as a more relevant end point when considering a drug's impact on survival. It is also worth noting that the new EOL criteria is not restricted to OS as the key endpoint for showing a survival benefit. The updated criteria states that:

- *the estimates of the extension to life are sufficiently robust and can be shown or reasonably inferred from either progression-free survival or overall survival*

As the criteria stands, PFS could be also considered when assessing treatments for EOL. In addition it is clinically implausible not to expect some OS benefit from a treatment that offers a statistically significant PFS improvement of 4.6 months in the advanced metastatic stage of disease. As was shown from the BOLERO-2 trial, everolimus showed a clinically meaningful OS benefit of 4.4 months. We therefore believe that everolimus meets the new EOL criteria as there is sufficient evidence either via PFS or OS that the treatment an additional 3 months of survival. We suggest that the Committee uses its discretion when interpreting the uncertainty in the survival benefit. Everolimus has also been approved by the SMC in Scotland under similar EOL considerations. To avoid a situation where English patients are denied access to an effective treatment that is available in Scotland, we urge the Committee to consider both the significant PAS offered and the fact that the indication meets EOL when making a decision.

Priority request: Kaplan-Meier data. Please provide the following Kaplan-Meier analyses (listed in a to c below) to the following specification:

Population: Use the ITT population including all patients lost to follow-up or withdrawing from trial.

Censoring: Censor lost to follow-up and withdrawn patients at the date recorded. Patients alive and still at risk of the target event at the date of data cut-off should be censored at the date of data cut-off; i.e. not when last known to be alive (OS/PPS), and not at the date of last tumour assessment (PFS). Please use the format of the table provided below.

Format: Please present analysis outputs using the format of the sample table shown below.

Trial data set: BOLERO-2, latest data cut (3 October 2013 or later, if available). N.B. if any patients crossed over or moved to an extension trial in the latest data cut, please censor them at the time they moved from the original trial or their randomised trial arm.

a. Time to death from any cause (OS) Kaplan-Meier analysis stratified by treatment arm (everolimus+exemestane vs placebo+exemestane).
b. Time to disease progression or death (PFS) Kaplan-Meier analysis based on investigator assessment, stratified by treatment arm (everolimus+exemestane vs placebo+exemestane).
c. Time from disease progression by investigator assessment to death from any cause (PPS) Kaplan-Meier analysis stratified by treatment arm (everolimus+exemestane vs placebo+exemestane).

The rationale for this request is as follows:

All Kaplan-Meier analyses are specified to use the alternative censoring rule:

When trials are stopped early or subject to early analysis, the conventional censoring rule (censor when last contacted/reviewed) always understates the time patients are exposed to risk but is much less likely to understate events, especially deaths. The result is that the inter-event period hazard rates calculated by Kaplan-Meier algorithm are exaggerated when multiple patients are censored in any period. The resulting Kaplan-Meier estimated time-to-event trends may therefore be distorted by 'informative censoring' and poorly reflect the true profile of time-to-event hazards. In some of the specified analyses (especially OS) there are suggestive indications that such effects are present towards the end of the follow-up period when heavy right-censoring is present, but it is not possible to confirm or refute this hypothesis without having access to re-analysis using the alternative censoring rule.

Survival gain for everolimus+exemestane vs placebo+exemestane is the most important parameter governing cost effectiveness. Careful analysis of OS and its components (PFS and Post-Progression Survival) is essential to validation of the survival gains estimated by the decision model.

Sample table: Example of output (SAS) required from specified Kaplan-Meier analyses

- The LIFETEST Procedure

Product-Limit Survival Estimates						
DAYS		**Survival**	**Failure**	**Survival Standard Error**	**Number Failed**	**Number Left**
0.000		1.0000	0	0	0	62
1.000		.	.	.	1	61
1.000		0.9677	0.0323	0.0224	2	60
3.000		0.9516	0.0484	0.0273	3	59
7.000		0.9355	0.0645	0.0312	4	58
8.000		.	.	.	5	57
8.000		.	.	.	6	56
8.000		0.8871	0.1129	0.0402	7	55
10.000		0.8710	0.1290	0.0426	8	54
SKIP...		.....	.....	.....	...	...
389.000		0.1010	0.8990	0.0417	52	5
411.000		0.0808	0.9192	0.0379	53	4
467.000		0.0606	0.9394	0.0334	54	3
587.000		0.0404	0.9596	0.0277	55	2
991.000		0.0202	0.9798	0.0199	56	1
999.000		0	1.0000	0	57	0

Novartis response to clarification questions

PRIORITY REQUEST: KAPLAN-MEIER DATA. Please provide the following Kaplan-Meier analyses (listed in a to c below) to the following specification:

Population: Use the ITT population including all patients lost to follow-up or withdrawing from trial.

Censoring: Censor lost to follow-up and withdrawn patients at the date recorded. Patients alive and still at risk of the target event at the date of data cut-off should be censored at the date of data cut-off; i.e. not when last known to be alive (OS/PPS), and not at the date of last tumour assessment (PFS).

Trial data set: BOLERO-2, latest data cut (3 October 2013 or later, if available). N.B. if any patients crossed over or moved to an extension trial in the latest data cut, please censor them at the time they moved from the original trial or their randomised trial arm.

a. **Time to death from any cause (OS) Kaplan-Meier analysis stratified by treatment arm (everolimus+exemestane vs placebo+exemestane).**
b. **Time to disease progression or death (PFS) Kaplan-Meier analysis based on investigator assessment, stratified by treatment arm (everolimus+exemestane vs placebo+exemestane).**
c. **Time from disease progression by investigator assessment to death from any cause (PPS) Kaplan-Meier analysis stratified by treatment arm (everolimus+exemestane vs placebo+exemestane).**

NOVARTIS RESPONSE: CENSORING IN GENERAL

The censoring method used in BOLERO-2 trial (that is, to censor patients the earliest of the event date or the date of last observation) represents the conventional approach to censoring of survival endpoints in clinical trials in oncology (Green S, Benedetti J, Smith A, et al. Clinical Trials in Oncology, Second Edition. Taylor & Francis, (2002). This approach is premised on the assumption that the likelihood of experiencing an event after censoring is the same for patients who were censored (for whom the events would be unobserved) and those who were not (for whom the events would be observed). This assumption would be violated, and censoring would be informative, if the actual (unobserved) risk of the event between the last observation and the data cut-off for patients who were censored was actually zero. This would be true if all events during that period are recorded spontaneously for all patients.

The approach proposed by the ERG is premised on the assumption that the risk of an event between the last observation and the data cut-off is known and is zero for those without a recorded event. Stated differently, it assumes that all events that occurred between the last observation and the data cut-off are recorded.

If all patients who experience an event after the last assessment are captured by spontaneous reporting, then the use of the conventional censoring rule may yield Kaplan Meier estimates that overestimate the risk of the event and underestimate survival. On the other hand, if there are some events that occur after the last observation, but which are not captured by spontaneous reporting, then the censoring rule proposed by the ERG may yield Kaplan Meier estimates that underestimate the risk of the event and

overestimate survival. The relative magnitude of the potential biases depend on the likelihood that events between the last observation and the data cut-off are recorded.

In consideration of the reasons discussed above, Novartis believes that the censoring method is not a standard approach to analysing K-M data and neither is it specified in the NICE methods guide. However, Novartis has conducted the requested analyses for PFS and OS using the approach to censoring described below.

***Population*: Use the ITT population including all patients lost to follow-up or withdrawing from trial.**

NOVARTIS RESPONSE:
Full Analysis Set is used for all requested analyses. The Full Analysis Set (FAS-population) consists of all randomized patients. Following the intent-to-treat principle patients are analysed according to the treatment and stratum they were assigned to at randomization.

***Censoring*: Censor lost to follow-up and withdrawn patients at the date recorded. Patients alive and still at risk of the target event at the date of data cut-off should be censored at the date of data cut-off; i.e. not when last known to be alive (OS/PPS), and not at the date of last tumour assessment (PFS).**

NOVARTIS RESPONSE:
In BOLEO 2 study treatment discontinuation due to lost to follow-up or withdraw of consent is collected on the End Of Treatment visit (EOT) page and study discontinuation on the Study Evaluation Completion (SEC) page. The corresponding date recorded is either the date of last treatment (EOT) or the visit date (SEC).

In case of withdraw of consent the patient could have also decided to discontinue treatment but accepted to be followed for Post treatment evaluation (which includes tumour assessments as per protocol schedule so that a PFS event can still be captured after treatment discontinuation) and/or for survival follow-up. In such cases, if patient later decided to completely withdraw of consent and stop any study assessment, the date of final withdraw of consent is difficult to identify.

Therefore, due to the way data were collected, a way of applying the recommendation was as follow separately for PFS and OS.

PFS :
- Patients who did not have a PFS event at the date of data cut-off and for whom the distance between their last adequate tumour assessment and the analysis cut-off date is shorter than D2 (please see definition below): These patients are considered still at risk of having a PFS event and their censor date will be equal to cut off date
- Patients who did not have a PFS event at the date of data cut-off and for whom the distance between their last adequate tumour assessment and the analysis cut-off date is greater or equal to D2 (please see definition below) : These patients are considered as lost to follow-up and censor date will be equal to the date of last adequate tumour assessment

where the threshold D2 is the one used in the original PFS censoring rules, pre-specified in the analysis plan, and defined as followed: D2 is formed based on two times the protocol specified interval between the tumor assessments plus the protocol allowed window around the assessments (D2 =14 weeks).

OS :

- Patients alive at the date of data cut-off and the distance between their last contact date and the analysis cut-off date is shorter than D2' (please see definition below) : These patients are considered still at risk of having an OS event and their censor date will be equal to cut off date
- Patients alive at the date of data cut-off and the distance between their last contact date and the analysis cut-off date is greater or equal to D2' (please see definition below) : These patient are considered as lost to follow up and censor date will be equal to the last contact date

where the threshold D2' is the one defined in the protocol as two times the schedule of survival follow up visits plus the allowed time window (D2'=3 months and 2 weeks).

***Trial data set*: BOLERO-2, latest data cut (3 October 2013 or later, if available). N.B. if any patients crossed over or moved to an extension trial in the latest data cut, please censor them at the time they moved from the original trial or their randomised trial arm.**

NOVARTIS RESPONSE:

Data cut-off date for OS was 3 Oct 2013. For PFS the last cut-off date used for the final PFS analysis (15 Dec 2011) was used (no further PFS analysis have been conducted beyond this cut-off date).

a. Time to death from any cause (OS) Kaplan-Meier analysis stratified by treatment arm (everolimus+exemestane vs placebo+exemestane).

NOVARTIS RESPONSE:

Please refer to table [redacted] attached.

b. Time to disease progression or death (PFS) Kaplan-Meier analysis based on investigator assessment, stratified by treatment arm (everolimus+exemestane vs placebo+exemestane).

NOVARTIS RESPONSE:

Please refer to table [redacted] attached.

c. Time from disease progression by investigator assessment to death from any cause (PPS) Kaplan-Meier analysis stratified by treatment arm (everolimus+exemestane vs placebo+exemestane).

NOVARTIS RESPONSE:

We could not perform the analysis of (Post Progression Survival (PPS) because the results from such an analysis would lack statistical validity due to the following reasons:

- Only patients who did progress are included in this analysis so for example those who died before and those who were censored for PFS are not included. This selection introduces bias as we are effectively choosing our population and therefore losing the benefit of randomisation. Different selections of the population might lead to different results
- Another source of bias is introduced by the selection of the starting point of the observation period, unlike usual time to event analysis where the start time is randomisation, here it was

time of disease progression, which is already impacted by the treatment (i.e. more progression in the placebo than in the Everolimus group).

- Because the PPS analysis will be performed on a post-randomisation sub-sample (no randomisation to ensure balance between two treatment groups), results from such an analysis can be misleading and not informative.
- The PFS assessment was based on cutoff 15DEC2011 and OS assessment was on cutoff 03OCT2013. As mentioned above patients who were censored for PFS were not included in the analysis, but if some have had an event between those cutoffs, then theoretically they should have or could have been included.
- Patients who died without progression at the time of the cutoff date of the 15DEC2011 were not included in the analysis , once again these patients should have or could have been included as time to death=0 days.

Appendix F - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

CDF Rapid reconsideration process

TA295 - Everolimus in combination with exemestane for treating advanced HER2-negative hormone-receptor-positive breast cancer after endocrine therapy

Thank you for agreeing to make a submission 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 submission, 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: Association of Breast Surgery
Are you (tick all that apply):

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

Appendix F - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

CDF Rapid reconsideration process

TA295 - Everolimus in combination with exemestane for treating advanced HER2-negative hormone-receptor-positive breast cancer after endocrine therapy

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.

The Association of Breast Surgery has noted the guidance and does not have anything specific to add.

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.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

CDF Rapid reconsideration process

TA295 - Everolimus in combination with exemestane for treating advanced HER2-negative hormone-receptor-positive breast cancer after endocrine therapy

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?

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.

Implementation issues

The NHS is required by the Department of Health 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 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)?

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.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission

TA295 - Everolimus in combination with exemestane for treating advanced HER2-negative hormone-receptor-positive breast cancer after endocrine therapy

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, and including health-related quality of life)
- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The length of your response should not normally exceed 10 pages.

1. About you and your organisation

Your name: [redacted]

Name of your organisation: Breast Cancer Now

Your position in the organisation: Senior Policy Officer

Brief description of the organisation: Breast Cancer Now is the UK's largest breast cancer charity, dedicated to funding ground-breaking research into the disease. Our ambition is that by 2050, everyone who develops breast cancer will live. We're bringing together all those affected by the disease to improve the way we prevent, detect, treat and stop breast cancer. And we're committed to working with the NHS and governments across the UK to ensure that breast cancer services are as good as they can be, and that breast cancer patients benefit from advances in research as quickly as possible.

This submission reflects the views of Breast Cancer Now, based on our experience of working with people who are affected by breast cancer. We know that access to effective drugs is hugely important to our supporters and that quality of life is valued just as much as length of life.

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

2. Living with the condition

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

Metastatic breast cancer is when cancer originating in the breast has spread to distant parts of the body, most commonly the lungs, brain, bones and liver. There is no cure for metastatic breast cancer, so most medicines aim to extend the length of life or to improve quality of life for patients. A patient can be diagnosed with metastatic (stage 4) cancer to begin with or they can develop the condition many years after treatment for their primary breast cancer has ended. Living with metastatic breast cancer is difficult to come to terms with for both the patient and their family. Patients' time is limited and the treatments usually have some side effects. Patients therefore tell us that

quality of life is just as important to take into account as length of life, as this means that they would be able to spend quality time with their loved ones.

3. Current practice in treating the condition

Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most important? If possible, please explain why.

As mentioned above, both quality of life and extension of life are important to patients with metastatic breast cancer. Patients also value knowing that additional treatment options are available, as it gives them some comfort to know that there are more options available once their cancer progresses on current treatment.

What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these treatments and which are preferred and why?

In clinical practice, women with metastatic ER+ breast cancer are often offered endocrine therapies, including aromatase inhibitors (exemestane, anastrozole, letrozole) and tamoxifen. These treatments do not have the side effects associated with traditional chemotherapies, because they target the hormones in the body to control the cancer's growth. However, AIs can have some significant side effects, including strong menopausal symptoms, such as night sweats and hot flushes. The intensity of side effects varies from patient to patient.

4. What do patients or carers consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)

- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that patients or carers expect to gain from using the treatment being appraised.

This review considers everolimus in combination with an aromatase inhibitor for the treatment of women with HER2 negative, oestrogen receptor positive local advanced or metastatic breast cancer, whose disease has progressed after prior endocrine therapy. Progression of the cancer is caused by the woman developing resistance to the endocrine therapy One mechanism of resistance to endocrine therapy is caused by the activation of the mammalian target of rapamycin (mTOR) signalling pathway. Everolimus works by blocking this pathway and allowing endocrine therapy to continue to work. This means that progression of disease can be slowed and women may be able to avoid or delay chemotherapy treatment.

Results the phase III BOLERO-2 trial shows promising results with up to 10.6 months progression free survival for women in the everolimus and exemestane arm of the trial. This compares with 4.1 months for women in the placebo and exemestane arm of the trial. This is an important result and shows that everolimus can greatly increase the length of time before metastatic breast cancer progresses. Whilst eventually all metastatic ER+ cancers develop resistance to endocrine treatments, some cancers are particularly aggressive and these patients in particular might benefit from more time to spend with their families in a reasonably good state of health.

Please explain any advantages that patients or carers think this treatment has over other NHS treatments in England.

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 this progression may bring. Maintaining a high quality of life for as long as possible is currently the best outcome for this patient group.

As metastatic breast cancer is not curable, it is essential that treatment options which could delay progression are made available to this patient group. Patients typically have limited treatment options in the metastatic setting and therefore the need for safe and effective new medicines in this patient group is important. If treatments can slow disease progression, they may also allow the patient to be able to continue to carry out some normal daily activities such as caring for their families, continuing to work or simply enjoying spending quality time with their loved ones. For patients with metastatic breast cancer the importance of this should not be underestimated.

Everolimus is taken in combination with an aromatase inhibitor in tablet form once a day. This means that women may be able to collect a number of tablets at a time and may not need to go into hospital on a regular basis to have the drug administered. This means that women who can tolerate this treatment well may be able to continue with their normal life with very little impact on their families. This would also mean that women and their families are not burdened with the additional cost of travelling to and from hospital and paying for car parking on a regular basis.

The BOLERO-2 trial of everolimus in combination with exemestane excluded women who had already taken exemestane. This scope is considering everolimus in combination with any aromatase inhibitor which may provide treatment options for those women who have received exemestane previously.

Overall survival data for everolimus has not been shown to be significant.[1]

If you know of any differences in opinion between patients or carers about the benefits of the treatment being appraised, please tell us about them.

We are not aware of any differences in opinion between patients, as generally patients prefer having additional options available after they stop responding to aromatase inhibitors, which are available as standard treatments on the NHS.

[1] http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4080643/

5. What do patients and/or carers consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns patients or carers have about current NHS treatments in England.

For women who have HER2 negative, oestrogen receptor positive locally advanced or metastatic breast cancer whose disease has progressed on prior endocrine therapy, NICE recommends chemotherapy treatment. Patients and carers are concerned that once their cancer becomes resistant to the endocrine therapies, they will need to move on to general chemotherapy, which is known to have some very strong side effects and is likely to negatively affect the patient's quality of life.

Please list any concerns patients or carers have about the treatment being appraised.

Everolimus has a high toxicity when compared to exemestane. Three of the most common side effects are stomatitis (inflammation of mucous lining of structures in the mouth), rash and fatigue.

Stomatitis is relatively well tolerated by patients and can be treated through oral hygiene and other measures such as avoiding alcohol. In addition, the trials found the many patients with stomatitis reacted well to a reduction in dose or a short break from the medication.

Rash is also relatively well tolerated and can be treated using common creams such as topical corticosteroids.

Other side effects of everolimus are potentially very serious but are quite rare. Pneumonitis (inflammation of the lung tissues) affected 16% of patients in the BOLERO-2 trial experienced pneumonitis. However, only 3% experienced grade 3 pneumonitis and no patients experienced grade 4 pneumonitis.

If everolimus is to be offered to patients, it is essential that women fully understand the potential risks and benefits of the treatment and are able to make an informed choice about whether to take it. It is important that women are provided with adequate information to make an informed choice and are given an opportunity to ask questions about the treatment. It is also important that women receiving everolimus are monitored closely to ensure that any side effects are noticed and treated as soon as possible.

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

Patients will differ in their willingness to accept risks. It is very important that they fully understand the possible risks and benefits before making a decision about treatment.

6. Patient population

Are there any groups of patients who might benefit more from the treatment than others? If so, please describe them and explain why.

The patient population as described in the final scope sounds sensible.

Are there any groups of patients who might benefit less from the treatment than others? If so, please describe them and explain why.

Everolimus in combination with an aromatase inhibitor will only benefit patients with hormone receptor positive breast cancer. Patients with hormone receptor negative breast cancer will not benefit from this treatment.

7. Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for

the treatment?

☐ Yes

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether patients' experience of using the treatment as part of their routine NHS care reflects the experiences of patients in the clinical trials.

As far as we are aware.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

Whilst clinical trials focus on reporting toxicity, this does not always accurately reflect quality of life for patients on a particular treatment. We could not find detailed results on quality of life from the trial so cannot comment in greater detail.

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

Not that we are aware of.

Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example, qualitative studies, surveys and polls)?

☐ No

If yes, please provide references to the relevant studies.

8. Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Protected characteristics are: age; being or becoming a transsexual person; being married or in a civil partnership; being pregnant or having a child; disability; race including colour, nationality, ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;
- having 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 treatment;
- any adverse impact on people with a particular disability or disabilities.

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

None, to the best of our knowledge.

Are there groups of patients who would have difficulties using the treatment or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

Not to the best of our knowledge. Everolimus is taken orally and therefore has the advantage of patients not needing to travel to hospital to receive the treatment.

9. Other issues

Do you consider the treatment to be innovative?

☐ Yes

If yes, please explain what makes it significantly different from other treatments for the condition.

When everolimus was launched, it was the first medicine of its kind to use a target of rapamycin (mTOR) signalling pathway. This has the potential to help patients who have become resistant to aromatase inhibitors and to give them an extra option of a treatment before they have to move on to general chemotherapy.

Are there any other issues that you would like the Appraisal Committee to consider?

10. Key messages

In no more than 5 bullet points, please summarise the key messages of

your submission.

- Everolimus gives ER+, HER- metastatic breast cancer patients an extra option of treatment, once their cancer becomes resistant to standard NHS treatment.
- Eventually all metastatic ER+ cancers develop resistance to endocrine treatments, but some cancers are particularly aggressive and these patients in particular might benefit from more time to spend with their families.
- Everolimus uses an innovative signalling pathway to block the resistance developed to endocrine treatments.
- This treatment may help to delay the associated debilitating symptoms and emotional distress that cancer progression may bring to a patient and their families.
- Everolimus is more toxic than exemestane alone, but this does not always equate to a lower quality of life for the patient. It is important that any patient given the treatment understand and are happy to accept the extra risks that this treatment has.

Appendix K – patient expert statement declaration form

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

CDF Rapid Reconsideration

Everolimus in combination with exemestane for treating advanced HER2-negative hormone-receptor-positive breast cancer after endocrine therapy (review of TA295) [ID1011]

Please sign and return via NICE Docs/Appraisals.

I confirm that:

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

Name: ....

Signed: ..

Date: .....

ERG REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Cancer Drugs Fund rapid reconsideration of NICE Guidance TA295

Everolimus in combination with exemestane for treating advanced HER2-negative hormone-receptor-positive breast cancer after endocrine therapy

[ID1011]

Confidential until published

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

Completed 13th June 2016
Amended for Factual Accuracy Checks 12th July 2016
CONTAINS CIC/AIC

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 NICE Guidance TA295. The original Single Technology Appraisal (STA) was conducted in 2012-13 and final NICE guidance was issued in August, 2013 and did not recommend everolimus in combination with exemestane for treating advanced HER2-negative hormone-receptor-positive breast cancer after endocrine therapy for use in the NHS.

2 CONTEXT AND APPROACH TO RAPID RECONSIDERATION

To allow these rapid reconsideration exercises to proceed with the minimum risk of delay, the expected 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 CS. It is assumed that the primary clinical effectiveness data will remain essentially unchanged from the original appraisal and therefore no additional clinical evidence will be accepted by NICE. The cost effectiveness analyses included in the CS needs to reflect the assumptions that determined the most plausible incremental cost-effectiveness ratio(s) (ICERs) as identified in the published guidance. It is anticipated that the main areas to be considered by the AC will relate to changes in the costs associated with treatment including any special NHS pricing agreements that have been agreed since the original STA was carried out.

3 SPECIFIC DIFFICULTIES WITH THIS RAPID RECONSIDERATION

An outline of process is provided to companies that are planning to make a submission to NICE for reconsideration of a treatment previously not recommended for general NHS use.

In contrast to this outline of process, the company indicated that they wished to submit updated survival data from the key clinical trial (BOLERO-2), as these data were now available. The ERG advised NICE that these updated survival data could only be accommodated within the defined process, if the ERG were permitted access to additional detailed evidence related to the latest trial survival results in the form of a request for clarification. NICE therefore approached the company and asked them to provide specific information as put in writing by the ERG.

4 MODEL ALTERATIONS

The company has submitted a revised version of the decision model developed for the original appraisal. In addition to implementing amendments identified previously by the ERG, the company has employed a different approach to estimating time-to-event patterns (especially overall survival [OS]) and this has led to structural changes to parts of their model.

4.1 Implementing ERG recommended amendments

The NICE guidance issued in 2013 included a detailed list of preferences as expressed by the AC that identified features of the cost effectiveness model and model parameters that formed the basis for their decision. The ERG has examined the revised version of the company model and sought to verify whether the company has implemented the required alterations. Within the time available, the ERG can confirm, as far as it is able, that all required changes have been applied by substitution of revised parameter values or by coding modifications.

One issue of concern with the version of the company model submitted for this Rapid Reconsideration is that the time horizon for the model calculation has been reset to 15 years, contrary to the setting in the original model (10 years). This has the effect of artificially reducing the size of estimated ICER by between £3,000 and £6,000 per quality adjusted life year (QALY) gained.

However, closer examination of the model coding has revealed an error in the implementation of the time horizon so that the model results are generated for the wrong time period to that specified by the user. The ERG has corrected this error and then explored the sensitivity of the model results to different time horizons. The ERG considers that the estimated ICER per QALY gained is generally stable across a wide range of time horizons, but that the incremental OS is more accurately represented when results are calculated for

extended periods. For the purposes of generating cost effectiveness results in this Rapid Reconsideration, the ERG has adopted a time horizon of 20 years.

4.2 Survival extrapolation

In view of the inclusion of new survival data relating to extended follow-up to the key BOLERO-2 clinical trial in the new submission, the ERG forwarded a clarification request via NICE for detailed Kaplan-Meier (K-M) analysis results for three variables: OS, progression-free survival (PFS) and post-progression survival (PPS), using an alternative censoring rule to avoid a type of right-censoring bias can occur in trials with a substantial proportion of patients who are censored at data cut-off. This is similar to the clarification requests made during the original STA, which the company did not carry out.

The company noted that the alternative censoring method is not the standard approach to analysing K-M data, and identified difficulties in applying it because of the way BOLERO-2 data were captured and recorded (especially for patients withdrawing consent). However, the company adapted the ERG requests to the BOLERO-2 data as best as possible, and provided recensored results for PFS and OS. However, the company did not provide the requested PPS analysis as they considered this to lack statistical validity.

The ERG understands that there is a balance to be struck between possibly unrecorded events prior to data cut-off, and excessive under-attribution of exposure time prior to data cut-off. However, in a well conducted clinical trial, patient status ascertainment, especially at a planned analysis milestone, should be a priority and therefore subject to a relatively low risk of event omission (especially for deaths). In reported results from a number of clinical trials submitted as evidence in previous NICE appraisals, the ERG has observed patterns of survival consistent with excessive 'undercounting' of exposure time prior to data cut-off leading to distortion of survival curves and the consequent miscalibration of parametric survival functions. Only by comparing results using alternative censoring definitions is it possible to assess whether significant differences in outcomes may be related to the method of censoring, and, if so, to quantify the likely impact of such differences on estimated cost effectiveness.

4.2.1 Progression-free survival

The two sets of trial data were compared to assess the influence of censoring method on PFS outcomes.

In the everolimus treatment arm, the PFS survival estimates are identical up to 302 days from randomisation, but then begin to separate to a maximum difference of [redacted] ([redacted]

[redacted]) in the 2016 analysis compared to the earlier analysis. This then reduces steadily to [redacted] at the end of the observed data set. A similar pattern of PFS estimates in the exemestane only arm is observed, although the maximum difference is [redacted], reducing to [redacted]. Thus the influence of using an alternative censoring in small, but tends to favour treatment with everolimus+exemestane.

In this report, the ERG has chosen to base its estimates on the recensored trial results.

Analysis of the BOLERO-2 trial K-M data for PFS confirms that a simple exponential model (i.e. constant risk of disease progression or death) fits both arms of the trial closely. The ERG has therefore used the K-M data directly to populate the decision model, until a point beyond the strong cyclic behaviour associated with scheduled assessments at which the trial data and exponential model are closely aligned, after which the modelled extrapolation was applied. This occurred after 12 months in the intervention arm and after 11 months in the control arm as illustrated in Figure 1.

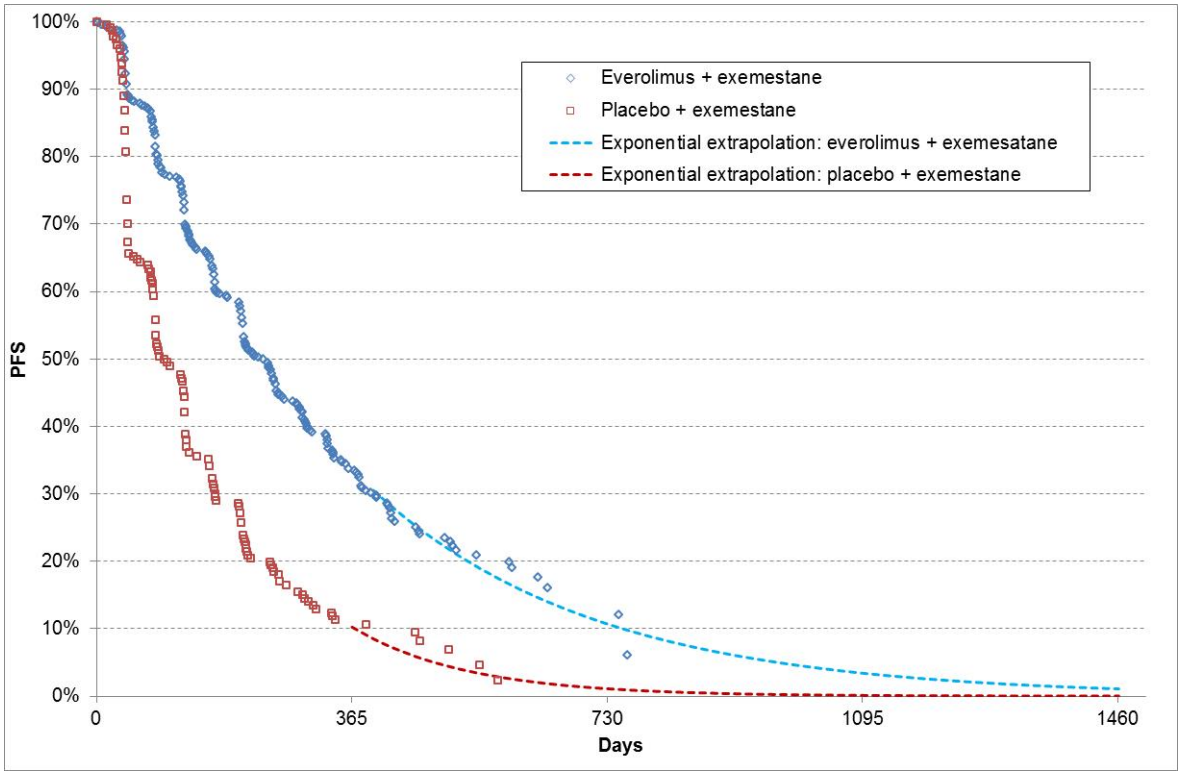


Figure 1 Progression-free survival K-M estimates (BOLERO-2 clinical trial) with exponential extrapolation curves applied in the decision model after 11 or 12 months

4.2.2 Overall survival

In the absence of direct evidence on the relative prognosis for BOLERO-2 trial patients beyond disease progression (PPS), the ERG has tested a conservative assumption of efficacy i.e., that the survival benefit from everolimus+exemestane versus

placebo+exemestame is limited to the pre-progression phase, so that thereafter mortality rates are the same in the two trial arms. This hypothesis would imply that mortality would be delayed in the intervention arm by use of everolimus, so that the survival curve would be moved forward in time (i.e. to the right in the OS chart), so that the gap between the two curves reflects the mean survival gain attributable to everolimus. However, this hypothesis also implies that over time as the proportion of surviving patients still progression-free reduces towards zero, the pattern of mortality should become similar in the two trial arms.

The ERG carried out an exploratory analysis by progressively shifting the survival plot of the BOLERO-2 placebo arm until the best fit was obtained to the later stage of the everolimus arm by visual inspection. This is illustrated in Figure 2, and suggests that there is a close correspondence of long-term survival trends beyond the point at which estimated OS is 62% (point C).

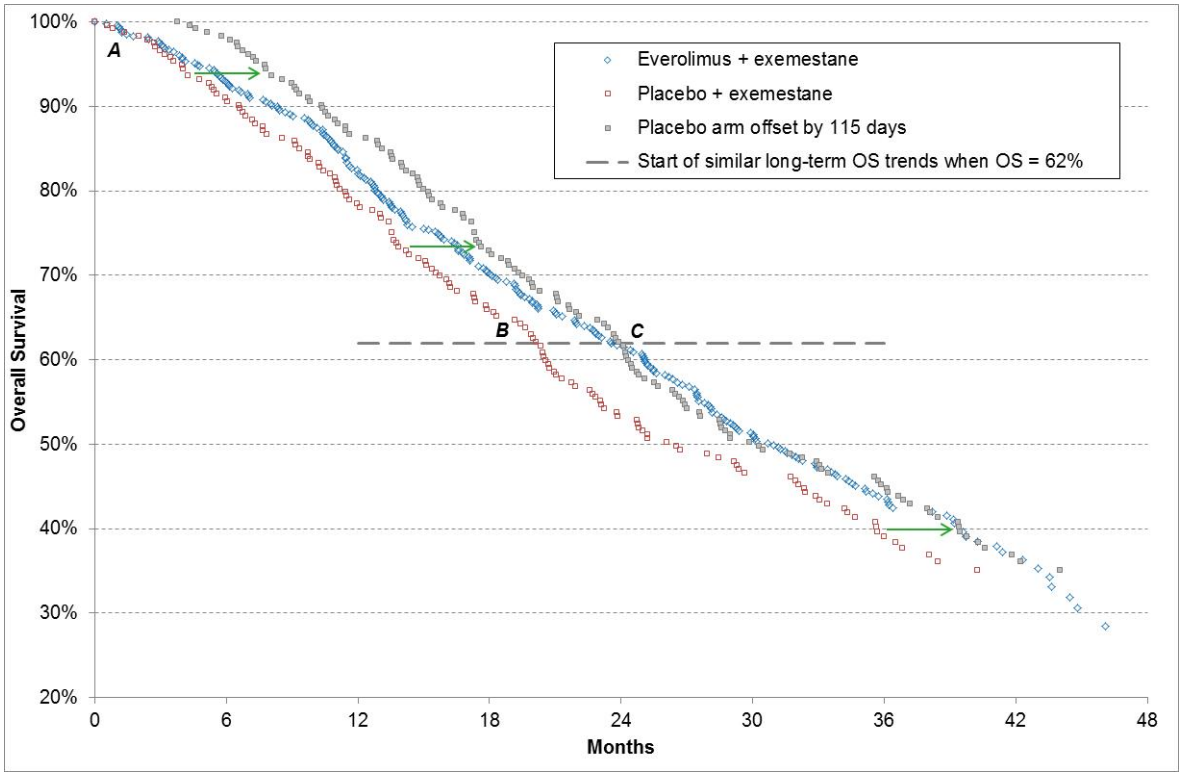


Figure 2 Overall survival in BOLERO-2 clinical trial, with offset placebo arm to compare long-term survival patterns

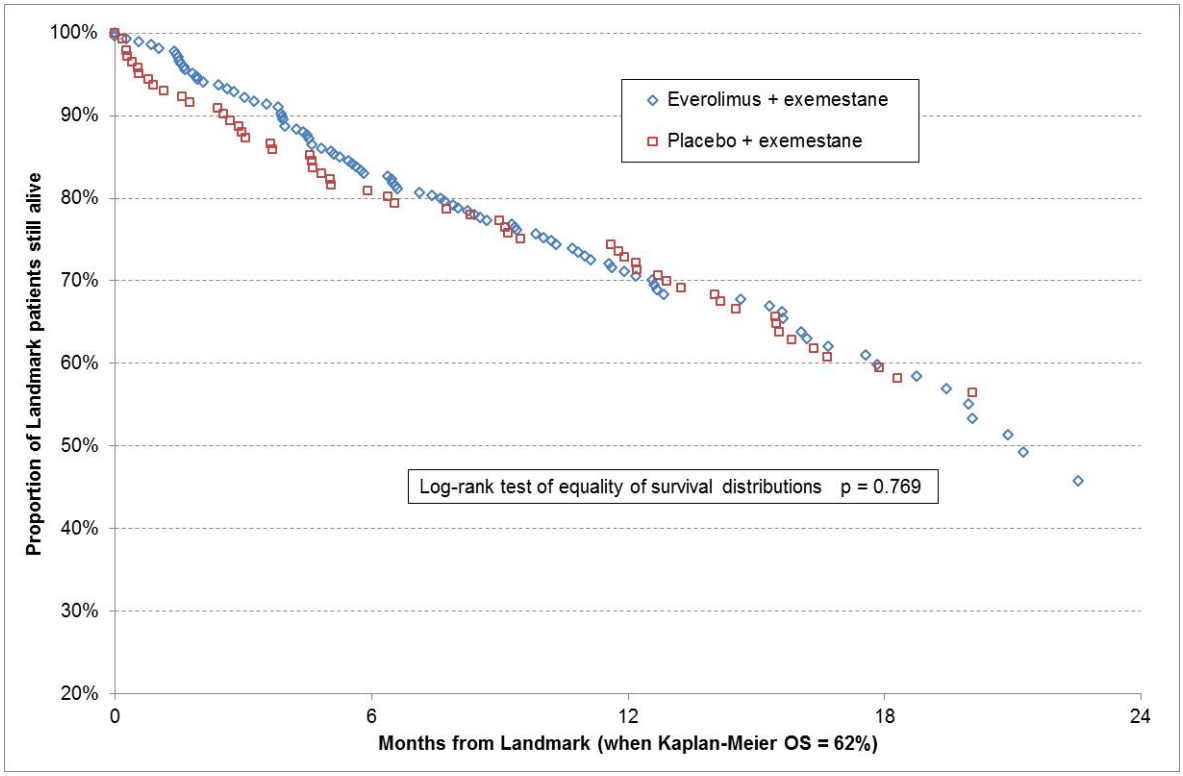


Figure 3 Landmark analysis of long-term survival for patients still alive when estimated OS is 62% in the BOLERO-2 clinical trial

This was confirmed by a K-M landmark analysis of all patients still at risk at the times corresponding to the 62% OS landmark (Everolimus+exemestane [redacted] patients and [redacted] events, Placebo+exemestane [redacted] patients and [redacted] events) (Figure 3). The estimated mean conditional OS was estimated at [redacted] days ([redacted]) for Everolimus+exemestane versus [redacted] days ([redacted]) for Placebo+exemestane.

However, the Log Rank (Mantel-Cox) test of equivalence indicated that there was no statistical basis for considering that patients in the Placebo+exemestane arm experienced a greater long-term survival (Chi2 = 0.0861,1 degree of freedom, p=0.7692). Therefore it was assumed that a common survival trend applied to all patients beyond the landmark point. This is consistent with an assumption that all patients who suffer a non-fatal progression event have the same prognosis irrespective of prior treatment, with an estimated mean conditional survival of [redacted] days ([redacted]).

A direct consequence of this finding is that the difference in OS attributable to everolimus can be accurately estimated directly from the trial results, without any recourse to parametric survival modelling. This is because the long-term survival of the 62% of everolimus+exemestane patients alive at point B in Figure 2 is can be considered identical to

the long-term survival of the 62% of placebo+exemestane patients at point C in Figure 2 so that long-term survival makes no contribution to the net difference in OS, regardless of the form of the common long-term survival trend. As a consequence, the true OS gain is simply calculated as the difference between the area under the intervention survival curve from point A to point C and the area under the control survival curve from point A to point B. This amounts to [redacted] months (95% CI [redacted] months).

The choice of 62% as the starting point for the long-term phase of survival is convenient because a common starting point for extrapolation excludes any risk of starting-point bias. Many other choices might be considered, but would require more time than was available to the ERG.

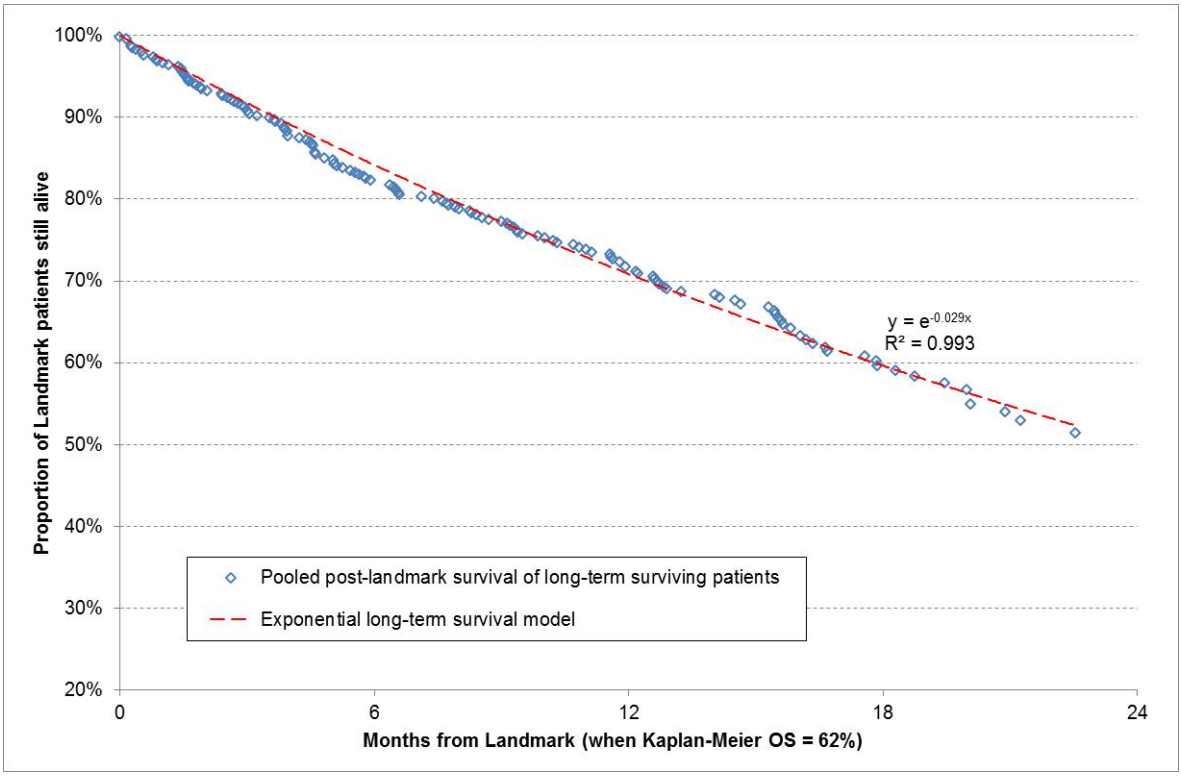


Figure 4 Exponential parametric model fitted to pooled long-term OS data (beyond the landmark) from BOLERO-2 clinical trial

For the purpose of reproducing these findings in the decision model it is necessary to identify a representative projective function for long-term survival (equivalent to post-progression survival). Figure 4 shows the results of a K-M landmark analysis of the BOLERO-2 long-term trial data pooled across the two trial arms (assuming equivalence). It is clear that a simple exponential provides an excellent fit, indicating a constant annual mortality rate of [redacted],

equivalent to an expected mean long-term survival (for patients surviving at the landmark) of [redacted] years.

4.3 'End of Life' criteria

The company refers to evidence from clinical trials to support a case for the application of NICE 'End of Life' criteria:

- In the BOLERO-2 clinical trial, the reported difference in median OS of 4.4 months (31.0 versus 26.6 months) indicates that a survival benefit greater than 3 months is confirmed.

- In the SoFEA clinical trial, the median OS in both arms of the trial was less than 24 months.

The use of the median as a measure of survival benefit is problematic on several grounds. First, the median is not the natural metric for cost effectiveness analysis; cost effectiveness analysis relies on mean outcomes and mean costs. Second, the median is calibrated on only a subset of the trial data (i.e. the first 50% to suffer the measured event) and ignores the remaining trial data. Third, the median is a completely arbitrary reference point as any other percentile could be used and may give very different results.

Figure 5 shows how the estimated OS gain varies in the BOLERO-2 clinical trial depending on which measure is selected to represent the whole data set. Clearly the median (50%) suggests the greatest benefit, but other options all appear to show less advantageous results. The ERG estimated mean lies centrally within the range of percentile measures, since it takes account of the whole available data set and is therefore representative of the overall experience of the patient population. For example, if the 45th percentile is used (based on 3-4 months additional data), the estimated OS gain falls to only [redacted] months.

Figure 5 Comparison of estimated OS gain attributable to everolimus for a range of survival percentile points.

The ERG notes that the company used the SoFEA trial to demonstrate that life expectancy in this patient group is less than 24 months. The company has based this justification on two grounds:

1. The SoFEA trail provides a robust analysis of survival specific to the UK

2. The SoFEA was used in the original submission and the company has had the SoFEA data set re-analysed to remove the HER2+ve patient population.

However, based on the analyses described above, the ERG estimates the mean OS in the control arm of the BOLERO-2 trial to be [redacted] months (compared to [redacted] months for the everolimus arm). The ERG therefore considers that there is substantial uncertainty since, on the basis of the available evidence, everolimus+exemestane does not fulfil the criteria for consideration as an 'End of Life' treatment. This conclusion accords with the assessment made during the original STA.

5 RESULTS

Table 1 summarises the cost effectiveness results obtained using the revised decision model submitted by the company, alongside results using the ERG corrected and revised model including the ERG remodelled OS and PFS estimates. In all scenarios the reduced price of everolimus improves the size of the estimated ICER per QALY gained, as does the correction made by the ERG to the time horizon model logic. The reworking of the PFS evidence by the ERG substantially increases the size of the ICER per QALY gained (as it both increases net costs and reduces QALYs in the everolimus+exemestane arm), whereas the OS remodelling has only a minor effect (reducing both costs and QALYs in parallel).

Table 1 Revised cost and outcome effects of ERG model amendments relative to the company's base case analysis, with and without PAS price

Model Scenario	Company revised model (no PAS)	Company revised model (with PAS)	ERG corrected model (no PAS)	ERG corrected model (with PAS)	ERG model + PFS revision (with PAS)	ERG model + OS revision (with PAS)	ERG model + both revisions (with PAS)
Everolimus Cost	£49,748	[redacted]	£63,498	[redacted]	[redacted]	[redacted]	[redacted]
Everolimus QALYs	1.581	[redacted]	2.082	[redacted]	[redacted]	[redacted]	[redacted]
Everolimus Life years	2.796	[redacted]	4.090	[redacted]	[redacted]	[redacted]	[redacted]
Exemestane Cost	£36,677	[redacted]	£51,177	[redacted]	[redacted]	[redacted]	[redacted]
Exemestane QALYs	1.367	[redacted]	1.825	[redacted]	[redacted]	[redacted]	[redacted]
Exemestane Life years	2.636	[redacted]	3.899	[redacted]	[redacted]	[redacted]	[redacted]
Incremental Cost	**+£13,070**	[redacted]	**+£12,321**	[redacted]	[redacted]	[redacted]	[redacted]
Incremental QALYs	**+0.214**	[redacted]	**+0.256**	[redacted]	[redacted]	[redacted]	[redacted]
Incremental Life years	**+0.160**	[redacted]	**+0.191**	[redacted]	[redacted]	[redacted]	[redacted]
Estimated ICER	**£61,046**	[redacted]	**£48,073**	[redacted]	[redacted]	[redacted]	[redacted]
ICER change	-	[redacted]	-£12,973	[redacted]	[redacted]	[redacted]	[redacted]

ERG model estimates are for 20 year time horizon. Life years are undiscounted

6 CONCLUSION

The revised decision model submitted by the company includes a new module to include additional parametric modelling undertaken since the original STA. In order for the ERG to take account of the survival outcome data for extended follow-up of the BOLERO-2 clinical trial, it was necessary for the ERG to undertake additional analyses. The results of the analyses revealed that conventional survival modelling using standard parametric functions was neither accurate nor in fact necessary in order to obtain robust estimates of mean expected patient survival times. ERG re-estimation of PFS was found to both increase incremental costs and reduce incremental QALYs, thus increasing the size of the ICER per QALY for everolimus+exemestane versus exemestane, whereas the amended OS data led to only minor changes in model costs and outcomes.

In the course of implementing the results of the ERG investigations within the company model, a logic error was identified relating to misspecification of the model time horizon which prevented long-term survival from being accurately estimated within the model. This has been corrected and all of the model results from the ERG corrected version are based on a 20 year time horizon in order to capture all future effects.

7 REFERENCES

1. National Institute for Health and Care Excellence (NICE). NICE Technology Appraisal Guidance[TA295]. 2013 [August]; Available from: https://www.nice.org.uk/guidance/ta295
2. Baselga J, Campone M, Piccart M, Burris HA, Rugo HS, Sahmoud T, et al. Everolimus in Postmenopausal Hormone-Receptor–Positive Advanced Breast Cancer. *N Engl J Med* 2012;366(6):520-9
3. Johnston SRD, Kilburn LS, Ellis P, et al. 2015 Fulvestrant plus anastrozole or placebo versus exemestane alone after progression on non-steroidal aromatase inhibitors in postmenopausal patients with hormone-receptor-positive locally advanced or metastatic breast cancer (SoFEA): a composite, multicentre, phase 3 randomised trial Lancet Oncology 14;10:989-998

APPENDIX: MODEL AMENDMENTS

Details of amendments made by the ERG to the company's revised decision model

Time horizon referencing logic

This revision corrects a referencing error which sets the time horizon 12 months shorter than is selected by the user.

Select range Results!D113:E120. Copy and paste to range D112:E119

Set value in Cell Results!B120 to 10

Set value in Cell Results!C120 to '30 years

Set value in Cell Results!D120 to 360

Set value in Cell Results!B120 to 10

ERG OS and PFS estimates

A new table of ERG PFS and OS estimates has been copied into worksheet 'Survival' with top-left of the new table located at cell AM7.

The table is provided in a separate confidential Excel file.

Two binary switch variables should be created on the 'Results' worksheet, with names 'ERG_1' and 'ERG_2'.

ERG_1 is set by the user to either 0 or 1 and determines which values are used to estimate PFS (0 gives the original company survival, 1 gives the ERG survival estimates)

ERG_2 is set by the user to either 0 or 1 and determines which values are used to estimate OS (0 gives the original company survival, 1 gives the ERG survival estimates)

On Worksheet 'Effectiveness':

Edit the formula in **Cell W35** as follows:

=IF(ERG_1=0,MIN(CHOOSE(index_pfs_function_EVE,Survival!D9,Survival!E9,Survival!F9,Survival!G9,Survival!H9),X35),Survival!AN9)

Edit the formula in **Cell X35** as follows:

=IF(ERG_2=0,CHOOSE(index_os_function_EVE,Survival!I9,Survival!J9,Survival!K9,Survival!L9,Survival!M9),Survival!AO9)

Edit the formula in Cell **Y35** as follows:

=IF(ERG_1=0,MIN(CHOOSE(index_pfs_function_COMP,Survival!P9,Survival!Q9,Survival!R9,Survival!S9,Survival!T9),Z35),Survival!AP9)

Edit the formula in Cell **Z35** as follows:

=IF(ERG_2=0,CHOOSE(index_os_function_COMP,Survival!U9,Survival!V9,Survival!W9,Survival!X9,Survival!Y9),Survival!AQ9)

Select & Copy Range Effectiveness!**W35:Z35**

Paste formulae to Range Effectiveness!**W36:Z635**

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Everolimus in combination with exemestane for treating advanced HER2-negative hormone-receptor-positive breast cancer after endocrine therapy (review of TA295) [ID1011]

You are asked to check the ERG report from LRIG (Liverpool Reviews and Implementation Group) to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm, Monday 20 June 2016** 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 Survival censoring

Description of problem	Description of proposed amendment	Justification for amendment	ERG response & Amendments to ERG report
<u>Page 4</u> This is similar to the clarification requests made during the original STA, which the company refused to carry out. using an alternative censoring rule to avoid a type of right-censoring bias that is often observed in trials with a substantial proportion of patients who are censored at data cut-off.	This is similar to the clarification requests made during the original STA, which the company provided a clear justification for not performing this analysis. using an alternative censoring rule, as defined by LiRG, for which the ERG believes that this alternative censoring approach avoids a type of right-censoring bias observed in trials with a substantial proportion if patients who are censored at data cut-off.	Factual inaccuracy. The wording in the current statement is inflammatory and misleading as Novartis did not refuse to carry out the requested alternative censoring analysis when requested in the original submission. Novartis, however, did provide a response with justification as to why they did not perform the ERG's request. Statement is misleading. The alternative censoring approach, as requested from the ERG, is not a standard approach to trial data analysis. The right-censoring approach is the standard approach. Novartis have only ever received the alternative censoring approach request from LiRG and no other ERG. There is no clear justification for the inclusion of "bias that is often observed"	*Text changes **in bold** in Section 4.2 paragraph 1:* In view of the inclusion of new survival data relating to extended follow-up to the key BOLERO-2 clinical trial in the new submission, the ERG forwarded a clarification request via NICE for detailed Kaplan-Meier (K-M) analysis results for three variables: overall survival (OS), progression-free survival (PFS) and post-progression survival (PPS), using an alternative censoring rule to avoid a type of right-censoring bias that **can occur** in trials with a substantial proportion of patients who are censored at data cut-off. This is similar to the clarification requests made during the original STA, which the company **did not** carry out.

The company has contested the ERG's current request on two grounds: - That the alternative censoring rule defined by the ERG is not appropriate and assumes that all events that occurred between the last observation and the data cut-off are recorded. - That the results from such an analysis would lack statistical validity and they cite a number of potential sources of bias. Therefore, the ERG received K-M analyses in respect of OS and PFS, but not using the requested censoring rule, and did not receive any PPS results at all. The ERG is disappointed with this response to what it regards as reasonable requests aimed at exploring the sensitivity of trial outcomes to different methods of analysis, recognising the various potential sources of analytic bias.	Novartis raised the point that the alternative censoring approach is not a standard approach to analysing K-M data and neither is it specified in the NICE methods guide. However, Novartis considered the ERG clarification request for the alternative censoring approach defined by LiRG in respect to the way the BOLERO-2 data were captured in the database and the ability to perform the requested analysis. Due to a limitation in respect of patient withdrawing consent, Novartis felt that they were unable to perform the request as per the LiRG definition; however the company did adapt the ERG requests to the BOLERO-2 data sets as best as possible in order to ensure that the approach to alternative censoring approach is answered. Novartis was able to provide the re-censored analysis to the ERG for both the PFS and OS; however Novartis did not perform the alternative censoring approach to the PPS due to the lack of statistical validity of such an analysis for this population.	Novartis did respond to the ERG request and provided analysis based on the alternative censoring approach. The justification of approach and the applicability to the BOLERO-2 clinical trial data is contained in *response to ERG clarification questions 3 June 16* Factual inaccuracy. "Therefore, the ERG received K-M analyses in respect of OS and PFS, but not using the requested censoring rule" – Novartis did provide OS and PFS analyses using the alternative censoring approach appropriate for the BOLERO-2 clinical trial data. Explanation is contained in *response to ERG clarification questions 3 June 16*	*Replace Section 4.2 paragraph 2 & 3 as follows:* **The company noted that the alternative censoring method is not the standard approach to analysing K-M data, and identified difficulties in applying it because of the way BOLERO-2 data were captured and recorded (especially for patients withdrawing consent). However, the company adapted the ERG requests to the BOLERO-2 data as best as possible, and provided recensored results for PFS and OS. However, the company did not provide the requested PPS analysis as they considered this to lack statistical validity.**

Issue 2 Progression-free survival: data interpretation and extrapolation

Description of problem	Description of proposed amendment	Justification for amendment	ERG response & Amendments to ERG report
Page 5 It is instructive to compare these two sets of results directly, which would be expected to be identical. In the everolimus treatment arm, the PFS survival estimates are identical up to 302 days from randomisation, but then begin to separate to a maximum discrepancy of [redacted] ([redacted]) in the 2016 analysis compared to the earlier analysis when they begin to separate after 594 days. This then reduces steadily to [redacted] at the end of the observed data set. This pattern of divergence between two analyses of what should be the same data raises concerns about the reliability of either data set. Moreover, the ERG's concerns about the potential uncertainty surrounding different censoring practices and the extent to which this may affect estimates of long-term survival when the data are used to calibrate projective survival models cannot be resolved. In this report, the ERG	It is instructive to compare these two sets of results directly, which would not be expected to be strictly identical, due to the re-censored analysis performed by Novartis, as per the ERG's request. Due to this difference in the censoring rules between the original and alternative analysis, it can be expected that the PFS Kaplan-Meier estimates may differ. However, it is important to assess the magnitude of the difference in order to evaluate the robustness of the original censoring rules. The Kaplan-Meier PFS estimates based on the original and alternative censoring rules are identical up to Day 300 from randomization when the difference is then less than [redacted]. After day 300, the difference of Kaplan-Meier estimates between the two analysis approaches remains small and is strictly less than [redacted] up to Day 378 and strictly less than [redacted] up to Day 508. The maximum difference of [redacted] is observed at Day 594 when the number of patients remaining at risk is very small in both the original and alternative analyses. Interpretation of PFS estimates based on small number of patients remaining at risk should be	Novartis feels that the current statement from the ERG calls into question the reliability of the data; however the divergence between the two analyses for Everolimus can be explained through the alternative censoring approach, as per the request from the ERG.	*Replace Section 4.2.1 as follows:* **The two sets of trial data were compared to assess the influence of censoring method on PFS outcomes.** **In the everolimus treatment arm, the PFS survival estimates are identical up to 302 days from randomisation, but then begin to separate to a maximum difference of [redacted] ([redacted]) in the 2016 analysis compared to the earlier analysis. This then reduces steadily to [redacted] at the end of the observed data set. A similar pattern of PFS estimates in the exemestane only arm is observed, although the maximum difference is [redacted], reducing to [redacted].** **Thus the influence of using an alternative censoring in**

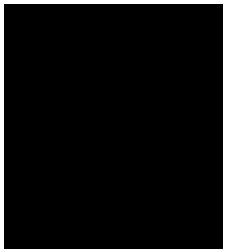
has chosen to rely only on the most recent data received from the company, in the hope that this is most likely to be accurate. The ERG has therefore used the K-M data directly to populate the decision model, until small numbers of patients still at risk make the K-M estimates unstable at which point the exponential extrapolation was applied (after 12 months in the intervention arm and after 11 months in the control arm) as illustrated in **Error! Reference source not found.**.	made with caution as the Kaplan-Meier estimates can be very sensitive to any subtle change made in the analysis method. As stated above, the PFS estimates obtained using the alternative censoring rules were consistent with the original PFS estimates with only small differences observed at late time points. Therefore, Novartis considers that this alternative PFS analysis confirms the robustness of the censoring rules used in the original PFS analysis. The ERG has therefore used the K-M data directly to populate the decision model, until month 12 in the intervention arm and month 11 in the control arm, as illustrated in Figure 1.	Novartis is unclear of the ERG's justification that there are a small number of patients at risk at 12 months in the intervention arm. Due to the significant impact that the PFS state plays within the model, the choice at which to apply the chosen extrapolation model is key. This is an arbitrary point selected, and no ICERs were presented for using the extrapolation from time point 0 as a comparison to the impact of a different starting extrapolation point. The ERG did not provide Novartis with key information to enable validation and checks to be performed in the model as to the impact of a different time point at which to apply the extrapolation model.	**small, but tends to favour treatment with everolimus+exemestane.** **In this report, the ERG has chosen to base its estimates on the recensored trial results.** **Analysis of the BOLERO-2 trial K-M data for PFS confirms that a simple exponential model (i.e. constant risk of disease progression or death) fits both arms of the trial closely. The ERG has therefore used the K-M data directly to populate the decision model, until a point beyond the strong cyclic behaviour associated with scheduled assessments at which the trial data and exponential model are closely aligned, after which the modelled extrapolation was applied. This occurred after 12 months in the intervention arm and after 11 months in the control arm as illustrated in Figure 1.**

Issue 3 Overall survival

Description of problem	Description of proposed amendment	Justification for amendment	ERG response & Amendments to ERG report
Page 6 The ERG carried out an exploratory analysis by progressively shifting the survival plot of the BOLERO-2 placebo arm until the best fit was obtained to the later stage of the everolimus arm. This is illustrated in Figure 2, and suggests that there is a close correspondence on long-term survival trends beyond the point at which estimated OS is 62% (point C). **Page 8** This is because the long-term survival of the 62% of everolimus+exemestane patients alive at point B in Figure 2 is identical to the long-term survival of the 62% of placebo+exemestane patients at point C in Figure 2	The ERG to include further supporting evidence as to the point where the control arm, placebo + exemenstane, survival plot is similar to the intervention arm, Everolimus + exemestane. This is because the long-term survival of 62% of Everolimus + exemestane patients alive at point B in Figure 2 is similar to the long term survival of 62% of placebo + exemestane patients at point C in Figure 2	The ERG offset the placebo + exemestane survival plot 115 days, which is shown in Figure 2. However, it is not clear to Novartis the justification for choosing 115 days. The ERG did not provide the analysis performed and Novartis was unable to validate that at point C on Figure 2, in the ERG report, 62% of the patients alive for exemestane is identical to point B and 62% for Everolimus + exemestane. The ERG mentions that the long-term survival is identical between the two arms (both at 62% of patients being alive), however, visual inspection of Figure 2 suggests that there is still a difference between the Everolimus + exemestane arm and placebo + exemestane arm after point C. Novartis would suggest that on visual	*Replace the text in Section 4.2.2 paragraphs 2,3 & 4 with the following:* **The ERG carried out an exploratory analysis by progressively shifting the survival plot of the BOLERO-2 placebo arm until the best fit was obtained to the later stage of the everolimus arm by visual inspection. This is illustrated in Figure 2, and suggests that there is a close correspondence of long-term survival trends beyond the point at which estimated OS is 62% (point C).** **This was confirmed by a K-M landmark analysis of all patients still at risk at the times corresponding to the 62% OS landmark (Everolimus+exemestane [redacted] patients and [redacted] events, Placebo+exemestane [redacted] patients and [redacted] events) (Figure 3). The estimated mean conditional OS was estimated at [redacted] days ([redacted]) for Everolimus+exemestane versus [redacted] days ([redacted]) for Placebo+exemestane.** **However, the Log Rank (Mantel-Cox) test of equivalence indicated that there was no statistical basis for considering that patients in the Placebo+exemestane arm experienced a greater long-term survival (Chi^2 = 0.0861,1 degree of freedom, p=0.7692). Therefore it was assumed that a common survival trend applied to all patients beyond the landmark**

		inspection the long-term survival between the two arms are closer when there are 50% of the patients alive.	**point. This is consistent with an assumption that all patients who suffer a non-fatal progression event have the same prognosis irrespective of prior treatment, with an estimated mean conditional survival of [redacted] days ([redacted]).** **A direct consequence of this finding is that the difference in OS attributable to everolimus can be accurately estimated directly from the trial results, without any recourse to parametric survival modelling. This is because the long-term survival of the 62% of everolimus+exemestane patients alive at point B in Figure 2 is can be considered identical to the long-term survival of the 62% of placebo+exemestane patients at point C in Figure 2 so that long-term survival makes no contribution to the net difference in OS, regardless of the form of the common long-term survival trend. As a consequence, the true OS gain is simply calculated as the difference between the area under the intervention survival curve from point A to point C and the area under the control survival curve from point A to point B. This amounts to [redacted] months (95% CI [redacted] to [redacted] months).** **The choice of 62% as the starting point for the long-term phase of survival is convenient because a common starting point for extrapolation excludes any risk of starting-point bias. Many other choices might be considered, but would require more time than was available to the ERG.**

Issue 4 'End of Life' criteria

Description of problem	Description of proposed amendment	Justification for amendment	ERG response & Amendments to ERG report
Page 9 The use of the median as a measure of survival benefit is problematic on several grounds. First, the median is not the natural metric for cost effectiveness analysis; cost effectiveness analysis relies on mean outcomes and mean costs. Second, the median is calibrated on only a subset of the trial data (i.e. the first 50% to suffer the measured event) and ignores the remaining trial data. Third, the median is a completely arbitrary reference point as any other percentile could be used and may give very different results.	Novartis does not agree with the assertion that the use of the median as a measure of survival benefit is problematic in the end of life assessment.	There are examples where NICE has previously accepted the use of the median overall survival to assess life expectancy. See for example TAG371 for trastuzumab emtansine published in December 2015 (https://www.nice.org.uk/guidance/ta371) : *'after review of the reported median survival from several trials of lapatinib plus capecitabine, it was prepared to accept that trastuzumab emtansine fulfilled this criterion'*	Overall survival K-M data from the BOLERO-2 trial show very variable estimated OS gain estimates depending on which percentile is selected as follows: Percentile OS gain (months)  The committee uses whatever data it has to hand at the time of a particular appraisal – a decision made on uncertain evidence in one appraisal is not a binding precedent for all other appraisals.

Page 10 It is surprising that the company relies on the SoFEA trial as the basis for asserting that that life expectancy in this patient group is less than 24 months, and ignores the BOLERO-2 trial.	The ERG notes that the company used the SoFEA trial to demonstrate that life expectancy in this patient group is less than 24 months. The company has based this justification on two reasons: 1. The SoFEA trail provides a robust analysis of survival specific to the UK 2. The SoFEA was used in the original submission and the company has had the SoFIA data set re-analysed to remove the HER2+ve patient population. The company does not ignore BOLERO-2 data, but uses SoFEA as it appears to be the most relevant UK specific data available to assess life expectancy in this patient group.	Novartis does not ignore BOLERO-2 data, but uses SoFEA as it appears to be the most relevant UK specific data available to assess life expectancy in this patient group. Novartis, in accordance with clinical experts, proposes that the data set from **SoFEA provides a more robust analysis of survival specific to the UK**: - Of the 724 patients randomised into BOLERO-2, only [redacted] were UK patients. [redacted] Global distribution of age-standardised 5-year net survival for women diagnosed with breast cancer during 1995–99, 2000–04, and 2005–09 in these countries exceed that of the UK (Allemani et al. Lancet 2015). It is therefore logical to assume that this improved survival will be reflected in BOLERO-2 when compared to the UK population. - On the contrary, SoFEA was mainly a UK specific study. This phase 3 multicentre	*ERG report amended, adding a final sentence:* **"For example, if the 45th percentile is used (based on 3-4 months additional data), the estimated OS gain falls to only [redacted] months."** *ERG report amended **in bold** as follows:* **The ERG notes that the company used the SoFEA trial to demonstrate that life expectancy in this patient group is less than 24 months. The company has based this justification on two grounds:** **1. The SoFEA trail provides a robust analysis of survival specific to the UK** **2. The SoFEA was used in the original submission and the company has had the SoFEA data set re-analysed to remove the HER2+ve patient population.** **However,** based on the analyses described above, the

		randomised controlled trial was conducted in [redacted]. The Committee noted in its previous guidance (TA 295) that a proportion of patients in the SoFEA trial had HER2-positive tumours and as a consequence the Committee concluded that this trial was not relevant in determining life expectancy in women with HR-positive tumours because it mixed breast cancer populations with different survival patterns. In response to this feedback, **Novartis has had the SoFEA data set re-analysed with the HER2+ve patient population removed from the dataset**. The median overall survival for patients receiving exemestane alone is [redacted] months in the SoFEA trial. Novartis believes this is the most accurate estimate of median OS in the UK for this patient population, in agreement with clinical experts. Novartis also adds a note of caution that OS from economic models tends to have higher OS due to extrapolations over the life time horizon. It would therefore reasonable to use trial reported results where possible. It was also shown in BOLERO-2 data the exemestane arm had 26.6 months OS with CI of 22.6 to 33.1.	ERG estimates the mean OS in the control arm of the BOLERO-2 trial to be [redacted] months (compared to [redacted] months for the everolimus arm). The ERG therefore considers that there is substantial uncertainty since, on the basis of the available evidence, everolimus+exemestane does not fulfil the criteria for consideration as an 'End of Life' treatment. This conclusion accords with the assessment made during the original STA.

NICE National Institute for Health and Care Excellence

NICE guidance

Everolimus in combination with exemestane for treating advanced HER2-negative hormone-receptor-positive breast cancer after endocrine therapy

Technology appraisal guidance

Published: 28 August 2013
nice.org.uk/guidance/ta295

Contents

1 Guidance

1.1 Everolimus, in combination with exemestane, is not recommended within its marketing authorisation for treating postmenopausal women with advanced human epidermal growth factor receptor 2 (HER2) negative hormone-receptor-positive breast cancer that has recurred or progressed following treatment with a non-steroidal aromatase inhibitor.

1.2 Women currently receiving everolimus for advanced breast cancer should be able to continue treatment until they and their clinician consider it appropriate to stop.

2 The technology

2.1 Everolimus (Afinitor, Novartis Pharmaceuticals) inhibits the mammalian target of rapamycin, a protein that regulates the division of tumour cells and growth of blood vessels. Everolimus has a UK marketing authorisation for the 'treatment of hormone receptor-positive, HER2/neu negative advanced breast cancer, in combination with exemestane, in postmenopausal women without symptomatic visceral disease after recurrence or progression following a non-steroidal aromatase inhibitor'.

2.2 Everolimus is contraindicated in people who are hypersensitive to the active substance, to derivatives of rapamycin, or to any of the excipients used to make everolimus. The summary of product characteristics lists the following as the most frequently reported grade 3 or 4 adverse reactions: anaemia, fatigue, diarrhoea, infections, stomatitis, hyperglycaemia, thrombocytopenia, lymphopenia, neutropenia, hypophosphataemia, hypercholesterolaemia, diabetes mellitus and pneumonitis. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3 Everolimus is administered orally. The recommended dosage is 10 mg once daily and treatment should continue as long as patients benefit clinically, or until they experience unacceptable adverse reactions. Adverse reactions that are severe and/or intolerable may be managed by reducing the dosage to 5 mg daily or temporarily stopping treatment followed by reintroducing it at 5 mg daily. The price for a pack (30 tablets per pack) of 10 mg tablets and 5 mg tablets is £2970 and £2250 respectively (excluding VAT; 'British National Formulary' [BNF] edition 65). Costs may vary in different settings because of negotiated procurement discounts. The manufacturer of everolimus has agreed a patient access scheme with the Department of Health, in which the first month of treatment with everolimus is free (including the option to offer the 5 mg tablet pack if there is a need to reduce the dose). The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

3 The manufacturer's submission

The Appraisal Committee (section 8) considered evidence submitted by the manufacturer of everolimus and a review of this submission by the Evidence Review Group (ERG; section 9).

Clinical effectiveness

3.1 The manufacturer conducted a systematic review of the literature to identify studies evaluating the clinical effectiveness and safety of everolimus in combination with another endocrine treatment (including exemestane, fulvestrant or tamoxifen) compared with endocrine treatment alone. Eligible studies included postmenopausal women with locally advanced or metastatic human epidermal growth factor receptor 2 (HER2) negative hormone-receptor-positive breast cancer after endocrine treatment. The manufacturer identified 2 randomised controlled trials (RCTs): a phase III trial (BOLERO-2) and a phase II trial (TAMRAD).

3.2 The BOLERO-2 trial was an international multicentre (189 centres in 24 countries) double-blind phase III RCT in postmenopausal women with locally advanced or metastatic HER2-negative hormone-receptor-positive breast cancer refractory to a non-steroidal aromatase inhibitor (letrozole or anastrozole). Refractory cancer was defined as cancer that recurred during or within 12 months of stopping adjuvant treatment (that is, treatment that is given in addition to the primary treatment), or cancer that progressed during or within 1 month of stopping treatment for advanced disease. Patients were stratified at randomisation according to the presence or absence of visceral metastasis and whether their cancer had previously been sensitive or insensitive to endocrine therapy, and randomised in a 2:1 ratio to everolimus 10 mg daily plus exemestane 25 mg daily (n=485) or placebo plus exemestane 25 mg daily (n=239). Treatment continued until patients' disease progressed, they experienced unacceptable toxicity or they withdrew consent. The trial protocol did not allow crossing over between the 2 treatment arms.

3.3 The primary outcome measure in the BOLERO-2 trial was progression-free survival (defined as time to disease progression or death) based on local radiological assessment of scans, which included CT scanning or MRI of the chest, abdomen and pelvis at baseline and every 6 weeks until disease progression. Using an intention-to-treat analysis, the primary analysis was a

log-rank test based on local radiological assessment according to the factors at randomisation on which patients had been stratified. The statistical analysis plan included a 'two-look' Lan-DeMets group design with an interim analysis after 317 (60%) progression-free survival events (progression or death) that occurred after a median follow-up of 7 months, and a final analysis after 528 progression-free survival events, which occurred after a median follow-up of 18 months. In addition, the manufacturer submitted an additional analysis of progression-free survival requested by the US Food and Drugs Administration (after a median follow-up of 12 months; 457 events). Data from an independent central radiological assessment (assessed by 2 independent radiologists) of progression-free survival were used, according to the trial's statistical analysis plan, for secondary supportive analyses. These analyses included a log-rank test at time to first tumour assessment by intention to treat and also, because of the possibility of informative censoring (loss to follow-up because of reasons related to the trial), by marginal structural Cox Proportional Hazards Modelling using the Inverse Probability of Censoring Weighting. In the BOLERO-2 trial, progression-free survival based on central assessment had the potential to be affected by informative censoring when local progression could not be confirmed centrally and the patient was censored because of the absence of radiological imaging after local progression or because the patient had started another anticancer therapy.

3.4 Most patients in the BOLERO-2 trial were white and had an Eastern Cooperative Oncology Group performance status of either 0 or 1. Approximately 84% of patients had tumours deemed to be sensitive to prior endocrine therapy and 75% of patients had received a non-steroidal aromatase inhibitor as their most recent treatment. Over half of the patients had received 3 or more prior therapies and 26% of patients had received chemotherapy for metastatic disease. Visceral metastases were present in 56% of patients at baseline. The manufacturer stated that the characteristics of the patients enrolled in the BOLERO-2 trial were well balanced between the 2 treatment arms.

3.5 Median progression-free survival after a median of 18 months' follow-up was longer with everolimus plus exemestane than with exemestane plus placebo, for the primary end point assessed by clinicians locally (7.8 compared with 3.2 months; hazard ratio [HR] 0.45, 95% confidence interval [CI] 0.38 to 0.54). The manufacturer noted that, at the median 18-month follow-up, 16.7% of

patients in the everolimus plus exemestane arm and 4.2% in the exemestane arm continued to receive treatment. The manufacturer also reported median progression-free survival when assessed centrally, which was also longer with everolimus plus exemestane than with exemestane alone (11.0 compared with 4.1 months; HR 0.38, 95% CI 0.31 to 0.48). During consultation, the manufacturer submitted a sensitivity analysis for the centrally assessed progression-free survival analysis. For patients in the everolimus plus exemestane arm whose cancer was deemed to have progressed at local review and who were censored because of a 'new cancer therapy added' by central reviewers, the censoring was replaced by a progression-free survival event. This assumes that the patient's cancer would have progressed at the next tumour assessment. The manufacturer did not apply this replacement to the exemestane alone arm and therefore these patients remained censored. The manufacturer suggested that the hazard ratio from this sensitivity analysis of centrally-assessed progression-free survival shows that the overall treatment effect is robust (median progression-free survival in months not reported; HR 0.55, 95% CI 0.43 to 0.70). The manufacturer presented analyses of results for locally-assessed progression-free survival for 12 of the 13 pre-specified exploratory subgroups at the median 7-month time point. Each analysis favoured everolimus plus exemestane compared with exemestane alone. No tests of interaction were pre-specified in the statistical analysis plan.

3.6 Secondary outcomes reported in the BOLERO-2 trial included overall survival, overall response rate and clinical benefit rate. The manufacturer included 3 planned analyses for overall survival in its statistical analysis plan and included the analysis it performed after a median follow-up of 16 months in its submission. In this analysis, 112 patients (23%) in the everolimus plus exemestane arm had died, compared with 70 patients (29%) in the exemestane alone arm (HR 0.77, 95% CI 0.57 to 1.04). At that point in the trial, because over half of the women remained alive, the median overall survival had not been reached.

3.7 The reported results for overall response rate (defined as complete or partial response) and clinical benefit rate (defined as complete or partial response or stable disease) for everolimus plus exemestane compared with exemestane alone at the 7-, 12- and 18-month median follow-up analyses were presented by the manufacturer. The reported clinical benefit rate at the 18-month median follow-up analysis was 51.3% and 26.4% for the everolimus plus exemestane

and exemestane alone arms respectively, and the overall response rate was 12.6% and 1.7% respectively.

3.8 The investigators measured health-related quality of life in the BOLERO-2 trial using the EORTC (European Organization for Research and Treatment of Cancer) QLQ-C30 questionnaire every 6 weeks until disease progression. The manufacturer provided data for the median time to definitive deterioration in months of the global health-related quality-of-life domain score, defining a minimally important difference as greater than or equal to a 5% change. At each follow-up point, the manufacturer reported the results of those patients who had experienced a deterioration in health-related quality of life. At the median follow-up of 7 months, the results for everolimus plus exemestane compared with exemestane alone were 4.5 months and 4.4 months respectively (p=0.217), at 12 months, they were 7.0 months and 5.6 months respectively (p=0.040) and, at 18 months, they were 8.3 months and 5.8 months respectively (p=0.0084). The manufacturer did not provide the number of patients who completed this analysis or describe how it adjusted for missing data.

3.9 The manufacturer presented 6- and 12-week data for the rate of bone turnover, which suggested that bone turnover was suppressed by adding everolimus to exemestane and that the increase in bone absorption associated with exemestane was reversed. The manufacturer reported that, at a median follow-up of 18 months, 2.3% of patients receiving everolimus plus exemestane and 3.8% of patients receiving exemestane alone had fractures.

3.10 Adverse event data from the BOLERO-2 trial at the 7-month median follow-up analysis were presented in the manufacturer's submission. The manufacturer reported grade 3 or 4 adverse events in 211 out of 482 patients taking everolimus plus exemestane compared with 61 out of 238 patients receiving everolimus alone. Thirty-two patients taking everolimus plus exemestane and 7 patients taking exemestane alone stopped treatment because of adverse events. Over a median follow-up of 7 months, 58% of patients receiving everolimus interrupted or reduced their dose because of adverse events. The most common grade 3 or 4 adverse events reported for everolimus plus exemestane compared with exemestane alone were stomatitis (7.7% and 0.8% respectively) and anaemia (5.8% and 0.8% respectively).

3.11 TAMRAD was a multicentre open-label phase II RCT carried out in France. Postmenopausal women with metastatic HER2-negative hormone-receptor-positive breast cancer whose disease was refractory to treatment with an aromatase inhibitor were randomised to 10 mg of everolimus daily plus 20 mg of tamoxifen daily (n=54), or 20 mg of tamoxifen daily (tamoxifen alone, n=57).

3.12 The manufacturer submitted results of the TAMRAD trial as supporting evidence. The primary outcome in the trial was the 'clinical benefit rate' at 6 months, which was 61.1% in the everolimus plus tamoxifen arm and 42.1% in the tamoxifen alone arm (p=0.045). Secondary outcomes included overall survival, time to progression, overall response rate and safety. At a median follow-up of 24 months, 29.6% of patients in the everolimus plus tamoxifen arm and 54.4% in the tamoxifen alone arm had died (HR 0.45, 95% CI 0.24 to 0.81; p=0.007). The median time to progression for patients receiving everolimus plus tamoxifen was 8.6 months and for tamoxifen alone was 4.5 months (HR 0.54, 95% CI 0.36 to 0.81; p=0.0021).

3.13 In the absence of head-to-head data comparing everolimus plus exemestane with comparators other than exemestane alone, namely fulvestrant, the manufacturer conducted a Bayesian fixed-effects indirect treatment comparison for 2 outcomes: progression-free survival and overall survival. The manufacturer systematically searched the literature and identified the BOLERO-2 trial plus 3 additional multicentre double-blind phase III RCTs, which compared either fulvestrant with exemestane (EFECT and SoFEA) or 1 dose of fulvestrant with a different dose of fulvestrant (CONFIRM). The manufacturer's searches did not identify any evidence that allowed tamoxifen or chemotherapy to be included in the indirect treatment comparison.

3.14 The manufacturer's indirect treatment comparison compared everolimus plus exemestane with fulvestrant, and exemestane alone with fulvestrant. The number of patients enrolled in each of the 4 trials was between 693 and 736. All patients were postmenopausal women with locally advanced or metastatic breast cancer and with hormone-receptor-positive tumours. However, the EFECT and CONFIRM trials did not provide data on HER2 status, whereas SoFEA also included women who had HER2-positive tumours. In all trials, patients had received prior therapy; in 3 of the trials, patients received prior treatment with a non-steroidal aromatase inhibitor. All trials reported progression-free survival or time to progression as the primary outcome and

included overall survival among the secondary outcomes. The manufacturer included progression-free survival based on central assessment from the BOLERO-2 trial. The manufacturer did not include the overall survival findings from the EFECT trial in the indirect treatment comparison. A reason for this was not provided.

3.15 The results of the manufacturer's indirect treatment comparison for progression-free survival suggested that everolimus is more effective than fulvestrant (at doses of either 250 mg or 500 mg). The manufacturer labelled the hazard ratios comparing everolimus plus exemestane and fulvestrant as academic in confidence, so they cannot be presented here. The manufacturer stated that it was not possible to provide a complete assessment of heterogeneity because of the small number of comparisons.

Cost effectiveness

3.16 The manufacturer did not identify any published studies of cost effectiveness relevant to the decision problem. It developed an Excel-based cost-effectiveness model. It chose a state-transition Markov model with a cycle length of 1 month to represent the progressive nature of locally advanced or metastatic breast cancer. The model includes a half-cycle correction and uses 3 mutually exclusive health states: stable disease, progressed disease and death. The model assumes that a patient could be offered 1 of 7 treatments: everolimus plus exemestane, exemestane alone, tamoxifen or fulvestrant, or 1 of 3 chemotherapy agents: docetaxel, doxorubicin or capecitabine. The primary outcome of the model is the quality-adjusted life year (QALY). Costs (from the perspective of the NHS) and outcomes (QALYs) are discounted over a patient's lifetime (10-year) time horizon by 3.5% per annum.

3.17 When entering the model, all patients are in the 'stable disease' health state. When a patient's disease progresses, the patient enters the 'progressed disease' state, unless the patient dies before the disease progresses. Patients can move during each cycle from 'stable disease' to 'progressed disease', or from 'stable disease' and 'progressed disease' to 'death'. The health state 'death' captures mortality from any cause (including non-disease-related death). The model calculates the proportion of patients in each health state according to survival functions for progression-free survival and overall survival.

3.18 To estimate the proportion of patients in the 'stable disease' health state over time, the manufacturer used progression-free survival based on data from the BOLERO-2 trial, which were available up to a median follow-up of 18 months. The manufacturer fitted a series of parametric curves to the BOLERO-2-derived Kaplan–Meier analysis using the exponential, Gompertz, log-logistic and Weibull functions. The manufacturer found that the curve estimated from the log-logistic function provided the best statistical fit. However, in its base-case analysis, the manufacturer used the Weibull function, noting that it had visually inspected the fit of the curve and took advice from clinical specialists, who suggested that the Weibull curve better reflected reality.

3.19 To estimate the proportion of patients treated with everolimus plus exemestane or with exemestane alone who were alive over time, the manufacturer used overall survival data from the BOLERO-2 trial, which were available up to a median follow-up of 16 months. The data, however, were not mature (see section 3.6); that is, at any time point, few women had died and an estimate of median overall survival needs at least half of the patients to have died. The log-logistic function provided the best statistical fit, but the manufacturer again used the Weibull function, guiding its decision, in part, on the advice of clinical specialists.

3.20 To calculate the number of patients in the 'progressed disease' health state, the manufacturer subtracted the number of patients in the 'stable disease' health state (before progression) from the number of patients estimated to be alive. However, the manufacturer stated that, in some of its comparisons of everolimus plus exemestane with the treatments included in its economic model, this led to negative numbers of patients in the 'progressed disease' health state, which the manufacturer interpreted as being caused by the overall survival data being immature. The manufacturer therefore chose to adjust the hazard for mortality in a way that lengthened overall survival. The manufacturer reduced the hazard for mortality in all time periods by 20% in the original parametric function that models the effectiveness of everolimus plus exemestane. The manufacturer applied the multiplication factor to the everolimus plus exemestane survival curve, but not to the curves for the comparators. The manufacturer considered that the 20% factor was supported by a review presented as a conference poster (Beauchemin et al. 2012). This study used a regression analysis to correlate the relationship between median progression-free survival and median overall survival from 144 trials, and

reported an average linear relationship in which, for women with metastatic breast cancer, 1 month of progression-free survival resulted in 1.7 months of overall survival. In addition, the manufacturer added age-related mortality for the general female population based on data from the Office for National Statistics, but only after 48 months in the economic model.

3.21 For other comparisons, because no head-to-head trials were available for everolimus plus exemestane compared with tamoxifen, fulvestrant or chemotherapy, the manufacturer used other methods to estimate progression-free survival and overall survival in the economic model.

3.22 For the analysis of everolimus plus exemestane compared with tamoxifen, the manufacturer used data from the TAMRAD trial. However, the manufacturer did not explain in its submission how these data were used in the economic model. For the analysis of everolimus plus exemestane compared with fulvestrant, the manufacturer used the hazard ratios from its indirect treatment comparison (see sections 3.13 to 3.15), but excluded the CONFIRM trial, which linked fulvestrant 250 mg and fulvestrant 500 mg (the licensed dose). The manufacturer stated that this reduced uncertainty because the BOLERO-2, EFECT and SoFEA trials have similar populations and a common comparator (that is, exemestane).

3.23 To obtain an estimate of overall survival for everolimus plus exemestane compared with chemotherapy for the economic model, the manufacturer conducted a second indirect analysis (described by the manufacturer as a 'naive chained indirect analysis'). The manufacturer took the hazard ratio for overall survival reported for endocrine therapy compared with chemotherapy (from 6 trials in a systematic review by Wilcken et al. 2003) and multiplied it by the hazard ratio for tamoxifen alone compared with everolimus plus tamoxifen (taken from the TAMRAD trial). To estimate overall survival for everolimus plus exemestane compared with chemotherapy from the naive chained indirect analysis, the manufacturer assumed that:

- the chemotherapy agents doxorubicin, docetaxel and capecitabine have equal clinical effectiveness
- overall survival for tamoxifen equals that of all other endocrine therapies

- the relative effectiveness of everolimus plus exemestane compared with exemestane alone is the same as everolimus plus tamoxifen compared with tamoxifen alone.

  The manufacturer could not estimate progression-free survival using this approach because of a lack of data, so assumed that the effectiveness of chemotherapy for progression-free survival (compared with everolimus plus exemestane) was the same as the effectiveness of tamoxifen (compared with everolimus plus exemestane) and used the hazard ratio estimated from the TAMRAD trial.

3.24 To estimate health-related quality of life, the manufacturer conducted a systematic literature review of utility studies for locally advanced or metastatic breast cancer. Although the searches identified 5 relevant studies, the manufacturer noted that none provided an estimate for the 'stable disease' health state, and that all 5 studies had limitations. In its original submission, the manufacturer considered that the study by Lloyd et al. (2006) provided the most appropriate utility values. This study calculated utility values for both stable and progressed disease, and had been used by other manufacturers in previous technology appraisals for metastatic breast cancer (Fulvestrant for the treatment of locally advanced or metastatic breast cancer [NICE technology appraisal guidance 239], Eribulin for the treatment of locally advanced or metastatic breast cancer [NICE technology appraisal guidance 250] and Lapatinib or trastuzumab in combination with an aromatase inhibitor for the first-line treatment of metastatic hormone-receptor-positive breast cancer that overexpresses HER2 [NICE technology appraisal guidance 257]). In Lloyd et al. (2006), utility values were collected from a sample of the general public in the UK (n=100) using the standard gamble technique. The manufacturer adjusted these published utilities for:

- age (to be consistent with the average age of patients used to estimate UK EQ-5D tariffs) and
- the degree of response to treatment, based on the clinical benefit rate observed in the BOLERO-2 trial (this adjustment was only made for the 'stable disease' health state).

  This provided utility values in the original submission of 0.798 and 0.496 for the 'stable disease' and 'progressed disease' health states respectively. However, the manufacturer provided comments during the consultation period expressing the view that a utility value for the 'stable disease' state should be based on 'disease stabilisation', which is incorporated in the BOLERO-2 trial 'clinical benefit rate' end

point but not in the 'overall response rate' end point. The manufacturer expressed the view that the post-progression utility value from Lloyd et al. (2006) was 'low compared with post-progression values from other studies' (of other cancers). In revised modelling after consultation, the manufacturer estimated a separate 'stable disease' utility value based on the clinical benefit rate from the BOLERO-2 trial. Furthermore, the manufacturer included a utility value for the 'progressed disease' health state from Launois et al. (1997) that estimated a utility value of 0.65 for 'progression' in metastatic breast cancer using the standard gamble technique in a sample of 20 French oncology nurses. The manufacturer considered that the Launois et al. (1997) utility value more accurately represents the likely quality of life of progressed advanced breast cancer.

3.25 Resource use and costs in the economic model include those related to treating disease, and those associated with managing disease in both the 'stable disease' and 'progressed disease' health states. The manufacturer assumed that patients would receive treatment with everolimus plus exemestane or exemestane alone only when in the 'stable disease' health state. Once progressed, patients would stop treatment with everolimus plus exemestane or exemestane alone. However, the manufacturer acknowledged that some patients stop taking treatment with everolimus plus exemestane or exemestane alone while in the 'stable disease' state and assumed they would do so at the rate observed in the BOLERO-2 trial. The unit costs for each of the drugs and their administration were taken from the 'British National Formulary 63' and 'NHS Reference Costs 2010-2011'. For the 'stable disease' health state, the manufacturer estimated resource use from Advanced breast cancer: diagnosis and treatment (NICE clinical guideline 81; package 1). Once disease had progressed, the manufacturer assumed the patients would receive package 2 from NICE clinical guideline 81, which includes visits from a community home nurse, appointments with a clinical nurse specialist, home visits from a GP and appointments with a therapist. The manufacturer took unit costs for these packages from the Personal Social Services Research Unit, Unit Costs of Health and Social Care, and estimated packages 1 and 2 to cost approximately £200 and £800 per patient in the 'stable disease' and 'progressed disease' health states respectively. These costs are incurred in each monthly cycle of the economic model. In the additional evidence provided with its response to consultation, the manufacturer's economic model included the costs of 4 subsequent chemotherapies: bevacizumab, paclitaxel, capecitabine and vinorelbine, that patients might be offered after everolimus (plus exemestane) or after one of the other therapies listed among the comparators.

3.26 The economic model did not include disutilities or costs associated with adverse events in the base-case analysis when comparing everolimus plus exemestane with endocrine therapy. The manufacturer stated that this was because 'very few' adverse events were reported in the BOLERO-2 trial and because NICE technology appraisal 239 (Fulvestrant for the treatment of locally advanced or metastatic breast cancer), although a different comparison, had excluded adverse events in the base-case cost-effectiveness analysis. However, the manufacturer did include disutilities and costs associated with adverse events in the base-case analysis when comparing everolimus plus exemestane with chemotherapies.

3.27 The manufacturer's economic model estimated a mean overall survival of 45.8 months and 28.9 months for everolimus plus exemestane and exemestane alone respectively. For (centrally assessed) progression-free survival, the model estimated a mean result of 17.3 months and 7.2 months for everolimus plus exemestane and exemestane alone respectively (base-case analysis). The mean (centrally assessed) progression-free survival data observed in the BOLERO-2 trial were 13.5 months and 6.7 months for everolimus plus exemestane and exemestane alone respectively. For (locally assessed) progression-free survival, the model estimated a mean of 10.8 months and 5.5 months for everolimus plus exemestane and exemestane alone respectively (scenario analysis). The mean (locally assessed) progression-free survival data from the BOLERO-2 trial were 10.3 months and 5.3 months for everolimus plus exemestane and exemestane alone respectively. However, not everyone in the BOLERO-2 trial reached the primary end point of progressed disease, and the manufacturer did not provide details on how it had calculated these mean values for observations from the trial in its original submission. In its response to consultation, the manufacturer explained that mean progression-free survival from the trial was estimated using the area under the curve approach and correcting for the largest observation if censored. It stated this method is likely to underestimate the mean progression-free survival because the estimation was restricted to the largest observation, which was censored.

3.28 The manufacturer presented pairwise incremental cost-effectiveness ratios (ICERs) for everolimus plus exemestane compared with each of the treatments included in the economic model. For everolimus plus exemestane compared with exemestane alone, the manufacturer estimated incremental costs of £27,086 and 0.84 incremental QALYs gained with an ICER of £32,417 per QALY

gained. For everolimus plus exemestane compared with tamoxifen, the manufacturer estimated incremental costs of £34,256 and 1.18 incremental QALYs gained with an ICER of £29,109 per QALY gained. For everolimus plus exemestane compared with fulvestrant, the manufacturer estimated incremental costs of £20,937 and 0.77 incremental QALYs gained with an ICER of £27,147 per QALY gained. For everolimus plus exemestane compared with docetaxel, the manufacturer estimated incremental costs of £13,364 and 1.21 incremental QALYs gained with an ICER of £11,000 per QALY gained. For everolimus plus exemestane compared with doxorubicin, the manufacturer estimated incremental costs of £25,227 and 1.25 incremental QALYs gained with an ICER of £20,253 per QALY gained. For everolimus plus exemestane compared with capecitabine, the manufacturer estimated incremental costs of £29,597 and 1.21 incremental QALYs gained with an ICER of £24,362 per QALY gained.

3.29 The manufacturer did not present the results of univariate sensitivity analysis, but instead reported results from several scenario analyses. The scenarios explored, and the comparisons for which the ICER changed most, included:

- Using overall survival data from the BOLERO-2 trial (removing the adjustment to overall survival taken from Beauchemin et al. 2012; see section 3.20). This increased the ICER from £32,417 to £37,719 per QALY gained for everolimus plus exemestane compared with exemestane alone. In this scenario, the incremental survival was estimated to be 10.5 months.
- Using the same estimate of post-progression survival for everolimus plus exemestane and the comparators, as opposed to treatment-specific estimates. This increased the ICER from £29,109 to £42,348 per QALY gained for everolimus plus exemestane compared with tamoxifen.
- Using estimates of progression-free survival for everolimus plus exemestane measured in the BOLERO-2 trial by the primary end point, local radiological assessment, instead of central radiological assessment. This increased the ICER from £11,000 to £15,195 per QALY gained for everolimus plus exemestane compared with docetaxel.
- Using the log-logistic survival function to extrapolate progression-free survival and overall survival. This decreased the ICER from £32,417 to £26,329 per QALY gained for everolimus plus exemestane compared with exemestane alone.

3.30 The manufacturer also presented probabilistic base-case ICERs that were similar to the deterministic estimates. The results of the manufacturer's probabilistic sensitivity analysis showed that, at £30,000 per QALY gained, there is a 41.6% probability of everolimus plus exemestane being cost effective when compared with exemestane alone. When everolimus plus exemestane is compared with the other treatments, the probability of everolimus plus exemestane representing a cost-effective use of NHS resources ranges between 52.4% and 99.1%, at £30,000 per QALY gained.

3.31 In its response to consultation, the manufacturer provided revised cost-effectiveness analyses comparing everolimus plus exemestane with exemestane alone, with capecitabine and with vinorelbine. The effectiveness of vinorelbine was assumed to be equal to the effectiveness of the other chemotherapies included in its economic model, based on the results of the naive chained indirect analysis (see section 3.23). It presented 2 scenarios: scenario 1 in which progression-free survival was based on central assessment from the BOLERO-2 trial; and scenario 2 in which progression-free survival was based on local assessment from the BOLERO-2 trial. The manufacturer updated its original economic model:

- combining 7 of the ERG's exploratory analyses (see sections 3.46 to 3.52) in the scenario with central assessment (scenario 1)
- combining 8 of the ERG's exploratory analyses (see sections 3.46 to 3.53) in the scenario with local assessment scenario (scenario 2)
- changing the utility values for 'stable disease' and 'progressed disease' (see section 3.24)
- introducing the costs associated with chemotherapies used post-progression (see section 3.25)
- including a patient access scheme for everolimus (see section 2.3).

3.32 The manufacturer presented pairwise ICERs incorporating the patient access scheme, updated utility values and costs associated with chemotherapies offered post-progression for scenario 1 (central assessment). For everolimus plus exemestane compared with exemestane alone, the manufacturer estimated incremental costs of £18,087 and 0.59 incremental QALYs gained with an ICER of £30,896 per QALY gained. For everolimus plus exemestane compared with

capecitabine, the manufacturer estimated incremental costs of £20,044 and 1.09 incremental QALYs gained with an ICER of £18,340 per QALY gained. For everolimus plus exemestane compared with vinorelbine, the manufacturer estimated incremental costs of £7105 and 1.09 incremental QALYs gained with an ICER of £6501 per QALY gained.

3.33 The manufacturer presented pairwise ICERs incorporating the patient access scheme, updated utility values and costs associated with chemotherapies offered post-progression for scenario 2 (local assessment). For everolimus plus exemestane compared with exemestane alone, the manufacturer estimated incremental costs of £20,280 and 0.53 incremental QALYs gained with an ICER of £38,012 per QALY gained. For everolimus plus exemestane compared with capecitabine, the manufacturer estimated incremental costs of £22,516 and 1.05 incremental QALYs gained with an ICER of £21,362 per QALY gained. For everolimus plus exemestane compared with vinorelbine, the manufacturer estimated incremental costs of £14,408 and 1.05 incremental QALYs gained and an ICER of £13,669 per QALY gained.

Evidence Review Group comments on clinical effectiveness

3.34 The ERG noted that the manufacturer appropriately addressed the final scope in its submission and that changes it made to the decision problem reflected the marketing authorisation for everolimus. The ERG stated that the manufacturer had identified generally appropriate comparators, but noted that the manufacturer had excluded vinorelbine as a comparator. The ERG reported that clinicians suggested that vinorelbine is the fourth most commonly used chemotherapy treatment in the UK for advanced breast cancer.

3.35 The ERG commented that the BOLERO-2 trial was well designed, had a low risk of bias and was relevant to the decision problem for this technology appraisal. It noted that, because everolimus causes stomatitis and rash, investigators may have guessed which treatment the patients were taking, compromising the blinding. The ERG commented that the baseline characteristics of the patients in the trial were well balanced between the treatment arms. However, compared with the exemestane alone arm, fewer patients in the everolimus plus exemestane arm had most recently been treated for metastatic disease (79% compared with 84%) or received a non-steroidal aromatase inhibitor for

metastatic disease (71% compared with 76%), and fewer were younger than 65 years of age (60% compared with 66%).

3.36 The ERG noted that the BOLERO-2 trial included patients with visceral disease (approximately 56% of all patients), but the manufacturer's submission did not state whether these patients were also 'symptomatic'. The manufacturer clarified that the licence wording specified 'without symptomatic visceral disease' to exclude patients with immediately life-threatening visceral disease, for whom chemotherapy may be the preferred treatment option. The ERG noted that the patients included in the BOLERO-2 trial did not appear to have life-threatening visceral disease.

3.37 The ERG commented that the point estimates of median progression-free survival measured by central radiological assessment were longer than when measured by local radiological assessment. It noted that the manufacturer had clarified that some patients deemed to have progressed by local radiological review, were deemed not to have progressed by central radiological review. Analyses based on central review 'censored' data from such patients (that is, the event of interest, in this case disease progression, was recorded as not having been observed; see section 3.3). The ERG noted that, although the results of both analyses showed similar results favouring everolimus plus exemestane, local assessment of progression better reflects clinical practice.

3.38 In its critique of the additional evidence provided by the manufacturer after consultation, the ERG explored whether bias existed in the BOLERO-2 trial by analysing whether local investigators might have known which treatment arm patients had been allocated to on the basis of typical adverse event symptoms and then acted differently by offering chemotherapy preferentially to patients taking placebo (exemestane alone). Using the data of the 'summary of censoring reasons' in the European Public Assessment Report, the ERG reported no significant differences in the proportion of patients censored for 'new cancer treatment added' between the 2 treatment arms. This did not differ whether the progression-free survival was assessed locally or centrally. The ERG concluded that this suggested treatment decisions based on local assessment were not significantly biased in the BOLERO-2 trial because the data did not indicate that the investigator was more likely to switch treatment in the exemestane alone arm. However, the ERG reported a statistically significantly higher rate of censoring using central assessment than local assessment, indicating that the

estimates of progression-free survival based on central assessment are subject to greater uncertainty.

3.39 The ERG considered the treatments for breast cancer received by patients after their disease had progressed. Data from a median of 7 months' follow-up in the European Public Assessment Report showed that chemotherapy was the most common cancer therapy offered after disease progression. The ERG observed that patients previously randomised to exemestane alone were more likely to receive chemotherapy and 'targeted therapies' than patients randomised to everolimus plus exemestane at a median of 7 months' follow-up.

3.40 The ERG noted that, in general, patients tolerate everolimus, but it highlighted that patients taking everolimus (plus exemestane) experienced more grade 3 or 4 adverse events, and more withdrew from the trial because of adverse events compared with patients in the exemestane alone treatment arm. The ERG acknowledged that most data on adverse events provided in the manufacturer's submission were from the analyses performed at 7 months' median follow-up, at which point patients had received everolimus for a median of 14.6 weeks compared with 12.0 weeks for placebo.

3.41 The ERG commented that the manufacturer's search strategies and methodology were appropriate for the indirect treatment comparison. The ERG noted that the analysis included estimates for median progression-free survival from the BOLERO-2 trial measured by central assessment, whereas the estimates of median progression-free survival from the other trials used local assessment. The ERG highlighted that the hazard ratios for progression-free survival were more favourable for everolimus plus exemestane with central assessment than with local assessment. The ERG noted differences between the studies, such as the proportion of patients previously treated with an aromatase inhibitor. It considered that this was potentially important because, in the CONFIRM trial, patients whose last treatment was an aromatase inhibitor had a worse prognosis compared with patients last treated with an anti-oestrogen therapy. In addition, 2 of the 4 studies did not provide information on the patients' HER2 status, and this markedly differed between the other 2 studies (BOLERO-2 and SoFEA). The ERG noted that including patients with HER2-positive tumours may lower progression-free and overall survival. Given the potential differences in the patient populations included in the indirect treatment comparison, as well as the use of central assessment estimates for

progression-free survival for everolimus plus exemestane, the ERG stated that the findings of the indirect comparison should be interpreted with caution.

3.42 The ERG stated that, because the Wilcken et al. review was published in 2003, it did not include endocrine therapies that reflect current practice; for example, the review included no trials of aromatase inhibitors. In addition, none of the studies included docetaxel or capecitabine. The ERG further noted that the results of the naive chained indirect analysis were based on several untested assumptions (for example, the relative effectiveness of everolimus plus tamoxifen compared with tamoxifen alone is the same as everolimus plus exemestane compared with exemestane alone). The ERG stated that the findings of the naive chained indirect comparison should be interpreted with extreme caution.

Evidence Review Group comments on cost effectiveness

3.43 The ERG noted that the economic model structure adopted by the manufacturer to address the decision problem of this technology appraisal had been used previously for several metastatic cancer-related NICE single technology appraisals (for example, in Fulvestrant for the treatment of locally advanced or metastatic breast cancer [NICE technology appraisal guidance 239] and Eribulin for the treatment of locally advanced or metastatic breast cancer [NICE technology appraisal guidance 250]).

3.44 The exploratory analyses undertaken by the ERG (see sections 3.45 to 3.54) focused on the comparison of everolimus plus exemestane with exemestane alone because it considered this to be the only reliable comparison.

3.45 The ERG conducted several exploratory sensitivity analyses using the manufacturer's economic model. The ERG commented that the manufacturer calculated drug costs for everolimus and exemestane on the basis of the average number of patients in the 'stable disease' health state each month, whereas it would have been more appropriate to calculate the costs on the basis of the number of patients in the 'stable disease' health state at the start of each month when the supply of tablets would be prescribed. Calculating the treatment costs for everolimus and exemestane at the beginning of each month resulted in an increase in the ICER for everolimus plus exemestane compared with exemestane alone from £32,417 (base case) to £33,113 per QALY gained.

3.46 The ERG noted that the manufacturer's approach to modelling time on treatment gave anomalous results. The manufacturer's model estimated that all patients completed treatment by month 32 in the everolimus plus exemestane arm, but that some patients continued to receive exemestane for more than 10 years in the exemestane alone arm. Using the BOLERO-2 data for time on treatment provided by the manufacturer, the ERG calculated lower treatment costs in both arms. The ICER decreased from £32,417 (base case) to £30,810 per QALY gained. Amending the model to include the BOLERO-2 data in this way means that the ERG's adjustment described in section 3.45 is no longer needed.

3.47 The ERG did not consider it appropriate for the manufacturer to exclude adverse reactions for everolimus plus exemestane in the base-case analysis because of the differences in the profile of adverse reactions between everolimus and the comparators. The ERG updated the frequencies of treatment-related adverse reactions to reflect data from the European Public Assessment Report and estimated an additional incremental cost of £142 and a loss of 0.029 incremental QALYs, and the ICER increased from £32,417 (base case) to £33,742 per QALY gained. The ERG noted uncertainty associated with the unit costs of treating adverse reactions in hospital because the ERG could verify only 2 of the 9 values included in the manufacturer's economic model.

3.48 The ERG commented that the manufacturer's economic model did not include any costs associated with assessing response to treatment or disease progression while patients remain in the 'stable disease' health state. The ERG investigated a scenario that included patients seeing an oncologist and getting a CT scan every 3 months. This increased the ICER from £32,417 (base case) to £33,372 per QALY gained.

3.49 With respect to the manufacturer's adjustment to the overall survival of everolimus plus exemestane based on the data from Beauchemin et al. (2012), the ERG highlighted several limitations, in particular:

- An average relationship obtained across a heterogeneous selection of 144 trials does not provide a better estimate of overall survival than does a single well-conducted trial (that is, the BOLERO-2 trial).
- The conference poster was based on meta-analysing median values, and averaging median values does not estimate an overall median.

- The manufacturer applied the adjustment to survival only in the everolimus plus exemestane arm, ensuring that the results favour everolimus.

  The ERG considered that this adjustment was not appropriate. The ERG ran an exploratory analysis that removed the adjustment, which resulted in a decrease in the incremental costs and QALYs during the post-progression phase. The ICER increased from £32,417 (base case) to £37,719 per QALY gained.

3.50 The ERG commented that the manufacturer discounted costs and outcomes on a monthly basis. When the ERG discounted the costs and outcomes annually, it resulted in a small decrease in the ICER from £32,417 (base case) to £32,326 per QALY gained.

3.51 The ERG commented that the manufacturer included deaths from any cause when estimating overall survival observed in the BOLERO-2 trial and therefore, by also including age-related mortality in the model after 4 years, the manufacturer had double-counted deaths. Also, because virtually all patients in the exemestane arm were estimated to have died by 4 years, this increased the rate of mortality only in the everolimus plus exemestane arm, leading to lower estimates of costs and outcomes. The ERG modelled a scenario that removed the age-related mortality and this decreased the ICER from £32,417 (base case) to £32,248 per QALY gained.

3.52 The ERG stated that the manufacturer incorrectly calculated the utility values from Lloyd et al. (2006) for progression-free survival. The ERG explained that it would have been more appropriate to estimate separate utility values for both everolimus plus exemestane and exemestane alone, taking into account the different levels of overall response rate (that is, complete or partial response) in each arm of the BOLERO-2 trial. The ERG estimated that the utility values for progression-free survival using Lloyd et al. (2006) were 0.7644 and 0.7571 for everolimus plus exemestane and exemestane respectively. This increased the ICER from £32,417 (base case) to £33,299 per QALY gained.

3.53 With respect to radiologically assessing the progression of cancer, the ERG considered that locally assessing progression of the cancer is more appropriate than doing it centrally because it more closely reflects clinical practice. By using locally assessed progression-free survival in the model, the ERG estimated an increase in the ICER from £32,417 (base case) to £34,684 per QALY gained.

3.54 The ERG considered that a significant area of uncertainty was the extent to which the manufacturer's economic model reflected the natural history of treated disease in the BOLERO-2 trial. The ERG had requested Kaplan–Meier analyses of progression-free survival, post-progression survival and overall survival using different censoring rules from the manufacturer to validate the survival models used in the manufacturer's base-case analysis. However, the manufacturer did not provide these data, so the ERG fitted exponential models to locally assessed data of progression-free survival obtained from a conference poster reporting the BOLERO-2 trial results (Piccart et al. 2012) and from data in the manufacturer's submission. The available data on overall survival did not allow the ERG to calculate the median overall survival from either arm of the BOLERO-2 trial because 50% of patients had not died. Instead, the ERG fitted a piecewise exponential model to the overall survival data up to 16 months, which showed that, beyond 10 months, patients on both treatments have similar mortality rates (the ERG described this as the parallel exponential model). It chose a 'piecewise approach' to reflect the change in mortality following disease progression when treatment stops, which may exhibit a 'kink' in the survival curve. In the ERG's view, attempts to fit conventional smooth parametric curves to kinked data are rarely successful. The ERG considered that a 'kink' occurred at a median follow-up of 18 months from baseline in the BOLERO-2 trial, and restricted its curve-fitting to the time period before this. The ERG used this analysis to replace the Weibull survival function used by the manufacturer in the ERG's base-case analysis. The ERG's exploratory analysis resulted in lower estimates for progression-free survival and overall survival for the everolimus plus exemestane arm, but not for the exemestane alone arm. The ICER increased from £32,417 (base case) to £39,978 per QALY gained.

3.55 When the exploratory sensitivity analyses described in sections 3.46 to 3.52 were combined, the ICER increased from £32,417 (base case) to £39,320 per QALY gained. Combining the exploratory sensitivity analyses described in sections 3.46 to 3.53 resulted in the ICER increasing from £32,417 (base case) to £52,285 per QALY gained. Combining the exploratory sensitivity analyses described in sections 3.46 to 3.52 and section 3.54 resulted in an increase in the ICER from £32,417 (base case) to £66,476 per QALY gained. The 2 changes that had the most influence on the ICER were removing the 20% hazard ratio reduction to the modelled overall survival, and replacing the manufacturer's survival analysis (Weibull) with the ERG's (piecewise parallel exponential model).

3.56 The ERG considered whether everolimus plus exemestane offered a cost-effective use of NHS resources for any of the patients subgroups analysed by the manufacturer. The ERG thought it worthwhile to consider the impact to the estimated ICER for everolimus plus exemestane compared with exemestane alone for 3 subgroups (median progression-free survival at a median follow-up of 18 months are presented in brackets):

- Visceral metastases (8.4 months for everolimus plus exemestane compared with 4.9 months for exemestane alone), and for non-visceral metastases (11.0 months for everolimus plus exemestane compared with 5.7 months for exemestane alone). The ERG suggested that the estimated ICER could be higher in patients with visceral metastases than in patients with non-visceral metastases.
- Bone-only metastases (12.9 months for everolimus plus exemestane compared with 5.2 months for exemestane alone). The ERG suggested that the estimated ICER could be lower in patients with 'bone-only metastases' than in the overall population.

  However, the ERG could not complete any exploratory analyses without access to data on overall survival and post-progression survival data for these subgroups.

3.57 In its critique of the additional evidence provided by the manufacturer after consultation, the ERG updated the 'stable disease' utility values to reflect the clinical benefit rates (that is, complete or partial response or stable disease) rather than overall response rates, from the latest cut-off of the BOLERO-2 trial data (that is, a median follow-up of 18 months). This increased the 'stable disease' utility values from 0.7644 to 0.7724 in the everolimus plus exemestane arm and from 0.7571 to 0.7603 in the exemestane alone arm. The ERG stated that the utility value for 'progressed disease' taken from Launois et al. (1997) suggested by the manufacturer in its response to consultation was derived from a small sample size that was not representative of the general UK population. The ERG concluded that its preferred source for the 'progressed disease' utility value remained Lloyd et al. (2006).

3.58 The ERG commented that, of the 4 post-progression chemotherapies included by the manufacturer in its revised cost-effectiveness analyses, only the dose level for vinorelbine was calculated based on the mean body surface area or mean body weight of the BOLERO-2 population. It stated this approach tends to underestimate treatment acquisition costs and does not allow for wastage. The ERG also noted that the unit costs used by the manufacturer did not reflect the

prices available for different sized vials or tablet packs, and that the cost of capecitabine did not include docetaxel as stated in its summary of product characteristics. The ERG was concerned that the manufacturer's approach did not represent the true lifetime cost of post-progression chemotherapy. The ERG explained that, up to the point when the trial stopped, the longer the patient remained in the pre-progression health state, the shorter the time spent in the post-progression health state. Therefore, the ERG suggested that it is reasonable to expect that a higher proportion of patients in the exemestane alone arm would have received post-progression therapies at a median follow-up of 7 months (see section 3.39). The ERG suggested that the probability of receiving post-progression therapies may not significantly differ between the 2 trial arms. The ERG considered that the post-progression cost amendment to the model was not well-founded.

3.59 In its critique of the additional evidence provided by the manufacturer after consultation, the ERG identified and corrected an error in its own exploratory piecewise exponential modelling of progression-free survival and overall survival in the exemestane alone arm. In its critique of the manufacturer's original submission, the ERG's (preferred) piecewise exponential modelling of overall survival assumed that both treatment arms were subject to the same mortality risk when in the 'progressed disease' health state ('parallel exponential model'). The ERG commented that similar linear trend coefficients observed in the post-progression phase of the BOLERO-2 trial supported the parallel modelling. The ERG also presented an alternative exploratory model of overall survival that relaxed the assumption of parallel-hazards, which assumed that everolimus plus exemestane provides a small continued survival gain once treatment is stopped compared with exemestane alone ('non-parallel exponential model').

3.60 The ERG presented revised ICERs comparing everolimus plus exemestane and exemestane alone, which:

- combined 7 of its exploratory analyses (see sections 3.46 to 3.51); and updated the utility value for the 'stable disease' health state (see section 3.57)
- corrected piecewise exponential modelling of progression-free survival (based on local assessment)

- incorporated the patient access scheme for everolimus.

Using the corrected 'parallel exponential model' of overall survival, the ERG estimated incremental costs of £16,127 and 0.155 incremental QALYs gained with a pairwise ICER of £104,100 per QALY gained. It estimated the incremental survival in the 'parallel exponential model' to be 1.4 months. Using the 'non-parallel exponential' model of overall survival, the ERG estimated an incremental survival of 4.6 months, incremental costs of £18,278 and 0.269 incremental QALYs gained with a pairwise ICER of £67,909 per QALY gained.

3.61 Full details of all the evidence are in the manufacturer's submission and the ERG report, which are available from www.nice.org.uk/guidance/TA295

4 Consideration of the evidence

4.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of everolimus plus exemestane, having considered evidence on the nature of locally advanced or metastatic human epidermal growth factor receptor 2 (HER2) negative hormone-receptor-positive breast cancer after endocrine therapy and the value placed on the benefits of everolimus plus exemestane by people with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.

4.2 The Committee considered the views of the patient expert on their experience of everolimus as a treatment for advanced breast cancer. It heard from the patient expert that patients would value everolimus plus exemestane as a treatment option because it is offered when limited treatment options exist after a woman's disease becomes resistant to endocrine therapy, and because everolimus plus exemestane may delay the need for chemotherapy and its associated toxicity. The Committee also heard from the patient expert that patients value increased survival and improved quality of life. The Committee was aware of comments from consultees that everolimus is considered to be the 'biggest development in years for treating breast cancer' and also that 'length of life is only worth having if there is a quality of life as well'. The Committee recognised the importance of having a range of treatment options for postmenopausal women with locally advanced or metastatic breast cancer.

4.3 The Committee considered the marketing authorisation, which specifies that everolimus can be used for 'postmenopausal women without symptomatic visceral disease after recurrence or progression following a non-steroidal aromatase inhibitor'. The Committee noted that patients in the BOLERO-2 trial may have had visceral disease, but that it was unclear whether these patients were also symptomatic. The Committee heard from the clinical specialists that patients with visceral disease may or may not have symptoms but that, for patients with life-threatening symptomatic visceral disease, chemotherapy is the preferred treatment option, usually with an anthracycline-containing regimen (doxorubicin or epirubicin) or a taxane. The Committee understood that, in accordance with the marketing authorisation, everolimus was not being appraised for patients with symptomatic visceral disease.

4.4 The Committee considered the likely position of everolimus plus exemestane in the treatment pathway for women with locally advanced or metastatic HER2-negative hormone-receptor-positive breast cancer. The Committee heard from the clinical specialists that, in general, clinical practice reflects the recommendations in Advanced breast cancer: diagnosis and treatment (NICE clinical guideline 81), but that patients whose disease progresses after a non-steroidal aromatase inhibitor (such as anastrozole or letrozole) are often offered further endocrine treatments rather than chemotherapy. The clinical specialists confirmed that everolimus plus exemestane would be offered to patients whose disease has progressed on a non-steroidal aromatase inhibitor at a point when a patient might otherwise receive either further endocrine therapy or chemotherapy.

4.5 The Committee considered the chemotherapy treatments that the manufacturer had included as comparators in its submission. It understood that the scope listed 'chemotherapy in accordance with NICE guidance' and that the manufacturer had included comparisons with docetaxel, doxorubicin and capecitabine, and after consultation, vinorelbine. The Committee heard from the clinical specialists that the most relevant chemotherapeutic comparators for everolimus plus exemestane are likely to be capecitabine and vinorelbine because anthracyclines (doxorubicin) and taxanes (docetaxel) are generally used to treat patients with metastatic breast cancer who have symptomatic and life-threatening visceral disease (see section 4.3). The Committee concluded that, of the chemotherapies, the comparison of everolimus plus exemestane with capecitabine was the most relevant for the population in the appraisal, and that a comparison with vinorelbine was also appropriate.

4.6 The Committee then discussed the endocrine treatments included as comparators by the manufacturer. It heard from the clinical specialists that, although fulvestrant is available through the Cancer Drugs Fund, NICE has not recommended it. The Committee did not hear any evidence that fulvestrant can be considered routine practice when non-steroidal aromatase inhibitors have failed. The clinical specialists stated that tamoxifen and exemestane (alone) were appropriate comparators for everolimus plus exemestane, although tamoxifen is often offered after exemestane. Also, the Committee understood from the clinical specialists that, although exemestane is used, there are concerns that it is not effective in the population considered in this appraisal because the disease will have already progressed on a non-steroidal aromatase

inhibitor. The Committee noted that this concern was acknowledged by the European Medicines Agency in the European Public Assessment Report, which stated that patients in the exemestane arm of the BOLERO-2 trial may have received suboptimal treatment. On this basis, the European Medicines Agency requested that the manufacturer complete a trial comparing everolimus plus exemestane with everolimus alone and with capecitabine alone. Despite these issues, the Committee concluded that exemestane alone was the most relevant endocrine comparator for everolimus plus exemestane for the purpose of this appraisal.

Clinical effectiveness

4.7 The Committee discussed the data on clinical effectiveness from the BOLERO-2 trial. It heard from the clinical specialists that the trial population represented patients who would be offered everolimus in the UK. The Committee understood from the trial publication and from the statistical analysis plan of the trial that the primary end point of the trial was progression-free survival based on radiographic assessment by local investigators, and that central assessment by an independent radiology committee was used in supportive analyses. However, in its submission, and at the Committee meeting, the manufacturer stated that the primary end point was progression-free survival based both on local and central radiological assessment. The Committee noted that the manufacturer's statistical analysis plan stated that the primary end point of BOLERO-2 was amended to local assessment from central assessment 5 months after the original protocol was approved. The manufacturer explained that this protocol amendment was implemented after approximately 100 events, but could not provide the reasons for the change. The Committee was aware that median progression-free survival was longer (both relatively and absolutely) when estimated using central rather than local assessment (see section 3.5) and that the manufacturer had chosen to use centrally assessed estimates of progression-free survival in its economic model. The Committee heard from the manufacturer that central assessment was associated with fewer biases. However, it was aware that women in the UK who would receive everolimus plus exemestane would have progression assessed locally, not centrally. The manufacturer agreed with the Committee that disease progression would be assessed locally in routine clinical practice. The Committee was aware that, ideally, trials give unbiased estimates of relative treatment effects, but that biases with central assessment may have existed in

this particular trial. The Committee agreed that it was important to consider in detail the different approaches related to, and issues around, local and central assessment.

4.8 The Committee then discussed the approaches to analysing the BOLERO-2 trial data when assessed locally or centrally. It was aware that the trial protocol stipulated that, once a patient's disease was assessed locally as having progressed, study treatment would have stopped (and the patient may have gone on to other treatments), whether or not the central radiological committee had considered the disease to have progressed. The Committee heard from the manufacturer that the analysis followed the statistical analysis plan, that patients deemed to have progressed only by local assessment were censored in Kaplan–Meier analyses based on central assessment, and that the manufacturer's statistical analysis plan acknowledged the potential for informative censoring when the analysis was based on central review. The Committee understood that censoring occurs in a trial when the event of interest, in this case, disease progression, is not observed during the follow-up. It appreciated that censoring in some circumstances can be 'informative', that is, patients censored for one reason are more likely to experience progression of their disease than patients censored for another reason. The censoring in the analysis based on central assessment may have been informative because these patients would plausibly fare more poorly (given that they had disease severe enough for the local radiologists to have deemed their disease to have progressed) than would patients censored by other means. The Committee heard from the Evidence Review Group (ERG) that informative censoring may have biased the treatment effect because it violates the statistical assumption that censoring is random and therefore unrelated to prognosis. The ERG noted that this is of greater concern in unblinded trials, but the Committee was also aware of the analysis provided by the ERG that concluded there was no evidence to suggest that local investigators acted in a way to suggest that unblinding occurred in the BOLERO-2 trial (see section 3.38). The Committee was also aware of analyses presented by the manufacturer after consultation, in which patients randomised to everolimus and censored by central review were instead 'imputed' to have progressed which, according to the manufacturer, did not reveal informative censoring. However, the Committee noted that these sensitivity analyses resulted in a hazard ratio of 0.55, reflecting a smaller treatment effect compared with when effectiveness was addressed centrally (0.36) or locally (0.43). The ERG explained to the Committee that it could not

verify the sensitivity analysis described by the manufacturer without access to the Kaplan–Meier analyses requested at the clarification stage. It concluded that, as a means to avoid informative censoring, local assessment without risk of informative censoring was superior to central assessment with imputed data. In addition, the Committee was aware of a meta-analysis by Amit et al. (2011), which showed that local evaluation provides a reliable measure of treatment effect when compared with central assessment, even when trials are unblinded. The Committee concluded that it was more appropriate to use effectiveness data derived from local assessment in the modelling than from central assessment because local assessment represented the primary end point of the trial, reflected clinical practice and minimised the potential for bias from informative censoring. Overall, the Committee concluded that everolimus plus exemestane is effective in prolonging progression-free survival compared with exemestane alone.

4.9 The Committee considered the results for overall survival in the BOLERO-2 trial and that the median overall survival had not yet been reached. It therefore agreed that the immaturity of the data resulted in considerable uncertainty associated with the longer-term benefits of everolimus plus exemestane.

4.10 The Committee considered the safety data from the BOLERO-2 trial, which showed that patients receiving everolimus plus exemestane experienced more adverse reactions, specifically stomatitis and anaemia, than patients receiving exemestane alone. The Committee heard from the clinical specialists that, although everolimus can lead to several different adverse reactions, it is generally well tolerated. The clinical specialists noted that, because everolimus was associated with pneumonitis, it was likely that patients would need additional monitoring. The Committee heard from the patient expert that people vary in their willingness to accept the risks of treatment with chemotherapy because it can significantly worsen a patient's health-related quality of life, and highlighted the importance of providing information on treatments to patients.

4.11 The Committee discussed the results of the indirect treatment comparison that estimates the clinical effectiveness of everolimus plus exemestane compared with fulvestrant. It heard from the ERG that it should regard the results with caution (see section 3.41). The Committee was aware that the manufacturer's indirect treatment comparison included studies that may have assessed

progression-free survival locally (which differed from the manufacturer's preference for central assessment for everolimus plus exemestane), and that the estimated incremental cost-effectiveness ratio (ICER) of everolimus plus exemestane compared with fulvestrant was dependent on the results of the indirect treatment comparison. The Committee noted its previous conclusion that, because fulvestrant is not used routinely in clinical practice (see section 4.6), and is not currently recommended by NICE (NICE's appraisal of fulvestrant included a different patient population; Fulvestrant for the treatment of locally advanced or metastatic breast cancer [NICE technology appraisal guidance 239]), it did not consider fulvestrant to be a relevant comparator. The Committee concluded that, for this technology appraisal, the results of the indirect treatment comparison were not key to its decision-making.

4.12 The Committee discussed the manufacturer's approach of using the TAMRAD trial, which compared everolimus plus tamoxifen with tamoxifen alone, to inform a comparison of everolimus plus exemestane with tamoxifen alone. The Committee understood from the manufacturer that it used the hazard ratios from the TAMRAD trial in its economic model and assumed that the hazard ratios for everolimus plus exemestane compared with tamoxifen alone would be the same as those for everolimus plus tamoxifen compared with tamoxifen alone. The clinical specialists noted that they could not ascertain whether the assumption was valid because exemestane and tamoxifen have different mechanisms of action. The Committee concluded that there was considerable uncertainty about the validity of the comparison of everolimus plus exemestane with tamoxifen, and that therefore no conclusions were possible on the effectiveness of everolimus plus exemestane compared with tamoxifen.

4.13 The Committee considered the results of the naive chained indirect analysis, which estimated the clinical effectiveness of everolimus plus exemestane compared with chemotherapy. It heard from the ERG that it had several concerns about the methodology associated with this analysis, which relied on untested assumptions and on a systematic review (Wilcken et al. 2003) that included studies that no longer reflect clinical practice (see section 3.42). The clinical specialists agreed that the studies in the systematic review reflect outdated clinical practice, but also stated there was little evidence comparing endocrine therapies with chemotherapies. Indeed, the ERG had not identified any evidence that would have allowed the manufacturer to have completed a more appropriate analysis. The Committee concluded that it was not possible to

make robust comparisons between everolimus plus exemestane and chemotherapies based on the available evidence, and that it was therefore not possible to separately develop recommendations for everolimus plus exemestane compared with chemotherapy.

Cost effectiveness

4.14 The Committee considered the manufacturer's economic model and the ERG's critique of the manufacturer's comparison of everolimus plus exemestane and exemestane alone. Firstly, it discussed the manufacturer's economic model and the manufacturer's choice of a Weibull function to extrapolate overall survival data from the BOLERO-2 trial. It noted that the Weibull function did not provide the best statistical fit, but heard from the manufacturer that its clinical advisers suggested that the Weibull function estimated the proportion of patients alive over time more accurately than the other functions explored. The Committee was aware that numerous uncertainties existed regarding extrapolating survival beyond the end of the BOLERO-2 trial, for example, that few patients died during the median 18-month follow-up of the BOLERO-2 trial, making data sparse, and whether mortality rates would plausibly differ after treatment stops between postmenopausal women who were or were not previously treated with everolimus. The Committee concluded that statistical fit is only one way to choose a parametric function, and that how well a curve fits the natural history of locally advanced and metastatic breast cancer treated with standard treatment would also be important, particularly when overall survival data are immature.

4.15 The Committee discussed whether it was appropriate for the manufacturer to adjust overall survival with a factor it took from Beauchemin et al. (2012) to address the anomalous result when estimating the number of women in the 'progressed disease' health state from the progression-free survival and overall survival data (see section 3.20), and whether it was appropriate to apply this adjustment only to people treated with everolimus plus exemestane. The Committee heard from the ERG that this adjustment increased the length of overall survival in the everolimus plus exemestane arm of the economic model by 17%. The manufacturer clarified that it took the factor from a conference poster, which it considered to the most up-to-date source of evidence. The Committee understood that the most recent evidence was not necessarily the most robust, and that other studies exist and had been reviewed by the NICE

Decision Support Unit (A review of studies examining the relationship between progression-free survival and overall survival in advanced or metastatic cancer). Furthermore, the Committee concluded that it was not reasonable for the manufacturer to apply this adjustment factor only to the everolimus plus exemestane arm of the economic model, and that the anomalous result for post-progression survival showed that the manufacturer had either used the wrong parametric model or had applied the functions incorrectly in the model. The Committee noted that the manufacturer had removed the adjustment in the additional analyses it provided after consultation.

4.16 The Committee noted that the manufacturer had originally applied a background mortality rate (age-related mortality) after 4 years in the economic model. It heard from the ERG (see section 3.51) that this double counted deaths from causes other than locally advanced or metastatic breast cancer because these were observed in the BOLERO-2 trial. The Committee concluded that it was not appropriate for the manufacturer to model additional background mortality and noted that this was removed in the additional analyses provided by the manufacturer after consultation.

4.17 The Committee discussed the implications of using local or central assessment for progression-free survival in the modelling (see section 3.27). It would expect progression-free survival from the economic model and the trial to be similar, but noted that the centrally assessed mean progression-free survival with everolimus plus exemestane was 3.8 months longer than that observed in the BOLERO-2 trial, whereas progression-free survival for exemestane alone was only 0.5 months longer in the economic model than in the trial. The Committee noted that this indicated that the economic model did not reflect the patient population in the BOLERO-2 trial. Furthermore, the Committee noted that the estimates for locally assessed progression-free survival were similar between the economic model and the trial. The Committee concluded that the manufacturer's economic model based on centrally assessed progression-free survival is unlikely to provide a robust basis for calculating a valid estimate of cost effectiveness.

4.18 The Committee discussed the ERG's exploratory survival analyses. The ERG chose a 'piecewise approach' because the mortality risk associated with advanced breast cancer is likely to be different before progression than it is after progression when a treatment has stopped. The Committee understood

from the ERG that the manufacturer did not provide the post-progression survival data that it requested and therefore the ERG could not assess whether everolimus prolongs survival after disease progression. The Committee agreed that fitting multiple parametric curves to the overall survival data may be appropriate when there is a high degree of uncertainty associated with estimating the survival gain from immature data. However, the Committee could not be confident that this markedly diminished the uncertainty inherent in the data. It noted the ERG's observation that mortality rates were similar in both treatment arms after approximately 10 months, and so the ERG fitted an exponential model that assumed parallel long-term hazard trends and, after consultation, an alternative scenario that assumed everolimus plus exemestane provides a survival benefit compared with exemestane alone (that is, the 'non-parallel exponential model'). The Committee heard from the ERG that it was unable to assess the goodness of fit of the exploratory survival analyses because the manufacturer did not provide access to the patient-level data. It agreed that the manufacturer's estimated 10.5 months' survival benefit with the Weibull analysis was likely to be optimistic, and that the estimated 1.4 months' survival benefit with the ERG's exploratory parallel exponential model was likely to be pessimistic. The Committee acknowledged that the overall survival benefit of everolimus plus exemestane is uncertain but probably lies between these estimates, as seen in the overall survival benefit from the ERG's non-parallel exponential model (4.6 months), which reflects the longer progression-free survival with everolimus plus exemestane compared with exemestane alone. The Committee agreed to use the ERG's exploratory non-parallel exponential survival analyses in its deliberations.

4.19 The Committee discussed the utility values for the 'stable disease' health state used by the manufacturer in its economic model. It noted that, in its original submission, the manufacturer had chosen utility values (taken from Lloyd et al. 2006) for the health states that were not estimated in line with the NICE reference case because it used vignettes to describe the health states and the standard gamble technique to estimate the utility values. The Committee was aware that these utility values had been used by other manufacturers in a previous appraisal of breast cancer (Fulvestrant for the treatment of locally advanced or metastatic breast cancer [NICE technology appraisal guidance 239]). The ERG noted that the manufacturer had incorrectly calculated the utility estimate for 'stable disease' in its original submission because it had not calculated utility separately for each treatment. The Committee understood

that correcting this had a small impact on the ICER. It understood that the manufacturer had measured health-related quality of life using a disease-specific instrument, but made no attempt to map this to the preferred generic EQ-5D instrument, despite several algorithms being available. It heard from the manufacturer that this was because the BOLERO-2 trial evaluated health-related quality of life only until disease progressed. The Committee acknowledged this limitation, but concluded that it would have been appropriate for the manufacturer to present estimates for the 'stable disease' health state from the BOLERO-2 trial alongside its base-case analysis.

4.20 In its meeting after consultation, the Committee discussed the alternative utility value from Launois et al. (1997) included by the manufacturer for the 'progressed disease' health state (see section 3.24). The Committee heard from the manufacturer that it had increased the utility value for 'progressed disease' after deliberations with the Scottish Medicines Consortium. The manufacturer explained that Launois et al. (1997) was the only publication relevant to advanced breast cancer that it could find. The Committee discussed the anomalous finding in Launois et al. (1997), which showed a lower quality of life for 'early progression' compared with 'progression'. It heard from the clinical specialists that this was unlikely to reflect reality. The Committee further discussed whether it is more valid to assume a decrease in utility from stable to progressed disease of approximately 0.28 (if using Lloyd et al. 2006) or approximately 0.12 (if using Launois et al. 1997). The patient expert commented that they were unable to approximate the decrease in quality of life resulting from disease progression in patients with advanced breast cancer. The Committee stated that the estimates for quality of life for the 'progressed disease' from both Lloyd et al. (2006) and Launois et al. (1997) relied on the descriptions used for the vignettes in the studies but the manufacturer could not provide information on how the vignettes had been described. The Committee heard from the ERG that Lloyd et al. (2006) better reflected NICE's Guide to the methods of technology appraisal (2008), in that it used valuations from the UK general public, than did Launois et al. (1997), which surveyed French nurses. The Committee concluded that neither valuation of utility for the 'progressed disease' health state was without uncertainty, but that the data from Lloyd et al. (2006) were more appropriate than the data from Launois et al. (1997).

4.21 The Committee discussed whether the manufacturer provided valid cost inputs for the 'stable' and 'progressed' health states in its economic model. It was aware that the manufacturer may have used drug costs of chemotherapy (particularly docetaxel) that were higher than the costs in the NHS, achieved through national agreements. The Committee agreed with the ERG's decision to adjust the time on treatment to reflect the longer follow-up period of the BOLERO-2 trial, and to include costs for a quarterly appointment to assess whether patients with stable disease had progressed. The Committee was aware that these exploratory analyses decreased and increased the base-case ICER respectively. It noted that the univariate sensitivity analysis included in the manufacturer's economic model (although not presented in its written submission) showed that the ICERs were sensitive to the costs for the 'progressed disease' health state but that this did not include costs associated with subsequent therapies (namely, chemotherapy). After consultation, the manufacturer included the costs associated with subsequent therapies in its economic model. It heard from the ERG that there is no evidence to suggest the probability of receiving subsequent therapies after disease progression differed significantly between treatment arms (see section 3.58). The Committee concluded that the inclusion of costs associated with subsequent therapies would have a small impact on the estimation of the ICER.

4.22 The Committee discussed whether it was appropriate to include costs and disutilities associated with adverse events in the model, noting that the manufacturer had included adverse events in its analyses of everolimus plus exemestane compared with chemotherapies, but not when compared with endocrine therapies. The Committee heard from the clinical specialists that mild adverse events would not lead to a break from treatment, but that patients may need other medicines (for example, mouthwash for stomatitis). The clinical specialists noted that patients who experience grade 3 or 4 adverse events would need a temporary break in treatment and that the cost of pneumonitis appeared to be underestimated in the manufacturer's model with respect both to diagnosis and treatment. Having previously concluded that, given the side effect profile of everolimus, costs and disutilities associated with adverse events should be included for each of the comparisons in its economic model, the Committee noted that the manufacturer included them in the additional analyses it provided after consultation.

4.23 The Committee discussed the most plausible ICER, noting that a robust comparison was available only for everolimus plus exemestane compared with exemestane alone. It agreed that the most plausible ICER should be based on an analysis using the following assumptions: using exponential functions to estimate progression-free survival and the non-parallel model of overall survival; omitting the adjustment factor from Beauchemin et al. (2012); using locally assessed trial data; including adverse reactions; using rates of adverse reactions as documented in the European Public Assessment Report; recalculating time on treatment; including costs of monitoring disease that has not progressed; correcting discounting and utility values for stable disease; using the utility value for 'progressed disease' from Lloyd et al. (2006); and omitting extra mortality from non-cancer causes. The Committee noted that the ICER was most sensitive to the modelling of overall survival and the progression-free survival assessment method. The Committee concluded that the ERG's estimate of the ICER (including the patient access scheme for everolimus) of £68,000 per quality-adjusted life year (QALY) gained for everolimus plus exemestane compared with exemestane alone was more plausible than the manufacturer's base-case estimate. The Committee concluded that everolimus (plus exemestane) could not be considered a cost-effective use of NHS resources for the treatment of locally advanced or metastatic HER2-negative hormone-receptor-positive breast cancer, after recurrence or progression following a non-steroidal aromatase inhibitor.

4.24 The Committee discussed the innovative nature of everolimus and whether the economic analysis had captured all changes in health-related quality of life. In its submission, the manufacturer stated that everolimus was innovative because it is administered orally, may slow the rate of disease progression in the bone, increases productivity and reduces healthcare-resource use when compared with chemotherapy. The Committee noted that a number of the comparator treatments are also administered orally, that bone markers were only an exploratory end point in the BOLERO-2 trial, and that gains in productivity were currently outside of the NICE reference case. The Committee considered that differences in the use of healthcare resource are expected to be adequately captured in the manufacturer's economic model. Although the Committee acknowledged that the mechanism of action of everolimus may offer a step change in treatment by restoring sensitivity of the tumour to endocrine therapy, it concluded that the manufacturer had not submitted convincing evidence that everolimus (plus exemestane) provides health-related quality-of-life benefits

exceeding that calculated in the QALY, as defined in NICE's Guide to the methods of technology appraisal (2008). The Committee concluded that the case for innovation made by the manufacturer did not change the Committee's conclusions about the cost effectiveness of everolimus plus exemestane.

4.25 The Committee considered supplementary advice from NICE, which should be taken into account when appraising treatments that may extend the life of patients with a short life expectancy and that are licensed for indications that affect small numbers of people with incurable illnesses. For this advice to be applied, all of the following criteria must be met:

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months.
- There is sufficient evidence to show that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment.
- The treatment is licensed or otherwise indicated for small patient populations.

In addition, when taking these criteria into account, the Committee must be persuaded that the estimates of the extension to life are robust and that the assumptions used in the reference case of the economic modelling are plausible, objective and robust.

4.26 The Committee discussed whether everolimus plus exemestane fulfilled the criteria for a life-extending end-of-life treatment. It acknowledged the uncertainty associated with estimated life expectancy but, given that the manufacturer model estimated a mean overall survival of 28.9 months for exemestane alone, the Committee was not convinced that the life expectancy of women to whom everolimus plus exemestane could be offered based on the marketing authorisation was convincingly less than 24 months. The Committee heard from the manufacturer that it chose not to present a case for end-of-life treatment in its original submission because discussions with the clinical specialists identified no clinically plausible subgroups of patients with a life expectancy of less than 24 months. The Committee was aware that the meta-analysis of the SoFEA and EFECT trials provided by the manufacturer during consultation suggested a median survival of 22.6 months in patients with advanced breast cancer treated with exemestane alone. However, the Committee understood that the manufacturer's original submission showed at least a third of the patients in the SoFEA trial had HER2-positive tumours (the

EFECT trial did not report the proportion of patients with HER2-negative tumours), and heard from the clinical specialists that HER2-positive tumours have a worse prognosis, that is, patients with HER2-positive tumours on average die sooner than patients with HER2-negative tumours. The Committee concluded that these 2 trials were not relevant in determining life expectancy in women with HER2-negative tumours, and that everolimus plus exemestane did not convincingly fulfil this criterion for an end-of-life therapy as defined. Having established that everolimus did not meet the short life expectancy criterion, the Committee decided that it was not necessary to make a decision about the extension-to-life or population size criteria. It concluded that, on this basis, everolimus plus exemestane did not fulfil the criteria for being a life-extending, end-of-life treatment.

4.27 The Committee discussed whether subgroups existed in which everolimus plus exemestane offered a cost-effective use of NHS resources. The ERG had identified 3 subgroups (see section 3.56). The Committee noted that, although the statistical analysis plan of the trial included no plans to test for interaction, the manufacturer had stated that it had not identified any statistically significant differences in progression-free survival between subgroups. The Committee heard from the ERG that it believed these subgroups may be relevant because, even though the relative effectiveness of everolimus plus exemestane might be similar across subgroups, differences in baseline risk could improve the cost effectiveness. The Committee noted that the ERG had been unable to quantify the effect on the ICER of the different subgroups. The Committee was also aware that the efficacy analyses in subgroups performed by the manufacturer were purely exploratory and intended to explore the uniformity of any overall treatment effects, and that the manufacturer had not included any cost-effectiveness analyses for subgroups in its original or revised submission. The Committee concluded that the available evidence did not allow it to make any recommendations specific to subgroups of patients.

Summary of Appraisal Committee's key conclusions

TA295	Appraisal title: Everolimus in combination with exemestane for treating advanced HER2-negative hormone-receptor-positive breast cancer after endocrine therapy	Section
Key conclusion		

Everolimus, in combination with exemestane, is not recommended within its marketing authorisation for treating postmenopausal women with advanced human epidermal growth factor receptor 2 (HER2) negative hormone receptor positive breast cancer that has recurred or progressed following treatment with a non-steroidal aromatase inhibitor.		1.1
With its preferred choice of survival modelling (the ERG's non-parallel exponential model) and progression-free survival measured locally, the Committee concluded that the ERG's estimate of the ICER (including the patient access scheme for everolimus) of £68,000 per QALY gained for everolimus plus exemestane compared with exemestane alone was more plausible than the manufacturer's base-case estimate, and therefore everolimus, in combination with exemestane, could not be considered a cost-effective use of NHS resources.		4.23
Current practice		
Clinical need of patients, including the availability of alternative treatments	The Committee heard from the patient expert that patients would value everolimus as a treatment option because it is offered when limited treatment options exist after a woman's disease becomes resistant to endocrine therapy, and because everolimus may delay the need for chemotherapy and its associated toxicity. The Committee also heard from the patient expert that patients value increased survival and improved quality of life.	4.2
	The Committee heard from clinical specialists that the most relevant chemotherapy comparators for everolimus are likely to be capecitabine and vinorelbine because anthracyclines (doxorubicin) and taxanes (docetaxel) are generally used to treat patients with metastatic breast cancer who have symptomatic and life-threatening visceral disease.	4.5

	The Committee heard from clinical specialists that, although fulvestrant is available through the Cancer Drugs Fund, NICE has not recommended fulvestrant following treatment with tamoxifen. Also, the Committee did not hear any evidence that fulvestrant can be considered routine practice when non-steroidal aromatase inhibitors have failed. The clinical specialists stated that tamoxifen and exemestane (alone) were appropriate comparators for everolimus plus exemestane, although tamoxifen is often offered after exemestane. The Committee concluded that exemestane alone was the most relevant endocrine comparator for everolimus plus exemestane.	4.6
The technology		
Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	The Committee acknowledged that the mechanism of action of everolimus may offer a step change in treatment by restoring sensitivity of the tumour to endocrine therapy.	4.24
What is the position of the treatment in the pathway of care for the condition?	The clinical specialists confirmed that everolimus plus exemestane would be offered to patients whose disease has progressed on a non-steroidal aromatase inhibitor at a point when a patient might receive either further endocrine therapy or chemotherapy.	4.4
Adverse reactions	The Committee noted that the BOLERO-2 trial showed that patients receiving everolimus plus exemestane experienced more adverse reactions, specifically stomatitis and anaemia, than patients receiving exemestane alone. However, the Committee heard that everolimus is generally well tolerated.	4.10
Evidence for clinical effectiveness		

Availability, nature and quality of evidence	The Committee concluded that the indirect treatment comparison that estimated the clinical effectiveness of everolimus plus exemestane compared with fulvestrant should be regarded with caution.	4.11
	The Committee noted that the TAMRAD trial did not compare everolimus within its licensed indication (that is, in combination with exemestane) with tamoxifen. The Committee noted that no conclusions on the effectiveness of everolimus plus exemestane compared with tamoxifen were possible.	4.12
	The Committee concluded that the 'naive chained indirect analysis', which estimated the clinical effectiveness of everolimus plus exemestane compared with chemotherapy relied on untested assumptions and on a systematic review that included studies that no longer reflect clinical practice	4.13
Relevance to general clinical practice in the NHS	The Committee heard from the clinical specialists that the BOLERO-2 trial population represented patients who would be offered everolimus plus exemestane in the UK.	4.7
Uncertainties generated by the evidence	The Committee agreed that the immaturity of the overall survival data from the BOLERO-2 trial generated considerable uncertainty associated with the longer-term benefits of everolimus plus exemestane.	4.9
	The Committee concluded that there was considerable uncertainty about the validity of the comparison of everolimus plus exemestane with tamoxifen, but noted its previous conclusions that, of the endocrine therapies, the comparison of everolimus plus exemestane with exemestane alone was the most relevant to the appraisal.	4.12
	The Committee concluded that it was not possible to make robust comparisons between everolimus plus exemestane and chemotherapies based on the available evidence.	4.13

Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	The Committee noted that, although the manufacturer included no plans to test for interaction in its statistical analysis plan, it had stated that it had not identified any statistically significant differences in progression-free survival between subgroups.	4.27
Estimate of the size of the clinical effectiveness including strength of supporting evidence	The Committee concluded that everolimus plus exemestane is effective in prolonging progression-free survival compared with exemestane alone.	4.8
	The Committee agreed that the immaturity of the overall survival data resulted in considerable uncertainty associated with the longer-term benefits of everolimus plus exemestane.	4.9
Evidence for cost effectiveness		
Availability and nature of evidence	The Committee considered the manufacturer's economic model and the ERG's critique of the manufacturer's comparison of everolimus plus exemestane and exemestane alone.	4.14
	The Committee noted that the ICERs were most sensitive to the modelling of overall survival and progression-free survival assessment method.	4.23
Uncertainties around and plausibility of assumptions and inputs in the economic model	The Committee agreed that the most plausible ICER should be based on an analysis using the following assumptions: using exponential functions to estimate progression-free survival and the non-parallel model of overall survival; omitting the adjustment factor from Beauchemin et al. (2012); using locally assessed trial data; including adverse reactions; using rates of adverse reactions as documented in the European Public Assessment Report; recalculating time on treatment; including costs of monitoring disease that has not progressed; correcting discounting and utility values for stable disease; using the utility value for 'progressed disease' from Lloyd et al. (2006); and omitting extra mortality from non-cancer causes.	4.23

Incorporation of health-related quality-of-life benefits and utility values Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?	The Committee concluded that neither valuation of utility for the 'progressed disease' health state was without uncertainty, but that the data from Lloyd et al. (2006) were more appropriate than the data from Launois et al. (1997).	4.20
	Although the Committee acknowledged that the mechanism of action of everolimus may offer a step change in treatment by restoring sensitivity of the tumour to endocrine therapy, it concluded that the manufacturer had not submitted convincing evidence that everolimus (plus exemestane) provides health-related quality-of-life benefits exceeding that calculated in the QALY.	4.24
Are there specific groups of people for whom the technology is particularly cost effective?	The Committee concluded that the available evidence did not allow it to make any recommendations specific to subgroups of patients.	4.27
What are the key drivers of cost effectiveness?	Using local or central assessment for progression-free survival in the modelling: The Committee concluded that it was more appropriate to use effectiveness data derived from local assessment in the modelling than from central assessment because local assessment represented the primary end point of the trial, reflected clinical practice and minimised the potential for bias from informative censoring.	4.8 4.17

	Choice of survival modelling: The Committee agreed that the manufacturer's estimated 10.5 months' survival benefit with the Weibull analysis was likely to be optimistic, and that the estimated 1.4 months' survival benefit with the ERG's exploratory parallel exponential model was likely to be pessimistic. It acknowledged that the overall survival benefit of everolimus plus exemestane is uncertain but probably lies between these estimates. The Committee noted that it is also similar to the overall survival benefit from the ERG's non parallel exponential model (4.6 months), which reflects the longer progression-free survival with everolimus plus exemestane than with exemestane alone.	4.18
Most likely cost-effectiveness estimate (given as an ICER)	The Committee concluded that the ERG's estimate of the ICER (including the patient access scheme for everolimus) of £68,000 per QALY gained for everolimus plus exemestane compared with exemestane alone was more plausible than the manufacturer's base-case estimate.	4.23
Additional factors taken into account		
Patient access schemes (PPRS)	The manufacturer of everolimus has agreed a patient access scheme with the Department of Health, in which the first month of treatment with everolimus is free (including the option to offer the 5 mg tablet pack if there is a need to reduce the dose). The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.	2.3
End-of-life considerations	The Committee acknowledged the uncertainty associated with estimated life expectancy but, given that the manufacturer's model estimated a mean overall survival of 28.9 months for exemestane alone, the Committee was not convinced that the life expectancy of women to whom everolimus plus exemestane would be offered was convincingly less than 24 months. The Committee therefore concluded that everolimus plus exemestane did not fulfil the criteria for an end-of-life therapy.	4.25 4.26

Equalities considerations and social value judgements	The only potential issue raised was that everolimus should be available to male patients. However, the UK marketing authorisation includes only postmenopausal women and therefore this issue could not be addressed within the remit of this NICE technology appraisal.	n/a

5 Implementation

5.1 NICE has developed a costing statement explaining the resource impact of this guidance.

6 Related NICE guidance

Details are correct at the time of publication. Further information is available on the NICE website.

Published

- Fulvestrant for the treatment of locally advanced or metastatic breast cancer. NICE technology appraisal guidance 239 (2011).
- Breast cancer (advanced): diagnosis and treatment. NICE clinical guideline 81 (2009).

NICE Pathways

- NICE has developed a pathway on advanced breast cancer.

7 Review of guidance

7.1 The guidance on this technology will be considered for review in June 2016. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Andrew Dillon
Chief Executive
August 2013

8 Appraisal Committee members, guideline representatives and NICE project team

8.1 Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Dr Amanda Adler (Chair)
Consultant Physician, Addenbrooke's Hospital

Professor Ken Stein (Vice Chair)
Professor of Public Health, Peninsula Technology Assessment Group (PenTAG), University of Exeter

Dr Ray Armstrong
Consultant Rheumatologist, Southampton General Hospital

Dr Jeff Aronson
Reader in Clinical Pharmacology, University Department of Primary Health Care, University of Oxford

Professor John Cairns
Professor of Health Economics Public Health and Policy, London School of Hygiene and Tropical Medicine

David Chandler
Lay Member

Mark Chapman
Health Economics and Market Access Manager, Medtronic UK

Professor Fergus Gleeson
Consultant Radiologist, Churchill Hospital, Oxford

Robert Hinchliffe
HEFCE Clinical Senior Lecturer in Vascular Surgery and Honorary Consultant Vascular Surgeon, St George's Vascular Institute

Professor Daniel Hochhauser
Consultant in Medical Oncology, UCL Cancer Institute

Dr Neil Iosson
General Practitioner

Anne Joshua
Associate Director of Pharmacy, NHS Direct

Dr Rebecca Kearney
Clinical Lecturer, University of Warwick

Terence Lewis
Lay Member

Professor Ruairidh Milne
Director of Strategy and Development and Director for Public Health Research at the National Institute for Health Research (NIHR) Evaluation, Trials and Studies Coordinating Centre at the University of Southampton

Dr Elizabeth Murray
Reader in Primary Care, University College London

Dr Peter Norrie
Principal Lecturer in Nursing, DeMontfort University

Professor Stephen Palmer
Professor of Health Economics, Centre for Health Economics, University of York

Dr Sanjeev Patel
Consultant Physician & Senior Lecturer in Rheumatology, St Helier University Hospital

Dr John Pounsford
Consultant Physician, Frenchay Hospital, Bristol

Dr Danielle Preedy
Lay Member

Cliff Snelling
Lay Member

Marta Soares
Research Fellow, Centre for Health Economics, University of York

Professor Andrew Stevens
Professor of Public Health, Department of Public Health and Epidemiology, University of Birmingham

Dr Nerys Woolacott
Senior Research Fellow, Centre for Health Economics, University of York

Dr Nicky Welton
Senior Lecturer in Biostatistics/Health Technology Assessment, University of Bristol

8.2 NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Martyn Burke
Technical Lead

Zoe Garrett
Technical Adviser

Jeremy Powell
Project Manager

9 Sources of evidence considered by the Committee

A. The Evidence Review Group (ERG) report for this appraisal was prepared by the Liverpool Reviews and Implementation Group:

- Fleeman N, Bagust A et al., Everolimus in combination with an aromatase inhibitor for the treatment of breast cancer after prior endocrine therapy, February 2013

B. The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Organisations listed in I were also invited to make written submissions. Organisations listed in II and III had the opportunity to give their expert views. Organisations listed in I, II and III also have the opportunity to appeal against the final appraisal determination.

I. Manufacturer/sponsor:

- Novartis

II. Professional/specialist and patient/carer groups:

- Breakthrough Breast Cancer
- Breast Cancer Campaign
- Breast Cancer Care
- Cancer Research UK
- Royal College of Nursing
- Royal College of Physicians
- Royal College of Pathologists

III. Other consultees:

- Department of Health
- Welsh Government

IV. Commentator organisations (did not provide written evidence and without the right of appeal):

- Bristol-Myers Squibb
- British National Formulary
- Commissioning Support Appraisals Service
- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland
- Pfizer
- Pierre Fabre
- Roche

C. The following individuals were selected from clinical specialist and patient expert nominations from the consultees and commentators. They gave their expert personal view on everolimus by attending the Committee discussion and providing written evidence to the Committee. They were also invited to comment on the ACD.

- Dr Mark Beresford, Consultant Oncologist, Royal United Hospital, Bath, nominated by the Royal College of Physicians on behalf of the NCRI Breast CSG/RCP/RCR/ACP/JCCO - clinical specialist
- Dr Alistair Ring, Senior Lecturer in Oncology, Brighton and Sussex Medical School, nominated by the Royal College of Physicians on behalf of the NCRI Breast CSG/RCP/RCR/ACP/JCCO - clinical specialist
- Sally Greenbrook, Senior Policy Officer, Breakthrough Breast Cancer, nominated by Breakthrough Breast Cancer – patient expert

D. Representatives from the following manufacturer/sponsor attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Novartis

E. Other sources of evidence considered by the Committee that was not included or considered in the manufacturer's submission or ERG's critique:

- Amit O, Mannino F, Stone AM et al. (2011) Blinded independent central review of progression in cancer clinical trials: Results from a meta-analysis. European Journal of Cancer 47: 1772-8

About this guidance

NICE technology appraisal guidance is about the use of new and existing medicines and treatments in the NHS in England and Wales.

This guidance was developed using the NICE single technology appraisal process.

It has been incorporated into the NICE pathway on advanced breast cancer along with other related guidance and products.

We have produced a summary of this guidance for patients and carers. Tools to help you put the guidance into practice and information about the evidence it is based on are also available.

Your responsibility

This guidance represents the views of NICE and was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.

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