NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Fulvestrant for untreated hormone-receptor positive locally advanced or metastatic breast cancer [ID951]

The following documents are made available to the consultees and commentators:

1. **Company response to ACD by AstraZeneca**
   - Additional submission
   - Supplementary material

2. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - Breast Cancer Now
   - Department of Health – no comment

3. **ERG's report addendum for company additional evidence submission**

4. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

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

Fulvestrant for untreated locally advanced or metastatic oestrogen-receptor positive breast cancer

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Consultation on the appraisal consultation document – deadline for comments 5pm Friday 25 September 2017 on **email:** [insert TACommA@nice.org.uk /NICE DOCS

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	AstraZeneca UK
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	Kevin Lock

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Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	**Section 3.3 – Patient experience** It should be noted that the patient representative described how she had experience of different treatment options (including anastrozole and fulvestrant) and that she *"felt most well or normal when on fulvestrant."* Furthermore, although she acknowledged that the injections could sometimes be painful, she was of the opinion that this discomfort *"was probably related to the competency or training of the nurse involved."* This testimony was also provided in Sections 2, 4 and 5 of the Patient/carer expert statement.
2	**Section 3.3 – Characteristics of eligible patients** It is disappointing that the ACD does not make any reference to the extensive discussion about the types of patient likely to be eligible for treatment in this setting. The clinical expert described in their submission and in the meeting itself that: *"…patients presenting with de novo advanced disease are more likely to be vulnerable patients." (Response to question 7)* *"Many patients presenting with untreated locally advanced or metastatic breast cancer are atypical compared to the early disease patient, older, more frail, more comorbidities, socially, economically deprived or psychologically compromised hence presenting late." (Response to question 23a)*
3	**Section 3.3 – Route of administration** With regards to the route of administration for treatments in this setting, the statement (as reported in the ACD) from the patient expert that *"having a monthly injection may be preferable to daily tablets (such as aromatase inhibitors) for some people."* may suggest that the benefit of fulvestrant is confined to patient preference. It is important to note that there are clear clinical reasons for treating physicians to consider the route of administration of medicines when choosing a treatment regime. These were discussed by the clinical expert during the meeting and in the pre-meeting submission, where he explained that: *"…the population includes some vulnerable patients who may find compliance with daily medicine difficult so supervised monthly IM treatment will aid compliance."* These considerations have not been reflected sufficiently in the current draft recommendations.
4	**Section 3.4 – Influence of study design on reliability of outcomes of FIRST** The Committee noted that FIRST was an open-label study where both investigators and patients were aware of treatment allocation and the observation was made that this could potentially lead to bias. However, this assertion is only true for subjective outcomes (such as patient reported outcomes or physician assessed disease outcomes) which may be influenced by knowledge of the intervention received. There is empirical evidence that the bias in intervention effect estimates in clinical trials, resulting from lack of blinding, varies according to the type of outcome assessed. A combined analysis of data from 3 meta-epidemiological studies containing 146 meta-analyses of 1346 trials measured the ratio of odds ratios quantifying the degree of bias associated with a lack of blinding (Wood, 2007). A ratio of odds ratios <1 implies non-blinded trials exaggerate intervention effect estimates. The bias

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	associated with lack of blinding was greater (interaction P = 0.011) in trials assessing outcomes other than all cause mortality (ratio of odds ratios 0.83 (0.70 to 0.98)) than in those assessing all cause mortality outcomes (1.04 (0.95 to 1.14)). In the case of the FIRST study, certain precautions were taken with the study design to minimise the potential for bias where possible (Robertson 2012). The clinical study team were unaware of the randomisation scheme until the data had been collected and locked for analysis. To prevent biasing the results of the tumour assessments, a blinded independent review was performed by an external radiologist. More supportive evidence will be provided in the Appendix.
5	**Section 3.5 – Dropouts in FIRST study** The Committee state that the PFS/TTP results in FIRST should be interpreted with caution because of the concerns set out in section 3.4 and a high dropout rate (37% (38/102) of patients in fulvestrant arm and 49% (50/103) in the anastrozole arm). It is important to note that the dropout rates quoted included those who had stopped treatment because of disease progression and were measured at the time of the first data cut off (DCO1 – Jan 10, 2008), 6 months after the last patient was randomised. At this time, 29.4% (30/102) of fulvestrant-treated patients had progressed compared with 41.7% (43/103) of those in the anastrozole group and were therefore no longer on study treatment (Robertson 2009). Thus, approximately the same number of patients randomised to treatment in FIRST had stopped treatment for a reason other than disease progression at the time of DCO1 (8 [38-30=8] patients randomised to receive fulvestrant vs 7 [50-43=7] patients receiving anastrozole). At the time of the second data cut off (DCO2 – March 26, 2010), when the PFS/TTP results used in the submission were measured, 14.7% (15/102) of patients in the fulvestrant group and 19.4% (20/103) of patients in the anastrozole group had discontinued study treatment for reasons other than disease progression or death (Robertson, 2012).
6	**Section 3.8 – Risk of breaking randomisation during matching process** The ACD reports that *"The ERG commented that this approach reduced the sample size of the comparator studies and broke randomisation in all studies except for FALCON."* This is inaccurate. The ERG report contains the following comment: *"… the ERG is concerned about potential disadvantages (of the matching process), for example if matching creates scope for bias as randomisation has been broken."(p55 of ERG report version 1)* We do not believe that the matching process led to randomisation being broken. We applied a combination of 2 critical inclusion criteria from FALCON (i.e. endocrine treatment naïve AND ER/PgR+ve status) to each arm of FIRST and NorthAmerica:TARGET, individually. The inclusion criteria applied in the matching analysis were pre-randomisation variables in all the trials included in the network (FALCON, FIRST and NorthAmerica:TARGET); that is, variables that were measured at baseline, before randomisation. It is important to note that a subgroup analysis of endocrine naïve patients in the FIRST study has already been presented for OS (Ellis 2012) and this subgroup is equivalent to the matched subgroup used in the original submission. With regards to NorthAmerica:TARGET, subgroup analysis of the ER/PgR+ve patients has been presented for PFS and OS (Bonneterre 2001 and Nabholtz 2003) – the matched patients in the submission are effectively a further sub-group of this cohort which were endocrine naïve. Sub-dividing the patient population on pre-randomised variables, as we did in the initial submission, does not break randomisation, and any differences in treatment group numbers in the subgroups produced, are obtained by chance (expert opinion from Professor of Biostatistics, Harvard). More evidence supporting this is provided in the Appendix.

Insert extra rows as needed

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- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Fulvestrant for untreated hormone-receptor positive locally advanced or metastatic breast cancer [ID951]

Company additional evidence submission

January 2017

File name	Version	Contains confidential information	Date
AZ Response to ACD [ID951] – Appendix_CiC	1	Yes	25th September 2017

Contents

Tables and figures

1 Appendices

1.1 Influence of study design on reliability of outcomes of FIRST

Estimates of overall survival are unlikely to be biased in open label studies

The Committee expressed a deep concern that the results of the FIRST study were unreliable because it was an open-label study. There are a number of studies which have explored the influence of study design, including blinding, on treatment effects from RCTs (1-3). These have consistently found that there is no evidence that mortality outcomes are influenced by blinding (i.e. no difference in mortality outcomes in studies with inadequate or unclear blinding of participants compared to studies with adequate blinding).

The results of the study by Page et al., for example, which relate to the impact of open-label versus double blind studies are presented in Figure 1 and demonstrate that whilst intervention effects on subjective outcomes may be exaggerated in studies with inadequate blinding, there is little evidence of a statistically significant influence on mortality outcomes (3).

Figure 1: RE meta-analysis of "Ratio of Odds Ratios" associated with lack of/unclear blinding (versus double blinding) (3)

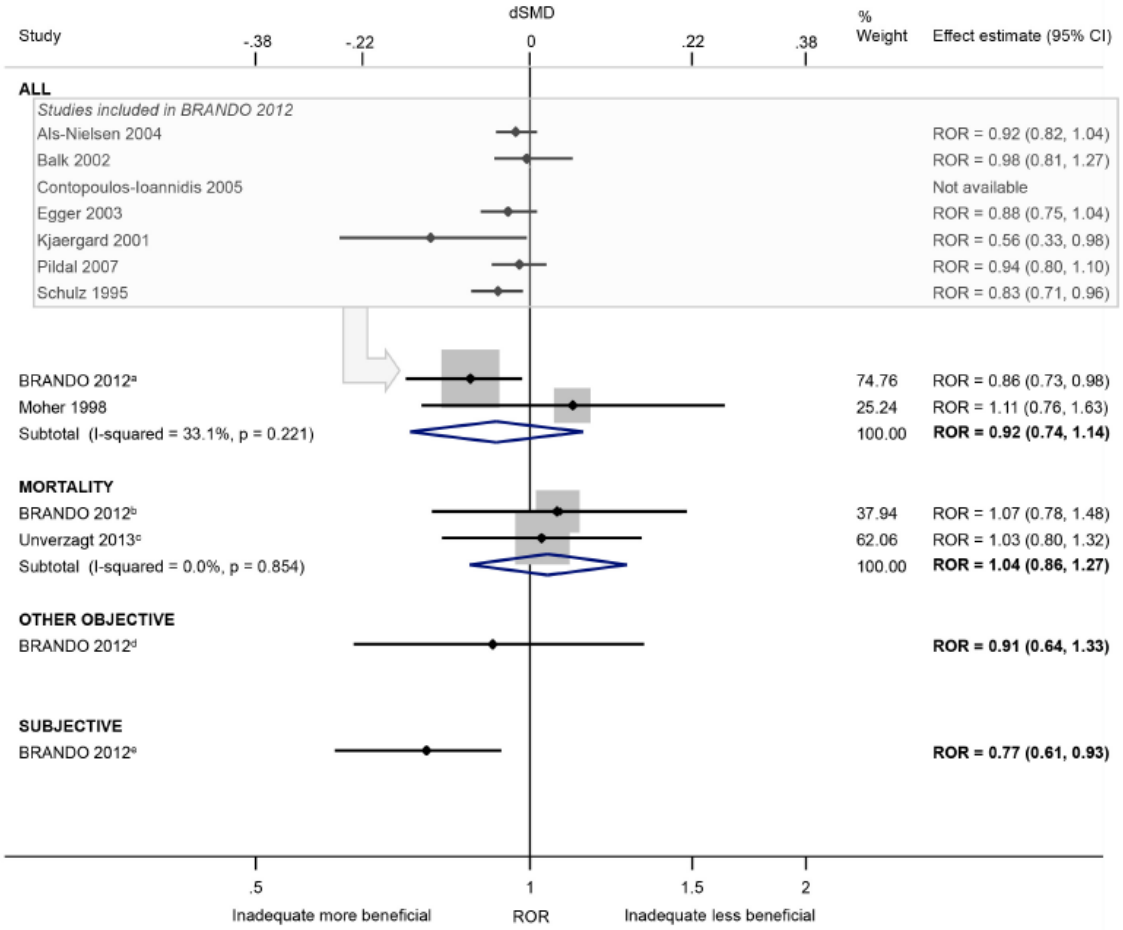


Fig 10. Random-effects meta-analysis of RORs associated with lack of/unclear double blinding (versus double blinding). The boxed section displays the average bias estimates, where available, from the seven meta-epidemiological studies contributing to the BRANDO 2012[a] study (however only the BRANDO 2012[a] ROR was included in our meta-analysis). The BRANDO 2012[a] ROR is based on a multivariable analysis with adjustment for sequence generation and allocation concealment [the corresponding univariable ROR (95% CrI) is 0.87 (0.79, 0.96)]. The BRANDO 2012[b] ROR is based on a multivariable analysis with adjustment for sequence generation and allocation concealment [the corresponding univariable ROR (95% CrI) is 0.92 (0.80, 1.04)]. The Unverzagt 2013[c] ROR is based on a multivariable analysis with adjustment for sequence generation, allocation concealment, attrition, selective outcome reporting, early stopping, pre-intervention, competing interests, baseline imbalance, switching interventions, sufficient follow-up, and single- versus multi-centre status [the corresponding univariable ROR (95% CI) is 0.84 (0.69, 1.02)]. The BRANDO 2012[d] ROR is based on a multivariable analysis with adjustment for sequence generation and allocation concealment [the corresponding univariable ROR (95% CrI) is 0.93 (0.74, 1.18)]. The BRANDO 2012[e] ROR is based on a multivariable analysis with adjustment for sequence generation and allocation concealment [the corresponding univariable ROR (95% CrI) is 0.78 (0.65, 0.92)].

doi:10.1371/journal.pone.0159267.g010

The overall survival estimate in FIRST is legitimate.

In the course of the appraisal meeting, it was suggested that the results of the FIRST study were particularly uncertain because a proportion of the ITT patients had not given consent to participate in the long term follow-up required to inform the overall survival outcome (4).

We have executed a number of sensitivity analyses to explore the hypothesis that these patients may influence the OS estimates for the ITT population. Firstly, it is important to test whether these 35 patients have any differences in baseline characteristics compared to the full ITT population. The data in Table 1 do not

suggest a difference in the types of patient who did not participate in the OS follow-up and the ITT patient between the two treatment arms.

Table 1: Key baseline characteristics of patients who did not participate in the OS follow-up

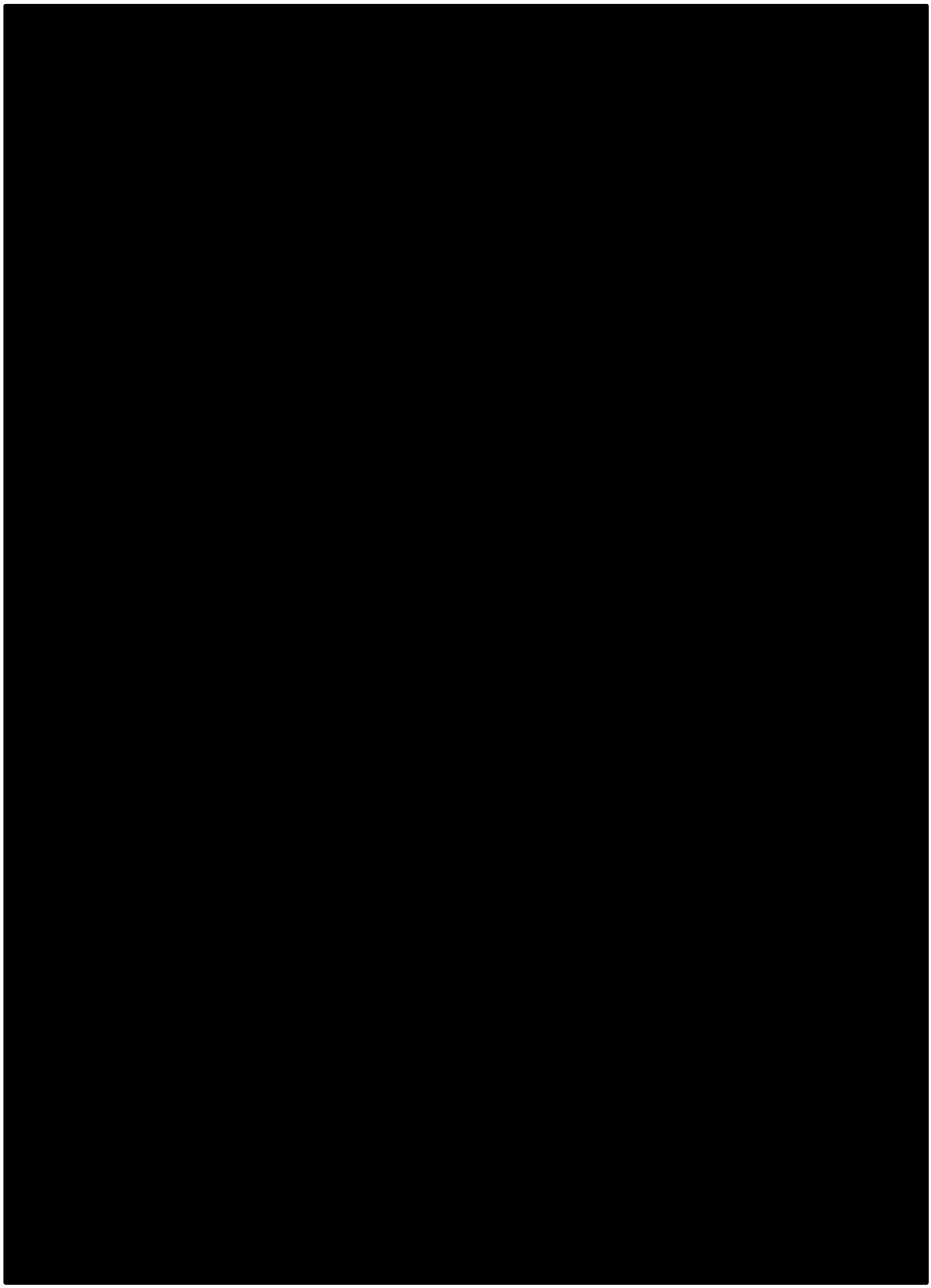
Baseline characteristic	Patients not consenting to OS follow-up		ITT	
	Fulvestrant	Anastrozole	Fulvestrant	Anastrozole
	N=16	N=19	N=102	N=103
Visceral involvement				
No	[redacted]	[redacted]	54 (53%)	45 (44%)
Yes	[redacted]	[redacted]	48 (47%)	58 (56%)
Prior chemotherapy				
No	[redacted]	[redacted]	73 (72%	78 (76%)
Yes	[redacted]	[redacted]	29 (28%)	25 (24%)
Measurable disease				
No	[redacted]	[redacted]	14 (13%)	10 (10%)
Yes	[redacted]	[redacted]	89 (87%)	93 (90%)
Prior endocrine therapy				
No	[redacted]	[redacted]	73 (72%)	80 (78%)
Yes	[redacted]	[redacted]	29 (28%)	23 (22%)

An analysis of the PFS for those who provided consent to participate in the OS follow-up versus those who did not (Table 2 and Figure 2) does not suggest that these patients exert any bias on the relative efficacy of fulvestrant compared with anastrozole, with regards to PFS/TTP.

Table 2: Sensitivity analysis of PFS/TTP for patients in FIRST who provided consent or not for OS follow-up

	N	Fulvestrant	Anastrozole	
PFS		Median PFS (months)	Median PFS (months)	HR (95% CI)
Full population	205	23.41 (16.67 – 33.99)	13.15 (9.93 – 18.90)	0.66 (0.47 – 0.92)
Consent to OS follow-up: Yes	170	[redacted]	[redacted]	[redacted]
Consent to OS follow-up: No	35	[redacted]	[redacted]	[redacted]

Figure 2: TTP of patients in FIRST - A) ITT population, B) Patients consenting to OS follow-up, C) Patients not consenting to OS follow-up



Similar sensitivity analyses for OS in this study (Table 3) are clearly not possible for the sub-group of patients who did not provide consent to participate in the follow-up

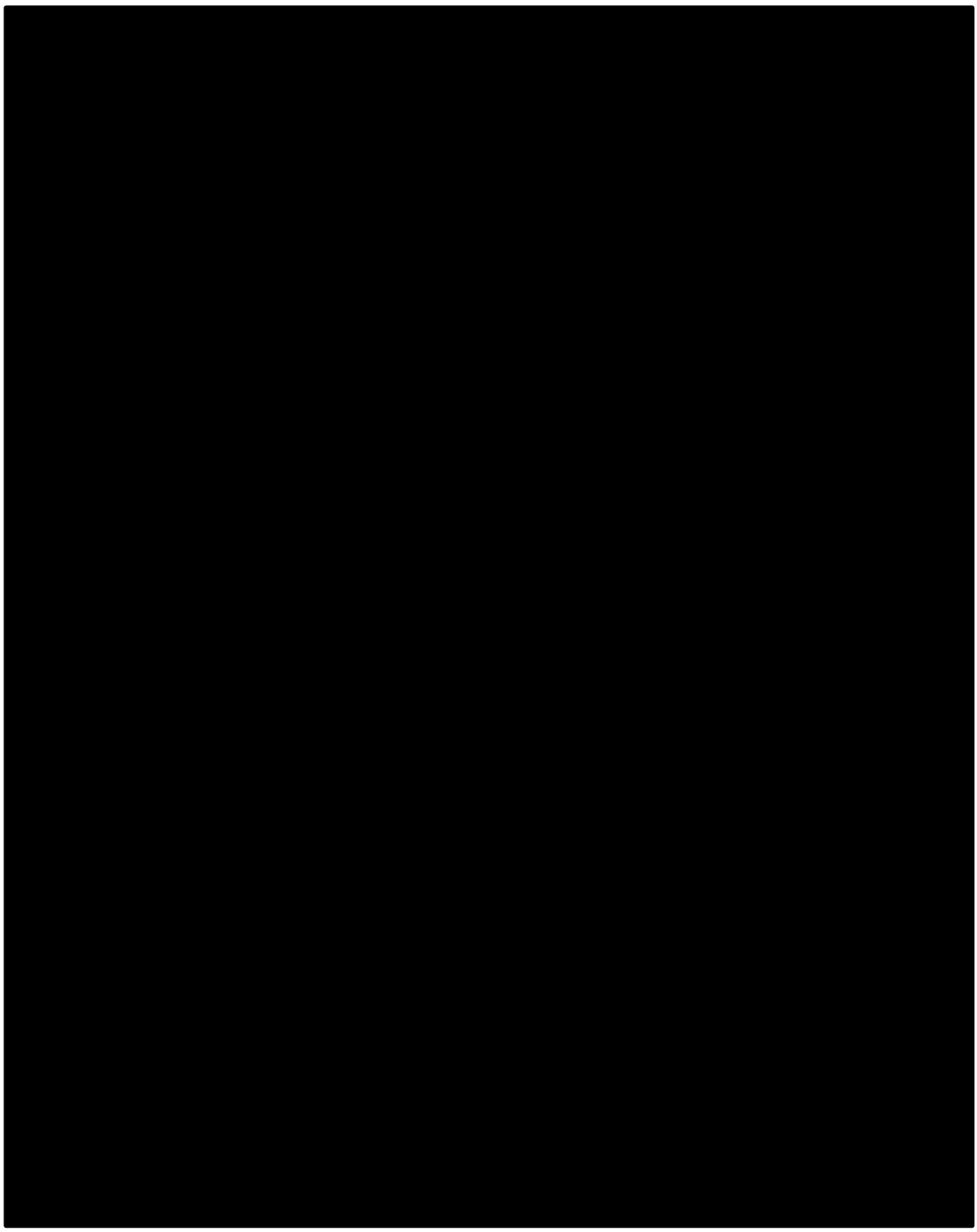
phase and so an alternative sensitivity analysis has been carried out where all patients in FIRST who did not provide consent, were censored at final data cut-off (DCO3). The results suggest that such a scenario would give a (non-significant) HR of [redacted]. Therefore, the OS benefit of fulvestrant compared to anastrozole observed in FIRST is unlikely to be significantly influenced by the missing data from 35 patients who did not provide informed consent to participate in the OS follow-up.

Table 3: Sensitivity analysis of OS for patients in FIRST who provided consent for OS follow-up

	N	Fulvestrant	Anastrozole	
OS		Median OS (months)	Median OS (months)	HR (95% CI)
Full population	205	54.15 (43.69 – 76.64)	48.39 (35.61 – 57.63)	0.705 (0.50 – 0.99)
Consent to OS follow-up: Yes	170	[redacted]	[redacted]	[redacted]
All non-consented OS follow-up patients set to DCO*	205	[redacted]	[redacted]	[redacted]

* An analysis of OS for patients who did not consent to participate in the OS follow-up study, is not possible in the same way as for PFS. This alternative sensitivity analysis explores the impact of assuming that all patients not consenting to follow-up are still alive at final DCO.

Figure 3: OS of patients in FIRST - A) ITT population, B) Patients consenting to OS follow-up, C) All non-consented OS follow-up patients set to DCO



OS benefit in fulvestrant studies require high level of maturity

Evidence from other studies using fulvestrant in metastatic breast cancer support the expectation of a sustained OS benefit in FALCON. The CONFIRM study established the efficacy of fulvestrant 500mg compared to 250mg in hormone receptor positive patients who had progressed after endocrine therapy (5, 6). This was after previous

studies had shown no difference between fulvestrant 250mg and anastrozole 1mg (7, 8) and therefore the CONFIRM study is actually a comparison between fulvestrant 500mg and anastrozole 1mg.

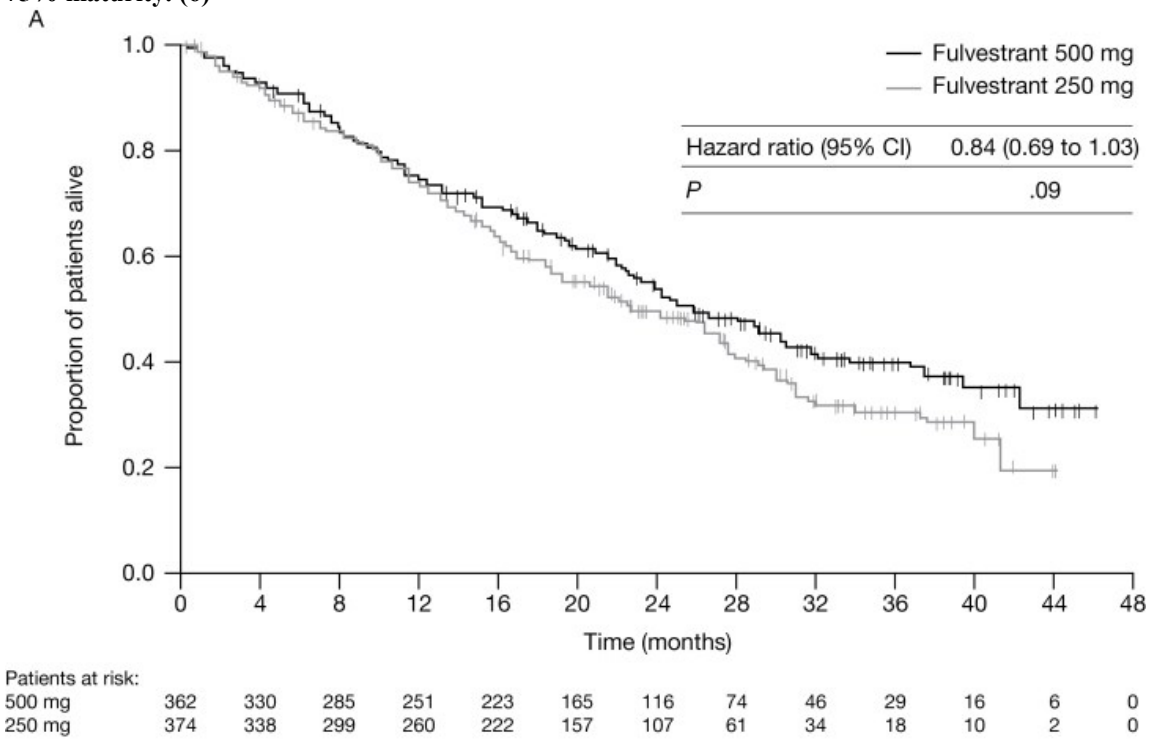
At first DCO, when 84% of patients had progressed and a significant effect on PFS had been observed (HR = 0.80 [0.68 – 0.94]), OS data was only 50% mature and not significant. At DCO2, when 75% of patients had died, the OS benefit was statistically significant (HR = 0.81 [0.69 – 0.96]) (Table 4 and Figure 4).

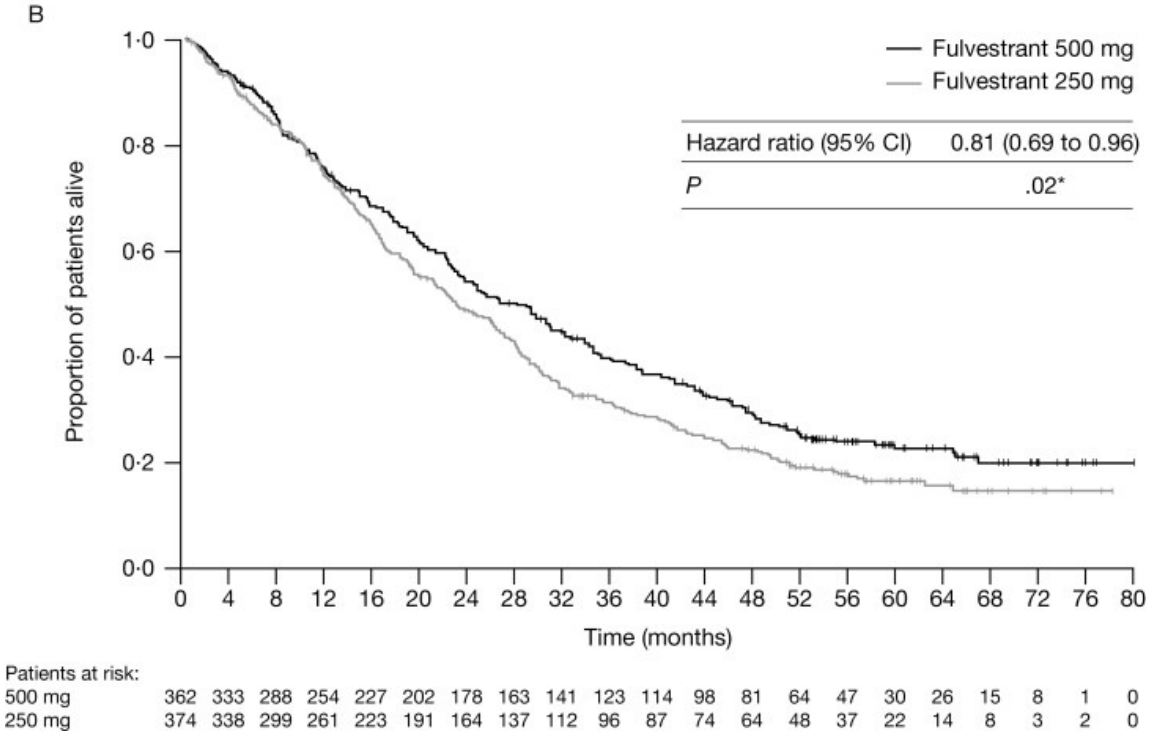
Table 4: The efficacy of fulvestrant 500mg compared to 250mg in CONFIRM (5, 6).

		Fulvestrant 500	Fulvestrant 250	HR (95% CI)
		N=362	N=374	
Median PFS	84% maturity	6.5 months	5.5 months	0.80 (0.68 – 0.94)
Median OS	50% maturity	25.1 months	22.8 months	0.84 (0.69 – 1.03)
	75% maturity	26.4 months	22.3 months	0.81 (0.69 – 0.96)

It is important to note that in the mature survival curves for CONFIRM (75% maturity), there is no separation until at least 12 months (Figure 4B) and a separation of survival curves at a similar time is clearly observed in data from FIRST (69% maturity, Figure 3). This further supports the hypothesis that an OS treatment effect is observable for fulvestrant 500mg with mature data (>50%).

Figure 4: Overall survival from date of randomisation in CONFIRM. A) OS at 50% maturity. B) OS at 75% maturity. (6)





1.2 The matching process used in the submission was robust

Applying selection criteria on FIRST and NorthAmerica:TARGET does not break randomisation

The Committee had a number of concerns about the way in which outcomes from adjusted populations from FIRST and NorthAmerica:TARGET were used in the NMA. It is important to note that, as stated in our response to Clarification Questions,

"… *data for ER/PR+ patients plus endocrine naive patients would be included and hence these patients were selected from FIRST and North American and Target." Response to question A8.*

All patients in FIRST were hormone receptor positive (i.e. ER/PgR+ve) and endocrine naivety was a pre-randomisation variable (Figure 5). Thus, the application of a filter on the basis of previous exposure to endocrine therapy to the ITT population will not break randomisation.

The North America and TARGET studies both recruited patients with metastatic breast cancer who were eligible for endocrine therapy. Although both studies excluded patients who were HR-ve, they included patients whose HR status was unknown (55% of North America study and 11% of TARGET). All efficacy analyses were performed on an ITT basis and were adjusted for the covariates of age, previous endocrine therapy(yes or no), extent of disease at entry and hormonal receptor status at diagnosis. Thus, endocrine naivety was a pre-randomisation variable and the application of a filter on this basis to the ER/PgR+ve subgroup (Figure 5) will not break randomisation.

This is further supported by the fact that baseline characteristics of patients in FIRST (Table 5) and NorthAmerica:TARGET (Table 6) are balanced before and after application of one or two filters based on pre-randomisation variables, respectively.

Figure 5: Number of patients in subgroups of the 3 key studies (Grey shading = ITT populations in studies, White shading = published subgroup, stripes = subgroup of a subgroup)

Patient characteristics	NorthAmerica: TARGET	FIRST	FALCON
Untreated mBC	ITT N=1021	-	-
-ER/PgR+ve	N=611	ITT N=205	-
-Endocrine naïve	N=513	N=153	ITT N=462

Alignment to decision problem

Table 5: Baseline characteristics of participants in the FIRST study (ITT and matched to FALCON study)

	fulvestrant ITT N=102	anastrozole ITT N=103	fulvestrant endocrine naïve subgroup N=73	anastrozole endocrine naïve subgroup N=80
Median age (years)	66	68	67	69
ER and/or PR +ve	**102 (100%)**	**103 (100%)**	**73 (100%)**	**80 (100%)**
Visceral disease	48 (47%)	58 (56%)	33 (45%)	43 (54%)
Bone only disease	10 (10%)	8 (8%)	2 (3%)	2 (3%)
Soft tissue only disease	1 (1%)	0 (0%)	0 (0%)	0 (0%)
No prior chemo	73 (72%)	78 (76%)	63 (86%)	68 (85%)
Prior adjuvant chemo	29 (28%)	25 (24%)	10 (14%)	12 (15%)
Prior endocrine therapy	**29 (28%)**	**23 (22%)**	**0 (0%)**	**0 (0%)**
Measurable disease	89 (87%)	93 (90%)	69 (95%)	78 (98%)
Locally advanced	19 (19%)	18 (18%)	19 (26%)	18 (23%)

Table 6: Baseline characteristics of participants in the North America:TARGET study (ITT and matched to FALCON study)

	anastrozole ITT N=511	Tamoxifen ITT N=510	anastrozole HR+ / endocrine naïve subgroup N=251	Tamoxifen HR+ / endocrine naïve subgroup N=262
Median age (years)	67	67	67	66
ER and/or PR +ve	**305 (60%)**	**306 (60%)**	**251 (100%)**	**262 (100%)**
Visceral disease	186 (36%)	211 (41%)	103 (41%)	132 (50%)
Bone only disease	101 (20%)	86 (17%)	53 (21%)	50 (19%)
Soft tissue only disease	142 (28%)	138 (27%)	53 (21%)	45 (17%)
No prior chemo	391 (77%)	385 (75%)	191 (76%)	198 (76%)
Prior adjuvant chemo	120 (23%)	125 (25%)	60 (24%)	65 (25%)
Prior endocrine therapy	**78 (15%)**	**68 (13%)**	**0**	**0**
Measurable disease	418 (82%)	425 (83%)	195 (78%)	208 (79%)
Locally advanced	-	-	-	-

Results for the matched patients are consistent with published outcomes

We are confident that the application of either one, or two, subgroup filters to the ITT data set for FIRST, or NorthAmerica:TARGET studies, respectively, provides a fair and robust comparison of the relative efficacy of fulvestrant in ER/PgR+ve, endocrine naïve patients with locally advanced or metastatic breast cancer.

Table 7 provides the Cox proportional hazard ratios for PFS and OS in the three key studies for ITT and key subgroup populations as reported in published literature or calculated from the raw data (in the case of the HR+ve and endocrine naïve patients in NorthAmerica:TARGET) used in the network meta-analysis in the submission.

Attention should be drawn to the following observations in particular.

- For both FIRST and NorthAmerica:TARGET studies, the relative efficacy of the investigational drug (against the comparator) increases as the patient population becomes more similar to the FACLON ITT patients.
    - PFS HR for fulvestrant versus anastrozole is 0.66 (0.47 – 0.92) for HR+ve patients in FIRST, but 0.52 (0.35 – 0.77) for the endocrine naïve subgroup.
    - PFS HR for tamoxifen versus anastrozole is 1.13 (1.00 - NR) for untreated mBC patients in NorthAmerica:TARGET, but 1.25 (1.03 - 1.51) for HR+ve patients, and [redacted] for the endocrine naïve subgroup.
- The relative efficacy of fulvestrant compared to anastrozole with respect to OS similarly increases as the patient population in FIRST becomes more similar to the FACLON ITT patients (HR = 0.70 (0.50 - 0.98) for HR+ve patients, compared to 0.63 (0.42 - 0.93) for the endocrine naïve subgroup).
- There is no evidence of an OS improvement in patients recruited to either arm of the NorthAmerica:TARGET study in either the ITT (HR = 0.97, lower 95% confidence interval = 0.84) or ER/PgR+ve subgroup (HR = 1.00, lower 95% confidence interval = 0.83). The endocrine-naïve subgroup of these patients

similarly have no evidence of a survival benefit for tamoxifen compared to anastrozole [redacted].

These observations support our position that the use of data from populations in FIRST and NorthAmerica:TARGET which are matched to the ITT population of FALCON and closely aligned with the decision problem for this appraisal is justified and does not produce results inconsistent with published data.

Table 7: Relative treatment effects of tamoxifen, anastrozole and fulvestrant calculated from parametric curves are aligned with published outcomes.

	NorthAmerica:TARGET		FIRST		FALCON	
PFS	**TAM vs ANA**	**Source**	**FUL vs ANA**	**Source**	**FUL vs ANA**	**Source**
Maturity of ITT	**73%**		**69%**		**59%**	
untreated mBC	1.13 (1.00 - NR)	Bonneterre 2001				
HR+ve	1.25 (1.03 - 1.51)	Bonneterre 2001	0.66 (0.47 - 0.92)	Robertson 2010		
HR+ve and endocrine naïve	[redacted]	Calculated	0.52 (0.35 - 0.77)	Ouwens 2016	0.80 (0.64 - 1.00)	Robertson 2016
OS	**TAM vs ANA**	**Source**	**FUL vs ANA**	**Source**	**FUL vs ANA**	**Source**
Maturity of ITT	**56%**		**65%**		**31%**	
untreated mBC	0.97 (0.84 - NR)	Nabholtz 2003				
HR+ve	1.00 (0.83 - NR)	Nabholtz 2003	0.70 (0.50 - 0.98)	Ellis 2014		
HR+ve and endocrine naïve	[redacted]	Calculated	0.63 (0.42 - 0.93)	Ellis 2014	0.88 (0.63 - 1.22)	Robertson 2016

Matching provides supportive evidence for FIRST results

A visual comparison of the KM survival curves for patients receiving anastrozole in the three key studies provides supportive evidence for the improvement in homogeneity in the NMA from the use of the subgroup data.

The PFS curves for the ITT patients in FALCON and FIRST are overlapping and almost equivalent, whilst the survival curve for ITT patients in NorthAmerica:TARGET is substantially worse and appears to be an outlier relative to the other two studies (Figure 6). The effect of considering only the data for the HR+ve and endocrine naïve patients in NorthAmerica:TARGET is to bring the performance of patients in that study receiving anastrozole in line with FALCON and FIRST (Figure 6)).

Similarly, the OS KM curve for anastrozole-treated ITT patients in NorthAmerica:TARGET is slightly under the KM curves for FALCON and FIRST (Figure 7). Indeed, survival curves for NorthAmerica:TARGET and FALCON studies are approximately equivalent until between 18 and 20 months. The effect of considering only the data for the HR+ve and endocrine naïve patients in NorthAmerica:TARGET is to bring the performance of patients in that study receiving anastrozole in line with FALCON ITT for almost the entire length of follow-up.

These observations suggest that a key determinant of outcomes for patients with advanced breast cancer who are treated with AIs, is the presence of hormone receptors on the tumour cells. FIRST and FALCON studies both recruited only patients who were ER/PgR+ve and the outcomes for patients in both studies are similar despite approximately 25% of patients in FIRST having previously been treated with endocrine therapy. The data also suggests that estimates of OS and PFS for patients treated with anastrozole in the open-label FIRST study are appropriate supporting the use of this study in the network of evidence (i.e. survival curves for anastrozole-treated patients in FIRST are similar to survival curves in 2 independent double-blinded RCTs).

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Figure 6: Visual comparison of PFS outcomes in ITT and matched cohorts of patients treated with anastrozole

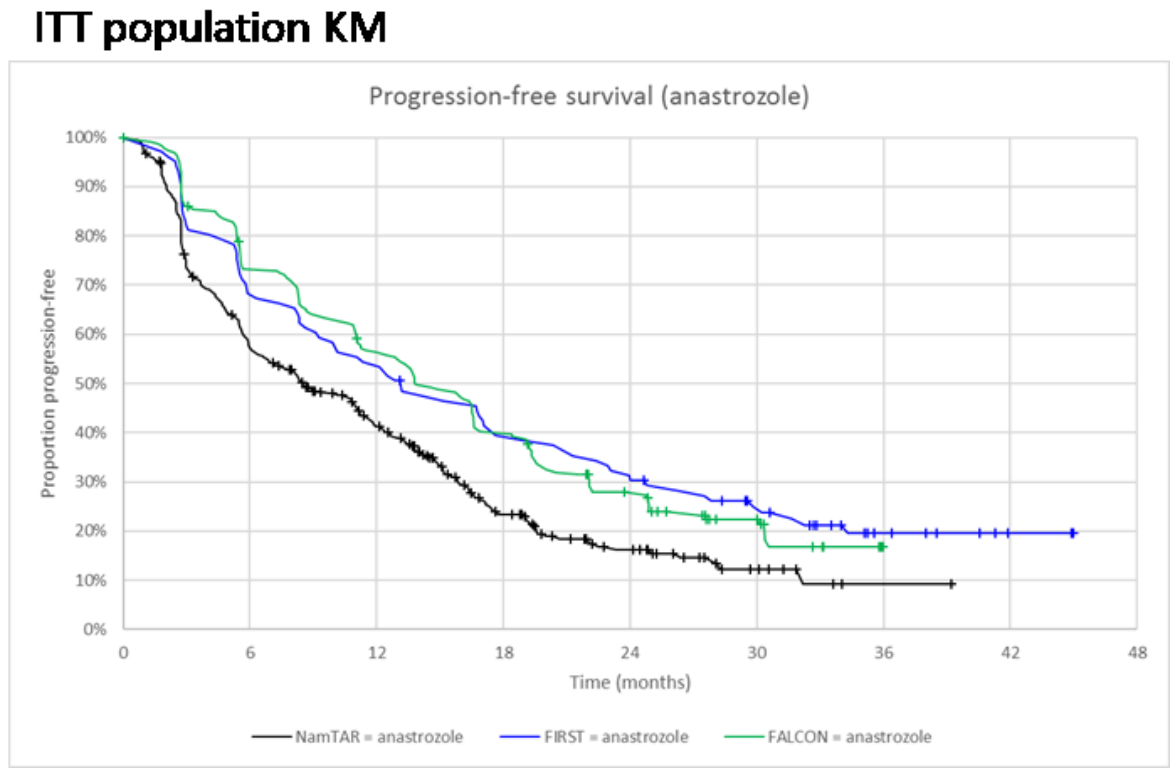

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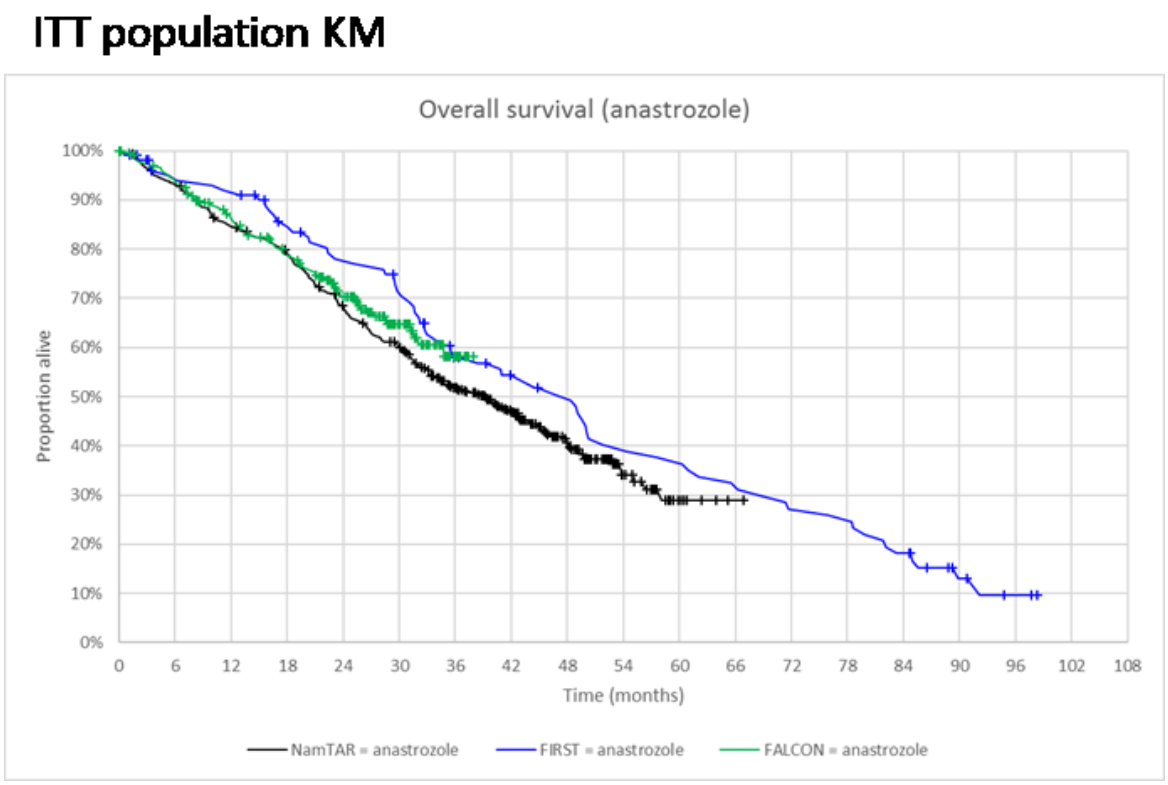
Figure 7: Visual comparison of OS outcomes in ITT and matched cohorts of patients treated with anastrozole



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A previously published subgroup analysis of NorthAmerica:TARGET demonstrated that median PFS for anastrozole for patients with confirmed HR+ status was improved relative to the ITT patients (median PFS = 10.7 vs 8.5 months respectively), whilst the median PFS for patients receiving tamoxifen was unchanged by HR status (6.4 for HR+ve confirmed versus 7.0 for ITT). This demonstrates that patients with HR+ve tumours respond significantly better to AIs than tamoxifen.

The impact of further sub-group analysis of this study according to previous exposure to endocrine therapy, is to improve median PFS for those patients on AIs to 14.8 months, versus 10.4 months for patients treated with tamoxifen (Figure 8). In other words, an average increase in median PFS of approximately 4 months in both treatment arms.Thus, the overall conclusion is that patients receiving endocrine therapy for the first time (either AIs or tamoxifen) experience better outcomes with regards to PFS than patients who have previously been treated with endocrine therapy.

Figure 8: PFS/TTP survival curves for ITT and Matched patients in NorthAmerica:TARGET study

There is little impact of previous endocrine therapy on the relative OS benefits for patients receiving either tamoxifen or an AI, but a trend for both treatment options to

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improve OS in HR+ve and endocrine naïve patients compared to the complete ITT population of NorthAmerica:TARGET (Figure 9).

Figure 9: OS for ITT and Matched patients in NorthAmerica:TARGET study

For the comparison of PFS outcomes for patients treated with fulvestrant, the effect of considering only endocrine-naïve patients on the KM curve for FIRST is relatively muted (Figure 10): patients in FIRST receiving fulvestrant were observed to progress more slowly than similar patients in FALCON (considering similar levels of maturity for FIRST [69%] and FALCON [59%]). Assessment visits in FALCON were scheduled to occur every 3 months until first data cut-off which explains the characteristic step-wise appearance of the survival curve. In contrast, regular (3 monthly) scheduled assessment visits in FIRST were only mandated for the first 6 months after the last patient was recruited and this is reflected in the step-wise appearance of the survival curves for the earliest period of this study. After about 6 months, progression was confirmed by an independent, blinded assessor of scans which were initiated by the treating physician on the basis of symptoms reported by the patient.

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Taken together with the observations for PFS in patients treated with anastrozole (Figure 6), it seems plausible that the PFS gain for patients treated with fulvestrant in FIRST is potentially subject to some bias associated with patients and/or physicians being unblinded to treatment allocation.

In contrast, the OS survival curve for patients treated with fulvestrant in FIRST (at 65% maturity) appears to be a reasonable estimation for what might be expected in FALCON when mature OS data are published given the censoring of observations in FALCON (at 31% maturity) from approximately 20 months (Figure 11).

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Figure 10: Visual comparison of PFS outcomes in ITT and matched cohorts of patients treated with fulvestrant

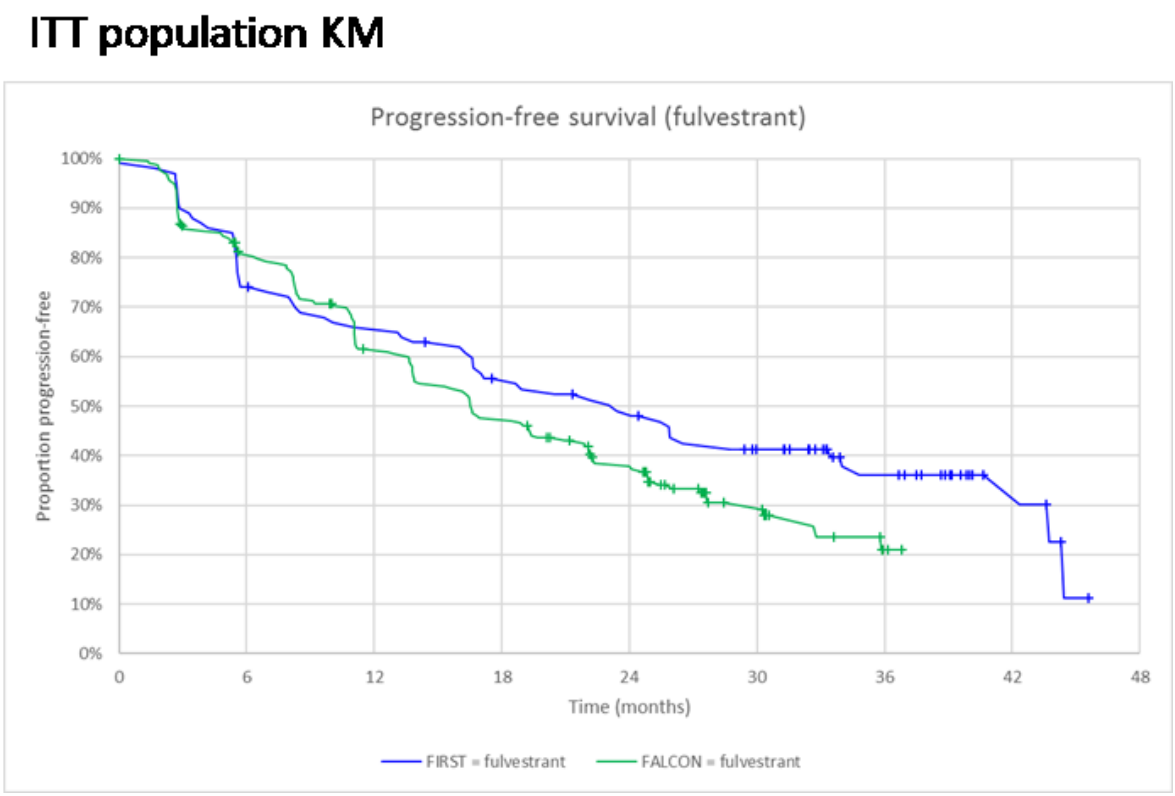

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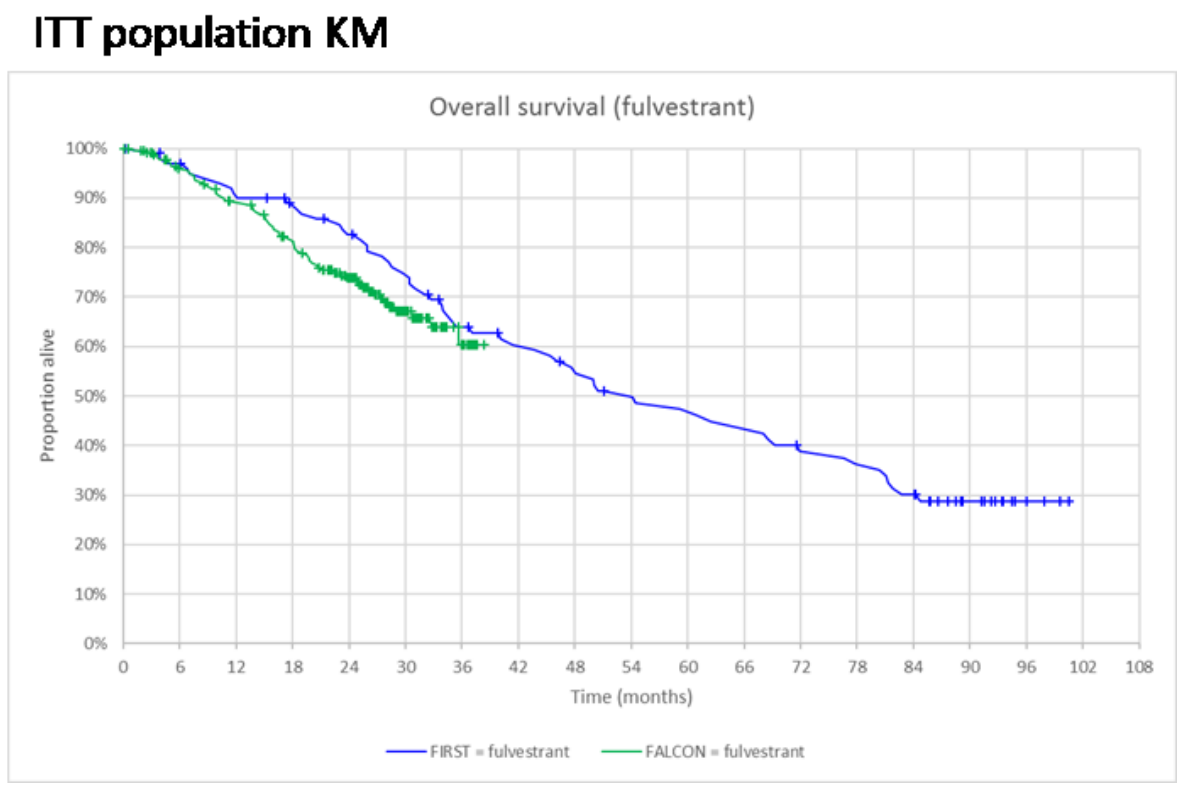
Figure 11: Visual comparison of OS outcomes in ITT and matched cohorts of patients treated with fulvestrant



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1.3 Indirect and mixed treatment comparisons

Method of network meta-analysis

Patient-level data was available for the following studies: FALCON, FIRST, and the combined North American and TARGET trials (hereafter referred to as NorthAmTarget). In line with the ERG's recommendation and Committee's decision, the PO25 trial is omitted from the network of evidence and the aromatase inhibitors (anastrozole and letrozole) were assumed to be clinically equivalent. In response to concerns raised by the Committee concerning the validity of the matching analysis undertaken in the original submission, the following analyses use the full ITT populations from the trials listed above.

The Kaplan-Meier plots of PFS and OS from FALCON, FIRST and NorthAmTarget are presented in Figure 12 and Figure 13, respectively. Visual inspection of the PFS Kaplan-Meier plots indicated that the treatment arms separated and remained separated over the course of the FALCON and FIRST trials, whilst the treatment arms in NorthAmTarget are observed to initially separate then converge and cross in the tail. Visual inspection of the OS Kaplan-Meier plots indicated that the treatment arms in the NorthAmTarget trial crossed.

Evaluation of the log cumulative hazard plots for PFS for FALCON, FIRST and NorthAmTarget (see Figure 14) suggest that the assumption of proportional hazards is not reasonable across all three trials; a similar conclusion was reached for OS (see Figure 15).

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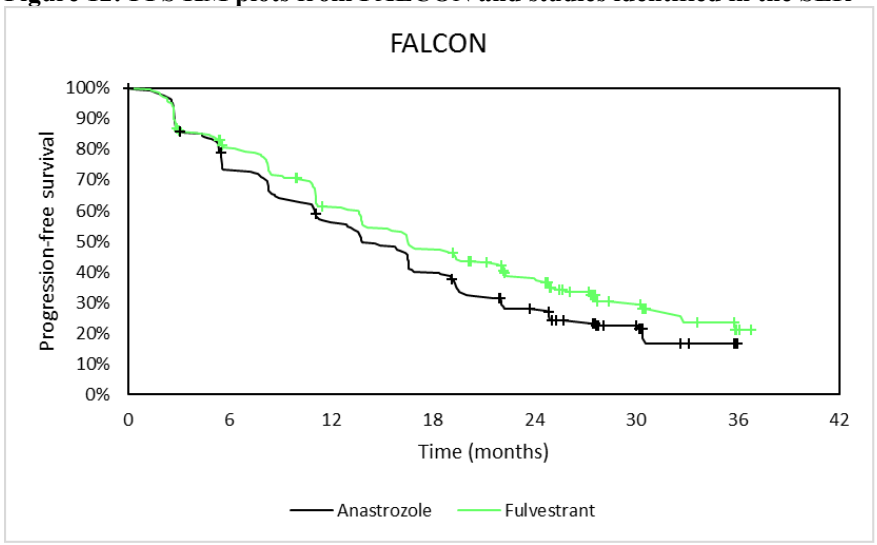
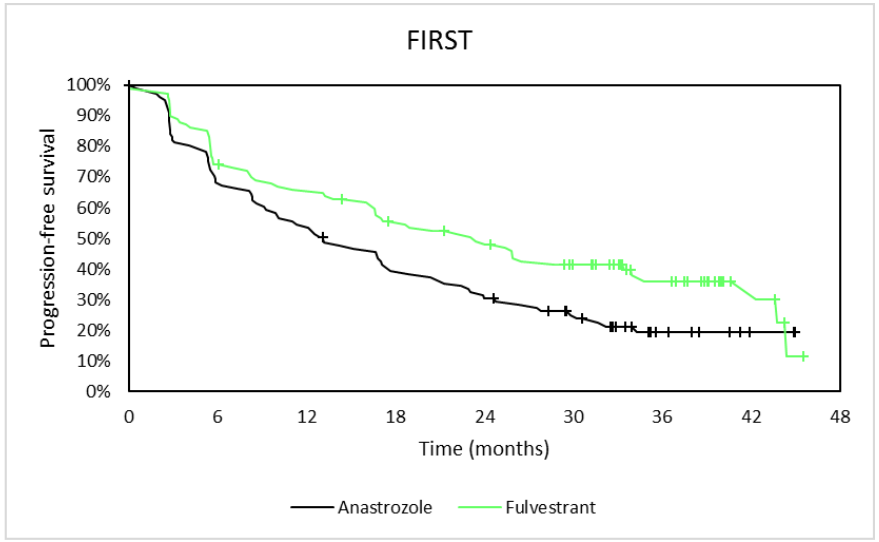
Figure 12: PFS KM plots from FALCON and studies identified in the SLR





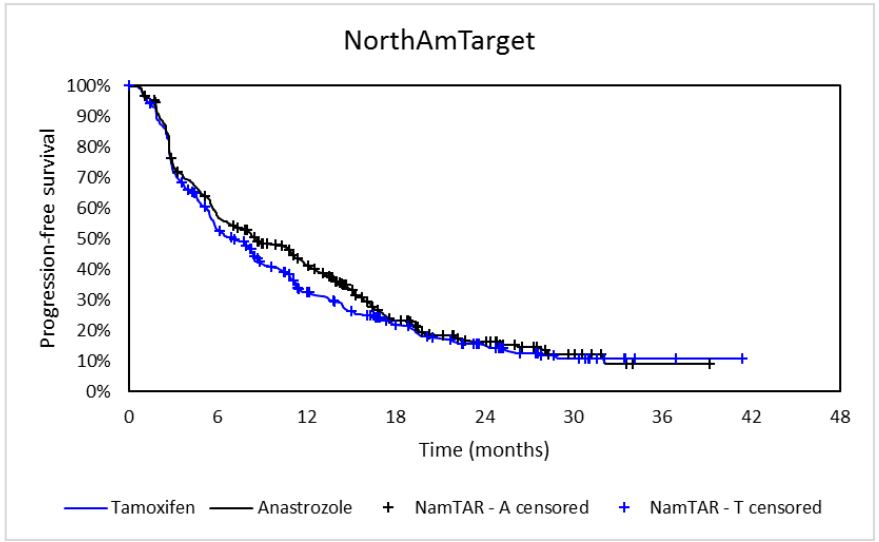


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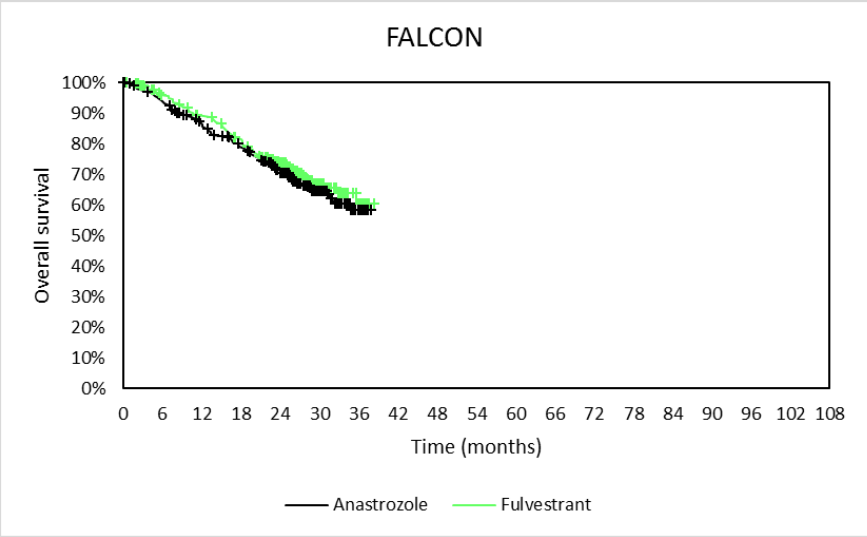
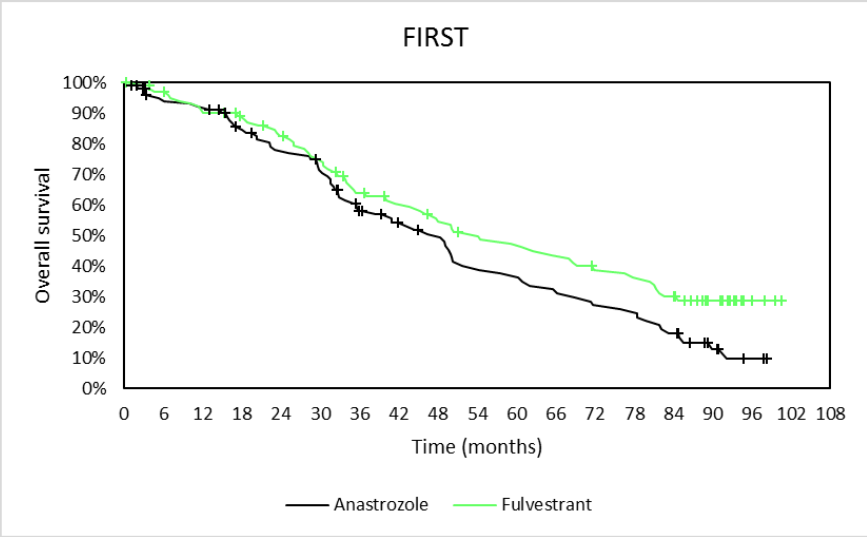
Figure 13: OS KM plots from FALCON and studies identified in the SLR





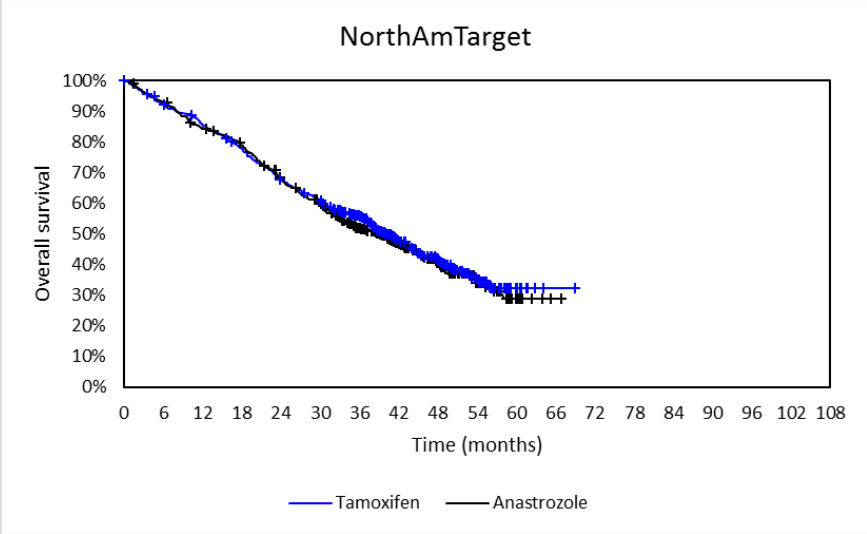


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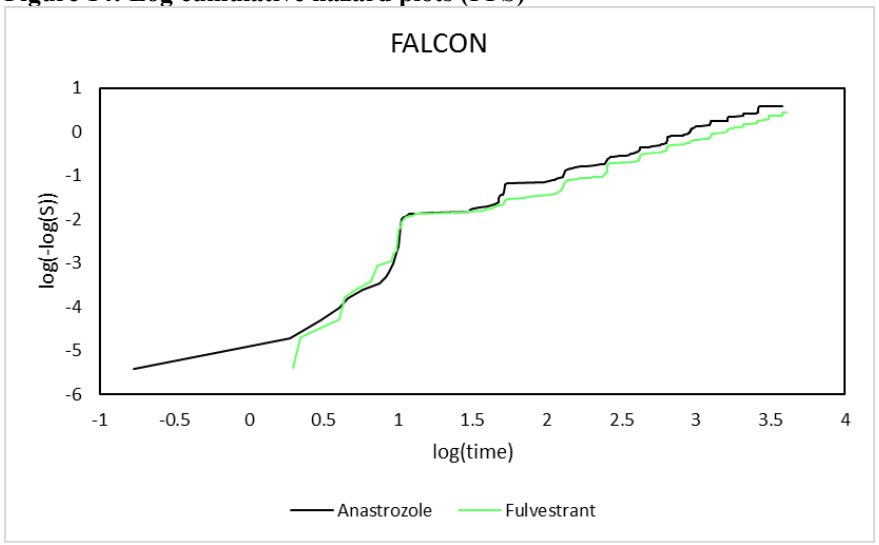
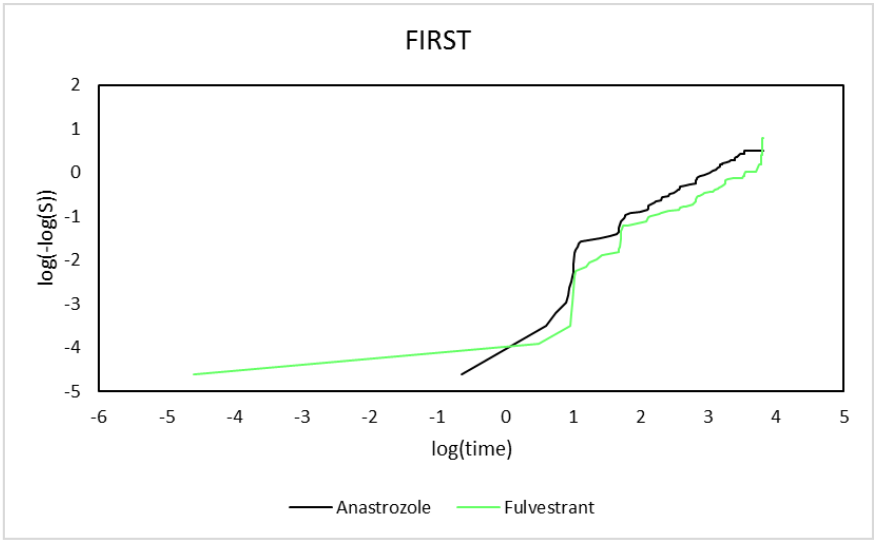
Figure 14: Log cumulative hazard plots (PFS)





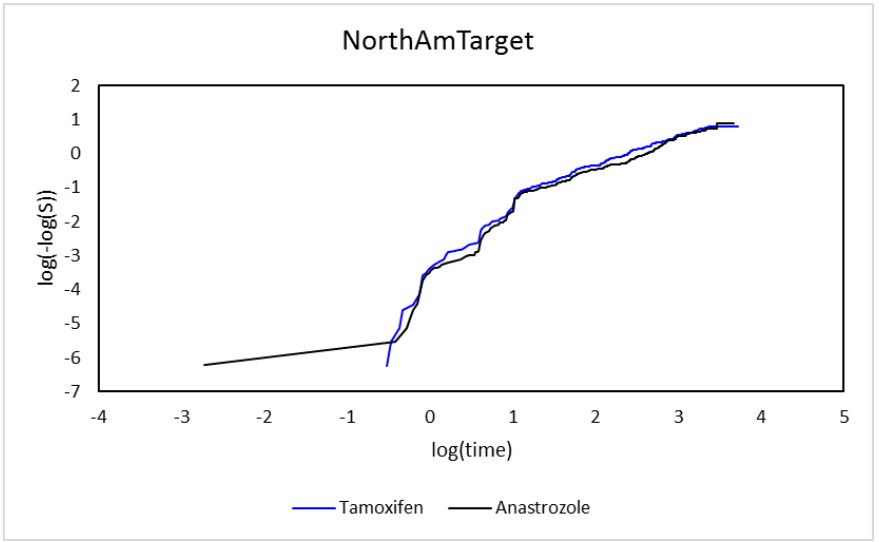


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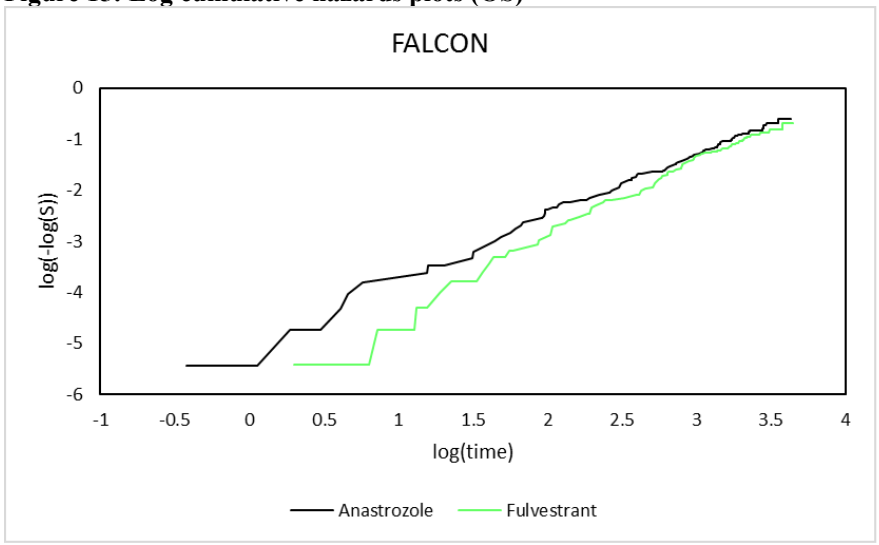
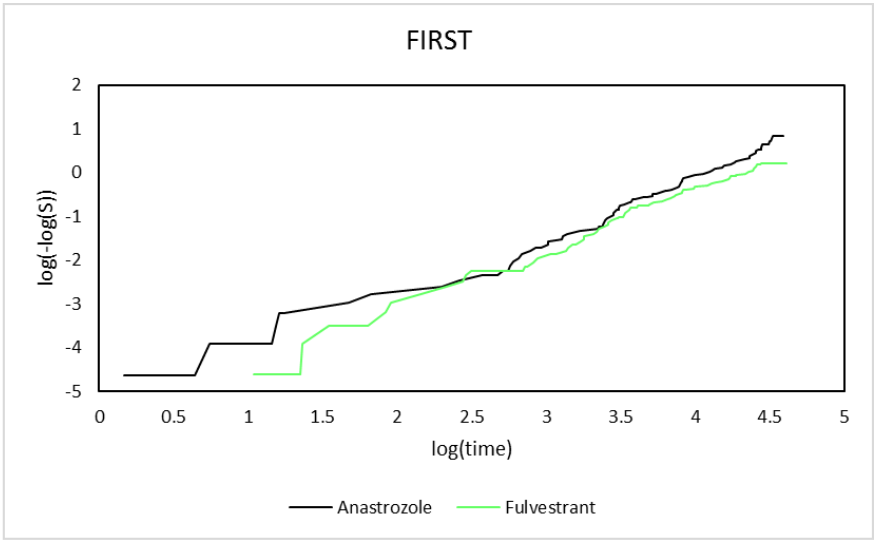
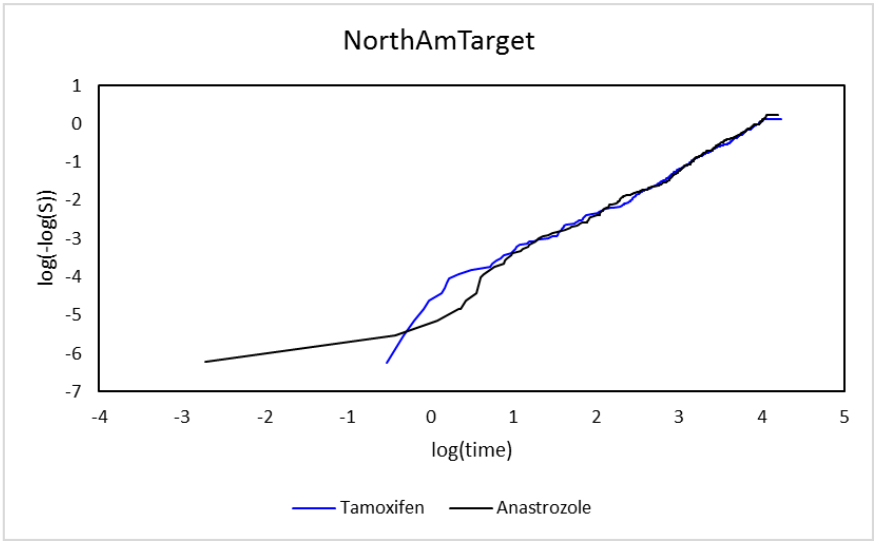
Figure 15: Log cumulative hazards plots (OS)







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As per the original submission, the methodology developed by Ouwens et al (9) was used to undertake a simultaneous extrapolation and network meta-analysis (NMA) of Kaplan-Meier curves for all relevant comparators. This is achieved by relating the Kaplan-Meier curves of each of the competing interventions directly to the parameters of each of the parametric distributions tested.

As agreed upon in the original submission, a fixed-effects meta-analysis was judged to be more appropriate due to the small number of trials (x3) in the networks of evidence. The analysis was undertaken using a frequentist framework in the R software platform. Both 'all shapes' (non-proportional hazards/ proportional acceleration factor [non-proportional treatment effect]) and the 'no shape arm' (proportional treatment effect) models were undertaken.

The 'no shape arm' model is more assumptive and restrictive than the 'all shapes' model as it does not allow the shape parameter to differ between treatment arms. This model does not appear to lend itself to the synthesis and extrapolation of either PFS or OS; the analysis was therefore undertaken using the 'all shapes' models.

Network meta-analysis results

Table 8 presents the results of the PFS ITT-population NMA 'all shapes' models. Base line shape and scale and difference from base line for each of the treatment alternatives versus anastrozole (from the reference trial – FALCON). Fulvestrant demonstrated statistically significant differences in the scale parameter for the Weibull, log-logistic, lognormal and generalised gamma distributions; fulvestrant also demonstrated statistically significant differences for the lognormal and generalised gamma distributions. Tamoxifen did not demonstrate any statistically significant differences in either shape or scale across any of the distributions when compared with anastrozole. Statistically significant results are highlighted with a grey background.

Table 9 presents the results of the OS ITT-population NMA 'all shapes' models. Neither fulvestrant or tamoxifen demonstrated statistically significant differences in the scale or shape parameters for any of the distributions analysed.

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Table 8: Fixed-effects network meta-analysis PFS results: baseline parametric distribution parameters and difference from baseline for treatment alternatives versus (FALCON) anastrozole ('all shapes' models)

Weibull	Scale			Shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Anastrozole (reference)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Difference in log scale			Difference in log shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Fulvestrant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tamoxifen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	Scale			Shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Anastrozole (reference)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Difference in log scale			Difference in log shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Fulvestrant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tamoxifen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	Scale			Shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Anastrozole (reference)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Difference in log scale			Difference in log shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Fulvestrant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tamoxifen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	Scale			Shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Anastrozole (reference)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Difference in log scale			Difference in log shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Fulvestrant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tamoxifen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	Scale			Shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Anastrozole (reference)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Difference in log scale			Difference in log shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Fulvestrant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tamoxifen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Common parameter	Estimate	L95%	U95%	-	-	-
Q	[redacted]	[redacted]	[redacted]	-	-	-

Abbreviations: L, lower; PFS, progression-free survival; U, upper.

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Table 9: Fixed effect network meta-analysis OS results: baseline parametric distribution parameters and difference from baseline for treatment alternatives versus (FALCON) anastrozole ('all shapes' models)

Weibull	Scale			Shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Anastrozole (reference)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Difference in log scale			Difference in log shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Fulvestrant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tamoxifen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	Scale			Shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Anastrozole (reference)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Difference in log scale			Difference in log shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Fulvestrant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tamoxifen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	Scale			Shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Anastrozole (reference)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Difference in log scale			Difference in log shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Fulvestrant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tamoxifen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	Scale			Shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Anastrozole (reference)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Difference in log scale			Difference in log shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Fulvestrant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tamoxifen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	Scale			Shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Anastrozole (reference)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Difference in log scale			Difference in log shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Fulvestrant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tamoxifen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Common parameter	Estimate	L95%	U95%	-	-	-
Q	[redacted]	[redacted]	[redacted]	-	-	-

Abbreviations: L, lower; OS, overall survival; U, upper.

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1.4 Comparison of ERG base case NMA (matched population; exclusion of the PO25 trial) and the ITT-population NMA

Progression-free survival

The Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) results from the ERG base case matched-population NMA are presented in Table 10. For comparison, the fitting statistics from the ITT-population NMA are presented in Table 11.

Table 10: AIC and BIC statistics for PFS based on fixed-effects NMA (ERG base case)

Distribution	AIC	AIC rank	BIC	BIC rank
Generalised gamma	5546.512	1	5601.822	2
Lognormal	5549.671	2	5599.953	1
Log-logistic	5555.259	3	5605.541	3
Weibull	5573.932	4	5624.214	4
Gompertz	5597.020	5	5647.302	5

Abbreviations: AIC, Akaike's Information Criterion; BIC, Bayesian Information Criterion; NMA, network meta-analysis; PFS, progression-free survival.

Table 11: AIC and BIC statistics for PFS based on fixed-effects NMA (ITT population)

Distribution	AIC	AIC rank	BIC	BIC rank
Lognormal	8875.586	1	8929.911	1
Generalised gamma	8876.912	2	8936.669	2
Log-logistic	8907.062	3	8961.387	3
Weibull	8993.253	4	9047.578	4
Gompertz	8998.024	5	9052.349	5

Abbreviations: AIC, Akaike's Information Criterion; BIC, Bayesian Information Criterion; NMA, network meta-analysis; PFS, progression-free survival.

The AIC and BIC statistics for the fixed-effects ITT-population NMA for PFS, concur with the fixed-effects matched-population NMA for PFS for the log-logistic, Weibull and Gompertz distributions: in both instances, the distributions are ranked as the 3rd, 4th and 5th best fit, respectively. In contrast, the lognormal distribution is now ranked as the best-fitting distribution in the ITT NMA with the generalised gamma ranked as second best.

Figure 16 presents a graphical comparison between the matched- and ITT-population NMA generalised gamma PFS survival curves for fulvestrant, the AIs and tamoxifen. The dotted lines represent the matched-population NMA survival curves and the solid lines represent the ITT-population NMA survival curves. The result of using the ITT populations in the NMA is an inflationary effect on the predicted PFS

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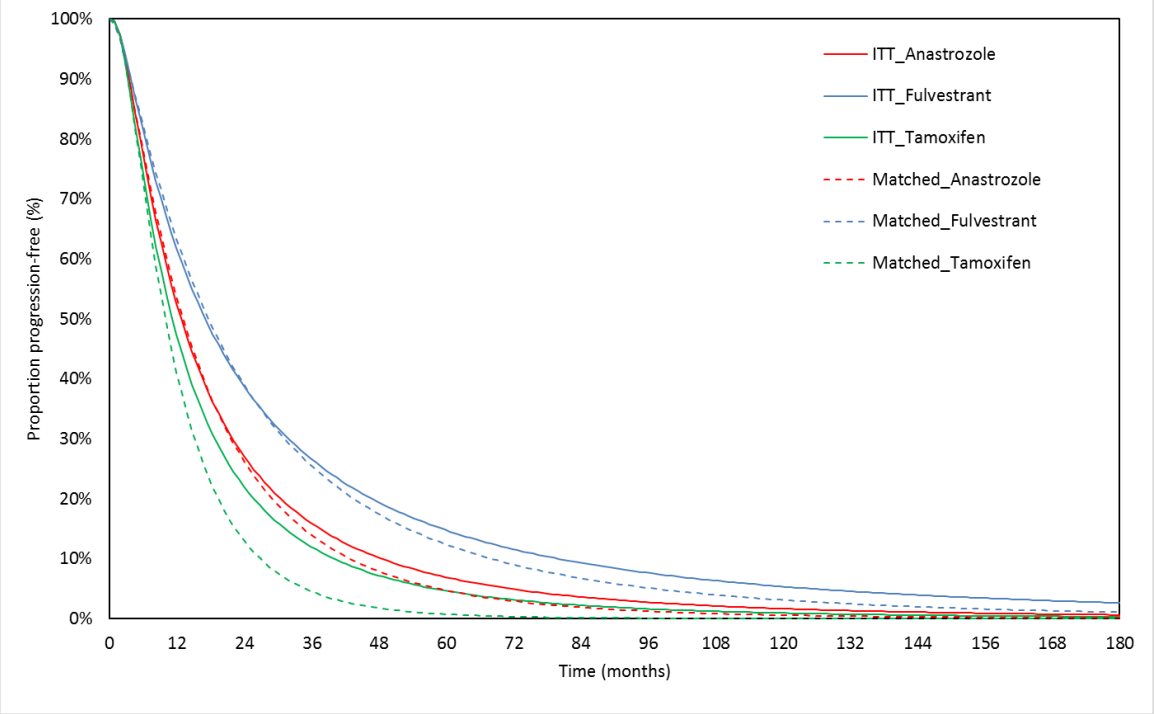
for fulvestrant, the AIs and tamoxifen, with the largest effect seen for tamoxifen. A comparison of the median and mean time spent in PFS for the matched- and ITT-population NMAs is presented in Table 13.

Figure 16: Comparison of matched-population and ITT-population NMA generalised gamma PFS curves



For reference, the KOL opinion on the proportion of those patients included in the FALCON trial who are expected to be progression-free at 1, 2, 5 and 10 years when treated with anastrozole[1] is presented in Table 12. Clinical expert opinion indicates that the choice of generalised gamma distribution still provides a realistic projection of PFS at 5 and 10 years for those patients treated with anastrozole when using the ITT populations in the NMA.

Table 12: KOL opinion on PFS at 1, 2, 5 and 10 years

	1 year	2 years	5 years	10 years
KOL estimate	50-60%	30-40%	5-10%	1-5%

Abbreviation: KOL, key opinion leader.

[1] AstraZeneca. Data on File: Minutes from the Breast cancer HTA advisory board (23 Feb 2017). 2017.

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Table 13: Time in PFS (mean and median [months]), undiscounted, generalised gamma

Treatment	Matched-population NMA		ITT-population NMA	
	Median	Mean	Median	Mean
Fulvestrant	16.56	29.63	16.56	34.25
Anastrozole	11.96	19.58	11.96	22.04
Letrozole				
Tamoxifen	9.20	13.17	10.12	18.46

The use of the ITT populations in the NMA appears to have little to no impact on the median PFS estimates for fulvestrant, the AIs and tamoxifen. However, the mean PFS for all treatments has increased.

Overall survival

The AIC and BIC results from the ERG base case matched-population NMA are presented in Table 14. For comparison, the fitting statistics from the ITT-population NMA are presented in Table 15.

Table 14: AIC and BIC statistics for OS based on fixed-effects NMA (ERG base case)

Distribution	AIC	AIC rank	BIC	BIC rank
Weibull	5242.794	1	5293.076	1
Generalised gamma	5244.528	2	5299.839	3
Gompertz	5246.951	3	5297.233	2
Log-logistic	5256.334	4	5306.616	4
Lognormal	5278.057	5	5328.339	5

Abbreviations: AIC, Akaike's Information Criterion; BIC, Bayesian Information Criterion; NMA, network meta-analysis; OS, overall survival.

Table 15: AIC and BIC statistics for OS based on fixed-effects NMA (ITT population)

Distribution	AIC	AIC rank	BIC	BIC rank
Weibull	8661.593	1	8715.918	1
Generalised gamma	8663.411	2	8723.168	2
Gompertz	8672.420	3	8726.745	3
Log-logistic	8681.871	4	8736.196	4
Lognormal	8735.678	5	8790.003	5

Abbreviations: AIC, Akaike's Information Criterion; BIC, Bayesian Information Criterion; NMA, network meta-analysis; OS, overall survival.

The ranking of distributions based on the AIC statistics for OS based on the ITT-population NMA match the rankling under the matched-population NMA. The BIC statistics produce a near identical ranking but, in the ITT-population NMA, the generalised gamma and Gompertz distributions are ranked 2nd and 3rd respectively, this ranking is reversed in the matched-ITT NMA BIC results.

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Figure 17 presents a graphical comparison between the matched- and ITT-population NMA Weibull OS survival curves for fulvestrant, the AIs and tamoxifen. The dotted lines represent the matched-population NMA survival curves and the solid lines represent the ITT-population NMA survival curves. The result of using the ITT populations in the NMA has, visually, a minimal impact on the predicted OS for fulvestrant and the AIs. For tamoxifen, the result is more pronounced, with the predicted OS curve now sitting above that for the AIs across the time horizon. Neither fulvestrant or tamoxifen demonstrated statistically significant differences in the scale or shape parameters for any of the distributions analysed (see Table 9).

For reference, the KOL opinion on the proportion of those patients included in the FALCON trial who are expected to be alive at 1, 2, 5 and 10 years when treated with anastrozole[2] is presented in Table 16. Clinical expert opinion indicates that the Weibull distribution provides a realistic OS projection for those patients treated with anastrozole at 5 and 10 years when using the ITT populations in the NMA.

A comparison of the median and mean time spent in OS for the matched- and ITT-population NMAs is presented in Table 17.

[2] AstraZeneca. Data on File: Minutes from the Breast cancer HTA advisory board (23 Feb 2017). 2017.

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Figure 17: Comparison of matched-population and ITT-population NMA Weibull OS curves

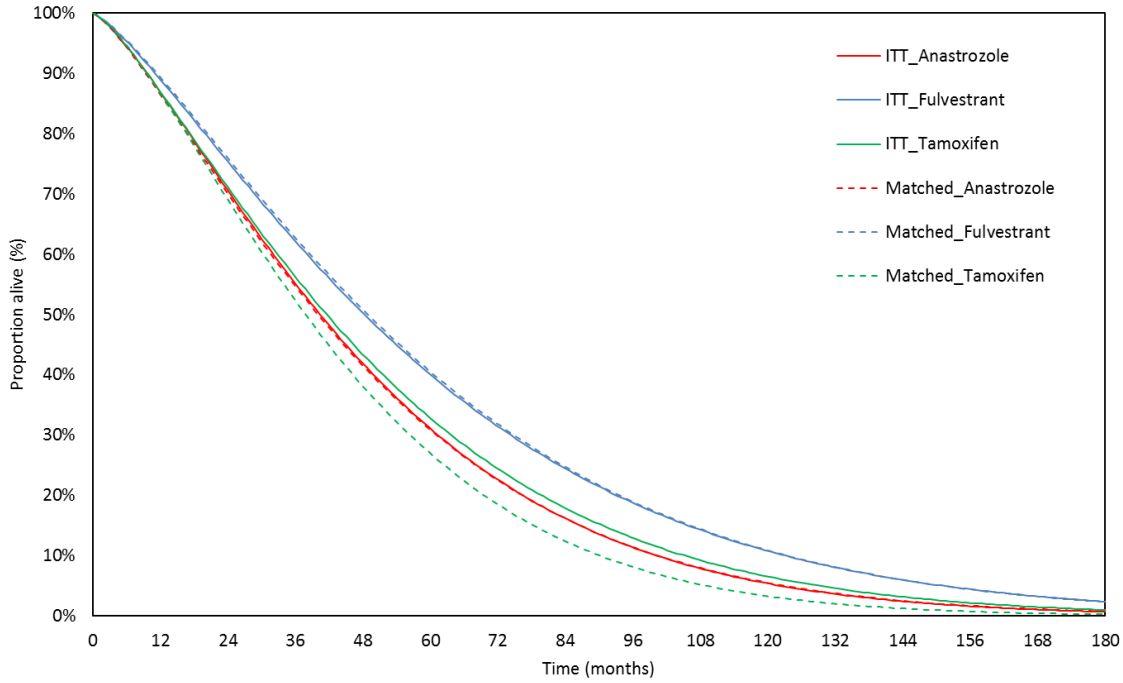

Table 16: KOL opinion on OS at 1, 2, 5 and 10 years

	1 year	2 years	5 years	10 years
KOL estimate	75-85%	55-70%	20-30%	5-10%

Abbreviation: KOL, key opinion leader.

Table 17: Time in OS (mean and median [months]), undiscounted, Weibull

Treatment	Matched-population NMA		ITT-population NMA	
	Median	Mean	Median	Mean
Fulvestrant	47.84	60.09	47.84	61.11
Anastrozole	39.56	48.95	39.56	49.40
Letrozole				
Tamoxifen	36.80	45.05	40.48	51.12

The use of the ITT populations in the NMA appears to have little to no impact on the median OS estimates for fulvestrant and the AIs. For tamoxifen, the use of the ITT populations results in an increase in the predicted median OS of 3.68 months. As with PFS, the mean estimates of OS increase for all treatments, with the largest increase, 6.07 months, predicted for tamoxifen.

1.5 Impact of FIRST in the matched-population and ITT-population NMAs

The committee has stated that the FALCON data is more applicable to the evaluation of clinical effectiveness of fulvestrant than the FIRST data because the FALCON trial population directly reflects the wording of the license for fulvestrant,

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and because FALCON's double-blind trial design reduces the likelihood of bias. As stated previously, there is empirical evidence that the bias in intervention effect estimates in randomised clinical trials, resulting from lack of blinding, varies according to the type of outcome assessed, with non-blinded trials exaggerating intervention effect estimates in all outcomes other than all-cause mortality(3).

The Kaplan-Meier curves, for each comparator, from each trial included in the networks of evidence for PFS and OS have been overlaid with parametric curves, fitted to each trial arm individually, and the corresponding network meta-analysed parametric curve. This has been undertaken for both the matched and ITT populations. A visual examination and comparison of the Kaplan-Meier curves, the projected PFS and OS for the parametric curves fitted to each trial arm individually and the network meta-analysed parametric curves was undertaken to try and ascertain 1) the potential heterogeneity in the trial populations and 2) to visualise the potential impact of each trial, but especially FIRST, on the long-term PFS and OS projections.

Figure 18 presents the anastrozole PFS Kaplan-Meier data from the FALCON, FIRST and NorthAmTarget trials in (A), the matched populations and (B), the ITT populations. In both plots, the Kaplan-Meier data has been overlaid with the generalised gamma distribution fitted to the trials individually (dotted lines in both plots), and from the resulting meta-analysed generalised gamma distribution (solid yellow line in both plots).

Visual comparison of the two plots highlights the impact of the matching analysis: in (A), the Kaplan-Meier survival curves from all three trials are more closely aligned than those in (B). The plots also provide an estimate of the extent to which the individual trials are impacting the meta-analysed survival curve. For PFS, the FALCON data is relatively mature (67%), and it appears that the greatest weight is applied to this data in the NMA.

Figure 19 presents the same comparison, but for fulvestrant. In this instance, it can be observed that the meta-analysed curve is predominantly influenced by the FALCON data, given the level of data maturity. It could be argued that the impact of FIRST is marginally greater in the ITT-population NMA (see Figure 19 [B]).

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Figure 20 presents the same comparison for tamoxifen. The ITT-population NMA curve (generalised gamma) appears to be a poor fit to the observed ITT population Kaplan-Meier plot, due to the heterogeneity between the FALCON ITT and NorthAmTarget ITT populations

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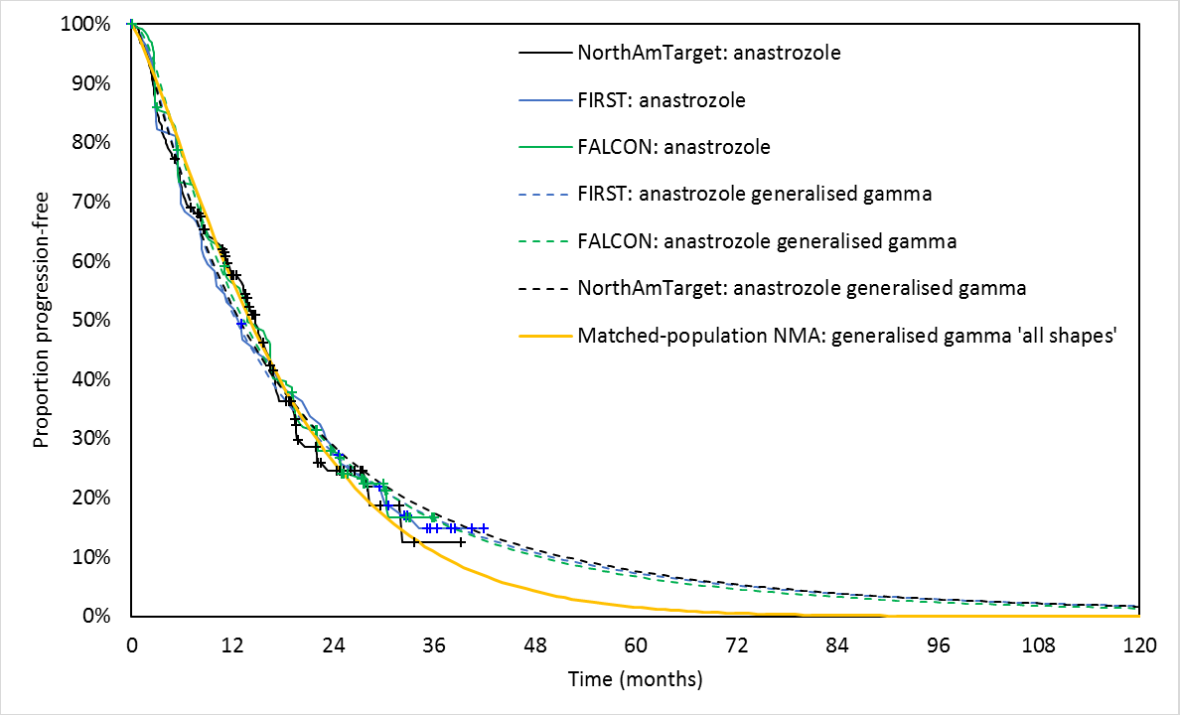
Figure 18: Kaplan-Meier, individual and fixed-effects network meta-analysis 'all shapes' PFS survival curves for anastrozole

A – matched populations



B – ITT populations

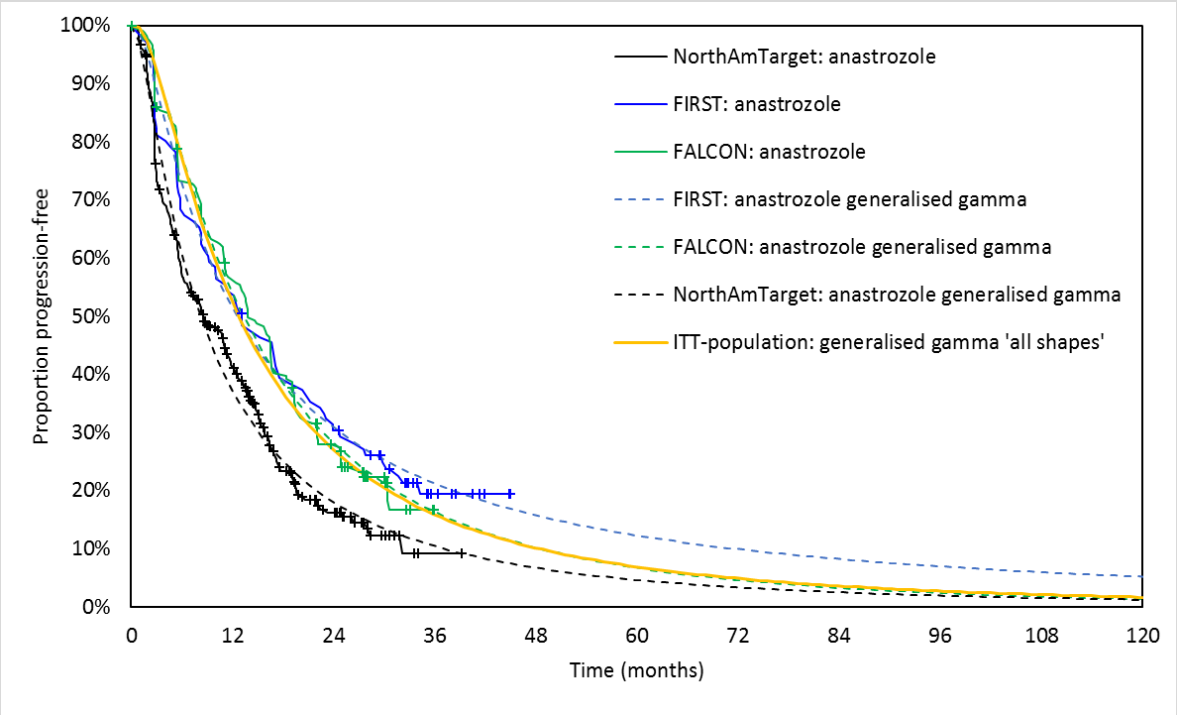


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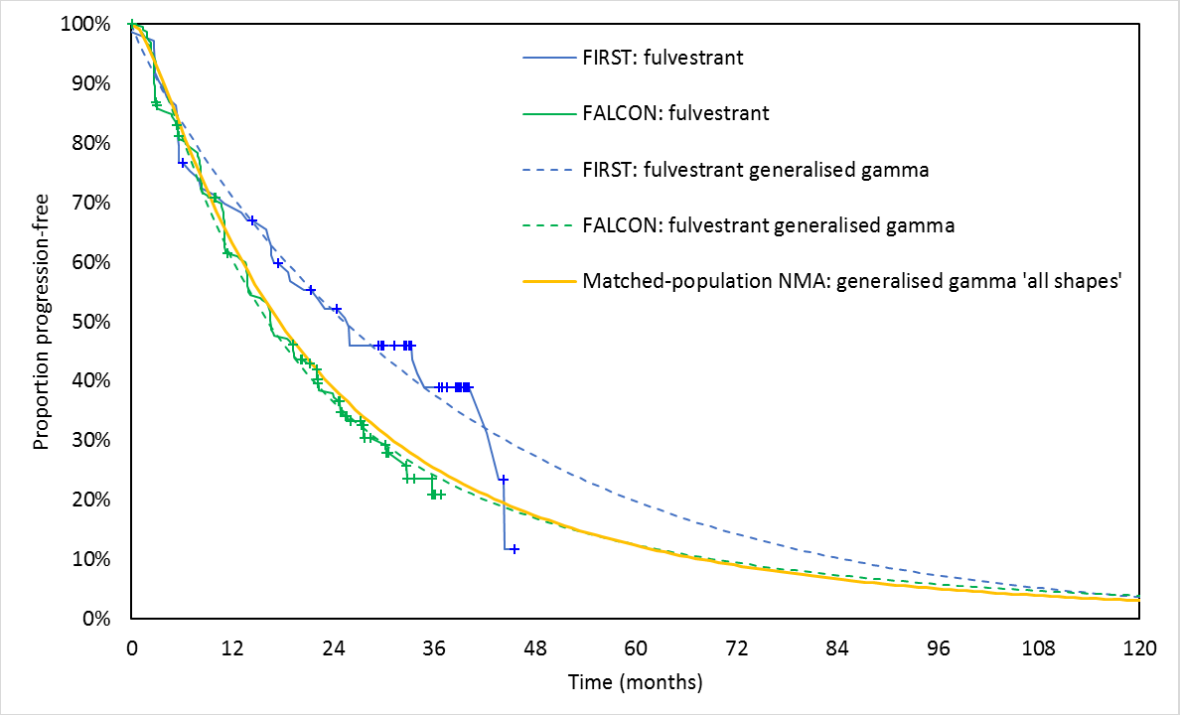
Figure 19: Kaplan-Meier, individual and fixed-effects network meta-analysis 'all shapes' PFS survival curves for fulvestrant

A – matched populations



B – ITT populations

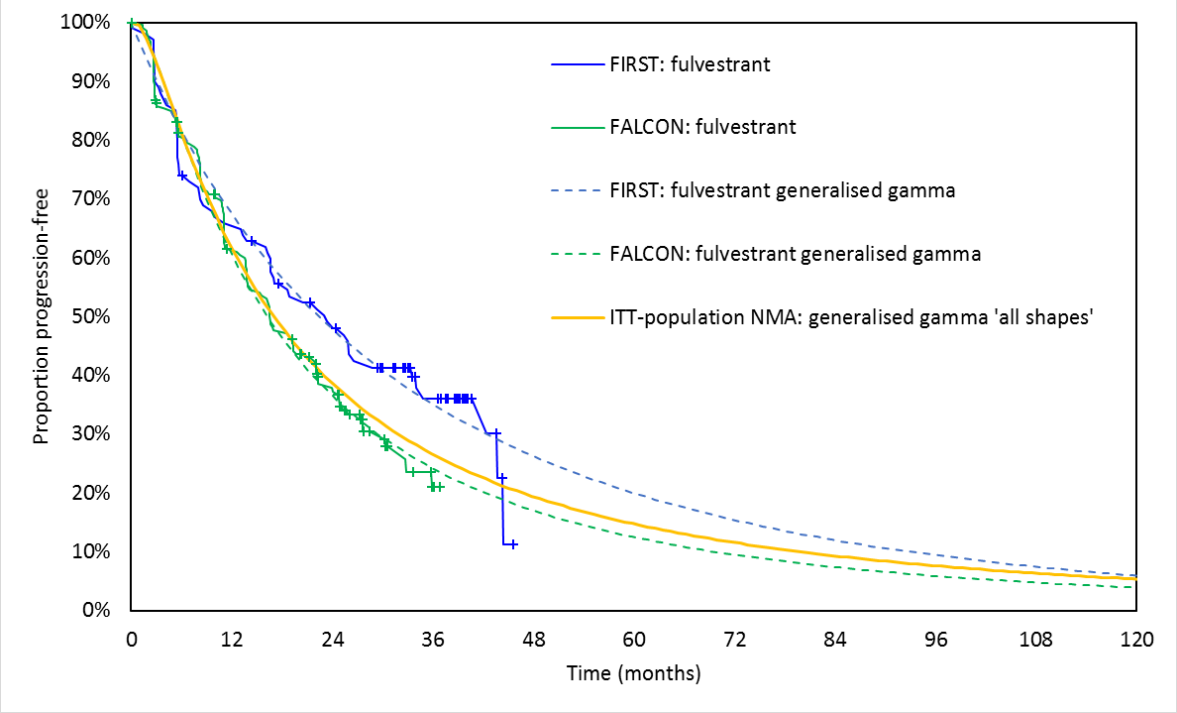


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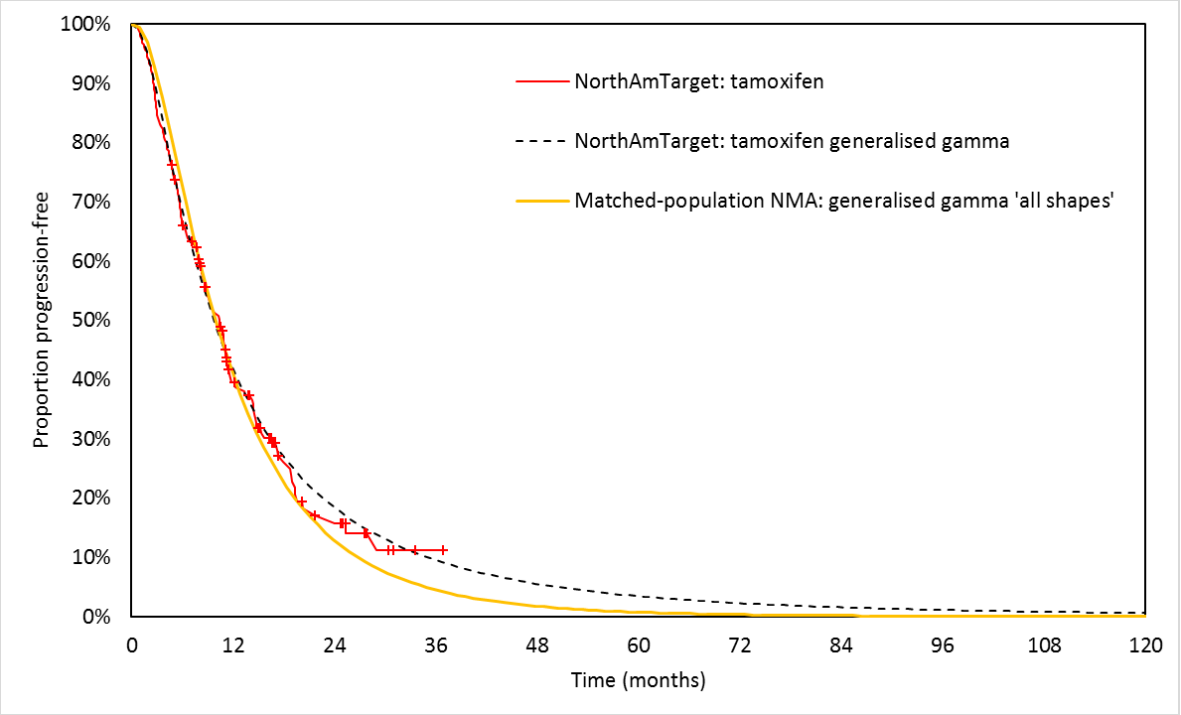
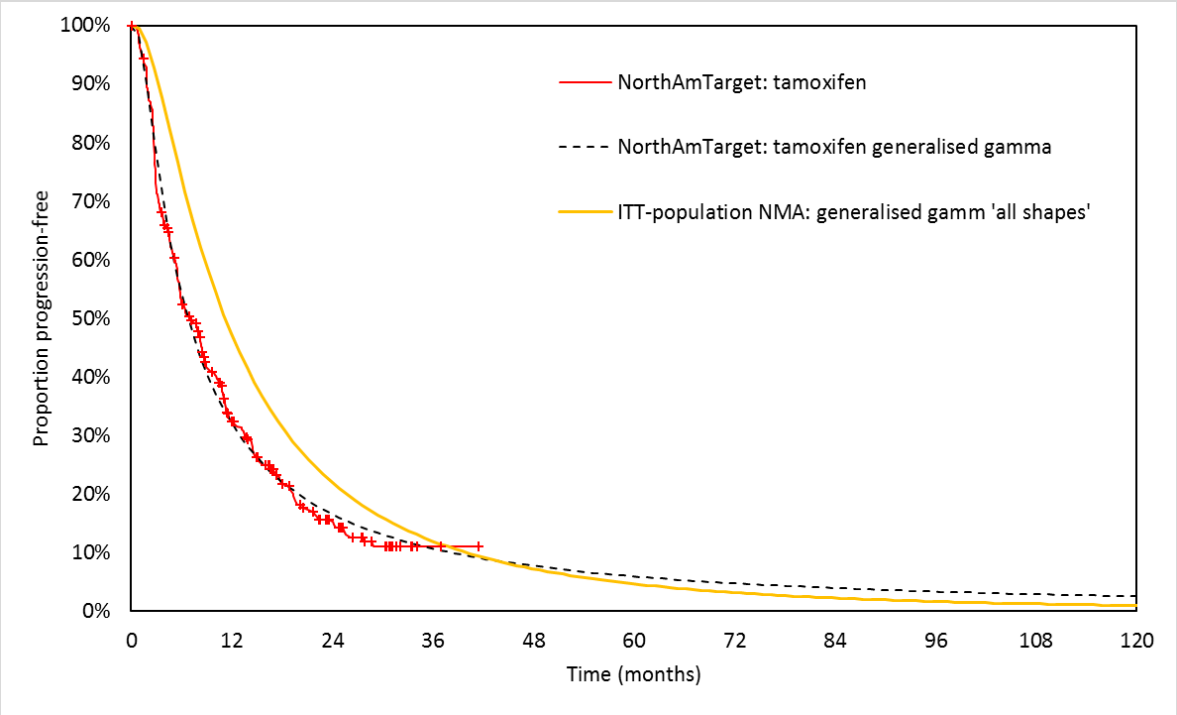
Figure 20: Kaplan-Meier, individual and fixed-effects network meta-analysis 'all shapes' PFS survival curves for tamoxifen

A – matched populations



B – ITT populations



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Both Figure 18 and Figure 19 indicate that FIRST trial has a limited impact on the projected PFS for anastrozole and fulvestrant, given the level of maturity in the FALCON data.

Figure 21 presents the anastrozole OS Kaplan-Meier data from the FALCON, FIRST and NorthAmTarget trials in (A), the matched populations and (B), the ITT populations. In both plots, the Kaplan-Meier data has been overlaid with the Weibull distribution fitted to the trials individually (dotted lines in both plots), and from the resulting meta-analysed Weibull distribution (solid yellow line in both plots).

As with PFS, a visual inspection of both plots indicates that the Kaplan-Meier survival curves from the trials are more closely aligned in the matched populations (A) than those from the ITT populations (B). For OS, the data in FALCON are immature (31%), and the impact of FIRST and NorthAmTarget is, as expected, more pronounced after 36 months (the limit of the observed FALCON OS data).

Figure 22 presents the same comparison as Figure 21, but for fulvestrant. The plots reflect the Committee's opinion that the OS projections for fulvestrant after 36 months are informed by the relative effect (two-dimensional [shape and scale]) estimated from FIRST.

Figure 23 presents the same comparison for tamoxifen. A key difference between the predicted OS for tamoxifen is that, using the matched population, the projected OS for tamoxifen is inferior to that of anastrozole across the time horizon. This result is reversed when the ITT population for NorthAmTarget is used. It is questionable whether the predicted superiority of tamoxifen over anastrozole with regards to OS is clinically valid.

The lack of blinding in FIRST is an understandable concern regarding the potential for bias in the intervention effect estimates; however, there is published evidence, using a large number of trials (1,346), which concludes that non-blinded evidence does not result in exaggerated all-cause intervention-effect mortality estimates.

The Phase II study FIRST represents the only long-term OS data for fulvestrant in the licensed population and, in agreement with long-term OS data for fulvestrant in

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the second-line metastatic breast cancer setting (CONFIRM), indicates that fulvestrant is associated with an OS benefit in metastatic breast cancer patients.

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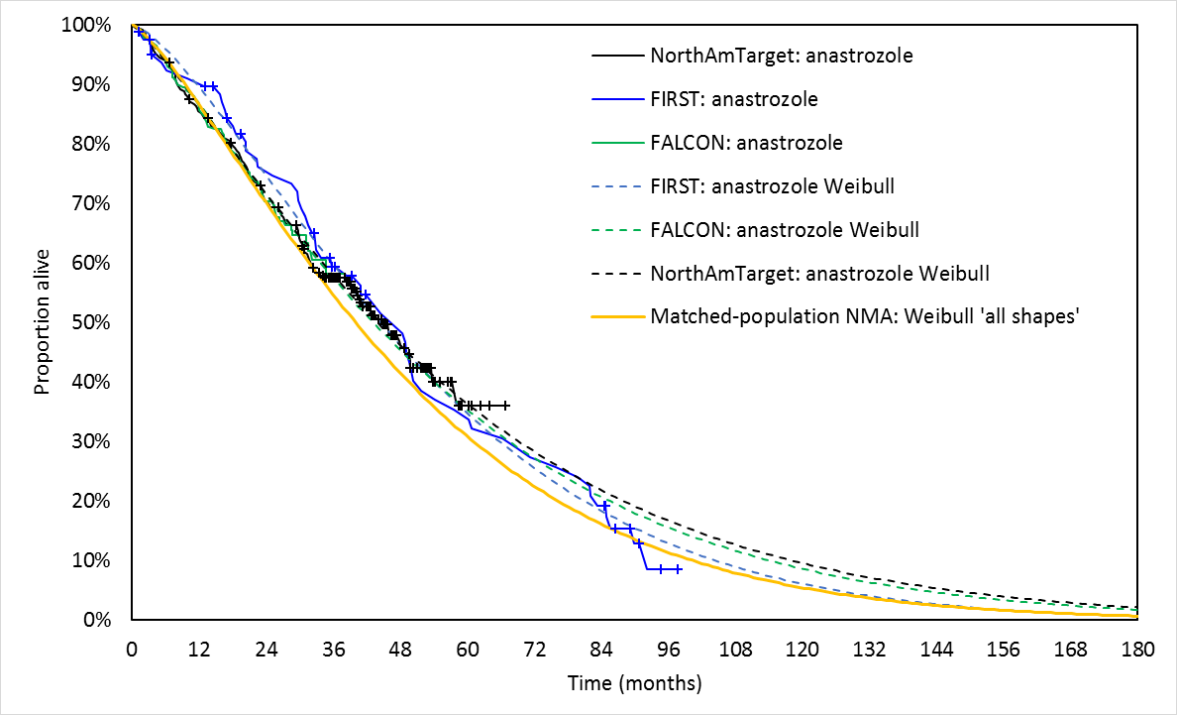
Figure 21: Kaplan-Meier, individual and fixed-effects network meta-analysis 'all shapes' OS survival curves for anastrozole

A – matched populations



B – ITT populations

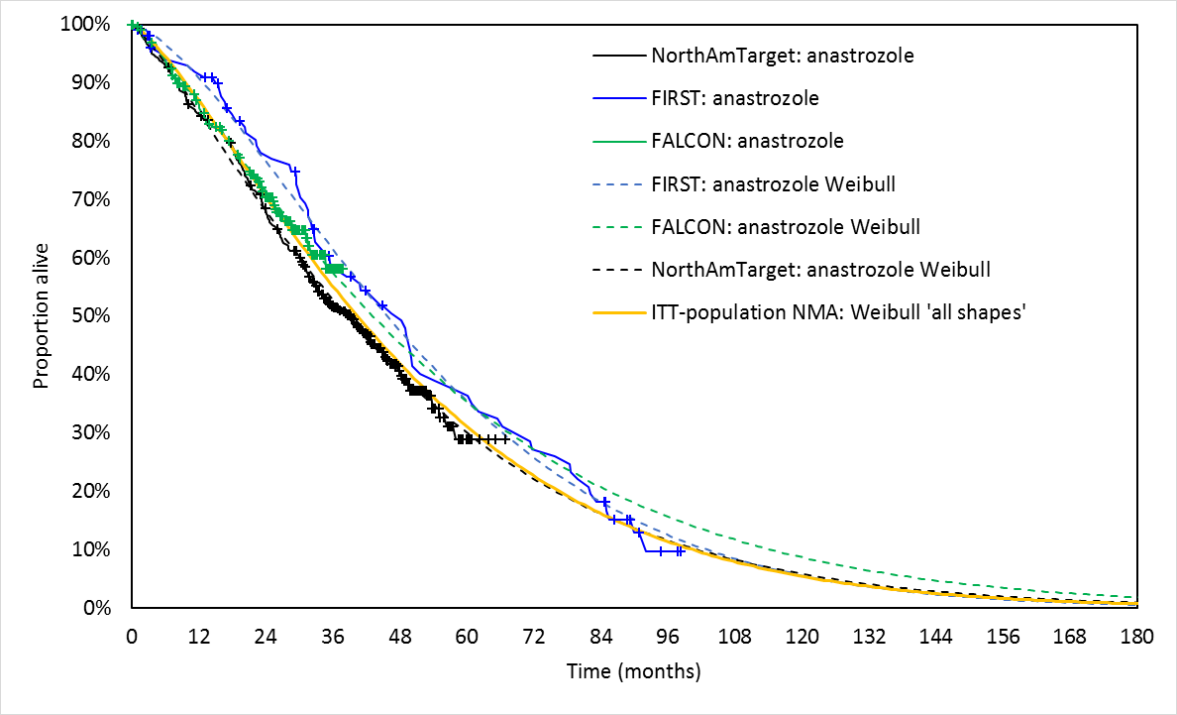


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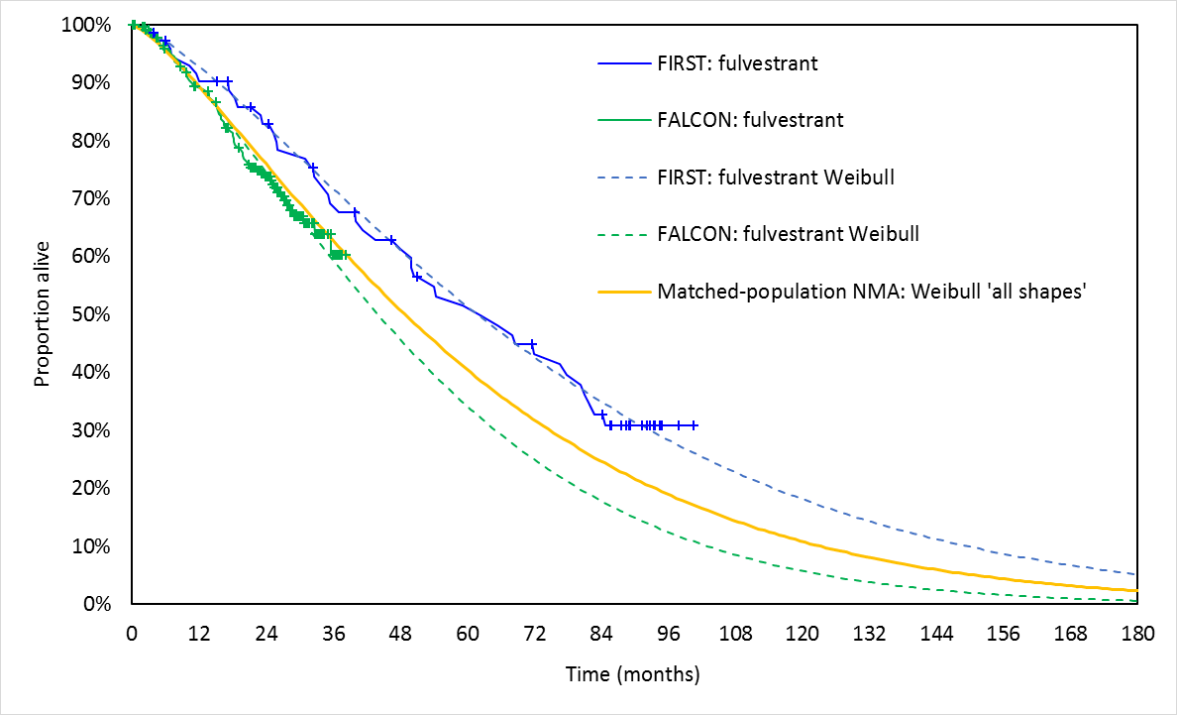
Figure 22: Kaplan-Meier, individual and fixed-effects network meta-analysis 'all shapes' OS survival curves for fulvestrant

A – matched populations



B – ITT populations

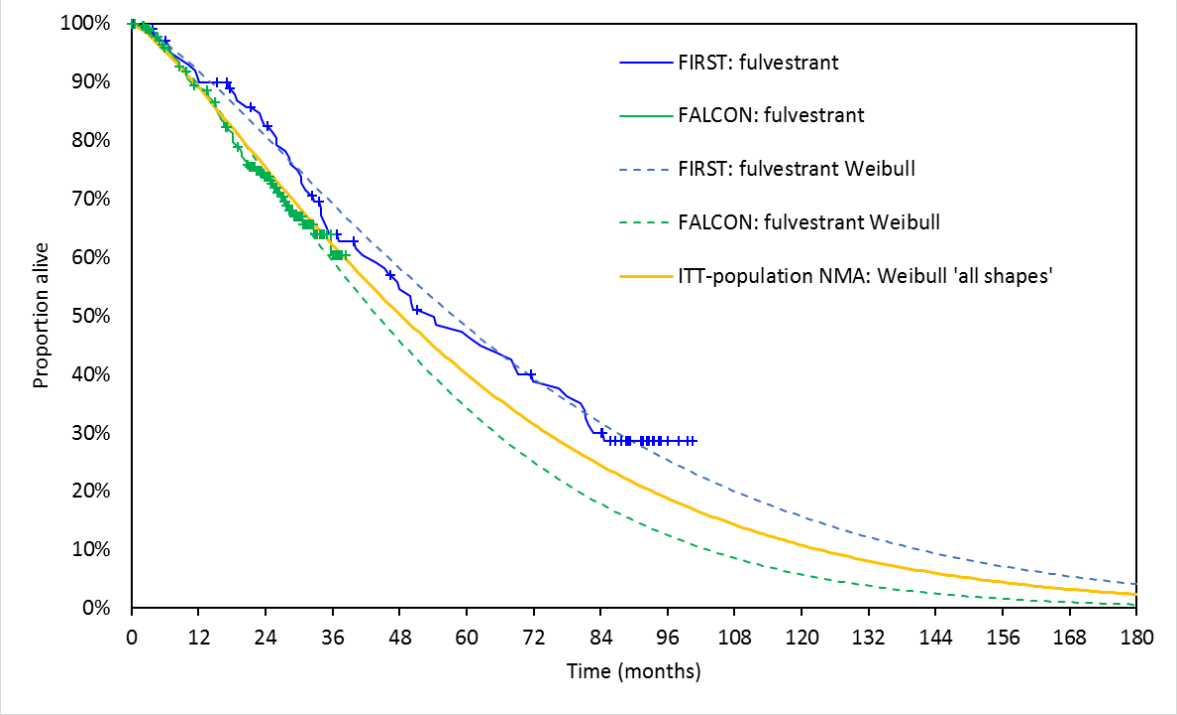


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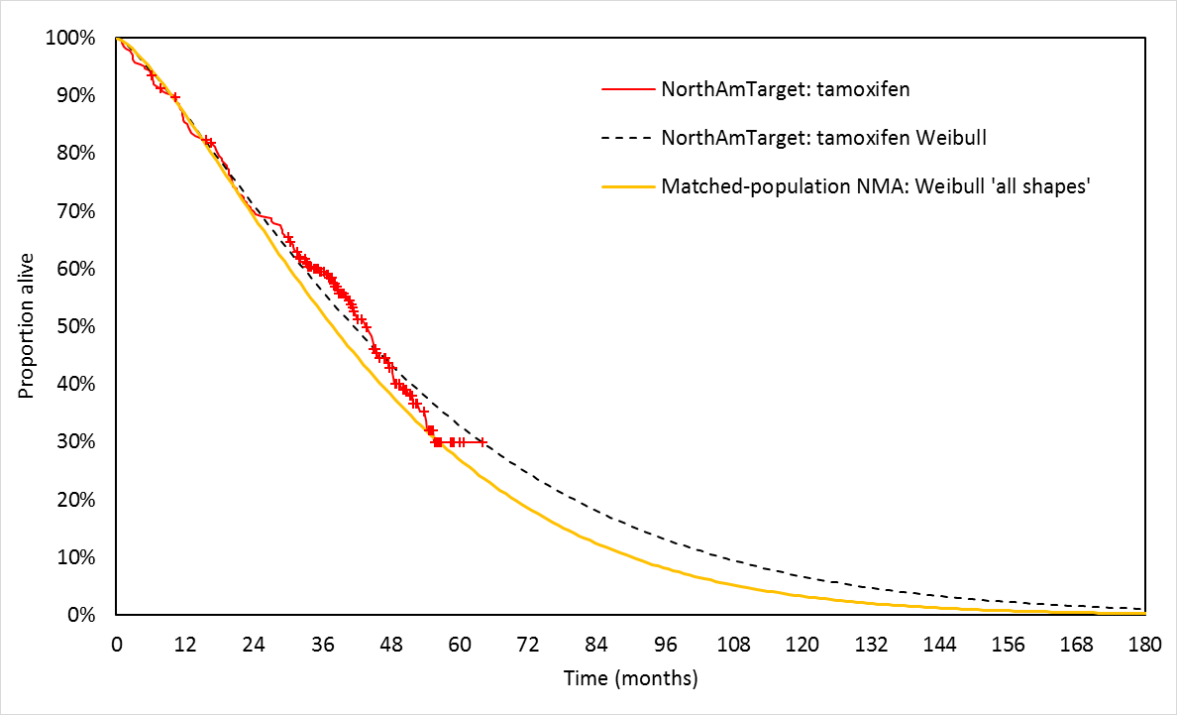
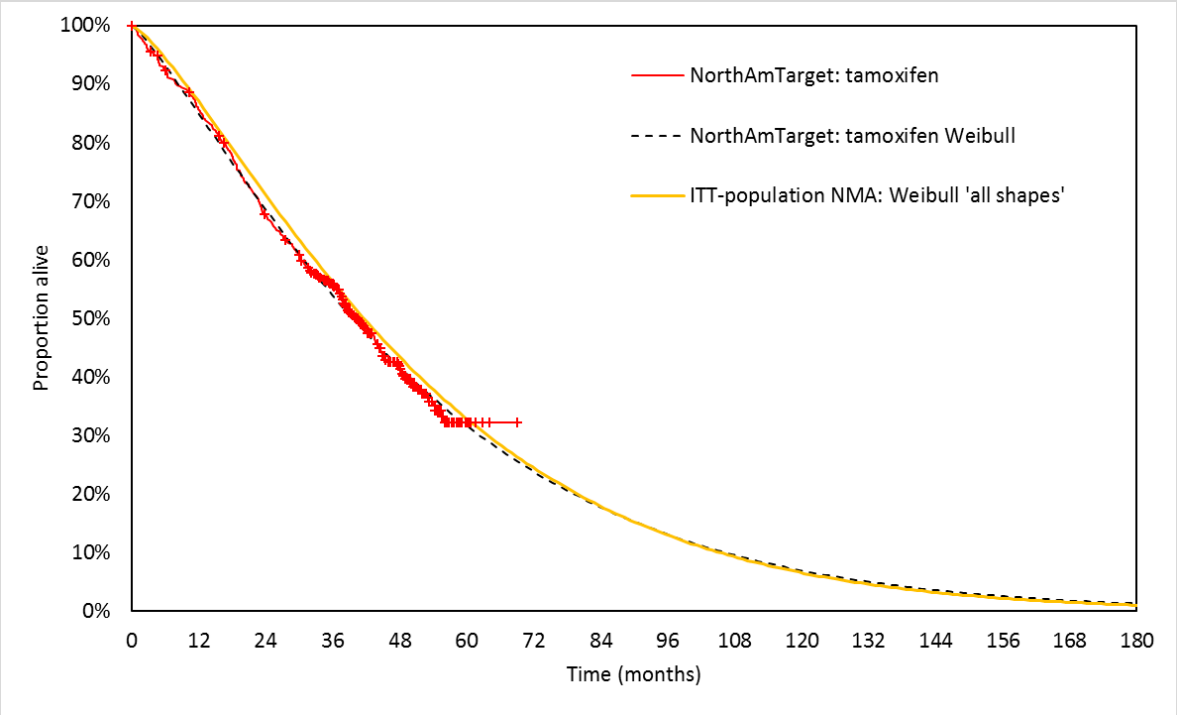
Figure 23: Kaplan-Meier, individual and fixed-effects network meta-analysis 'all shapes' OS survival curves for tamoxifen

A – matched populations



B – ITT populations



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1.6 ITT-population NMA cost-effective results

Incremental cost-effectiveness analysis results

Total costs, life years gained (LYG), QALYs and incremental cost per QALY for patients on either the intervention treatment (fulvestrant 500mg), or the comparator treatments (anastrozole, letrozole and for those patients in which aromatase inhibitors (AIs) are not tolerated or are contraindicated, tamoxifen), over the model time horizon (30 years, lifetime). The Weibull distribution from the fixed-effects NMA was used to extrapolate overall survival (OS) and the generalised gamma distribution estimated from the fixed-effects NMA was used to extrapolate progression-free survival (PFS).

The results section presents the results of fulvestrant when compared against the AIs (anastrozole and letrozole) and the results of fulvestrant when compared against tamoxifen (in those patients in which AIs are not tolerated or are contraindicated) separately.

Pair-wise comparisons of fulvestrant vs AIs and tamoxifen are presented in Table 18 and Table 19.

Table 18: Fulvestrant vs AIs

Technologies	Total			Incremental			ICER
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
AIs	£11,441	3.762	2.70	-	-	-	-
Fulvestrant	£31,890	4.502	3.26	£20,448	0.739	0.559	£36,565

Abbreviation: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years.

Table 19: Fulvestrant vs tamoxifen

Technologies	Total			Incremental			ICER
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Tamoxifen	£12,034	3.880	2.77	-	-	-	-
Fulvestrant	£31,890	4.502	3.26	£19,856	0.622	0.494	£40,196

Abbreviation: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years.

The ICER for fulvestrant compared with the AIs (anastrozole and letrozole) is £36,565 when the ITT-population NMA is used to populate the economic model. The corresponding results from the ERG base case analysis in the original submission was £33,455 based on the comparison of fulvestrant vs anastrozole. The results

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using the ITT-population NMA are in-line with expectations given a visual examination of the comparison predicted PFS and OS curves using the matched-population and ITT-population NMAs.

The ICER for fulvestrant compared with tamoxifen using the ITT-population NMA is £40,196 which, when compared with the results from the ERG base case (£23,687), is an increase of £16,509. The results are, again, in-line with expectations given a visual comparison of the results PFS and OS plots using the matched- and ITT-population NMAs. However, as stated throughout this document, it is AstraZeneca's belief that the results of the ITT-population NMA present potentially biased estimates of efficacy for the intervention and the comparators, especially for tamoxifen, given the heterogeneity in trial populations, and that the matched-population NMA should be considered the more valid estimator of efficacy.

Clinical outcomes from the model

The predicted mean and median time to progression, time in progressed disease and time alive for each arm of the simulation are summarized in Table 20.

Table 20: Survival outcomes; time (mean and median) spent in health states, undiscounted

Treatment	Time in PFS (months)		Time in PD (months)		Time alive (months)	
	Median	Mean	Median	Mean	Median	Mean
Fulvestrant	16.56	34.25	31.28	26.85	47.84	61.11
AIs	11.96	22.04	27.60	27.36	39.56	49.40
Tamoxifen	10.12	18.46	30.36	32.66	40.48	51.12

Abbreviation: PD, progressed disease; PFS, progression-free survival.

Table 21 and Table 22 summarises the breakdown of QALYs for each health state over the model time horizon in the base case analysis for fulvestrant vs anastrozole and, for those patients in which aromatase inhibitors are not tolerated or contraindicated, tamoxifen, respectively.

Table 21: Summary of QALY gain by health state; fulvestrant vs AIs

Health state	QALY intervention (fulvestrant)	QALY comparator (AIs)	Incremental QALYs	% absolute incremental QALYs
PF	1.90	1.29	0.61	108.31%
PD	1.36	1.41	-0.05	-8.29%
AE disutility	0.00	0.00	0.00	-0.02%
Total	3.26	2.70	0.56	100.00%

Abbreviation: AE, adverse events; PD, progressed disease; PF, progression-free.

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Table 22: Summary of QALY gain by health state; fulvestrant vs tamoxifen

Health state	QALY intervention (fulvestrant)	QALY comparator (tamoxifen)	Incremental QALYs	% absolute incremental QALYs
PF	1.90	1.10	0.80	161.55%
PD	1.36	1.67	-0.30	-61.62%
AE disutility	0.00	0.00	0.00	0.08%
Total	3.26	2.77	0.49	100.00%

Abbreviation: AE, adverse events; PD, progressed disease; PF, progression-free.

Table 23 and Table 24 summarises the breakdown of costs in the base case analysis.

Table 23: Summary of costs by health state; fulvestrant vs AIs

Health state	Cost intervention (fulvestrant)	Cost comparator (AIs)	Incremental costs	% absolute increment
Disease management: PF	£2,989	£2,035	£953	4.66%
Disease management: PD	£2,332	£2,411	-£79	-0.39%
Terminal care	£3,761	£3,881	-£120	-0.59%
Treatment acquisition	£17,562	£17	£17,545	85.80%
Administration and monitoring	£3,560	£789	£2,771	13.55%
Subsequent treatment	£1,575	£2,257	-£682	-3.34%
Adverse events	£112	£52	£60	0.29%
Total	£31,890	£11,441	£20,448	100.00%

Abbreviation: PD, progressed disease; PF, progression-free.

Table 24: Summary of costs by health state; fulvestrant vs tamoxifen

Health state	Cost intervention (fulvestrant)	Cost comparator (tamoxifen)	Incremental costs	% absolute increment
Disease management: PF	£2,989	£1,733	£1,256	6.32%
Disease management: PD	£2,332	£2,852	-£520	-2.62%
Terminal care	£3,761	£3,864	-£103	-0.52%
Treatment acquisition	£17,562	£29	£17,533	88.30%
Administration and monitoring	£3,560	£701	£2,859	14.40%
Subsequent treatment	£1,575	£2,547	-£972	-4.90%
Adverse events	£112	£309	-£197	-0.99%
Total	£31,890	£12,034	£19,856	100.00%

Abbreviation: PD, progressed disease; PF, progression-free.

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Sensitivity analyses

Probabilistic sensitivity analysis was conducted to assess the parametric uncertainty associated with the base case model results. Those parameters where estimates of uncertainty were available were assigned probability distributions and point estimates were drawn using Monte Carlo simulation techniques. Where available, known correlation between parameters was preserved; e.g., the correlations for the baseline survival curve parameters (PFS and OS) were available from the survival analysis and included in the model (assuming a multivariate normal distribution). The parameters to which there was uncertainty, and the choice of distribution used is presented in Table 25.

Table 25: PSA distributions per parameter

Parameter	Distribution	Comment
Survival distributions	Cholesky decomposition	Decomposition of a Hermitian, positive-definite matrix into the product of a lower triangular matrix and its conjugate transpose
Survival curve (shape, scale, and covariate parameters)	Multinomial normal	Incorporates the covariance between parameters estimated in a survival regression analysis
Costs	Gamma	Likely skewed nature of health care costs, and their constraint to positive values
AE rates (incidence)	Beta	Bounded between 0 and 1
Distribution of subsequent treatments	Dirichlet distribution	Normalised sum of independent gamma variables
Duration of subsequent treatment	Gamma	Bounded between 0 and infinity, and skewed
Utilities	Beta	Constrained to values between minus infinity and 1. Modelled as a disutility
AE disutilities	Lognormal	Bounded between 0 and infinity, and skewed

Abbreviation: AE, adverse event; PSA, probabilistic sensitivity analysis.

The PSA was run for 10,000 iterations for the base case analysis. Results from the PSA are presented in Table 26 and Table 27 for fulvestrant vs AIs and fulvestrant vs tamoxifen, respectively.

Table 26: Average results based on the probabilistic sensitivity analysis (10,000 iterations); fulvestrant vs AIs

Technologies	Total			Incremental			ICER
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
AIs	£11,446	3.771	2.715	-	-	-	-
Fulvestrant	£32,038	4.543	3.298	£20,592	0.772	0.583	£35,310

Abbreviation: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years.

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Table 27: Average results based on the probabilistic sensitivity analysis (10,000 iterations); fulvestrant vs tamoxifen

Technologies	Total			Incremental			ICER
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Tamoxifen	£12,041	3.895	2.784	-	-	-	-
Fulvestrant	£32,038	4.543	3.298	£19,997	0.648	0.514	£38,895

Abbreviation: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years.

The cost-effectiveness planes (CEP) for fulvestrant compared with anastrozole and tamoxifen are presented in

Figure **24** and Figure **25**, respectively.

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Figure 24: Cost-effectiveness plane for fulvestrant vs AIs

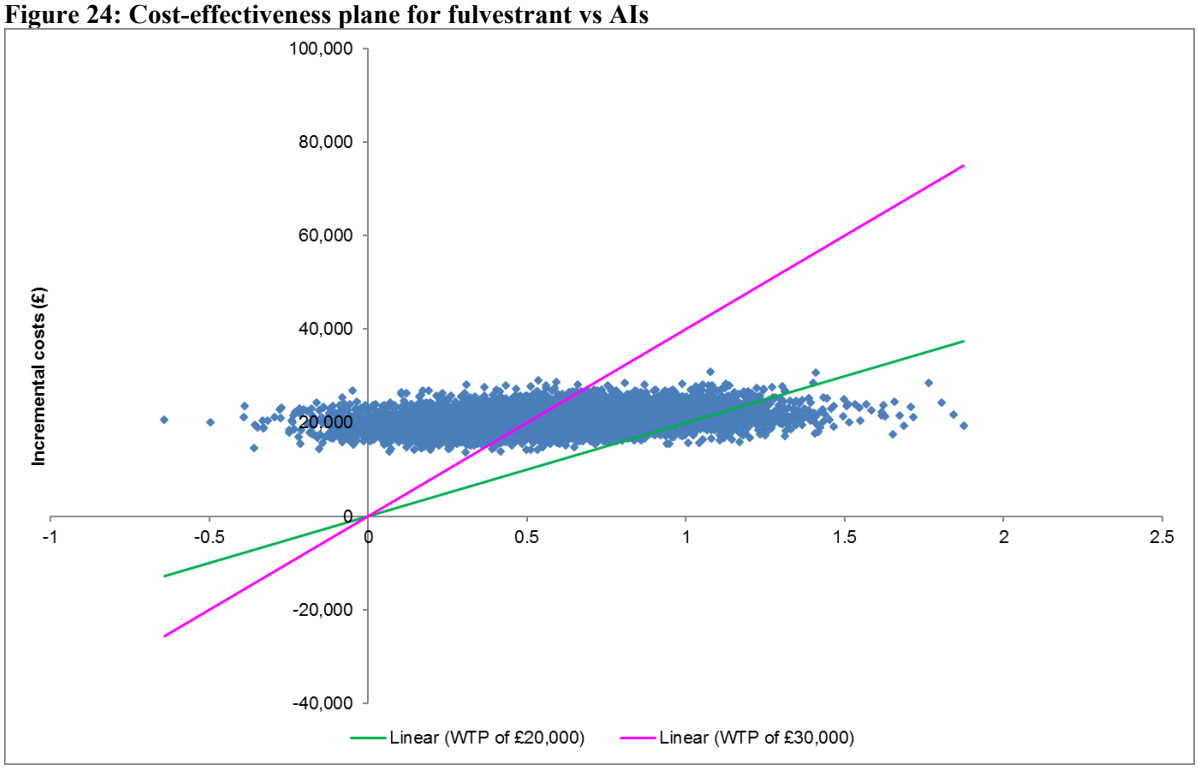

Figure 25: Cost-effectiveness plane for fulvestrant vs tamoxifen

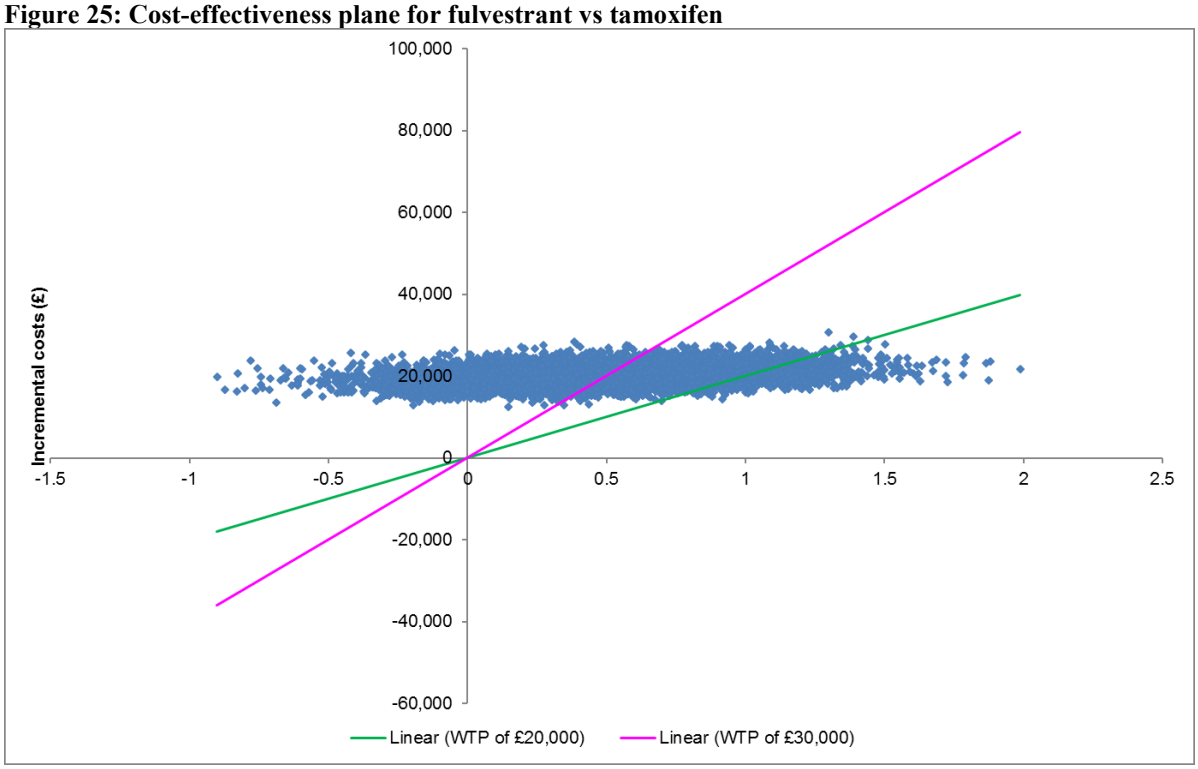

Table 28 and Figure 26 present the probability of fulvestrant and the AIs being the most cost-effective at a series of WTP thresholds.

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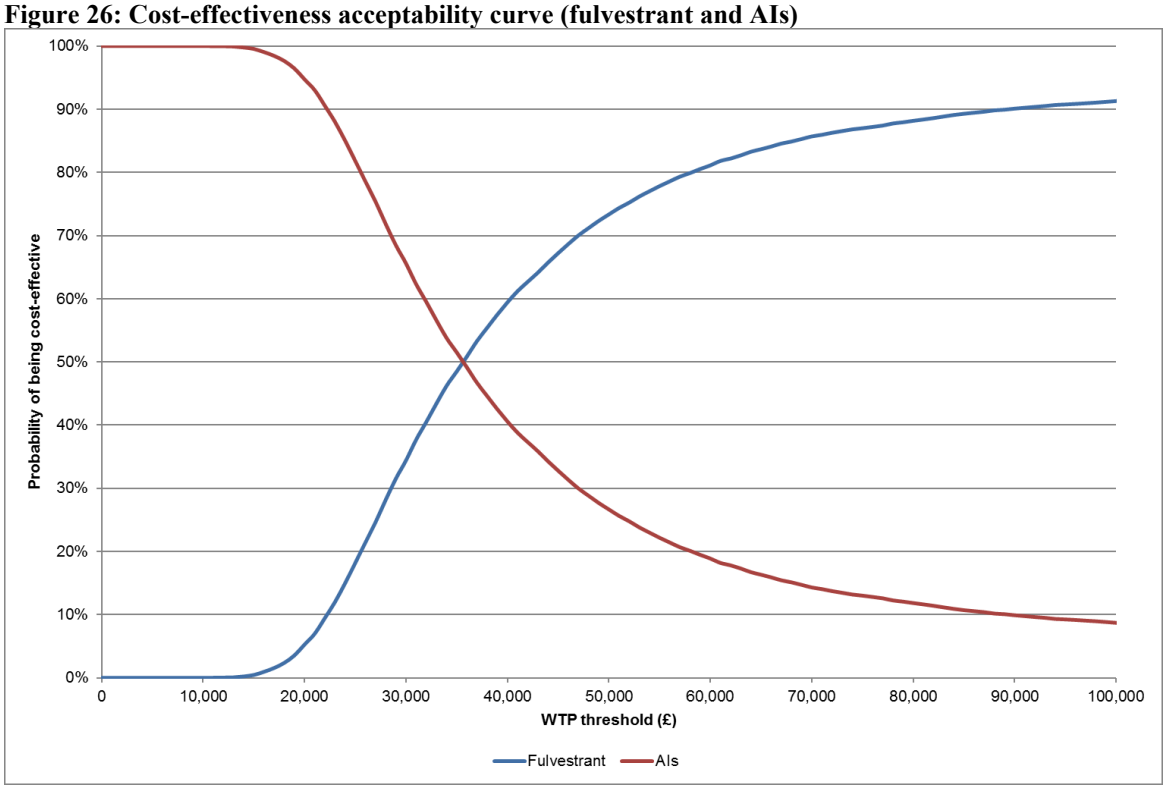
Table 28: Probability of being the most cost-effective treatment (fulvestrant and AIs) at WTP thresholds

Technology	WTP threshold		
	£20,000	£30,000	£50,000
Fulvestrant	5.3%	34.4%	73.4%
AIs	94.7%	65.6%	26.7%

Abbreviation: WTP, willingness to pay.

Figure 26: Cost-effectiveness acceptability curve (fulvestrant and AIs)



Abbreviation: WTP, willingness to pay.

Table 29 and Figure 27 present the probability of fulvestrant and tamoxifen being the most cost-effective at a series of WTP thresholds.

Table 29: Probability of being the most cost-effective treatment (fulvestrant, tamoxifen) at WTP thresholds

Technology	WTP threshold		
	£20,000	£30,000	£50,000
Fulvestrant	7.2%	33.4%	63.8%
Tamoxifen	92.8%	66.6%	36.2%

Abbreviation: WTP, willingness to pay.

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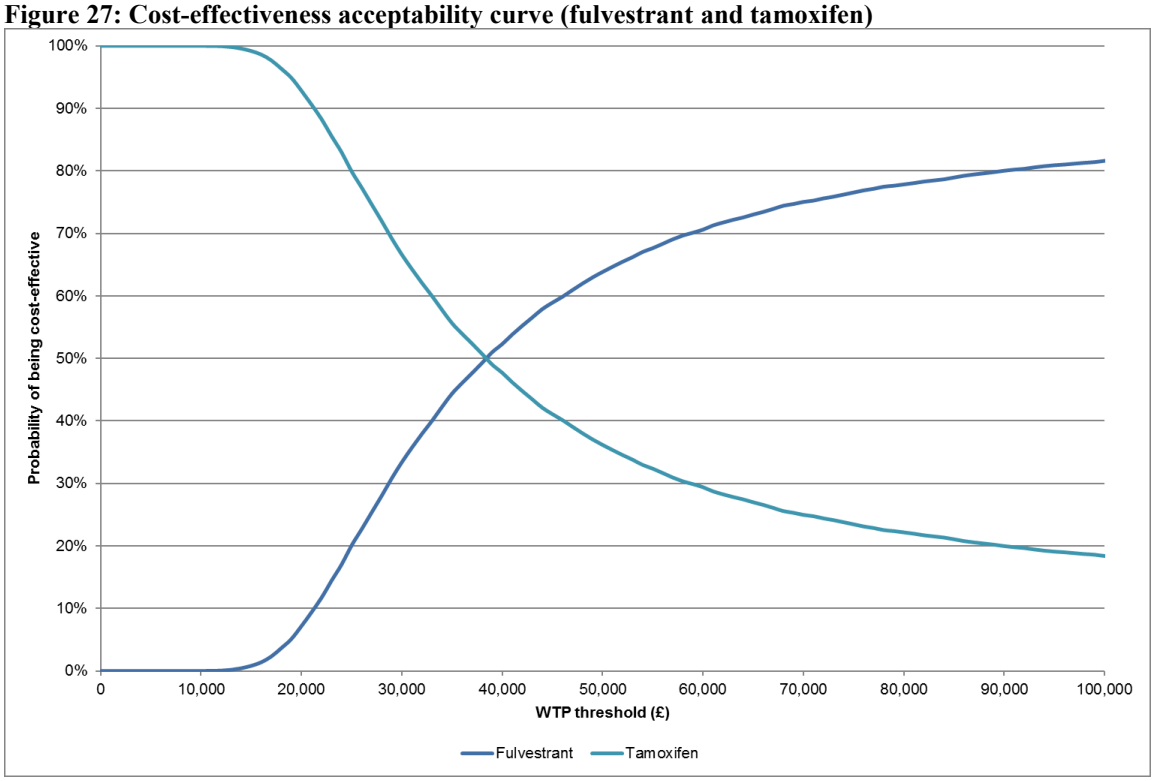
Figure 27: Cost-effectiveness acceptability curve (fulvestrant and tamoxifen)



Abbreviation: WTP, willingness to pay.

Conclusions

The ITT-population NMA presented in this document has the potential to provide biased estimates of the efficacy of all treatments considered in this appraisal, due to the heterogeneity of trial populations. Given that AstraZeneca is in the relatively unique position of having patient-level data (PLD) for all the trials informing the networks of evidence, and because a random-effects meta-analysis could not be undertaken, an attempt was made to mitigate the impact of heterogeneity by sub-dividing the data on pre-randomisation variables; this allowed for both the preservation of randomisation and a greater degree of homogeneity between FALCON (which fully represents the licensed population for fulvestrant) and FIRST and NorthAmTarget.

The matched-population NMA, which informed the initial submission, is considered to provide more accurate estimates of long-term PFS and OS for anastrozole as well as treatment effects (relative to anastrozole) for fulvestrant and tamoxifen, and is therefore thought to provide a more realistic estimate of the cost-effectiveness of fulvestrant.

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Appendix 3 – Alternative cost-effectiveness results

The following scenario analysis explores the cost-effectiveness of fulvestrant under an alternative pricing assumption, where the net price of fulvestrant in the base case model proposed by the ERG is [redacted] instead of the list price of £522.41. All other assumptions in the ERG's preferred model, which they *"consider to be the most representative analysis of the available evidence"*, are retained.

- Resource use for PFS and PD health states are based on the study by Karnon et al, 2003
- Revised proportion of patients receiving second-line treatment
- Exclusion of PO25 trial from the NMA network and assuming similar efficacy for letrozole and anastrozole
- All patients receiving fulvestrant administered in an outpatient setting

The Weibull distribution from the fixed-effects NMA was used to extrapolate OS and the generalised gamma distribution estimated from the fixed-effects NMA was used to extrapolate PFS in the base case analysis.

The incremental results of the ERG base case from the report (Table 59, p140) are reproduced in

Table 1: Incremental results for the ERG base case (Table 59, p140 ERG report)

Treatments	Total Costs	Total QALYs	Incremental costs	Incremental QALYs	Incremental ICER (cost per QALY)
Letrozole	£11,336	2.68			
Anastrozole	£11,356	2.68			
Tamoxifen	£11,852	2.47	£496	-0.21	Dominated
Fulvestrant	£29,866	3.23	£18,510	0.54	£33,455

The results section presents the results of fulvestrant when compared against the AIs (anastrozole and letrozole) and the results of fulvestrant when compared against tamoxifen (in those patients in which AIs are not tolerated or are contraindicated) separately.

Pair-wise comparisons of fulvestrant vs AIs and fulvestrant vs tamoxifen are presented in Table 2 and Table 3.

Table 2: Fulvestrant vs AIs

Technologies	Total			Incremental			ICER
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
AIs	£11,356	3.736	2.68	-	-	-	-
Fulvestrant	[redacted]	4.475	3.23	[redacted]	0.739	0.553	[redacted]

Abbreviation: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years.

Table 3: Fulvestrant vs tamoxifen

Technologies	Total			Incremental			ICER
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Tamoxifen	£11,853	3.479	2.47	-	-	-	-
Fulvestrant	[redacted]	4.475	3.23	[redacted]	0.996	0.761	[redacted]

Abbreviation: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years.

Clinical outcomes from the model

The predicted mean and median time to progression, time in progressed disease and time alive for each arm of the simulation are summarized in Table 4 and are unchanged from those in the original submission.

Table 4: survival outcomes; time (mean and median) spent in health states, undiscounted

Treatment	Time in PFS (months)		Time in PD (months)		Time alive (months)	
	Median	Mean	Median	Mean	Median	Mean
Fulvestrant	16.56	29.63	31.28	30.46	47.84	60.09
AIs	11.96	19.58	27.60	29.37	39.56	48.95
Tamoxifen	9.20	13.17	27.60	31.89	36.80	45.05

Abbreviation: PD, progressed disease; PFS, progression-free survival.

Table 5 and Table 6 summarises the breakdown of QALYs for each health state over the model time horizon in the base case analysis for fulvestrant vs anastrozole and, for those patients in which aromatase inhibitors are not tolerated or contraindicated, tamoxifen, respectively.

Table 5: Summary of QALY gain by health state; fulvestrant vs AIs

Health state	QALY intervention (fulvestrant)	QALY comparator (AIs)	Incremental QALYs	% absolute incremental QALYs
PF	1.71	1.18	0.53	96.05%
PD	1.52	1.50	0.02	3.97%
AE disutility	0.00	0.00	0.00	-0.02%
Total	3.23	2.68	0.55	100.00%

Abbreviation: AE, adverse events; PD, progressed disease; PF, progression-free.

Table 6: Summary of QALY gain by health state; fulvestrant vs tamoxifen

Health state	QALY intervention (fulvestrant)	QALY comparator (tamoxifen)	Incremental QALYs	% absolute incremental QALYs
PF	1.71	0.81	0.90	118.05%
PD	1.52	1.66	-0.14	-18.10%
AE disutility	0.00	0.00	0.00	0.05%
Total	3.23	2.47	0.76	100.00%

Abbreviation: AE, adverse events; PD, progressed disease; PF, progression-free.

Economic outcomes from the model

Table 7 and Table 8 summarise the breakdown of costs in the base case analysis.

Table 7: summary of costs by health state; fulvestrant vs AIs

Health state	Cost intervention (fulvestrant)	Cost comparator (AIs)	Incremental costs	% absolute increment
Disease management: PF	£2,690	£1,854	£836	5.18%
Disease management: PD	£2,598	£2,561	£38	0.23%
Terminal care	£3,773	£3,886	-£113	-0.70%
Treatment acquisition	[redacted]	£15	[redacted]	[redacted]
Administration and monitoring	£3,234	£733	£2,501	15.50%
Subsequent treatment	£1,598	£2,255	-£657	-4.07%
Adverse events	£112	£52	£60	0.37%
Total	[redacted]	£11,356	[redacted]	100.00%

Abbreviation: PD, progressed disease; PF, progression-free.

Table 8: summary of costs by health state; fulvestrant vs tamoxifen

Health state	Cost intervention (fulvestrant)	Cost comparator (tamoxifen)	Incremental costs	% absolute increment
Disease management: PF	£2,690	£1,278	£1,413	9.03%
Disease management: PD	£2,598	£2,834	-£235	-1.50%
Terminal care	£3,773	£3,925	-£151	-0.97%
Treatment acquisition	[redacted]	£21	[redacted]	[redacted]
Administration and monitoring	£3,234	£561	£2,673	17.10%
Subsequent treatment	£1,598	£2,926	-£1,328	-8.49%
Adverse events	£112	£309	-£197	-1.26%
Total	[redacted]	£11,853	[redacted]	100.00%

Abbreviation: PD, progressed disease; PF, progression-free.

Sensitivity analyses

Probabilistic sensitivity analysis

The PSA was run for 10,000 iterations. Results from the PSA are presented in and for fulvestrant vs AIs and fulvestrant vs tamoxifen, respectively.

Table 9: Average results based on the probabilistic sensitivity analysis (10,000 iterations); fulvestrant vs AIs

Technologies	Total			Incremental			ICER
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
AIs	£11,362	3.741	2.682	-	-	-	-
Fulvestrant	[redacted]	4.512	3.258	[redacted]	0.771	0.575	[redacted]

Abbreviation: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years.

Table 10: Average results based on the probabilistic sensitivity analysis (10,000 iterations); fulvestrant vs tamoxifen

Technologies	Total			Incremental			ICER
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Tamoxifen	£11,877	3.504	2.489	-	-	-	-
Fulvestrant	[redacted]	4.512	3.258	[redacted]	1.008	0.768	[redacted]

Abbreviation: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years.

The cost-effectiveness planes (CEP) for fulvestrant compared with anastrozole and tamoxifen are presented in Figure 1 and Figure 2, respectively.

Figure 1: Cost-effectiveness plane for fulvestrant vs AIs

Figure 2: Cost-effectiveness plane for fulvestrant vs tamoxifen

Table 11 and Figure 3 present the probability of fulvestrant and the AIs being the most cost-effective at a series of WTP thresholds.

Table 11:Probability of being the most cost-effective treatment (fulvestrant and AIs) at WTP thresholds

Technology	WTP threshold		
	£20,000	£30,000	£50,000
Fulvestrant	[redacted]	[redacted]	[redacted]
AIs	[redacted]	[redacted]	[redacted]

Abbreviation: WTP, willingness to pay.

Figure 3: Cost-effectiveness acceptability curve (fulvestrant and AIs)

Table 12 and Figure 4 present the probability of fulvestrant and tamoxifen being the most cost-effective at a series of WTP thresholds.

Table 12: Probability of being the most cost-effective treatment (fulvestrant and tamoxifen) at WTP thresholds

Technology	WTP threshold		
	£20,000	£30,000	£50,000
Fulvestrant	[redacted]	[redacted]	[redacted]
Tamoxifen	[redacted]	[redacted]	[redacted]

Abbreviation: WTP, willingness to pay.

Figure 4: Cost-effectiveness acceptability curve (fulvestrant and tamoxifen)

Comparison with original base case

A comparison of the deterministic base case and point estimates from the average probabilistic results reported by the ERG (Table 60, page 141) are summarised in Table 13, along with results for the proposed pricing scenario.

Table 13: Comparison of point estimates from the deterministic and probabilistic analyses of the ERG base case and new scenario

Intervention vs comparator	Deterministic ICER		Probabilistic ICER	
	Base case	Scenario 1	Base case	Scenario 1
Fulvestrant vs anastrozole	£33,455	[redacted]	£32,956	[redacted]
Fulvestrant vs tamoxifen	£23,687	[redacted]	£23,999	[redacted]

The result of the scenario presented in this appendix shows that fulvestrant has the potential to be considered cost-effective under the proposed pricing assumption.

Fulvestrant for untreated locally advanced or metastatic oestrogen-receptor positive breast cancer

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments 5pm Friday 25 September 2017 on **email:** [insert TACommA@nice.org.uk /NICE DOCS

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? 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 the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Breast Cancer Now
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
Name of commentator person completing form:	[redacted]

Please return to: **[insert email address]** / NICE DOCS

Fulvestrant for untreated locally advanced or metastatic oestrogen-receptor positive breast cancer

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments 5pm Friday 25 September 2017 on **email:** [insert TACommA@nice.org.uk /NICE DOCS

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	Breast Cancer Now was disappointed in the committee's decision not to recommend fulvestrant for use in this population. Fulvestrant provides a valuable treatment option for women with ER+ advanced breast cancer and we believe that patients who could benefit from this treatment should have access to it. Evidence shows that fulvestrant can add nearly three months progression free survival when compared to the standard treatment in this patient group (anastrozole). Metastatic breast cancer is a terminal diagnosis and any additional time, especially with a good quality of life, is extremely valuable to breast cancer patients and their families.
2	The side effect profile of fulvestrant is similar to that of aromatase inhibitors, with many people experiencing only mild side effects with fulvestrant. However, some patients may have a preference as the treatments are delivered differently. Aromatase inhibitors are delivered by a daily tablet while fulvestrant is delivered through monthly intramuscular injections into the buttocks. Some patients may prefer to have injections once a month and then not to have to worry about their treatment for the rest of the month, rather than having to remember to take tablets every day. In addition, some patients find swallowing tablets very difficult and so may prefer to have their medication delivered via injection.
3	Fulvestrant may allow patients to delay the start of chemotherapy. Chemotherapy treatment is associated with side effects such as nausea, vomiting and hair loss. These side effects can have a significant impact on a patient's quality of life, something that is highly valued as patients near the end of their lives.
4	Patients with locally advanced or metastatic oestrogen-receptor positive breast cancer are in need of new treatment options. While new treatments (such as palbociclib and ribociclib) have been developed for this patient group, it is not yet clear whether these treatments will be made routinely available on the NHS. Other innovative breast cancer treatments (such as trastuzumab emtansine) are not suitable for patients with this type of breast cancer.
5	Women with metastatic breast cancer have a terminal disease and wish to extend their lives as long as possible. We know from talking to breast cancer patients that they also value progression free survival with minimal side effects as it allows them a good quality of life so they are able to continue to spend time with their friends and families and do the things they enjoy. It is therefore vital that as many treatment options as possible are available to these patients so that they are able to make the most of the limited time they have left. While we appreciate that there is a lack of overall survival data for fulvestrant, it has been shown to extend progression free survival.
6	It is disappointing that this drug could not be considered for funding through the Cancer Drugs Fund. Most cancer drugs which have uncertain survival data could be eligible for Cancer Drugs Fund funding while more mature data are collected. However, because

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments 5pm Friday 25 September 2017 on **email:** [insert TACommA@nice.org.uk /NICE DOCS

	fulvestrant is an endocrine therapy rather than a chemotherapy and therefore is commissioned locally rather than centrally, fulvestrant is not eligible for the CDF. This split in commissioning is not logical and is now having a real impact on patients as it means that they won't be able to access a treatment that may provide benefit to them. We will be taking the issue of the eligibility criteria for the Cancer Drugs Fund up with NHS England.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Single technology appraisal

Fulvestrant for untreated hormone-receptor positive locally advanced or metastatic breast cancer [ID951]

ADDENDUM TO THE ERG REPORT

ERG's summary of and comments on the 'Company additional evidence submission' submitted by AstraZeneca to NICE in response to the ACD

Produced by Southampton Health Technology Assessments Centre (SHTAC)

Addendum date 13th October 2017

Key to colour highlighting used in this addendum

[redacted]

TABLE OF CONTENTS

1 Introduction

After the first Appraisal Committee Meeting (ACM) for the Single Technology Appraisal (STA) of fulvestrant for untreated hormone-receptor positive locally advanced or metastatic breast cancer NICE produced an appraisal consultation document (ACD). The ACD did not recommend fulvestrant, within its marketing authorisation, for treating locally advanced or metastatic oestrogen-receptor positive breast cancer in postmenopausal women that have not previously been treated with endocrine therapy. The reasons why the committee made this negative recommendation are provided in full within the ACD but in summary, the main areas of concern were that:

- the final results on overall survival (OS) from the FALCON trial are not available yet, so it is unclear whether fulvestrant will extend OS compared with aromatase inhibitors which are currently used for first-line management.
- the 'matching' approach adopted by the company when undertaking the indirect treatment comparison may not have been appropriate. The committee would have liked to have compared the results using the 'matched' population with those for the full 'unmatched' population to assess the robustness of the results. The committee was not confident that the results of the indirect treatment comparison were reliable.
- The projections for OS are highly uncertain and this is the main area of uncertainty in the cost-effectiveness analysis. The committee was concerned that much of the OS projection for fulvestrant was driven by data from the FIRST trial, which the committee had already concluded was less relevant than FALCON

When the ACD was produced, NICE invited comments from the consultees and commentators for the appraisal as well as comments from the public.

2 Company additional evidence submission

In response to the ACD the company has submitted further evidence (document titled 'Company additional evidence submission') which addresses five elements in an addendum (Company addendum sections 2.1 to 2.5) and presents intention to treat (ITT)-population cost-effectiveness results (Company addendum section 2.6). The company also submitted results from the ITT population network meta-analysis (NMA) for OS and progression-free survival (PFS) and instructions for including these results in the economic model. On 9th October 2017 the ERG received an additional document "Appendix 3 - Alternative cost-effectiveness results"

which contains an exploration of the cost-effectiveness of fulvestrant under an alternative pricing assumption.

The ERG has read the additional evidence submission and provides comments on each of its sections below, focussing on the aspects that seem to mostly closely align to the NICE committee's main areas of concern.

2.1 Influence of study design on reliability of outcomes of FIRST

The company states that estimates of OS are unlikely to be biased in open label studies such as FIRST. The ERG agrees, that objective outcomes such as all-cause mortality are less likely to be biased in open label studies than subjective outcomes.

The company goes on to address a further area of concern for the NICE committee which related to the OS estimate in FIRST. This was the degree to which the OS outcome could have been affected by missing data. As noted in the ERG report (section 3.3.2) the analysis of OS was not originally specified in the trial. The published paper presenting the analysis of OS in the FIRST RCT[1] explains that trial sites were invited to request written consent from patients for the collection of additional data. Consequently 35 patients did not contribute data to this outcome, for the majority (20 patients, 57%) this was because they attended centres that declined to contribute to the OS follow-up phase. The other 15 patients (from 9 different centres) did not consent to follow-up.

The missing data were split almost equally between the two study arms (16 from the fulvestrant arm; 19 from the anastrozole arm). This may in part have been because, as stated in the clinical study report (CSR) for FIRST,

[redacted]. The company presents sensitivity analysis to explore the hypothesis that the missing 35 patients may have influenced the OS estimates for the ITT FIRST population. The company does this by:

i) testing whether the 35 patients have any differences in baseline characteristics compared to the full ITT population

ii) presenting an analysis of the PFS for those who provided consent to participate in the OS follow up versus those who did not
iii) presenting an analysis where all patients in FIRST who did not provide consent, were censored at final data cut-off and assumed to be still alive.

The results of the analysis of baseline characteristics show that for the four baseline characteristics in the company's addendum Table 1 (Visceral involvement, Prior chemotherapy, Measurable disease and Prior endocrine therapy) three are well balanced between the trial arms for the patients not consenting to OS follow-up and one, Measurable disease, shows a slight imbalance [redacted]. The comparison of the baseline characteristics for the patients not consenting to OS follow-up with those of the ITT population also display some slight differences (the largest being for Visceral involvement in the anastrozole arm which in patients not consenting to OS follow-up was [redacted], but in the ITT population was no: 44% and yes: 56%).

The analysis of PFS (company's addendum Table 2) demonstrates that median PFS was [redacted] in the anastrozole arm among those who did not consent to OS follow-up [redacted] than it was for those who did consent to OS follow-up ([redacted]) and consequently the HR for the 35 participants who did not consent to OS follow-up is [redacted] than it is for the subgroup of 170 participants who did consent to OS follow-up [redacted]. The PFS results for the ITT population (HR 0.66 95% CI 0.47 to 0.92, n=205) are similar to those for the 170 participants who consented to follow-up so the company suggests that subgroup of 35 participants do not exert any great influence over the overall PFS outcome.

In the company's final analysis to investigate the potential impact of the missing 35 participants on OS, the 35 participants who did not provide consent, were censored at final data cut-off and all of them were assumed to be still alive (i.e. the OS outcome is set to be identical in both trial arms for the missing participants). This is one example of the use of an extreme option to account for the missing OS data and the ERG would have welcomed an extension of this to explore other extreme options (i.e. an assumption that all those in the fulvestrant arm had died and all those in the anastrozole arm were alive or vice versa, and an assumption that all 35

participants have died). The ERG recognises however that other extreme options, which assume the missing patients have died, would require assumptions to be made about when deaths occurred. The effect of assuming all the missing participants were alive at final data cut off was to generate a hazard ratio that was not statistically significant ([redacted]); in comparison to the HR of 0.705 95% CI 0.50 to 0.99 in the analysis where data for the missing 35 participants were censored at the point each patient was last known to be alive (company's addendum Table 3). The company state that the analysis indicates that the OS benefit of fulvestrant compared to anastrozole observed in FIRST is unlikely to be significantly influenced by the missing data from the 35 patients who did not participate in the OS follow-up. The ERG observes that the company's analysis assuming all missing participants are alive at final data cut off shifts the hazard ratio from 0.705 to [redacted] and the outcome moves from one with statistical significance to one that is not statistically significant. The ERG finds it difficult to know how realistic the assumption of having all patients still alive is, and thus concludes that there is still uncertainty regarding the impact of the missing 35 patients on the OS outcome.

The final part of the company's exploration of the issues regarding the 'Influence of study design on the reliability of outcomes from FIRST' looked at the impact of data maturity. The company point to the CONFIRM study which, at first data cut off, showed a significant PFS effect but a non-significant effect in OS which had data that was only 50% mature. However, by the second data cut off when 75% of participants had died the OS benefit was statistically significant. Furthermore the company point out that the survival curves for the 75% mature CONFIRM data do not separate until at least 12 months, which is similar to the separation of the FIRST survival curves at 69% maturity. Thus the company have confidence that a treatment effect on OS will be observable in the FALCON study once data are mature (>50%). The ERG note that the participants in the CONFIRM trial were postmenopausal women who had either locally advanced or metastatic ER-positive breast cancer. All had received prior adjuvant endocrine therapy (in contrast all participants in the FALCON trial and 74.6% of participants in the FIRST trial were endocrine therapy naive). Furthermore CONFIRM was a comparison of fulvestrant 500mg and fulvestrant 250mg but the company make the case that since studies have shown no difference between fulvestrant 250mg and anastrozole 1mg the CONFIRM study can be considered a comparison of fulvestrant 500mg and anastrozole 1mg. In the ERG's view the differences between the CONFIRM trial and the FALCON trial make it difficult to generalise between the two.

ERG Summary

The company have presented the case that the OS estimate in the FIRST trial is valid because i) OS was unlikely to be biased despite the open-label design of the trial and ii) because the missing OS data for 35 of the 205 participants had not significantly influenced the overall OS outcome. The ERG agrees with the first of these two points but would have liked to have seen a more wide ranging exploration of the impact of missing data on the OS outcome as the ERG is still uncertain about the extent to which the missing data could have altered the OS outcome. Furthermore the company assert that the FIRST trial, and another fulvestrant trial CONFIRM, both point to the likelihood that a treatment effect on OS will be observable in the FALCON study when data are mature. On this final point the ERG also have some reservations. This is because of the differences between the CONFIRM trial population and the FALCON trial population and because it is still unclear to the ERG what the relationship is between PFS and OS is i.e. how well PFS predicts OS in the relevant population for this appraisal (post-menopausal people with locally advanced or metastatic hormone receptor-positive breast cancer, who have not received endocrine therapy). As stated in the main ERG report, the ERG is concerned that the OS benefit in FALCON may mirror that of PFS in FALCON and not be as great as observed in the FIRST study.

2.2 The matching process used in the submission was robust

In this section of the company's additional evidence submission the company address the concerns of the NICE committee that the 'matching' approach undertaken by the company for the indirect treatment comparison may not have been appropriate.

The company assert that applying selection criteria to the FIRST and NorthAmerica:TARGET trial populations does not break randomisation. The company state that this is because in both the studies endocrine naivety was a pre-randomisation variable. In the ERG's view, to be certain not to break randomisation the initial randomisation would have to have been stratified for the characteristics subsequently used for the 'matching' process. The company presents data to demonstrate that baseline characteristics are balanced before and after the 'matching' process, and indeed the ERG and NICE had already sought baseline characteristics for the matched trial populations (clarification question A9) and the ERG report (section 3.1.7) states ""Where possible the ERG has compared the baseline characteristics for the matched trial populations and those for the whole trial populations reported in CS Tables 26-28. Where the

ERG is confident that the definition of characteristics correspond (e.g. age, visceral disease, measurable disease) the baseline characteristics of the matched and whole trial population data are very similar."

The company then present evidence to show that the results for the matched trial populations are not inconsistent with existing published outcomes and that matching provides supportive evidence for FIRST results. The ERG has noted this evidence.

ERG Summary

Although the ERG believes that only stratification of the initial randomisation on the baseline characteristics used for matching would avoid breaking randomisation, it is reassuring that the baseline characteristics of the matched and whole trial population data are so similar. Further reassurance comes from the results of the indirect treatment comparison conducted using the ITT data (this addendum section 2.3).

2.3 Indirect and mixed treatment comparisons

The ACD stated that the NICE committee would have liked to have compared the results using the 'matched' population with those for the full 'unmatched' population to assess the robustness of the results of the indirect treatment comparison and indeed NICE and the ERG had previously requested these data in clarification question A12 but the company declined to provide the information because it would have included participants not covered by the expected marketing authorisation for fulvestrant.

The company have now presented analyses using the unmatched (ITT) populations from the FALCON, FIRST and NorthAmTarget trials in their additional evidence submission. The same methodology has been used as in the original company submission in which a simultaneous extrapolation and network meta-analysis was undertaken. The PFS results are presented in Table 8 of the company's additional evidence submission and the OS results in Table 9.

In these analyses the PO25 trial was omitted from the network and anastrozole and letrozole were assumed to be clinically equivalent. Therefore these analyses would appear to be most analogous to the 'matched' population analyses reported in response to Clarification question A13 (clarification response Table 18 for PFS using the generalised gamma distribution and

Table 23 for OS using the Weibull distribution) which also excluded the PO25 trial. A comparison between the full ITT and the most similar 'matched' analyses for PFS is presented in Table 1 and for OS in Table 2. The ERG observes, from visual inspection of the pairs of tables, that the results from the ITT indirect treatment comparison and the 'matched' population indirect treatment comparison are similar.

Table 1: Comparison of NMA for PFS using the ITT population with the NMA for PFS using the matched population

PFS - NMA using ITT population

Source: Company additional evidence submission
Excerpt from Table 8: Fixed-effects network meta-analysis PFS results: baseline parametric distribution parameters and difference from baseline for treatment alternatives versus (FALCON) anastrozole ('all shapes' models)

Generalised gamma	Scale			Shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Anastrozole (reference)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Difference in log scale			Difference in log shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Fulvestrant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tamoxifen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Common parameter	Estimate	L95%	U95%	-	-	-
Q	[redacted]	[redacted]	[redacted]	-	-	-

Abbreviations: L, lower; PFS, progression-free survival; U, upper.

PFS - NMA using matched population

Source: response to clarification question 13
Table 18: Generalised gamma parameter estimates for PFS based on fixed-effects NMA (excluding PO25 trial)

Generalised gamma	Scale			Shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Anastrozole (reference)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Difference in log scale			Difference in log shape		
	Estimate	L95%	U95%	Estimate	L95%	U95%
Fulvestrant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Letrozole	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tamoxifen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Common parameter	Estimate	L95%	U95%	-	-	-
	Q	[redacted]	[redacted]	[redacted]	-	-	-

Table 2: Comparison of NMA for OS using the ITT population with the NMA for OS using the matched population

	OS - NMA using ITT population						
Source: Company additional evidence submission **Excerpt from Table 9:** Fixed effect network meta-analysis OS results: baseline parametric distribution parameters and difference from baseline for treatment alternatives versus (FALCON) anastrozole ('all shapes' models)	**Weibull**	Scale			Shape		
		Estimate	L95%	U95%	Estimate	L95%	U95%
	Anastrozole (reference)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Difference in log scale			Difference in log shape		
		Estimate	L95%	U95%	Estimate	L95%	U95%
	Fulvestrant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Tamoxifen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	OS - NMA using matched population						
Source: response to clarification question 13 **Table 23:** Weibull parameter estimates for OS based on fixed-effects NMA (excluding PO25 trial)	**Weibull**	Scale			Shape		
		Estimate	L95%	U95%	Estimate	L95%	U95%
	Anastrozole (reference)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Difference in log scale			Difference in log shape		
		Estimate	L95%	U95%	Estimate	L95%	U95%
	Fulvestrant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Letrozole	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Tamoxifen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ERG Summary

The ERG is pleased to be able to compare the results of the indirect treatment comparison conducted using the ITT data with those obtained from the matched data and is reassured to find that these appear similar.

2.4 Comparison of ERG base case NMA (matched population; exclusion of the PO25 trial) and the ITT-population NMA

The company present the AIC and BIC statistics for PFS and for OS and compare these for the ERG base-case matched population indirect treatment comparison and for the newly presented ITT (unmatched) population indirect treatment comparison. Although there are a couple of changes to the rankings of the distributions these did not change the company's view regarding the most appropriate choices of extrapolation models (generalised gamma for PFS and Weibull for OS).

The company concludes that the use of ITT populations has little to no impact on the median PFS and median OS estimates for fulvestrant and anastrozole/letrozole. For tamoxifen there is no effect on the PFS estimate but with an ITT population, predicted median OS increases by 3.68 months. The use of the ITT population results in the OS for tamoxifen being greater than that for anastrozole (as shown in the company's additional submission Table 17), whereas in the matched-population OS is greater with anastrozole. The company do not discuss why this might be but the ERG note that the analysis of OS in the combined North American and Target trials publication indicated equal efficacy between anastrozole and tamoxifen. For both PFS and OS the mean values increase for all treatments when the ITT data are used.

2.5 Impact of FIRST in the matched-population and ITT-population NMAs

In the penultimate section of the company's additional evidence submission the company present the work they have conducted to i) ascertain the potential heterogeneity in the trial populations and ii) visualise the potential impact of each trial, but especially FIRST, on the long-term PFS and OS projections.

A series of pairs of Kaplan-Meier (KM) plots are presented in which the upper panel (A) is an illustration of the individual and NMA survival curves for the matched populations and the lower

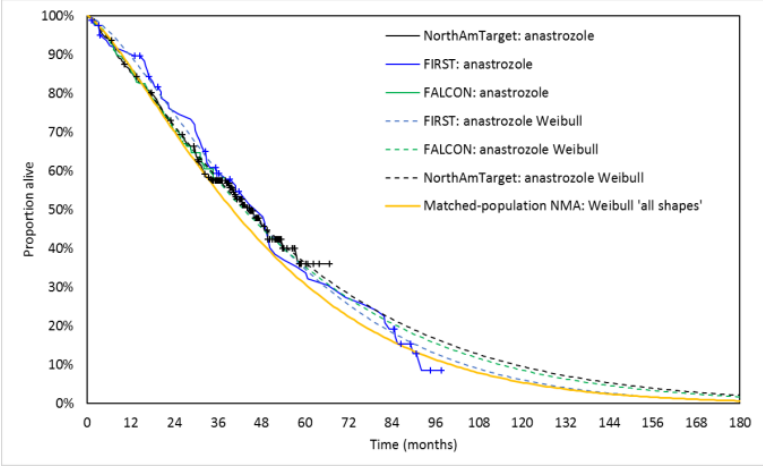
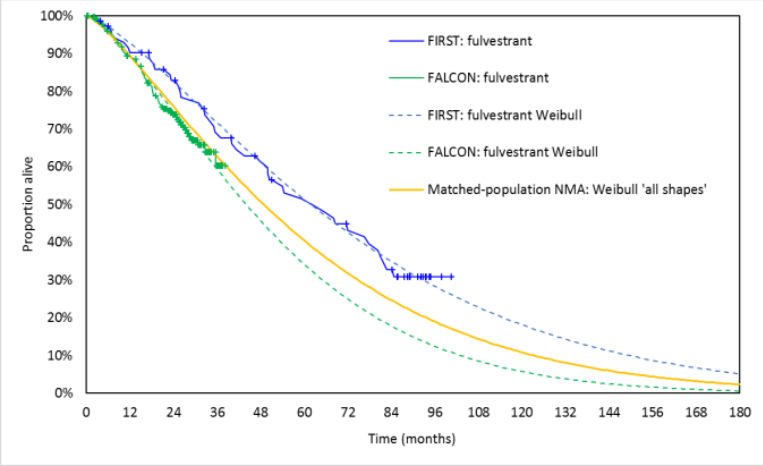
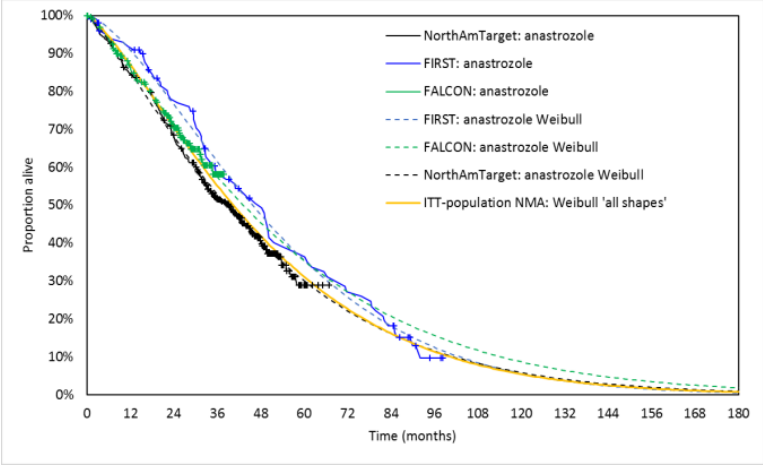
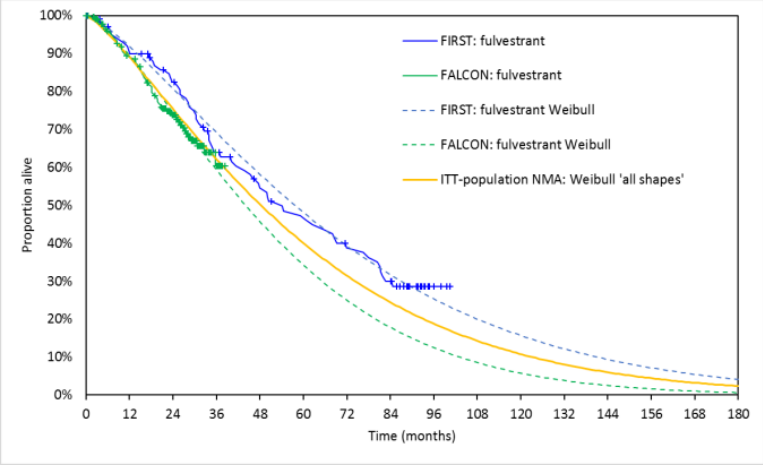
panel (B) presents the curves for the ITT populations. The two plots can then be visually compared, which inherently involves some subjective judgement, to gain an understanding of the impact of the matching analysis. Within each panel the trial KM plot is presented along with the extrapolated curve for that data as a dotted line. A solid yellow line represents the overall NMA extrapolation for that outcome. Visual inspection of the position of the yellow line for the NMA extrapolation in relation to the extrapolated curves for the individual trials may help the reader to make a judgement about which of the component trials have the greatest influence on the overall NMA curve.

In the ACD the area of greatest concern reported for the NICE committee was the uncertainty in the projections for OS. The committee was concerned that much of the OS projection for fulvestrant was driven by data from FIRST, which the committee had already concluded was less relevant than FALCON to the decision problem.

In the company's additional evidence submission the plots for anastrozole OS (company additional submission Figure 21) and fulvestrant OS (company additional submission Figure 22) are presented and these are reproduced, inevitably in a smaller size, in Figure 1 below. In these figures the KM plots are shown together with the Weibull distribution fitted to the individual trials (the dotted lines) and finally the meta-analysed Weibull distribution from the NMA (a solid yellow line). The company state that for anastrozole the KM survival curves from the trials are more closely aligned in the matched populations (panel A) than in the ITT populations (B). From visual inspection the ERG agrees that this is the case. For the comparison of the fulvestrant curves however (company additional submission Figure 22 panels A and B) the KM survival plots from the trials appear further apart in the matched populations than in the ITT populations. In Figure 22, both in panel A and in panel B, the yellow curve of the meta-analysed Weibull distribution for fulvestrant OS is initially closely aligned with the fulvestrant Kaplan-Meier plot and the individual Weibull distribution fitted to this, but at the limit of the observed FALCON data (about 36 months) the path of the yellow meta-analysed Weibull curve lies between the distributions fitted to the individual trials. The company state that "the plots reflect the Committee's opinion that the OS projections for fulvestrant after 36 months are informed by the relative effect (two-dimensional [shape and scale]) estimate from FIRST."

The ERG remains concerned about the reliability of the fitted OS curve for FALCON (given the immaturity of the OS data) and the interplay between this curve and the fitted OS curve for FIRST in generating the meta-analysed OS curve (in yellow).

Figure 1: Comparison of the matched population and ITT population OS curves for anastrozole and fulvestrant

KM, individual and fixed-effects network meta-analysis 'all shapes' OS survival curves for anastrozole (Figure 21)	KM, individual and fixed-effects network meta-analysis 'all shapes' OS survival curves for fulvestrant (Figure 22)
A - matched populations anastrozole	**A - matched populations fulvestrant**
	
B– ITT populations anastrozole	**B– ITT populations fulvestrant**
	

2.6 ITT-population NMA cost-effectiveness results

The company presented new sets of results in terms of total costs, life years gained, QALYs and incremental cost per QALY based on the NMA conducted on ITT population. Results were presented as pair-wise comparisons of fulvestrant versus aromatase inhibitors (AIs) and tamoxifen (Additional submission Tables 18 and 19). The results are reproduced below in Table 3 and Table 4.

Table 3: Company's ITT analysis: Fulvestrant vs AIs

Technologies	Total			Incremental			ICER
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
AIs	£11,441	3.762	2.70	-	-	-	-
Fulvestrant	£31,890	4.502	3.26	£20,448	0.739	0.559	£36,565

Abbreviation: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years.

Table 4: Company's ITT analysis: Fulvestrant vs tamoxifen

Technologies	Total			Incremental			ICER
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Tamoxifen	£12,034	3.880	2.77	-	-	-	-
Fulvestrant	£31,890	4.502	3.26	£19,856	0.622	0.494	£40,196

Abbreviation: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years.

The company has not clearly stated which version of the model (i.e. company's base case or the ERG's base case) was used to perform these additional analyses. Due to lack of clarity, we assumed that the version used for these additional analyses was the ERG base case and therefore attempted to replicate the company's ITT analysis by incorporating the parameter estimates for OS and PFS obtained from the "all shapes" fixed effects ITT population NMA model as the company outlined in the document titled "Instructions for inclusion of ITT-population NMA output into the economic model". The results we obtained from the analyses are summarised below in Table 5 and Table 6.

Table 5: ERG's replication of the company's ITT analysis: Fulvestrant vs AIs

Technologies	Total			Incremental			ICER
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
AIs	£11,398	3.752	2.687	-	-	-	-
Fulvestrant	£29,737	4.446	3.209	£18,338	0.694	0.522	£35,160

Abbreviation: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years.

Table 6: ERG's replication of the company's ITT analysis: Fulvestrant vs tamoxifen

Technologies	Total			Incremental			ICER
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Tamoxifen	£12,028	3.878	2.761	-	-	-	-
Fulvestrant	£29,737	4.446	3.209	£17,708	0.568	0.448	£39,515

Abbreviation: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years.

As can be seen from the above tables, the results we obtained from incorporating the revised NMA estimates into the ERG base case model differed slightly from those reported by the company. The company did not provide a version of the model that included the ITT analyses and so the ERG is unclear for the reasons between the discrepancies in the results. The ERG did not perform any further checks on the additional results reported by the company in Table 20- 29 in the document titled "Company additional evidence submission" as these will also contain discrepancies.

2.7 Alternative pricing assumption for fulvestrant

The company submitted an alternative pricing assumption consisting of a simple discount with a new price of fulvestrant of [redacted] instead of the list price of £522.41. The company stated that that they have provided an updated analysis with the assumptions in the ERG's preferred model which includes the following:

- Resource use for PFS and PD health states were based on Karnon et al.[2]
- Revised proportion of patients receiving second-line treatment
- Exclusion of PO25 trial from the NMA network and assuming similar efficacy for letrozole and anastrozole
- All patients receiving fulvestrant administered in an outpatient setting.

The company analyses from the revised price of fulvestrant using the matched NMA is reproduced below in Table 7 and Table 8.

Table 7: Fulvestrant vs AIs (Appendix 3-Table 2)

Technologies	Total			Incremental			ICER
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
AIs	£11,356	3.736	2.68	-	-	-	-
Fulvestrant	[redacted]	4.475	3.23	[redacted]	0.739	0.553	[redacted]

Abbreviation: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years.

Table 8: Fulvestrant vs Tamoxifen (Appendix 3- Table 3)

Technologies	Total			Incremental			ICER
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Tamoxifen	£11,853	3.479	2.47	-	-	-	-
Fulvestrant	[redacted]	4.475	3.23	[redacted]	0.996	0.761	[redacted]

Abbreviation: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years.

The ERG replicated the above analyses and confirms that they were able to replicate the company's cost-effectiveness results based on the alternative pricing assumption for fulvestrant.

The ERG has also calculated the ICER using the ERG's preferred base case using the ITT NMA and the company's alternative price for fulvestrant. The results are shown below in Table 9 and Table 10.

Table 9: ERG's base case with the ITT NMA and the alternative price for fulvestrant (Fulvestrant vs AIs)

Technologies	Total			Incremental			ICER
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	

AIs	£11,398	3.752	2.687	-	-	-	-
Fulvestrant	[redacted]	4.446	3.209	[redacted]	0.694	0.522	[redacted]

Abbreviation: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years.

Table 10: ERG's base case with the ITT NMA and the alternative price for fulvestrant (Fulvestrant vs Tamoxifen)

Technologies	Total			Incremental			ICER
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
Tamoxifen	£12,028	3.878	2.761	-	-	-	-
Fulvestrant	[redacted]	4.446	3.209	[redacted]	0.568	0.448	[redacted]

Abbreviation: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years.

2.8 ERG Summary

In the introduction to this addendum (Section 1) the ERG summarised what it believed were the NICE appraisal committee's main areas of concern which are set out in full in the ACD. These are:

- the final results on OS from the FALCON trial are not available yet, so it is unclear whether fulvestrant will extend OS compared with aromatase inhibitors which are currently used for first-line management.
- the 'matching' approach adopted by the company when undertaking the indirect treatment comparison may not have been appropriate. The committee would have liked to have compared the results using the 'matched' population with those for the full 'unmatched' population to assess the robustness of the results. The committee was not confident that the results of the indirect treatment comparison were reliable.
- The projections for OS are highly uncertain and this is the main area of uncertainty in the cost-effectiveness analysis. The committee was concerned that much of the OS projection for fulvestrant was driven by data from FIRST, which the committee had already concluded was less relevant than FALCON

The 'Company additional evidence submission' has sought to address the NICE Committee's concerns by providing further supporting evidence for the efficacy of fulvestrant in the population relevant to this appraisal.

The ERG believes it is still unclear whether fulvestrant will extend OS compared with aromatase inhibitors and concerns remain over both the projection of OS for fulvestrant in the FALCON trial (due to the immaturity of the data) and proportional contributions made by the projected OS curve for FALCON and the curve fitted to the mature FIRST OS data to the overall meta-analysed fulvestrant OS curve that contributes to the cost-effectiveness model.

The ERG is somewhat reassured that, although the 'matching' approach adopted by the company for the indirect comparison may not have been appropriate, the company have provided results for the full 'unmatched' population and these results appear similar.

References

1. Ellis MJ, Llombart-Cussac A, Feltl D, et al. Fulvestrant 500 mg Versus Anastrozole 1 mg for the First-Line Treatment of Advanced Breast Cancer: Overall Survival Analysis From the Phase II FIRST Study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2015;**33**(32):3781-7.
2. Karnon J. A trial-based cost-effectiveness analysis of letrozole followed by tamoxifen versus tamoxifen followed by letrozole for postmenopausal advanced breast cancer. Annals of Oncology 2003;**14**(11):1629-33.

Fulvestrant for untreated locally advanced or metastatic oestrogen-receptor positive breast cancer

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal determination (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation.

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Consultee	AstraZeneca UK	**Section 3.3 – Patient experience** It should be noted that the patient representative described how she had experience of different treatment options (including anastrozole and fulvestrant) and that she *"felt most well or normal when on fulvestrant."* Furthermore, although she acknowledged that the injections could sometimes be painful, she was of the opinion that this discomfort *"was probably related to the competency or training of the nurse involved."* This testimony was also provided in Sections 2, 4 and 5 of the Patient/carer expert statement.	Comment noted. Patients' experience has been described in section 3.3 of the FAD.
2	Consultee	AstraZeneca UK	**Section 3.3 – Characteristics of eligible patients** It is disappointing that the ACD does not make any reference to the extensive discussion about the types of patient likely to be eligible for treatment in this setting. The clinical expert described in their submission and in the meeting itself that: *"…patients presenting with de novo advanced disease are more likely to be vulnerable patients." (Response to question 7)* *"Many patients presenting with untreated locally advanced or metastatic breast cancer are atypical compared to the early disease patient, older, more frail, more comorbidities, socially, economically deprived or psychologically compromised hence presenting late." (Response to question 23a)*	Comment noted. Section 3.3 has been updated to reflect the experience of vulnerable people.
3	Consultee	AstraZeneca UK	**Section 3.3 – Route of administration** With regards to the route of administration for treatments in this setting, the statement (as reported in the ACD) from the patient expert that *"having a monthly injection may be preferable to daily tablets (such as aromatase inhibitors) for some people."* may suggest that the benefit of fulvestrant is confined to patient preference. It is important to note that there are clear clinical reasons for treating physicians to consider the route of administration of medicines when choosing a treatment regime. These were discussed by the clinical expert	Comment noted. Section 3.3 has been updated with information from the clinical expert that monthly injections may improve compliance.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			during the meeting and in the pre-meeting submission, where he explained that: *"…the population includes some vulnerable patients who may find compliance with daily medicine difficult so supervised monthly IM treatment will aid compliance."* These considerations have not been reflected sufficiently in the current draft recommendations.	
4	Consultee	AstraZeneca UK	**Section 3.4 – Influence of study design on reliability of outcomes of FIRST** The Committee noted that FIRST was an open-label study where both investigators and patients were aware of treatment allocation and the observation was made that this could potentially lead to bias. However, this assertion is only true for subjective outcomes (such as patient reported outcomes or physician assessed disease outcomes) which may be influenced by knowledge of the intervention received. There is empirical evidence that the bias in intervention effect estimates in clinical trials, resulting from lack of blinding, varies according to the type of outcome assessed. A combined analysis of data from 3 meta-epidemiological studies containing 146 meta-analyses of 1346 trials measured the ratio of odds ratios quantifying the degree of bias associated with a lack of blinding (Wood, 2007). A ratio of odds ratios <1 implies non-blinded trials exaggerate intervention effect estimates. The bias associated with lack of blinding was greater (interaction P = 0.011) in trials assessing outcomes other than all cause mortality (ratio of odds ratios 0.83 (0.70 to 0.98)) than in those assessing all cause mortality outcomes (1.04 (0.95 to 1.14)). In the case of the FIRST study, certain precautions were taken with the study design to minimise the potential for bias where possible (Robertson 2012). The clinical study team were unaware of the randomisation scheme until the data had been collected and locked for analysis. To prevent biasing the results of the tumour assessments, a blinded independent review was performed by an external radiologist. More supportive evidence will be provided in the Appendix.	Comment noted. The committee concluded that the FALCON data are more applicable to the evaluation of the clinical effectiveness of fulvestrant than the FIRST data because: • the trial population directly reflects the licence (that is, postmenopausal women with endocrine-naive oestrogen-receptor positive disease) • the double-blind trial design reduces the likelihood of bias (see section 3.4 of the FAD) For overall survival, section 3.6 of the FAD now states that data from FIRST should be interpreted cautiously because they may not be generalisable to the licensed population.
5	Consultee	AstraZeneca	**Section 3.5 – Dropouts in FIRST study**	Comment noted. Reference to the

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
		UK	The Committee state that the PFS/TTP results in FIRST should be interpreted with caution because of the concerns set out in section 3.4 and a high dropout rate (37% (38/102) of patients in fulvestrant arm and 49% (50/103) in the anastrozole arm). It is important to note that the dropout rates quoted included those who had stopped treatment because of disease progression and were measured at the time of the first data cut off (DCO1 – Jan 10, 2008), 6 months after the last patient was randomised. At this time, 29.4% (30/102) of fulvestrant-treated patients had progressed compared with 41.7% (43/103) of those in the anastrozole group and were therefore no longer on study treatment (Robertson 2009). Thus, approximately the same number of patients randomised to treatment in FIRST had stopped treatment for a reason other than disease progression at the time of DCO1 (8 [38-30=8] patients randomised to receive fulvestrant vs 7 [50-43=7] patients receiving anastrozole). At the time of the second data cut off (DCO2 – March 26, 2010), when the PFS/TTP results used in the submission were measured, 14.7% (15/102) of patients in the fulvestrant group and 19.4% (20/103) of patients in the anastrozole group had discontinued study treatment for reasons other than disease progression or death (Robertson, 2012).	dropout rates has been removed from the FAD section 3.5.
6	Consultee	AstraZeneca UK	**Section 3.8 – Risk of breaking randomisation during matching process** The ACD reports that *"The ERG commented that this approach reduced the sample size of the comparator studies and broke randomisation in all studies except for FALCON."* This is inaccurate. The ERG report contains the following comment: *"… the ERG is concerned about potential disadvantages (of the matching process), for example if matching creates scope for bias as randomisation has been broken."(p55 of ERG report version 1)* We do not believe that the matching process led to randomisation being broken. We applied a combination of 2 critical inclusion criteria from FALCON (i.e. endocrine treatment naïve AND ER/PgR+ve status) to each arm of FIRST and NorthAmerica:TARGET, individually. The inclusion criteria applied in the matching analysis were pre-randomisation variables in all the trials included in the network (FALCON,	Comment noted and reflected in the FAD. Please see section 3.8 of the FAD.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			FIRST and NorthAmerica:TARGET); that is, variables that were measured at baseline, before randomisation. It is important to note that a subgroup analysis of endocrine naïve patients in the FIRST study has already been presented for OS (Ellis 2012) and this subgroup is equivalent to the matched subgroup used in the original submission. With regards to NorthAmerica:TARGET, subgroup analysis of the ER/PgR+ve patients has been presented for PFS and OS (Bonneterre 2001 and Nabholtz 2003) – the matched patients in the submission are effectively a further sub-group of this cohort which were endocrine naïve. Sub-dividing the patient population on pre-randomised variables, as we did in the initial submission, does not break randomisation, and any differences in treatment group numbers in the subgroups produced, are obtained by chance (expert opinion from Professor of Biostatistics, Harvard). More evidence supporting this is provided in the Appendix.	
7	Consultee	Breast Cancer Now	Breast Cancer Now was disappointed in the committee's decision not to recommend fulvestrant for use in this population. Fulvestrant provides a valuable treatment option for women with ER+ advanced breast cancer and we believe that patients who could benefit from this treatment should have access to it. Evidence shows that fulvestrant can add nearly three months progression free survival when compared to the standard treatment in this patient group (anastrozole). Metastatic breast cancer is a terminal diagnosis and any additional time, especially with a good quality of life, is extremely valuable to breast cancer patients and their families.	Comment noted. The committee reconsidered the evidence but could not recommend fulvestrant as a cost effective use of NHS resources.
8	Consultee	Breast Cancer Now	The side effect profile of fulvestrant is similar to that of aromatase inhibitors, with many people experiencing only mild side effects with fulvestrant. However, some patients may have a preference as the treatments are delivered differently. Aromatase inhibitors are delivered by a daily tablet while fulvestrant is delivered through monthly intramuscular injections into the buttocks. Some patients may prefer to have injections once a month and then not to have to worry about their treatment for the rest of the month, rather than having to remember to take tablets every day. In addition, some patients find swallowing tablets very difficult and so may prefer to have their medication delivered via injection.	Comment noted. Patients' compliance to drug administration regime is described in section 3.3 of the FAD.
9	Consultee	Breast	Fulvestrant may allow patients to delay the start of chemotherapy.	Comment noted. The committee

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		Cancer Now	Chemotherapy treatment is associated with side effects such as nausea, vomiting and hair loss. These side effects can have a significant impact on a patient's quality of life, something that is highly valued as patients near the end of their lives.	understood that effective treatments that delay the need for chemotherapy are needed, see section 3.1 of the FAD.
10	Consultee	Breast Cancer Now	Patients with locally advanced or metastatic oestrogen-receptor positive breast cancer are in need of new treatment options. While new treatments (such as palbociclib and ribociclib) have been developed for this patient group, it is not yet clear whether these treatments will be made routinely available on the NHS. Other innovative breast cancer treatments (such as trastuzumab emtansine) are not suitable for patients with this type of breast cancer.	Comment noted. The need for new treatment options is discussed in section 3.1 of the FAD.
11	Consultee	Breast Cancer Now	Women with metastatic breast cancer have a terminal disease and wish to extend their lives as long as possible. We know from talking to breast cancer patients that they also value progression free survival with minimal side effects as it allows them a good quality of life so they are able to continue to spend time with their friends and families and do the things they enjoy. It is therefore vital that as many treatment options as possible are available to these patients so that they are able to make the most of the limited time they have left. While we appreciate that there is a lack of overall survival data for fulvestrant, it has been shown to extend progression free survival.	Comment noted. The committee noted the evidence on progression free survival in section 3.12 of the FAD.
12	Consultee	Breast Cancer Now	It is disappointing that this drug could not be considered for funding through the Cancer Drugs Fund. Most cancer drugs which have uncertain survival data could be eligible for Cancer Drugs Fund funding while more mature data are collected. However, because fulvestrant is an endocrine therapy rather than a chemotherapy and therefore is commissioned locally rather than centrally, fulvestrant is not eligible for the CDF. This split in commissioning is not logical and is now having a real impact on patients as it means that they won't be able to access a treatment that may provide benefit to them. We will be taking the issue of the eligibility criteria for the Cancer Drugs Fund up with NHS England.	Comment noted.