Chair's presentation

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

2nd Appraisal Committee meeting

Committee A

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ERG/AG: Southampton Health Technology Assessment Centre

Company: AstraZeneca

2nd November 2017

Fulvestrant (faslodex), AstraZeneca

Marketing authorisation	Treatment of oestrogen-receptor positive, locally advanced or metastatic breast cancer in postmenopausal women: • not previously treated with endocrine therapy (indication of interest for appraisal) • with disease relapse on or after adjuvant anti-oestrogen therapy, or disease progression on anti-oestrogen therapy (not recommended under NICE technology appraisal 239)

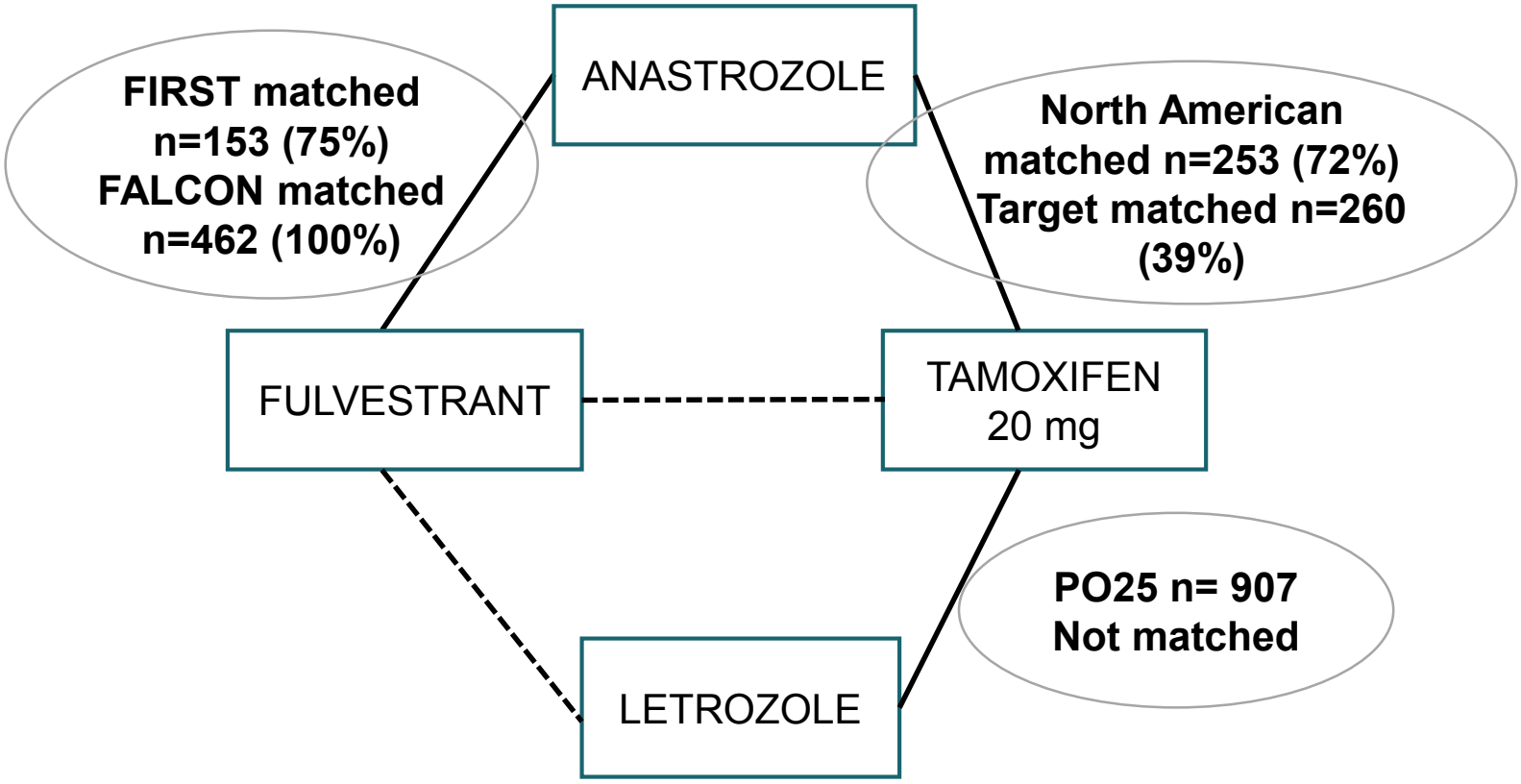
2 trials of fulvestrant vs anastrozole

	FIRST		FALCON	
	Fulvestrant (n=102)	Anastrozole (n=103)	Fulvestrant (n=230)	Anastrozole (n=232)
Trial design	Open label		Double blind	
Population	25% prior endocrine therapy 18.5% HER2 +ve (34% HER -/+ve unknown)		<1% prior endocrine therapy <1% HER2 +ve	
Maturity of OS data at cut off	Mature (65% of events reached)		Immature (31% of events reached)	
Median TTP/PFS	23.4 months (TTP)	13.1 months (TTP)	16.6 months (PFS)	13.8 months (PFS)
difference	**10.3** months		**2.8** months	
HR (95% CI)	0.66 (0.47, 0.92)		0.797 (0.637, 0.999)	
Median OS	54.1 months	48.4 months	-	-
difference	**5.7** months		-	
HR (95% CI)	0.70 (0.50, 0.98)		0.875 (0.629, 1.217)	

Key: TTP, time-to-progression; PFS, progression-free survival; OS, overall survival; HR, hazard ratio; HR <1 favours fulvestrant

Indirect treatment comparison (ITC): network of evidence

- Inclusion and exclusion criteria from FALCON were applied to the included studies to better 'match' the trial population in FALCON



ACD: preliminary recommendation

- Fulvestrant is not recommended, within its marketing authorisation, for treating locally advanced or metastatic oestrogen-receptor positive breast cancer in postmenopausal women that has not previously been treated with endocrine therapy

Key conclusions in ACD

Clinical effectiveness

- FALCON favoured over FIRST:
  - trial population directly reflected the licence
  - the double-blind trial design reduced the likelihood of bias (no blinding of investigators or patients in FIRST)
- Modest gain in progression-free survival (PFS) of 2.8 months in FALCON but uncertain whether fulvestrant extends overall survival (OS) because data were immature
- Indirect comparisons to tamoxifen and letrozole may not be reliable:
  - 'matching' characteristics to FALCON may not be appropriate as it breaks randomisation and reduces the sample size of the comparator studies
  - unclear whether people with HER2+ disease in some studies (i.e. for the comparison with tamoxifen) were excluded
  - letrozole should be assumed equivalent to anastrozole

Key conclusions in ACD

Cost effectiveness

- OS projections are highly uncertain
  - OS data from FALCON were immature and so modelled OS results for fulvestrant were driven by FIRST, which should be interpreted cautiously
- Cost-effectiveness results are therefore very uncertain
  - ICERs for fulvestrant compared with anastrozole were above the range normally considered a cost effective use of NHS resources (company's base case ICER £34,099; ERG's analysis £33,455)
  - in a scenario analysis assuming no OS benefit for fulvestrant over anastrozole, the ICER increased to £208,231
  - ICERs for fulvestrant compared with tamoxifen were between £20,000 and £30,000 per QALY gained but concerns about:
    - results of the ITC
    - immaturity of the OS data (assuming no OS benefit increased the ICER to £39,027)

ACD consultation responses

- Consultee comments from:
  - Breast Cancer Now
  - AstraZeneca
- Additional evidence from the company:
  - Robustness of survival estimates from FIRST
    - risk of bias for objective outcomes in open label studies
    - analysis of population who did not give consent for long term follow up for OS and impact on survival outcomes
    - impact of data maturity in fulvestrant trials
  - ITC
    - robustness of matched data
    - new ITC using ITT data
    - cost effectiveness results incorporating new ITC
  - Alternative cost effectiveness results with a different pricing assumption

Consultation comments: Breast Cancer Now

- Fulvestrant is a valuable treatment option and patients who could benefit should have access. Metastatic breast cancer is a terminal diagnosis and any additional time is extremely important to patients and their families
- Fulvestrant extends PFS with minimal side effects which patients value as it allows them a good quality of life
- Fulvestrant may delay chemotherapy and its associated side effects such as nausea, vomiting and hair loss, which can have a significant impact on a patient's quality of life
- Patients need new treatment options and some prefer monthly injections
- Disappointing that fulvestrant is not eligible for consideration in the Cancer Drugs Fund because it is an endocrine therapy rather than a chemotherapy and is therefore commissioned locally. Would allow more mature data to be collected

Consultation comments: company (1)

- Committee commented that results in FIRST should be treated with caution because of high drop out rate (37% (**38/102**) patients in fulvestrant arm and 49% (**50/103**) in the anastrozole arm).
- Company: these data included people who stopped treatment because of disease progression and the proportion of people who stopped treatment for reasons other than disease progression was similar in both treatment arms
- Drop out rate in FIRST for reasons other than disease progression:

	Fulvestrant	Anastrozole
Data cut off 1 (Jan 2008)	8/102	7/103
Data cut off 2 (March 2010, when results in the submission were measured)	15/102	20/103

Consultation comments: company (2)

- Patient experience was not fully reflected in ACD:
  - patient expert “felt most well or normal when on fulvestrant”…and discomfort from injections “was probably related to the competency or training of the nurse involved”
  - the benefit of a monthly injection of fulvestrant (rather than a daily tablet) is not just patient preference - the clinical expert stated that for some vulnerable patients monthly supervised injections will aid compliance
- Characteristics of patients presenting with de novo advanced disease not reflected in ACD:
  - Cited clinical expert statement “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”
    - Influence of FIRST study design on reliability of outcomes (discussed in detail in additional analyses)
    - Randomisation during matching process for ITC (discussed in detail in additional analyses)

Company’s additional analyses

Estimates of OS are unlikely to be biased in open label studies

- Company cites 3 studies that found 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)
- Presented data from Page et al. showing 'Ratio of Odds Ratios' associated with lack of/unclear blinding vs double blinding (a value of 1 implying no difference)
  - for mortality the Ratio of Odds Ratio was 1.04 (0.86,1.27)
  - for 'subjective outcomes' the Ratio of Odds Ratio was 0.77 (0.61,0.93)
- **ERG** agrees that objective outcomes such as all-cause mortality are less likely to be biased in open label studies than subjective outcomes

The estimate of OS in FIRST is legitimate: impact of population not consenting to OS follow up

- **Company**: No difference in baseline characteristics of 35 people who did not give consent to OS follow up in FIRST and full ITT population

Baseline characteristic	Patients not consenting to OS follow-up		ITT	
	Fulvestrant N=16	Anastrozole N=19	Fulvestrant N=102	Anastrozole N=103
Visceral involvement	[redacted]	[redacted]	48 (47%)	58 (56%)
Prior chemotherapy	[redacted]	[redacted]	29 (28%)	25 (24%)
Measurable disease	[redacted]	[redacted]	89 (87%)	93 (90%)
Prior endocrine therapy	[redacted]	[redacted]	29 (28%)	23 (22%)

Source: Table 1 of the company's additional analyses

- **ERG:** missing data were split almost equally between study arms. Slight imbalance in measurable disease between the trial arms for the patients not consenting to OS follow-up

PFS and OS estimates in FIRST by OS follow up consent status

- **Company:** PFS & OS are unlikely to be biased by the missing data:
  - Analysis of PFS for those consenting versus those not consenting, does not suggest that these patients exert any bias on the relative efficacy of fulvestrant compared with anastrozole.
  - Company carried out an analysis where all non consenting patients were assumed to be alive at final data cut-off. Results suggest that the OS benefit of fulvestrant compared to anastrozole is unlikely to be significantly influenced.
- **ERG:** would have liked to see a wider ranging exploration of the impact of the missing data – still uncertain about the extent to which the missing data could have altered the OS outcome.

Mature data needed to detect benefit of fulvestrant on overall survival

- Company stated that evidence from other studies using fulvestrant in metastatic breast cancer supports the expectation of a sustained OS benefit in FALCON
- The CONFIRM study (fulvestrant 500 mg vs fulvestrant 250 mg in patients whose disease had progressed after endocrine therapy) showed:
  - a statistically significant benefit in OS after 75% of patients had died, but not after 50% of patients had died
  - in the survival curves (75% maturity) there was no separation until after 12 months
- **ERG:** difficult to generalise the results of CONFIRM to FALCON because of differences in the trial populations
- Unclear what the relationship is between PFS and OS
- Concern that the OS benefit in FALCON may mirror that of PFS in FALCON and not be as great as observed in the FIRST study

ITC: matching process was robust

- Company highlights that applying selection criteria to the FIRST and NorthAmerica:TARGET trial populations does not break randomisation because endocrine naivety was a pre-randomisation variable
- Relative treatment effects for the matched subgroups are consistent with published data
- Supported by baseline characteristics remaining balanced in matched subgroups
- **ERG:** only stratification of the initial randomisation on the baseline characteristics used for matching would avoid breaking randomisation
- Reassuring that the baseline characteristics of the matched and whole trial population data are so similar. Further reassurance comes from the results of the ITC conducted using the ITT data

Company's new ITC using ITT data

- Included FALCON, FIRST and combined North American and TARGET trials. Omitted PO25 trial reflecting the committee's previous conclusion that equal efficacy of anastrozole and letrozole could be assumed
- Used the same methods as in original submission
- Compared results with ERG exploratory base case which used matched population and also excluded PO25 trial*
- Company believes the results are potentially biased given the heterogeneity in trial populations. The matched-population ITC should be considered the more valid estimator of efficacy

*ERG exploratory base case also made different assumptions for resource use in PFS + PD health states, proportion of patients receiving second-line treatment, setting for fulvestrant administration

Company's new ITC: results

- **Using ITT rather than the 'matched' population led to:**
  - no change in median PFS or OS for fulvestrant and AIs
  - increases in mean PFS and OS for all treatments
  - a higher mean OS with tamoxifen than AIs

PFS	Matched population		ITT population	
	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

OS	Matched population		ITT population	
	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

Source: Tables 13 and 17 of the company's additional analyses

ERG's comments on the company's new ITC

- Reassured that the results from the ITCs using ITT data and 'matched' data are similar
- 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
- Still unclear whether fulvestrant will extend OS compared with aromatase inhibitors

Cost effectiveness results*

	ICER vs aromatase inhibitors	ICER vs tamoxifen
Company base case using matched ITC	£34,099	£22,498
ERG exploratory base case using matched ITC	£33,455	£23,687
New analyses		
Company additional analyses using ITT ITC	£36,565	£40,196
ERG's replication using company's ITT ITC	£35,160	£39,515
Company's results using matched ITC and alternative pricing assumption†	[redacted]	[redacted]
ERG's results using ITT NMA and alternative pricing assumption	[redacted]	[redacted]

*Deterministic

†included committee's preferred assumptions from ERG exploratory base case on: resource use for PFS and PD health states; proportion of patients receiving second-line treatment; administration setting for fulvestrant and exclusion of PO25 trial from the ITC network

Key issues for consideration

- Are overall survival estimates from open label studies subject to bias?
- Which are the most robust data for determining overall survival with fulvestrant?
  - mature open label data from FIRST not reflecting MA population
  - immature double blind data from FALCON reflecting MA population
  - data matched to patient characteristics in FALCON
- Which are the most reliable data to use in the ITC?
  - ITT?
  - Matched?