NICE National Institute for Health and Care Excellence

Abemaciclib with fulvestrant for treating advanced hormone-receptor positive, HER2-negative breast cancer after endocrine therapy

Pre-meeting briefing

PART 1

This slide set is the pre-meeting briefing for this appraisal. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report

It highlights key issues for discussion at the first appraisal committee meeting and should be read with the full supporting documents for this appraisal

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies

The lead team may use, or amend, some of these slides for their presentation at the committee meeting

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Key issues for consideration - clinical

- As the treatment pathway has recently changed with the availability of ribociclib and palbociclib, is the decision problem relevant?
  - ERG's clinical experts noted that people treated with palbociclib and ribociclib first line would be unlikely to be given another combination treatment
- What is the most relevant comparator?
- Is the network meta-analysis robust for overall survival, given the immaturity of the overall survival data in the MONARCH 2 trial?
- Is abemaciclib plus fulvestrant clinically effective?
- Which network meta-analysis should be used to compare treatments?
  - Hazard ratio NMA
  - Company's fractional polynomial NMA
  - ERG's fractional polynomial NMA

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Advanced breast cancer background

- Breast cancer is the most common cancer amongst women in the UK
- The cancer is said to be 'advanced' if it has spread to other parts of the body such as the bones, liver, and lungs (metastatic cancer), or if it has grown directly into nearby tissues and cannot be completely removed by surgery.
- Approximately 13% of women with breast cancer have advanced disease when they are diagnosed, and around 35% of people with early or locally advanced disease will progress to metastatic breast cancer in the 10 years following diagnosis.
- Approximately 64% of women with metastatic breast cancer in the UK have HR+/HER2− disease.
- In 2016 in England, around 45,960 people were diagnosed with breast cancer and there were 9,685 deaths from breast cancer.

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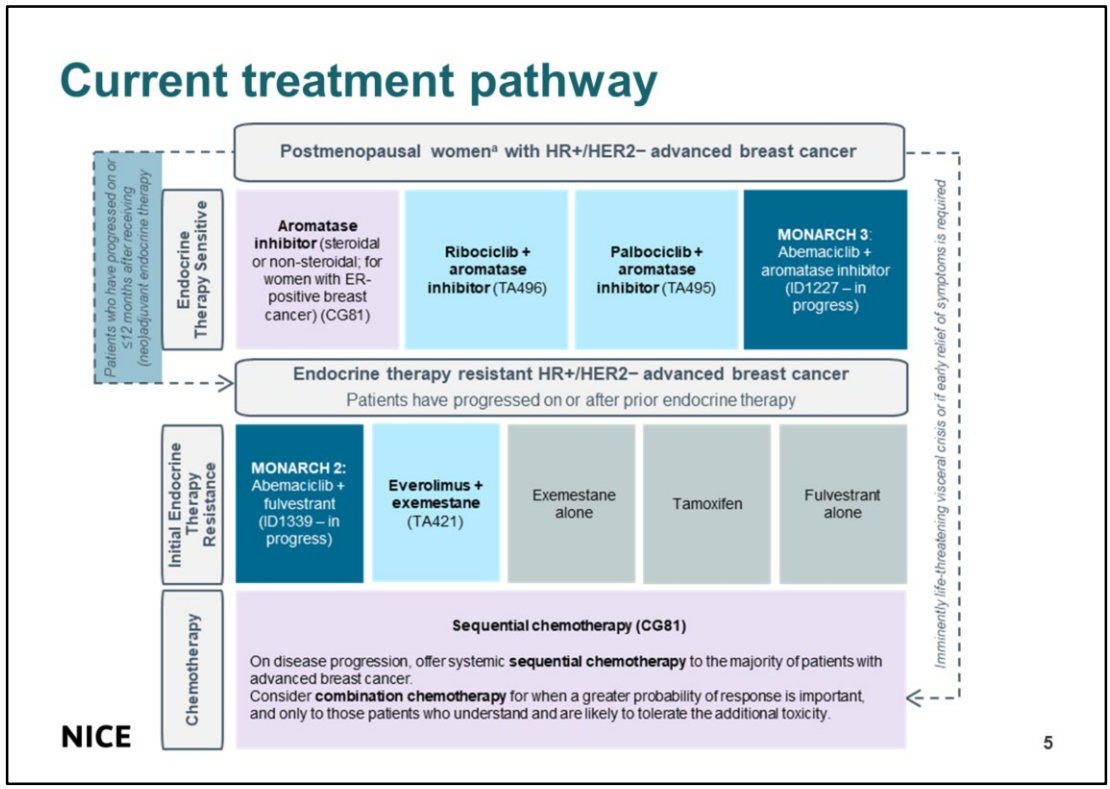
Source: company submission section B.1.3.1; NICE final scope



Source: company submission figure 2

Patient Issues (Breast Cancer Now. Breast Cancer Care)

- Diagnosis of incurable, advanced breast cancer is difficult to accept.
- The disease and its treatment impact on mental & physical health, & QoL.
- Abemaciclib combined with fulvestrant is a potential additional treatment option for disease that has progressed on previous endocrine therapy.
- Benefits include:
  - postponing or avoiding need for chemotherapy
  - limited side effects compared with chemotherapy – improved quality of life
  - extended progression-free survival – allowing people to spend more quality time with family and friends.
- Disadvantages (which may be outweighed by increased PFS) include:
  - Fulvestrant is administered by injection requiring hospital/ GP visits
  - Potential increased side effects.

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Source: Submissions from Breast Cancer Now and Breast Cancer Care

Comments from clinical experts

- Abemaciclib+fulvestrant shows a clinically important improvement in progression-free survival, likely to improve overall survival
- Could help to delay initiation of chemotherapy
- Improved quality of life with manageable side effects
- However, could be a further strain on metastatic breast cancer services

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Source: Submissions from clinical experts

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Abemaciclib (Verzenios, Eli Lilly)

Marketing authorisation (October 2018)	Indicated for the treatment of women with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative locally advanced or metastatic breast cancer in combination with an aromatase inhibitor or **fulvestrant** as initial endocrine-based therapy, or **in women who have received prior endocrine therapy.**
Mechanism of action	Inhibitor of cyclin-dependent kinases 4 and 6 (CDK4 and CDK6), blocking cell cycle progression and leading to suppression of tumour growth
Administration and dosage	Abemaciclib administered orally, 150 mg twice daily when used in combination with endocrine therapy on a continuous 28 day cycle. Fulvestrant administered intramuscularly*, 500mg on day 1 and 15 of first cycle, day 1 of subsequent cycles.
List price	List price of abemaciclib: £[redacted] per 28-day cycle Mean time on treatment: [redacted] months (modelled) Cost per mean time on treatment (based on list price): £[redacted] A confidential patient access scheme has been proposed.

**Corrected after committee meeting*

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Source: company submission B.1.2; summary of product characteristics.

Decision problem

	Final scope issued by NICE	Decision problem in the company's submission	Rationale if different
Population	People with advanced HR+/HER2− breast cancer that has progressed on or after endocrine therapy	Women with locally advanced or metastatic HR+/HER2− breast cancer who had progressed while receiving (neo)adjuvant ET, ≤ 12 months from the end of adjuvant therapy, or while receiving first-line ET for locally advanced or metastatic disease	Company consider patients untreated or who have progressed after ET in the advanced setting to be part of one population for this submission.
Intervention	Abemaciclib with fulvestrant	Abemaciclib with fulvestrant	N/A
Outcomes	OS PFS Response rate Adverse effects of treatment HRQoL	OS and OS rated PFS Response rates Adverse effects of treatment Patient reported outcomes	N/A

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Source: company submission B.1.1

Notes:

- There are 2 appraisals for abemaciclib
  - People with untreated advanced HR+/HER2− breast cancer (ID1227)
  - People with advanced HR+/HER2− breast cancer that has progressed on or after endocrine therapy (ID1339 – this appraisal)

Decision problem

	Final scope issued by NICE	Decision problem in the company's submission	Rationale if different
Comparators	For people with advanced hormone-receptor positive HER2-negative breast cancer that has progressed after one line of prior endocrine therapy: • Exemestane • Everolimus and exemestane • Tamoxifen • Fulvestrant • Chemotherapy	• Exemestane (EXE) • Everolimus and exemestane (EXE-EVE) • Tamoxifen (TMX) • Fulvestrant (FUL) • Capecitabine (CAP) (considered in response to clarification questions)	Company note that: • Chemotherapy is the last resort • Fulvestrant monotherapy not NICE recommended but may be used

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Source: company submission B.1.1, B1.3.3 page 23, response to clarification A3b

ERG comments on decision problem and treatment pathway

- Company's decision problem focused on the endocrine therapy-resistant population - narrower than population in final scope but the ERG considers this appropriate based on feedback from clinical experts
- ERG's clinical experts consider chemotherapy to be a relevant comparator for some patients
- ERG's clinical experts suggest that clinicians will not use abemaciclib+fulvestrant after another CDK 4/6 inhibitor (e.g. palbociclib or ribociclib with an aromatase inhibitor (AI)), because of:
  - intensity of a second combined treatment regimen
  - lack of evidence of response or reversal of endocrine therapy resistance
- Currently, most common first line treatment is a CDK 4/6 inhibitor + AI, but if abemaciclib+fulvestrant were to be recommended, a small number of patients may be given AI alone as first line treatment

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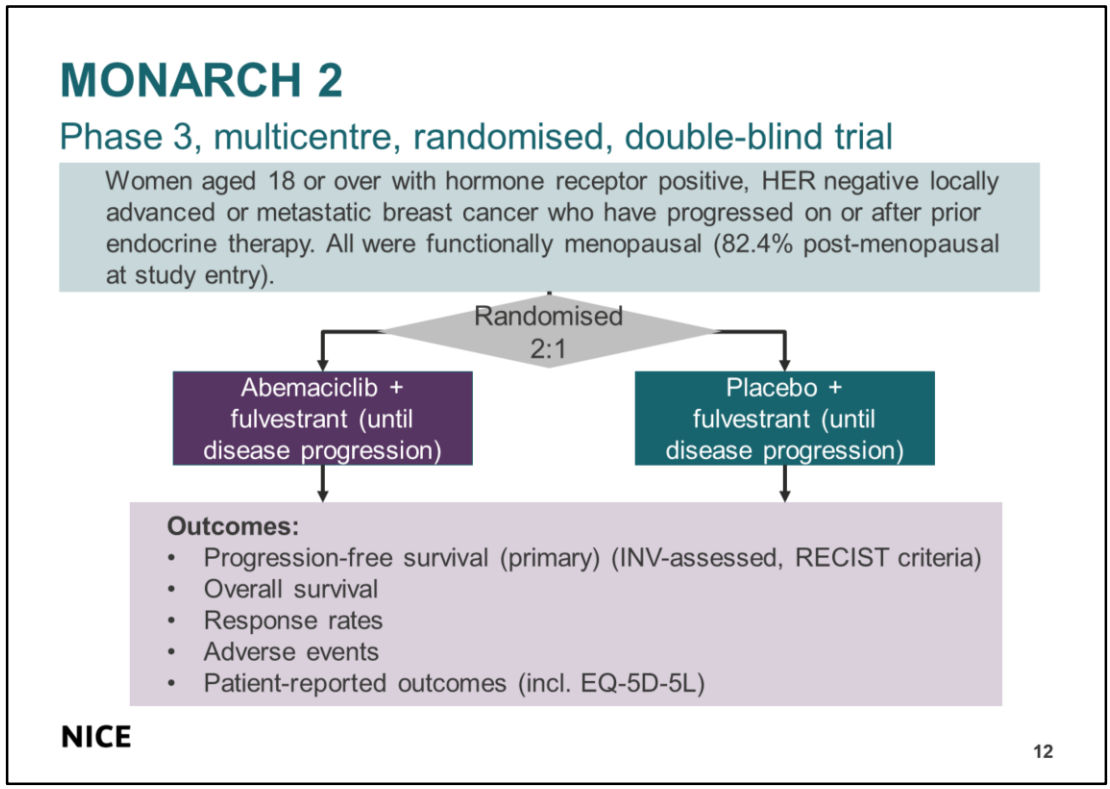
Source: ERG report section 2.2.2, 3.1



Source: company submission B.2.3

Notes

- 142 centres across 19 countries, including Australia, Belgium, Canada, Denmark, Finland, France, Germany, Italy, Japan, Republic of Korea, Mexico, Poland, Puerto Rica, Romania, Russia, Spain, Switzerland, Taiwan and United States of America
- Patients were not permitted to switch treatment groups
- If either abemaciclib or placebo was discontinued, patients were permitted to continue receiving fulvestrant. If fulvestrant required discontinuation, patients were permitted to continue receiving abemaciclib or placebo

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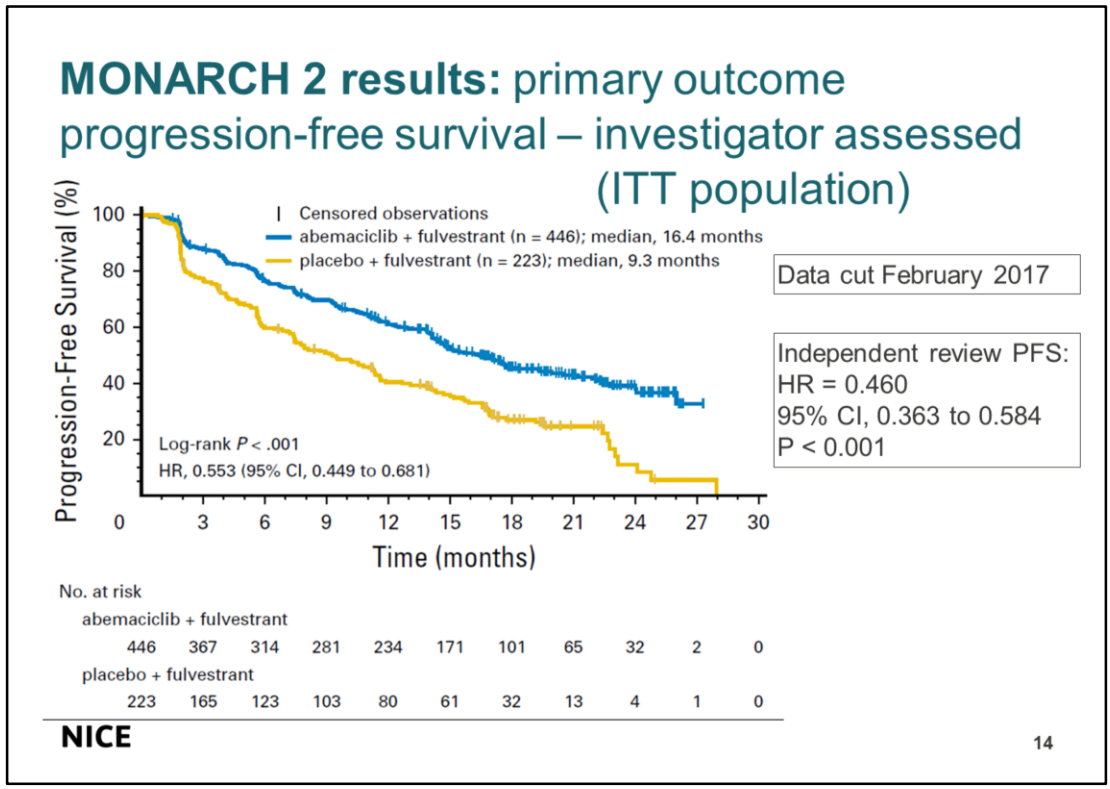
MONARCH 2 selected baseline characteristics

Baseline characteristic		AB+FUL (N=446)	Placebo+FUL (N=223)
Age, median (range)		59 (32 to 91)	62 (32 to 87)
Menopausal status, n (%)	Pre- or peri-menopause	72 (16.1)	42 (18.8)
	Post-menopause	371 (83.2)	180 (80.7)
	Natural	[redacted]	[redacted]
	Surgical	[redacted]	[redacted]
Race, n (%)	Asian	149 (33.4)	65 (29.1)
	Caucasian	237 (53.1)	136 (61.0)
	Other	29 (6.5)	13 (5.8)
ECOG performance status	0	264 (59.2)	136 (61.0)
	1	176 (39.5)	87 (39.0)
Region, n (%)	Europe	[redacted]	[redacted]
	Asia	[redacted]	[redacted]
	North America	[redacted]	[redacted]
Metastatic site, n (%)	Visceral	245 (54.9)	128 (57.4)
	Bone only	123 (27.6)	57 (25.6)
	Other	75 (16.8)	38 (17.0)
ET resistance, n (%)	Primary	111 (24.9)	58 (26.0)
	Secondary	326 (73.1)	163 (73.1)
Prior AI, n (%)	Yes	316 (70.9)	149 (66.8)
	No	130 (29.1)	74 (33.2)
Prior chemotherapy for (neo)adjuvant treatment, n (%)	Yes	267 (59.9)	134 (60.1)
	No	179 (40.1)	89 (39.9)

Source: company submission table 6



Source: company submission figure 4

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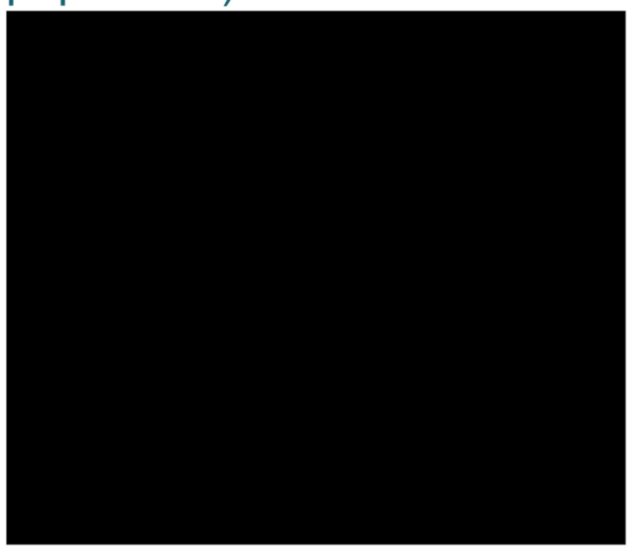
MONARCH 2 results: Overall survival (ITT population)



Data cut 14th Feb 2017
- OS data still immature
- Median OS not reached
- OS data cut-off expected April 2019
- Estimated study completion date February 2020

HR = [redacted]
95% CI [redacted]
Log-rank test p-value = [redacted]

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Source: company submission B.2.6.2, figure 7

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MONARCH 2 results: Response rates

ITT population n=669	Abemaciclib + fulvestrant (n, %)	Placebo + fulvestrant (n, %)	Odds ratio
Complete response (CR)	14 (3.1)	1 (0.4)	NA
Partial response (PR)	143 (32.1)	35 (15.7)	NA
Stable disease (SD)	213 (47.8)	133 (59.6)	NA
≥6 months	165 (37.0)	89 (39.9)	NA
Progressive disease	40 (9.0)	45 (20.2)	NA
Not evaluable	36 (8.1)	9 (4.0)	NA
Overall response rate (CR + PR)	157 (35.2)	36 (16.1)	2.82 (p<0.001)
Disease control rate (CR + PR + SD)	370 (83.0)	169 (75.8)	1.56 (p=0.025)
Clinical benefit rate (CR + PR + SD ≥6 months)	322 (72.2)	125 (56.1)	2.04 (p<0.001)

ERG notes that median time to response was [redacted] in abemaciclib+fulvestrant group and [redacted] in the placebo+fulvestrant group (based on CSR)

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Source: company submission B.2.6.3, table 12; ERG report 4.3.3

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MONARCH 2 results: Duration of response

Median duration of response:
ABE-FUL Not reached
PBO-FUL [redacted]
Patients whose disease responded who were progression-free at 12 months:
ABE-FUL 67.8%
PBO-FUL 66.9%

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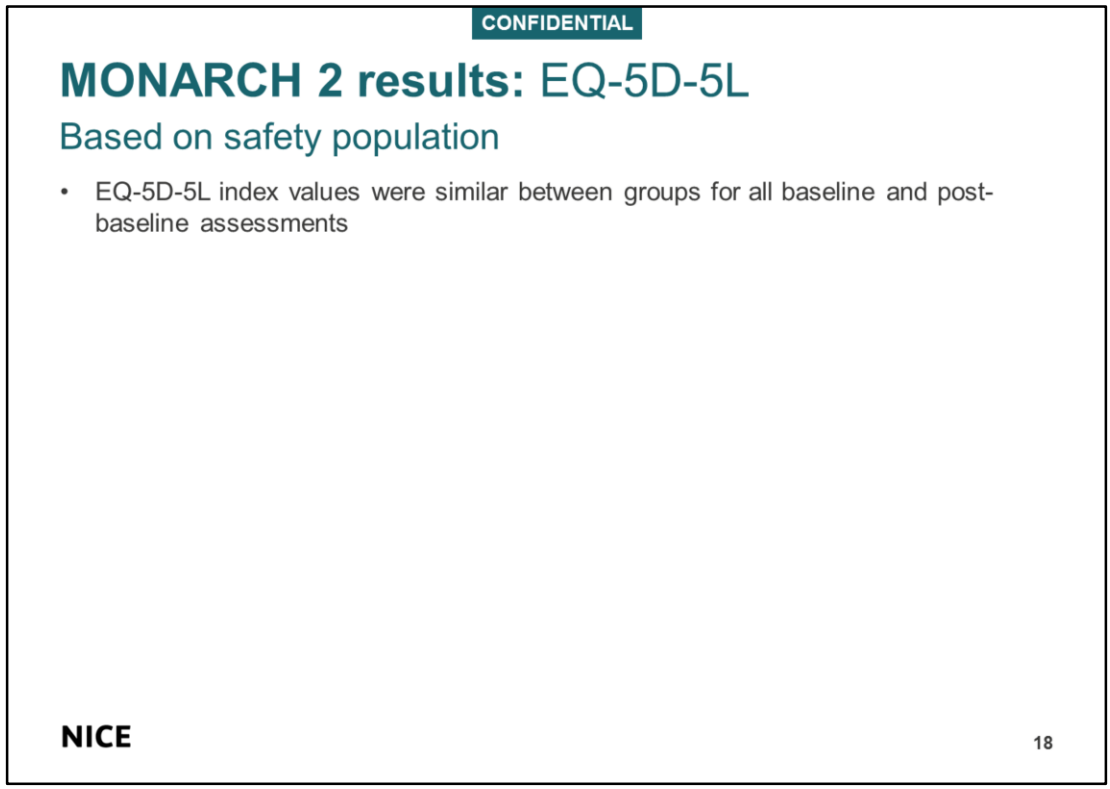
Source: company submission figure 8



Source: company submission B.2.6.7

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Treatment-emergent adverse events

	Pre-amendment population	Post-amendment population	Intent-to-treat population	
	ABE 200 mg (N=121)	ABE 150 mg (N=320)	ABE-FUL (N=441)	PBO-FUL (N=223)
Incidence of diarrhoea				
Grade 2, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Grade 3, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Incidence of neutropenia				
Grade 3, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Grade 4, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Dose reductions due to TEAEs (%)	[redacted]	[redacted]	[redacted]	[redacted]
Dose reduced due to diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Dose reduced due to neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued any study drug due to AE (%)	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued due to diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued due to neutropenia	[redacted]	[redacted]	[redacted]	[redacted]

- Treatment discontinuations due to adverse events were more common with abemeciclib+fulvestrant compared with placebo+fulvestrant
- Diarrhoea was the most common adverse event in the abemaciclib+fulvestrant group and led to reductions in dose – after a review of preliminary safety data, the trial protocol was changed from an abemaciclib starting dose of 200 mg to 150 mg

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Source: company submission table 19

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ERG comments on MONARCH 2

- Well-designed and well-conducted trial
- Protocol amendment reduced starting dose from 200 mg to 150 mg twice daily after trial had started, based on review of preliminary safety data – potential impact on efficacy and safety results
  - Subgroup analysis showed interaction between 200 mg and 150 mg subgroup was [redacted]. However, mean relative treatment effect of abemaciclib+fulvestrant was [redacted] in 200 mg subgroup even though patients enrolled before amendment only received a median 34 days of treatment before all doses were reduced to 150 mg
- Baseline characteristics well balanced across treatment groups
  - No patients from UK but clinical experts reported the population appears representative of people in England who are likely to be eligible for treatment with abemaciclib
- Independent review of progression-free survival was done retrospectively
- Company used PFS Kaplan-Meier data adjusted for interval censoring in its base case economic model – not what is presented in the clinical effectiveness results
- Overall survival data immature – 19.1% patients had died in the abemaciclib+fulvestrant group and 21.5% in the placebo+fulvestrant group

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Source: ERG report sections 4.2, 4.3.2, 4.3.5

Company's hazard ratio network meta-analysis

Included trials	Intervention A (ITT n)	Connected to network of evidence?			
		ORR	CBR	OS	PFS
Baselga 2012 (BOLERO-2)	EXE-EVE (485), EXE (239)	✓	✓	✓	✓
*Buzdar 1997	ANAS 1 mg (128), ANAS 10 mg (130), MGA 160 mg (128)	✓	✓	✓	✓
*Buzdar 2001	LTZ 0.5 mg (202), LTZ 2.5 mg (199), MGA 160 mg (201)	✓	×	✓	✓
‡Campos 2009	EXE (65), ANAS 1 mg (65)	×	✓	✓	✓
Chia 2008 (EFECT)	FUL 250 mg (351), EXE (342)	✓	✓	×	×
Di Leo 2010 (CONFIRM)	FUL 500 mg (362), FUL 250 mg (374)	✓	✓	✓	✓
**Dombernowsky 1998	LTZ 0.5 mg (188), LTZ 2.5 mg (174), MGA 160 mg (189)	✓	✓	✓	×
Nishimura 2017 (Hi-FAIR fx)	FUL 500 mg (52), TOR (53)	✓	✓	✓	✓
‡Howell 2002	FUL 250 mg (222), ANAS 1 mg (229)	✓	✓	✓	✓
Johnston 2013 (SoFEA)	FUL 250 mg (231), EXE (249)	✓	✓	✓	✓
*Jonat 1996	ANAS 1 mg (135), ANAS 10 mg (118), MGA 160 mg 125)	✓	✓	✓	✓
**Kaufmann 2000	EXE (366), MGA 160 mg (403)	✓	✓	✓	×
**Muss 1990	MGA 160 mg (86), MGA 800 mg (84)	✓	×	✓	×
‡Osborne 2002 (Trial 0021)	FUL 250 mg (206), ANAS 1 mg (194)	✓	✓	✓	✓
**Rose 2003	LTZ 2.5 mg (356), ANAS 1 mg (357)	✓	✓	✓	×
Sledge 2017 (MONARCH 2)	ABE-FUL (446), FUL 500 mg (223)	✓	✓	✓	✓
*Turner 2015 (PALOMA 3)	PAL-FUL (347), FUL 500 mg (174)	✓	✓	✓	✓
Yamamoto 2013	TOR (46), EXE (45)	✓	✓	✓	✓
Zhang 2016	FUL 500 mg (111), FUL 250 mg (110)	✓	✓	×	✓

Subsequent FP NMA: Removed from FP NMA **Removed from OS FP NMA ‡Used in scenario analysis only

Source: company submission appendix D table 19

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HR NMA results vs fulvestrant 500mg

Heterogeneity – other trials multiple ET / prior chemotherapy vs. MONARCH 2)

PFS (random effects) | OS (fixed effects)

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Source: company submission figures 9 and 10

Notes:

- ABE+FUL, abemaciclib + fulvestrant
- EXE+EVE, exemestane + everolimus
- FUL 500, fulvestrant 500mg
- FUL 250, fulvestrant 250mg
- EXE, exemestane

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Adjusted indirect comparison

- Tamoxifen not included in NMA due to lack of evidence – adjusted indirect comparison subsequently done using Milla-Santos (2001)

	OS, HR (CrI)	PFS/TTP, HR (CrI)	Source
Toremifene vs tamoxifen	[redacted]	[redacted]	Milla-Santos 2001
Toremifene vs fulvestrant 500 mg	[redacted]	[redacted]	NMA, company submission
Adjusted indirect comparison tamoxifen vs fulvestrant 500 mg	[redacted]	[redacted]	Company submission

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Source: company submission table 16

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ERG comments on company's NMA

- Not clear why company analysed the tamoxifen trial and the NMA results in a separate analysis rather than including the trial in the original network
- Heterogeneity due to lack of published data in a similar patient population to MONARCH 2
  - all studies except MONARCH 2 (who reported it) allowed for prior chemotherapy in the advanced setting and some studies allowed for more than one prior ET in the advanced setting
- BOLERO-6 – open-label study with some imbalances in baseline characteristics. PFS benefit of capecitabine over exemestane+everolimus may be overestimated
- Subsequent therapies only reported in 4 trials. In Hi-FAIR fx and Yamamoto 2013, patients could switch to the other treatment group on progression – likely to confound OS estimates
- Proportional hazards not met for all trials for PFS and OS
  - Therefore ERG considers results of HR NMA to be misleading and challenging to interpret

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Source: ERG report section 4.4

Fractional polynomial method

- Method uses parametric survival functions, including survival distributions such as Weibull or Gompertz, together with **more flexible** fractional polynomials (FP)
- Allows for **change of hazards over time** and offers more freedom in distribution selection
- With 1st or 2nd order fractional polynomials:
  - Model hazard functions of the interventions compared in a trial
  - Consider difference in the parameters of these fractional polynomials within a trial
  - Synthesise multidimensional treatment effect (and indirectly compare) across studies
- Therefore, treatment effects are represented with multiple parameters rather than a single parameter or outcome

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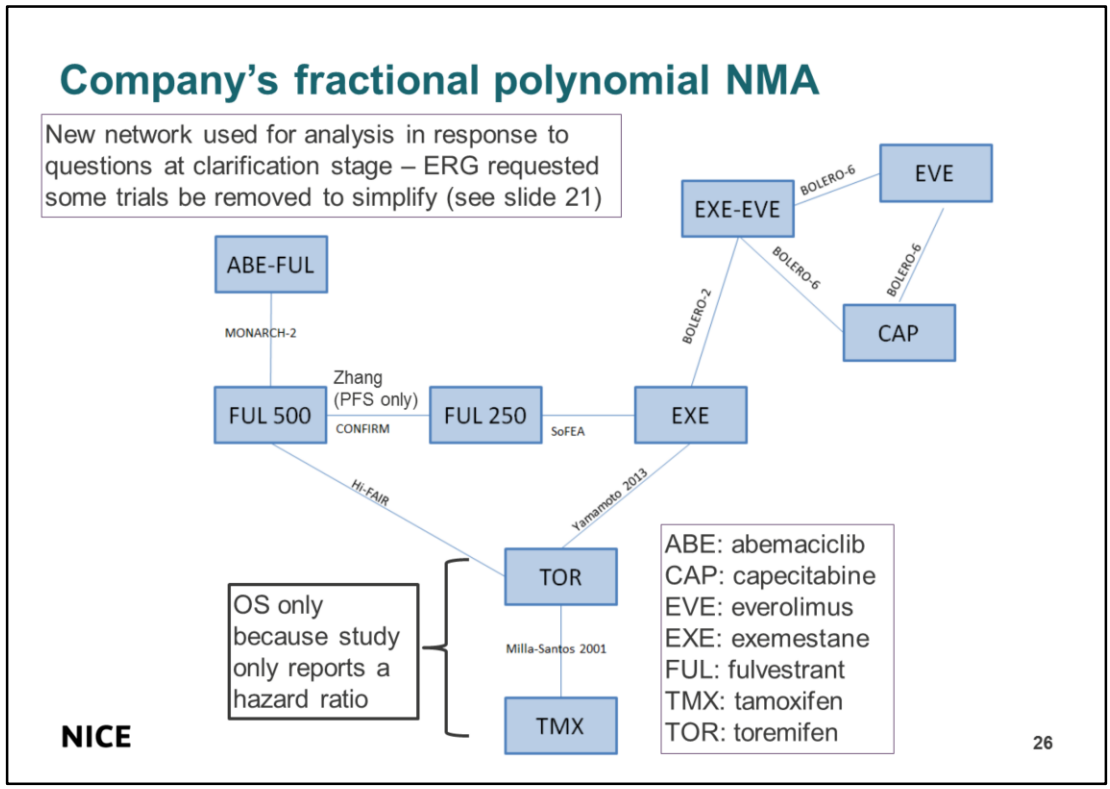

Source: company response to clarification question A3b

FP NMA (including tamoxifen for OS)

Methods

- Proportional hazards assumption did not hold for all of the trials in the revised NMA (for PFS and OS) and therefore company used a fractional polynomial approach
- Patient populations broadly similar in trial BUT MONARCH 2 more specific - people who have progressed on or after endocrine therapy and had less previous treatment. These factors could not be adjusted for.

Trial	Design	N	Intervention
BOLERO-2	Double blind	485+239	EXE-EVE, EXE
BOLERO-6	Open label	104+103+102	EXE-EVE, EVE, CAP
CONFIRM	Double blind	362+374	FUL500, FUL250
Hi-FAIR fx	Open label	53+52	TOR, FUL
Milla-Santos 2001	Double blind	106+111	TOR, TMX
MONARCH 2	Double blind	446+223	ABE-FUL, FUL
SoFEA	Partially blinded	231+249	FUL250, EXE
Yamamoto 2013	Open label	46+45	TOR, EXE
Zhang 2016	Double blind	111+110	FUL500, FUL250

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Source: company response to clarification question A3, A4

ERG comments on NMA

Hazard ratio NMA

- ERG considers it challenging to meaningfully interpret the results of the NMA based on hazard ratios when the proportional hazards assumption did not hold for all studies
- 95% credible intervals relatively wide for each comparison, particularly in overall survival

Company's PFS FP NMA

Fractional polynomial NMA

Curves presented by company do not match the curves used in the economic model – ERG unable to validate

- All models lack clinical plausibility because the plateau is not in line with the clinical trial data
- PFS curve crosses OS curve for several of the treatments, which is not biologically possible

ERG ran own NMA using fractional polynomial method

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Source: ERG report section 4.4, 4.4.3

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ERG revised FP NMA

- Excluded Hi-FAIR fx and Yamamoto 2013 and everolimus monotherapy arm from BOLERO-6 (not required to connect interventions of interest) to simplify network
- Tamoxifen not included
- Relative treatment effectiveness for capecitabine likely to have been overestimated in the BOLERO-6 trial and therefore in the FP NMA

Progression-free survival

- Consider first order FP with p=0 to have most plausible tails
- Fit to KM data may look poor but fit statistics are best average fit across the network

Overall survival

- p = -1.5 used in scenario analysis
- p = -0.5 chosen as base case based on DIC statistics, clinical plausibility and consistency in relative order of treatments compared with underlying trial data
- May be a poor fit to MONARCH 2 due to immaturity of OS data

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Source: ERG report 4.6.1, figure 19, figure 22

Cost effectiveness

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Key issues for consideration - cost

- How should treatment effectiveness be extrapolated in the model?
  - PFS and OS
  - Which NMA should be used?
- Which data should be used for time to treatment discontinuation?
- Which utility values should be used for progression-free survival and post-progression survival?
- Should adverse event-related disutilities be used in the model?
- Should age-related utility decrements be included in the model?
- What distribution of subsequent treatments should be modelled?
- How long should patients receive subsequent treatments in the model?
- How should the costs of fulvestrant and capecatibine be modelled?
- How should follow-up care costs be modelled?
- Is abemaciclib plus fulvestrant cost effective?

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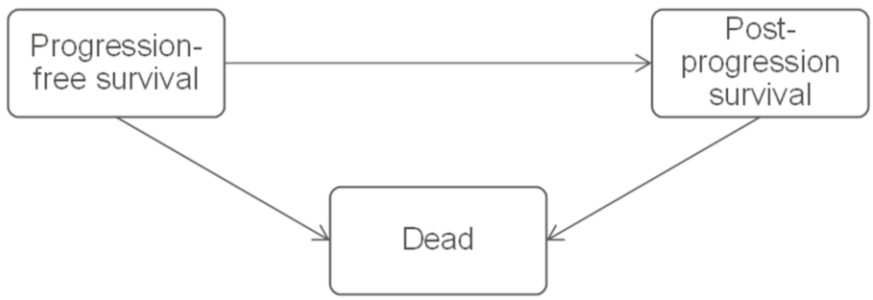
Company's economic model

- Partitioned survival model
- 3 health states
- Weekly cycle, 25 year time horizon (equivalent to lifetime)
  - ERG comment – 20 year time horizon actually used in model



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Source: company submission figure 13

Treatment effectiveness in the model

Progression-free survival - MONARCH 2

Abemaciclib+fulvestrant

[redacted]

Fulvestrant

[redacted]

Investigator assessed progression-free survival. Joint Weibull distribution fitted in the base case, chosen based on AIC/BIC statistics, fit to Kaplan-Meier data and plausibility of long-term extrapolations compared with trial data (e.g. 45 month FUL 500mg data from CONFIRM)

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Source: company submission figures 16 and 17

Treatment effectiveness in the model

Overall survival – MONARCH 2

Abemaciclib+fulvestrant

Fulvestrant

Weibull distribution chosen for both in the base case, based on AIC/BIC statistics, fit to Kaplan-Meier data and plausibility of long-term extrapolations compared to trial (CONFIRM) data. Long-term OS for abemaciclib+fulvestrant and fulvestrant was assumed to be the same after [redacted] months, after which, extrapolation was informed by CONFIRM data.

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Source: company submission figures 21 and 22

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Treatment effectiveness in the model

PFS and OS for other comparators

- Network meta-analysis used in model for progression-free survival and overall survival (original NMA used in company base case)
- Hazard ratios estimated by the NMA and applied to the fulvestrant curve based on MONARCH-2:

Comparator	PFS HR (CrI)	OS HR (CrI)
EXE (25 mg)	[redacted]	[redacted]
EXE (25 mg)-EVE (10 mg)	[redacted]	[redacted]
FUL (500 mg)	Reference	Reference

- Hazard ratios for tamoxifen compared to fulvestrant 500mg, estimated by the adjusted indirect comparison

Comparator	TTP/PFS HR (CrI)	OS HR (CrI)
TMX	[redacted]	[redacted]
FUL (500 mg)	Reference	Reference

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Source: company submission B.3.3.4, tables 26 and 27; B.3.3.5, tables 28 and 29; ERG report 5.4.5

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PFS extrapolations in company's base case

Investigator-assessed

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Source: company submission figure 19

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OS extrapolations in company's base case

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Source: company submission figure 24

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Treatment effectiveness in the model

Time to treatment discontinuation

Abemaciclib+fulvestrant

Placebo+fulvestrant

- Based on data from MONARCH 2 and used to estimate drug acquisition costs
- Joint Weibull distribution jointly fitted to MONARCH 2 KM data in base case
- Duration of therapy for comparators estimated from median duration of therapy and median PFS reported in the trial publications – HR applied to PFS distribution in model

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Source: company submission figures 26 and 27

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Utility values in the model

Health state	Utilities used in the model	Source
Pre-progression	[redacted] (company and ERG base case)	EQ-5D-5L collected in MONARCH-2 and mapped to EQ-5D-3L (van Hout approach)
Post-progression	0.505 (company's base case)	Lloyd (2006) (Company used due to immaturity of MONARCH-2 data. Used in TA421, everolimus with exemestane, in a similar population)
	[redacted] (ERG base case)	Estimated using Mitra et al. 2016
	[redacted] (ERG scenario analysis)	MONARCH 2

Company included utility decrements for adverse events. ERG removed – minimal impact on ICER

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Source: company submission B.3.2.2, B.3.4

Notes:

- The utility value from Lloyd (2006) was used for post-progression survival in the appraisals for palbociclib (TA495), ribociclib (TA496) and abemaciclib+aromatase inhibitor (ID1227)

Costs and resource use in the model

	Source for components/frequency	Source for costs
Follow-up care	NICE guidelines/ Pre-progression: MONARCH-2 Post-progression: MONARCH-1	NHS Reference costs 2016-17 / PSSRU
Subsequent therapies	Weighted average cost based on treatments in MONARCH-2 and BOLERO-2	eMIT / BNF

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Source: company submission B.3.5.3

ERG comments

Comparators

- Tamoxifen modelled as 40 mg daily while 20 mg usually used in UK

Modelling approach and structure

- Company's base case estimates that 5% patients in abemaciclib+fulvestrant group are still alive at 10 years – may suggest overestimation of long-term survival in model

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Source: ERG report 5.4.3, 5.4.4

ERG comments

Treatment effectiveness

- Company did not use hazard ratio obtained in NMA to estimate the PFS and OS abemaciclib+fulvestrant curves – used fitted curves to KM data instead
- ERG considers that models should not have been fitted jointly for treatment groups for time to treatment discontinuation, progression-free survival or overall survival because proportional hazards assumption does not hold
  - This relies even further on validity of proportional hazards assumption – ERG considers this inappropriate.
- PSA flawed because company did not account for correlation between different HRs when sampling clinical effectiveness data from HRs (and 95% credible intervals) in base case analysis
- Base case economic model uses PFS Kaplan-Meier data adjusted for interval censoring – not what is presented in the clinical effectiveness results
  - ERG does not think adjusting for interval censoring is necessary
- **Immaturity of overall survival data provides uncertainty in all results** – not accounted for through probabilistic sensitivity analyses

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Source: ERG report 5.4.3, 5.4.5

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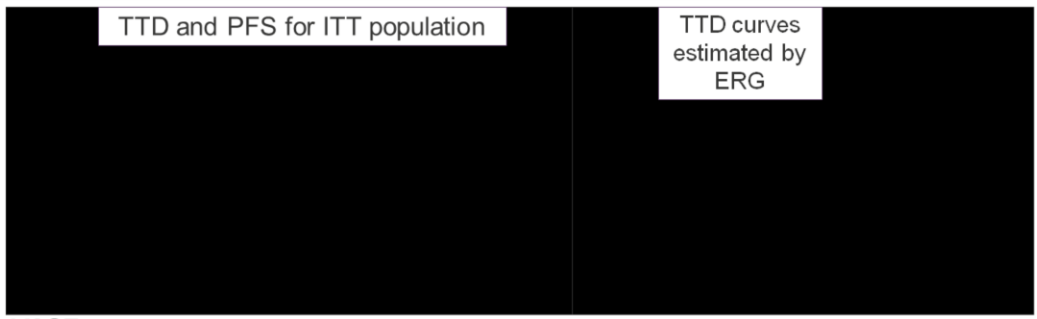
ERG comments

Time to treatment discontinuation (TTD)

- Company's base case treatment discontinuation (for EXE, EXE-EVE, TMX and chemotherapy) estimated by a ratio between median PFS and median TTD within each trial (not HRs)
- Median PFS and TTD were similar for exemestane (BOLERO 2), tamoxifen (Milla-Santos) and chemotherapy (BOLERO 6) so ERG used PFS curves as proxies to estimate TTD
- ERG estimated hazard ratio (for abemaciclib+fulvestrant, fulvestrant, and exemestane+everolimus) between cumulative survival at median duration of therapy and PFS at median TTD from trial publications (company's scenario analysis), but with PFS curves from MONARCH 2 and BOLERO 2 not the hazard ratio NMA



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Source: ERG report 5.4.5.5; figure F, G

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ERG comments

Time to treatment discontinuation

- A lot of withdrawals among patients who started on the 200mg dose. The difference between PFS and TTD KM curves is greater in the ITT population than those started on 150mg abemaciclib
- **Using the ITT TTD data underestimates the costs of ABE-FUL** compared to using the 150 mg TTD data and ERG considers is not representative of NHS clinical practice or in line with marketing authorisation of abemaciclib
- Because 150mg data not provided by company, ERG did scenario analyses varying the HR between PFS and TTD

TTD curves by abemaciclib starting dose (MONARCH 2)

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Source: ERG report 5.4.5.5; figure I

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ERG comments

Health-related quality of life

- Company stated p-values and 95% confidence intervals associated with coefficients obtained in regression models were not available, therefore ERG not able to validate
- Lloyd et al. elicited utility values from general public, rather than patients with HR positive HER2 negative advanced breast cancer, as in MONARCH 2
  - PFS utility in Lloyd [redacted] than PFS utility in MONARCH 2 so ERG considers the substantial difference between PFS and PPS in Lloyd not easily explained – used utility values from MONARCH 2 in **scenario analysis** (PFS = [redacted], PPS = [redacted])
- Alternative **ERG scenario analysis** used data from cross-sectional study, Mitra et al 2016, to apply -11% decrement to PFS utility value in MONARCH 2 to estimate PPS utility of [redacted]
- ERG also conducted **scenario analysis** to include age-related utility decrements

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Source: ERG report 5.4.8

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ERG comments: Resource and costs

Post-progression treatments

- Data on subsequent therapies in MONARCH 2 are incomplete (70% in abemaciblib+fulvestrant group had progressed or left study at end of follow-up)
- Clinical opinion that distribution of subsequent treatment would be different to company's assumptions e.g. paclitaxel use would be higher; bevacizumab not available in NHS, tamoxifen available but not included **> ERG scenario analysis**

Treatment	Time on treatment (months)		Total time in PPS (months)
	Base case	ERG scenario	
ABE-FUL	[redacted]	[redacted]	[redacted]
FUL	[redacted]	[redacted]	[redacted]
EXE	[redacted]	[redacted]	[redacted]
EXE-EVE	[redacted]	[redacted]	[redacted]
TMX	[redacted]	[redacted]	[redacted]

- Company model assumes patients on subsequent treatment for 37% of time in post-progression survival **> ERG scenario analysis** where patients remain on subsequent treatment for all but the last 3 months of life
- **Decreasing costs of subsequent treatment increases the ICER**

Treatment costs

- Fulvestrant assumed to be administered as part of consultation with oncologist and only loading dose has an associated administration cost - **ERG scenario analysis** where 32.3% subsequent fulvestrant administrations delivered in primary care and 67.7% as outpatient and administration costs applied to every treatment cycle

Follow-up care costs

- Clinical opinion that costs in model overestimate UK costs as patients would not have ECGs and would have less frequent CT scans, community nurse and oncologist visits **> ERG scenario analysis** using follow-up care costs accepted in TA496

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Source: ERG report section 5.4.9

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Company's base case results (deterministic)

Includes PAS discount for abemaciclib

Uses company's hazard ratio network meta-analysis (preferred company base case)

Technology	Total costs (£)	Total QALYs	Incremental ICER (£/QALY)	Pairwise ICER vs ABE-FUL (£/QALY)
TMX	[redacted]	[redacted]	Referent	£62,548
FUL	[redacted]	[redacted]	Dominated	£41,702
EXE	[redacted]	[redacted]	Dominated	£18,754
ABE-FUL	[redacted]	[redacted]	£62,548	-
EXE-EVE	[redacted]	[redacted]	Dominated	Dominated

Based on the latest PAS price of abemaciclib and list prices of comparators. (PAS price of abemaciclib increased after clarification.)

- **Results with the PAS discount for everolimus are presented in the part 2 confidential appendix to the PMB**
- Probablistic results are consistent with the deterministic results
- Scenario analyses show the ICER to be largely stable when varying model assumptions

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Source: company's response to clarification table 0

ERG's scenario analyses

All include PAS for abemaciclib

1. Using ERG's FP NMA-derived curves (PFS power of 0, OS power of -1.5), including ERG's estimated TTD curves
2. Using both PFS and PPS-related utility values from MONARCH 2
3. Using utility value derived using Mitra et al. 2016
4. Removing adverse event-related disutilities (ERG considers already included in PFS value from MONARCH 2)
5. Including age-related utility decrements
6. Alternative distribution of subsequent treatments
7. Patients receive subsequent treatments for all except last 3 months of PPS
8. Limited time on fulvestrant and exemestane-everolimus as subsequent treatments
9. Resource use for follow-up care from TA496 (ribociclib)
10. Fulvestrant administration costs from TA496 applied for every treatment cycle
11. Excluding cost of non-AE-related hospitalisations from analysis
12. Removing half-cycle correction
13. As scenario 1 but including first-order FP OS* curve with power -0.5

NICE **Corrected after committee meeting* 48

Source: ERG report section 6.2

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ERG alternative base case analysis [1]

	Results per patient	Incremental value ABE-FUL vs comparator ‡			
		FUL	EXE	EXE-EVE	CAP*
0	Company's base case corrected by ERG				
	Costs (£)	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]
	ICER (compared with base case)	£50,687	£57,247	Dominant	£82,621**
1	Using the ERG's FP NMA results for OS and PFS and adjusting TTD curves				
	Costs (£)	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]
	ICER (compared with base case)	£41,719	£44,089	Dominant	Dominated
3	PPS utility using a -11% relative decrement (Mitra et al. 2016) on PFS utility				
	Costs (£)	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]
	ICER (compared with base case)	[redacted]	[redacted]	[redacted]	[redacted]
	ICER with all above changes	£52,288	£51,578	Dominant	Dominated
4	Removed AE-related disutilities				
	Costs (£)	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]
	ICER (compared with base case)	[redacted]	[redacted]	[redacted]	[redacted]
	ICER with all above changes	£52,210	£51,525	Dominant	Dominated

*This refers to TMX instead of CAP for the scenario using the company's corrected base case (0)
**ABE-FUL is compared to TMX instead of CAP when the ICER is compared with the base case
‡ *Corrected after committee meeting*

Source: ERG report table 55

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ERG alternative base case analysis [2]

	Results per patient	Incremental value ABE-FUL vs comparator ‡			
		FUL	EXE	EXE-EVE	CAP*
5	Age-related utility decrements included				
	Costs (£)	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]
	ICER (compared with base case)	£51,757	£58,360	Dominant	£84,299**
	ICER with all above changes	£53,668	£52,778	Dominant	Dominated
6+7+8	Post-progression treatment in PPS from 37% to up to 3 months before death				
	Costs (£)	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]
	ICER (compared with base case)	£29,786	£53,150	Dominant	£8,384**
	ICER with all changes	£45,168	£46,116	Dominant	Dominated
9	TA496 health state costs				
	Costs (£)	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]
	ICER (compared with base case)	£62,737	£65,459	Dominant	£111,549**
	ICER with all above changes	£47,885	£45,994	Dominant	Dominated
10	TA496 FUL administration costs				
	Costs (£)	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]
	ICER (compared with base case)	£52,348	£59,546	Dominant	£88,566**
	ICER with all above changes	£49,254	£47,637	Dominant	Dominated

Source: ERG report table 55

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ERG alternative base case analysis [3]

	Results per patient	Incremental value ABE-FUL vs comparator ‡			
		FUL	EXE	EXE-EVE	CAP
11	Removing non-AE-related hospitalisation costs				
	Costs (£)	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]
	ICER (compared with base case)	£54,054	£59,797	Dominant	£89,595**
	ICER with all above changes	£50,725	£48,406	Dominant	Dominated
12	Remove half-cycle correction				
	Costs (£)	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]
	ICER (compared with base case)	£51,432	£57,790	Dominant	£84,139**
	ICER with all above changes	£52,351	£52,002	Dominant	Dominated
13	Using first-order FP OS curve with a power of -0.5 (compared to p = -1.5)				
	Costs (£)	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]
	ICER (compared with base case)	£42,065	£44,258	Dominant	Dominated
	ICER with all above changes	£70,634	£63,436	Dominant	Dominated
ERG base case with PFS and PPS utility values from MONARCH (OS FP p= -0.5)					
	ICER	£80,604	£68,116	Dominant	Dominated
ERG base case with PFS and PPS utility values from MONARCH (OS FP p= -1.5)					
	ICER	£55,448	£54,038	Dominant	Dominated

**ABE-FUL is compared to TMX instead of CAP when the ICER is compared with the base case

Source: ERG report table 55

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ERG scenario analysis

Using alternative HRs to estimate TTD curve for ABE-FUL

	Results per patient	Incremental value ABE-FUL vs comparator ‡			
		FUL	EXE	EXE-EVE	CAP
0	ERG base case				
	Costs (£)	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	£70,634	£63,436	Dominant	Dominated
a	HR=1 for PFS vs TTD curve				
	Costs (£)	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	£120,775	£87,152	Dominant	Dominated
b	Reduce HR by 5% ([redacted])				
	Costs (£)	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	£78,996	£67,391	Dominant	Dominated
c	Reduce HR by 10% ([redacted])				
	Costs (£)	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	£88,353	£71,817	Dominant	Dominated

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Source: ERG report table 56

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ERG scenario analysis

Varying the time patients spend on FUL and EXE-EVE as subsequent treatments

	Results per patient	Incremental value ABE-FUL vs comparator ‡			
		FUL	EXE	EVE-EXE	CAP
0	ERG base case				
	Costs (£)	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	£70,634	£63,436	Dominant	Dominated
d	Decreasing time spent in FUL and EXE-EVE as subsequent treatments by 5%				
	Costs (£)	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	£70,634	£63,477	Dominant	Dominated
e	Decreasing time spent in FUL and EXE-EVE as subsequent treatments by 10%				
	Costs (£)	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	£72,634	£63,518	Dominant	Dominated
f	Decreasing time spent in FUL and EXE-EVE as subsequent treatments by 25%				
	Costs (£)	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]
	ICER	£74,448	£60,649	Dominant	Dominated

Source: ERG report table 57

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