NICE National Institute for Health and Care Excellence

Abemaciclib with an aromatase inhibitor for untreated advanced HR-positive, HER2-negative breast cancer [ID1227]:

Lead team presentation

Committee A
Lead team: Brian Shine, Pamela Rees, and Paul Robinson
ERG: Southampton Health Technology Assessments Centre
NICE technical team: Marcela Haasova and Joanna Richardson
18th September 2018

For public - ACiC information redacted

Background and Clinical Effectiveness

[redacted]

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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.

[redacted]

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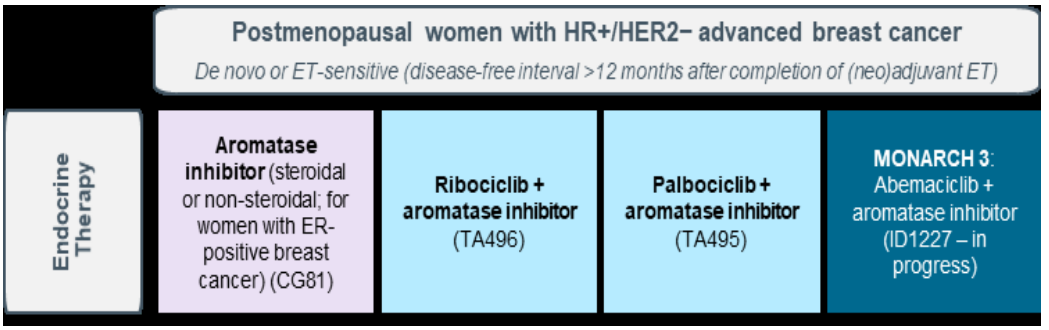
Key: HER2-, human epidermal growth factor receptor 2-negative; HR+, hormone receptor-positive.

Company: treatment pathway 1st line



- Sequential chemotherapy for imminently life-threatening disease or if early relief of symptoms is required (CG81)

ERG: The pathway is reflective of current clinical practice. However, aromatase inhibitor (AI) monotherapy would only now be used in a minority of patients given that ribociclib and palbociclib have been recommended by NICE for use in the NHS.

[redacted]

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Decision problem

	Final scope	Company
Population	People with advanced HR+/HER2− breast cancer that has not been previously treated with endocrine therapy	Postmenopausal women with advanced HR+/HER2− locoregionally recurrent or metastatic breast cancer who have had no prior systemic therapy for advanced disease
Intervention	Abemaciclib in combination with an aromatase inhibitor	Abemaciclib + non-steroidal aromatase inhibitor [i.e. anastrozole or letrozole]
Comparators	• Palbociclib with an aromatase inhibitor • Ribociclib with an aromatase inhibitor	• Palbociclib + aromatase inhibitor (letrozole) • Ribociclib + aromatase inhibitor (letrozole)
Outcomes	OS, PFS, RR, AE, HRQoL	OS, OS rate, PFS, RRs (ORR, DCR, CBR, DoR), AE, EORTC QLQ-C30, EQ-5D-5L

ERG: The company's decision problem reflects the final scope.

[redacted]

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Preview: clinical effectiveness and treatment pathway issues

- How generalisable are MONARCH 3 results?
  - Is MONARCH 3 population representative of postmenopausal women with advanced or metastatic HR+/HER2- breast cancer previously untreated in the advanced setting?
- Does the committee have a preference for the investigator assessed or the independent review of the outcome PFS?
- Network meta-analyses (NMA1) estimated the clinical effectiveness (PFS and OS) of abemaciclib+NSAI compared with ribociclib+NSAI, and palbociclib+NSAI.
  - Is the level of clinical heterogeneity in the NMA1 acceptable?
  - Overall survival in MONARCH 3 (and other studies) is immature.
  - Networks for AEs, treatment discontinuation and HRQoL were not possible.
  - What is the committee's view of the NMA1 results?
- Does the committee consider the effectiveness of the 3 CDK 4/6 inhibitors to be similar? Is a class effect for CDK 4/6 inhibitors likely?

[redacted]

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Abemaciclib (Verzenios, Eli Lilly)

Positive CHMP opinion	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 as initial endocrine-based therapy.**
Mechanism of action	Selective dual inhibitor of cyclin-dependent kinase 4 and 6 (CDK 4/6).
Administration	• 150 mg oral tablet twice daily for 28-days, in combination with aromatase inhibitor. • Women must be in a postmenopausal state prior to therapy.
Acquisition cost	List price of abemaciclib: [redacted] per 28-day cycle.
Cost of a course of treatment	• Mean Time on Treatment: [redacted] months (modelled). • Cost per mean Time on Treatment: [redacted]. • PAS submitted to Department of Health and Social Care.

[redacted]

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Impact on Patients

Breast Cancer Now

- Diagnosis of metastatic breast cancer is difficult to come to terms with.
- Pain; Fear; Uncertainty; Living from “scan to scan”.
- Limited treatment options.
- Patients want treatments that will halt progression, extend life and have few or manageable side effects and
- To be able to continue with “normal” life as much as possible.
- As a first line treatment, it has an important role in extending the time that hormone treatments work; delaying progression; delaying commencing chemotherapy.
- Oral medication taken in the comforts of home.
- Associated with more side effects than an aromatase inhibitor as a monotherapy.
- However, patients vary in their attitudes to risk.
- Importance of patient involvement in informed discussions & decisions.

[redacted]

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Clinical evidence: MONARCH 3

Design	Phase III, multi-centre, placebo-controlled, randomised, double-blinded.
Location	International: 158 sites & 22 countries; 4 sites in UK ([redacted]).
Population	Postmenopausal women with HR+/HER2− locoregionally recurrent or metastatic breast cancer who had no prior systemic therapy in the advanced setting. Randomisation stratified by: • site of metastases: visceral (lung, liver, pleural, peritoneal, or adrenal gland involvement); bone only, or other; • prior (neo)adjuvant endocrine therapy: AI therapy (e.g. anastrozole, exemestane and letrozole), other, or no prior endocrine therapy.
Intervention and comparator	• Abemaciclib (N=328) 300mg/day for 28day cycle with a NSAI (either anastrozole or letrozole). • Placebo (N=165) with a NSAI (as above). • Dose interruptions and sequential dose permitted for treatment-related toxicities. If dose reduction beyond 50 mg twice daily needed, drug discontinued.
Outcomes	**Investigator-assessed PFS (primary),** OS, OS rate, RRs (ORR, DCR, CBR, DoR), TEAE, EORTC QLQ-C30, EQ-5D-5L**, also independent review PFS.**

[redacted]

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MONARCH 3: selected baseline characteristics

Baseline characteristic		Abemaciclib + NSAI, N=328	Placebo + NSAI, N=165
Mean age, years (SD)		[redacted]	[redacted]
Race, n (%)	White	186 (56.7)	102 (61.8)
	Asian	103 (31.4)	45 (27.3)
	Other	11 (3.4)	7 (4.2)
Region, n (%)	Europe	[redacted]	[redacted]
	Asia	[redacted]	[redacted]
	North America	[redacted]	[redacted]
ECOG performance status	ECOG 0	192 (58.5)	104 (63.0)
	ECOG 1	136 (41.5)	61 (37.0)
Disease setting, n (%)	De novo metastatic	135 (41.2)	61 (37.0)
	Metastatic recurrent	182 (55.5)	99 (60.0)
	Locoregionally recurrent	11 (3.4)	5 (3.0)
Metastatic site, n (%)	Visceral	172 (52.4)	89 (53.9)
	Bone only	70 (21.3)	39 (23.6)
	Other	86 (26.2)	37 (22.4)

[redacted]

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MONARCH 3: Investigator-assessed PFS

- Final PFS analysis ITT population (3rd November 2017):

- **HR=**
- Sensitivity analysis censoring patients at a start of a new anticancer therapy: **HR=**
- Similar result were shown in pre-planned and exploratory subgroup analyses.
- **Independent review PFS:**

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MONARCH 3: Overall Survival

- At PFS final analysis ITT population (3rd November 2017):

- OS data still immature, with events (deaths) in abemaciclib+ NSAI arm and events (deaths) in placebo +NSAI arm and with median OS OS Kaplan-Meier curves over the 36 month observation period.
- HR=

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MONARCH 3: Survival at final PFS analysis

	Abemaciclib + NSAI (n=328)	Placebo + NSAI (n=165)	Treatment Effect /p-value
Progression-free survival			
Median PFS, months Investigator assessed	[redacted]	[redacted]	[redacted]
24 month PFS rate, % Investigator assessed	[redacted]	[redacted]	[redacted]
Median PFS, months Independent Review	[redacted]	[redacted]	[redacted]
24 month PFS rate, % Independent Review	[redacted]	[redacted]	[redacted]
Overall survival			
Median OS, months	[redacted]	[redacted]	[redacted]
24 month OS rate, % (95% CI)	[redacted]	[redacted]	[redacted]
Number of deaths, n (%)	[redacted]	[redacted]	-

[redacted]

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MONARCH 3: health-related quality of life

- **EQ-5D-5level:**
  - [redacted] differences were observed in change from baseline between arms for both the EQ-5D-5L index ([redacted]) and VAS ([redacted]).

	Baseline score mean (SD)		Change from baseline across all visits LS Mean (SE)		Difference in change between arms a LS mean (SE)	p-value
Treatment	Abemaciclib + NSAI N=327	Placebo + NSAI N=161	Abemaciclib + NSAI N=327	Placebo + NSAI N=161		
Index value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visual analogue scale	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

- **EORTC QLQ-C30**:
  - [redacted] of the diarrhoea symptom scale in abemaciclib plus NSAI arm relative to the placebo+NSAI arm ([redacted]) and a [redacted] in global health status in the placebo +NSAI arm relative to abemaciclib +NSAI ([redacted]).

[redacted]

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MONARCH 3: Treatment emergent adverse events (TEAE, safety population)

Percent of participants (patients may be counted in >1 category)	Abemaciclib + NSAI (n=327)	Placebo + NSAI (n=161)
TEAEs related to study treatment [b]	[redacted]	[redacted]
Grade 3 or higher TEAE related to study treatment [b]		
Serious Adverse Events related to study treatment [b]		
Discontinuations of all study treatment due to an AE		
Deaths due to adverse event		

- **Company**: For abemaciclib + NSAI diarrhoea, infection/infestations, neutropenia, fatigue and nausea were the most frequent TEAEs. Diarrhoea was predominantly of low grade and largely managed through medication.

ERG: agrees with company's conclusion, but notes that the relatively high proportion of patients receiving abemaciclib reporting grade 3 diarrhoea ([redacted]) is clinically important.

[redacted]

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Key: [b] Includes events that were considered related to study treatment as judged by the investigator.

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ERG: MONARCH 3

- Well conducted trial, but high frequency of AE such as diarrhoea could lead to unblinding. Therefore the independent review PFS may be a better measure of PFS. Antidiarrhoeal medications used in [redacted] of patients experiencing diarrhoea; [redacted] had dose reduction, [redacted] dose omission, and [redacted] discontinued treatment due to diarrhoea.
- Median duration of disease was [redacted] in ABE+NSAI vs. placebo ([redacted] months) and proportion of patients with treatment-free interval of ≥36 months was higher (62.7 % vs 50.0%). This suggests that ABE+NSAI arm had some better prognostic factors at baseline, potentially favouring treatment effects.
- ABE+NSAI : Withdrawals due to AE [redacted] and withdrawals due to progressive disease [redacted] (vs placebo).
- No cross-over permitted, but ABE/placebo or NSAI could be discontinued. [redacted] in ABE+NSAI and [redacted] in placebo+NSAI received post-discontinuation therapy. Endocrine therapy ([redacted]) (e.g. fulvestrant) and chemotherapy ([redacted]; e.g. paclitaxel) were most common.
- The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Breast 23 (EORTC QLQ-BR23) was specified in CSR but results are not reported. There is a risk of selective reporting bias.
- OS results are immature.

[redacted]

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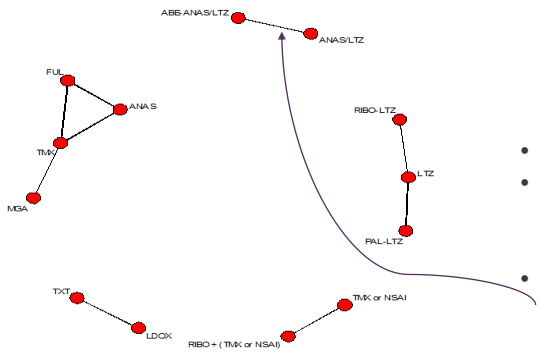
Network meta-analysis for 1st line: NMA1



- 18 Studies including abemaciclib, anastrozole, exemestane, fulvestrant, letrozole, megestrol acetate, palbociclib, ribociclib, tamoxifen, toremifene, liposomal doxorubicin, and docetaxel
- Analyses included PFS, OS, ORR & CR
- Networks for AEs, treatment discontinuation and HRQoL not possible due to limited data in primary studies.
- MONARCH 3: ANAS or LTZ (investigator's choice). ANAS & LTZ pooled to connect the network.

- Company: heterogeneity in MONARCH 3, MONALEESA-2, PALOMA-1 & -2:
  1. Disease-free interval following adjuvant therapy: was the same for ABE, PAL and RIBO, unclear for some others in network
  2. Visceral involvement: Proportion of patients varied between arms and studies: 44% to 59%, & only MONARCH 3 reported proportion of patients with liver metastases

[redacted]

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NMA1: results summary

- Treatment effects relative to placebo+NSAI:

Outcome, FE/RE and N	Abemaciclib + NSAI	Palbociclib + NSAI	Ribociclib + NSAI
PFS, FE 8 studies, HR (95% CrI)	[redacted]	[redacted]	[redacted]
PFS, RE 8 studies, HR (95% CrI)	[redacted]	[redacted]	[redacted]
OS, FE 15 studies, HR (95% CrI)	[redacted]	[redacted]	[redacted]
ORR, RE 17 studies, OR (95% CrI)	[redacted]	[redacted]	[redacted]
CBR, FE 10 studies, OR (95% CrI)	[redacted]	[redacted]	[redacted]
CR, RE 15 studies, OR (95% CrI)	[redacted]	[redacted]	[redacted]

- Similar estimates observed for ABE-ANAS/LTZ and comparators for PFS and response rates.
- Final OS data only from PALOMA-1, MONARCH 3, MONALEESA-2, and PALOMA-2 immature OS. Treatment effects are highly uncertain.

[redacted]

Key: N, **number of studies in NMA;** FE, fixed effects model; RE, random effects model.

ERG: NMA1 critique

- NMA1 has been adequately conducted.
- However, there are some limitations and uncertainties
- For many trials it was not possible to ascertain similarity, or otherwise, of patient characteristics. Notably, there is variation between trials in the proportion of patients with visceral metastases, and the effect of this on the results is uncertain.
- The methods used assumes proportional hazards assumption. However, proportional hazards assumption did not hold for OS. Alternative approach assuming time-varying hazards should been used (albeit with immature OS data).
- Considers included trials similar in terms of age and previous treatment history for advanced cancer. However, due to reporting limitations a full assessment of clinical heterogeneity is not possible.
- The impact of this on the NMA1 is not clear and results of the NMA1 should be interpreted with caution. In addition, due to immaturity of OS data, OS NMA1 results are highly uncertain.
- Although there were limitations to the NMA1, the results were considered by clinical experts advising the ERG to be clinically plausible.

[redacted]

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Clinical effectiveness and treatment pathway issues

- How generalisable are MONARCH 3 results?
  - Is MONARCH 3 population representative of postmenopausal women with advanced or metastatic HR+/HER2- breast cancer previously untreated in the advanced setting?
- Does the committee have a preference for the investigator assessed or the independent review of the outcome PFS?
- Network meta-analyses (NMA1) estimated the clinical effectiveness (PFS and OS) of abemaciclib+NSAI compared with ribociclib+NSAI, and palbociclib+NSAI.
  - Is the level of clinical heterogeneity in the NMA1 acceptable?
  - Overall survival in MONARCH 3 (and other studies) is immature.
  - Networks for AEs, treatment discontinuation and HRQoL were not possible.
  - What is the committee's view of the NMA1 results?
- Does the committee consider the effectiveness of the 3 CDK 4/6 inhibitors to be similar? Is a class effect for CDK 4/6 inhibitors likely?

[redacted]

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Cost-Effectiveness

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Preview: cost-effectiveness issues

- What is the committee's view of the company's model?
  - Is the committee minded to consider that abemaciclib, ribociclib and palbociclib are similar?
    - If so is the use of this model appropriate for decision making, or would a cost comparison approach be reasonable?
    - If so what is the committee's view of the company's approach to modelling the cost of treatments?
- What is the committee's view of the company's data and assumptions?
  - Is the ERG's or the company's approach to time to treatment progression (TTP1) , progression free survival deaths (PFSD1), overall survival on 2nd line treatments (OS2) and utilities (PFS2) more appropriate?
  - Is the company's assumption of 27.5% PFS/OS gain appropriate?
  - OS data are immature, results from NMAs need to be interpreted with caution. What is the committee's view of the uncertainty of the cost-effectiveness estimates?

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Introduction

Recent models used to appraise CDK 4/6 inhibitors for this indication:

- TA495 palbociclib: conventional 3-state (PFS, PD, death) partitioned survival model.
- TA496 ribociclib: individual patient based state-transition model (PFS1, PFS2, PD, death).
- DSU report: explored TA496 model structure, data and assumptions.
- Abemaciclib: Cohort state-transition model with "fixed pay-off" sub-model. Sub-model is included to reduce uncertainty over immature 1st-line OS data.
  - This is a new model that similarly to TA496 explicitly models a second-line of treatment and time to second progression (PFS2).
  - The key data inputs and assumptions are discussed on the following slides. No one-way sensitivity analysis for model parameters has been submitted so it is difficult to identify key drivers of the model.

[redacted]

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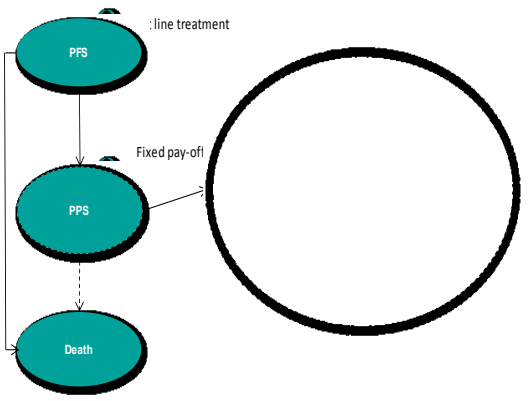
Company: model structure

- **Cohort state-transition model** with 2 health states (PFS1 & PPS1) and death, with **'fixed pay-off' sub-model**, a separate state-transition model with 2 health states (PFS2 & PPS2) and death, representing health outcomes and costs incurred on 2nd line and subsequent treatments applied post progression.



- Calibration is used to adjust the time spent in the pay-off sub-model to reflect an assumed relationship between PFS and OS:
  - in the base case, 'partial surrogacy' relationship is set at 27.5% PFS/OS gain
- monthly cycles with half-cycle correction
- Life time horizon (35 years)

[redacted]

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Key: OS, overall survival; PFS, progression-free survival; PPS, post-progression survival.

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Summary: inputs for 1st line and utilities

	Treatment	Values	Company	ERG	Source
TTP1 (TTP≤OS)	NSAI rate	[redacted]	✓	✓	MONARCH 3: exponential
	ABE+NSAI rate		✓	✗	
	ABE-NSAI vs NSAI		✗	✓	NMA1
	PAL-NSAI vs NSAI		✓	✓	
	RIBO-NSAI vs NSAI		✓	✓	
PFD1	NSAI rate	0.002 per month	✓	✓	MONARCH 3: Negative binomial
	ABE-NSAI rate	0.005 per month	✓	✗	
	ABE-NSAI vs NSAI	[redacted]	✗	✓	NMA1
	PAL-NSAI vs NSAI		✓	✓	
	RIBO-NSAI vs NSAI		✓	✓	
TTD1 (TTD≤TTP)	NSAI		✓	✓	MONARCH 3: Generalised gamma
	ABE-NSAI		✓	✓	
	PAL-NSAI vs ABE	19.8 months: HR 0.81	✓	✓	PAL SmPC
	RIBO-NSAI vs ABE	20.3 months: HR 0.79	✓	✓	RIBO EMA assessment
Utilities	PFS1	[redacted]	✓	✓	MONARCH 3
	PFS2 endocrine	0.774	✓	✗	TA496-BOLERO 2
	PFS2 chemo	0.661	✓	✗	TA496-BOLERO 2
	PFS2 endocrine	0.690	✗	✓	TA496 DSU
	PFS2 chemo	0.577	✗	✓	TA496 DSU
	PPS	0.505	✓	✓	TA496 Lloyd, 2006

[redacted]

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Summary: inputs for 2nd line

	Treatment	values	Company	ERG	Source
PFS2	FUL rate	[redacted]	✓	✓	MONARCH 2 SG: exponential
	ANAS vs FUL		✓	✓	NMA2
	LTZ vs FUL		✓	✓	
	EXE vs FUL		✓	✓	
	EVE+EXE vs FUL		✓	✓	
	TMX vs FUL		✓	✓	Mila-Santos 2001
	Chemo vs FUL	1.64 (0.85, 3.15)	✓	✓	Li et al 2015
OS2	FUL rate	[redacted]	✓	✗	MONARCH 2+ CONFIRM: exponential
	FUL rate		✗	✓	MONARCH: Gompertz
	ANAS vs FUL		✓	✓	NMA 2
	LTZ vs FUL		✓	✓	
	EXE vs FUL		✓	✓	
	EVE+EXE vs FUL		✓	✓	
	TMX vs FUL		✓	✓	Mila-Santos 2001
	Chemo vs FUL	HR 1.89 (0.72, 5.00)	✓	✓	Li et al 2015
PFD2	EVE+EXE	0.005 per month	✓	✓	BOLERO-2
	EXE	0.003 per month	✓	✓	
	Chemo vs FUL	1.64 (0.85 ,3.15)	✓	✓	Li et al 2015
TTD2	FUL	[redacted]	✓	✓	MONARCH 2: exponential
	ANAS	5.6 months: [redacted]	✓	✓	Rose 2003
	LTZ	5.9 months: [redacted]	✓	✓	Rose 2003
	EXE and TMX	4.4 months: [redacted]	✓	✓	Baselga 201, TMX assumed equal EXE.
	EVE+EXE	7.8 months: [redacted]	✓	✓	BOLERO 2
	Chemo	4.8 months: [redacted]	✓	✓	Smorenburg 2014

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ERG: preferred assumptions and changes to model

- Corrected 4 minor errors in the coding of the model. These made very little difference to the company's results.
- ERG preferred analysis included the following changes to company's base case:
  - Estimation of time to progression (TTP1) and pre-progression deaths (PFD1) for ABE+NSAI estimated relative to fitted curves for NSAI using hazard ratios from NMA1 (as for the comparators).
  - A Gompertz OS curve from second-line treatment. This was more pessimistic than the company's assumption of exponential with CONFIRM trial extrapolation.
  - A utility of 0.69 for people free of progression at second line – as per the assumption suggested by the Decision Support unit in the NICE appraisal of ribociclib (TA496).

[redacted]

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Issues: time to progression (TTP1) ~ PFS1

[redacted]

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Issues: progression-free death rate (PFD1)

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Issues: fulvestrant OS2 modelling

- **Company:** Extrapolations uncertain due to the immaturity of data. OS estimated from MONARCH 2 (exponential curve) and CONFIRM trial (Weibull).

OS2	Year	FUL	ANAS	LTZ	EXE	TMX	EVE+EXE	Chemo
Exponential + CONFIRM	1							
	3							
	5							
	10							
Gompertz	1							
	3							
	5							
	10							

ERG: Gompertz is better fit for MONACH 2 and is clinically plausible. Has concerns about the use of CONFIRM trial in the model.

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Issues: utilities

- **Company**: utilities for PFS1 were assumed to be the same for all treatments

Health state		Utilities	Notes	Source
Company's base-case	PFS1	[redacted]	-	MONARCH 3
	PFS2	0.774/0.661/0.745	Endocrine/chemo/ average	TA496-BOLERO 2
	PPS	0.505	-	Lloyd, 2006
MONARCH 3	PFS1	[redacted]	Overall/NSAI/ABE+NSAI	MONARCH 3
	PFS2/PPS	[redacted] (some patients may have experienced 2nd progression)		
MONARCH 2	PFS2	[redacted]	Endocrine/chemo/ average	MONARCH 2
	PPS	[redacted]	-	MONARCH 2
TA495	PFS1	0.72/0.71/0.74	Overall/NSAI/PAL+NSAI	PALOMA 2
	PFS2/PPS	0.505	-	Lloyd, 2006
TA496	PFS2	0.774 initial and 0.690 final		DSU
	PPS	0.505	-	Lloyd, 2006

ERG: Due to inconsistency between PFS1 and PFS2 (PFS2 >PFS1) ERG uses TA496 PFS2 value of 0.690.

[redacted]

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Company: TTD1 summary

- **Abemaciclib + NSAI and NSAI**: TTD KM data from MONARCH 3 modelled. Gamma distribution was chosen (lognormal, Gompertz & exponential in scenario analyses). Where TTD exceeded TTP, TTD was set equal to TTP.
- **Comparators:** TTD not reported in primary publications. TTD estimated from HR between median TTD provided in EMA publication for RIBO (20.30 months), SmPC for PAL (19 months), relative to NSAI from MONARCH 3 ([redacted] months).

TTD1 (months)	ABE+NSAI	NSAI	PAL+NSAI	RIBO+NSAI
Modelled mean	[redacted]	[redacted]	[redacted]	[redacted]
Modelled median	[redacted]	[redacted]	[redacted]	[redacted]
Reported median (trial)	(MONARCH 3)	(MONARCH 3)	13.81/19.82 (PALOMA-1/2)	13.00 (MONALEESA-2)

ERG: agrees with the company's choice of curves.
- However, as the company notes, lower costs of ABE are driven by shorter time on treatment with ABE+NSAI. This difference is based on weak evidence.
- The company notes that including dose intensity of [redacted] for ABE, 93% for PAL and 88% for RIBO increased ICERs by ≥15% in sensitivity analyses.

[redacted]

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Model: clinical outcomes (ERG updated)

Treatment	Median PFS (months)			Median ToT (months)			Median OS (months)		
	Modelled		Reported (Trial)	Modelled		Reported (Trial/document)	Modelled		Reported (Trial)
	CS	ERG		CS	ERG		CS (no calibration)	ERG (no calibration)	
ABE-NSAI	[redacted]	[redacted]	[redacted] (MONARCH 3)	[redacted]	[redacted]	[redacted] (MONARCH 3)	[redacted]	[redacted]	NR (MONARCH 3)
PAL-NSAI	[redacted]	[redacted]	20.20 (PALOMA-1) 27.60 (PALOMA-2)	[redacted]	[redacted]	13.81 (PALOMA-1) 19.82 (PALOMA-2) 19.00 (SmPC)	[redacted]	[redacted]	37.5 (PALOMA-1)
RIBO-NSAI	[redacted]	[redacted]	25.30 (MONALEESA-2)	[redacted]	[redacted]	13.00 (MONALEESA-2) 15.10 (MONALEESA-7) 20.30 (EMA)	[redacted]	[redacted]	NR (MONALEESA-2)
NSAI	[redacted]	[redacted]	[redacted] (MONARCH 3) 8.50-18.00 (see CS table 65 for trials)	[redacted]	[redacted]	[redacted] (MONARCH 3) 6.10-13.90 (see CS table 65 for trials)	[redacted]	[redacted]	NR (MONARCH 3) 17.40-60.10 (see CS table 65 for trials)

[redacted]

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ERG: other issues

- AE: disutilities for adverse drug reactions are included in the model, but as the size and duration of the effects assumed are low, these have a negligible impact on cost-effectiveness results.
- 2nd and 3rd-line treatments:
  - clinical advice to the ERG is that it would be unusual for patients to spend as much as 63% of time after a second disease progression without treatment. Thus, the cost of treatment in the PPS health state is probably underestimated.
  - concern that the estimated use of second and third-line treatments does not reflect current NHS practice. In particular, the company includes fulvestrant which is not recommended by NICE in this context.
- Clinical data:
  - NMA1 should be interpreted with caution due to uncertainties. In addition, due to immaturity of OS data, OS NMA1 results are highly uncertain.
  - NMA2 conducted for wider population. Results should be interpreted with caution due to uncertainties.

[redacted]

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Results

- All results presented below were calculated using list prices.
- Results with confidential patient access scheme discounts and commercial access agreements for the intervention, comparators and subsequent treatments are presented in a separate confidential appendix.
- The confidential appendix [cPAS] cannot be presented here.

[redacted]

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Company: base-case results using list prices (before ERG error corrections)

- **Deterministic results**

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
ABE+NSAI	£129,803	5.08	3.29	-	-	-	-	-
RIBO+NSAI	£148,170	5.02	3.22	£18,367.14	−0.06	−0.068	Dominated	Dominated
PAL+NSAI	£145,266	5.03	3.23	−£2,904.53	0.02	0.003	Dominated	Dominated

ERG: probabilistic analysis did not reflect correlations between NMA parameters.

[redacted]

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Company: summary of sensitivity analyses

- In scenario analyses, results were largely stable when varying model assumptions, with consistent ICER estimates, demonstrating the robustness of the model:

Decrease in base case ICER of ≥15%	Increase in base case ICER of ≥15%
1. Apply PFS–OS surrogacy (base case: partial [27.5%]; scenario: full [100%])	1. Source of ABE-NSAI treatment effect for PFS
2. Source of clinical outcomes in PPS (base case: from MONARCH 2; scenario: from BOLERO-2)	2. PPS utility source (base case: from Lloyd 2006 [0.505]; scenario: from MONARCH 2 [redacted])
3. Distribution for extrapolating 2nd -line OS, scenario 3 (base case: exponential with CONFIRM data extrapolation; scenario: Gompertz)	3. Distribution for extrapolating TTP, scenario 2 (base case: exponential; scenario: Gompertz)
4. Relative dose intensity (base case: off; scenario: on)	

ERG: Results consistent across company's analyses, and our results were similar.
- However, difference in QALYs between CDK 4/6 inhibitors was very small, and ranking of ABE, RIBO and PAL changed between scenarios.
- Company did not present one-way sensitivity analysis for model parameters, or tornado diagram so it is difficult to identify key drivers of the model.

[redacted]

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ERG: results with cumulative changes (ranked by QALY gains)

Analysis		Treatments	Total costs	Total QALYs	ICERs (£/QALY)	
					Incremental	ABE vs. comparator
ERG corrected company base case		**NSAI**	**£56,152**	**2.997**	**Referent**	**£250,352**
		PAL+NSAI	**£152,268**	**3.273**	**Dominated**	**ABE+NSAI dom.**
		RIBO+NSAI	**£154,559**	**3.285**	**Dominated**	**ABE+NSAI dom.**
		ABE+NSAI	**£129,590**	**3.291**	**£250,352**	-
+	**ABE+NSAI TTP1 from NMA**	NSAI	£56,152	2.997	Referent	£341,663
		ABE+NSAI	£130,514	3.215	£341,663	-
		PAL+NSAI	£152,268	3.273	Ext. dom.	£376,720 (SW)
		RIBO+NSAI	£154,559	3.285	£343,915	£343,915 (SW)
+	**ABE+NSAI PFD1 from NMA**	NSAI	£56,152	2.997	Referent	£289,982
		PAL+NSAI	£152,268	3.273	Dominated	ABE+NSAI dom.
		ABE+NSAI	£138,597	3.282	£289,982	-
		RIBO+NSAI	£154,559	3.285	£4,909,402	£4,909,402 (SW)
+	**OS2 Gompertz**	NSAI	£40,049	2.350	Referent	£208,333
		RIBO+NSAI	£142,614	2.750	Dominated	ABE+NSAI dom.
		PAL+NSAI	£140,748	2.761	Dominated	ABE+NSAI dom.
		ABE+NSAI	£127,062	2.768	£208,333	-
+	**PFS2 utility 0.69 ~ERG preferred analysis**	**NSAI**	**£40,049**	**2.283**	**Referent**	**£192,356**
		RIBO+NSAI	**£142,614**	**2.719**	**Dominated**	**ABE+NSAI dom.**
		PAL+NSAI	**£140,748**	**2.727**	**Dominated**	**ABE+NSAI dom.**
		ABE+NSAI	**£127,062**	**2.735**	**£192,356**	-

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Innovation and equality consideration

Innovation:

- The company states that abemaciclib plus NSAI is a oral therapy with a tolerable safety profile that allows for continuous dosing which may be preferred by patients:
  - In the MONARCH 3 trial, the most frequently observed TEAE was diarrhoea ([redacted]); [redacted] and [redacted] experienced a grade 3 and 4 event, respectively. The majority of abemaciclib plus NSAI patients (76.3%) who experienced diarrhoea did not undergo any treatment modifications during the study, [redacted] had a dose reduction and [redacted] had a dose omission.
  - It may be noted that the comparators palbociclib and ribociclib are associated with high levels of neutropenia: 55.3% grade 3 and 59.6% grade 3 or 4, respectively. As a result, treatment with palbociclib or ribociclib requires regular blood count monitoring and a seven-day treatment gap following every 21 days of treatment to allow for recovery.

Equality consideration

- No equality issues were raised.

[redacted]

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Cost-effectiveness issues

- What is the committee's view of the company's model?
  - Is the committee minded to consider that abemaciclib, ribociclib and palbociclib are similar?
    - If so is the use of this model appropriate for decision making, or would a cost comparison approach be reasonable?
    - If so what is the committee's view of the company's approach to modelling the cost of treatments?
- What is the committee's view of the company's data and assumptions?
  - Is the ERG's or the company's approach to time to treatment progression (TTP1) , progression free survival deaths (PFSD1), overall survival on 2nd line treatments (OS2) and utilities (PFS2) more appropriate?
  - Is the company's assumption of 27.5% PFS/OS gain appropriate?
  - OS data are immature, results from NMAs need to be interpreted with caution. What is the committee's view of the uncertainty of the cost-effectiveness estimates?

[redacted]

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