NICE National Institute for Health and Care Excellence

Abemaciclib in combination with fulvestrant for treating advanced hormone receptor-positive, HER2-negative breast cancer (CDF review of TA579)

Lead team presentation

Committee A chair: Jane Adam

Lead team: Mohit Sharma, Rita Faria, Pam Rees

ERG: BMJ-TAG

Technical team: Emily Eaton Turner, Sue Harnan, Janet Robertson

Company: Eli Lilly

1st Appraisal post CDF Committee Meeting: 5th January 2021

Key clinical issues

- **Key issue 1:** Subgroup data by abemaciclib starting dose
  - Should the ITT population or the post-amendment (150 mg) subgroup be used to estimate efficacy?
  - *NB: this was not a key issue in TA579, has been raised subsequently by ERG; this issue also relates to:*
  - ***Key issue 4*** *(Time to treatment discontinuation estimate for abemaciclib plus fulvestrant)*

- **Key issue 9 (un-numbered in the ERG report):** SACT data
  - Is the SACT data too immature to be informative for decision making?

Abemaciclib (Verzenios, Eli Lilly) with fulvestrant (Faslodex, AstraZeneca)

Marketing authorisation (Oct 2018)	For 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" **Note only recommended for CDF in a subpopulation of MA: In combination with fulvestrant, after endocrine therapy, and if exemestane/everolimus is the comparator**
Mechanism of action	(CDK4/6) inhibitor. Blocks cell cycle progression leading to suppression of tumour growth
Dosage and administration	• **Abemaciclib**: 1 x 150 mg orally, twice daily for 28-day cycle. • **Fulvestrant:** intramuscular injection, 500 mg on days 1 & 15 of the first cycle, and day 1 of subsequent cycles • Use for as long as the patient is deriving clinical benefit or until unacceptable toxicity
List Price	• **Abemaciclib**: £2,950 per 28-day cycle. Approved simple discount PAS • **Fulvestrant:** £522.41 per 2 x 250mg/5ml solution for injection

Appraisal of abemaciclib with fulvestrant

TA579 published May 2019 (optimised recommendation):
Abemaciclib with fulvestrant is **recommended for use within the Cancer Drugs Fund** in **people who have had endocrine therapy** only if exemestane plus everolimus is the most appropriate alternative

ID2727

- **Sept 2020:** Company submission
- **Nov-Dec 2020:** Technical engagement

Further data collection

1) Managed access agreement
2) Additional data from MONARCH-2
3) Real world data (SACT)

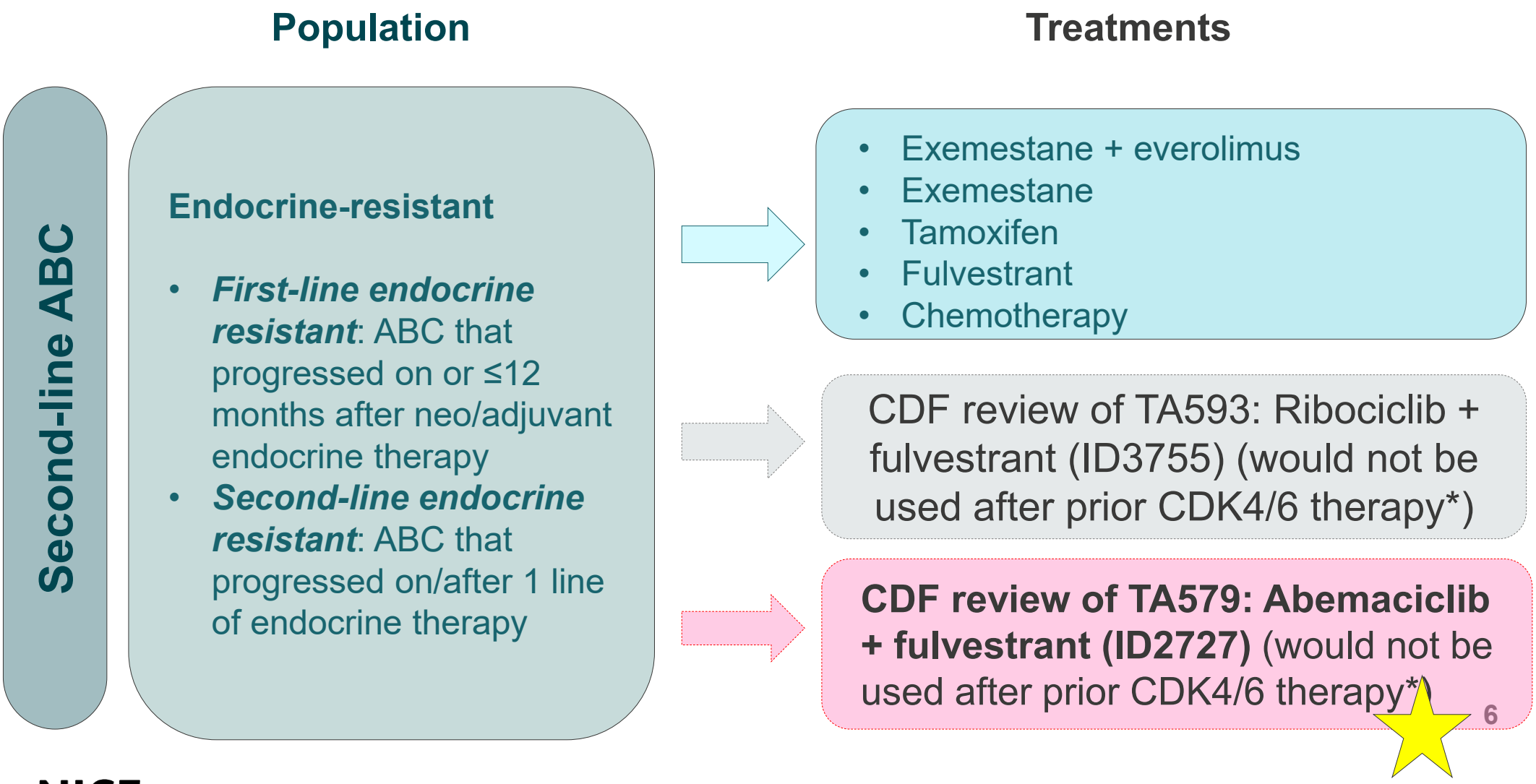
CDF review January 2021

Abbreviations: ACM, appraisal committee meeting; CDF, cancer drugs fund; CDK, cyclin-dependent kinase; SACT, systemic anti-caner therapy

Advanced breast cancer

- Breast cancer – most common cancer among women in UK
- Advanced breast cancer – cancer has spread to other parts of body such as bones, liver, and lungs, or directly into nearby tissues and cannot be completely removed by surgery
- About 13% of people have advanced breast cancer at diagnosis
- About 35% of people with early or locally advanced disease will progress to metastatic cancer within 10 years of diagnosis
- About 64% of people with metastatic breast cancer in UK have HR+/HER2− disease
- In 2016 in England, around 46,000 people were diagnosed with breast cancer and there were nearly 10,000 deaths

2nd line treatment pathway for HR-positive, HER2-negative ABC



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Patient group perspectives (1)

Breast Cancer Now

- Abemaciclib with fulvestrant hugely welcomed by the patient community
    - A significant backwards step if not recommended
- Availability of different treatment options means that switching is an option if have tolerability issues
- Previously CDK4/6 inhibitors were only available to those newly diagnosed with locally advanced or metastatic breast cancer
    - Abemaciclib with fulvestrant available to thousands more
- Everolimus with exemestane (comparator) is often poorly tolerated and side effects can be on a par with chemotherapy
- **Advantages of the treatment:**
    - can give valuable extra time with friends and family by delaying progression and extending survival
    - can also delay the need for chemotherapy, thereby improving quality of life and allowing patients to continue doing the activities they enjoy and lead a more or less normal day to day life

Patient group perspectives (2)

"My treatment goes on for as long as it works and this is my life now. Constant 'scanxiety', endless hospital appointments and the struggle with day to-day living that others either don't see or understand"
Patient statement (Breast Cancer Now)

"I've been on this treatment combination for over 15 months now. So that shows the treatment is keeping things under control, which is the main thing!"
Patient statement (Breast Cancer Now)

"If this treatment had not been available, I would have had to go on chemotherapy, which was something I wanted to avoid as long as possible."
Patient statement (Breast Cancer Now)

"My oncologist suggested that I have my dose reduced and I was pleased to do this. I still have diarrhoea and nausea…but I found the treatment more tolerable… I rarely feel really well. However, I would rather be on this treatment than chemotherapy"
Patient statement (Breast Cancer Now)

Patient group perspectives (3)

Treatment challenges:

- Side effects do occur, but not in all patients; every treatment for breast cancer has some side effects
- In the trial, the most common side effects were diarrhoea, neutropenia, nausea, fatigue and abdominal pain, but were mostly grade 1 or 2 in severity
- Diarrhoea is the most common side effect, but this usually occurs in the first or second cycle and can usually be managed with anti-diarrhoea medication or dose adjustments
- Need to attend hospital or in some areas a GP surgery for treatment. For many, the inconvenience caused is outweighed by an increase in progression free survival

Clinical expert perspective

- Useful to have more than one CDK4/6 treatment option since they have different adverse event profiles
  - Neutropenia can occur with ribociclib and palbociclib, whereas abemaciclib tends to induce lower grade neutropenia
  - Abemacicilib can cause debilitating diarrhoea, mostly ameliorated with anti-diarrhoea treatments and dose reductions, but some will still experience problems
  - Switching occurs between CDK4/6 treatments due to adverse events

Primary clinical evidence: MONARCH 2

Design	Phase III, multicentre, randomised, placebo-controlled, double-blind trial
Location	International: 142 centres, 19 countries: 0 in UK, 10 in Europe
Population	Women with HR+/HER2− locally advanced or metastatic BC who had progressed while receiving neoadjuvant or adjuvant endocrine therapy (ET), ≤12 months from the end of adjuvant ET, or while receiving first-line ET for metastatic disease
Intervention	Abemaciclib with fulvestrant
Comparator	Placebo with fulvestrant
Outcomes	**Primary:** Investigator-assessed PFS (RECIST criteria) **Secondary:** OS, overall response rate, disease control rate, duration of response, clinical benefit rate

Abbreviations: BC, breast cancer; HR+, hormone receptor positive; OS, overall survivalPFS, progression free survival

Key committee assumptions from TA579 (1)

Topic	Committee consideration from TA579 appraisal
PFS and OS	**Abemaciclib plus fulvestrant increases progression-free survival compared with fulvestrant alone but the overall survival data are immature**
Adverse events	Patients would prefer abemaciclib with fulvestrant to chemotherapy as chemotherapy is likely to have worse side effects. **The safety profile of abemaciclib plus fulvestrant is acceptable to patients**
Network meta-analysis	**The ERG's fractional polynomial method was preferred, but both the company's and the ERG's network meta-analyses are associated with heterogeneity and uncertainty**
Model structure	**The model structure is appropriate for decision making but the overall survival data used in the model are immature**
Treatment duration for abemaciclib with fulvestrant	**The company model underestimates the treatment duration and therefore costs of abemaciclib plus fulvestrant, although some people do stop before progression. Committee suggested time on treatment should be based on the licensed 150 mg dose not the early 200 mg dose which was reduced as a protocol amendment because of adverse effects**

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Abbreviations: PFS, progression free survival; OS, overall survival; NHS, national health service

CDF recommendation

CDF and data collection

- Further data on **overall survival** would likely reduce the uncertainty in the long-term benefit of abemaciclib plus fulvestrant
- Further data may make it clearer which method is the most appropriate for doing the **network meta-analysis**
- More data may be able to be collected on **time on treatment. The committee considered that the licensed dose time on treatment was the relevant data**

Abbreviations: ERG, evidence review group; ICER, incremental cost effectiveness ratio

Updated clinical evidence: progression-free survival

Additional 28 months of data collection from MONARCH 2

Results from MONARCH 2 presented in TA579 (DCO 14th Feb 2017)

ITT population	ABE-FUL n=446	PBO-FUL n=223
Patients with event, n (%)	222 (49.8)	157 (70.4)
Median PFS, months (95% CI)	16.4 ([redacted])	9.3 ([redacted])
Hazard ratio (95% CI) p-value	0.553 (0.449 to 0.681) p<0.001	

Results from MONARCH 2 presented in CDF review (DCO 20th June 2019)

ITT population	ABE-FUL n=446	PBO-FUL n=223
Patients with event, n (%)	297 ([redacted])	193 ([redacted])
Median PFS, months (95% CI)	16.87 ([redacted])	9.27 ([redacted])
Hazard ratio (95% CI) p-value	0.536 (0.445, 0.645) [redacted]	

Abbreviations: ABE-FUL: abemaciclib with fulvestrant; CDF, cancer drugs fund; CI, confidence interval; DCO, data cut off; PBO-FUL: placebo with fulvestrant; PFS, progression free survival; ITT, intention to treat

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Updated PFS (ITT & post-amendment) from MONARCH 2 (DCO 20th June 2019)

NB: the ITT population includes patients who received 200 mg unlicensed dose (26.6% of patients), the PA population excludes these patients.

Abbreviations: ABE: abemaciclib; CI: confidence interval; DCO: data cut-off; ITT: intention-to-treat; PA, post amendment; PBO-FUL; placebo with fulvestrant; PBO: placebo; PFS: progression free survival.

Updated clinical evidence: overall survival

Additional 28 months of data collection from MONARCH 2

Results from MONARCH 2 presented in TA579 (DCO 14th Feb 2017)

ITT population	ABE-FUL n=446	PBO-FUL n=223
Patients with event, n	85 (19.1)	48 (21.5)
Median OS, months (95% CI)	[redacted]	[redacted]
Hazard ratio (95% CI) p value	[redacted]	

Results from MONARCH 2 presented in CDF review (DCO 20th June 2019)

ITT population	ABE-FUL n=446	PBO-FUL n=223
Patients with event, n	211 (47.3)	127 (57.0)
Median OS, months (95% CI)	46.72 [redacted]	37.25 [redacted]
Hazard ratio (95% CI) p value	0.757 (0.606, 0.945) p=0.0137	

Updated DCO: Hazard ratio is statistically significant and suggests a 24% reduction in the risk of death with abemaciclib with fulvestrant

Abbreviations: ABE-FUL: abemaciclib with fulvestrant; CDF, cancer drugs fund; CI, confidence interval; DCO, data cut off; PBO-FUL: placebo with fulvestrant; OS, overall survival; ITT, intention to treat

Updated OS (ITT & post-amendment) from MONARCH 2 (DCO 20th June 2019)

Abbreviations: ABE: abemaciclib; DCO: data cut-off; ITT: intention-to-treat; OS: overall survival; PA, post amendment; PBO-FUL: placebo with fulvestrant.

Systemic anti-cancer therapy (SACT) data

- Latest date of follow-up 31st December 2019
- 876 patients received abemaciclib with fulvestrant
- Treatment duration
  - 4.4 months (maximum 10 months) median follow-up
  - 10.2 months median duration
- Median OS was not reached
  - 8.5 months median follow-up
  - Decreased OS compared to MONARCH 2
    - 75% vs 91.8% of patients surviving at 12 months respectively

Abbreviations: OS, overall survival

Key issue 1(new): Subgroup data by abemaciclib starting dose (1)

Background

- MONARCH 2: protocol amendment reduced 200mg to 150 mg due to adverse events (diarrhoea). 150 mg is the licensed dose.
- 26.6% enrolled before the amendment
- Company's network meta-analysis used efficacy estimates from all patients irrespective of starting dose (ITT population)
- Company's model uses estimates from the post-amendment (150 mg) subgroup for time to discontinuation, but from the ITT population for PFS and OS as per committee recommendation

Company comments:

- Pre- and post-amendment groups not intended as head to head comparison
- Median [redacted] days before dose reduction
- Median dose was [redacted] and [redacted]
- Interaction test [redacted] after adjustments for multiplicity and baseline confounding factors
- Placebo arm in pre and post groups had [redacted] OS [redacted]
- Worldwide regulators use ITT population
- Clinical advice indicates not appropriate to analyse separately

 Abbreviations: ITT, intention to treat; OS, overall survival; PFS, progression free survival

Key issue 1: Subgroup data by abemaciclib starting dose (2)

	HR (95% CI) DCO 14th Feb 2017	HR (95% CI) DCO 20th June 2019
Progression-free survival		
ITT	0.553 (0.449 to 0.681) p<0.001	0.536 (0.445, 0.645) [redacted]
Pre-amendment (200 mg), n=178	[redacted]	NR
Post-amendment (150 mg), n=491	[redacted]	NR, KM curve supplied
Interaction test	[redacted]	NR
Overall survival		
ITT	[redacted]	0.757 (0.606, 0.945) p = 0.0137
Pre-amendment (200 mg), n=178	NR	[redacted]
Post-amendment (150 mg), n=491	NR	[redacted]
Interaction test	NR	NR

Abbreviations: CI, confidence interval; DCO, data cut off; HR, hazard ratio; ITT, intention to treat, KM, Kaplan-Meier, NR, not reported

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Key issue 1 Subgroup data by abemaciclib starting dose (3)

ERG's comments:

- The ERG considers post-amendment (150 mg) subgroup may better reflect use in clinical practice. The company did not provide full post-amendment subgroup data needed to explore the cost effectiveness of abemaciclib at the licensed 150 mg dose
- Post-amendment (150 mg) subgroup was adequately powered and should be internally valid due to randomisation
- Not possible to validate the company's explanation relating to baseline differences without baseline data
- Mismatch between efficacy data (ITT population) and time to discontinuation data (post-amendment, 150 mg, subgroup) which may underestimate treatment costs and/or overestimate efficacy

Clinical expert comments:

- Clinicians don't expect 200 mg to be different to 150 mg
- Patients appear to do as well in clinical practice

Abbreviations: ITT, intention to treat

Key issue 1: Subgroup data by abemaciclib starting dose (4)

Company comments post-TE:

- Company re-iterate that the ITT population should be used for the reasons previously given (see **Key Issue 1**, slide 1)
- Letter from clinician highlighted that disregarding the ITT population would not reflect the intention of MONARCH 2
- [redacted]
- [redacted]
- Alternative results incorporating the post-amendment data are provided as an exploratory scenario analysis

Key issue 1: Subgroup data by abemaciclib starting dose (5)

ERG comments post-technical engagement:

- ERG reiterate post-amendment subgroup was given dose which reflects marketing authorisation and which will be used in clinical practice
- Subgroup methodologically robust as more patients recruited to ensure adequate power and patients were randomised
- The 95% CI for the HRs for the 150 mg and 200 mg subgroups only overlap by a small amount
- Contrary to the company assertion
  - [redacted]
  - [redacted]
    - [redacted] efficacy similar for primary and secondary resistance, [redacted]
    - [redacted]
- ERG use the post-amendment subgroup in its base case

Should the ITT or post- amendment (150 mg) subgroup be used to estimate efficacy?

Abbreviations: ABE-FUL, abemaciclib with fulvestrant; CI, confidence interval; ERG, evidence review group; HR, hazard ratio; PBO-FUL, placebo with fulvestrant

Key Issue 9: SACT data (1)

Background

- SACT data was collected to
  - support generalisability of MONARCH 2
  - Provide evidence of time on treatment in clinical practice

Company comments

- Patient spectrum
  - Baseline data indicate older and frailer in SACT
  - Early enrollers usually the most ill – only 9 months of recruitment
  - May have recruited patients who had had chemotherapy
  - May be given to those with visceral disease preferentially over other CDK4/6 options
- No comparator, relative effect may be the same
- Data immature, expect OS to improve over time as it did in MONARCH 2

	Median follow-up	Outcome
OS, months	8.5	Median not reached Alive at 6 months: 88% Alive at 12 months: 75%
Treatment duration, months	4.4 (maximum 10)	Median: 10.2

Compared to MONARCH 2:

- OS: 75% compared with 91.8% of patients surviving at 12 months
- Treatment duration 10.2 months, compared with [redacted] in MONARCH 2

Abbreviations: CDK, cytokine dependent kinase; OS, overall survival; SACT, systematic anticancer therapy

Key Issue 9: SACT data (2)

ERG's comments:

- ERG agree with most of the company's observations relating to patient selection (see next slide)
- Agree data is immature
- Notes it is striking that the OS is substantially lower, even though immature
- Notes it is unclear if the relative efficacy would be the same in SACT as there is no comparator arm

ERG's conclusions:

- Concludes MONARCH 2 most robust estimate of comparative efficacy
- But there is uncertainty around the generalisability of MONARCH 2 to clinical practice
- Outcome validation using SACT limited due to short follow-up and data immaturity

Clinical expert comments:

- Clinical trials tend to exclude patients that would be included in real life, e.g. those at high risk of early progression
- Therefore absolute OS likely to be shorter in real life
- But relative efficacy from MONARCH 2 likely to be generalisable

Is the SACT data too immature to be informative for decision making?

Abbreviations: OS, overall survival; SACT, systematic anticancer therapy

Key clinical issues

- **Key issue 1:** Subgroup data by abemaciclib starting dose
  - Should the ITT population or the post-amendment (150 mg) subgroup be used to estimate efficacy?
  - *NB: this was not a key issue in TA579; this issue also relates to **Key issue 4** (Time to treatment discontinuation estimate for abemaciclib plus fulvestrant)*

- **Key issue 9 (un-numbered in the ERG report):** SACT data
  - Is the SACT data too immature to be informative for decision making?

Cost effectiveness

Key cost effectiveness issues

- **Key issue 1:** Subgroup data by abemaciclib starting dose
  - Should data from the ITT population or the post-amendment subgroup be used in the FP NMA that informs the cost-effectiveness model?
- **Key issue 4:** Time to treatment discontinuation (TTD) estimate for abemaciclib plus fulvestrant (ABE-FUL)
  - Should the PFS and TTD that inform the TTD HR be drawn from the ITT population, the post-amendment (150 mg) population, or a mixture of the two (ITT PFS with post-amendment (150 mg) TTD)?
  - Is the restricted mean or extrapolated data preferable?
- **Key issue 5:** TTD estimated for exemestane with everolimus (EXE-EVE)
  - Should the observed data from BOLERO 2 be used to estimate the HR for TTD?
    - If observed data is used, should the TTD for exemestane or everolimus be used to estimate the HR for TTD?
    - If the observed data is not used, is scenario 1, 2 or 3 the most clinically plausible?

Abbreviations: ABE-FUL: abemaciclib with fulvestrant; EXE-EVE, exemestane with everolimus; HR, hazard ratio; ITT, intention to treat; OS, overall survival; PFS, progression free survival; TTD, time to discontinuation, ERG, evidence review group; HRQoL, health related quality of life

Key Issue 1: Subgroup data by abemaciclib starting dose (1)

- Company performed a fractional polynomial network meta-analysis (FP NMA) to provide data about the comparator EXE-EVE, since MONARCH 2 compared to PBO-FUL for use in the model
  - There were some uncertainties that could not be resolved in the network, since published studies did not report required data

- As discussed in the clinical section, the ERG favours the use of the 150 mg subgroup in the FP NMA for ABE-FUL in its base case

Should data from the ITT population or the post-amendment subgroup be used in the FP NMA that informs the cost-effectiveness model?

Abbreviations: ABE-FUL, abemaciclib with fulvestrant; ERG, evidence review group; FP NMA, fractional polynomial network meta analysis; HR, hazard ratio; ITT, intention to treat; PFS, progression free survival; TTD: time to treatment discontinuation

Key Issue 4: Time to treatment discontinuation (TTD) estimate for abemaciclib plus fulvestrant (ABE-FUL) (1)

- **Company estimated TTD for ABE-FUL:**
  - Estimated HR of observed PFS of ITT population vs TTD for post-amendment subgroup at the time of median TTD = [redacted]
  - Applied HR to FP NMA PFS curve of ITT population

- **ERG concerned that this approach underestimates TTD, because:**
  - Inconsistency in data sources
  - Similar post-amendment TTD and ITT PFS curves suggest that post-amendment TTD is closer to post-amendment PFS than what is implied by estimated HR
  - No evidence post-amendment subgroup discontinues at same rate as 200 mg subgroup (who had high discontinuations due to AEs)
  - Modelled curves show wide separation after 6 months and don't track close together until 16 years – not supported by available TTD and PFS data
- ERG presented analysis using HR=1

Abbreviations: ABE-FUL, abemaciclib with fulvestrant; ERG, evidence review group; FP NMA, fractional polynomial network meta analysis; HR, hazard ratio; ITT, intention to treat; PFS, progression free survival; TTD: time to treatment discontinuation

Key Issue 4: Time to treatment discontinuation (TTD) estimate for abemaciclib plus fulvestrant (ABE-FUL) (2)

Company

- HR=1 too conservative.
- HR=1 clinically implausible as some patients discontinue for reasons other than progression.

- Calculates 6 HRs:
  - Based on lifetime survival model vs restricted means
  - Using ITT PFS vs ITT TTD, ITT PFS vs PA TTD, PA PFS vs PA TTD
  - HR = **** to ****

- Company prefers HR = ****
  - ITT PFS vs PA TTD based on lifetime survival model

ERG

- Agrees that HR=1 not supported by PA PFS
- Maintains that using ITT PFS with PA TTD underestimates TTD because PA PFS is under ITT PFS
- HRs calculated using lifetime survival model produce similar TTD curves to using HR=**** → same concerns apply
- Restricted means analysis results in modelled curves more aligned to KM curves

- Prefers HR = ****
  - PA PFS vs PA TTD, based on restricted mean analysis over MONARCH 2 observation period

Key Issue 4: Time to treatment discontinuation (TTD) estimate for abemaciclib plus fulvestrant (ABE-FUL) (3)

Modelled and KM curves for HR of **** (lifetime extrapolation method), based on post-amendment (150 mg) TTD, and ITT PFS

Abbreviations: ABE-FUL, abemaciclib with fulvestrant; FP NMA, fractional polynomial network meta analysis; ITT, intention to treat; PFS, progression free survival; TTD, time to discontinuation

Key Issue 4: Time to treatment discontinuation (TTD) estimate for abemaciclib plus fulvestrant (ABE-FUL) (4)

Modelled and KM curves for HR of **** (restricted means method), based on post-amendment (150 mg) TTD and PFS

Abbreviations: ABE-FUL, abemaciclib with fulvestrant; FP NMA, fractional polynomial network meta analysis; ITT, intention to treat; PFS, progression free survival; TTD, time to discontinuation

Key Issue 4: Time to treatment discontinuation (TTD) estimate for abemaciclib plus fulvestrant (ABE-FUL) (5)

Clinical expert comments

- Patients on CDK4/6 inhibitors tend to discontinue due to progression, not adverse events
- 1.6% discontinued due to diarrhoea in MONARCH 2 after dose change
- Those that discontinue ABE-FUL due to diarrhoea tend to do so in first or second cycle
- <10%, possibly <5% discontinue due to diarrhoea
- Tend to then switch to another CDK4/6
- If no other CDK4/6 available, likely to stay on treatment for longer despite AEs

Should the PFS and TTD that inform the TTD HR be drawn from the ITT population, the post-amendment (150 mg) population, or a mixture of the two (ITT PFS with post-amendment (150 mg) TTD)?

Is the restricted mean (as per ERG preference) or extrapolated data preferable (as per company preference)?

Abbreviations: AE, adverse event; ABE-FUL, abemaciclib with fulvestrant; CDK, cyclin-dependent kinase; HR, hazard ratio; ITT, intention to treat; PFS, progression free survival; TTD, time to discontinuation

Key issue 5: Time to treatment discontinuation (TTD) estimated for exemestane with everolimus (EXE-EVE)

1. Company

- Original base-case: all patients treated until disease progression

2. ERG

- EVE is usually discontinued first and is more costly.
- Estimated HR TTD for EVE vs PFS EXE-EVE = 1.61

3. Company

- Estimated HR TTD for EVE vs PFS EXE-EVE = 1.58
  - Used in company's revised base-case
- Presented alternative scenarios
  1. 20% discontinue EVE after 6 months but continue EXE until disease progression
  2. As 2), 70% of remainder have EVE dose reduced (10 mg to 5 mg) at 6 months → company's preferred
  3. All patients treated until disease progression (original Ribociclib company base case)

4. ERG

- ERG revised base-case uses same HR as company's base-case = 1.58
- Disagreed with scenario 3 as inconsistent with clinical advice that patients discontinue due to AEs
- Key issue for committee's consideration

Key issue 5: Time to treatment discontinuation (TTD) estimated for exemestane with everolimus (EXE-EVE) (4)

Abbreviations: ERG, evidence review group; EVE, everolimus; EXE-EVE, exemestane with everolimus; PFS, progression free survival; TTD, time to discontinuation

Should the observed data from BOLERO 2 be used to estimate the HR for TTD?

- **If observed data is used, should the TTD for exemestane or everolimus be used to estimate the HR for TTD?**
- **If the observed data is not used, is scenario 1, 2 or 3 the most clinically plausible?**

Additional areas of uncertainty

Issue	Why issue is important	Impact on ICER
Heterogeneity in the FP NMA	The FP NMA informs the efficacy and TTD inputs to the model. Heterogeneity between studies unresolvable since more data unlikely to become available	Unclear
Chemotherapy postponement was a key element to the value proposition	• The ERG noted chemotherapy was second line for [redacted] for ABE-FUL and PBO-FUL, respectively, indicating ABE-FUL does not allow another line of therapy before chemotherapy. • Company supplied time to chemotherapy (median, 50.2 months vs 22.1 months), and chemotherapy free-survival (median, 25.5 months versus 18.2 months) for ABE-FUL and PBO-FUL respectively at TE	None, only impacts the value proposition
Source of quality of life data	ERG requested updated MONARCH 2 QoL data, but the company confirmed this data was not updated in the 2019 DCO	Unclear

Abbreviations: ABE-FUL, abemaciclib with fulvestrant; ERG, evidence review group; ICER, incremental cost effectiveness ratio; PBO-FUL, placebo with fulvestrant; TE, technical engagement

Key cost effectiveness issues

- **Key issue 1:** Subgroup data by abemaciclib starting dose
  - Should data from the ITT population or the post-amendment subgroup be used in the FP NMA that informs the cost-effectiveness model?
- **Key issue 4:** Time to treatment discontinuation (TTD) estimate for abemaciclib plus fulvestrant (ABE-FUL)
  - Should the PFS and TTD that inform the TTD HR be drawn from the ITT population, the post-amendment (150 mg) population, or a mixture of the two (ITT PFS with post-amendment (150 mg) TTD)?
  - Is the restricted mean or extrapolated data preferable?
- **Key issue 5:** TTD estimated for exemestane with everolimus (EXE-EVE)
  - Should the observed data from BOLERO 2 be used to estimate the HR for TTD?
    - If observed data is used, should the TTD for exemestane or everolimus be used to estimate the HR for TTD?
    - If the observed data is not used, is scenario 1, 2 or 3 the most clinically plausible?

Abbreviations: ABE-FUL: abemaciclib with fulvestrant; EXE-EVE, exemestane with everolimus; HR, hazard ratio; ITT, intention to treat; OS, overall survival; PFS, progression free survival; TTD, time to discontinuation, ERG, evidence review group; HRQoL, health related quality of life

Cost-effectiveness results

Decision making ICERs are reported in part 2 slides for the closed committee discussion because they include confidential discounts.

The following slides show the ICERs including the simple discount patient access scheme for abemaciclib only.

ERG base-case vs company's base-case

Element	Company	ERG
PFS and OS	NMA with 200 mg data	Updated NMA with post-amendment 150 mg data
TTD for ABE-FIL	HR [redacted](post-amendment TTD vs ITT PFS)	HR [redacted]
TTD for EXE-EVE	HR 1.58 (median time-on-treatment vs PFS from BOLERO 2)	2 scenarios: • HR=1.58 as per company • Scenario (2) from company
Fulvestrant list price	[redacted] price reduction	List price
Half-cycle correction	Yes	No

Scenario (2): Assuming that 20% of progression-free patients receiving EVE-EXE will discontinue everolimus at six months after the initiation of treatment, and that 70% of the patients remaining on everolimus will have their dose reduced from 10 mg to 5 mg daily at month six, and assuming that exemestane was given until disease progression (ERG corrected company's implementation of its issue 5 scenario 2)

Cost effectiveness results: company base case

- Updated company base case after technical engagement includes:
  - TTD for ABE-FUL based on HR [redacted] (post-amendment TTD, ITT PFS)
  - TTD for EXE-EVE estimated using the digitized BOLERO 2 KM PFS curve and PFS at median time-on-treatment in BOLERO2 (giving a HR of 1.58)
  - [redacted] price reduction on the list price for fulvestrant
  - Half-cycle correction

	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Deterministic results			
ABE-FUL versus EXE-EVE	[redacted]	[redacted]	£6,593
Probabilistic results			
ABE-FUL versus EXE-EVE	[redacted]	[redacted]	£8,119

Abbreviations: ABE-FUL: abemaciclib with fulvestrant; DCO, data cut off; EXE-EVE, exemestane with everolimus; HR, hazard ratio; ICER, incremental cost effectiveness ratio; KM, Kaplan Meier; PFS, progression free survival; QALYs, quality adjusted life years; TTD, time to discontinuation;

Cost effectiveness results: ERG base case

- ERG base case includes:
  - Half-cycle correction removed (as per original ERG base case)
  - Updated NMA with post-amendment 150 mg data
  - Using HR of **** to estimate TTD for ABE-FUL
  - List price for fulvestrant (confidential discount applied in part 2 ICERs)
- And two alternative scenarios to model TTD for EXE-EVE

a) Applying the 1.58 HR to the EXE-EVE FP NMA PFS curve to obtain a TTD curve for EXE-EVE in order to cost treatment with everolimus, and assuming that exemestane was given until disease progression (company base case assumption)

b) Assuming that 20% of progression-free patients receiving EVE-EXE will discontinue everolimus at six months after the initiation of treatment, and that 70% of the patients remaining on everolimus will have their dose reduced from 10 mg to 5 mg daily at month six, and assuming that exemestane was given until disease progression (ERG corrected company's implementation of its issue 5 scenario 2)

Abbreviations: ABE-FUL: abemaciclib with fulvestrant; EXE-EVE, exemestane with everolimus, ICER, incremental cost effectiveness ratio; QALYs, quality adjusted life years

Cost effectiveness results: ERG's alternative base case analyses

	Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
1+2+3+ 4 +5a	**Issue 5:** Applying 1.58 HR to the EXE-EVE PFS curve to obtain a TTD curve for EXE-EVE and costing EXE until disease progression	[redacted]	[redacted]	£49,556
1+2+3+ 4+5b	**Issue 5:** 20% of patients receiving EVE-EXE discontinue EVE at six months, and 70% of patients remaining will have a dose reduction	[redacted]	[redacted]	Dominant

Abbreviations: ABE-FUL, abemaciclib with fulvestrant; EXE-EVE, exemestane with everolimus; EXE, exemestane; ICER, incremental cost effectiveness ratio; NMA, network meta analysis; OS, overall survival; PFS, progression free survival; QALYs, quality adjusted life years; TE, technical engagement; TTD, time to discontinuation

Back-up slides

Updated clinical evidence from MONARCH 2: Progression free survival and overall survival

	DCO 14th Feb 2017		DCO 20th June 2019	
ITT population	ABE-FUL n=446	PBO-FUL n=223	ABE-FUL n=446	PBO-FUL n=223
Progression free survival				
Patients with event, n (%)	222 (49.8)	157 (70.4)	297 [redacted]	193 [redacted]
Median PFS, months (95% CI)	16.4 (NR)	9.3 (NR)	16.87 [redacted]	9.27 [redacted]
Hazard ratio (95% CI) p- value	0.553 (0.449 to 0.681) p<0.001		0.536 (0.445, 0.645) [redacted]	
Overall survival				
Patients with event, n (%)	85 (19.1)	48 (21.5)	211 (47.3)	127 (57.0)
Median PFS, months (95% CI)	[redacted]	[redacted]	46.72 [redacted]	37.25 [redacted]
Hazard ratio (95% CI) p- value	[redacted]		0.757 (0.606, 0.945) P=0.0137	

Updated clinical evidence: Time to discontinuation

Additional 28 months of data collection from MONARCH 2

Results from MONARCH 2 presented in TA579 (DCO 14th Feb 2017)

Results from MONARCH 2 presented in CDF review (DCO 20th June 2019)

Abbreviations: ABE-FUL: abemaciclib with fulvestrant; CDF, cancer drugs fund; DCO, data cut off; PBO-FUL: placebo with fulvestrant; OS, overall survival; ToT, time on treatment (equivalent to time to discontinuation)

Key issue 1: Subgroup data by abemaciclib starting dose

Baseline characteristics for pre-amendment, post-amendment and ITT populations

	Pre-amendment population		PA population		ITT Population	
	Abemaciclib 200 mg	Placebo 200 mg	Abemaciclib 150 mg	Placebo 150 mg	Abemaciclib	Placebo
Key baseline characteristics (N)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median age (min, max)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race ≥10%, n (%)						
White	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Menopausal status, n (%)						
Postmenopausal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre or perimenopausal (ovarian suppression)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Primary resistance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visceral disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bone only disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key issue 1: Subgroup data by abemaciclib starting dose

OS summary statistics from the updated FP NMA survival

	FUL	EXE	EXE-EVE	ABE-FUL
Mean OS, months	[redacted]	[redacted]	[redacted]	[redacted]
Median OS, months	[redacted]	[redacted]	[redacted]	[redacted]
Alive at 12 months, %	[redacted]	[redacted]	[redacted]	[redacted]
Alive at 60 months, %	[redacted]	[redacted]	[redacted]	[redacted]
Alive at 120 months, %	[redacted]	[redacted]	[redacted]	[redacted]

Estimated OS summary statistics from the FP NMA including the PA population data

	FUL	EXE	EXE-EVE	ABE-FUL
Mean OS, months	[redacted]	[redacted]	[redacted]	[redacted]
Median OS, months	[redacted]	[redacted]	[redacted]	[redacted]
Alive at 12 months, %	[redacted]	[redacted]	[redacted]	[redacted]
Alive at 60 months, %	[redacted]	[redacted]	[redacted]	[redacted]
Alive at 120 months, %	[redacted]	[redacted]	[redacted]	[redacted]

PFS summary statistics from the FP NMA

	FUL	EXE	EXE-EVE	ABE-FUL
Median PFS, months	[redacted]	[redacted]	[redacted]	[redacted]
Progression-free at 12 months, %	[redacted]	[redacted]	[redacted]	[redacted]
Progression-free at 60 months, %	[redacted]	[redacted]	[redacted]	[redacted]
Progression-free at 120 months, %	[redacted]	[redacted]	[redacted]	[redacted]

Estimated PFS summary statistics from the FP NMA including the PA population data

	FUL	EXE	EXE-EVE	ABE-FUL
Mean PFS, months	[redacted]	[redacted]	[redacted]	[redacted]
Median PFS, months	[redacted]	[redacted]	[redacted]	[redacted]
Progression-free at 12 months, %	[redacted]	[redacted]	[redacted]	[redacted]
Progression-free at 60 months, %	[redacted]	[redacted]	[redacted]	[redacted]
Progression-free at 120 months, %	[redacted]	[redacted]	[redacted]	[redacted]

NICE

OS summary statistics from FP NMA

	Post-amendment population				ITT population			
	FUL	EXE	EXE-EVE	ABE-FUL	FUL	EXE	EXE-EVE	ABE-FUL
Mean OS, months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median OS, months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alive at 12 months, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alive at 60 months, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alive at 120 months, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ABE: abemaciclib; EVE: everolimus; EXE: exemestane; FP: fractional polynomial; FUL: fulvestrant; ITT, intention to treat; NMA: network meta-analysis; OS: overall survival.

PFS summary statistics from FP NMA

	post-amendment population				ITT population			
	FUL	EXE	EXE-EVE	ABE-FUL	FUL	EXE	EXE-EVE	ABE-FUL
Mean PFS, months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median PFS, months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progression-free at 12 months, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progression-free at 60 months, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progression-free at 120 months, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ABE: abemaciclib; EVE: everolimus; EXE: exemestane; FP: fractional polynomial; FUL: fulvestrant; ITT, intention to treat; NMA: network meta-analysis; PFS, progression-free survival.

Key Issue 9: SACT data baseline characteristics ABE-FUL

Characteristics	SACT Patients receiving ABE-FUL (n = 876)	MONARCH 2 ABE-FUL (n=446)	MONARCH 2 (n=669)
Gender			
Female, n (%)	865 (99)	NR	669 (100.0)
Age		NR	
<40, n (%)	21 (2)	NR	NR
40–49, n (%)	92 (11)	NR	NR
50–59, n (%)	208 (24)	NR	NR
60–69, n (%)	235 (27)	NR	NR
70–79, n (%)	248 (28)	NR	NR
≥80, n (%)	72 (8)	NR	NR
Median age (overall), years	65	59 (32 to 91)	****
Median age (women)	64		NR
Median age (men)	68		NR
Performance status			
0	273 (31)	264 (59.2)	400 (59.8)
1	416 (47)	176 (39.5)	263 (39.3)
2	66 (8)	****	****
3	4 (<1)	****	-
4	1 (<1)		-
Missing	116 (13)	NR	****
Previous endocrine therapy, n (%)	876 (100)	NR	
Progressive disease whilst still receiving adjuvant or neoadjuvant endocrine therapy for EBC	302 (34%)	NR	NR
Has progressive disease within 12 or less months of completing adjuvant endocrine therapy for EBC	32 (4)	NR	NR
Has progressive disease on first line endocrine therapy for advanced/metastatic breast cancer	542 (62)	NR	NR

Key conclusions from TA579

TA579 recommendation:

Abemaciclib with fulvestrant is recommended for use within the Cancer Drugs Fund as an option for treating hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer in people who have had endocrine therapy only if:

- *exemestane plus everolimus would be the most appropriate alternative and*
- *the conditions in the managed access agreement for abemaciclib with fulvestrant are followed.*

Issues resolved after technical engagement

	Summary	Stakeholder responses	Technical team consideration	Included in updated base case?
2	Issue 6: Prices used model - ERG: update NHS reference costs should be used	Company updated the costs and incorporated them into the revised base case analysis	The ERG corrected some minor errors, minimal impact on ICERs	Company ✓ ERG ✓ **(corrected)**
3	Fulvestrant cost	Company's base case (after technical engagement) included **** discount	NHS England confirmed a cost to use in appraisal (confidential, not to be discussed in part 1)	Company ✓ ERG ✓ (cPAS appendix)

Changes to model parameters in CDF review

	Committee preference from TA579	Company CDF base case after technical engagement	Company justification for change
Modelling of OS and PFS (FP NMA)	Company should explore NMA methodology and most appropriate trials to include	FP NMA based on ITT population and a restricted network, using DCO 2019	Proportional hazards assumption not met; restricted network reduces heterogeneity
TTD for ABE-FUL	Company should explore most appropriate method and base extrapolations on post-amendment (150 mg) subgroup	TTD for ABE-FUL and PBO-FUL estimated by jointly fitting Weibull curves to the ToT discontinuation data from post-amendment (150 mg) population and ITT PFS KM population, HR applied to FP NMA PFS	Use of the post-amendment (150 mg) population in MONARCH 2 is aligned with the committee's preferred assumption
TTD for EXE-EVE	Based on HR between the published median duration of therapy and median PFS from BOLERO 2	HR based on digitised KM curve for BOLERO 2 TTD for EVE Three additional new scenarios supplied	In accordance with ERG preferred methodology. Three additional scenarios due to uncertainty in ERG preferred methodology

Abbreviations: ABE-FUL: abemaciclib with fulvestrant; CDF, cancer drugs fund; ERG, evidence review group; FP NMA, fractional polynomial network meta-analysis; KM, Kaplan Meier; OS, overall survival; PBO-FUL, placebo with fulvestrant, ITT, intention to treat; TTD, time to discontinuation; ToT, time on treatment

Changes to model parameters in CDF review

	Committee preference from TA579	Company CDF base case after technical engagement	Company justification for change
Post-progression utilities	Company should use Mitra et al or MONARCH 2	Used MONARCH 2 (2017 DCO) after technical engagement	In line with committee's preferred approach; data not updated in 2019 DCO
Subsequent therapy	Company should use the ERG's changes to modelling of subsequent treatments	Updated base case is fully aligned with the ERG's preferred changes to the modelling of subsequent treatments	Use of the ERG's preferred changes is in line with the committee's preferred assumptions
Resource use	Not an issue in TA579	Costs and codes updated with National Schedule of NHS cost 2018-2019, or inflated cost based on the consumer price index or health price index to 2019. BNF and eMIT checked for drug prices	In accordance with ERG preferred methods
Rebate for Fulvestrant	Not addressed in TA579	Assume a [redacted] price reduction for fulvestrant	Fulvestrant will lose exclusivity in near future

Abbreviations: BNF, British National Formulary; DCO, data cut off; eMIT, Drugs and pharmaceutical electronic market information tool; ERG, evidence review group

Data used in the company's model

	Company's model	Technical team's preference
PFS	Latest datacut from MONARCH 2 for ITT population	Latest data cut from post-amendment (150 mg) group (ERG base case)
OS		
NMA	Updated MONARCH 2 data for the ITT population	Results using the updated MONARCH 2 data for the post-amendment (150 mg) group
TTD ABE-FUL	Estimated by applying a HR to the updated FP PFS NMA curve. HR based on updated post-amendment TTD and ITT PFS	HR based on updated, post-amendment (150 mg) data for PFS and TTD from MONARCH 2
TTD EXE-EVE	Digitised plot from BOLERO 2 Three alternative scenarios provided	Digitised plot from BOLERO 2
Costs	Updated resource costs and cost codes	ERG base case, corrected some minor errors in company's updated costs
Utilities	MONARCH 2 (DCO 2017)	MONARCH 2 (DCO 2017)

Abbreviations: ABE-FUL: abemaciclib with fulvestrant; DCO, data cut-off; ITT, intention to treat; NMA, network meta-analysis; OS, overall survival; PFS, progression free survival; TTD, time to discontinuation

Key Issue 4: Time to treatment discontinuation (TTD) estimate for abemaciclib plus fulvestrant (ABE-FUL) (3)

[redacted]

Abbreviations: ABE-FUL, abemaciclib with fulvestrant; ITT, intention to treat; KM, Kaplan Meier; TTD, time to treatment discontinuation

Key Issue 4: Time to treatment discontinuation (TTD) estimate for abemaciclib plus fulvestrant (ABE-FUL) (6)

Abbreviations: ABE-FUL, abemaciclib with fulvestrant; ITT, intention to treat; PFS, progression free survival; TTD, time to discontinuation

Key Issue 4: Time to treatment discontinuation (TTD) estimate for abemaciclib plus fulvestrant (ABE-FUL) (8)

Modelled and KM curves for HR of **** (lifetime extrapolation method), based on post-amendment (150 mg) TTD and PFS

Abbreviations: ABE-FUL, abemaciclib with fulvestrant; FP NMA, fractional polynomial network meta analysis; ITT, intention to treat; PFS, progression free survival; TTD, time to discontinuation

Key issue 5: Time to treatment discontinuation (TTD) estimated for exemestane with everolimus (EXE-EVE) (1)

Background

- TTD for EXE-EVE estimated using published median TTD and PFS from BOLERO 2 (RCT)
- EVE is poorly tolerated: usually discontinued first, but continue with EXE
- EVE more expensive
- BOLERO 2 reported TTD for EXE and EVE separately (6.8 and 5.5 months respectively)
- ERG originally (TA579) preferred use of 6.8 months (EXE) to estimate TTD for EXE-EVE

ERG comments

- Model not set up for EXE and EVE TTD to be modelled separately
- Since EVE is more expensive, TTD for EVE (5.5 months) is better for estimating costs for EXE-EVE
- EXE-EVE TTD curve estimated in the model by applying an HR to the FP NMA PFS EXE-EVE curve
- ERG used published median PFS and TTD to calculate HR due to data availability
- Digitisation of the PFS curve from BOLERO 2 is its preferred approach for estimating the HR

Clinical expert comments

- Tolerability of EVE-EXE poor
- Mouth ulcers a particular problem
- Patients often discontinue EVE first, this adversely effects efficacy

Abbreviations: EVE, everolimus; EXE-EVE, exemestane with everolimus; ERG, evidence review group; HR, hazard ratio; ITT, intention to treat; PFS, progression free survival; RCT, randomised controlled trial; TTD, time to discontinuation

Cost effectiveness results: company scenario analysis (1)

Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Key Issue 5: EXE-EVE TTD			
Digitised BOLERO 2 KM PFS curve and uses PFS at median time-on-treatment in BOLERO 2 (company base case)	[redacted]	[redacted]	£16,683
• Scenario 1: 20% discontinue EVE after 6 months	[redacted]	[redacted]	Dominant
• Scenario 2: 20% discontinue EVE after 6 months, 70% reduce dose to 5 mg from month 7	[redacted]	[redacted]	Dominant
• Scenario 3: EXE-EVE PFS equal to TOT	[redacted]	[redacted]	Dominant
Key issue 6: Updated prices in the model			
Updated resource cost and cost codes used	[redacted]	[redacted]	£13,587

Abbreviations: EVE, everolimus; EXE-EVE; exemestane with everolimus; HR, hazard ratio; ICER, incremental cost effectiveness ratio; KM, Kaplan Meier, PFS, progression free survival; QALYs, quality adjusted life years; TTD, time to discontinuation; TOT, time on treatment

Cost effectiveness results: company scenario analysis (2)

Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Additional issue 1: Fulvestrant costs			
Applied **** price reduction to fulvestrant (estimate following loss of exclusivity)	****	****	£3,893
Other changes			
Post-progression utility value based on data derived from MONARCH 2 (DCO 2017)	*****	*****	£13,580

Abbreviations: ICER, incremental cost effectiveness ratio; QALYs, quality adjusted life years

Cost effectiveness results: ERG scenarios using post-amendment (150 mg) subgroup

	Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
	Company base case after TE	[redacted]	[redacted]	£6,593
1	Removing fulvestrant discount	[redacted]	[redacted]	£16,327
2	Removal of half-cycle correction	[redacted]	[redacted]	£15,850
3	**Issue 1:** Using the company's NMA PFS and OS curves for the post amendment population	[redacted]	[redacted]	£10,146
4	**Issue 4:** Applying the [redacted] HR to the ABE-FUL NMA PFS curve to obtain a TTD curve	[redacted]	[redacted]	£33,906
5a	**Issue 5:** Applying 1.58 HR to the EXE-EVE PFS curve to obtain a TTD curve for EXE-EVE and costing EXE until disease progression	[redacted]	[redacted]	£15,626
5b	**Issue 5:** 20% of patients receiving EVE-EXE discontinue EVE at six months, and 70% of patients remaining will have a dose reduction and costing EXE until disease progression	[redacted]	[redacted]	Dominant

Cost effectiveness results: Cumulative changes to ERG scenarios using post-amendment (150 mg) subgroup

	Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
0	Company base case	[redacted]	[redacted]	£6,593
1	Removing fulvestrant discount	[redacted]	[redacted]	£16,327
1+2	Removal of the half-cycle correction from the model	[redacted]	[redacted]	£15,850
1+2+3	Using the company's NMA PFS and OS curves for the post amendment population	[redacted]	[redacted]	£9,086
1+2+3+4	Applying the [redacted] HR to the ABE-FUL NMA PFS curve to obtain a TTD curve	[redacted]	[redacted]	£49,879
1+2+3+4+a	Applying the 1.58 HR to the EXE-EVE PFS curve to obtain a TTD curve for EXE-EVE and costing EXE until disease progression	[redacted]	[redacted]	£49,556
1+2+3+4+b	Assuming that 20% of patients receiving EVE-EXE will discontinue EVE at six months after the initiation of treatment, and that 70% of the of the patients remaining on EVE will have a dose reduction	[redacted]	[redacted]	Dominant

Cost effectiveness results: Cumulative changes to ERG scenarios using ITT data

	Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
	Company base case after TE	[redacted]	[redacted]	£6,593
1	Removing fulvestrant discount	[redacted]	[redacted]	£16,327
1+2	Removal of half-cycle correction	[redacted]	[redacted]	£15,850
1+2+4	**Issue 4**: Applying the [redacted] HR to the ABE-FUL NMA PFS curve to obtain a TTD curve	[redacted]	[redacted]	£33,431
1+2+4+5a	**Issue 5a:** Applying the 1.58 HR to the EXE-EVE PFS curve to obtain a TTD curve for EXE-EVE and costing EXE until disease progression	[redacted]	[redacted]	£33,310
1+2+4+5b	**Issue 5b:** Assuming that 20% of patients receiving EVE-EXE will discontinue EVE at six months after the initiation of treatment, and that 70% of the of the patients remaining on EVE will have a dose reduction	[redacted]	[redacted]	£9,237