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)

Chair's presentation

2nd Appraisal Committee meeting

Lead team: Mohit Sharma, Rita Faria, Pam Rees

ERG: BMJ-TAG

Technical team: Jane Adam, Janet Robertson, Mary Hughes, Summaya Mohammad

Company: Eli Lilly

6th July 2021

Key clinical and cost-effectiveness issues

- **Issue 1: TTD estimate for exemestane plus everolimus (KEY DRIVER of ICER estimates)**

  What is the best approach to estimating TTD for exemestane plus everolimus?

- **Issue 2: Time to treatment discontinuation (TTD) estimate for abemaciclib plus fulvestrant**

  What is the best approach to estimating TTD for abemaciclib plus fulvestrant?

- **Issue 3: Post-amendment data versus intention to treat (ITT) population in MONARCH 2**

  Company has revised its base case to use post-amendment data. Should the ITT results be taken into account?

- **Issue 4: New company scenario around fulvestrant administration costs**

  Are the modelled administration costs of fulvestrant appropriate?

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 CDF review of TA579

- **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 ACM1 January 2021

ID2727 Appraisal consultation document draft recommendations:
Abemaciclib plus fulvestrant is not recommended, within its marketing authorisation, for treating hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer in adults who have had endocrine therapy

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

Recap from 1st meeting

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

Abemaciclib

Marketing authorisation	For hormone receptor (HR) positive, (HER2) negative, advanced breast cancer in combination with an aromatase inhibitor **or** fulvestrant as initial endocrine-based therapy, or in women who have received prior endocrine therapy. It is a CDK4/6 inhibitor **TA579 - abemaciclib was recommended for CDF in a subpopulation of MA:** • **in combination with fulvestrant, after endocrine therapy, and if exemestane + everolimus is the comparator.**
Dosage and administration	• **Abemaciclib**: 1 x 150 mg orally, twice daily for 28-day cycle • **Fulvestrant:** intramuscular injection, 500 mg • Use for as long as the patient is deriving clinical benefit or until unacceptable toxicity
Patient access scheme	A commercial access agreement has been approved which provides a simple discount to the list price • **Increased discount for abemaciclib included post ACD consultation**

Abbreviations: ACD: Appraisal consultation document

Treatment pathway

Second-line advanced breast cancer

Population

Endocrine-resistant

- ***First-line endocrine resistant***: Advanced breast cancer that progressed ≤12 months after neo/adjuvant endocrine therapy
- ***Second-line endocrine resistant***: Advanced breast cancer that progressed on/after 1 line of endocrine therapy

Treatments

- **Exemestane + everolimus**
- Exemestane
- Tamoxifen
- Fulvestrant
- Chemotherapy

TA 687: Ribociclib + fulvestrant recommended if exemestane + everolimus alternative (issued March 2021 CDF review of TA593)

Today's discussion CDF review of TA579: Abemaciclib + fulvestrant (ID2727)

- **Exemestane + everolimus is the comparator in Scope for CDF review**
- Abemaciclib (and ribociclib) are cyclin-dependent kinase 4 and 6 inhibitors and would not be used after prior CDK4/6 therapy

Primary clinical evidence: MONARCH 2

Design	Phase III, multicentre, double-blind randomised controlled trial
Location	International: 142 centres, 19 countries: 10 in Europe (0 in UK)
Population	Women with HR+/HER2-, locally advanced/metastatic breast cancer with progression during neoadjuvant/adjuvant endocrine therapy (ET), ≤12 months from end of adjuvant ET, or during first-line ET for metastatic disease
Intervention	Abemaciclib with fulvestrant
Comparator	Placebo with fulvestrant
Outcomes	**Primary:** Investigator-assessed progression-free survival (RECIST criteria)
Protocol amendment	Dose reduction due to adverse events (diarrhoea): from 200 mg to 150 mg twice a day (licenced dose). Before amendment, 26.6% of patients enrolled
Follow up for CDF review	Overall survival data immature during TA579. Additional 28 months of data collection presented.

Abbreviations: HR+: hormone receptor positive, HER2-: human epidermal growth factor receptor 2 negative

MONARCH 2: updated data

The improvement in overall survival was smaller in the post-amendment group than in the pre-amendment group (ACD: 3.4)

	HR (95% CI) data cut off 20th June 2019
• Progression-free survival (PFS)	
ITT, n=669	0.536 (0.445, 0.645) [redacted]
• Overall survival (OS)	
ITT, n=669	0.757 (0.606, 0.945) p = 0.0137
Pre-amendment (200 mg), n=178	[redacted]
Post-amendment (150 mg), n=491	[redacted]
Interaction test	NR

Abbreviations: CI: confidence interval, HR: hazard ratio, ITT: intention to treat, NR: not reported

MONARCH 2 progression-free survival: ITT & post-amendment 150mg abemaciclib

June 2019 data

NB:

- ITT population includes 26.6% of patients **starting on** 200 mg unlicensed dose.
- Post-amendment population: **only 150 mg dose** (anyone on 200 mg dose at protocol amendment reduced dose to 150 mg).

NICE **Abbreviations**: ITT: intention-to-treat; ABE: abemaciclib, FUL: fulvestrant

MONARCH 2 overall survival: ITT & post-amendment 150mg abemaciclib

June 2019 data

NB:

- ITT population includes 26.6% of patients **starting on** 200 mg unlicensed dose.
- Post-amendment population: **only 150 mg dose** (anyone on 200 mg dose at protocol amendment reduced dose to 150 mg).

Abbreviations: ITT: intention-to-treat; ABE: abemaciclib, FUL: fulvestrant

Committee conclusions on ITT vs. post-amendment population (ACD 3.3, 3.4)

ERG preferred post-amendment subgroup data:

- Adequately powered should be internally valid + reflects marketing authorisation
- Should be used consistently for time to treatment discontinuation and overall survival (inappropriate to use data from different groups for these outcomes)

Company:

- Not an issue in pre CDF entry appraisal and raised subsequently by ERG
- ITT used in regulatory submission
- Performed interaction test + did not consider starting dose was a treatment effect modifier

Clinical experts at 1st meeting:

- A higher dose for a short time at start of treatment not likely to confer a long-term advantage. CDK4/6 inhibitors work through long-term suppression of tumour growth

Committee conclusions

- Excluding data from 26.6% of people recruited before amendment was justified → post-amendment group more relevant than ITT (ACD 3.3)
- Explanation for different clinical results between the pre- and post-amendment groups uncertain – could not be determined if differences due to genuine dose effect, chance or baseline characteristic imbalances (ACD3.4)

Cost effectiveness: partitioned survival model

	Company's preferences	ERG's preferences	Committee's preference
PFS and OS data source	NMA with MONARCH ITT	NMA with MONARCH post amendment (PA)	Post amendment (PA) (ACD 3.3)
Time to treatment discontinuation (TTD) abemaciclib + fulvestrant (ABE-FUL)	Estimated HR [redacted] observed PFS (ITT) vs. TTD (PA) applied to NMA curve of ITT population.	Estimated HR [redacted] PFS (PA) vs TTD (PA) restricted means over MONARCH 2 observation period	Post amendment (PA) data more relevant than ITT (ACD3.3) Most appropriate modelling approach uncertain (ACD 3.8)
TTD exemestane + everolimus (EXE-EVE)	HR 1.58 (median time-on-treatment vs PFS from BOLERO 2) + clinical opinion scenario (20% discontinue EVE at 6 months + 70% of remainder have EVE dose reduced. Continue EXE to disease progression)		Most appropriate method remains uncertain (ACD 3.9)

- **BOLERO 2**: Phase 3, randomised controlled trial comparing exemestane + everolimus with exemestane + placebo

NICE **Abbreviations**: PFS: progression free survival; OS: overall survival; NMA: network meta-analysis; ITT: intention-to-treat, PA: post amendment, HR: hazard ratio

Appraisal consultation document: cost-effectiveness results

Considering confidential discounts and the committee's preference for post-amendment efficacy data for abemaciclib + fulvestrant, the company and ERG's ICERs were **over £30,000 per quality-adjusted life year** (QALY) **gained** (ACD 3.10)

Summary of responses to appraisal consultation document (ACD)

ACD consultation responses:

Received consultation responses from:

- Company – Eli Lilly & Company Ltd
- Professional organisation – United Kingdom Breast Cancer Group (UKBCG)
- Patient organisation – Breast Cancer Now
- Web comments

Consultation responses: Breast Cancer now

Comments on recommendations:

- Urge Lilly UK, NICE and NHS England to work together to see if cost-effectiveness of abemaciclib + fulvestrant could be improved
- Access concerns across the UK → this treatment available in Scotland

Treatment options:

- Draft recommendation a step backwards in treatment options…everyone deserves best available treatments…self funding not an option for many
- Ribociclib + fulvestrant has been approved but different CDK4/6 inhibitors suit patients better → crucial for quality of life and adherence
- Exemestane + everolimus can be sub-optimal for some patients given the toxicities and needing to reduce the dose or stop everolimus

Comments on post-amendment group

- Understand that committee needs to look at what is used in clinical practice but suggest committee consider more flexible approach
- not uncommon to see dose reductions across all CDK 4/6 inhibitors, yet still hear from patients the benefits they are receiving from the treatments
- Elaboration needed on how clinical expert comments that outcomes of 2 doses expected to be similar and that a higher dose for short term at start of treatment not likely to confer advantage considered by committee

Consultation responses: Breast Cancer now

Provided statements from people with experience of taking abemaciclib + fulvestrant:

- Can function sufficiently on a daily basis including independently and working fulltime
- Feeling normal and not like a cancer sufferer
- Minimal side effects even on max 150 mg dose
- A few injections per month easier compared to other treatments
- Reduced/stable spread of cancer and symptoms (including reduced 100 mg dose)
- Adverse symptoms using alternative ribociclib and palbociclib including vomiting and low white blood cell count

Consultation responses: UKBCG

Comments on using post amendment data:

- Concerns preliminary recommendation based on unplanned analysis of trial population in MONARCH 2 (amended protocol)
- Dose change can lead to uncertainty in how drug works – but supporting evidence for abemaciclib 150 mg from MONARCH 3 trial (abemaciclib 150 mg 2x daily with aromatase inhibitor HR-positive, HER2-negative advanced breast cancer with no prior systemic therapy in the advanced setting)
- The HR for PFS for the ITT population of MONARCH 2 is 0.536 which corresponds with the PFS HR MONARCH 3 of 0.54

Indirect comparison to assess clinical effectiveness should not be a barrier to treatment

- Fulvestrant and ribociclib approved by NICE (TA687), with indirect treatment comparison evaluation

Treatment options:

- Class effect with three CDK 4/6 inhibitors seem to perform similarly in endocrine sensitive/resistant disease (supported by latest ESO-ESMO international guidelines for advanced breast cancer, Cardoso et al. 2020)
- Abemaciclib + fulvestrant alternative to other CDK 4/6 inhibitors for side effects management
- No budget impact to NHS if clinicians choose most appropriate CDK 4/6 inhibitor with fulvestrant for patients → individualised treatment and optimised side effect management

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Abbreviations: CDK: cyclin-dependent kinase, ITT: intention-to-treat, PFS: progression-free survival, HR: hazard ratio

Consultation responses: web comments

Comments on recommendation:

- There is a population who can benefit from abemaciclib +fulvestrant
- Further review after 3 years is too long – treatment and trials have been delayed by Covid-19
- Average life expectancy of patient with secondary breast cancer is 3-5 years → delay will have direct impact
- Currently undertaking 2 studies to look at quality of life in secondary breast cancer patients → results in 12 months

Treatment options:

- Indirect (abemaciclib + fulvestrant) vs. (exemestane + everolimus) comparison suggests longer life and time before disease progression
- Different treatment options can avoid chemotherapy
- Hoping for a few years extra quality of life…may have to resort to private care

ACD committee preferred assumptions & company's new evidence post consultation

Company has agreed revised patient access scheme for abemaciclib

Issue	Committee conclusion	Company post ACD
Population	Data from post-amendment population who start on the licensed dose are the most relevant and should be used in model	Post-amendment data used in updated base case for the purposes of this appraisal • but it does not agree that ITT population should not be considered
Abemaciclib + fulvestrant	The appropriate modelling approach for time to treatment discontinuation for abemaciclib + fulvestrant is uncertain	New HR PFS vs. TTD
Exemestane + everolimus	The appropriate modelling approach for time to treatment discontinuation for exemestane plus everolimus is uncertain	New HR PFS vs. TTD

TTD exemestane and everolimus consistency with TA687

TA687 (ribociclib + fulvestrant) committee presented with same approaches to estimate hazard ratio for stopping everolimus; comments from meeting attendees differed between 2 appraisals

	Clinical opinion scenario: *20% stop everolimus after 6 months, 70% remaining have 10 mg to 5 mg dose reduction, but continue exemestane until disease progression*	**Hazard ratio calculated from median time on treatment from BOLERO 2**
Abemaciclib + fulvestrant (ACD 3.9)	Clinical experts: change at 6 months seemed implausible, more likely to stop gradually throughout the first 6 months	Committee: BOLERO 2 data preferable to 1 clinician opinion, even if not based on individual patient data
Committee conclusions	Uncertainty on most appropriate method to estimate TTD exemestane plus everolimus	
Ribociclib + fulvestrant (TA 687 section 3.9)	ERGs clinical expert suggested the scenario Clinical expert at meeting thought more plausible.	CDF clinical lead: ERG's model using BOLERO-2 data more plausible. ERG: does not take into account the large proportion of patients stopping treatment early – uses summary statistic
Committee conclusions	TTD everolimus likely to be between clinical opinion and the ERG's model using BOLERO-2 data	

Company's updated model TTD exemestane + everolimus

Company

- Noted conclusions in TA687 (ribociclib + fulvestrant) CDF review, committee agreed TTD likely to be between:
  - HR=1.58 (median time-on-treatment vs PFS from BOLERO 2)
  - ERG clinical opinion scenario (assume [redacted])
- **New estimate in response to ACD** restricted mean analysis of BOLERO 2 data used to determine PFS and TTD relationship → assuming fit on exponential model
- Estimate HR of [redacted] (Company note value between [redacted] and 1.58)
- Used new estimate HR [redacted] in the company's revised base-case to estimate treatment costs with everolimus

ERG

- Disagrees with HR of [redacted]: company's approach is flawed and could **underestimate the HR**
- Assumes PFS and TTD data can be fitted on exponential curve
- Previous meeting: committee expressed preference for clinical data
- HR: **1.58** relies on fewest assumptions → based on BOLERO 2
- The choice between any of these three HRs is **one of the key model drivers**

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Abbreviations: ITT: intention to treat, OS: overall survival, PFS: progression free survival, TTD: time to treatment discontinuation

Modelled TTD exemestane + everolimus

PFS curves for EXE-EVE and alternative TTD curves for estimating treatment costs with everolimus

What is the best approach to estimating TTD for exemestane + everolimus?

Company's updated model: TTD abemaciclib + fulvestrant

Company

- ITT: HR: [redacted] is most plausible assumption (for ITT population) (N.B. company uses post amendment data in its revised base case)
- **Analyses in response to ACD**: Explored HRs between PFS and TTD in post amendment group using restricted mean survival time analysis:
- Over length of MONARCH 2 (54 months) HR = [redacted]
- Over 120 months HR= [redacted]
- Lifetime extrapolation HR = [redacted]
- HR of [redacted] is used in the company's revised base case
- HR of [redacted] and [redacted] are considered in scenario analyses

ERG

- ERG do not consider using the ITT population relevant
- HR: [redacted] is likely most appropriate value → relative positioning of TTD and PFS modelled curves seems to be aligned to observed TTD and PFS KM curves in the post-amendment.
  - ➢ Results from comparing the areas under the PFS and TTD curves for the period of time where KM data were available
- Acknowledges HR of [redacted] is a potentially valid estimate and includes this in scenario analyses

What is the best approach to estimating TTD for abemaciclib plus fulvestrant?

Abbreviations: ITT: intention to treat, OS: overall survival, PFS: progression free survival, TTD: time to treatment discontinuation, HR: hazard ratio, KM: Kaplan-Meier

Company updates base case to use post-amendment data, ITT data supportive

Company:

- Post-amendment population (PAP) in revised base case, **but ITT also relevant** → disregarding does not reflect MONARCH 2 intention
- Protocol updated to increase enrolment of patients for assessing ABE safety
- Worldwide regulators use ITT
- Clinical advice indicates not appropriate to analyse separately
- [redacted]

ERG:

- Acknowledges company's correction that sample size calculations for PAP based on safety outcomes rather than PFS
- PAP (n=491) is methodologically robust and provides the most appropriate results:
  - Is powered to detect **differences in PFS**
  - Matches **marketing authorisation**
  - **Exceeds initial sample size** plan
- [redacted]
  - Median PFS: [redacted] in PAP vs [redacted] in ITT
  - Medial OS: [redacted] in PAP vs [redacted] in ITT

Should date from the ITT population be considered as supportive evidence in this appraisal?

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Abbreviations: ITT: intention to treat; OS: overall survival; PFS: progression free survival, PBO: placebo, ABE: abemaciclib, FUL: fulvestrant; PAP: post-amendment population

Company revised base case vs ERG preferred assumptions

	Company	ERG
Population	Post-amendment data (new)	Post-amendment data (no change)
TTD abemaciclib + fulvestrant	HR of [redacted]– using post-amendment TTD & PFS • change from ACD HR of [redacted] - post amendment TTD vs ITT PFS • HR of [redacted] and [redacted] considered in scenario analyses	HR [redacted]- using post-amendment TTD & PFS (no change) • for completeness, company's scenario with HR of [redacted] included (new)
TTD exemestane + everolimus	HR of [redacted]- a value between [redacted] (~ ERG's ACD scenario 2) and 1.58 (BOLERO 2) • change from HR of 1.58 based on BOLERO 2 • HR of [redacted] and 1.58 considered in scenario analyses	2 scenarios (no change): 1. HR=1.58 as per company 2. 20% of patients receiving EVE-EXE discontinue EVE at six months, and 70% of patients remaining will have a dose reduction from 10 mg daily to 5 mg daily (ERG's ACD scenario 2)

Abbreviations: TTD: Time to discontinuation, PFS: progression free survival, HR: hazard ratio, EVE: everolimus, EXE: exemestane

Additional company scenario: fulvestrant administration cost

Company base case :

Administration costs based on TA496 (Ribociclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer), published 2018.

New scenario:

- Company states fulvestrant part of routine practice and considers reasonable to assume increased efficiency and reduced costs associated with fulvestrant injections over time.
- Unreasonable to suggest large proportion of patients attend hospital for fulvestrant
- Fulvestrant injections assumed to be taken in community, except initial loading dose
- Cost associated with administration assumed to equal cost of 15 minutes of Band 6 community nurse specialist time → £11.50 per 28-day cycle.

Are the modelled administration costs of fulvestrant appropriate?

Cost-effectiveness results – using post-amendment data from MONARCH 2

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** and list price for other treatments.

Company's updated base case

Treatment	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)
Deterministic results							
Exemestane with everolimus	[redacted]	[redacted]	[redacted]	-	-	-	-
Abemaciclib with fulvestrant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Probabilistic results							
Exemestane with everolimus	[redacted]	[redacted]	[redacted]	-	-	-	-
Abemaciclib with fulvestrant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£2,020

Abbreviations: LYG: life-years gained, QALY: quality-adjusted life year, ICER: incremental cost-effectiveness ratio

Company's scenario analyses around time to treatment discontinuation assumptions

ICERs		TTD: abemaciclib with fulvestrant Restricted means analysis of MONARCH 2		
		HR of [redacted]	HR of [redacted]	HR of [redacted]
TTD: everolimus with exemestane	**Clinical opinion scenario** **HR of [redacted]** (~ 20% of patients discontinue everolimus at six months, 70% of patients remaining on treatment have a dose reduction)	Dominant	Dominant	Dominant
	Company's new restricted means analysis of BOLERO 2 HR of [redacted] applied to progression-free curve for everolimus time to discontinuation, while exemestane is costed to disease progression	Dominant	Dominant **Company revised base case**	Dominant
	Median time-on-treatment vs PFS from BOLERO 2 HR of 1.58 applied to the PFS curve, costing exemestane to disease progression	£35,639 **ERG preferred**	£26,112	Dominant

Fulvestrant administration cost price scenario for abemaciclib + fulvestrant vs exemestane + everolimus = **dominant** ICER

Key clinical and cost-effectiveness issues

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  Are the modelled administration costs of fulvestrant appropriate?