NICE National Institute for Health and Care Excellence

Technology Appraisal

Palbociclib with fulvestrant for treating hormone receptor-positive, HER2-negative, advanced breast cancer (Review of TA619) [ID3779]

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

TECHNOLOGY APPRAISAL

Palbociclib with fulvestrant for treating hormone receptor-positive, HER2-negative, advanced breast cancer (Review of TA619) [ID3779]

Contents:

The following documents are made available to consultees and commentators:

The **final scope** and **final stakeholder list** are available on the NICE website.

1. **Company submission** from Pfizer
2. **Clarification questions and company responses**
3. **SACT report**
4. **Patient group, professional group and NHS organisation submissions** from:
   a. Breast Cancer Now
5. **Expert personal perspectives** from:
   a. Sukhi Kaur – patient expert, nominated by Breast Cancer Now
6. **Evidence Review Group report** prepared by Liverpool Reviews and Implementation Group (LRiG)

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Fast track appraisal: cost-comparison case

Palbociclib in combination with fulvestrant for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer that has become resistant to previous endocrine therapy [ID33779]
(Review of TA619)

Document B
Company evidence submission

March 2022

File name	Version	Contains confidential information	Date
ID3779_Palbociclib_DocumentB_18MAR22_(Redacted)	1.0	No	18/03/22

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Abbreviations

Abbreviation	Description
AACR	American Association for Cancer Research
aBC	Advanced breast cancer
AESI	Adverse events of special interest
AE	Adverse event
AI	Aromatase inhibitor
AIC	Akaike information criteria
ALT	Aminotransferase
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
BC	Breast cancer
BIC	Bayesian information criteria
BICR	Blinded Independent Central Review
BNF	British National Formulary
BPI-SF	Brief Pain Inventory-Short form
CBR	Clinical benefit response
CC	Clinical coding
CCG	Clinical commissioning group
CDF	Cancer drug fund
CDK	Cyclin dependent kinases
CDSR	Cochrane Database of Systematic Reviews
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence interval
CNS	Central nervous system
CT	Computerised tomography
DARE	Database of Abstracts of Reviews of Effectiveness
DOR	Duration of response
DSU	Decision Support Unit
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EORTC QLQ-BR23	QLQ Breast cancer module
EQ-5D	5-dimension EuroQol questionnaire
ER	Estrogen receptor
ERG	NICE Evidence Review Group
ESMO	European society for medical oncology
ET	Endocrine therapy
EU	European Union
FBC	Full blood count
FDA	Food and Drug Administration
FUL	Fulvestrant
GP	General practitioner
H_0	Null hypothesis
H_A	Alternative hypothesis
HER2	Human epidermal growth factor receptor 2
HR	Hazard ratio
HR	Hormone receptor
HRQoL	Health-related quality of life
HTA	Health technology assessment

Abbreviation	Description
ICER	Incremental cost-effectiveness ratio
IM	Intramuscular
IPD	Individual patient data
ITC	Indirect treatment comparison
ITT	Intention to treat
KM	Kaplan-Meier
LFT	Liver function test
LHRH	Luteinizing hormone-releasing hormone
MAIC	Matching-adjusted indirect comparison
mBC	Metastatic breast cancer
mBPI-sf	modified Brief Pain Inventory (short form)
MIMS	Monthly Index of Medical Specialties
mg	Milligrams
ml	Millilitres
N/A	Not applicable
NC	Not calculated
NHS	National health service
NHSE	National health service England
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NR	Not reported
OR	Objective response
ORR	Objective response rate
OS	Overall survival
OWSA	One-way sensitivity analysis
PAL	Palbociclib
PAS	Patient access scheme
PBO	Placebo
PD	Progressed disease
PDS	Personal Demographic Service
PFS	Progression-free survival
PgR	Progesterone receptor
PHE	Public Health England
PI3K-mTOR	Phosphoinositide 3 kinase – mammalian target of rapamycin
PR	Partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
PROs	Patient-reported outcomes
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
QOL	Quality of life
RCT	Randomised controlled trial
RECIST	Response evaluation criteria in solid tumors
RR	Response rate
RWE	Real-world evidence
SACT	Systemic Anti-Cancer Therapy Dataset
SD	Standard deviation
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
STA	Single Technology Appraisal
TA	Technology Appraisal
TEAEs	Treatment-emergent adverse events

Abbreviation	Description
TSD	Technical Support Document
TTD	Time to treatment discontinuation
TTR	Time to response
VAS	Visual analogue scale
VAT	Value Added Tax

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

Population

This submission focuses on **part** of the marketing authorisation for IBRANCE® (palbociclib) and comparators ribociclib and abemaciclib.

IBRANCE® (palbociclib) is indicated for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer (mBC):

1. in combination with an aromatase inhibitor (AI);
2. in combination with fulvestrant in women who have received prior endocrine therapy (ET).

In pre- or perimenopausal women, the ET should be combined with a luteinizing hormone-releasing hormone (LHRH) agonist.

The treatment indication covered in this submission is narrower than the full marketing authorisation for the technology because palbociclib has already been recommended by the National Institute for Health and Care Excellence (NICE) for the treatment of advanced breast cancer (aBC) in setting **1** (see NICE Technology Appraisal [TA] 495[1]), as have the two comparators ribociclib and abemaciclib.[2, 3]

Recent post-Cancer Drugs Fund (CDF) reviews published by NICE for the comparators now recommend ribociclib and abemaciclib for use in setting **2**, that is, in combination with fulvestrant for the treatment of HR-positive, HER2-negative aBC in women who have received prior ET. The recommendations are made providing:

- exemestane plus everolimus is the most appropriate alternative to a cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor, and;
- the manufacturer companies provide ribociclib and abemaciclib according to the commercial arrangement, involving a simple discount patient access scheme (PAS).[4, 5]

This submission aims to present a cost-comparison of palbociclib with ribociclib and abemaciclib within this second NICE-approved setting, for women who have received prior ET.

Comparator(s)

The two comparators ribociclib and abemaciclib are both to be considered for the purpose of the cost comparison, with assumed efficacy equivalence between them and palbociclib.

Table 1. The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Women with HR-positive, HER2-negative locally advanced or metastatic BC, who have received prior ET	Same as final scope issued by NICE.	
Intervention	Palbociclib in combination with fulvestrant	Same as final scope issued by NICE.	Not applicable (N/A)
Comparator(s)	• CDK4/6 inhibitors in combination with fulvestrant: – Abemaciclib – Ribociclib • Everolimus and exemestane	Ribociclib in combination with fulvestrant Abemaciclib in combination with fulvestrant	Ribociclib and abemaciclib are now both recommended by NICE in the same population and setting.[4, 5] Everolimus plus exemestane is a historical comparator for the STA of palbociclib, ribociclib and abemaciclib. Since ribociclib and abemaciclib were compared indirectly to everolimus plus exemestane in TA687[5] and TA725[4] and found to be cost-effective, and this fast-track submission aims to demonstrate equivalence with ribociclib and abemaciclib, everolimus and exemestane will not be considered as a comparator.
Outcomes	The outcome measures to be considered include: • overall survival (OS) • progression-free survival (PFS) • response rate (RR) • adverse effects (AE) of treatment • health-related quality of life (HRQoL)	Same as final scope issued by NICE, but also adding outcomes deemed critical to resolve cost-effectiveness uncertainty in the original STAs of palbociclib, ribociclib and abemaciclib: • Time to discontinuation (TTD) of treatment • Details of subsequent therapies, including the duration of these treatments • OS (extra evidence deemed necessary to better inform choice of model extrapolation method)	
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should	A cost comparison versus ribociclib and abemaciclib has been carried out. The	Palbociclib can be appropriately assessed through the Fast Track Appraisal process,

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	be expressed in terms of incremental cost per quality-adjusted life year (QALY) with a sufficiently long-time horizon for the estimation of clinical and cost-effectiveness to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services (PSS) perspective. The availability of any PASs for the intervention or comparator technologies will be taken into account.	time horizon for assessing costs was assumed to be 40 years (lifetime), consistent with that used in TA619[6], which is sufficiently long to capture the majority of costs associated with the use of palbociclib. Costs are considered from an NHS and PSS perspective. A PAS for palbociclib has been included as part of the analysis.	due to its similarity in terms of effectiveness with currently approved comparator therapies. As such, a cost comparison analysis was conducted. The cost comparison compares the drug acquisition, monitoring and AE costs for palbociclib versus ribociclib and abemaciclib. Ribociclib and abemaciclib were selected as the most appropriate comparators given their wide usage in clinical practice and belonging to the same class of CDK4/6 inhibitors.
Subgroups to be considered	This submission is for a subset of the licensed population.	No other subgroups are to be considered in the appraisal, in line with the final scope issued by NICE.	N/A
Special considerations including issues related to equity or equality	No special considerations	No special considerations	N/A

Abbreviations: AE, adverse effect; BC, breast cancer; CDK, cyclin dependent kinases; ET, endocrine therapy; HRQoL, health-related quality of life; HER-, human epidermal growth factor receptor 2 negative; HR, hormone receptor; N/A, not applicable; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; OS, overall survival; PAS, patient access scheme; PFS, progression-free survival; PSS, Personal Social Services; QALY, quality-adjusted life year; RR, response rate; STA, single technology appraisal;;

B.1.2 Description of the technology being appraised

Table 2. Technology being appraised

UK approved name and brand name	**Palbociclib (Ibrance®)**
Mechanism of action	Palbociclib is a first in class small molecule inhibitor of the CDK 4 and 6 that synergistically enhances the effect of ET leading to a significant improvement in PFS in patients with ER+/HER2- aBC with a generally manageable AE profile.[7-10] Through its mechanism of action palbociclib enhances the anti-proliferative efficacy of endocrine treatments through inhibition of the ER receptor in BC cells.[10]
Marketing authorisation/CE mark status	Palbociclib received a positive opinion from the Committee for Human Medicinal Products on 15th September 2016[11] collectively for both the indications set out in this table. European Marketing Authorisation was then granted on 9th November 2016 for the same indications.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Palbociclib is indicated for the treatment of HR-positive, HER2-negative locally advanced or metastatic BC in combination with an AI or in combination with fulvestrant in women who have received prior ET. In pre- or peri-menopausal women, the ET should be combined with a LHRH agonist.
Method of administration and dosage	<u>Forms</u> Palbociclib: Oral Fulvestrant: Intramuscular (IM) injection <u>Dosage</u> Palbociclib: 125 mg (also available in 100mg and 75mg, all priced the same) Fulvestrant: 500 mg given as two slow (i.e. 1-2 minutes) IM injections in the gluteal area <u>Dosing Frequency</u> Palbociclib: daily for 21 consecutive days, followed by 7 days off treatment (to complete one 28-day cycle), until disease progression Fulvestrant: on days 1, 15, and once monthly thereafter. <u>Cycle length</u> One cycle of palbociclib plus fulvestrant is 28 days. Within this, the course of palbociclib treatment is for the first 21 consecutive days (then a 7-day break) and for fulvestrant is once per month (but twice in the first 4 weeks).
Additional tests or investigations	None required

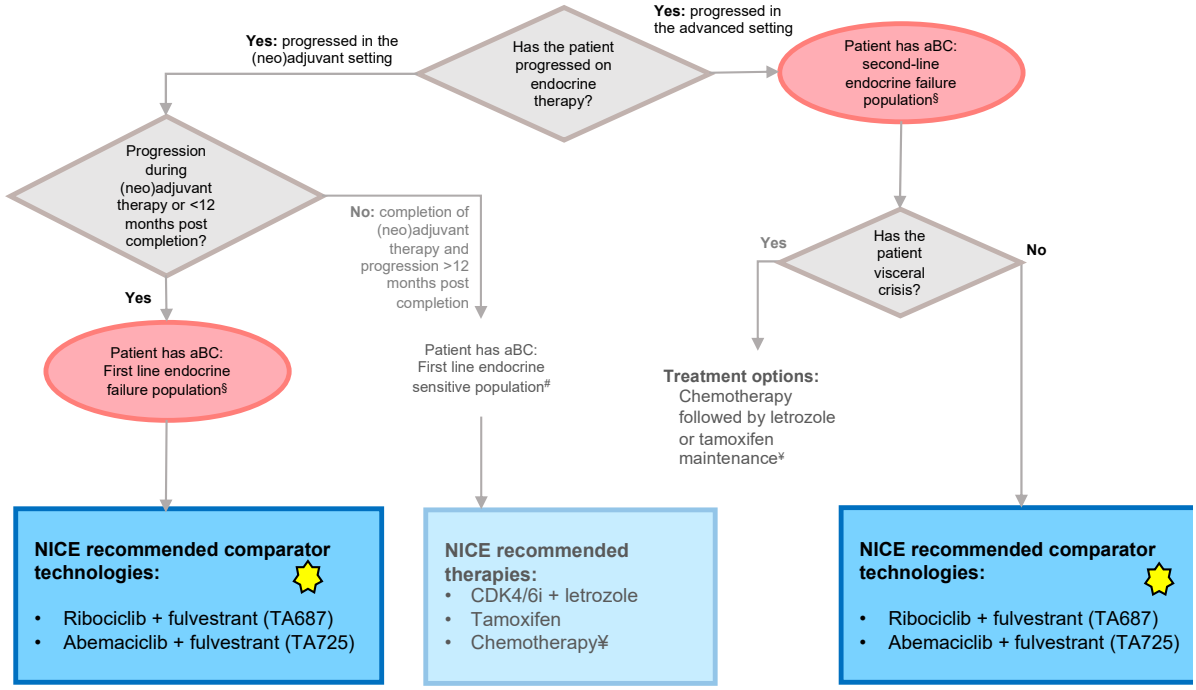
List price and average cost of a course of treatment	Palbociclib list price: £2,950 per pack of 21 tablets, which covers a 28-day treatment cycle. Fulvestrant: £261.21 per month at list price (but double dosed during the first month). At list price, per course the combined price cost is £3,211 (£3,472 in the first course due to fulvestrant's double dose).
PAS/commercial arrangement (if applicable)	Palbociclib price with simple PAS: [redacted] per pack of 21 tablets, which covers a 28-day/4-week treatment cycle. With palbociclib's PAS and fulvestrant's list price, the cost per course is [redacted] (or [redacted] in the first 4 weeks).

Abbreviations: aBC, advance breast cancer; AE, adverse effect; AI, aromatase inhibitor; BC, breast cancer; CDK, cyclin dependent kinases; ER, oestrogen receptor; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; LHRH, luteinizing hormone-releasing hormone; PAS, patient access scheme; PFS, progression-free survival; SmPC, Summary of Products Characteristics.

B.1.3 Health condition and position of the technology in the treatment pathway

The treatment pathway for the population of aBC patients who have received ET is summarised in Figure 1. This pathway is broadly consistent with the updated NICE Pathway for management of aBC, although fulvestrant is not NICE recommended but is used via variable Clinical Commissioning Group (CCG) commissioning.[12] Primarily, palbociclib is expected to be offered as a treatment option in the same position as ribociclib and abemaciclib are now recommended.

Figure 1. Position of the technology in the treatment pathway



aBC: advanced breast cancer (comprising locally advanced breast cancer or metastatic breast cancer).

CDK4/6i: CDK4/6 inhibitor therapy (palbociclib, ribociclib, abemaciclib)

§ Refers to the second licensed indication for palbociclib, namely "in combination with fulvestrant in women who have received prior endocrine therapy".

Refers to the first licensed indication for palbociclib, namely 'in combination with an aromatase inhibitor'. The use of palbociclib for this indication has been recommended by NICE (Nov 17, TA495).

¥ Chemotherapy used in visceral crisis or high tumour burden: capecitabine and paclitaxel are commonly used (non-inferiority studies show equal PFS; (ESMO).

Position of ribociclib, abemaciclib, and palbociclib in this appraisal

B.1.4 Equality considerations

There are no equality considerations to be made.

B.2 Key drivers of cost effectiveness of the comparator(s)

B.2.1 Clinical outcomes and measures

The clinical outcomes which drove cost-effectiveness analyses in TA687 (ribociclib)[5] and TA725 (abemaciclib)[4] are summarised in Table 3. Where relevant, additional context has been provided for outcomes explaining how additional data cuts from randomised clinical trials (RCTs) and real-world evidence (RWE) were used to address uncertainties identified prior to the CDF review.

Both ribociclib and abemaciclib appraisals used everolimus and exemestane as the comparator. Network meta-analyses (NMAs) estimated relative differences versus everolimus and exemestane for PFS and overall survival (OS) – however, the ribociclib appraisal did not contain an OS NMA, as the economic modelling assumed equivalence in post-progression survival between ribociclib and everolimus and exemestane.

Table 3. Clinical outcomes and measures in NICE TAs for the comparators ribociclib and abemaciclib (TA687, TA725)[4, 5]

Outcome	Measurement scale	Used in cost-effectiveness model?	Impact on ICER*	Committee's preferred assumptions	Uncertainties
Overall survival (OS)	Months (median) Hazard ratio (HR) (relative to everolimus and exemestane)	Yes	Major	ERG, manufacturer and NICE Committee extensively discussed their preferences regarding curve-fitting methodology and data sources.	NMA methodology Model curve-fitting and extrapolation methodology Maturity of RCT datasets informing model curves; changes to trial dosing protocol between datacuts for abemaciclib
Progression-free survival (PFS)	Months (median) HR (relative to everolimus and exemestane)	Yes	Major	ERG, manufacturer and NICE Committee extensively discussed their preferences regarding curve-fitting methodology and data sources.	
Response rate (RR)	Percentages	No	N/A		None
Adverse effects of treatment	Percentages	Yes	Minor	Use values from RCTs.	None
Health-related quality of life (HRQoL)	Utility scores	Yes	Medium	Use values from RCTs.	No common uncertainties
Time to discontinuation (TTD) for everolimus plus exemestane	Months (median)	Yes	Major	Several methods were discussed to accurately model this parameter. At the most recent appraisal TA725 (abemaciclib)[4] the ERG and Committee agreed that the true TTD value for everolimus plus exemestane is likely to lie somewhere between: • An estimate based on clinical opinion given in TA687 (ribociclib)[5], which assumed that 20% of people stopped everolimus after 6 months, and 70% of those remaining on treatment had a dose reduction (10 mg to 5 mg) but continued exemestane until disease progression; • An approach using median data from the BOLERO-2 study, which resulted in a HR of 1.58 between TTD curves of the appraised technology versus everolimus plus exemestane.	

Outcome	Measurement scale	Used in cost-effectiveness model?	Impact on ICER*	Committee's preferred assumptions	Uncertainties
Time to discontinuation for ribociclib and abemaciclib	Months (median)	Yes	Major	ERG, manufacturer and NICE Committee extensively discussed their preferences regarding curve-fitting methodology and data sources to support assumptions for TTD, both for the technologies as well as for everolimus plus exemestane.	As part of the Managed Access Agreements for ribociclib and abemaciclib, uncertainty around these Parameters for everolimus plus exemestane and the technologies were to be addressed via: • more mature data cuts from the pivotal clinical trials MONALEESA-3 and MONARCH 2; • data collection from the systemic anti-cancer therapy (SACT) dataset.
Progression-free survival (PFS)	Months (median)	Yes	Major		
OS (new data-cuts)	Months (median) HR (relative to everolimus plus exemestane)	Yes	Major	Data from SACT were not used in the final appraisals of ribociclib or abemaciclib, being judged to be too immature to add insight; the ERG and NICE Committee agreed with this approach.	
Subsequent treatments	Proportion of patients	Yes	Medium		A key driver of uncertainty relates to the costs of subsequent therapies after progression on ribociclib plus fulvestrant or abemaciclib plus fulvestrant, and the same applies to palbociclib plus fulvestrant. Unfortunately, the SACT data analysis provided a mixed picture of subsequent medication use which could not be used to further address this uncertainty.

Abbreviations: ERG, NICE Evidence Review Group; HR, hazard ratio; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival; RCT, randomised controlled trial; RR, response rate; SACT, Systemic Anti-Cancer Therapy Dataset; TTD, time to discontinuation.

B.2.1.1 Additional data collection and analysis agreed with NICE for palbociclib

Palbociclib and fulvestrant combination for treatment of the prior ET population was conditionally approved by NICE through a Managed Access Agreement (NICE TA619[6]). The appraisal guidance set out that palbociclib would be made available through the CDF until more evidence could be collected from the ongoing PALOMA-3 clinical study. The Managed Access Agreement also stipulated additional data collection to resolve uncertainties remaining in appraisal, including:

1. results of the NMA;
2. extrapolation of OS;
3. time to treatment discontinuation (TTD);
4. time on and details of subsequent therapies after discontinuation of palbociclib plus fulvestrant.

The Managed Access Agreement set out primary and secondary data sources to address the uncertainties as follows:

Primary source:

- Final data-cut from the PALOMA-3 trial (to resolve OS).

Secondary sources:

- Systemic Anti-Cancer Therapy (SACT) dataset (patient numbers receiving palbociclib plus fulvestrant, treatment duration and discontinuation, OS, details of subsequent treatments and in particular whether patients receive everolimus plus exemestane or exemestane monotherapy);
- National Health Service England (NHSE) Blueteq® data (patient numbers starting treatments, patient baseline characteristics).

This submission contains updated OS analyses from an extended data-cut of PALOMA-3 (section B.3.10), as well as a summary of findings from a report prepared by Public Health England (PHE) using linked Blueteq, SACT and Personal Demographic Service (PDS) data (see section B.3.8).

B.2.2 Resource use assumptions

The development of a preferred set of resource use statistics for ribociclib and abemaciclib varied per appraisal, as detailed below.

B.2.2.1 Ribociclib

For ribociclib, assumptions used in the manufacturer's original submission (TA593)[13] were accepted by the ERG and, aside from a few minor corrections, only unit costs were updated to reflect a 2018/19 cost year when the technology was reassessed in the 2021 CDF review (TA687).[5] The manufacturer's 2021 CDF review submission suggested that a 10% discount could be applied to fulvestrant pricing to reflect potential availability as a generic product after patent expiry, but this assumption was not accepted by the ERG or the NICE Committee.

B.2.2.2 Abemaciclib

For abemaciclib, manufacturer and ERG assumptions differed during the original appraisal (TA579).[14] However, the manufacturer's model was updated during the CDF review to allow selection of ERG-preferred assumptions. Base-case model results were presented in tandem, one set using original manufacturer assumptions and one using ERG assumptions.

B.2.2.3 Palbociclib

Unit costs for healthcare resources, and how their usage was affected by health state, as accepted by the committee in the original NICE STA submission for palbociclib plus fulvestrant[6] in Table 4 below.

Table 4. Healthcare resource use for the technology - as presented in original submission for TA619[6]

Administrative resources	**Unit cost (£)**	**Usage**	**Source**
Monitoring – 1 full blood count (FBC)[a]	£2.51	1 every month for 6 months, then every 3 months.	NHS Reference costs 2017/18[15]
Weighted fulvestrant administration cost comprised of: • Community nurse specialist 15 minutes at £45/hour (£11.25, 33.3% of the time) • Non-consultant led follow-up attendance medical oncology code 370 (£127.63, 66.7% of the time)	£88.84		PSSRU 2018[16] NHS Reference costs 2017/18[15]
Health state resources			
Community nurse visit	£65.36	Health state-specific usage for the following modelled health states, increasing with disease severity: • Pre-progression (stable disease) • Post-progression, first subsequent treatment • Post-progression, second subsequent treatment • Best supportive care Travel time to patient's home allocated where applicable.	PSSRU 2015[17] inflated using PSSRU 2018[16]
Community nurse travel time	£32.68		Assumption
Consultant visit (oncologist) – first visit	£187.30		NHS Reference costs 2017/18[15]
Consultant visit (oncologist) – follow-up visit	£132.10		NHS Reference costs 2017/18[15]
GP contact (surgery visit)	£34.00		PSSRU 2018[16]
GP contact (home visit)	£200.00		PSSRU 2018[16]
GP contact (home visit) – travel cost	£100.00		Assumption
Nurse (GP practice)	£39.00		PSSRU 2018[16]
Clinical nurse specialist	£111.00		PSSRU 2018[16]
Social worker visit	£72.50		PSSRU 2018[16]
Social worker travel time	£36.25		Assumption
Palliative care	£65.36		Assumption
CT scan	£122.22		NHS Reference costs 2017/18[15]
Occupational therapist	£39.50		PSSRU 2018[16]
Physiotherapist	£39.50		PSSRU 2018[16]
Lymphoedema nurse	£111.00		PSSRU 2018[16]

Notes: a, this reference cost is assumed to cover all healthcare resource use involved in the FBC laboratory test (i.e. staff time, testing kit costs etc), in addition to the cost of the actual test.
Abbreviations: CT, computerised tomography; GP, general practitioner; NHS, National Health Service; PSSRU, Personal and Social Services Research Unit.

B.3 Clinical effectiveness

B.3.1 Identification and selection of relevant studies

In the original submission for palbociclib plus fulvestrant (TA619[6]), relevant RCT evidence was sourced from a systematic literature review (SLR) up to March 2016, conducted by Wilson et al. (2017).[18] Two updates of the Wilson's SLR up to January 2018 and February 2019 were conducted to identify all relevant clinical data from the published literature regarding the clinical effectiveness of pre/peri/post-menopausal women with HR-positive, HER2-negative locally advanced or metastatic BC receiving first- or second-line therapy for their disease and who had been exposed to prior ET, either in the (neo)adjuvant or advanced/metastatic setting. Relevant comparators included several chemotherapies, as well as ETs (e.g. AI, selective oestrogen receptor [ER] modulators and ER antagonists).

As discussed in previous sections, recent post-CDF reviews published by NICE now recommend ribociclib and abemaciclib, both in combination with fulvestrant, for use in this patient population.[4, 5] To reflect these changes in clinical practice, a further update of the Wilson's SLR was conducted in January 2022; in this update, the search strategies were modified to exclusively identify publications reporting clinical trials of palbociclib plus fulvestrant versus fulvestrant in the population of interest, while all the other comparators previously searched where excluded. In addition, a *de novo* SLR of ribociclib and abemaciclib used in combination with fulvestrant in the population of interest was conducted.

Further details of the SLR are available in separate Appendix D.1.

B.3.1.1 Search strategy

The systematic reviews (the original search from 2015, the updates from 2016, 2018, 2019 and 2022, and the *de novo* review of ribociclib and abemaciclib conducted in 2022) were performed in accordance with the methodological principles of conducting systematic reviews as detailed in the University of York Centre for Reviews and Dissemination guidance for undertaking systematic reviews in health care and is reported here following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting checklist.[19, 20]

B.3.1.1.1 Wilson's SLR

The following electronic databases were searched for the original systematic review[18] from their inception dates until the date of the search, indicated below:

- MEDLINE, MEDLINE In-Process and MEDLINE Daily Update, 22 January 2015 (using Ovid SP platform)
- Embase, 22 January 2015 (using Elsevier Platform)
- The Cochrane Library (Wiley Online platform), 23 January 2015, specifically the following:
  - The Cochrane Central Register of Controlled Trials (CENTRAL)
  - The Cochrane Database of Systematic Reviews (CDSR)
  - Database of Abstracts of Reviews of Effectiveness (DARE)
  - Health Technology Assessment (HTA) Database

The same databases were searched again on 28 April 2016 as part of the first systematic review update.[18] However, the following minor changes were made:

- The Epub Ahead of Print database was searched alongside the MEDLINE databases, using the Ovid SP platform
- Embase was searched using the Ovid SP platform instead of Elsevier. This search was run simultaneously with the MEDLINE search. Search terms were translated and adapted as necessary for use in the Ovid SP platform.

No date limits were applied in the updated search; instead, the EndNote library of search results obtained in the April 2016 update was de-duplicated against the library obtained in the January 2015 search, prior to screening of titles and abstracts.

As well as the electronic database searches, the following conference proceedings were searched from 2012–2015 (2012–2014 in the original SLR, and 2015 in the systematic review update):

- American Society of Clinical Oncology (ASCO)
- American Association for Cancer Research (AACR), including the San Antonio Breast Cancer Symposium
- European Society of Medical Oncology (ESMO), including:
  - ESMO
  - IMPAKT-Breast Cancer
  - European Cancer Congress
  - ESMO Asia
  - Immuno-Oncology

The same databases from Wilson's SLR were searched on 26 January 2018 as part of the SLR update, as well as for the other update on 15 February 2019, with the following minor change:

- Embase was searched using the Elsevier instead of Ovid SP platform.

In addition, a search of conference proceedings identical to Chirila's SLR[21] was conducted for the years of 2016-2018 and in the update and adaptation in 2019 for the year 2018 and 2019. Finally, ClinicalTrials.gov and the International Clinical Trials Registry Platform were searched for relevant RCTs of palbociclib in Chirila's SLR. The search was extended to all relevant comparators in the update/adaptation of Wilson's SLR. The FDA website was also searched for the Summary Basis of Approvals in Chirila's SLR and in the update/adaptation of Wilson's SLR.

B.3.1.1.2 Wilson's SLR 2022 update for palbociclib and *de novo* SLR for ribociclib and abemaciclib

The same databases from Wilson's 2019 SLR update were searched on 26 January 2022 as part of the palbociclib update, as well as for the *de novo* SLR of ribociclib and abemaciclib, with the following minor changes:

- Embase was searched using the Ovid SP platform instead of Elsevier

Abstracts from relevant conferences indexed in Embase were retrieved via the electronic searches; relevant conferences not indexed in Embase were searched manually.

Searches on ClinicalTrials.gov and the International Clinical Trials Registry Platform were updated to identify completed and ongoing interventional studies of palbociclib with fulvestrant in HR-positive, HER2-negative, aBC patients. In addition, these clinical trial databases were

searched to identify relevant RCTs of ribociclib with fulvestrant and abemaciclib with fulvestrant in this population, without date limits.

The FDA website was searched to identify relevant documents in the Drug Approval Packages for palbociclib, ribociclib and abemaciclib (e.g. medical reviews, clinical reviews, multidisciplinary reviews, labels). The NICE website was also searched to identify published guidance on palbociclib, ribociclib and abemaciclib in combination with fulvestrant for BC.

Full details of the search strategies used in the original systematic review, the subsequent updates and the *de novo* SLR of ribociclib and abemaciclib are presented in separate Appendix D.1. In addition, a list of included studies relevant for the current submission, a list of excluded studies from the full-text screening and a list of excluded studies which were identified from ClinicalTrials.gov are provided.

B.3.1.2 Description of identified studies

A total number of 60 studies were included from Wilson's systematic review. The update/adaptation of Wilson's systematic review also included 38 publications of 23 unique studies, out of which 2 were subgroup analysis and updated publications of studies already included in the previous reviews. The 2019 update resulted in the inclusion of 44 publications, of which 22 unique studies. Of these unique studies, 13 were not identified before. Overall, 142 publications for 94 unique studies were included in the review.

However, only one of these studies was relevant to the current submission (PALOMA-3[10]), as it fulfilled the revised inclusion criteria in terms of intervention and comparators (i.e. including palbociclib with fulvestrant vs. placebo with fulvestrant). Twenty publications were identified in the Wilson's review and updates for PALOMA-3[10] up to 2019, while the 2022 update identified 23 further publications for this study.

The *de novo* SLR of ribociclib and abemaciclib in combination with fulvestrant identified 62 publications for four unique studies (MONARCH 2,[22] MONALEESA-3,[23] MONARCHplus[24] and FLIPPER[25]).

Overall, 85 publications for 5 unique studies (PALOMA-3,[10] MONARCH 2,[22] MONALEESA-3,[23] MONARCHplus[24] and FLIPPER[25]) were identified by the 2022 reviews. However, only three studies (PALOMA-3,[10] MONARCH 2,[22] and MONALEESA-3[23]) were eligible to be included in matching-adjusted indirect comparisons (MAIC) further presented in section B.3.12. More details on the excluded studies are presented in separate Appendix D.1.

B.3.2 List of relevant clinical effectiveness evidence

Study details are summarised for RCTs relevant to the assessment of palbociclib and comparators ribociclib and abemaciclib in the setting for this appraisal.

Table 5. Clinical effectiveness evidence - palbociclib

Study	PALOMA-3
Study design	International, multicentre, 2:1 randomised, double-blind, placebo-controlled, parallel-group, phase 3 clinical study
Population	Women 18 years of age or older and of any menopausal status,[a] with HR-positive, HER2-negative aBC not amenable to resection or radiation therapy with curative intent or mBC, whose disease progressed during or soon after completion of prior ET received in the (neo)adjuvant or advanced setting.

Study	PALOMA-3
Intervention(s)	Palbociclib in combination with fulvestrant
Comparator(s)	Fulvestrant
Indicate if trial supports application for marketing authorisation (yes/no)	Yes
Reported outcomes specified in the decision problem	PFS, OS, AEs HRQoL
All other reported outcomes	OR, CBR, DR, TTD

Notes: a. Pre- or peri-menopausal women are required to combine the fulvestrant treatment with an LHRH agonist.

Abbreviations: aBC, advanced breast cancer; AE, adverse event; CBR, clinical benefit response; DR, duration of response; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; HRQoL, health-related quality-of-life; LHRH, luteinizing hormone-releasing hormone; OR, objective response; OS, overall survival; PFS, progression-free survival; TTD, time to treatment discontinuation.

Table 6. Clinical effectiveness evidence - ribociclib

Study	MONALEESA-3
Study design	Phase III, multicentre, double blind RCT
Population	People (note only women recruited) with HR+, HER2- aBC who have received no or only one line of ET for aBC
Population considered in CDF review 2021	Population B (n=346 of total 726 subjects) - endocrine resistant disease defined as having progression on or ≤12 months after (neo)adjuvant ET (population Bi) & progression after one line of ET in advanced setting (population Bii+Biii)
Intervention(s)	Ribociclib with fulvestrant
Comparator(s)	Placebo with fulvestrant
Indicate if trial supports application for marketing authorisation (yes/no)	Yes
Reported outcomes specified in the decision problem	PFS, OS AEs HRQoL
All other reported outcomes	OR, CBR, DR, TTD, time to chemotherapy

Abbreviations: aBC, advanced breast cancer; AE, adverse event; CBR, clinical benefit response; DR, duration of response; ET, endocrine therapy; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; HRQoL, health-related quality-of-life; LHRH, luteinizing hormone-releasing hormone; OR, objective response; OS, overall survival; PFS, progression-free survival; RCT, randomised controlled trial; TTD, time to treatment discontinuation.

Table 7. Clinical effectiveness evidence – abemaciclib

Study	MONARCH 2
Study design	Phase III, multicentre, double blind RCT
Population	Women with HR+/HER2-, locally advanced or metastatic BC with progression during (neo)adjuvant ET, ≤12 months from end of adjuvant ET, or during first line ET for metastatic disease
Intervention(s)	Abemaciclib with fulvestrant
Comparator(s)	Placebo with fulvestrant
Indicate if trial supports application for marketing authorisation (yes/no)	Yes
Reported outcomes specified in the decision problem	PFS, OS AEs HRQoL
All other reported outcomes	OR, PR, CBR, DR, TTD, time to second disease progression chemotherapy-free survival

Abbreviations: BC, breast cancer; AE, adverse event; CBR, clinical benefit response; DR, duration of response; ET, endocrine therapy; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; HRQoL, health-related quality-of-life; OR, objective response; OS, overall survival; PFS, progression-free survival; PR, partial response; RCT, randomised controlled trial; TTD, time to treatment discontinuation.

B.3.3 Summary of methodology of the relevant clinical effectiveness evidence

The pivotal trials assessing ribociclib, abemaciclib and palbociclib in combination with fulvestrant for the treatment as set out in the appraisal scope have comparable methodology, with minor differences in patient selection and design, none of which materially alter the NICE Decision Problem applying either in the initial HTAs or in the post-CDF reviews (for ribociclib and abemaciclib). All were placebo-controlled, and all included a population of women with ER-positive HER2-negative aBC who had received and progressed during or soon after ET either in the (neo)adjuvant setting or as first-line therapy in the advanced setting. This information is summarised in Table 8.

In their initial HTAs, manufacturer submissions for ribociclib, abemaciclib and palbociclib all indirectly compared the technology with everolimus plus exemestane by means of NMA incorporating the pivotal RCTs together with the BOLERO-2 pivotal trial of everolimus plus exemestane[26] and several additional studies as required for evidence networks. These indirect comparisons were used to inform relative estimates of OS and PFS in cost-effectiveness analyses.

Uncertainty was raised around the results of these analyses, and their influence on the cost-effectiveness estimates. Some concerns were unique to single submissions, but a common concern across all three appraisals was the immaturity of trial data in respect of OS. During the post-CDF reviews of ribociclib and abemaciclib, the manufacturers updated their indirect comparison analyses in several ways, but both included updated data cuts from their RCTs.

Table 8. Comparative summary of trial methodology and design for palbociclib and comparators

	PALOMA-3 (palbociclib)	MONALEESA-3 (ribociclib)	MONARCH 2 (abemaciclib)
Location	Multicentre	Multicentre	Multicentre
Trial design	Phase III, double blind RCT	Phase III, double blind RCT	Phase III, double blind RCT
Number of subjects	521	726[§]	669
Eligibility **Inclusion criteria** **Age, gender**	Women 18 years or older	Male/female 18 years or older (only women recruited)	Women 18 years or older
Menopausal status	Pre, peri or post	Post	Pre, peri or post
Disease status	• HR+/HER2- aBC • Measurable disease defined by RECIST version 1.1, or bone-only disease • ECOG status 0 or 1	• HR+/HER2- aBC • Measurable disease defined by RECIST version 1.1, or ≥1 predominantly lytic bone lesion • ECOG status 0 or 1	• HR+/HER2- aBC • Measurable disease or bone-only disease • ECOG status 0 or 1
Progressed on or after ET in (neo)adjuvant or metastatic setting	Required	Not required	Required
Number of prior lines of ET for MBC	Any	≤1	≤1
Exclusion criteria **Visceral crisis**	Excluded	Excluded	Excluded
CNS metastasis that is symptomatic and/or not stable	Excluded	Excluded	Excluded
Prior chemotherapy for mBC	>1 excluded	Excluded	Excluded
QTc/QTcF interval	>480msec	Not reported	>450msec
Settings and locations where the data were collected	144 sites in 17 countries, 8 in Europe (including UK)	175 centres in 31 countries, 17 in Europe (including UK)	142 centres in 19 countries, 10 in Europe (0 in UK)

	PALOMA-3 (palbociclib)	MONALEESA-3 (ribociclib)	MONARCH 2 (abemaciclib)
Trial drugs **All given until discontinuation criteria are met (see below)**	Experimental arm (n=347) • Palbociclib 125mg daily oral (days 1 to 21 in a 28-day cycle). • Fulvestrant 500 mg intramuscularly on Days 1 and 15 of Cycle 1, and then on Day 1 of each subsequent 28-day cycle. Control arm (n= 174) • Fulvestrant as per experimental arm plus oral placebo given on same schedule as palbociclib.	Experimental arm (n=484) • Ribociclib 600mg daily oral (days 1 to 21 in a 28-day cycle) • Fulvestrant 500 mg intramuscularly on Days 1 and 15 of Cycle 1, and then on Day 1 of each subsequent 28-day cycle. Control arm (n=242) • Fulvestrant as per experimental arm plus oral placebo given on same schedule as ribociclib.	Experimental arm (n=446) • Abemaciclib 150mg daily oral (every day in a 28-day cycle). • Fulvestrant 500 mg intramuscularly on Days 1 and 15 of Cycle 1, and then on Day 1 of each subsequent 28-day cycle. Control arm (n=223) • Fulvestrant as per experimental arm plus oral placebo given on same schedule as abemaciclib.
Discontinuation criteria	Objective progression, symptomatic deterioration, unacceptable toxicity, death, or withdrawal of consent.	Objective progression, symptomatic deterioration, unacceptable toxicity, death, or withdrawal of consent.	Objective progression, symptomatic deterioration, unacceptable toxicity, death, or withdrawal of consent.
Concomitant medication rules	Not specified	Herbal preparations, medications or dietary supplements not allowed during or 7 days prior to start of trial.	Not specified
Primary outcomes (including scoring methods and timings of assessments)	PFS as assessed by the Investigator. Time Frame: from randomization date to date of first documentation of progression or death Assessment method: Progression is defined using Response Evaluation Criteria in Solid Tumors (RECIST v1.1).		
Secondary outcomes	• OS, OR, CBR, DOR • PROs including: – EORTC QLQ-C30 (change from baseline) – EORTC QLQ-BR23 (change from baseline) – Time to deterioration in pain score VAS – EQ-5D (Index score and VAS) • TEAEs • Biomarker and pharmacokinetics	• OS, ORR, CBR, DOR, TTR • PFS per blinded independent review committee (BIRC) • ECOG score deterioration • PROs including: – mBPI-sf (change from baseline) – EORTC QLQ-C30 (change from baseline and time to deterioration on subscales) – EQ-5D (Index score and VAS) • TEAEs	• OS, CR, PR, Stable Disease, ORR, DOR, CBR • PROs including – mBPI-sf (change from baseline) – EORTC QLQ-C30 (change from baseline) – EORTC QLQ-BR23 (change from baseline) – EQ-5D (index score and VAS) • Pharmacokinetics • TEAEs
Pre-planned subgroups (for PFS analysis)	• Age (<65 years, ≥65 years) • Race (White, Asian, Black, other) • Region (America, Europe, Asia)	• A random sample had secondary PFS analysis performed by BIRC. • Prespecified subgroups:[23]	• Endocrine resistance history (primary, secondary) • PgR status (positive, negative)

	PALOMA-3 (palbociclib)	MONALEESA-3 (ribociclib)	MONARCH 2 (abemaciclib)
	• Baseline ECOG score (0 or 1) • Menopausal status at study entry (pre/peri, post) • Metastatic site (visceral y/n) • Sensitivity to prior ET (yes, no) • Receptor status (ER+/PgR+, ER+/PgR-) • Disease-free interval (≤24 months, >24 months) • Bone-only disease (yes, no) • Number of disease sites (1, 2, ≥3) • Prior chemotherapy ((neo)adjuvant only, advanced/metastatic ± (neo)adjuvant, none) • Prior lines of therapy in metastatic setting (0, 1, 2, ≥3) • Most recent therapy setting ((neo)adjuvant, advanced/metastatic) • Most recent therapy by type of prior ET (AIs; anti-oestrogens; other)	• Age (<65 years, ≥65 years) • Race (Asian, White, Other) • Baseline ECOG score (0 or 1) • Prior ET (treatment naïve, up to one line) • Bone-only disease at baseline (yes, no) • Liver or lung involvement (yes, no) • Number of metastatic sites (<3, ≥3) • Prior tamoxifen (yes, no) • Prior AIs (yes, no)	• Metastatic site (visceral, bone only, other) • Measurable disease (yes, no) • Age (<65 years, ≥65 years) • Region (North America, Europe, Asia) • Race (Asian, White, Other) • Baseline ECOG score (0 or 1) • Menopausal status at study entry (pre/peri, post) • Number of disease sites (1, 2, ≥3)

Notes: §, an extended datacut from 'Population B' only was presented in the 2021 CDF review submission for RIB - this population comprises women with disease progression on/≤12 months after neo/adjuvant endocrine therapy (population Bi) & progression after 1 line of endocrine therapy in advanced setting (population Bii+Biii)

Abbreviations: aBC, advanced breast cancer; AI, aromatase inhibitor; BPI-SF, Brief Pain Inventory-Short form; CBR, clinical benefit response; CDK, cyclin-dependent kinase; CNS, central nervous system; CYP3A4, Cytochrome P450 3A4; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EORTC QLQ-BR23, QLQ Breast Cancer Module; EQ-5D, EuroQoL five dimension score; ER, oestrogen receptor; EU, European Union; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; LHRH, luteinizing hormone-releasing hormone; mBC, metastatic breast cancer; mBPI-sf, modified Brief Pain Inventory, short form; OR, objective response; ORR, objective response rate; OS, overall survival; PD, progressed disease; PI3K-mTOR, phosphoinositide 3 kinase – mammalian target of rapamycin; PFS, progression-free survival; PgR, progesterone receptor; PRO, patient-reported outcome; RCT, randomised controlled trial; RECIST, Response Evaluation Criteria in Solid Tumours; TEAEs, treatment-emergent adverse events; TTR, time to response; VAS, visual analogue scale.

B.3.4 Patient characteristics of relevant clinical effectiveness evidence

Patient baseline characteristics most relevant to a cross-trial comparison of key outcomes were summarised in a recent publication by Rugo et al., who developed a MAIC analysis of OS for palbociclib, ribociclib and abemaciclib.[27] This summary was used as the basis of Table 9.

The PALOMA-3 study had a lower proportion of patients aged over 65 than MONALEESA-3 and MONARCH 2, although patient populations were roughly similar in terms of Eastern Cooperative Oncology Group (ECOG) status, tumour location distribution and number of organs involved. Most patients presented with measurable disease in all studies.

PALOMA-3 patients had treatment histories involving more lines of therapy. Just 25% of patients in PALOMA-3 were chemotherapy-naïve compared to 44% in MONALEESA-3 and 40% in MONARCH 2. Around 86% of PALOMA-3 patients had received prior AI therapy compared to 52% in MONALEESA-3 and 70% in MONARCH 2. Prior ET was given in the metastatic setting for 75% of women in PALOMA-3 compared to 26% in MONALEESA-3 (MONARCH 2 did not report this distinction in its publication). For chemotherapy exposure, 35% of PALOMA-3 patients had two or more lines of prior therapy compared to 0% in the other two studies. Only 22% of patients in PALOMA-3 had received no prior therapy for mBC compared to 52% in MONALEESA-3 and 61% in MONARCH 2.

Table 9. Patient baseline characteristics in key clinical effectiveness evidence

Characteristic	Category	PALOMA-3 [a] (N = 521) n (%)	MONALEESA-3 (N = 726) n (%)	MONARCH 2 (N = 669) n (%)
Age group	<65	392 (75)	387 (53)	424 (63)
	>65	129 (25)	339 (47)	245 (37)
Race	White	385 (74)	619 (88)	373 (59)
	Asian	105 (20)	63 (9)	214 (34)
	Other	29 (6)	24 (3)	42 (7)
Region	North America	240 (46)	112 (15)	178 (27)
	Asia Pacific	114 (22)	56 (8)	-
	Other	167 (32)	558 (77)	-
	Europe	167 (32)	-	279 (42)
	Asia	114 (22)	-	212 (31)
ECOG	1	199 (38)	256 (35)	264 (40)
	0	322 (62)	468 (65)	400 (60)
Metastatic site	Visceral	304 (58)	439 (60)	373 (56)
	Bone only	124 (24)	154 (21)	180 (27)
	Other	93 (18)	133 (18)	113 (17)
Organs involved, number	1	171 (33)	224 (31)	263 (40)
	2	146 (28)	232 (32)	200 (30)
	3	106 (20)	162 (22)	-
	≥3	201 (39)	-	203 (30)
	4	66 (13)	72 (10)	-
	≥5	29 (6)	33 (5)	-
Measurable disease	Yes	405 (78)	560 (77)	483 (73)
	No	116 (22)	166 (23)	183 (27)
Prior AI	Yes	447 (86)	375 (52)	465 (70)
	No	74 (14)	350 (48)	204 (30)

Characteristic	Category	PALOMA-3 [a] (N = 521) n (%)	MONALEESA-3 (N = 726) n (%)	MONARCH 2 (N = 669) n (%)
Prior chemotherapy	(Neo)adjuvant	214 (41)	405 (56)	401 (60)
	Metastatic	177 (34)	0 (0)	0 (0)
	None	130 (25)	321 (44)	268 (40)
Previous lines of therapy for MBC	0	114 (22)	367 (52)	396 (61)
	1	225 (43)	345 (48)	256 (39)
	>2	182 (35)	0 (0)	0 (0)
Menopausal status	Pre or perimenopausal	108 (21)	0 (0)	114 (17)
	Postmenopausal	413 (79)	726 (100)	551 (83)
ER status	Negative	3 (1)	4 (1)	
	Positive	510 (99)	722 (99)	
PR status	Negative	142 (28)	206 (28)	
	Positive	361 (72)	520 (72)	
Disease-free Interval	< 12 months	13 (2)	31 (4)	
	>12 months	341 (65)	555 (76)	
	N/A	167 (32)	140 (19)	
Prior tamoxifen	No	207 (40)	428 (59)	
	Yes	314 (60)	297 (41)	
Prior ET setting	(Neo)adjuvant	134 (26)	431 (74)	396 (59) [b]
	Advanced or metastatic	387 (74)	150 (26)	256 (38) [b]
Sensitivity to prior ET	Yes	410 (79)		489 (74)
	No	111 (21)		169 (26)

Notes: Table layout derived from MAIC publication by Rugo et al, 2021.[9] a, values for PALOMA-3 calculated from individual patient data; b, please note prior ET setting percentages for MONARCH 2 do not add up to 100% because ET history was not reported for 12 patients in the abemaciclib plus fulvestrant arm and five patients in the placebo plus fulvestrant arm.[22]

Abbreviations: AI: Aromatase inhibitor; ECOG PS: Eastern Cooperative Oncology Group performance status; ER: Estrogen receptor; ET: Endocrine therapy; MAIC: Matching-adjusted indirect comparison; MBC: Metastatic breast cancer; N/A: Not applicable; PR: Progesterone receptor.

B.3.5 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

A brief overview of statistical methods for the three pivotal trials is shown in Table 10. A full account of the statistical methodology for the PALOMA-3 study of palbociclib plus fulvestrant, as presented in the original STA submission, has been repeated in a separate Appendix D.1.8.

Table 10. Statistical methods overview for palbociclib, ribociclib and abemaciclib pivotal studies on outcomes PFS and OS

Trial acronym (outcome)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
PALOMA-3 PFS	H_0: HR=1 H_A: HR<1 superiority	Log Rank Test (1-sided) for HR Stratified by sensitivity to prior hormonal therapy and the presence of visceral metastases	A sample size of at least 417 was required. The study was planned to have 90% power and control the type-I error rate at 0.025.	Data censored on date of last assessment, date of switching to a new anticancer medicine (if no progression observed). Patients with PD and 2 or more incomplete or non-evaluable assessments since last assessment were censored at the time of last objective assessment that no PD was found.
OS	H_0: HR=1 H_A: HR<1 superiority		No power calculation - OS hierarchically tested once PFS reached significance	The main objective of hierarchical testing was to test PFS (primary) and OS (secondary) hypotheses proposed in this study with the family-wise error rate strongly controlled at level 0.025.
MONALEESA-3 PFS	H_0: HR=1 H_A: HR<1 superiority	Log Rank Test for HR (one-sided)	Approximately 364 local PFS events needed to detect a HR of 0.67 with 95% power and a one-sided 0.025 level of significance	
OS	H_0: HR=1 H_A: HR<1 superiority	Stratified Log Rank Test for HR (one-sided)	No power calculation - OS hierarchically tested once PFS reached significance	
MONARCH 2 PFS	H_0: HR=1 H_A: HR≠1	Log Rank Test (2-sided) for HR Stratified by endocrine sensitivity and natural history of disease	The final analysis was planned at 378 PFS events, which would provide approximately 90% power assuming a HR of 0.703 at a one-sided α of 0.025.	
OS	H_0: HR=1 H_A: HR<1 superiority	Log Rank Test (1-sided) for HR		OS time was censored on the last date the participant is known to be alive.

Abbreviations: HR, hazard ratio; H_0, null hypothesis; H_A, alternative hypothesis; OS, overall survival; PD, progressed disease; PFS, progression-free survival.

B.3.6 Quality assessment of the relevant clinical effectiveness evidence

An overview of trial quality assessments carried out in the prior STAs of palbociclib, ribociclib and abemaciclib is given in Table 11.

Table 11. Quality assessment of key clinical trials

Trial acronym	PALOMA-3[28-30]	MONALEESA-3[31]	MONARCH 2[32, 33]
Was randomisation carried out appropriately?	Yes	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes	Yes
Were there any unexpected imbalances in drop-outs between groups?	No (see Appendix D.1)	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Yes, see Cristofanili et al. (2016)[28]	Yes	Yes
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes, Yes. No missing data for PFS.	Yes, Yes	Yes, Yes

Abbreviations: PFS, progression-free survival

B.3.7 Clinical effectiveness results of the relevant trials

Clinical data relevant to the Decision Problem in the ribociclib and abemaciclib appraisals were not used in their original form as reported in the clinical trials to inform the outcomes listed in Table 3. Instead, they were incorporated into economic models, via indirect comparison to everolimus plus exemestane, to derive predictions of relative long-term health benefit, cost and survival. These are not presented here due to differences in modelling methodology and source data, and the use of confidential patient-level data in some parts of the modelling. Furthermore, in the 2021 CDF review appraisals, the ribociclib and abemaciclib evidence base has been further extended through supplemental analyses performed on more recent data-cuts of clinical trials. The supplementary analyses are summarised in section B.3.10.

Table 12 aims to provide a brief, unadjusted summary of the key outcomes published from the PALOMA-3, MONALEESA-3 and MONARCH 2 trials. The table presents values from scientific publications or manufacturer CDF review submissions, whichever is more recent. In cases where values in the table do not match estimates submitted by manufacturers in the NICE CDF reviews TA687 and TA725, footnotes are provided for clarification.

The table results demonstrate that, in common patient populations with HER2-negative HR-positive aBC, palbociclib, ribociclib and abemaciclib all have clinically and statistically significant PFS benefit when used in combination with fulvestrant, compared to placebo with fulvestrant. The PALOMA-3 study had a broader patient population including a sizable subgroup that had extensive treatment history for mBC including prior chemotherapy (in both neo/adjuvant and metastatic settings). For their NICE CDF Reviews, manufacturers performed extended data analyses only on certain trial subpopulations in MONALEESA-3 and for MONARCH 2, new analysis subgroups were defined according to mid-trial dosing protocol amendments.[4, 5] However, relative treatment benefit for PFS versus placebo was maintained regardless of endocrine sensitivity or prior exposure, and HRs remained in a comparable range across all three trials despite differences in follow-up length.

Basic PFS and OS estimates differed between the three studies, with median PFS and OS markedly shorter for palbociclib (11.2 / 34.9 months) than for ribociclib (20.5 / 53.7 months) or abemaciclib (16.9 / 46.7 months). However, a similar difference in median PFS and OS was observed in the trial placebo arms, suggesting that the difference is likely explained mostly by the PALOMA-3 trial population, which had significantly greater numbers of patients who had received multiple lines of prior therapy (25% having chemotherapy in the metastatic setting, compared to 0% in MONALEESA-3 and MONARCH 2). These differences in OS prompt careful consideration of the methods selected to perform indirect treatment comparison involving the three studies, ensuring that these differences can be appropriately adjusted for. A recent publication used MAIC methodology to generate adjusted efficacy estimates for palbociclib, ribociclib and abemaciclib.[27]

Time to discontinuation (TTD) for the comparator everolimus plus exemestane – a key source of uncertainty in the ribociclib and abemaciclib appraisals – was not captured in those medicines' clinical trials, which were placebo-controlled. Instead, the NICE Committee supported an assumption for everolimus plus exemestane discontinuation that the TTD value for everolimus plus exemestane is likely to lie somewhere between:

- An estimate based on clinical opinion given in TA687 (ribociclib), which assumed that 20% of people stopped everolimus after 6 months, and 70% of those remaining on treatment had a dose reduction (10 mg to 5 mg) but continued exemestane until disease progression;
- An approach using median data from the BOLERO-2 study[26, 34], which resulted in a HR of 1.58 between TTD curves of the appraised technology versus everolimus plus exemestane.

Disease-specific HRQoL questionnaires were administered in the pivotal studies (as summarised in Table 3), but the preference in TAs and CDF reviews was to use generic 5-dimension EuroQoL questionnaire (EQ-5D) scores for economic modelling. Few published estimates of these EQ-5D scores exist – the TA papers for ribociclib and abemaciclib indicate that EQ-5D estimates were derived directly from trial datasets and supplied in confidence to NICE as part of the manufacturer economic models, so it has not been possible to clearly compare palbociclib with comparators on EQ-5D. The main published disease specific HRQoL

questionnaire results from the pivotal studies are shown in Table 13. Although the European Organisation for Research and Treatment of Cancer Quality of Life BC specific questionnaire (EORTC-QLQ-BR23) was analysed for publications on the PALOMA-3[35] and MONARCH 2[36] studies, these analyses were hampered by small sample sizes and found no significant differences between the placebo and active treatment arms except on the "upset by hair loss" item in PALOMA-3 where palbociclib plus fulvestrant patients had a significantly greater deterioration from baseline compared to placebo plus fulvestrant.[35]

Time to deterioration statistics both for global Quality of Life Questionnaire Core-30 (QLQ-C30) score as well as for pain (either captured as QLQ-C30 sub-score or via the BPI-SF questionnaire) revealed trends demonstrating that the active medication delayed deterioration of overall QoL and pain. The HRs associated with these comparisons were statistically significant in some analyses, namely, global QLQ-C30 score for palbociclib (HR versus placebo=0.641 [95% CI: 0.45,0.91]); QLQ-C30 pain score for palbociclib (HR versus placebo=0.642 [95% CI: 0.487, 0.846]) and QLQ-C30 pain score for abemaciclib (HR versus placebo=62 [95% CI: 0.48, 0.79]).

A recent analysis by Law et al. (2021)[37] used patient-level data from PALOMA-3 in combination with published summary statistics from MONARCH 2 to compare the relative impact of palbociclib and abemaciclib on patient-reported HRQoL outcomes QLQ-C30 and QLQ-BR23. Changes from baseline were examined for individual symptom scores as well as aggregate functional scales and global QoL score (for QLQ-C30). Estimates were calculated using MAIC methods, with a Bucher indirect treatment comparison being carried out for validation. For global QLQ-C30, the mean difference between active treatments was statistically significant, favouring palbociclib (mean difference = 6.95, 95% CI: 2.19, 11.71, p=0.004). Except for the "emotional functioning" scale from QLQ-C30 (mean difference = 5.40 favouring palbociclib, 95% CI: 0.78,10.02, p=0.022), other functional scales from QLQ-C30 and QLQ-BR23 did not differ notably between treatments. Statistically significant mean differences, favouring palbociclib, were also found on the following individual symptom scores: nausea/vomiting, appetite loss, systemic therapy side effects and diarrhoea, the latter having the greatest estimated difference (mean difference = -25.47, 95% CI: -29.81, -21.13, p<0.001).[37]

Table 12. Key clinical trial outcomes published for the technology and comparators

Outcome[a]	Group	PALOMA-3 (palbociclib)	MONALEESA-3 (ribociclib)	MONARCH 2 (abemaciclib)
PFS				
Median duration (months)	New medication + fulvestrant	11.2	20.5 [b]	16.9
	Placebo + fulvestrant	4.6	12.8 [b]	9.3
	HR	0.50 (95% CI: 0.40, 0.62)[29]	0.59 (95% CI: 0.48, 0.73)[23, 38]	0.54 (95% CI: 0.45, 0.65)[39]
OS				
Median duration (months)	New medication + fulvestrant	34.8	53.7 [c]	46.7
	Placebo + fulvestrant	28.0	41.5 [c]	37.3
	HR	0.81 (95% CI: 0.65, 0.99)[40]	0.73 (95% CI: 0.59,0.90)[41] [c]	0.76 (95% CI: 0.61, 0.95)[32]
TTD				
Median duration (months)	New medication + fulvestrant	PLD	NR	CiC
	Placebo + fulvestrant		29.5	
	HR		0.7 (95% CI: 0.55, 0.88)[e]	
HRQoL				
EQ-5D score whilst on treatment (mean)	New medication + fulvestrant	0.74 (95% CI: 0.72, 0.76)[d]	CiC	CiC
	Placebo + fulvestrant	0.69 (95% CI: 0.67, 0.72)[d]		
	p-value (difference)	p=0.0037		

Notes: a, relative effect sizes are shown versus the placebo plus fulvestrant arm for each study, using the main Intention To Treat (ITT) analysis populations; b, the estimates reported in the CDF review for ribociclib are referenced as derived from Data on File although they also appear to correspond to published values from Slamon 2018[23]; c, the ribociclib CDF review submission quoted values published in Slamon 2018[23], since this time a newer datacut for OS has been analysed in Slamon 2021[41]; d, values for palbociclib are from a conference poster by Loibl et al 2016[42] - however, the values used in the health technology assessments of palbociclib, ribociclib and abemaciclib were sourced directly from clinical trial data, separated according to disease state where possible (e.g. PFS, post-progression survival) and submitted in confidence to NICE for use in economic models; e, TTD outcome defined as "time to first chemotherapy" in the MONALEESA-3 study.

Abbreviations: CDF, Cancer Drugs Fund; CI, confidence interval; EQ-5D, 5-dimension EuroQoL questionnaire; HR, hazard ratio; HRQoL, health-related quality of life; ITT, intention to treat; NR, not reached; OS, overall survival; PFS, progression-free survival; PLD, patient-level data were used to estimate and extrapolate time to discontinuation, provided in confidence to NICE; TTD, time to discontinuation of treatment.

Table 13. HRQoL outcomes published for the technology and comparators

Outcome	Group	PALOMA-3 (palbociclib)[35]		MONALEESA-3 (ribociclib)[43]		MONARCH 2 (abemaciclib)[36]	
EORTC QLQ-C30 (global score, mean)		Baseline Mean	Follow-up [a] Mean (change from baseline)	Baseline Mean (SD)	Follow-up [c] Mean (SD)	Baseline Mean (SD)	Change from baseline [d] Mean (SD)
	New medication + FUL	65.9	66.1 (+0.2)	65.5 (19.1)	71.0 (18.5)	64.0 (22.4)	-1.4 (0.7)
	Placebo + fulvestrant	65.3	63.0 (-1.7)	68.4 (18.5)	73.5 (16.6)	63.5 (22.8)	+0.1 (1.0)
	p-value		p=0.0313 [b]		NC		
Time to deterioration in EORTC QLQ-C30 global score (median months)	New medication + fulvestrant	NR		35.9		-	
	Placebo + fulvestrant	NR		33.1		-	
	HR	0.641 (95% CI: 0.45,0.91) [e]		0.81 (95% CI: 0.62, 1.06) [e]		0.80 (95% CI: 0.63, 1.02) [f]	
Time to deterioration in QLQ-C30 pain score (median months)	New medication + fulvestrant	8.0 (95% CI: 5.6, NE)		41.9		-	
	Placebo + fulvestrant	2.8 (95% CI: 2.3, 5.4)		NR		-	
	HR	0.642 (95% CI: 0.487, 0.846)		1.06 (95% CI: 0.74, 1.52)		0.62 (95% CI: 0.48, 0.79)	
Time to deterioration in BPI-SF pain score (median months)	New medication + fulvestrant	-		42.7		16.83 [g]	
	Placebo + fulvestrant	-		35.9		11.93	
	HR	-		0.77 (95% CI: 0.57, 1.05)		0.90 (95% CI: 0.71, 1.15)	

Notes: a, changes from baseline were statistically analysed using a longitudinal multilevel model, the 'follow-up' mean reflects an adjusted average collected across a range of follow-up timepoints rather than a specific timepoint, the mean change from baseline value was manually calculated by subtracting two published means for illustrative purposes only; b, for difference in mean change from baseline as assessed by multilevel model; c, the mean from scores calculated at Cycle 15, day 1 is shown, however the main analysis presented multiple measurements taken over time, with 95% CIs suggesting that placebo and ribociclib mean scores did not differ statistically significantly; d, statistical test not carried out for the comparison of abemaciclib and placebo; e, definitive deterioration defined as a ≥10% reduction in the global QLQ-C30 score; f, deterioration defined as a ≥10-point reduction from baseline in global QLQ-C30 score; g, 'pain' outcome was a composite including a BPI-SF "worst pain" item score increase of ≥2 from baseline or an analgesic drug class increase of ≥1 level.

Abbreviations: BPI-SF, Brief Pain Inventory-Short form; CI, confidence interval; EORTC QLQ, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D, EuroQol 5 Dimension Questionnaire; FUL, fulvestrant; HR, hazard ratio; HRQoL, health-related quality of life; NC, not calculated; NR, not reached; QLQ, quality-of-life questionnaire; SD, standard deviation.

B.3.8 Subgroup analysis

The entire PALOMA-3 clinical trial population for palbociclib matches the Decision Problem, as do the populations from MONALEESA-3 and MONARCH 2. Prespecified subgroups were analysed as per trial study protocols, reported in key publications, and included in scenario analyses within manufacturers' original NICE submissions. However, no subgroups demonstrated differential efficacy or cost-effectiveness to the extent that CDF access or NICE recommendations post-CDF had to be restricted.

The ribociclib CDF review examined extended OS and PFS results for a trial subpopulation ("Population B", see Table 8) because that was the only group of study participants in MONALEESA-3 for whom longer-term survival data were collected. This ribociclib subpopulation was deemed by the NICE Committee to be relevant to decision-making, and the extended results reported for it were considered alongside the initial 2018 findings of the whole MONALEESA-3 trial.

Consequently, subgroup data in this submission have been limited to a presentation of refreshed estimates conducted as part of the new OS data-cut analysis, in section B.3.10.

B.3.9 Real-world evidence collected and reviewed as part of the CDF Review

B.3.9.1 History

PHE has conducted real-world evidence (RWE) reviews of palbociclib, ribociclib and abemaciclib in the post-ET setting approved by NICE for use on the CDF. The PHE reviews primarily aimed to address uncertainty around OS, but also around TTD. For palbociclib, the data collection brief also involved finding details of subsequent therapies received following discontinuation of palbociclib plus fulvestrant (in particular, whether everolimus plus exemestane or exemestane monotherapy are given).

All reviews used National Health Service (NHS) Blueteq records to identify patients whose physicians had applied to use the technology on the CDF; these records were then linked to the SACT and PDS datasets to develop analyses of OS, TTD and treatment patterns.

B.3.9.1.1 Ribociclib plus fulvestrant PHE review

After deduplication and linkage of Blueteq and SACT databases, 187 patient records were available for analysis. The median follow-up time was 3.7 months, and 141 patients (75%) remained on treatment whilst 46 patients (25%) had evidence that their treatment had stopped.

Median treatment duration for ribociclib plus fulvestrant was 9.4 months, and 72% (95% CI: 63 - 78) of patients were still receiving treatment at six months. Reasons for stopping treatment included disease progression (30%), death while not on treatment (24%), toxicity (15%), death while on treatment (9%), patient withdrawal (4%), or no evidence of treatment for 3 months or more on the SACT database.

OS could not be analysed meaningfully for ribociclib plus fulvestrant in the SACT database due to the low number of patients, short follow-up time and limited number of events.

B.3.9.1.2 Abemaciclib plus fulvestrant PHE review

A total 876 patient records were available for analysis. The median follow-up time was 4.4 months with a maximum follow-up of 10 months. Median treatment duration for abemaciclib plus fulvestrant was 10.2 months. Around 64% (95% CI: 60 - 67) were still receiving treatment at six months, whilst 24% of patients had evidence that their treatment had stopped.

Median OS was not reached in the SACT dataset. Six- and twelve-month OS rates were 88% (95% CI: 86 - 90) and 75% (95% CI: 70 - 79); substantially lower than the OS rates observed in the pivotal MONARCH 2 study of abemaciclib plus fulvestrant versus fulvestrant.

The manufacturer, ERG and NICE noted that patients treated with abemaciclib plus fulvestrant under the CDF were older and frailer (with higher ECOG scores on average) than those in MONARCH 2, and that OS results derived from SACT could not be incorporated into the economic evaluation.

B.3.9.2 Palbociclib plus fulvestrant PHE review

B.3.9.2.1 Data collection and management

Between 28 November 2019 and 27 February 2021, 1,265 applications for palbociclib with fulvestrant were identified in NHS England and NHS Improvement's Blueteq® system. After exclusions for duplicates (36), palbociclib plus fulvestrant usage outside CDF (15), and exclusions related to the linkage of Blueteq and SACT systems (36 deaths before treatment, 38 not receiving palbociclib plus fulvestrant or not in SACT database), 1,140 unique patient records were available for analysis.

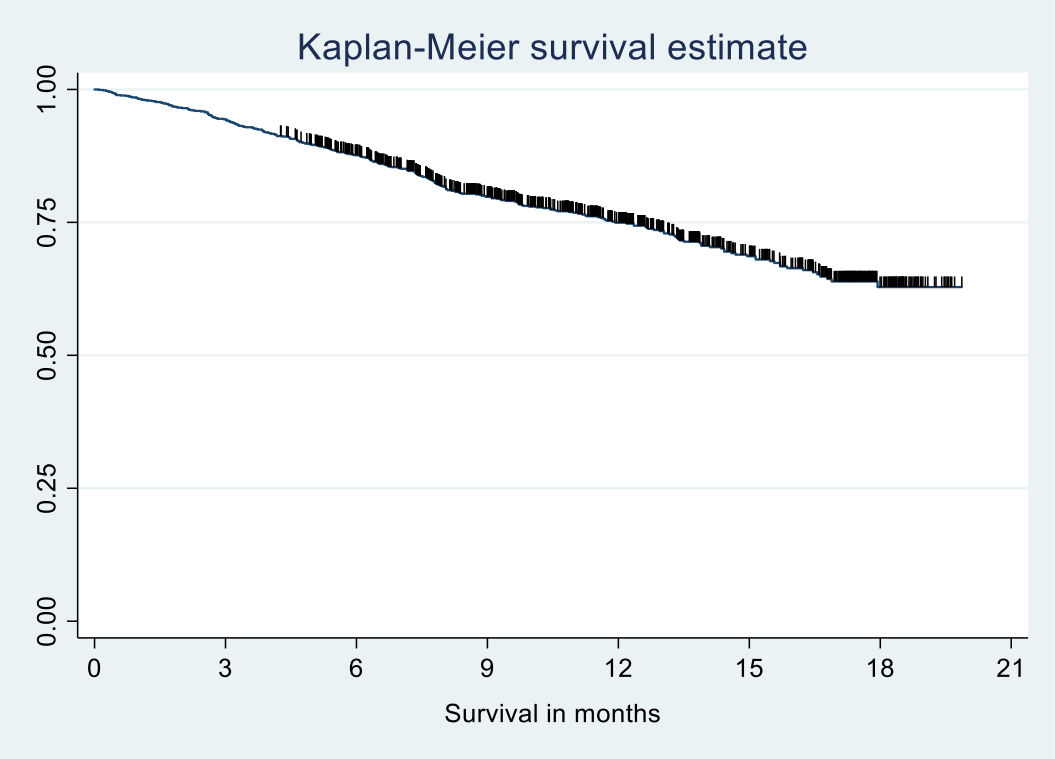
B.3.9.2.2 Patient demographics and characteristics

A full tabulation of patient characteristics is provided in separate Appendix D1.9.

B.3.9.2.3 Overall survival

The median follow-up time in SACT was 10 months (304 days). Median OS was not reached in the SACT analysis. At six months, OS was 88% (95% CI: 86 - 89), at 12 months 75% (95% CI: 72 - 78), and at 18 months 63% (95% CI: 59 - 67). These OS rates are consistently lower than those observed in either arm of PALOMA-3.[29]

Figure 2. OS for palbociclib plus fulvestrant based on SACT (n=1,140)



Abbreviations: OS, overall survival; SACT, systemic anti-cancer therapy.

B.3.9.2.4 Time to discontinuation

Records in the SACT dataset allowing assessment of treatment duration had a median follow-up time 5.5 months, with a maximum follow-up of 16.1 months.

In total, 494 patients (43%) were identified as having stopped treatment by the latest follow-up in SACT dataset (31st March 2021). Patients were assumed to have stopped treatment if they died, or had another relevant outcome recorded in the SACT dataset, or if there was no evidence of treatment with palbociclib plus fulvestrant for at least three months. The TTD analysis is represented graphically in a Kaplan-Meier (KM) plot in Figure 3.

The median treatment duration for all patients was 9.4 months (95% CI: 8.4, 10.8).

Of the 494 patients with evidence of having stopped treatment with palbociclib plus fulvestrant, the majority (21%) had died “not on treatment”, and 19% stopped treatment due to disease progression. A total of 138 patients (30%) stopped palbociclib plus fulvestrant after having received it as “palliative” treatment according to SACT. A full summary of stopping reasons recorded in SACT, separated by patients’ death status is provided in Table 14.

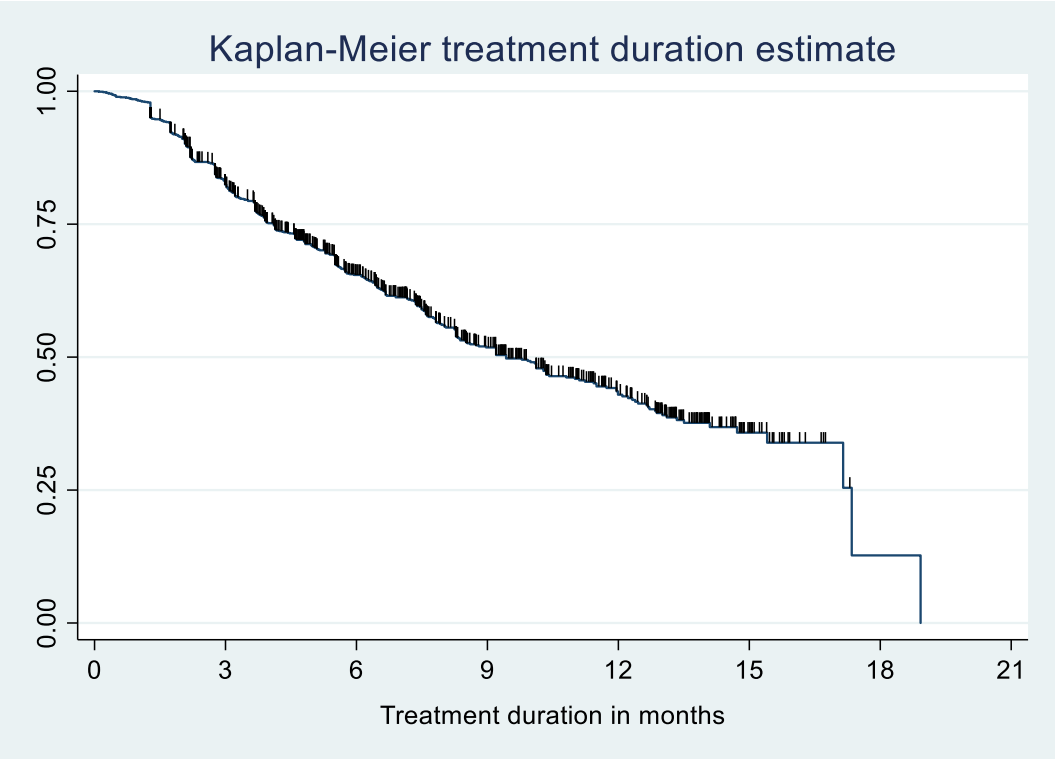
Table 14. Outcomes recorded for patients that have stopped treatment with palbociclib plus fulvestrant, separated by recorded death status (N=494)

	Recorded death status		
Treatment stopping outcome recorded in SACT	**Treatment stopped**	**Patient died not on treatment**	**Patient died on treatment**
Died not on treatment	104		
Progression of disease	54	42	
Palliative, patient did not benefit	47	30	
No treatment in at least 3 months		75	
Palliative, patient did benefit	28	33	
Died on treatment			45
Acute toxicity	7	14	
Patient choice	2	8	
COVID	2	2	
Completed as prescribed		1	
Total	244	205	45

Notes: Figures may not sum to 100% due to rounding. Table presents the outcome summary data reported by NHS Trusts. Deaths on treatment' and 'deaths not on treatment are explained in the methodology paper available on the SACT website.[44]

Abbreviations: COVID, coronavirus disease; SACT, systematic anti-cancer therapy

Figure 3. Treatment discontinuation for palbociclib plus fulvestrant based on SACT (n=1,140)



Abbreviations: SACT, systematic anti-cancer therapy

B.3.9.2.5 Subsequent therapies

Of 1,140 (21%) patients in the dataset, 240 received subsequent therapies after the patient's last palbociclib plus fulvestrant cycle; this represents 49% of the 494 patients in whom palbociclib plus fulvestrant discontinuation could be confirmed either by death, toxicity or another available code. The median time between these patients' last palbociclib plus fulvestrant cycle and their first subsequent therapy was 40.5 days. Some patients received

more than one subsequent therapy; the PHE report distinguishes therapies received first after palbociclib plus fulvestrant versus those received later, but it does not disaggregate these therapies by time, schedule or tumour type. The results of this analysis are presented by PHE as an illustrative analysis of the treatments given and were not validated with trusts or by the PHE data liaison team. To address a key question posed in the Managed Access Agreement for TA619, this analysis did not suggest widespread consistent use of everolimus plus exemestane or exemestane monotherapy following discontinuation of palbociclib plus fulvestrant. Rather, chemotherapies such as capecitabine and paclitaxel seemed to be predominant, as well as a notable 17/240 patients who went on to receive a second CDK4/6 inhibitor. A full breakdown of subsequent therapies from the PHE report is presented in the separate Appendix D1.9.

B.3.9.2.6 Sensitivity analysis

A sensitivity analysis for OS and TTD was performed, restricting the dataset to patients who had at least six months follow-up in SACT. Findings from this analysis were comparable to the whole-dataset findings.

B.3.9.2.7 Differences between SACT and PALOMA-3

The SACT analysis provides insight into the usage of palbociclib plus fulvestrant during its availability under the CDF following TA619. Of particular interest are the patient populations for whom Blueteq applications were made, and what treatments were given before and after palbociclib plus fulvestrant during its availability on the CDF from November 2019 to February 2021.

Data from SACT were not used in the final appraisals of ribociclib or abemaciclib, being judged by the NICE Committee to be insufficiently mature to add insight beyond that gained from the manufacturers' analyses of extended data-cuts in the MONALEESA-3 and MONARCH 2 studies. Although the SACT dataset for palbociclib plus fulvestrant is considerably larger and slightly more mature in terms of follow-up length, interpretation of OS and TTD findings is affected by similar issues as those raised in the CDF review of abemaciclib plus fulvestrant. A brief overview of these issues is recounted below:

- **Patient selection** – the context of the medicine's availability on the CDF may have led to palbociclib plus fulvestrant being prescribed to patients in a way that reflects neither the pivotal PALOMA-3 study nor the economic model assumptions considered by NICE in view of the Decision Problem. For example:
  - the Blueteq form does not list prior chemotherapy as an exclusion criterion, although the PALOMA-3 study excluded patients with >1 prior chemotherapy regimen;
  - in the SACT data, 10% of patients receiving palbociclib plus fulvestrant had "not ascertained" ET history;
  - In the SACT analysis, 19% of patients had indeterminate ECOG status.
- **Patient characteristics** - patients in SACT who received palbociclib plus fulvestrant were older and had poorer ECOG performance scores than those in PALOMA-3 and the economic models based on it.
  - In the SACT data, 69% of patients were over 60 and only 29% were aged under 60. In the PALOMA-3 population, 75% were aged under 65 and only 25% were over 65 years old.

  - In the SACT data, 30% of patients had ECOG score 0 and more than 50% had scores of 1 or higher; 19% had missing ECOG scores. In the PALOMA-3 population, 62% had ECOG score 0 and 38% had ECOG score 1.
- **Control arm** – the SACT data have no comparative control arm (e.g. fulvestrant monotherapy) meaning that relative treatment efficacy cannot be assessed, and only superficial comparison with PALOMA-3 results is possible. The absolute OS rate estimated for palbociclib plus fulvestrant in the SACT dataset was lower than that observed for fulvestrant plus placebo in the PALOMA-3 study.
- **Data maturity** – the median follow-up length for OS was 10 months in SACT. Median OS was not reached in the dataset. Patient record censoring began to occur from 3 months after treatment start and by 18 months all patients were either censored (56%) or had a confirmed discontinuation event (such as death).
- **Roll-out of CDK4/6 inhibitors** – it was noted in the manufacturer submission for the abemaciclib CDF review that because the three CDK4/6 inhibitor medicines were new technologies successively made available through the CDF, the allocation of patients to these treatments may not have reflected typical future use, but rather a set of priorities driven by urgent need for alternative therapies in patients who had exhausted other options. This was illustrated in part by the evidence in SACT of palbociclib plus fulvestrant being given in palliative settings, or as prior treatment to a second CDK4/6 inhibitor.

B.3.9.2.8 Conclusions

The PHE report authors acknowledge that the purpose of the SACT analysis is to provide a secondary source of evidence on real-world treatment patterns and outcomes observed for patients receiving palbociclib plus fulvestrant during the CDF period. To this end, the report has illustrated that in its early use through CDF, palbociclib plus fulvestrant was administered to an older and more impaired (in terms of ECOG score) population than that of PALOMA-3. The treatment was used in a range of settings, some of which appear to fall outside the scope of the NICE appraisal, and overall treatment duration was shorter than observed in PALOMA-3. OS results remain immature in the dataset extracted from SACT, and difficult to draw conclusions from based on the short median follow-up time.

B.3.9.3 Comparison of SACT outcomes from SACT reviews of the technology and comparators

The usage and setting of CDK4/6 inhibitors as observed in SACT may not reflect future real-world use, either in terms of patient selection nor placement within context of prior and subsequent therapy, as the NICE Committee acknowledged in the abemaciclib CDF review.[4] However, as presented in Table 15, it is noteworthy that OS and treatment duration outcomes estimated from SACT were almost identical for palbociclib, ribociclib and abemaciclib (OS not being calculable for ribociclib).

Table 15. Main SACT outcomes for the technology and comparators

Outcome	Palbociclib	Ribociclib	Abemaciclib
Median follow-up time for OS (months)	10	3.7	4.4
Median duration of treatment (months)	9.4	9.4	10.2
OS % at 6 months	88%	-	88%
OS % at 12 months	75%	-	75%

Abbreviations: OS, overall survival.

B.3.10 New OS data from PALOMA-3

Final analysis for OS was performed for the PALOMA-3 study in 2018 with 310 events (60% of 521 total randomised patients) based on an April 13, 2018 data cut-off.[29] The stratified analysis demonstrated superior OS for palbociclib plus fulvestrant versus placebo plus fulvestrant (HR=0.81, 95% CI: 0.64, 1.03) and 1-sided p=0.0429. This result did not reach the prespecified level of statistical significance. With a median follow-up time of 45 months, the median OS for the palbociclib plus fulvestrant arm was 34.9 months (95% CI: 28.8, 40.0) and the median OS for the placebo plus fulvestrant arm was 28.0 months (95% CI: 23.6, 34.6).

To address uncertainties around this parameter raised in TA619, an unplanned updated OS analysis was performed in Q4 2020 with 393 events (75% of 521 total randomised patients) based on an August 17, 2020 data cut-off.

Figure 4 summarises the updated analysis. A HR of palbociclib plus fulvestrant versus placebo plus fulvestrant of HR=0.806 (95% CI: 0.654, 0.994) was estimated with 1-sided nominal p=0.0221.[40]

With a median follow-up time of 73.3 months, the median OS for the palbociclib plus fulvestrant arm was 34.8 months (95% CI: 28.8, 39.9) and median OS for the placebo plus fulvestrant arm was 28.0 months (95% CI: 23.5, 33.8).[40] An improvement of 6.8 months was observed, consistent with the published final OS analysis from April 2018.[29, 40] The improvement in OS (HR <1) was observed in most of the pre-specified subgroups (Figure 5).

With longer follow-up and additional events, the improvement in OS is demonstrated with clear and lasting separation of the KM curves. Subgroup results of this updated analysis are consistent with the results from the final analysis. 5-year survival rates for the palbociclib + fulvestrant arm and the placebo + fulvestrant arm were 23.3% and 16.8%, respectively.[40]

Figure 4. Updated OS KM Curves from PALOMA-3

Abbreviations: CI, confidence interval; FUL, fulvestrant; HR, hazard ratio; KM, Kaplan-Meier; OS, overall survival; PAL, palbociclib; PBO, placebo.

Figure 5. Updated PALOMA-3 OS subgroup analyses

Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; ER, oestrogen-receptor; FUL, fulvestrant; HR, hazard ratio; ITT, intention-to-treat; OS, overall survival; PAL, palbociclib; PBO, placebo; PR, progesterone receptor.

B.3.11 New OS, PFS and TTD data from MONALEESA-3 and MONARCH 2 trials for comparators

As part of their CDF review submissions, the ribociclib and abemaciclib manufacturers supplied updated analyses of PFS and OS, based on more mature datasets from the pivotal trials MONALEESA-3 and MONARCH 2. For ribociclib, this took the form of reporting the latest published PFS and OS analyses from a prespecified data cut-off date of 3 June 2019. For abemaciclib, this involved a new analysis of the MONARCH 2 data using a data cut-off date of 20 June 2019. A top-line comparison of the most recent results is provided in Table 12.

Additional TTD (or "time to first chemotherapy") estimates were calculated and presented in the manufacturer CDF review submission for ribociclib[38]. Similar analyses for TTD (called "extent of exposure") were reported in confidence for abemaciclib, based on clinical study reports.[39]

B.3.12 Meta-analysis

No pairwise meta-analysis was conducted. Head-to-head evidence was not available comparing palbociclib with any of the comparators in the assessment scope; therefore, MAICs

for OS and PFS were conducted to estimate the relative efficacy of all relevant therapies (see section B.3.13).

B.3.13 Indirect and mixed treatment comparisons

As described in previous sections, several trials have demonstrated the clinical benefit of CDK4/6 inhibitors plus fulvestrant for the treatment of HR-positive, HER2-negative advanced breast cancer.[10, 22, 23] However, due to the lack of head-to-head evidence comparing the three interventions directly, we compared the clinical effectiveness of palbociclib, ribociclib, and abemaciclib via MAICs using the most recent available evidence for all comparators and following methodology explained in the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 18.[45] The primary outcomes considered in these analyses were OS and PFS.

Traditional anchored (unadjusted) indirect treatment comparisons (ITCs) are usually based on summary-level data and are the most widely used approach for indirect comparisons. However, the presence of clinical heterogeneity (in the form of patient characteristics and/or study design) across trials for treatments of interest may undermine the validity of ITCs based on summary-level data, since traditional ITC methodology does not allow for adjustment for such heterogeneity. Failure to account for these important differences in patient characteristics or study design can result in misleading (biased) comparisons of treatment effect given that it is not possible to adjust for between-trial heterogeneity using the traditional ITC methodology.

MAICs are often used to indirectly compare a treatment effect across studies by leveraging individual patient data (IPD) from one study to reduce cross-trial differences. In practice, this is achieved through selection and adjustment of the IPD to match the summary-level data of the comparator trial population(s). When a common comparator is present, anchored MAICs can be used to further adjust for cross-trial differences. By anchoring through the control arm, differences in known and unknown prognostic factors across trials are accounted for when determining the relative treatment effect.

Given the baseline population heterogeneity between PALOMA-3, MONARCH 2, and MONALEESA-3, and because we had access to IPD for PALOMA-3, we conducted MAICs on OS and PFS to account for between-trial differences that would otherwise cause bias under a traditional ITC framework. Details on the between-trial baseline population characteristics were previously presented in Table 9. Further information on the assessment of heterogeneity and the quality assessment of each clinical trial are further described in separate Appendix D, sections 1.5 and 1.7 respectively.

B.3.13.1 MAIC methods

The anchored MAICs between PALOMA-3, MONARCH 2 and MONALEESA-3 were carried out according to guidelines set out in the NICE DSU TSD 18.[45] The steps taken in the MAIC are described in separate Appendix, section D.2. Each step was implemented in the R software package, using code adapted from the examples provided in the NICE DSU TSD. R code for the MAICs versus MONARCH 2 and MONALEESA-3 is presented in a separate Appendix, section D.4.

With regards to the uncertainty around the MAIC results, we present measures of uncertainty, such as confidence intervals (CIs) derived from robust sandwich estimator, alongside the point

estimates in the following results sections (B.3.13.2 and B.3.13.3), as per guidance described in TSD18.[45]

In addition to the base-case analysis, scenarios assessing the impact of removing the adjustment factors in decreasing order of importance were implemented. Scenarios A-H were considered for the analysis versus MONALEESA-3 (

Table 16) and scenarios A-L were conducted for the analysis versus MONARCH 2 (Table 17).

Table 16. Description of scenarios for the MAIC analyses versus MONALEESA-3

Variables	Scenario A	Scenario B	Scenario C	Scenario D	Scenario E	Scenario F	Scenario G	Scenario H
Prior ET Setting (Advanced/Metastatic)	✓	✓	✓	✓	✓	✓	✓	✓
Region (Asia Pacific/ North American)	✓	✓	✓	✓	✓	✓	✓	
Organs Involved (2/3/4/≥5)	✓	✓	✓	✓	✓	✓		
Chemotherapy (Neoadjuvant/adjuvant)	✓	✓	✓	✓	✓			
ER Status (Positive)	✓	✓	✓	✓				
Race (Asian/White)	✓	✓	✓					
Disease-free interval (≤12 months/>12 months)	✓	✓						
Metastatic Site (Visceral/Bone only)	✓							

Notes: Scenario A adjusts for all characteristics. Consecutive scenarios drop the least important variable one at a time.

Abbreviations: ER, estrogen receptor; ET, endocrine therapy; MAIC, matching adjusted indirect comparison.

Table 17. Description of scenarios for the MAIC analyses versus MONARCH 2

Variables	Scenario A	Scenario B	Scenario C	Scenario D	Scenario E	Scenario F	Scenario G	Scenario H	Scenario I	Scenario J	Scenario K	Scenario L
Race (Asian/White)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Previous Lines of Therapy for MBC	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Organs Involved (2/≥3)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Region (Europe/North American)	✓	✓	✓	✓	✓	✓	✓	✓	✓			

Metastatic Site (Bone only/Visceral)	✓	✓	✓	✓	✓	✓	✓	✓				
Age Group (≥65)	✓	✓	✓	✓	✓	✓	✓					
Prior Chemotherapy (Neoadjuvant/adjuvant)	✓	✓	✓	✓	✓	✓						
Sensitivity to prior ET (Yes)	✓	✓	✓	✓	✓							
Measurable Disease (Yes)	✓	✓	✓	✓								
ECOG PS	✓	✓	✓									
Prior AI (Yes)	✓	✓										
Menopausal Status (Pre/perimenopausal)	✓											

Notes: Scenario A adjusts for all characteristics. Consecutive scenarios drop the least important variable one at a time.

Abbreviations: AI, aromatase inhibitor; ER, estrogen receptor; ET, endocrine therapy; MAIC, matching adjusted indirect comparison; MBC, metastatic breast cancer.

Further details on the treatment-effect modifiers for the MAICs versus MONALEESA-3 and MONARCH 2 are presented in separate Appendix D.2. Results are presented in the following sections for:

- an analysis without any adjustment ("unmatched and unadjusted"),
- an analysis with the matching of the inclusion criteria but without any further adjustment ("matched and unadjusted"),
- scenarios A-H for the analysis versus MONALEESA-3 and scenarios A-L for the analysis versus MONARCH 2.

B.3.13.2 MAIC results for PALOMA-3 vs MONALEESA-3

Base-case and scenario results for the OS and PFS MAIC analyses for PALOMA-3 versus MONALEESA-3 are presented in sections B.3.13.2.1 and B.3.13.2.2 below. Additional MAIC results, such as the distribution of rescaled weights, summary statistics of baseline characteristics before and after matching and adjusting to the population as well as the associated effective sample size (ESS), are presented in separate Appendix D.3.

B.3.13.2.1 OS results

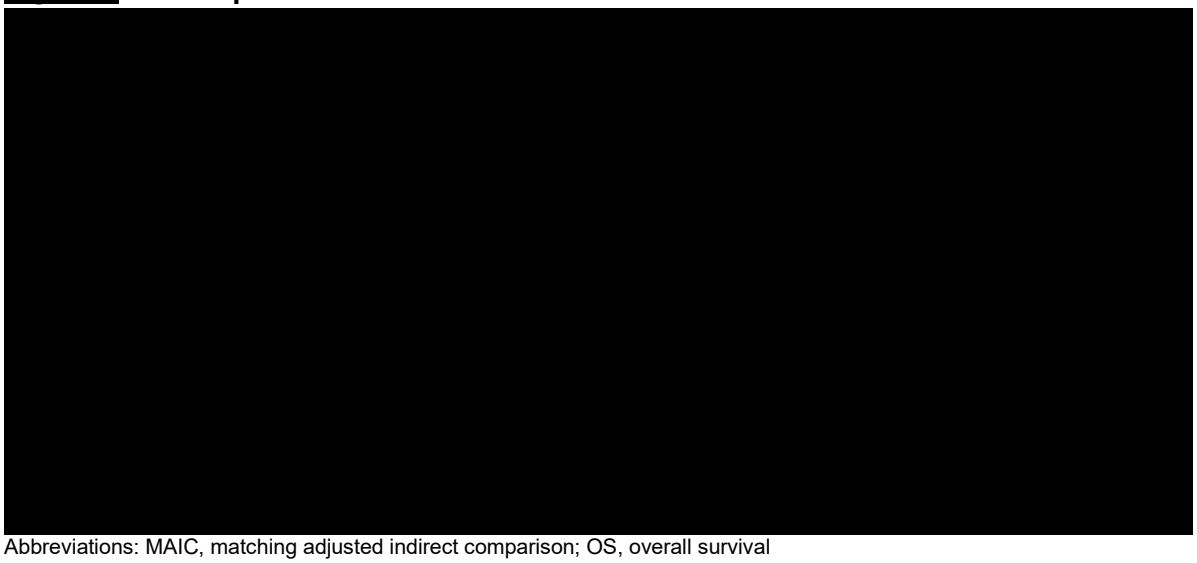
The results of the OS MAIC comparing palbociclib plus fulvestrant with ribociclib plus fulvestrant were [redacted], as can be seen in [redacted] 18 and [redacted] 6 [redacted]. The point estimates nearing 1 and the 95% CI confirm the clinical equivalence assumption for palbociclib plus fulvestrant and ribociclib plus fulvestrant with regards to the OS data.

Table 18. OS MAIC results for PALOMA-3 versus MONALEESA-3

Scenarios	HR (95% CI)
Unmatched and unadjusted	[redacted]
Matched and unadjusted	[redacted]
Scenario A	[redacted]
Scenario B	[redacted]
Scenario C	[redacted]
Scenario D	[redacted]
Scenario E	[redacted]
Scenario F	[redacted]
Scenario G	[redacted]
Scenario H	[redacted]

Abbreviations: CI, confidence interval; HR, hazard ratio; MAIC, matching adjusted indirect comparison; OS, overall survival

Figure 6. Forest plot: OS MAIC results PALOMA-3 versus MONALEESA-3



Abbreviations: MAIC, matching adjusted indirect comparison; OS, overall survival

B.3.13.2.2 PFS results

The majority of the results of the PFS MAIC comparing palbociclib plus fulvestrant with ribociclib plus fulvestrant were not statistically significant, as can be seen in 19 and 7 ( ). Scenario A and the . However, given the results of the remaining scenarios, which all report , indicate that it is reasonable and conservative to conclude that the two therapies are clinically equivalent in terms of PFS benefit.

Table 19. PFS MAIC results for PALOMA-3 versus MONALEESA-3

Scenarios	HR (95% CI)
Unmatched and unadjusted	
Matched and unadjusted	
Scenario A	
Scenario B	
Scenario C	
Scenario D	
Scenario E	
Scenario F	
Scenario G	
Scenario H	

Abbreviations: CI, confidence interval; HR, hazard ratio; MAIC, matching adjusted indirect comparison; PFS, progression-free survival

Figure 7. Forest plot: PFS MAIC results PALOMA-3 versus MONALEESA-3

Abbreviations: MAIC, matching adjusted indirect comparison; PFS, progression-free survival

B.3.13.3 MAIC results for PALOMA-3 vs MONARCH 2

Base-case and scenario results for the OS and PFS MAIC analyses for PALOMA-3 versus MONARCH 2 are presented in sections B.3.13.3.1 and B.3.13.3.2 below. Additional MAIC results, such as the distribution of rescaled weights, summary statistics of baseline characteristics before and after matching and adjusting to the population as well as the associated ESS, are presented in separate Appendix D.3.

B.3.13.3.1 OS results

The results of the OS MAIC comparing palbociclib plus fulvestrant with abemaciclib plus fulvestrant , as can be seen in 20 and 8 ( ). The point estimates nearing 1 and confirm the clinical equivalence assumption for palbociclib plus fulvestrant and abemaciclib plus fulvestrant with regards to the OS data.

Table 20. OS MAIC results for PALOMA-3 versus MONARCH 2

Scenarios	HR (95% CI)
Unmatched and unadjusted	
Matched and unadjusted	
Scenario A	
Scenario B	
Scenario C	
Scenario D	
Scenario E	
Scenario F	
Scenario G	
Scenario H	
Scenario I	
Scenario J	

Scenario K	[redacted]
Scenario L	[redacted]

Abbreviations: CI, confidence interval; HR, hazard ratio; MAIC, matching adjusted indirect comparison; OS, overall survival

Figure 8. Forest plot: OS MAIC results PALOMA-3 versus MONARCH 2

Abbreviations: MAIC, matching adjusted indirect comparison; OS, overall survival

B.3.13.3.2 PFS results

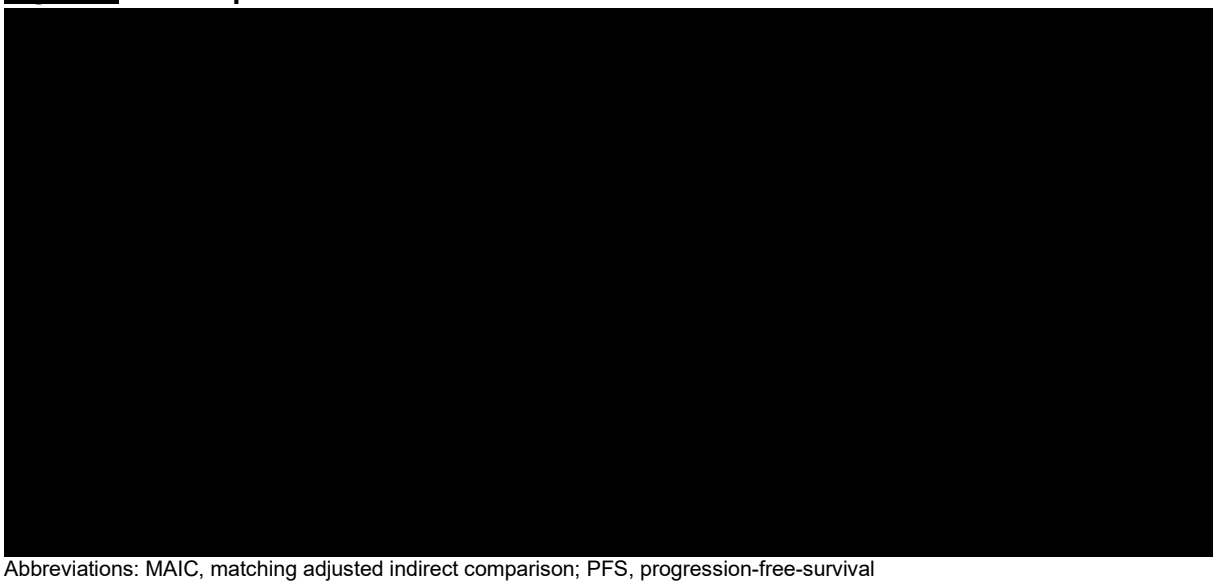
The results of the PFS MAIC comparing palbociclib plus fulvestrant with abemaciclib plus fulvestrant [redacted], as shown in [redacted] 21 and [redacted] 9 ([redacted]). As with the OS findings, these results support a clinical equivalence assumption for palbociclib and abemaciclib on PFS.

Table 21. PFS MAIC results for PALOMA-3 versus MONARCH 2

Scenarios	HR (95% CI)
Unmatched and unadjusted	[redacted]
Matched and unadjusted	[redacted]
Scenario A	[redacted]
Scenario B	[redacted]
Scenario C	[redacted]
Scenario D	[redacted]
Scenario E	[redacted]
Scenario F	[redacted]
Scenario G	[redacted]
Scenario H	[redacted]
Scenario I	[redacted]
Scenario J	[redacted]
Scenario K	[redacted]
Scenario L	[redacted]

Abbreviations: CI, confidence interval; HR, hazard ratio; MAIC, matching adjusted indirect comparison; PFS, progression-free survival

Figure 9. Forest plot: PFS MAIC results PALOMA-3 versus MONARCH 2



Abbreviations: MAIC, matching adjusted indirect comparison; PFS, progression-free-survival

B.3.14 Adverse reactions

The pivotal trials for palbociclib, ribociclib and abemaciclib remain the most comprehensive available assessments of drug safety profile. Accordingly, Table 22 aggregates and compares the adverse events (AEs) reported in the most recent publications from PALOMA-3, MONALEESA-3 and MONARCH 2. The MONALEESA-3 publication[41] reported AEs of special interest, irrespective of causality, by grouping and maximum grade (safety set). The MONARCH 2 publication[32] limited its summary to treatment-emergent AEs occurring in 10% or more subjects (grouped as grade 3, grade 4, and all grades combined). The original manufacturer submission for palbociclib (in TA619[6]) included a detailed AE summary taken directly from the PALOMA-3 clinical study report, which is difficult to compare with the publicly available AE summaries for ribociclib and abemaciclib. The summary for PALOMA-3 AEs in Table 22 is based on the Turner 2018[29] publication which provided more up-to-date statistics from the planned final analysis of PALOMA-3. AEs occurring with 10% or higher frequency in either arm of PALOMA-3 are reported, as well as any AEs which were reported in MONALEESA-3 and MONARCH 2, even if their relative frequency in the PALOMA-3 study was less than 10%.

All three CDK4/6 treatments have comparable adverse event profiles in terms of serious and life-threatening AEs. However, important differences can be seen on certain AEs of lower grades:

- Neutropenia can occur with ribociclib and palbociclib, whereas abemaciclib tends to induce less frequent and lower-grade neutropenia;
- Abemaciclib frequently causes diarrhoea, with over 14% of cases at grade 3/4 above.[22]

Given the level of impact these AEs can have, the safety findings present a strong case for making all three CDK4/6 inhibitors available on the NHS, so that treatment can be tailored, including treatment swich if necessary, to maximise patient safety, compliance and comfort. The benefit of having multiple CDK4/6 inhibitors available was recognised by the NICE Appraisal Committee in the post-CDF review of abemaciclib.[46]

Table 22. Summary of published AE frequency (%) from pivotal trials of palbociclib plus fulvestrant and comparators

Grade 3/4 AEs	Palbociclib + Fulvestrant[29]	Abemaciclib + Fulvestrant[32]	Ribociclib + Fulvestrant[41]
Neutropenia	69.57%	29.71%	58.18%
Leukopenia	38.26%	11.11%	16.98%
Diarrhoea	N/A	14.51%	N/A
Hepatobiliary toxicity	N/A	N/A	13.87%
Anaemia	4.35%	9.07%	3.93%
Infections	5.22%	N/A	8.07%
ALT increased	N/A	4.54%	N/A
Fatigue	2.61%	4.08%	N/A
Lymphopenia	N/A	4.08%	N/A
Thrombocytopenia	2.90%	3.40%	1.24%
AST increased	3.19%	2.72%	N/A
Rash	0.87%	3.17%	N/A
Abdominal pain	N/A	3.17%	N/A
QT interval prolongation	N/A	N/A	3.11%
Pulmonary embolism	N/A	N/A	2.90%
Nausea	0.58%	2.72%	N/A
Dyspnoea	0.58%	2.72%	N/A
Pulmonary toxicity	N/A	N/A	2.48%
Renal toxicity	N/A	N/A	1.66%
Back pain	1.45%	0.68%	N/A
Muscular weakness	N/A	1.36%	N/A
Decreased appetite	1.16%	1.13%	N/A
Pyrexia	0.29%	1.13%	N/A
Vomiting	0.58%	0.91%	N/A
Blood creatinine increased	N/A	0.91%	N/A
UTI	N/A	0.91%	N/A
Headache	0.87%	0.68%	N/A
Arthralgia	0.87%	0.68%	N/A
Stomatitis	0.87%	0.45%	N/A
Dizziness	0.58%	0.68%	N/A
Constipation	N/A	0.68%	N/A
Cough	0.29%	0.45%	N/A
Pain in extremity	0.29%	0.45%	N/A
Interstitial lung disease/pneumonitis	N/A	N/A	0.41%
Insomnia	0.29%	N/A	N/A
Musculoskeletal pain	0.29%	N/A	N/A
Dyspepsia	0.29%	N/A	N/A
Weight decreased	N/A	0.23%	N/A
Other	N/A	N/A	0.21%

Abbreviations: AEs, adverse events; ALT, alanine aminotransferase; AST, aspartate aminotransferases; N/A, not applicable; UTI, urinary tract infection

B.3.15 Conclusions about comparable health benefits and safety

As Table 12 summarises for OS and PFS, relative treatment effects of the three CDK4/6 inhibitors versus placebo are comparable, suggesting equivalence of palbociclib, ribociclib and abemaciclib in delaying disease progression and extending survival compared to fulvestrant monotherapy. This top-line finding has been further supported by recent MAICs considering PFS and/or OS.[27, 47, 48]

The results of the new MAICs comparing palbociclib plus fulvestrant versus ribociclib plus fulvestrant and abemaciclib plus fulvestrant (for OS and PFS, see section B.3.13) confirm the clinical equivalence assumption based on the best available evidence. These new MAIC analyses were based on PALOMA-3 IPD and the most recently published trial data for the two comparators, and consistently estimated statistically non-significant HRs between treatments.

Two pooled analyses were carried out by the US Food and Drug Administration (FDA) using the patient-level data from phase 3 RCTs which the FDA had received as part of the marketing applications for PAL, RIB and ABE. The first FDA analysis (by Gao et al 2020[47]) concentrated on PFS and aggregated data from seven RCTs including the PALOMA-3, MONALEESA-3 and MONARCH 2 studies as well as additional first-line studies (PALOMA-2, MONALEESA-2, MONALEESA-7 and MONARCH 3[47]) which the manufacturers had submitted to FDA. Significant PFS benefit was estimated for CDK4/6 inhibitors versus placebo, first using the entire pooled dataset (HR=0.59, 95% CI: 0.50, 0.61), and then for specific settings including the one most relevant to this appraisal: *CDK4/6i in combination with fulvestrant for "second-line and beyond" treatment* (HR=0.56, 95% CI: 0.49, 0.64).[47] The second FDA analysis (by Gao et al 2021[48]) used similar methodology to estimate CDK4/6i versus placebo HRs for OS, but only included patient-level data from trials with sufficient OS follow-up, namely PALOMA-3, MONALEESA-3 and MONARCH 2. Both the whole-dataset HR (HR=0.77, 95% CI: 0.68, 0.88) and a HR restricted to the *"second-line and later"* (HR=0.77, 95% CI: 0.67, 0.89) setting were statistically significant and demonstrated an OS benefit of CDK4/6 inhibitors.

To compare potential efficacy differences between the CDK4/6is whilst accounting for inter-trial differences in patient population and treatment setting, Rugo et al (2021)[27] designed a MAIC which used patient-level data from PALOMA-3 and published summary data from MONALEESA-3 and MONARCH 2. The authors calculated adjusted HRs comparing OS benefit between palbociclib vs ribociclib and palbociclib vs abemaciclib. For the setting *"combination with fulvestrant after endocrine therapy",* the MAIC reported small and statistically nonsignificant adjusted HRs comparing OS benefit of palbociclib versus ribociclib (HR=0.89, 95% CI: 0.48, 1.63), and for palbociclib versus abemaciclib (HR=0.87, 95% CI: 0.54, 1.40), reinforcing that CDK4/6 inhibitors have comparable efficacy on the outcomes of PFS and OS in the setting relevant to the Decision Problem.[27]

The main sources of uncertainty surrounding an assumption of equivalence between palbociclib and ribociclib/abemaciclib in this setting relate to whether each of the three trials has recruited a comparable population and administered treatments and assessments in a similar enough way that the benefits observed in these analyses would also be realised in real-world practice, as indicated by the SACT dataset that showed comparability amongst the CDK4/6 inhibitors (see section B.3.8). There were unique properties to each trial, including protocol amendments, differences in patient selection, and prior treatment history. However,

on balance the evidence collectively reinforces that each of the three CDK4/6 inhibitors confers significant PFS benefit and clinically, if not statistically, significant OS benefit.

The AEs of CDK4/6 inhibitors remain similar in terms of severity and overall frequency, but each has a slightly different profile of AE types.

B.3.16 Discussion

Evaluating the cost-effectiveness of ribociclib and abemaciclib has been a detailed process involving multiple rounds of review through NICE, with intensive consideration of the extrapolation methods used to forecast long-term health, survival benefit and cost based on available short- to medium-term trial data. The final decision of the NICE Appraisal Committee on both comparators was that they were clinically effective and could be funded on the NHS providing the manufacturer agreed to a simple PAS providing cost effectiveness versus everolimus plus exemestane as assessed using the Committee's preferred modelling assumptions. The Committee recognised the value to patients of having multiple CDK4/6 inhibitor options available, especially in respect of side-effect profile management. Although an assessment of incremental cost remains essential in the assessment of palbociclib plus fulvestrant, we feel that another clinical comparison to everolimus plus exemestane is not required and palbociclib should instead be evaluated on the basis of its equivalent efficacy to ribociclib and abemaciclib.

B.4 Cost-comparison analysis

B.4.1 Changes in service provision and management

Palbociclib and the comparators ribociclib and abemaciclib are all oral medications given in combination with fulvestrant, a solution for injection. There are no differences expected in the resources needed to administer each drug as the only administration cost incurred is for the preparation and injection of fulvestrant as discussed in section B.4.2.3.1. Drug acquisition costs between the comparators are very similar with the cost per 28-day cycle for both palbociclib and abemaciclib equal at £2,950.00 while the cost per 28-day cycle for ribociclib is £2,949.99. No meaningful differences are therefore expected in the associated drug acquisition costs.

Resource use required for monitoring patients on palbociclib is expected to be lower than for both abemaciclib and ribociclib. Treatment monitoring requirements for palbociclib are reduced as it only requires a full blood count (FBC),[7] whereas abemaciclib requires both FBC and monitoring of alanine aminotransferase (ALT) and aspartate aminotransferase (AST),[49] and ribociclib requires FBC, liver function test (LFT), serum electrolyte monitoring and electrocardiogram (ECG).[50] The frequency that patients on palbociclib require monitoring is expected to be reduced compared to both comparators, as discussed in section B.4.2.3.2.

It is expected that patients on palbociclib will experience fewer grade 3/4 AEs requiring treatment.[29] Therefore, patents receiving palbociclib are expected to consume fewer healthcare resources for the management of AEs, as will be discussed in section B.4.2.4.

No additional differences in drug-related costs or resource have been identified between the comparators. Consequently, the introduction of palbociclib into secondary care is expected to

improve service provision and decrease resource use by reducing the resources required for treatment monitoring in the proportion of patients who receive palbociclib.

B.4.2 Cost-comparison analysis inputs and assumptions

B.4.2.1 Features of the cost-comparison analysis

Cost inputs considered in the base-case analysis comprised drug acquisition costs, administration costs, monitoring costs and AE costs. Only direct medical costs were included in the model. Unit costs were sourced from the 2019/20 NHS reference costs,[51] the Monthly Index of Medical Specialties (MIMS)[52] and the British National Formulary (BNF).[53] The analyses also included the PAS applicable for palbociclib.

Costs were calculated over a lifetime horizon defined as a maximum of 40 years. This time horizon was considered long enough to capture the difference in costs of the drugs being compared as per the NICE reference case.[54] Future costs were not discounted in the base case as it is not required in a cost-comparison analysis, per the NICE cost comparison guidance.[55]

B.4.2.2 Clinical parameters – treatment duration

In accordance with its marketing authorisation, palbociclib plus fulvestrant was administered until disease progression or until unacceptable toxicity. PFS was used as a proxy for modelling treatment duration for palbociclib plus fulvestrant to align with the previous committee accepted assumption in the original company submission.

Six parametric distributions were fitted to the PALOMA-3 PFS (23rd October 2015 data-cut[56]) for the palbociclib plus fulvestrant arm following guidance from the NICE Decision Support Unit (DSU):[57] the exponential, Weibull, gompertz, log-logistic, log-normal, and generalised gamma. The model selection process included the following considerations:

- Ranking distributions based on their statistical goodness-of-fit to the observed data according to Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC);
- A visual inspection of the “observed vs predicted” plot. Kaplan-Meier (KM) were overlaid with parametric survival curves to assess the goodness-of-fit during the trial period, and during the long-term extrapolation period;
- Comparison of predicted median values and median to mean ratios.

The AIC and BIC for all models fit to the PALOMA-3 data are presented in Table 23. The best fitting distributions were the log-logistic, generalised gamma, Weibull and the log-normal. The exponential and gompertz were relatively poor in terms of statistical fit.

The extrapolated PALOMA-3 PFS means, medians, and the median to mean ratios are presented in Table 23. Although a good statistical fit, the log-logistic produced the highest mean PFS which suggested it may be less plausible as a result of this extremity due to its long tail. The medians in the observed data were similar between the majority of curves.

Table 23. PALOMA-3 PFS survival analysis measures for palbociclib plus fulvestrant

Measure	Exponential	Weibull	Log-normal	Log-logistic	Gompertz	Generalised Gamma
AIC	1501.62	1497.42	1489.91	1497.30	1500.70	1491.89
BIC	1505.47	1505.12	1497.60	1505.50	1508.40	1503.43
Estimated mean (months)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated median (months)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ratio of estimated median to mean (months)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; PFS, progression-free survival

In conclusion, given its plausible predictions and good fit statistically, the preferred base-case distribution was the log-normal distribution for the PALOMA-3 PFS data for the palbociclib plus fulvestrant arm.

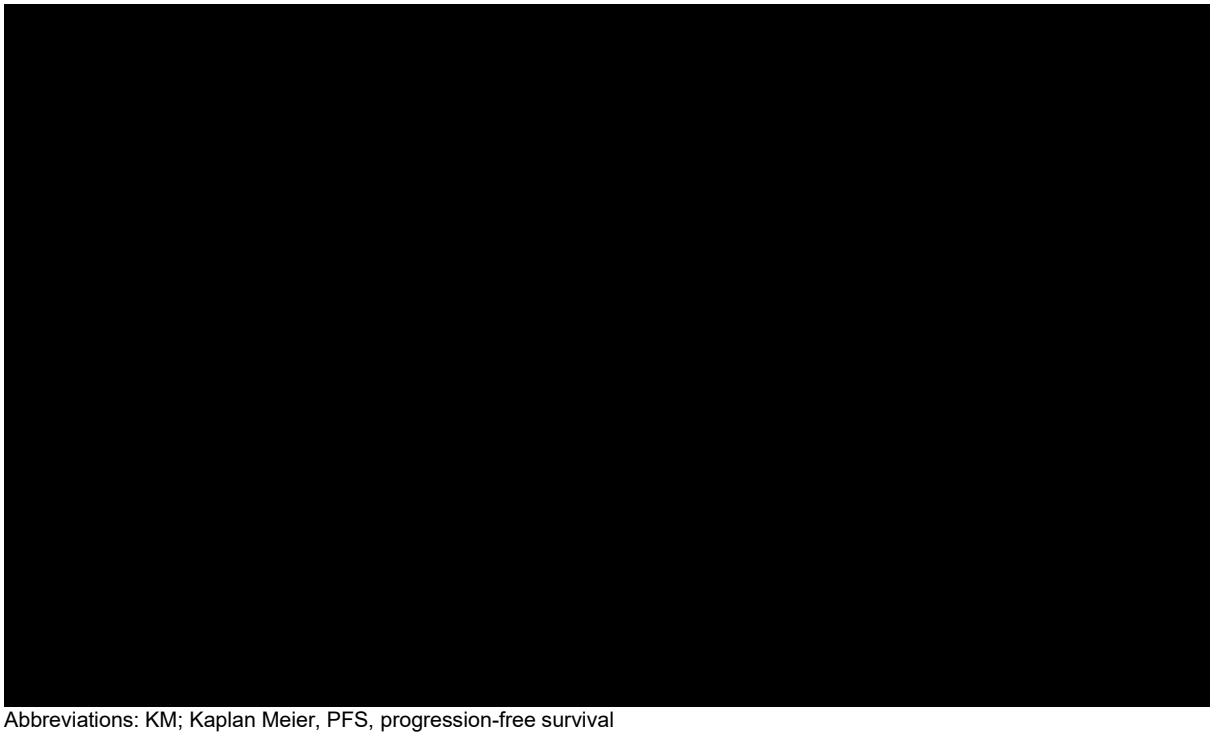
The visual fit of the log-normal distribution with respect to the PALOMA-3 KM data can be seen in Figure 10. A comparison of all the parametric models for PFS can be seen in Figure 11.

Given the clinical equivalence between the comparators, treatment duration of abemaciclib and ribociclib was assumed equal to palbociclib. Consequently, the choice of parametric model has limited impact on the results.

Figure 10. Comparison of PFS log-normal distribution with the KM curve

Abbreviations: KM, Kaplan Meier; PFS, progression-free survival

Figure 11. Base-case PFS for palbociclib plus fulvestrant showing all parametric distributions



Abbreviations: KM; Kaplan Meier, PFS, progression-free survival

B.4.2.2.1 Intervention and comparators' acquisition costs

Unit costs for drug acquisition for each comparator were sourced from the BNF and MIMS.[52, 53] Table 24 shows the pack cost for each treatment including fulvestrant. Costs for therapies, as used in the analysis, are summarized in Table 25 for palbociclib, abemaciclib, ribociclib and fulvestrant. The unit cost for fulvestrant which is given in combination with each of the comparators is also summarized in Table 25. The dose and posology of each treatment were taken from their respective Summary of Product Characteristics (SmPC).[7, 49, 50] Note that the lowest values reported in MIMS and the BNF were used for each drug in the cost comparison analysis.

Table 24. Drug acquisition costs (list prices) for each formulation of each comparator and fulvestrant

Technology	Licensed dose (mg)	Package information	Cost (£) per package	Source
Palbociclib	125 mg daily	125 mg, 21 tablets in pack	£2950.00	MIMS,[52] BNF,[53] Palbociclib SmPC[7]
Abemaciclib	150 mg twice daily	150 mg, 28 tablets per pack	£1475.00	MIMs,[52] BNF,[53] Abemaciclib SmPC[49]
Ribociclib	600 mg once daily	200 mg, 21 tablets per pack	£983.33	MIMs,[52] BNF,[53] Ribociclib SmPC[50]
Fulvestrant	500 mg at week 1, week 3 then at 1- month intervals.	250mg/5ml solution in pre-filled syringe, 2 in pack	£261.21	BNF,[53] Palbociclib SmPC,[7] Abemaciclib SmPC,[49]

Technology	Licensed dose (mg)	Package information	Cost (£) per package	Source
				Ribociclib SmPC[50]

Abbreviations: BNF, British national Formulary; mg, milligrams; MIMS, Monthly Index of Medical Specialities; SmPC, Summary of Product Characteristics

Table 25. Acquisition costs of the intervention and comparator technologies used in the cost comparison analysis

	Palbociclib	Abemaciclib	Ribociclib	Fulvestrant
Pharmaceutical formulation	125mg tablets, 21 tablets per pack [52, 53]	150mg tablets, 28 tablets per pack [52, 53]	200mg tablets. 21 tablets per pack [52, 53]	250mg/5ml solution in pre-filled syringe, 2 in pack[52, 53]
(Anticipated) care setting	Secondary care	Secondary care	Secondary care	Secondary care
Acquisition cost (excluding VAT) *	£2,950.00 (list price)[52, 53] [redacted] (PAS price)	£1,475.00 (list price)[52, 53]	£983.33 (list price)[52, 53]	£261.21 (list price)[52, 53]
Method of administration	Oral tablets	Oral tablets	Oral tablets	IM injection
Doses	125mg	150mg	600mg	500mg
Dosing frequency	Once daily for 21 consecutive days followed by 7 days off treatment[7]	Twice daily[49]	Once daily for 21 consecutive days followed by 7 days off treatment[50]	Administered on Days 1, 15, 29 and once monthly thereafter[7, 49, 50]
Dose adjustments	First dose reduction: 100mg/day. Second dose reduction: 75mg/day[7]	First dose reduction: 100mg/day. Second dose reduction: 50mg/day[49]	First dose reduction: 400mg/day. Second dose reduction: 200mg/day[50]	N/A
Average length of a course of treatment	Long term. Treatment should be continued as long as the patient is deriving clinical benefit from therapy or until unacceptable toxicity occurs [7, 49, 50]			
Average cost of a course of treatment (acquisition costs only)	Average cost over 1 year: £38,350.00 (list price). Average cost over 1 year: £[redacted] (PAS	Average cost over 1 year: £38,350.00	Average cost over 1 year: £38,349.87	Average cost over 1 year: £5,832.72
(Anticipated) number of repeat courses of treatment	Continuous	Continuous	Continuous	Continuous

Abbreviations: IM, intramuscular; mg, milligrams; ml, millilitres; N/A, not applicable; PAS, patient access scheme; VAT, Value Added Tax.

*Lowest available prices were used from the MIMS[52] and the BNF.[53] Doses and dosing frequency were taken from the SmPCs.[7, 49, 50]

B.4.2.2.2 Wastage costs

Patients receiving palbociclib or ribociclib are on treatment for 21 consecutive days followed by 7 days off treatment.[7, 50] One pack of palbociclib contains 28 days' treatment. It was

assumed that once a model cycle was started, the full cost of the pack is incurred and thus, there are no wastage costs for palbociclib. One pack of ribociclib contains 7 days' treatment and therefore the cost of three full packs are incurred during one model cycle. There is no wastage assumed for ribociclib. Patients receiving abemaciclib are on treatment continuously. One pack of abemaciclib contains 14 days' treatment and therefore the cost of two full packs of abemaciclib is incurred during one model cycle and thus there is no wastage for abemaciclib. No wastage is assumed to occur for fulvestrant.

B.4.2.3 Intervention and comparators' healthcare resource use and associated costs

B.4.2.3.1 Administration costs

Palbociclib, abemaciclib and ribociclib are oral treatments and are self-administered by the patient, therefore no administration costs are incurred. However, these treatments are given in combination with fulvestrant, a solution for injection, which does incur an administration cost. As the administration cost is equivalent for each comparator the cost comparison analysis contains the functionality to include or exclude administration costs. Please note that base-case results presented below include administration costs.

The administration cost of fulvestrant consisted of 33.3% delivered in the primary care setting and 66.7% delivered in the outpatient setting, details are provided in Table 26. This cost assumption was accepted in the original NICE appraisal for palbociclib for treatment of patients with HR-positive, HER2-negative advanced breast cancer (TA619).[6]

Table 26. Fulvestrant administration cost

Resource use	Weight	Unit cost (£)	Source
Community nurse specialist 15 minute – Cost per working hour (£55) Band 6	33.3%	£13.75	PSSRU 2021[58]
Non-Consultant Led: Follow up Attendance Non-Admitted Face to Face, Medical oncology Code 370	66.7%	£188.58	NHS reference costs 2019/20[51]
Total weighted administration cost		£130.31	

Abbreviations: NHS, National Health Service; PSSRU, Personal Social Services Research Unit

B.4.2.3.2 Monitoring costs

Palbociclib requires less intensive monitoring than both abemaciclib and ribociclib as it only requires patients to have a FBC. Both abemaciclib and ribociclib require further monitoring such as the requirement for LFT or an ECG. Treatment-related monitoring assumptions are presented in Table 27 for each treatment. The unit costs for each monitoring resource are listed in Table 28.

Table 27. Monitoring cost assumptions for each drug

Resource	Palbociclib[7]		Abemaciclib[49]		Ribociclib[50]	
	First 28-day cycle	After first cycle	First 28-day cycle	After first cycle	First 28-day cycle	After first cycle
FBC	2	4 (one every 3 months)	2	4 (one every 3 months)	2	6 (one every 2 months)

AST and ALT	N/A	N/A	2	4 (one every 3 months)	N/A	N/A
ECG	N/A	N/A	N/A	N/A	2	1 (one every 12 months)
Serum electrolytes	N/A	N/A	N/A	N/A	1	5 (one every 2.4 months)
LFT	N/A	N/A	N/A	N/A	2	6 (one every 2 months)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferases; ECG, electrocardiogram; FBC, full blood count; LFT, liver function test; N/A, not applicable.

Table 28. Unit costs of monitoring resources/services

Resource use	Unit cost (£)	Note about unit cost	Source
FBC	£2.53	DAPS05 Haematology, Directly accessed pathology services	NHS Reference costs 2019/20[51]
LFT	£1.20	Clinical biochemistry, Directly accessed pathology services	NHS Reference costs 2019/20[51]
ECG	£61.80	EY51Z Electrocardiogram Monitoring or stress testing, Directly accessed diagnostic services	NHS Reference costs 2019/20[51]
ALT and AST monitoring	£1.20	Clinical biochemistry, Directly accessed pathology services	NHS Reference costs 2019/20[51]
Serum electrolyte monitoring	£1.20	Clinical biochemistry, Directly accessed pathology services	NHS Reference costs 2019/20[51]

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferases; ECG, electrocardiogram; FBC, full blood count; LFT, liver function test; NHS, National Health Service.

B.4.2.4 Adverse reaction unit costs and resource use

It was assumed that all AEs occur concomitantly as one cost rather than cumulative costs for each event following expert opinion that indicated AEs are commonly experienced in the early cycles of treatment and so are often treated simultaneously. This approach is in line with the palbociclib plus fulvestrant NICE STA previously submitted (TA619). [6]

The most up-to-date publicly available AE data report frequencies and classifications differently for the modelled comparators. For example, all-cause grade 3/4 AEs occurring in at least 10% of patients was reported for palbociclib,[29] whilst abemaciclib reported grade 3/4 treatment emergent adverse events (TEAE) occurring in at least 10% of patients.[32] In contrast, ribociclib only reported data on grade 3/4 adverse events of special interest (AESI).[41] A complete list of the AEs used in the cost-comparison model was presented in Table 22.

Due to the difficulty in aligning criteria for AE selection across comparators, the approach taken was to use the most up-to-date publicly available data for each comparator and include all reported AEs. However, in using this approach there is the possibility that the cost of AEs for ribociclib are underestimated as the AESI occur in fewer patients than the all-cause AEs reported for palbociclib and the TEAEs reported for abemaciclib.

The costs of treatment of AEs were assumed to be independent of treatment strategy and were estimated using the 2019/20 NHS reference costs[51] and PSSRU 2021.[58] Guided by clinical expert opinion that AEs occur in early cycles, the AE cost for each comparator arm was applied in the first model cycle. The resource use costs associated with each grade 3/4 AE are listed in Table 29; all resource use assumptions were validated by clinical expert opinion. The total cost of AEs incurred by palbociclib, abemaciclib and ribociclib was £147.77, £284.13 and £589.13 respectively.

Table 29. Estimates of direct medical costs for treatment of grade 3/4 AEs

Grade 3/4 AEs	Cost (£)	Source	Notes
Neutropenia	£2.53	NHS Reference costs 2019/20: DAPS05 Haematology, Directly accessed pathology services[51]	Clinical expert opinion: grade 3+ neutropenia require repeat FBC.
Leukopenia	£0.00	Assume zero cost	Clinical expert opinion: asymptomatic event.
Infections	£681.19	NHS Reference costs 2019/20: Weighted average (based on frequency) of Non-Elective Short Stay: WH07A to WH07G - Infections or complications of procedures[51]	
Fatigue	£557.98	NHS Reference costs 2019/20: non-elective short stay: SA04K Iron deficiency Anaemia with CC score 2-5 non-elective short stay[51]	
Nausea	£1,101.87	NHS Reference costs 2019/20: Weighted average (based on frequency) of Non-Elective Short Stay: JA12D to JA12L, Malignant breast disorders[51]	
Anaemia	£607.95	NHS Reference costs 2019/20: Weighted average (based on frequency) of Non-Elective Short Stay: SA04G to SA04L, Iron deficiency anaemic with CC score 0 to 14+[51]	
Stomatitis	£485.11	NHS Reference costs 2019/20: Weighted average (based on frequency) of Non-Elective Short Stay: CB02A to CB02F with or without interventions with CC score 0-5+ Non-Malignant, Ear Nose, Mouth, throat neck disorders[51]	
Headache	£408.61	NHS Reference costs 2019/20: Weighted average (based on frequency) of Non-Elective Short Stay: AA31C to AA31E, Headache, migraine or cerebrospinal fluid leak with CC score 0 1to 11+ [51]	
Thrombocytopenia	£804.66	NHS Reference costs 2019/20: Weighted average (based on frequency) of Non-Elective Short Stay: SA12G to SA12K Thrombocytopenia[51]	
Cough	£55.00	PSSRU 2021, p. 116 of pdf, community nurse specialist (mean value = band 6)[58]	Clinical expert opinion: grade 3+ cough requires review by nurse.
Vomiting	£1,101.87	NHS Reference costs 2019/20: Weighted average (based on frequency) of Non-Elective Short Stay: JA12D to JA12L, Malignant breast disorders[51]	
Arthralgia	£507.44	NHS Reference costs 2019/20: Weighted average (based on frequency) of Non-Elective Short Stay: HD26D Musculoskeletal signs or symptoms with CC score 0 to 12+[51]	
Back pain	£507.44	NHS Reference costs 2019/20: Weighted average (based on frequency) of Non-Elective Short Stay: HD26D Musculoskeletal signs or symptoms with CC score 0 to 12+[51]	
Rash	£55.00	PSSRU 2021, p. 116 of pdf, community nurse specialist (mean value = band 6)[58]	Clinical expert opinion: grade 3+ rash requires review by nurse.

Grade 3/4 AEs	Cost (£)	Source	Notes
Decreased appetite	£92.00	PSSRU 2021, p. 90 of pdf. Community Services, Dietician, average cost per group session (one-to-one)[58]	Clinical expert opinion: grade 3+ decreased appetite requires dietician review.
Pain in extremity	£507.44	NHS Reference costs 2019/20: Weighted average (based on frequency) of Non-Elective Short Stay: HD26D Musculoskeletal signs or symptoms with CC score 0 to 12+[51]	
Dizziness	£635.43	NHS Reference costs 2019/20: Weighted average (based on frequency) of Non-Elective Short Stay: AA26 C to AA26H Muscular, Balance, Cranial or Peripheral Nerve Disorders, Epilepsy or Head Injury, with CC Score 0 to 15+[51]	
Dyspnoea	£421.74	NHS Reference costs 2019/20: Weighted average (based on frequency) of Non-Elective Short Stay: DZ19L to DZ19N Other respiratory disorders without interventions[51]	
Pyrexia	£519.66	NHS Reference costs 2019/20: Weighted average (based on frequency) of Non-Elective Short Stay: WJ07C to WJA07D Fever of unknown origin without interventions[51]	
Insomnia	£372.31	NHS Reference costs 2019/20: Weighted average (based on frequency) of Non-Elective Short Stay: AA43A to AA43B Sleep disorders, excluding deep apnoea with CC score 0 to 2+[51]	
Musculoskeletal pain	£507.44	NHS Reference costs 2019/20: Weighted average (based on frequency) of Non-Elective Short Stay: HD26D Musculoskeletal signs or symptoms with CC score 0 to 12+[51]	
AST increased	£2.53	NHS Reference costs 2019/20: DAPS05 Haematology, Directly accessed pathology services[51]	Clinical expert opinion: grade 3+ AST increased requires repeat FBC.
Dyspepsia	£137.00	PSSRU 2021, p. 90 of pdf. NHS reference costs for hospital services. Outpatient attendances weighted average of all outpatient attendances[58]	Clinical expert opinion: grade 3+ dyspepsia requires outpatient management.
Diarrhoea	£593.00	NHS Reference costs 2019/20: Weighted average (based on frequency) of Non-Elective Short Stay: FD01A to FD01J - Gastrointestinal infections non elective short stay[51]	
Abdominal pain	£137.00	NHS Reference costs 2019/20: Non-Elective Short Stay: FD05A, Abdominal pain with interventions[51]	
Constipation	£33.70	PSSRU 2021, p. 118 of pdf.[58]	Clinical expert opinion: grade 3+ constipation

Grade 3/4 AEs	Cost (£)	Source	Notes
		Mean value is average of GP per patient contact lasting 9.22 minutes, LLCI = without qualifications, excluding direct care staff costs, HLCI = with qualification costs, including direct care staff costs.	requires phone call consultation (GP)
Blood creatinine increased	£2.53	NHS Reference costs 2019/20: DAPS05 Haematology, Directly accessed pathology services[51]	Clinical expert opinion: grade 3+ blood creatinine increased require repeat FBC.
Weight decreased	£92.00	PSSRU 2021, p. 90 of pdf. Community Services, Dietician, average cost per group session (one-to-one)[58]	Clinical expert opinion: grade 3+ weight decreased requires dietician review.
Muscular weakness	£507.44	NHS Reference costs 2019/20: Weighted average (based on frequency) of Non-Elective Short Stay: HD26D Musculoskeletal signs or symptoms with CC score 0 to 12+[51]	
Lymphopenia	£0.00	Assume zero cost	Clinical expert opinion: asymptomatic event.
UTI	£137.00	PSSRU 2021, p. 90 of pdf. NHS reference costs for hospital services. Outpatient attendances weighted average of all outpatient attendances[58]	Clinical expert opinion: grade 3+ UTI require outpatient management.
Other	£0.00	Pfizer to confirm	
Pulmonary toxicity	£2,227.00	PSSRU 2021, p. 90 of pdf. NHS reference costs for hospital services. Average of non-elective inpatient stays (short stays, £827) and non-elective inpatient stays (long stays, £3,627)[58]	Clinical expert opinion: grade 3+ pulmonary toxicity requires review and hospital admission.
Hepatobiliary toxicity	£2,227.00	PSSRU 2021, p. 90 of pdf. NHS reference costs for hospital services. Average of non-elective inpatient stays (short stays, £827) and non-elective inpatient stays (long stays, £3,627)[58]	Clinical expert opinion: grade 3+ hepatobiliary toxicity requires review and hospital admission.
Renal toxicity	£2,227.00	PSSRU 2021, p. 90 of pdf. NHS reference costs for hospital services. Average of non-elective inpatient stays (short stays, £827) and non-elective inpatient stays (long stays, £3,627)[58]	Clinical expert opinion: grade renal toxicity requires review and hospital admission.
QT interval prolongation	£2,227.00	PSSRU 2021, p. 90 of pdf. NHS reference costs for hospital services. Average of non-elective inpatient stays (short stays, £827) and non-elective inpatient stays (long stays, £3,627)[58]	Clinical expert opinion: grade 3+ QT internal prolongation requires review and hospital admission.

Grade 3/4 AEs	Cost (£)	Source	Notes
Pulmonary embolism	£663.02	NHS Reference costs 2019/20: Weighted average (based on frequency) of Non-Elective Short Stay: DZ09J to DZ09Q, Pulmonary Embolus[51]	
Interstitial lung disease/pneumonitis	£2,227.00	PSSRU 2021, p. 90 of pdf. NHS reference costs for hospital services. Average of non-elective inpatient stays (short stays, £827) and non-elective inpatient stays (long stays, £3,627)[58]	Clinical expert opinion: grade 3+ interstitial lung disease/pneumonitis requires review and hospital admission.
ALT increased	£2.53	NHS Reference costs 2019/20: DAPS05 Haematology, Directly accessed pathology services[51]	Clinical expert opinion: grade 3+ ALT increased require repeat FBC.

Abbreviations: AEs, adverse events; ALT, alanine aminotransferase; AST, aspartate aminotransferases; CC, clinical coding; FBC, full blood count; GP, general practitioner; HLCI, higher limit confidence interval; LLCI, lower limit confidence interval; NHS, National Health Service; UTI, urinary tract infection

B.4.2.5 Miscellaneous unit costs and resource use

No further unit costs and resource use were identified as relevant or different between the comparator arms, given the clinical efficacy assumption.

B.4.2.6 Clinical expert validation

UK clinical expert opinion was sought to estimate and validate assumptions pertaining to the adverse event management and patient monitoring requirements, as well as using data from UK guidelines for breast cancer.

B.4.2.7 Uncertainties in the inputs and assumptions

One-way sensitivity analysis (OWSA) was carried out varying the relevant inputs between upper and lower values. The assumptions behind the OWSA parameter inputs are listed in separate Appendix I. The following inputs were varied in the OWSA:

- AE management costs
- AE incidence
- Monitoring frequency
- Monitoring costs
- PFS parametric model coefficients for the log-normal distribution

B.4.3 Results

B.4.3.1 Base-case results

The total costs over a lifetime horizon are presented for each of the interventions in Table 30. The base-case results show that total cost of palbociclib plus fulvestrant is cheaper than abemaciclib plus fulvestrant and ribociclib fulvestrant when both the list and PAS prices are used.

Table 30. Base-case results

Technology	Drug acquisition	Drug administration	Drug monitoring	AEs	Total cost	Incremental costs (palbociclib – comparator)
Palbociclib plus fulvestrant	£75,211.60 (list) [redacted] (PAS)	£2,920.48	£23.93	£147.77	£78,303.77 (list) [redacted] (PAS)	N/A
Abemaciclib plus fulvestrant	£75,211.60	£2,920.48	£35.27	£284.13	£78,451.47	-£147.70 (list) [redacted] (PAS)
Ribociclib plus fulvestrant	£75,211.37	£2,920.48	£300.19	£589.13	£79,021.16	-£717.39 (list) [redacted] (PAS)

Abbreviations: AE, adverse event; N/A, not applicable; PAS, patient access scheme.

B.4.3.2 Sensitivity and scenario analyses

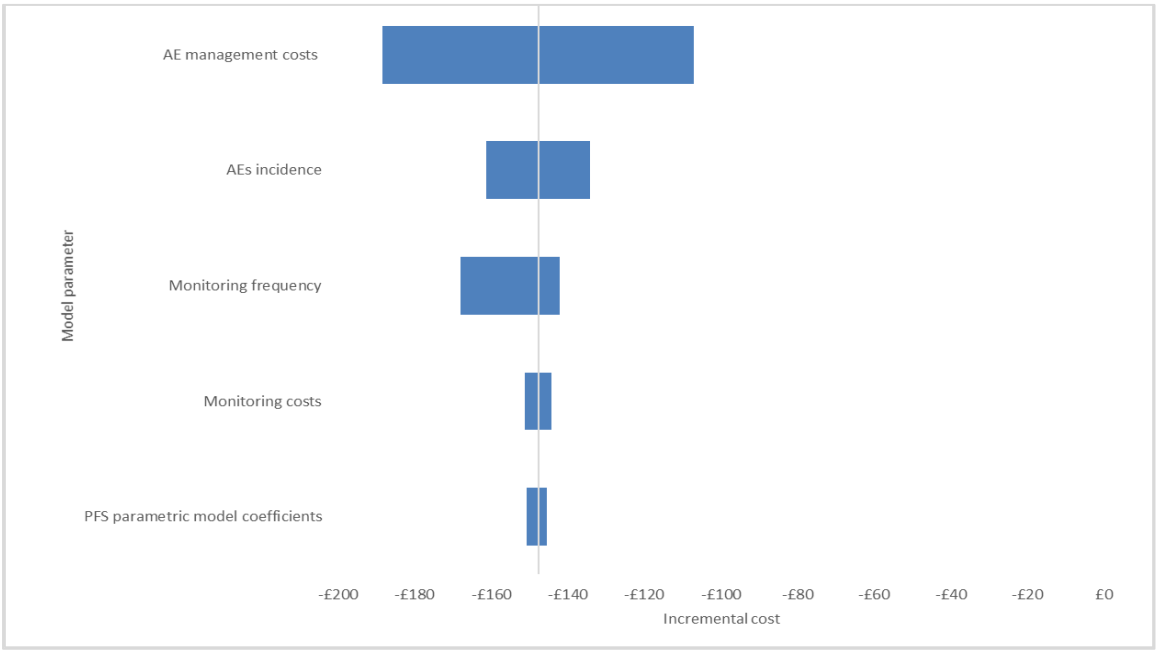
Table 31 to Table 34 present the results of the one-way sensitivity analysis. Tornado diagrams are presented in Figure 12 to Figure 15 for each comparison. For both comparisons with abemaciclib and ribociclib using the palbociclib list price or PAS price, the OWSA results did not change the conclusions dictated by the base-case results, palbociclib plus fulvestrant [redacted] to both abemaciclib plus fulvestrant and ribociclib plus fulvestrant. the results were not sensitive to changes in assumptions of the parameters included in the OWSA. Parameters that had a higher impact on the results were the assumptions around the AE management costs and monitoring frequency. Assumptions around the PFS parametric model coefficients, while showing an impact on results, were far from changing the ranking of the comparators cost (see tornados in Figure 14 and Figure 15), given that all comparators share the same time on treatment under the clinical equivalence assumption. Therefore, any changes to the PFS assumptions may change the absolute total costs, but not the ranking of them.

Table 31. OWSA results (incremental costs for palbociclib vs abemaciclib, palbociclib list price)

Model parameter	Low value	High value
Base-case incremental costs	*-£147.70*	
AE management cost	-£106.96	-£188.45
AE incidence	-£134.06	-£161.34
Monitoring frequency	-£142.03	-£167.98
Monitoring costs	-£144.30	-£151.10
PFS parametric model coefficients	-£145.50	-£150.78

Abbreviations: AE, adverse event; OWSA, one-way sensitivity analysis; PFS, progression-free survival; vs, versus

Figure 12. Tornado diagram: OWSA results (incremental costs for palbociclib vs abemaciclib, palbociclib list price)



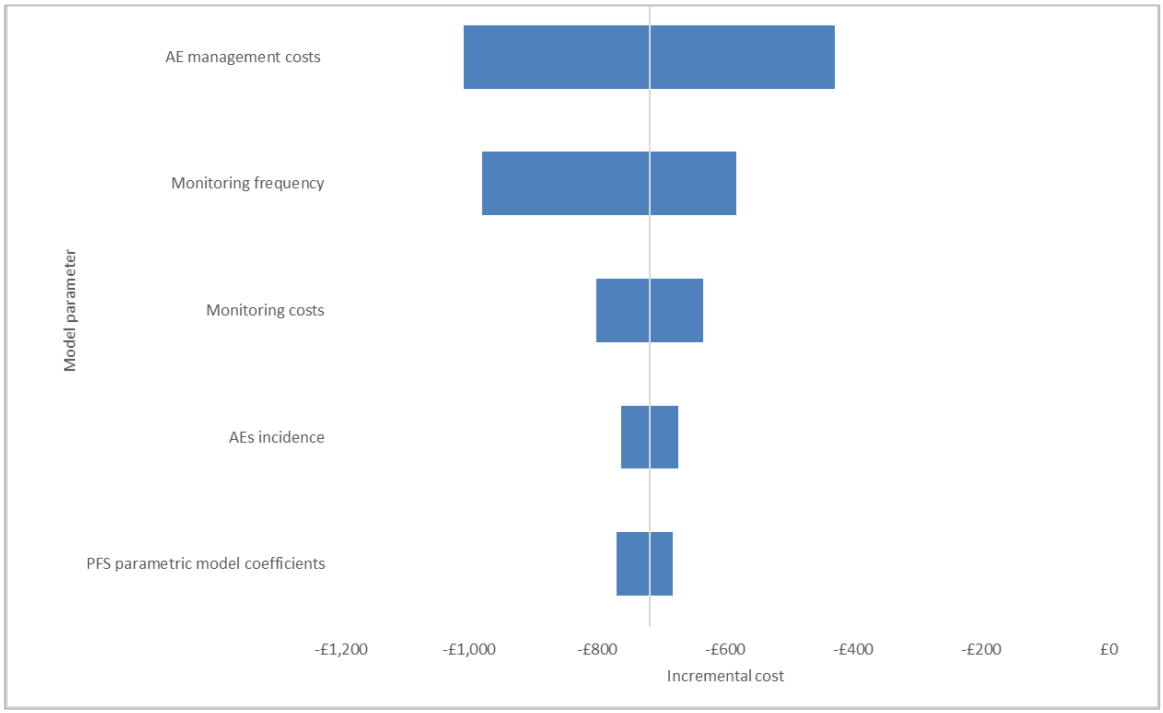
Abbreviations: AE, adverse event; OWSA, one-way sensitivity analysis; PFS, progression-free survival; vs, versus

Table 32. OWSA results (incremental costs for palbociclib vs ribociclib, palbociclib list price)

Model parameter	Low value	High value
Base-case incremental costs	*-£717.39*	
AE management costs	-£427.32	-£1,007.45
Monitoring frequency	-£582.25	-£979.25
Monitoring costs	-£634.51	-£800.27
AEs incidence	-£673.25	-£761.52
PFS parametric model coefficients	-£680.82	-£768.76

Abbreviations: AE, adverse event; OWSA, one-way sensitivity analysis; PFS, progression-free survival; vs, versus

Figure 13. Tornado diagram: OWSA results (incremental costs for palbociclib vs ribociclib, palbociclib list price)



Abbreviations: AE, adverse event; OWSA, one-way sensitivity analysis; PFS, progression-free survival; vs, versus

Table 33. OWSA results (incremental costs for palbociclib vs abemaciclib, palbociclib PAS price)

Model parameter	Low value	High value
Base-case incremental costs	[redacted]	[redacted]
PFS parametric model coefficients	[redacted]	[redacted]
AE management costs	[redacted]	[redacted]
AEs incidence	[redacted]	[redacted]
Monitoring frequency	[redacted]	[redacted]
Monitoring costs	[redacted]	[redacted]

Abbreviations: AE, adverse event; OWSA, one-way sensitivity analysis; PFS, progression-free survival; vs, versus

Figure 14. Tornado diagram: OWSA results (incremental costs for palbociclib vs abemaciclib, palbociclib PAS price)

Abbreviations: AE, adverse event; OWSA, one-way sensitivity analysis; PFS, progression-free survival; vs, versus

Table 34. OWSA results (incremental costs for palbociclib vs ribociclib, palbociclib PAS price)

Model parameter	Low value	High value
Base-case incremental costs	[redacted]	[redacted]
PFS parametric model coefficients	[redacted]	[redacted]
AE management costs	[redacted]	[redacted]
Monitoring frequency	[redacted]	[redacted]
Monitoring costs	[redacted]	[redacted]
AEs incidence	[redacted]	[redacted]

Abbreviations: AE, adverse event; OWSA, one-way sensitivity analysis; PFS, progression-free survival; vs, versus

Figure 15. Tornado diagram: OWSA results (incremental costs for palbociclib vs ribociclib, palbociclib PAS price)

[redacted]

Abbreviations: AE, adverse event; OWSA, one-way sensitivity analysis; PFS, progression-free survival; vs, versus

B.4.3.2.1 Scenario analysis

No scenario analyses were conducted.

B.4.3.2.2 Subgroup analysis

No subgroup analyses were conducted.

B.4.3.2.3 Interpretation and conclusions of economic evidence

A cost comparison analysis was developed for the economic evaluation of palbociclib plus fulvestrant versus abemaciclib plus fulvestrant and ribociclib plus fulvestrant. Given the similarities in efficacy between the comparators, only acquisition, administration, monitoring and AEs costs were considered in this analysis.

The results considered the confidential PAS in place for palbociclib and the list price for the comparators. The results showed that overall palbociclib generates less costs when compared to abemaciclib or to ribociclib. This conclusion is the same regardless of whether the PAS or list price for palbociclib is used in the cost comparison analysis. Deterministic sensitivity analyses showed that palbociclib remained the least costly option for these patients, despite changes to the inputs and assumptions.

In summary, it can be concluded that palbociclib would prove to be cost-saving for the NHS in the treatment of patients with HR-positive HER2-negative locally advanced or metastatic BC.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Palbociclib in combination with fulvestrant for treating advanced, hormone-receptor positive, HER2-negative breast cancer after endocrine therapy (review of TA619)

Clarification questions

April 2022

File name	Version	Contains confidential information	Date
ID3779 Palbociclib ERG clarification letter_CompanyResponse _04May22_(FullyRedacted)	1.0	Yes	04/05/2022

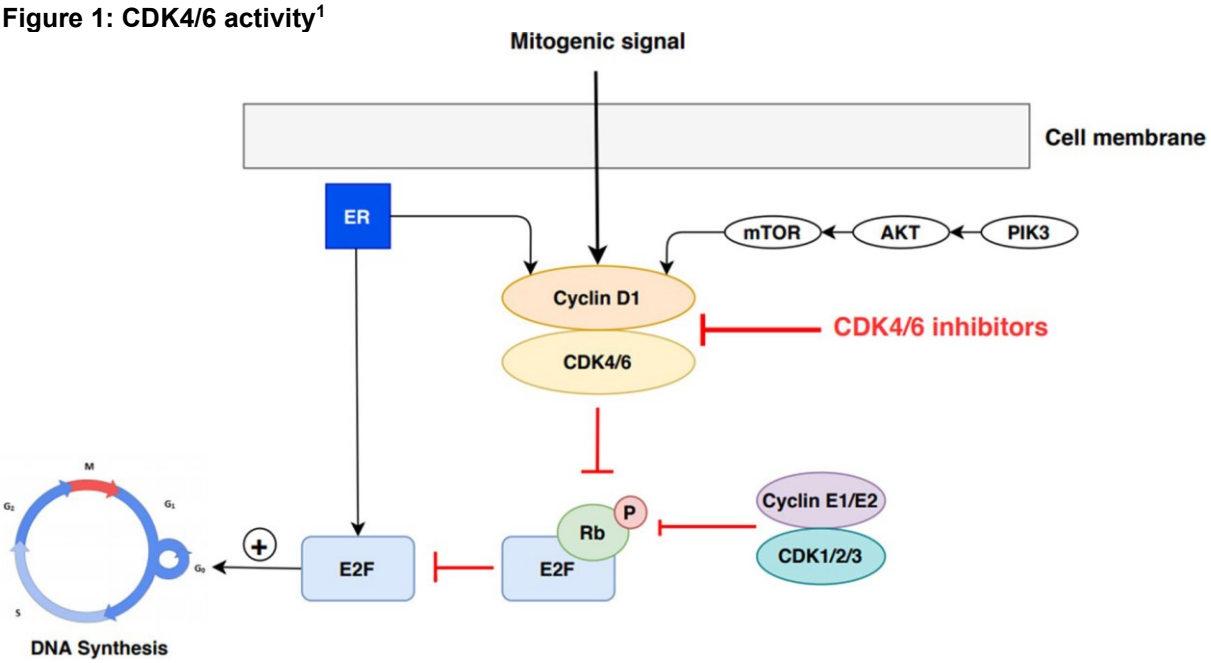
Section A: Clarification on effectiveness data

Clinical equivalence of intervention and comparators

A1. Priority question: Please provide more information about the similarities and differences between palbociclib, ribociclib and abemaciclib in respect of their pharmacokinetic properties and mechanisms of action.

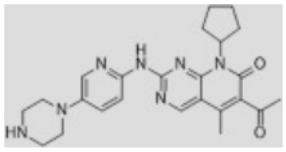
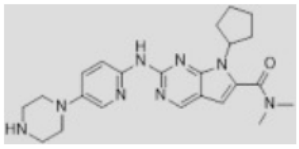
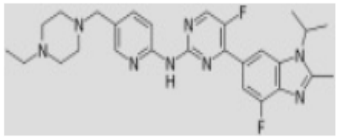
Cyclin dependent kinases (CDK) 4/6 activity regulates the cellular commitment towards mitotic cell cycling, however for this process to proceed phosphorylation, resulting in the inactivation of the retinoblastoma tumour-suppressor protein (Rb) needs to take place. A large part of the growth suppression properties of Rb is regulated by its binding to the E2 transcription factor (E2F). Phosphorylation of Rb results in a destabilising of its interactions with E2F and other transcription factors. In non-cancerous cells the phosphorylation of Rb is carried out by CDK4 or CDK6 kinases in a complex with D-type cyclin subunits followed by cyclin E/CDK2 complexes. In cancer cells this process is disrupted by the overexpression of cyclin d1, mutation of CDK4 or the loss of Rb amongst other cyclin inhibitors, resulting in how the cell responds to intracellular signalling but also the sequenced phosphorylation by the CDKs and the inactivation of Rb. Rb is the main target of all of the CDK4/6 inhibitors and it is this specificity of Rb targeting, regardless of the preclinical molecular differences, which provides their in vivo efficacy.

Figure 1: CDK4/6 activity[1]



Palbociclib was the first CDK4/6 inhibitor to demonstrate clinical efficacy[2], this was followed soon after by ribociclib which is structurally very similar to palbociclib, and abemaciclib which is less similar to the other two molecules (Table 1). *In vitro* studies using cyclin D1/CDK4 and various cyclin D/CDK6 kinases determined that both abemaciclib and ribociclib are more potent against CDK4 than CDK6 (Table 1)[3, 4]. Palbociclib, on the other hand, has similar potency when comparing its activity on cyclin D1/CDK4 and cyclin D2/CDK6[5]. In in vitro assays, abemaciclib also has modest activity, relative to its CDK4 inhibitory activity, against cyclin T1/CDK9, cyclin E2/CDK2, p25/CDK5, and p35/CDK5 (Table 1)[3]. However, the specificity of all these drugs to inhibit the proliferation of Rb-positive tumour cells but not Rb-negative tumour cells suggests that differences in the *in vitro* profiles might not contribute that much to their *in vivo* activity as it is the Rb function that leads to clinical utility. This is replicated in UK clinical practice where the three CDK4/6 inhibitors are used interchangeably with consideration given to their toxicity profile in clinical decision making.

Table 1: Comparison of the CDK4/6 inhibitor properties[3-5]

	Palbociclib	**Ribociclib**	**Abemaciclib**
			
CDK4/cyclin D1	11 nM	8 nM	2 nM
CDK4/cyclin D3	9 nM	NR	NR
CDK6/cyclin D1	NR	NR	9.9 nM
CDK6/cyclin D2	15 nM	NR	NR
CDK6/cyclin D3	NR	39 nM	NR
CDK1/cyclin B	>10 µM	>1.5 µM	1,627 nM

CDK2/cyclin A	>10 μM	>1.5 μM	NR
CDK2/cyclin E2	>10 μM	>1.5 μM	504 nM
CDK5/p25	>10 μM	>1.5 μM	355 nM
CDK5/p35	NR	>1.5 μM	287 nM
CDK7/cyclin H1	NR	>1.5 μM	3,910 nM
CDK9/cyclin T1	NR	1,510 nM	57 nM
C_{max} (nM)	200–260	4,000–7,000	500–600
t_{max} (hr)	4–8	2–5	4
$t_{1/2}$ (hr)	28	30-50	NR (21 hr for a single dose)
$K_{p,uu}$ in Mouse Models	0.01	0.12	0.03

All three CDK4/6 inhibitors are orally administered, with differing pharmacokinetics resulting in different dosing strategies. The main difference in the drugs reside in their toxicity profiles which is discussed in more detail in the company response to A2.

A2. Priority question: The company states (company submission, p53) that

> **"…the results of the new MAICs comparing palbociclib plus fulvestrant versus ribociclib plus fulvestrant and abemaciclib plus fulvestrant (for OS and PFS, see section B.3.13) confirm the clinical equivalence assumption based on the best available evidence."**

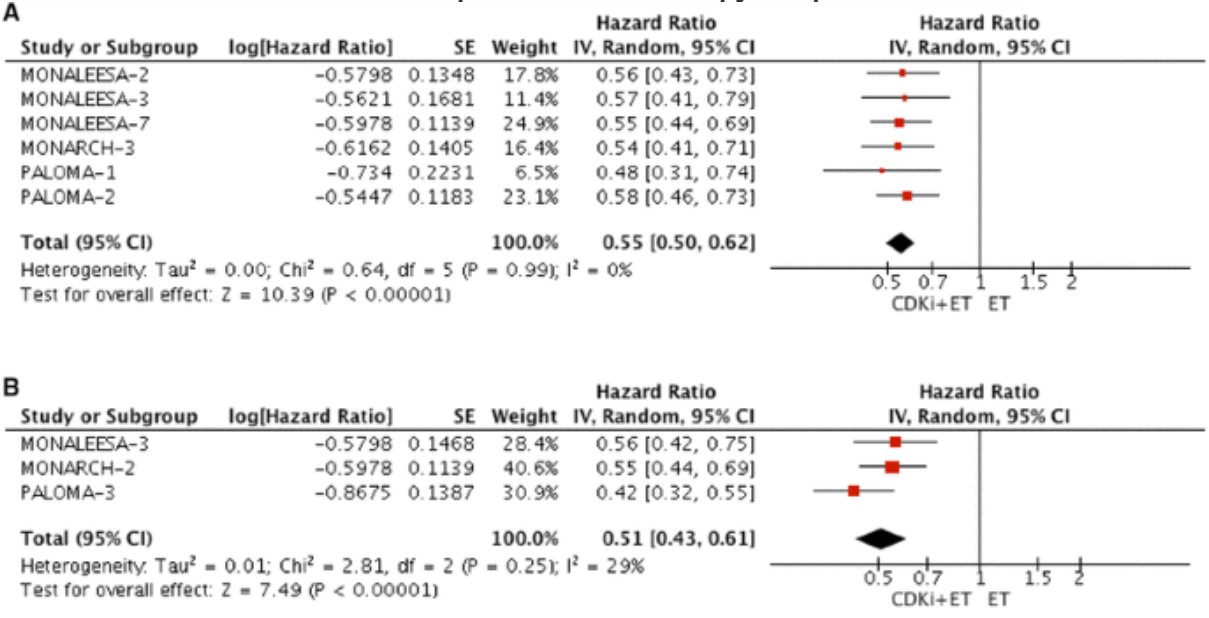
The company MAIC 95% CIs overlap 1 and are wide; these results suggest no evidence of difference. However, absence of evidence is not evidence of

absence and MAIC 95% CIs include potentially important advantages for palbociclib over the comparators, and vice versa.

Please provide any available further information to support the claims that the clinical effectiveness and safety profiles of palbociclib and ribociclib, and palbociclib and abemaciclib, are similar.

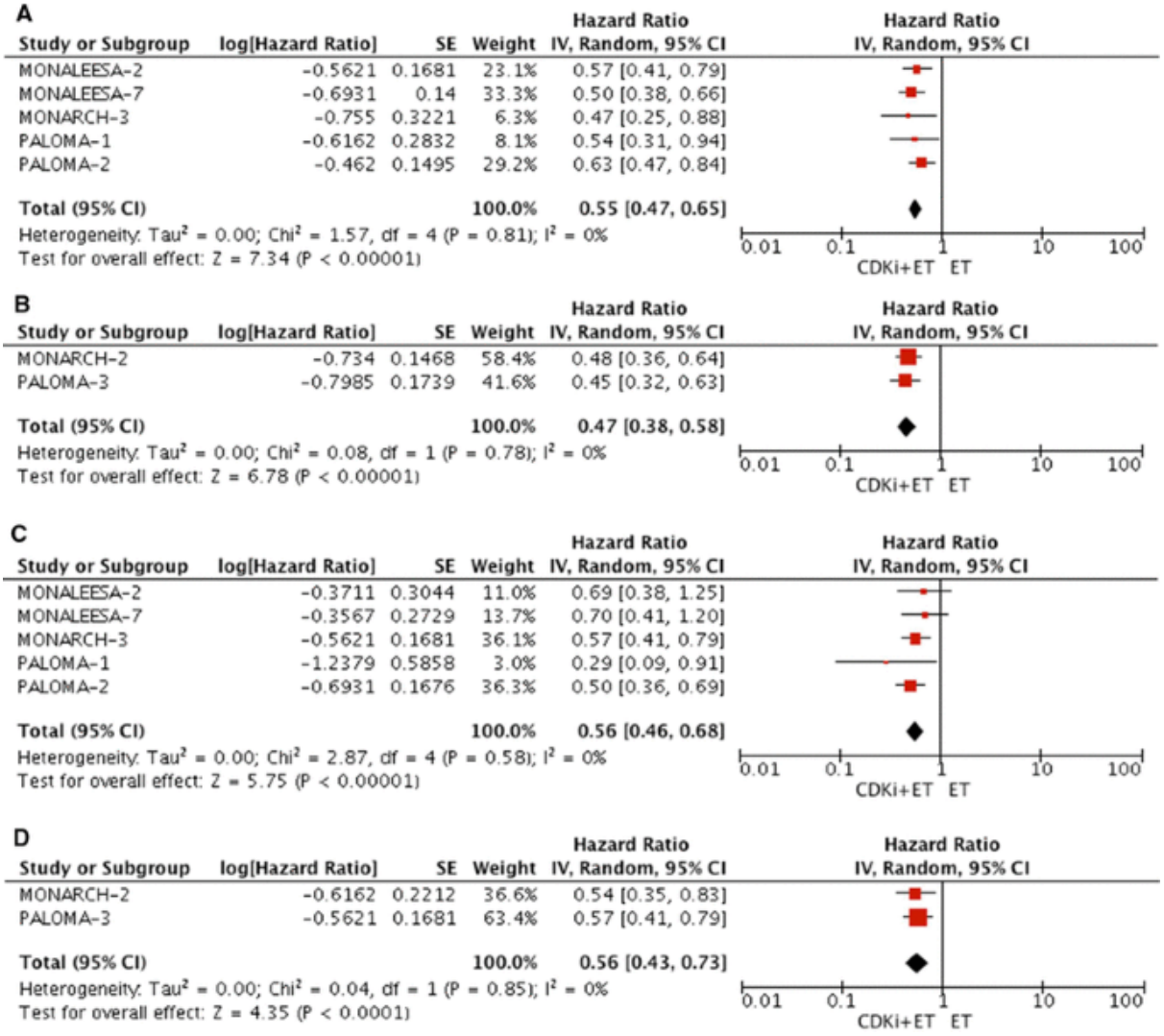
A number of reviews and meta-analyses of the CDK4/6 inhibitors in both first- and second-line indication have been undertaken and published since their launch[6-10]. Most notably in February 2020 the FDA carried out a pooled analysis of the data submitted to them[8]. The rationale for pooling the data was to examine less common subgroups and evaluate their hypothesis that being on a CDK4/6 inhibitor provides a better outcome compared to AI alone regardless of which CDK4/6 inhibitor a patient was placed on. They concluded that all subgroups derived a benefit from the addition of a CDK4/6 inhibitor to endocrine therapy irrespective of the endocrine partner or line of therapy. A meta-analysis carried out by Lin et al. in 2020 examined the different CDK4/6 inhibitors against each other comparing their efficacy and adverse event profiles[9]. Lin et al. demonstrated similar hazard ratios across the studies both in first- and second-line treatment[9]. Messina et al. 2018 also performed a meta-analysis of randomized clinical trials (RCTs) to better define the benefit and the risk of CDK4/6 inhibitors plus ET for endocrine-sensitive or endocrine-resistant population in metastatic HR+/HER2− breast cancer (Figure 2 Figure 4)[10].

Figure 2: Forest plot of hazard ratios (HRs) for progression-free survival (PFS) in eight randomized trials of CDK inhibitors plus endocrine therapy compared ET alone[10]



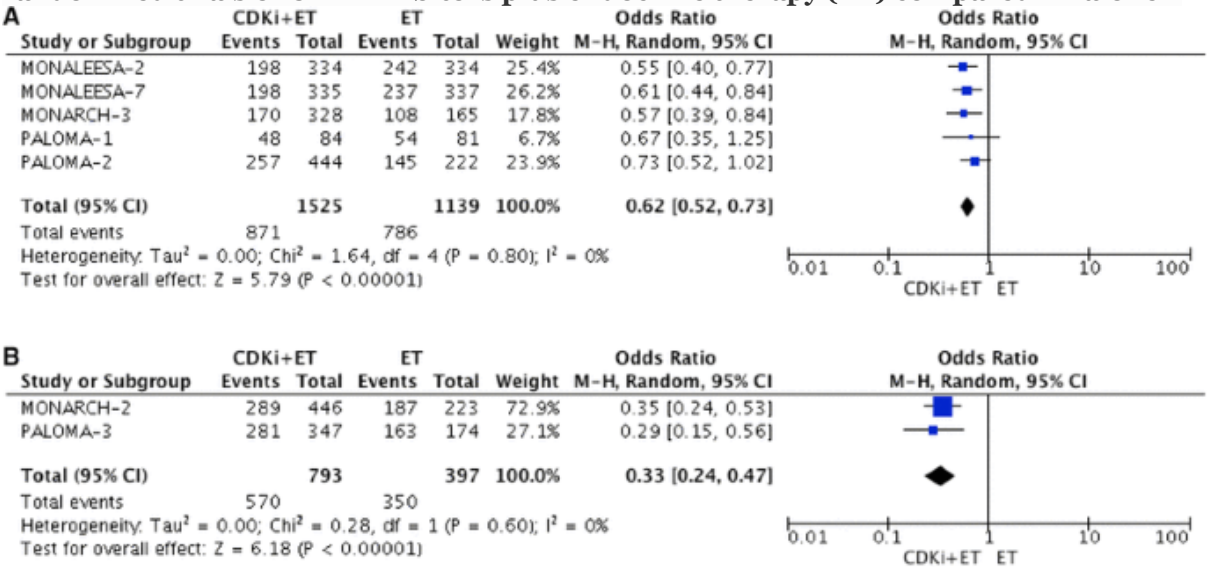
Women with advanced HR+ HER2- breast cancer: (A) endocrine-sensitive population, (B) endocrine-resistant population. Pooling HRs were computed using random-effects models. The bars indicate 95% confidence intervals.
Abbreviations: CDKi, cyclin-dependent kinase inhibitor; ET, endocrine therapy.

Figure 3: Forest plot of hazard ratios (HRs) for progression-free survival (PFS) in randomized trials of CDK inhibitors plus endocrine therapy compared ET alone[10]



Women with HR+ HER2− breast cancer with (A, B) visceral metastasis (C, D) non-visceral metastasis. Pooling HRs were computed using random-effects models. The bars indicate 95% confidence intervals.
Abbreviations: CDKi, cyclin-dependent kinase inhibitor; ET, endocrinal therapy.

Figure 4: Forest plot of Odds ratios (ORs) objective response rate (ORR) in seven randomized trials of CDK inhibitors plus endocrine therapy (ET) compared ET alone[10]



Women with HR+ HER2− breast cancer with (A) endocrine-sensitive disease (B) endocrine-resistant disease. Pooling ORs were computed using random-effects models. The bars indicate 95% confidence intervals.
Abbreviations: CDKi, cyclin-dependent kinase inhibitor; ET, endocrinal therapy; ORs, Odds ratios.

A further recent analysis in older patient populations concluded that even within these subgroups the efficacy across the three CDK4/6 inhibitors was comparable, with the main differentiator being their toxicity profiles amongst this older subgroup, replicating data from previous meta-analyses[11].

Table 2: Key efficacy and toxicity outcomes of CDK4/6 inhibitors in older patients based on available data from the pivotal trials[11]

Population	Outcome	Palbociclib	Ribociclib	Abemaciclib
Treatment naïve	PFS	PALOMA-2: 65+ years: HR 0.57 (95% CI 0.39 – 0.84)	MONALEESA-2: +AI, 65+ years: HR 0.658 (95% CI 0.466 – 0.928) MONALEESA-3 + fulvestrant, 65+ years: HR 0.597 (95% CI 0.436 – 0.818)*	MONACH-3: 65+ years: HR 0.57 (95% CI 0.36 – 0.90)
Pretreated	PFS	PALOMA-3: 65+ years: HR 0.35 (95% CI 0.19 – 9.62)	MONALEESA-3: + fulvestrant, 65+ years: HR 0.597 (95% CI 0.436 – 0.818)*	MONARCH-2: 65+ years: HR 0.620 (95% CI 0.447 – 0.860)

*The MONALEESA-3 study included treatment-naïve and pretreated patients.
Abbreviations: AI, aromatose inhibitor; CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.

The literature summarised here supports the results of the company MAIC and the assumption of equivalence included in the company submission. It should also be noted that palbociclib was statistically significant in one scenario of the submitted MAIC and therefore the assumption of clinical equivalence could be considered conservative.

As a correction, we have not considered the safety profiles of palbociclib, ribociclib and abemaciclib to be similar; in fact, all adverse events were included in the submission and costed out individually to avoid making any simplifying assumptions. The MONALEESA-3 publication (Slamon et al. 2021) reported AEs of special interest, irrespective of causality, by grouping and maximum grade (safety set)[12]. The MONARCH 2 publication (Sledge et al. 2020) limited its summary to treatment-emergent AEs occurring in 10% or more subjects (grouped as grade 3, grade 4, and all grades combined)[13]. The original manufacturer submission for palbociclib (in TA619) included a detailed AE summary taken directly from the PALOMA-3 clinical study report[14], which is difficult to compare with the publicly available AE summaries for ribociclib and abemaciclib. The AEs considered in the CS are based on the Turner 2018 publication which provided more up-to-date statistics from the planned final analysis of PALOMA-3[15]. AEs occurring with 10% or higher frequency in either arm of PALOMA-3 are reported, as well as any AEs which were reported in MONALEESA-3

and MONARCH 2, even if their relative frequency in the PALOMA-3 study was less than 10%.

We have explained in detail the safety profile selection criteria (CS, page 51), and have further highlighted important differences observed on certain AEs of lower grade:

- Neutropenia can occur with ribociclib and palbociclib, whereas abemaciclib tends to induce less frequent and lower-grade neutropenia;
- Abemaciclib frequently causes diarrhoea, with over 14% of cases at grade 3/4 above (Sledge et al. 2017)[16].

The safety findings present a strong case for making all three CDK4/6 inhibitors available on the NHS, so that treatment can be tailored, including treatment swich if necessary, to maximise patient safety, compliance, and comfort. The benefit of having multiple CDK4/6 inhibitors available was also recognised by the NICE Appraisal Committee in the post-CDF review of abemaciclib (NICE CDF Review for Abemaciclib TA725, 2021)[17].

PALOMA-3 trial

A3. Priority question: Using data from the most recent data-cuts of the PALOMA-3 trial, please provide the results of proportional hazards assessments (i.e., Schoenfeld residuals plots and tests) for the following outcomes:

- **progression-free survival**
- **overall survival**
- **time to treatment discontinuation**

For each outcome, please clarify which data-cut is the most recent.

Progression-free survival

Progression-free survival data was from the 23rd October 2015 data-cut from the PALOMA-3 trial.

The proportional hazards assumption was assessed using log cumulative hazard plots (Figure 5, parallel line suggested proportional hazards held) and Schoenfeld residual

(Figure 6, flat line with no systematic trend suggested proportional hazards held). The p-value from the proportional hazards test based on the Schoenfeld residuals is [redacted]. Based on this analysis it is observed that the assumption may not hold for the PALOMA-3 progression-free survival. Consequently, a traditional Bayesian network meta-analysis (NMA) would not have been suitable as it relies on a single hazard ratio to be applicable across the observed comparative survival in trials, which relies on proportionality.

Figure 5: Log-log plot for PFS from the PALOMA-3 trial (23rd October 2015 data-cut)

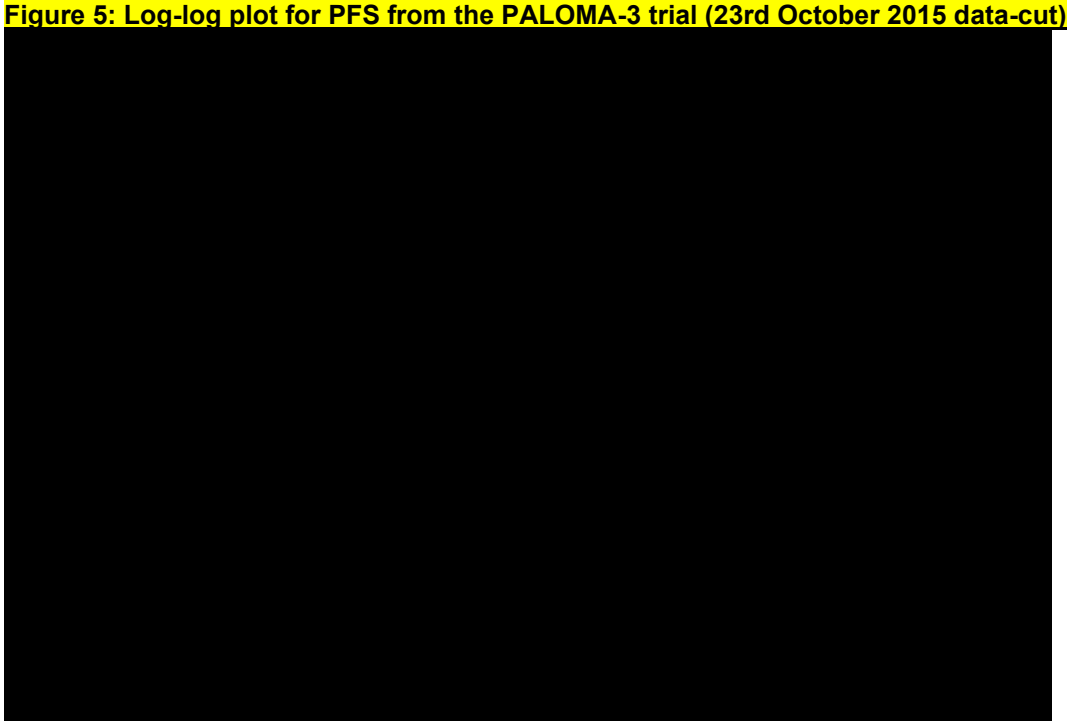
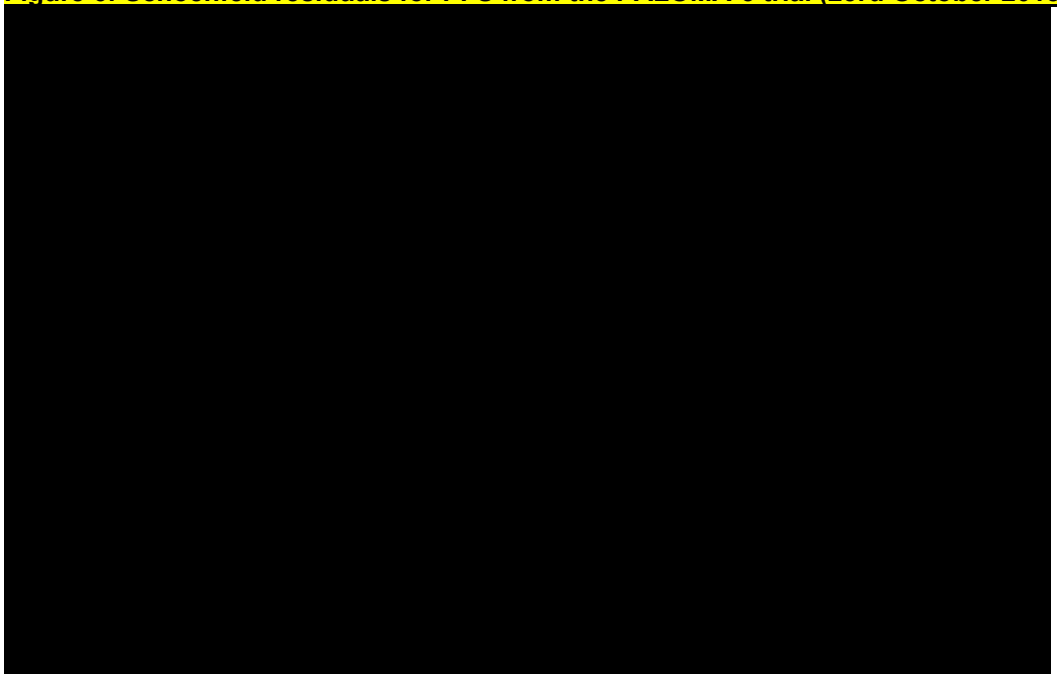


Figure 6: Schoenfeld residuals for PFS from the PALOMA-3 trial (23rd October 2015 data-cut)



Overall survival

Overall survival data was available from the 13th April 2018 data-cut from the PALOMA-3 trial.

The proportional hazards assumption was assessed using log cumulative hazard plots (Figure 7), Schoenfeld residual plots (Figure 8), and the p-value from the proportional hazards test based on the Schoenfeld residuals (p-value = [redacted]). Based on the analyses, the proportional hazards assumption is assumed to hold for PALOMA-3 for the 13th April 2018 data-cut.

Figure 7: Overall Survival PALOMA-3 trial - log-cumulative hazards plot (13th April 2018 data-cut)

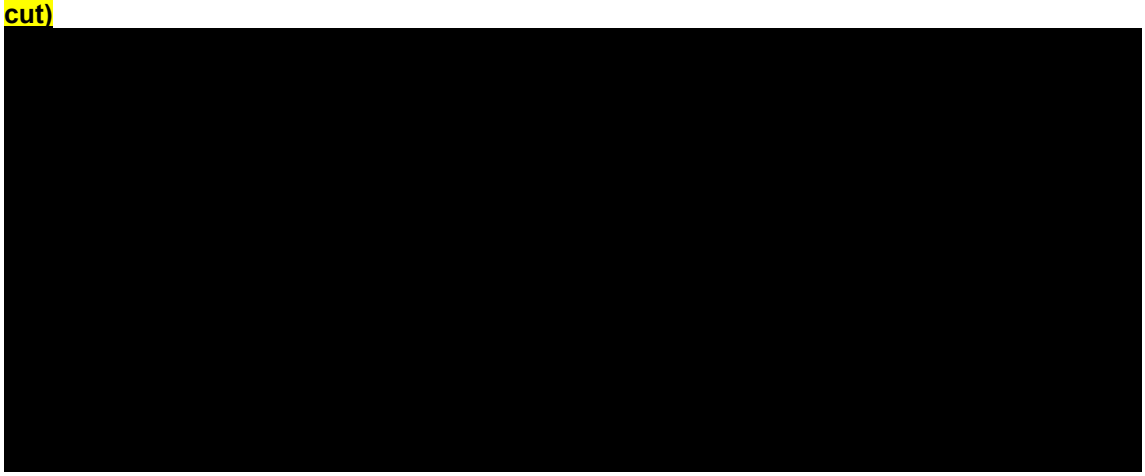
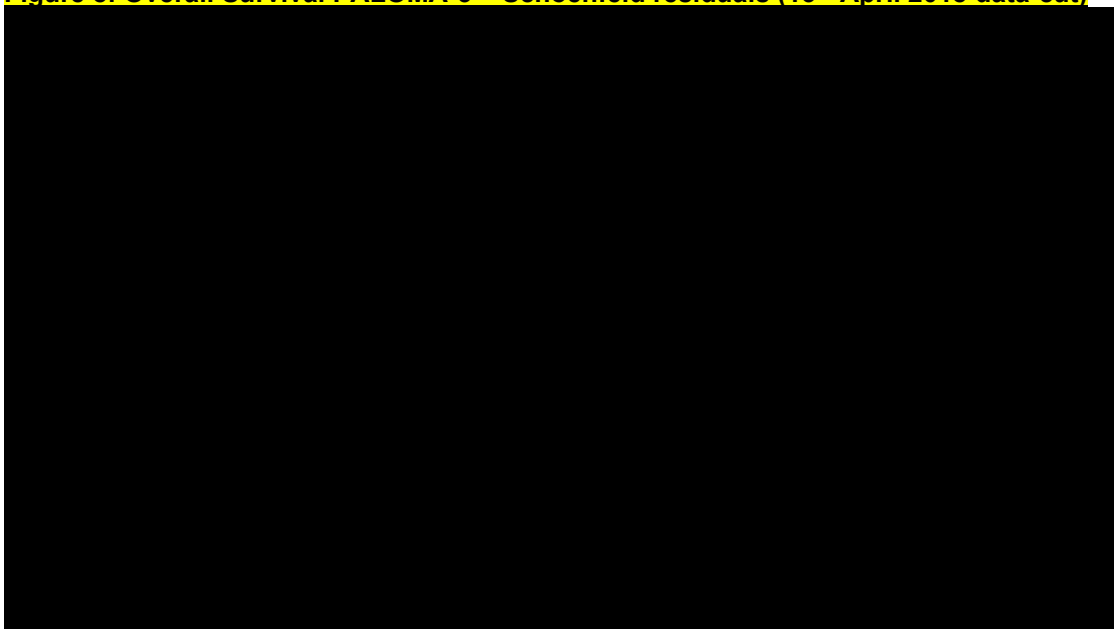


Figure 8: Overall Survival PALOMA-3 – Schoenfeld residuals (13th April 2018 data-cut)



Overall survival data was also available from a more recent data-cut from the PALOMA-3 trial, dated 17th August 2020.

The proportional hazards assumption was assessed using log cumulative hazard plots (Figure 9), Schoenfeld residual plots (Figure 10), as well as the proportional hazards test based on the Schoenfeld residuals (p-value = [redacted]). Based on the analyses, the proportional hazards assumption appears to hold for PALOMA-3 for the more recent 17th August 2020 data-cut.

Figure 9: Overall Survival PALOMA-3 trial - log-cumulative hazards plot (17th August 2020 data-cut)

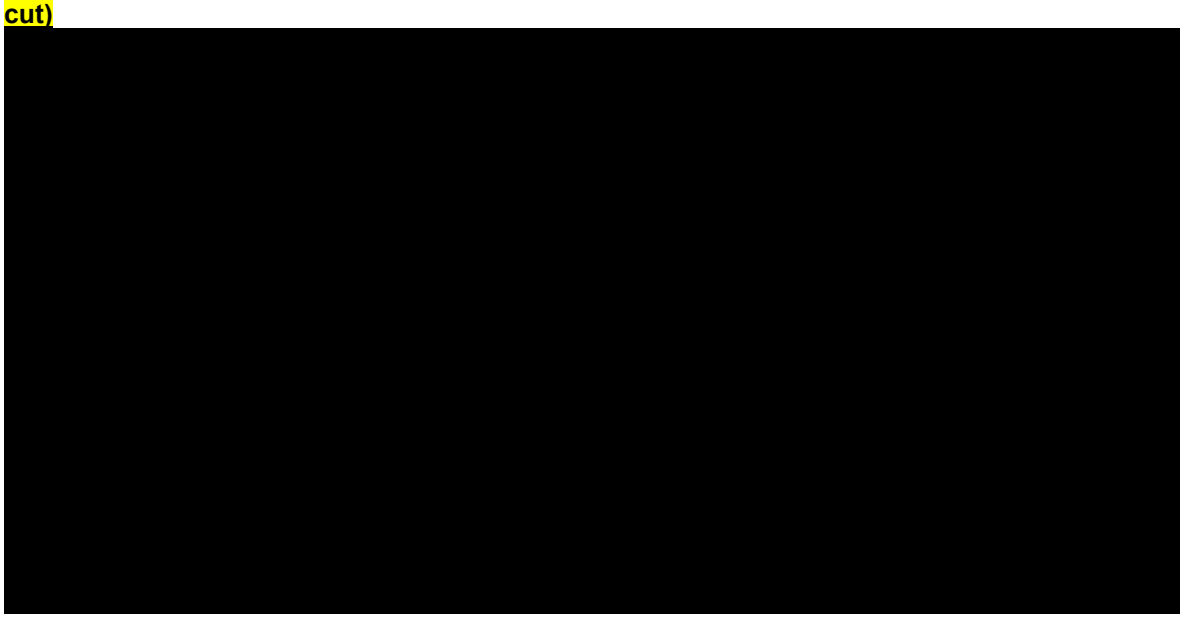
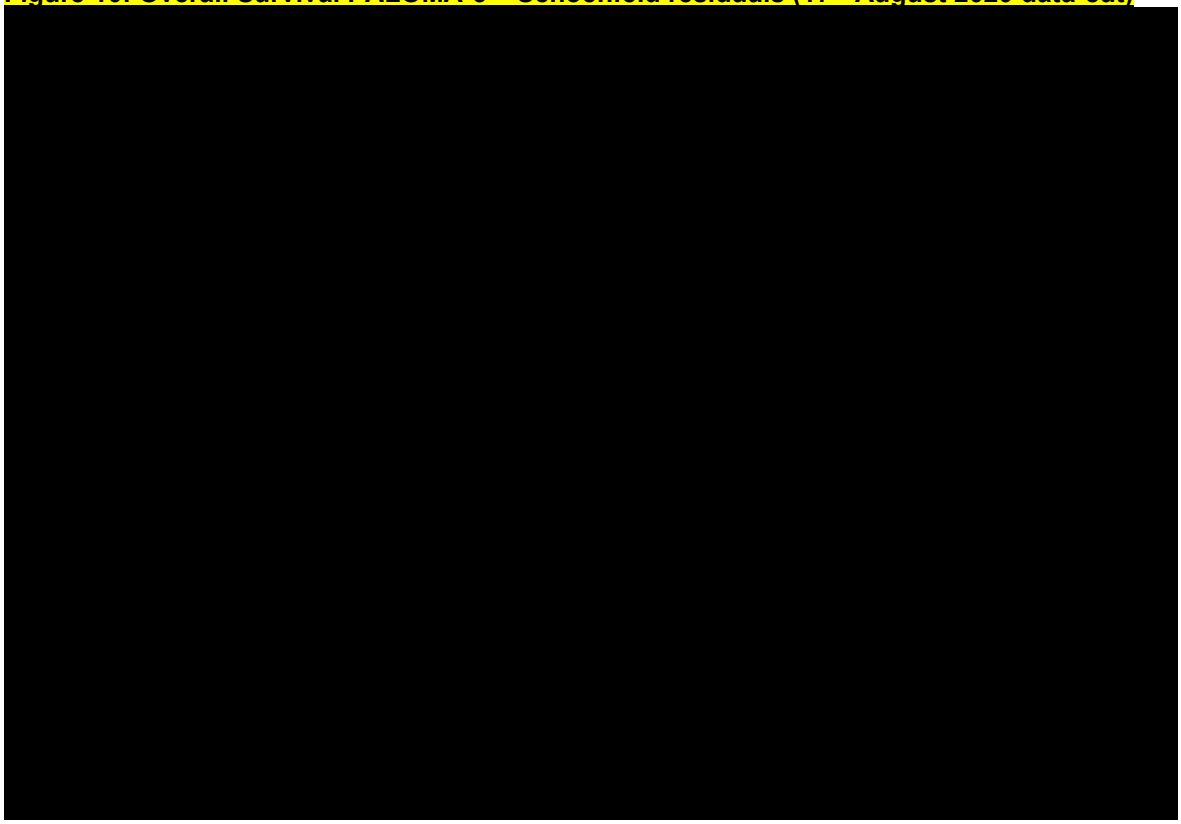


Figure 10: Overall Survival PALOMA-3 – Schoenfeld residuals (17th August 2020 data-cut)



Time to treatment discontinuation

Time to treatment discontinuation data was available for the 23rd October 2015 data-cut from the PALOMA-3 trial.

The proportional hazards assumption was assessed using log cumulative hazard plots (Figure 11), Schoenfeld residual plots (Figure 12), as well as the proportional hazards test based on the Schoenfeld residuals (p-value = [redacted]). Based on this analysis it is observed that the assumption may not hold for the PALOMA-3 time to treatment discontinuation.

Figure 11: Time to treatment discontinuation PALOMA-3 trial - log-cumulative hazards plot (23rd October 2015 data-cut)

Figure 12: Time to treatment discontinuation PALOMA-3 – Schoenfeld residuals (23rd October 2015 data-cut)

Time to treatment discontinuation data was also available from a more recent data-cut from the PALOMA-3 trial, dated 13th April 2018.

The proportional hazards assumption was assessed using log cumulative hazard plots (Figure 13), Schoenfeld residual plots (Figure 14), as well as the proportional hazards test based on the Schoenfeld residuals (p-value = [redacted]). Based on the analyses, the proportional hazards assumption is borderline for PALOMA-3 for the more recent 13th April 2018 data-cut.

Figure 13: Time to treatment discontinuation PALOMA-3 trial - log-cumulative hazards plot (13th April 2018 data-cut)

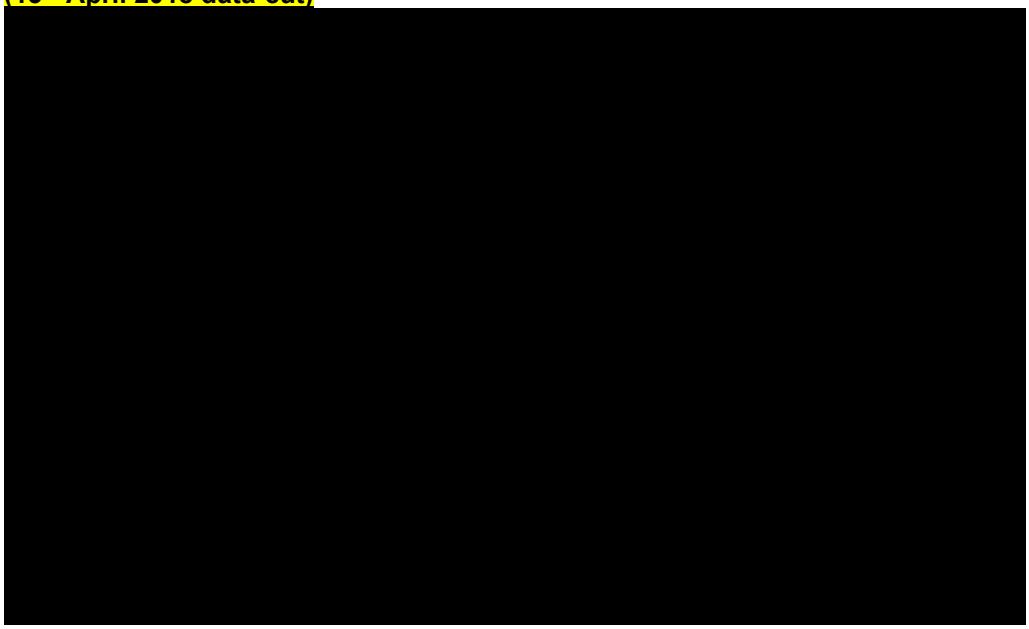


Figure 14: Time to treatment discontinuation PALOMA-3 – Schoenfeld residuals (13th April 2018 data-cut)

A4. Using data from the most recent data-cuts of the PALOMA-3 trial, please provide the number (proportion) of patients in each treatment arm who received anti-cancer treatment on disease progression. Please also specify the number (proportion) of patients by type of anti-cancer treatment received.

Table 3 presents a summary of the lines of subsequent therapy in each treatment arm from the 17th August 2020 data cut of the PALOMA-3 trial.

Table 3: Subsequent lines of treatment

	Palbociclib + Fulvestrant (n=347)				Placebo + Fulvestrant (n=174)			
	Lines of Subsequent Therapy							
Treatment,[a,b] n (%)	**Any line**	**First**	**Second**	**≥Third**	**Any line**	**First**	**Second**	**≥Third**
Any treatment received[c]	[redacted]							
Chemotherapy	[redacted]							
Eribulin	[redacted]							
Paclitaxel	[redacted]							
Capecitabine	[redacted]							
Doxorubicin	[redacted]							
Vinorelbine	[redacted]							
Gemcitabine	[redacted]							
Cyclophosphamide	[redacted]							
Carboplatin	[redacted]							
Fluorouracil	[redacted]							
Endocrine therapy	[redacted]							
Exemestane	[redacted]							
Letrozole	[redacted]							
Tamoxifen	[redacted]							
Fulvestrant	[redacted]							
mTOR kinase inhibitors	[redacted]							
Everolimus	[redacted]							
CDK4/6 inhibitors	[redacted]							
Palbociclib	[redacted]							
Ribociclib	[redacted]							
Abemaciclib	[redacted]							

Abbreviations: CDK4/6, cyclin-dependent kinase 4/6; mTOR, mechanistic target of rapamycin.
a) In >10% of patients in either treatment arm, except CDK4/6 inhibitors (all are listed).
b) Percentages calculated using the number of patients in the ITT population who received any treatment after treatment discontinuation.
c) One patient with missing/partial start/stop dates for reported follow-up therapies is not included.

Matching-adjusted indirect comparisons (MAICs)

A5. Please provide additional information about how adjustment factors for each MAIC were selected (company submission, Appendix D.2.1.1), specifically:

- list of literature reviewed
- how many clinicians were consulted
- how the individual patient data from the PALOMA-3 trial were examined
- how the rank-ordered list of treatment effect modifiers was produced for each MAIC.

List of literature reviewed: A systematic literature review up to March 2016 was conducted by Wilson et al. (2017). The list of studies is included in Appendix Table 2 of the publication. The lists of all literature reviewed, including those from the SLR updates, are provided in D.1.3.3.2 – D.1.3.3.5 of the appendix submitted by the company.

How many clinicians were consulted: Previous covariates and rankings with input from [redacted], and [redacted], for the "*progression-free survival in postmenopausal patients treated with palbociclib + letrozole and abemaciclib + letrozole/anastrozole, as initial therapy using MAIC",* were leveraged to help inform these analyses. In addition, [redacted] provided input in the selection and rankings of covariates in these analyses.

How the individual patient data from the PALOMA-3 trial were examined*:* Descriptive statistics (i.e. sample size and proportions) of all included baseline characteristics were examined prior to analysis. Imbalances between trials were assessed by calculating the percent differences in baseline characteristics between PALOMA-3 and the comparator trial. These were also examined after matching the PALOMA-3 IPD to the eligibility criteria of each comparator, and after aligning the

baseline characteristics of the remaining patients in PALOMA-3 to those of the comparator (through weighting).

How the rank-ordered list of treatment effect modifiers was produced for each MAIC: An evidence-informed process which considered both differences between trials and the strength of treatment effect on overall survival was used to produce a rank-ordered list of treatment-effect modifiers. The algorithm adjusted for one covariate at a time and estimated the comparative treatment effect of PAL+FUL versus the comparator treatment. The covariates were then ordered from largest to smallest absolute difference in comparative treatment effect relative to the unadjusted comparison. Larger differences indicate more significant treatment effect modification and differences across trials. Since differences in patient characteristics varied according to the population of the comparator trial, a rank-ordered list was produced for each comparator. The rank-ordered lists were validated by the clinical expert.

A6. Please provide results of the MAIC analyses performed using data from the PALOMA-3 and MONALEESA-3 trials which included measurable disease, prior tamoxifen, age group, ECOG performance status and ER status (CS, Appendix D.2.1.1)

The additional variables included in the scenarios requested, along with the ESS corresponding to each scenario, are provided in Table 4 below.

Table 4: Additional scenarios: ESS and variables included

	Variables	Additional Scenario 1	Additional Scenario 2	Additional Scenario 3	Additional Scenario 4	Additional Scenario 5
	N (ESS)	**48**	**49**	**52**	**56**	**62**
Variables previously included	Prior ET Setting	X	X	X	X	X
	Region	X	X	X	X	X
	Organs Involved	X	X	X	X	X
	Chemotherapy	X	X	X	X	X
	ER Status	X	X	X	X	X
	Race	X	X	X	X	X
	Disease-free interval	X	X	X	X	X
	Metastatic Site	X	X	X	X	X
Additional	Measurable disease	X	X	X	X	X
	Prior tamoxifen	X	X	X	X	

	Age group	X	X	X		
	ECOG PS	X	X			
	PR status	X				

The results of the MAIC scenarios requested are provided in Table 5 for both PFS and OS for palbociclib plus fulvestrant versus ribociclib plus fulvestrant. Some of the PFS scenarios generate [redacted] (see additional scenarios 1, 3, 4, and 5) where [redacted]. However, the ESS has been reduced considerably in these scenarios, so results should be interpreted with caution.

The results of the OS MAIC comparing palbociclib plus fulvestrant with ribociclib plus fulvestrant were [redacted], confirming the clinical equivalence assumption for palbociclib plus fulvestrant and ribociclib plus fulvestrant with regards to the OS data.

Table 5: MAIC results for additional scenarios requested, PALOMA-3 versus MONALEESA-3

Scenario	ESS	PFS HR (95% CI)	OS HR (95% CI)
Additional Scenario 1	[redacted]	[redacted]	[redacted]
Additional Scenario 2	[redacted]	[redacted]	[redacted]
Additional Scenario 3	[redacted]	[redacted]	[redacted]
Additional Scenario 4	[redacted]	[redacted]	[redacted]
Additional Scenario 5	[redacted]	[redacted]	[redacted]

Section B: Clarification on cost-effectiveness data

The ERG has no cost-effectiveness clarification questions.

Section C: Textual clarification and additional points

PALOMA-3 trial information

C1. If a clinical study report was prepared for the updated overall survival analysis (17 August 2020), please provide this.

A clinical study report was not prepared for the 17th August 2020 data cut.

C2. Figure 5 of the company submission presents an overall survival subgroup analysis stratified by most recent therapy. A proportion of patients received therapy classified as 'other' (i.e., patients who did not receive aromatase inhibitors or anti-oestrogen therapy). Please specify what 'other' treatment patients received.

Treatments classified as 'other' were defined as all treatments other than aromatose inhibitors and anti-estrogen therapy and included chemotherapy and investigational agents.

Quality assessment for included studies in the MAICs

C3. Please clarify how many independent reviewers were involved in the quality assessment of the trials in CS, Appendix D.1.7.

We can confirm that two independent reviewers were involved in the quality assessment of the trials considered in the CS.

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NDRS
NATIONAL DISEASE REGISTRATION SERVICE

NHS Digital

Palbociclib with fulvestrant for treating hormone receptor-positive, HER2-negative, advanced breast cancer – data review

Commissioned by NHS England and NHS Improvement

About the NDRS

The National Disease Registration Service (NDRS) is part of NHS Digital (NHSD). Its purpose is to collect and quality-assure high-quality, timely data on a wide range of diseases and provide robust surveillance to monitor and detect changes in health and disease in the population.

The NDRS includes:

- the National Cancer Registration and Analysis Service (NCRAS) and
- the National Congenital Anomaly and Rare Disease Registration Service (NCARDRS)

Healthcare professionals, researchers and policy makers use data to better understand population health and disease. The data is provided by patients and collected by the NHS as part of their care and support. The NDRS uses the data to help:

- understand cancer, rare diseases, and congenital anomalies
- improve diagnosis
- plan NHS services
- improve treatment
- evaluate policy
- improve genetic counselling

NDRS
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Contents

1. Executive summary

Introduction

The National Institute for Health and Care Excellence (NICE) appraised the clinical and cost effectiveness of palbociclib with fulvestrant for treating hormone receptor-positive, HER2-negative, advanced breast cancer. The appraisal committee highlighted clinical uncertainty around estimates of overall survival (OS) and duration of treatment in the evidence submission. As a result, they recommended the commissioning of palbociclib with fulvestrant through the Cancer Drugs Fund (CDF) to allow a period of managed access, supported by additional data collection to answer the clinical uncertainty.

NHS England and NHS Improvement commissioned NHS Digital (NHSD) to evaluate the real-world treatment effectiveness of palbociclib with fulvestrant in the CDF population, during the managed access period. This report presents the results of the use of palbociclib with fulvestrant in clinical practice in England, using the routinely collected Systemic Anti-Cancer Therapy (SACT) dataset.

This report, and the data presented, demonstrate the potential within the English health system to collect real-world data to inform decision-making about patient access to cancer treatments via the CDF. The opportunity to collect real-world data enables patients to access promising new treatments much earlier than might otherwise be the case, whilst further evidence is collected to address clinical uncertainty.

The NHS England and NHS Improvement and NHSD partnership for collecting and following up real-world SACT data for patients treated through the CDF in England has resulted in analysis being carried out on 99% of patients and 63% of patient outcomes reported in the SACT dataset. NHSD and NHS England and NHS Improvement are committed to providing world first, high-quality real-world data on CDF cancer treatments to be appraised alongside the outcome data from the relevant clinical trials.

Methods

NHS England and NHS Improvement's Blueteq® system was used to provide a reference list of all patients with an application for palbociclib with fulvestrant for treating hormone receptor-positive, HER2-negative, advanced breast cancer in the CDF. Patient NHS numbers were used to link Blueteq applications to NHSD's routinely collected SACT data to provide SACT treatment history.

Between 28 November 2019 and 27 February 2021, 1,265 applications for palbociclib with fulvestrant were identified in NHS England and NHS Improvement's Blueteq system. Following appropriate exclusions (see Figures 1 and 2), 1,140 unique patients

who received treatment were included in these analyses. All patients were traced to obtain their vital status using the personal demographics service (PDS).[1]

Results

1,140/1,151 (99%) unique patients with CDF applications were reported in the SACT dataset and were included in the final cohort.

Median treatment duration was 9.4 months [95% CI: 8.4, 10.8] (286 days). 65% of patients were still receiving treatment at 6 months [95% CI: 62%,68%] and 43% of patients were still receiving treatment at 12 months [95% CI: 39%, 47%].

At data cut off, 43% (N=494) of patients were identified as no longer being on treatment. Of these 494 patients:

- 21% (N=104) of patients died not on treatment
- 19% (N=96) of patients stopped treatment due to progression
- 16% (N=77) of patients who received palliative treatment did not benefit
- 15% (N=75) of patients did not have a treatment record in SACT in at least three months and are assumed to have completed treatment
- 12% (N=61) of patients who received palliative treatment did benefit
- 9% (N=45) of patients died on treatment
- 4% (N=21) of patients stopped treatment due to acute toxicity
- 2% (N=10) of patients chose to end their treatment, and
- 1% (N=4) of patients stopped treatment due to COVID and less than 1% (N=1) of patients completed treatment as prescribed.

The median OS was not reached. OS at 6 months was 88% [95% CI: 86%, 89%], 12 months OS was 75% [95% CI: 72%, 78%], OS at 18 months was 63% [95% CI: 59%, 67%].

A treatment duration sensitivity analysis was conducted for a cohort with at least 6 months' data follow-up in the SACT dataset. Results were consistent with the full analysis cohort.

Conclusion

This report analysed SACT real-world data for patients treated with palbociclib with fulvestrant for treating hormone receptor-positive, HER2-negative, advanced breast cancer in the CDF. It evaluates treatment duration, OS, treatment outcomes and subsequent treatments for all patients treated with palbociclib with fulvestrant for this indication.

Introduction

Breast cancer (ICD-10: 50) accounts for 15% of all cancer diagnoses in England. In 2018, 48,030 patients were diagnosed with Breast cancer (females 47,697, males 333).[2]

- Palbociclib 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 previous endocrine therapy only if:
    - exemestane plus everolimus is the most appropriate alternative to a cyclin-dependent kinase 4 and 6 (CDF 4/6) inhibitor and
    - the conditions in the managed access agreement for palbociclib with fulvestrant are followed.[3]

2. Background to this report

The NHS Digital and NHS England and NHS Improvement partnership on cancer data – using routinely collected data to support effective patient care

High quality and timely cancer data underpin NHS England and NHS Improvement and NHS Digital's (NHSD's) ambitions of monitoring cancer care and outcomes across the patient pathway. The objective of the NHSD and NHS England and NHS Improvement partnership on cancer data is to address mutually beneficial questions using Systemic Anti-Cancer Therapy (SACT) data collected by NHSD. This includes NHS England and NHS Improvement commissioning NHSD to produce routine outcome reports on patients receiving treatments funded through the Cancer Drugs Fund (CDF) during a period of managed access.

The CDF is a source of funding for cancer drugs in England[4]. From 29 July 2016 NHS England implemented a new approach to the appraisal of drugs funded by the CDF. The new CDF operates as a managed access scheme that provides patients with earlier access to new and promising treatments where there is uncertainty as to their clinical effectiveness. During this period of managed access, ongoing data collection is used to answer the clinical uncertainties raised by the NICE committee and inform drug reappraisal at the end of the CDF funding period[5].

NHSD analyse data derived from patient-level information collected in the NHS, as part of the care and support of cancer patients. The data is collated, maintained, quality-assured and analysed by the National Disease Registration Service (NDRS), which is part of NHSD.

NICE Appraisal Committee review of palbociclib with fulvestrant for treating hormone receptor-positive, HER2-negative, advanced breast cancer [TA619]

The NICE Appraisal Committee reviewed the clinical and cost effectiveness of palbociclib with fulvestrant (Pfizer Ltd) in treating hormone receptor-positive, HER2-negative, advanced breast cancer [TA619] and published guidance for this indication in January 2020.[6]

Due to the clinical uncertainties identified by the committee and outlined below, the committee recommended the commissioning of palbociclib with fulvestrant for treating hormone receptor-positive, HER2-negative, advanced breast cancer through the CDF for a period of 19 months, from November 2019 to June 2021.

During the CDF funding period, results from an ongoing clinical trial (PALOMA-3[7]) evaluating palbociclib with fulvestrant in the licensed indication are likely to answer the main clinical uncertainties raised by the NICE committee. Data collected from the PALOMA-3 clinical trial is the primary source of data collection.

Analysis of the SACT dataset provides information on real-world treatment patterns and outcomes for palbociclib with fulvestrant for treating hormone receptor-positive, HER2-negative, advanced breast cancer in England, during the CDF funding period. This acts as a secondary source of information alongside the results of the PALOMA-3[7].

The committee identified the key areas of uncertainty below for re-appraisal at the end of the CDF data collection. These are:

- treatment duration from the start of a patient's first treatment with palbociclib with fulvestrant
- overall survival from the start of a patient's first treatment with palbociclib with fulvestrant, and
- time on and details of subsequent therapies.

Approach

Upon entry to the CDF, representatives from NHS England and NHS Improvement, NICE, NHSD and the company (Pfizer Ltd) formed a working group to agree the Data Collection Agreement (DCA).[6] The DCA set out the real-world data to be collected and analysed to support the NICE re-appraisal of palbociclib with fulvestrant. It also detailed the eligibility criteria for patient access to palbociclib with fulvestrant through the CDF, and CDF entry and exit dates.

This report includes patients with approved CDF applications for palbociclib with fulvestrant, approved through Blueteq® and followed up in the SACT dataset collected by NHSD.

3. Methods

CDF applications – identification of the cohort of interest

NHS England and NHS Improvement collects applications for CDF treatments through their online prior approval system (Blueteq®). The Blueteq application form captures essential baseline demographic and clinical characteristics of patients needed for CDF evaluation purposes. Where appropriate, Blueteq data are included in this report.

Consultants must complete a Blueteq application form for every patient receiving a CDF funded treatment. As part of the application form, consultants must confirm that a patient satisfies all clinical eligibility criteria to commence treatment. NHSD has access to the Blueteq database and key data items such as NHS number, primary diagnosis and drug information of all patients with an approved CDF application (which therefore met the treatment eligibility criteria).

The lawfulness of this processing is covered under Article 6(1)(e) of the United Kingdom (UK) General Data Protection Regulations (GDPR) (processing is necessary for the performance of a task carried out in the public interest or in the exercise of official authority vested in the controller). NHS Digital (NHSD), through the National Disease Registration Service (NDRS), does have statutory authority to process confidential patient information (without prior patient consent) afforded through the National Disease Registries (NDRS) Directions 2021 issued to it by the Secretary of State for Health and Social Care, and has issued the NDRS Data Provision Notice under section 259 of the Health and Social Care Act 2012 regarding collection of the Blueteq data from NHS England and NHS Improvement.

NHSD collates data on all SACT prescribed drugs by NHS organisations in England, irrespective of the funding mechanism. The Blueteq extract is therefore essential to identify the cohort of patients whose treatment was funded by the CDF.

Palbociclib with fulvestrant clinical treatment criteria

- The application for palbociclib in combination with fulvestrant is made by and the first cycle of palbociclib plus fulvestrant will be prescribed by a consultant specialist specifically trained and accredited in the use of systemic anti-cancer therapy

- Patient has histologically or cytologically documented oestrogen receptor positive and HER-2 negative breast cancer

- Patient has metastatic breast cancer or locally advanced breast cancer which is not amenable to curative treatment

- Patient is male or is female and if female is either post-menopausal or if pre- or peri-menopausal has undergone ovarian ablation or suppression with LHRH agonist treatment

- Patient has an ECOG performance status of 0 or 1 or 2

- Patient has received previous endocrine therapy according to one of the three populations as set out below as these are the groups on which the NICE Technology Appraisal for palbociclib plus fulvestrant focused. Please record which population the patient falls into:

    - Patient has progressive disease whilst still receiving adjuvant or neoadjuvant endocrine therapy for early breast cancer with no subsequent endocrine therapy received following disease progression or,

    - Patient has progressive disease within 12 or less months of completing adjuvant endocrine therapy for early breast cancer with no subsequent endocrine therapy received following disease progression or,

    - Patient has progressive disease on 1st line endocrine therapy for advanced/metastatic breast cancer with no subsequent endocrine therapy received following disease progression.

- Patient has had no prior treatment with a CDK 4/6 inhibitor unless either abemaciclib (in combination with fulvestrant) or ribociclib (in combination with fulvestrant) has been stopped within 6 months of its start solely as a consequence of dose-limiting toxicity and in the clear absence of disease progression or palbociclib has been received as part of an early access scheme for the combination of palbociclib plus fulvestrant and the patient meets all the other criteria set out in this form

- Patient has had no prior treatment with fulvestrant

- Patient has had no prior treatment with everolimus

- Palbociclib will only be given in combination with a fulvestrant

- Treatment will continue until there is progressive disease or excessive toxicity or until the patient chooses to discontinue treatment, whichever is the sooner

- Treatment breaks of up to 6 weeks are allowed, but solely to allow toxicities to settle

- Palbociclib and fulvestrant will be otherwise used as set out in their Summaries of Product Characteristics (SPC)

CDF applications - de-duplication criteria

Before conducting any analysis on CDF treatments, the Blueteq data is examined to identify duplicate applications. The following de-duplication rules are applied:

1. If two trusts apply palbociclib with fulvestrant for the treatment of hormone receptor-positive, HER2-negative, advanced breast cancer for the same patient (identified using the patient's NHS number), and both applications have the same approval date, then the record where the CDF trust (the trust applying for CDF treatment) matches the SACT treating trust is selected.

2. If two trusts apply for palbociclib with fulvestrant for the treatment of hormone receptor-positive, HER2-negative, advanced breast cancer for the same patient, and the application dates are different, then the record where the approval date in the CDF is closest to the regimen start date in SACT is selected, even if the CDF trust did not match the SACT treating trust.

3. If two applications are submitted for palbociclib with fulvestrant for the treatment of hormone receptor-positive, HER2-negative, advanced breast cancer and the patient has no regimen start date in SACT capturing when the specific drug was delivered, then the earliest application in the CDF is selected.

Initial CDF cohorts

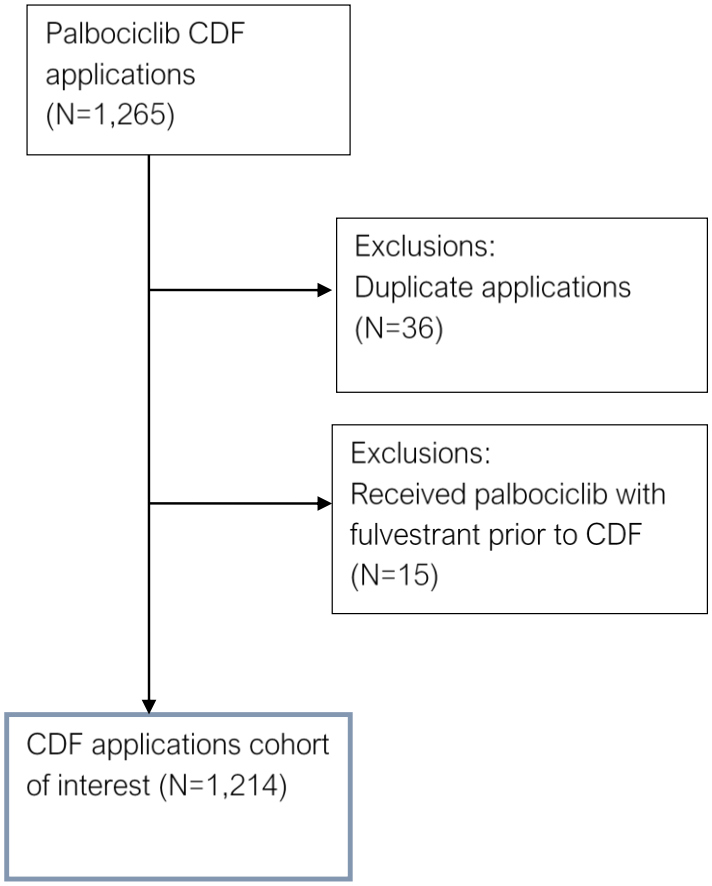
The analysis cohort is limited to the date palbociclib with fulvestrant entered the CDF for this indication, onwards. Any treatments delivered before the CDF entry date are excluded as they are likely to be patients receiving treatment via an Early Access to Medicines Scheme (EAMS) or a compassionate access scheme run by the company. These schemes may have different eligibility criteria compared to the clinical treatment criteria detailed in the CDF managed access agreement for this indication.

The CDF applications included in these analyses are from 28 November 2019 to 27 February 2021. A snapshot of SACT data was taken on 3 July 2021 and made available for analysis on 12 July 2021 and includes SACT activity up to 31 March 2021. Tracing the patients' vital status was carried out on 30 July 2021 using the Personal Demographics Service (PDS)[1].

There were 1,265 applications for CDF funding for palbociclib with fulvestrant for the treatment of hormone receptor-positive, HER2-negative, advanced breast cancer between 28 November 2019 and 27 February 2021 in the NHS England and NHS Improvement Blueteq database. Following de-duplication this relates to 1,229 unique

patients. Fifteen patients were excluded as they received palbociclib with fulvestrant prior to the drug being available through the CDF.

Figure 1. Derivation of the cohort of interest from all CDF (Blueteq) applications made for palbociclib with fulvestrant for the treatment of hormone receptor-positive, HER2-negative, advanced breast cancer between 28 November 2019 and 27 February 2021



Linking CDF cohort to SACT

NHS numbers were used to link SACT records to CDF applications for palbociclib with fulvestrant in NHS England and NHS Improvement's Blueteq system. Information on treatments in SACT were examined to ensure the correct SACT treatment records were matched to the CDF application; this includes information on treatment dates (regimen, cycle and administration dates) and primary diagnosis codes in SACT.

Addressing clinical uncertainties

Treatment duration

Treatment duration is calculated from the start of a patient's treatment to their last known treatment date in SACT.

Treatment start date is defined as the date the patient started their CDF treatment. This date is identified as the patient's earliest treatment date in the SACT dataset for the treatment of interest. Data items[8] used to determine a patient's earliest treatment date are:

- start date of regimen – SACT data item #22
- start date of cycle – SACT data item #27, and
- administration date – SACT data item #34.

The earliest of these dates is used as the treatment start date.

The same SACT data items (#22, #27, #34)8 are used to identify a patient's final treatment date. The latest of these three dates is used as the patient's final treatment date.

Additional explanation of these dates is provided below:

Start date of regimen

A regimen defines the drugs used, their dosage and frequency of treatment. A regimen may contain many cycles. This date is generally only used if cycle or administration dates are missing.

Start date of cycle

A cycle is a period of time over which treatment is delivered. A cycle may contain several administrations of treatment, after each treatment administration, separated by an appropriate time delay. For example; a patient may be on a 3-weekly cycle with treatment being administered on the 1st and 8th day, but nothing on days 2 to 7 and days 9 to 20. The 1st day would be recorded as the "start day of cycle". The patient's next cycle would start on the 21st day.

Administration date

An administration is the date a patient is administered the treatment, which should coincide with when they receive treatment. Using the above example, the administrations for a single 3-week cycle would be on the 1st and 8th day. The next administration would be on the 21st day, which would be the start of their next cycle.

The interval between treatment start date and final treatment date is the patient's time on treatment.

All patients are then allocated a 'prescription length', which is a set number of days added to the final treatment date to allow for the fact that they are effectively still 'on treatment' between administrations. The prescription length should correspond to the typical interval between treatment administrations.

If a patient dies between administrations, then their censor date is their date of death and these patients are deemed to have died on treatment unless an outcome summary is submitted to the SACT database confirming that the patient ended treatment due to disease progression or toxicity before death.

Palbociclib with fulvestrant is administered orally, treatment is generally prescribed in a healthcare facility and healthcare professionals are able to confirm that the prescribing of treatment has taken place on a specified date. A duration of 39-days (if within the first month of commencing treatment) or 28-days has been added to the final treatment date for all patients; this represents the duration from a patient's last cycle to their next[9]. Palbociclib with fulvestrant is a 28-day cycle consisting of one administration of 28 tablets.

Treatment duration is calculated for each patient as:

Treatment duration (days) = (Final treatment date – Treatment start date) + prescription length (days). This date would be the patients censored date, unless a patient dies in between their last treatment and the prescription length added, in this case, the censored date would be the patients date of death.

Once a patient's treatment duration has been calculated, the patient's treatment status is identified as one of the following:

No longer receiving treatment (event), if:

- the patient has died
- the outcome summary, detailing the reason for stopping treatment has been completed:
    - SACT v2.0 data item #41
    - SACT v3.0 data item #58 - #61
- there are no further SACT records for the patient following a three-month period.

If none of the above apply, the patient is assumed to still be on treatment and is censored.

Overall survival (OS)

OS is calculated from the CDF treatment start date, not the date of a patient's cancer diagnosis. Survival from the treatment start date is calculated using the patient's earliest treatment date, as described above, and the patient's date of death or the date the patient was traced for their vital status.

All patients in the cohort of interest are submitted to the PDS to check their vital status (dead or alive). Patients are traced before any analysis takes place. The date of tracing is used as the date of follow-up (censoring) for patients who have not died.

OS is calculated for each patient as the interval between the earliest treatment date where a specific drug was given to the date of death or date of follow-up (censoring).

OS (days) = Date of death (or follow up) - treatment start date

The patient is flagged as either:

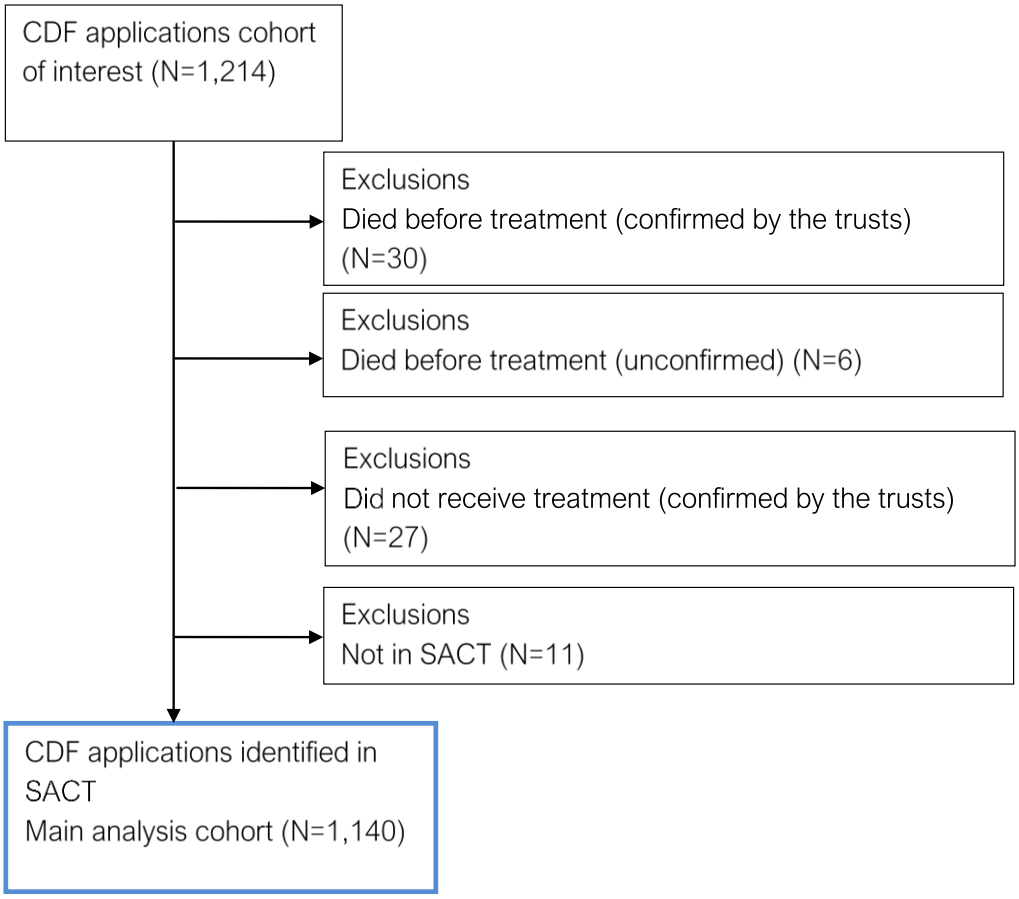
- dead (event):
    - at the date of death recorded on the PDS.
- alive (censored):
    - at the date patients were traced for their vital status as patients are confirmed as alive on this date.

4. Results

Cohort of interest

Of the 1,214 applications for CDF funding for palbociclib with fulvestrant for the treatment of hormone receptor-positive, HER2-negative, advanced breast cancer, 27 patients did not receive treatment, 36 patients died before treatment and 11 patients were missing from SACT[a] (see Figure 2).

Figure 2. Matched cohort - SACT data to CDF (Blueteq®) applications for palbociclib with fulvestrant for the treatment of hormone receptor-positive, HER2-negative, advanced breast cancer between 28 November 2019 and 27 February 2021



[a] Of the 27 patients that did not receive treatment, all were confirmed by the relevant trust by the NHSD data liaison team. Of the 36 patients that died before treatment, 30 were confirmed by the relevant trust by the NHSD data liaison team, 6 deaths were not confirmed by the trust as a death before treatment.

A maximum of 1,151 palbociclib with fulvestrant records are expected in SACT for patients who were alive, eligible and confirmed to have commenced treatment (Figure 2). 99% (1,140/1,151) of these applicants for CDF funding have a treatment record in SACT

Completeness of SACT key variables

Table 1 presents the completeness of key data items required from SACT. Completeness is 100% for primary diagnosis, date of birth, gender and treatment dates. Performance status at the start of regimen is 81% complete.

Table 1. Completeness of key SACT data items for the Palbociclib with fulvestrant cohort (N=1,140)

Variable	Completeness (%)
Primary diagnosis	100%
Date of birth (used to calculate age)	100%
Sex	100%
Start date of regimen	100%
Start date of cycle	100%
Administration date	100%
Performance status at start of regimen	81%

Table 2 presents the completeness of regimen outcome summary. A patient's outcome summary, detailing the reason why treatment was stopped, is only captured once a patient has completed their treatment. Therefore, the percentage completeness provided for outcome summary is for records where we assume treatment has stopped and an outcome is expected. Outcomes are expected if a patient has died, has an outcome in SACT stating why treatment has ended or has not received treatment with palbociclib with fulvestrant in at least three months[9]. These criteria are designed to identify all cases where a patient is likely to have finished treatment. Based on these criteria, outcomes are expected for 494 patients. Of these, 310 (63%) have an outcome summary recorded in the SACT dataset.

Table 2. Completeness of outcome summary for patients that have ended treatment (N=494)

Variable	Completeness (%)
Outcome summary of why treatment was stopped	63%

Completeness of Blueteq key variables

Table 3. Completeness of key data items required from Blueteq. Previous endocrine therapy is 100% complete (1,140/1,140).

Variable	Completeness (%)
Previous endocrine therapy	100%

Patient characteristics

The median age of the 1,140 patients receiving palbociclib with fulvestrant for the treatment of hormone receptor-positive, HER2-negative, advanced breast cancer was 66 years. The median age in females and males was 66 and 72.5 years respectively.

Table 4. Patient characteristics (N=1,140)

Patient characteristics[b]			
		N	%
Sex	Female	1,128	99%
	Male	12	1%
Age	<40	17	1%
	40 to 49	78	7%
	50 to 59	252	22%
	60 to 69	334	29%
	70 to 79	342	30%
	80+	117	10%
Performance status	0	344	30%
	1	474	42%
	2	106	9%
	3	2	Less than 1%
	4	0	0%
	Missing	214	19%

[b] Figures may not sum to 100% due to rounding.

Blueteq data items

Table 5 shows the distribution of Blueteq data items with 52% (N=596) of patients having progressive disease on 1st line endocrine therapy, 42% (N=480) of patients having progressive disease whilst still receiving adjuvant or neoadjuvant endocrine therapy and 6% (N=64) of patients have progressive disease within 12 months or less of completing adjuvant endocrine therapy.

Table 5. Distribution of key Blueteq data items (N=1,140)

Blueteq data items[c]		N	%
Previous endocrine therapy	progressive disease on 1st line endocrine therapy for advanced/metastatic breast cancer with no subsequent endocrine therapy received following disease progression	596	52%
	progressive disease whilst still receiving adjuvant or neoadjuvant endocrine therapy for early breast cancer with no subsequent endocrine therapy received following disease progression	480	42%
	progressive disease within 12 or less months of completing adjuvant endocrine therapy for early breast cancer with no subsequent endocrine therapy received following disease progression	64	6%

[c] Figures may not add to 100% due to rounding.

Time to subsequent treatments in SACT

240/1,140 (21%) unique patients treated with palbociclib with fulvestrant in the CDF have subsequent therapies recorded in the SACT dataset, received after the patient's last palbociclib with fulvestrant cycle. This includes all patients regardless of whether they have completed treatment or not.

240/494 (49%) of patients who have since completed treatment with palbociclib with fulvestrant went on to receive a subsequent therapy.

Table 6 reports regimens prescribed after palbociclib with fulvestrant, as recorded in the SACT dataset, some patients have more than one subsequent therapy, these regimens are shown in Table 7.

The median time from a patient's last palbociclib with fulvestrant cycle in SACT to their next treatment was 40.5 days[d].

The median time from a patient's first palbociclib with fulvestrant cycle in SACT to their next treatment was 141 days.

Distribution of subsequent treatments in SACT

Table 6. Distribution of first treatments prescribed after a patient's last palbociclib with fulvestrant cycle (N(Patients)=240)[e,f]

Regimen	Number of subsequent treatments
Capecitabine	119
Paclitaxel	52
Abemaciclib + fulvestrant	12
Everolimus	8
Eribulin	7
Vinorelbine	7
Epirubicin	5

[d] If a patient has > 1 subsequent regimen recorded in SACT, time to next treatment only includes regimen immediately after palbociclib with fulbestrant.
[e] Some patients will have received more than one subsequent therapy. Table 6 lists therapies prescribed immediately after a patient's last palbociclib with fulbestrant cycle. Subsequent therapies could be related to a second primary tumour.
[f] These data have not been validated/confirmed with trusts or by the NHSD data liaison team.

Regimen	Number of subsequent treatments
Everolimus + exemestane	4
Abemaciclib	3
Capecitabine + vinorelbine	3
Cyclophosphamide + epirubicin	3
Nab-paclitaxel	3
Docetaxel + pertuzumab + trastuzumab	2
Fulvestrant + ribociclib	2
Hormones	2
Pertuzumab + trastuzumab	2
Trial	2
Carboplatin	1
Carboplatin + gemcitabine	1
Carboplatin + paclitaxel	1
Trastuzumab emtansine	1
Total number of subsequent treatments	240

Table 7. Distribution of further lines of therapy following a patient's palbociclib with fulvestrant cycle (N(Patients)=240)[g,h]

Regimen	Number of subsequent treatments
Paclitaxel	14
Capecitabine	11
Vinorelbine	4
Epirubicin	3
Eribulin	3

[g] Some patients will have received more than one subsequent therapy. Table 7 lists further lines of therapies prescribed after a patient's last palbociclib with fulvestrant cycle in SACT. Subsequent therapies could be related to a second primary tumour.

[h] These data have not been validated/confirmed with trusts or by the NHSD data liaison team.

Regimen	Number of subsequent treatments
Pertuzumab + trastuzumab	3
Everolimus	2
Trial	2
Capecitabine + vinorelbine	1
Carboplatin	1
Carboplatin + gemcitabine	1
Cyclophosphamide + epirubicin	1
Cyclophosphamide + epirubicin + fluorouracil	1
Docetaxel	1
Everolimus + exemestane	1
Fulvestrant + ribociclib	1
Olaparib	1
Ribociclib	1
Trastuzumab emtansine	1
Total number of subsequent treatments	53

Treatment duration

Of the 1,140 patients with CDF applications, 494 (43%) were identified as having completed treatment by 31 March 2021 (latest follow up in SACT dataset). Patients are assumed to have completed treatment if they have died, have an outcome summary recorded in the SACT dataset or they have not received treatment with palbociclib with fulvestrant in at least three months (see Table 12). The median follow-up time in SACT was 5.5 months (167 days). The median treatment duration follow-up is the patients' median observed time from the start of their treatment to their last treatment date in SACT + prescription length.

Presently, 94% (N=132) of trusts submit their SACT return to the submission portal two months after the month's treatment activity has ended; this provides a maximum follow-up period of 16 months. 6% (N=9) of trusts submit their SACT return to the submission portal one month after the month's treatment activity has ended; this provides a maximum follow-up period of 17 months. SACT follow-up ends 31 March 2021.

Table 8. Breakdown by patients' treatment status[i,j,k]

Patient status	Frequency (N)	Percentage (%)
Patient died – not on treatment	244	21%
Patient died – on treatment	45	4%
Treatment stopped	205	18%
Treatment ongoing	646	57%
Total	1,140	100%

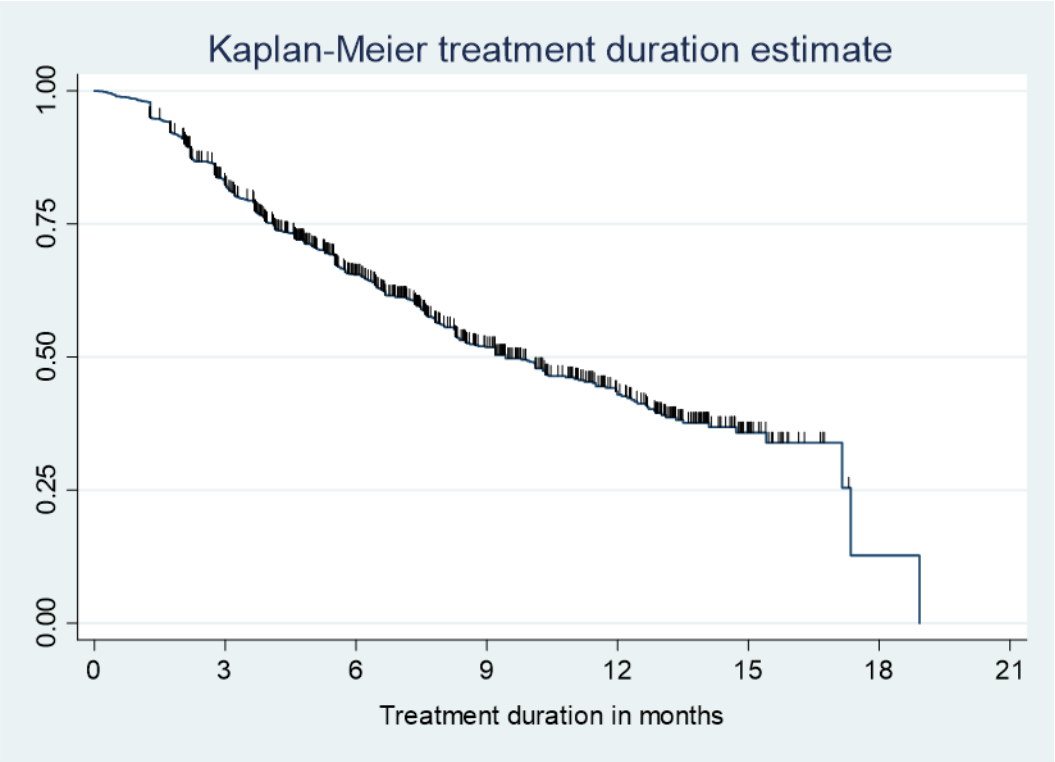
[i] Figures may not sum to 100% due to rounding.
[j] Table 12 presents the outcome summary data reported by trusts. This includes patients from Table 8 who 'died on treatment', 'died not on treatment' and 'stopped treatment'.
[k] 'Deaths on treatment' and 'deaths not on treatment' are explained in the methodology paper available on the SACT website: http://www.chemodataset.nhs.uk/nhse_partnership/.

Table 9. Treatment duration at 6 and 12-month intervals

Time period	Treatment duration (%)
6 months	65% [95% CI: 62%, 68%]
12 months	43% [95% CI: 39%, 47%]

The Kaplan-Meier curve for ongoing treatment is shown in Figure 3. The median treatment duration for all patients was 9.4 months [95% CI: 8.4, 10.8] (286 days) (N=1,140).

Figure 3. Kaplan-Meier treatment duration (N=1,140)



Tables 10 and 11 show the number of patients at risk, the number of patients that were censored and the number of patients that ended treatment (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for all patients for treatment duration was 16.1 months (490 days). SACT contains more follow-up for some patients.

Table 10. Number of patients at risk, by quarterly breakpoints

Time intervals (months)	0-18	3-18	6-18	9-18	12-18	15-18	18
Number at risk	1,140	841	504	256	135	23	1

Table 11 shows that for all patients who received treatment, 646 were still on treatment (censored) at the date of follow-up and 494 had ended treatment (events).

Table 11. Number of patients at risk, by quarterly breakpoints split between patients that have ended treatment (events) and patients that are still on treatment (censored)

Time intervals (months)	0-18	3-18	6-18	9-18	12-18	15-18	18
Censored	646	541	360	200	115	19	0
Events	494	300	144	56	20	4	1

Table 12 gives a breakdown of a patient's treatment outcome recorded in SACT when a patient's treatment has come to an end. 494 (43%) of patients had ended treatment at 31 March 2021.

Table 12: Treatment outcomes for patients that have ended treatment (N=494)[l,m]

Outcome	Frequency (N)	Percentage (%)
Stopped treatment – died not on treatment[n]	104	21%
Stopped treatment – progression of disease	96	19%
Stopped treatment – palliative, patient did not benefit	77	16%
Stopped treatment – no treatment in at least 3 months	75	15%
Stopped treatment – palliative, patient did benefit	61	12%
Stopped treatment – died on treatment	45	9%
Stopped treatment – acute toxicity	21	4%
Stopped treatment – patient choice	10	2%
Stopped treatment – COVID	4	1%
Stopped treatment – completed as prescribed	1	<1%
Total	494	100%

[l] Figures may not sum to 100% due to rounding.
[m] Table 12 presents the outcome summary data reported by trusts. This includes patients from Table 8 who 'died on treatment', 'died not on treatment' and 'stopped treatment'.

[n] Deaths on treatment' and 'deaths not on treatment are explained in the methodology paper available on the SACT website.

Table 13. Treatment outcomes and treatment status for patients that have ended treatment (N=494)

Outcome[o]	Patient died [p] not on treatment	Treatment stopped	Patient died on treatment
Stopped treatment – died not on treatment[q]	104		
Stopped treatment – progression of disease	54	42	
Stopped treatment – palliative, patient did not benefit	47	30	
Stopped treatment – no treatment in at least 3 months		75	
Stopped treatment – palliative, patient did benefit	28	33	
Stopped treatment – died on treatment			45
Stopped treatment – acute toxicity	7	14	
Stopped treatment – patient choice	2	8	
Stopped treatment – COVID	2	2	
Stopped treatment – completed as prescribed		1	
Total	244	205	45

[o] Relates to outcomes submitted by the trust in Table 12.

[p] Relates to treatment status in Table 8 for those that have ended treatment.

[q] Deaths on treatment' and 'deaths not on treatment are explained in the methodology paper available on the SACT website.

Overall survival (OS)

Of the 1,140 patients with a treatment record in SACT, the minimum follow-up was 5 months (152 days) from the last CDF application. Patients were traced for their vital status on 30 July 2021. This date was used as the follow-up date (censored date) if a patient is still alive. The median follow-up time in SACT was 10 months (304 days). The median follow-up is the patients' median observed time from the start of their treatment to death or censored date.

Table 14: OS at 6, 12 and 18-month intervals

Time period	OS (%)
6 months	88% [95% CI: 86%, 89%]
12 months	75% [95% CI: 72%, 78%]
18 months	63% [95% CI: 59%, 67%]

Figure 4 provides the Kaplan-Meier curve for OS, censored at 30 July 2021. The median OS was not reached.

Figure 4. Kaplan-Meier survival plot (N=1,140)

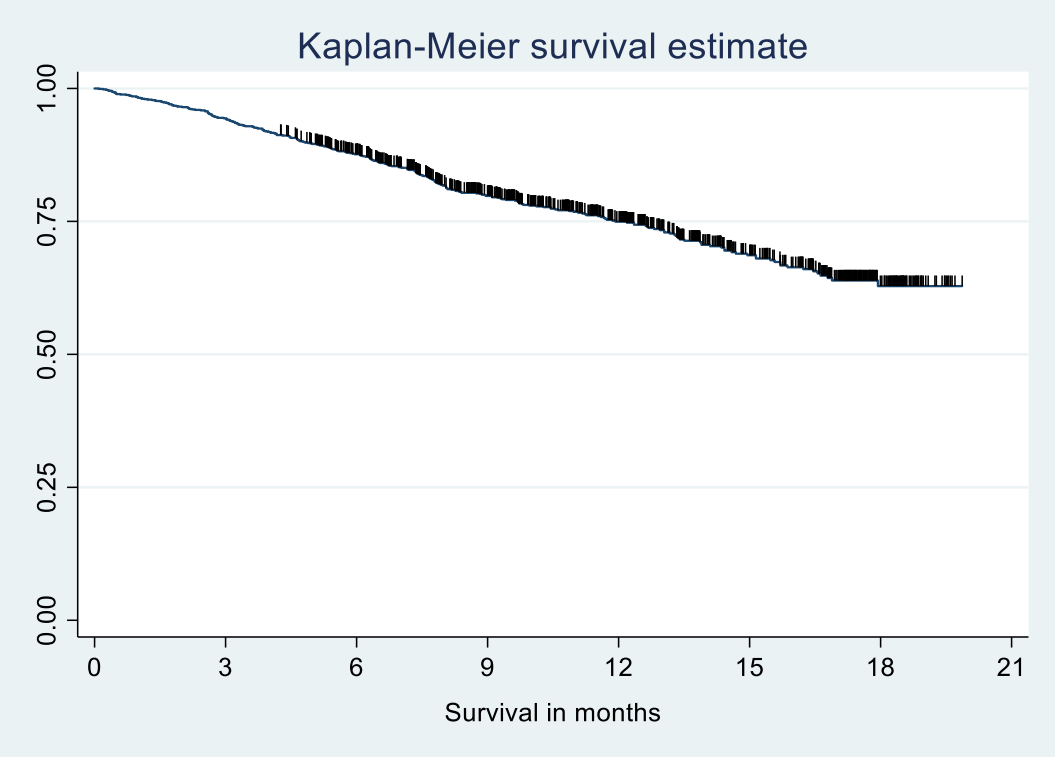


Table 15 and Table 16 show the number of patients at risk, the number of patients that were censored and the number of patients that died (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for survival was 20 months (608 days), all patients were traced on 30 July 2021.

Table 15. Includes the number of patients at risk, by quarterly breakpoints

Time intervals (months)	0-21	3-21	6-21	9-21	12-21	15-21	18-21
Number at risk	1,140	1,076	930	663	414	230	57

Table 16 shows that for all patients who received treatment, 851 were still alive (censored) at the date of follow-up and 289 had died (events).

Table 16. Number of patients at risk, those that have died (events) and those that are still alive (censored) by quarterly breakpoints

Time intervals (months)	0-21	3-21	6-21	9-21	12-21	15-21	18-21
Censored	851	851	781	589	373	216	57
Events	289	225	149	74	41	14	0

5. Sensitivity analyses

6-month SACT follow up

Treatment duration

Sensitivity analyses were carried out on a cohort with at least six months follow-up in SACT. To identify the treatment duration cohort, CDF applications were limited from 28 November 2019 to 30 September 2021 and SACT activity was followed up to the 31 March 2021.

Following the exclusions above, 753 patients (66%) were identified for inclusion. The median follow-up time in SACT was 7.5 months (228 days). The median treatment duration follow-up is the patients' median observed time from the start of their treatment to their last treatment date in SACT + prescription length.

The Kaplan-Meier curve for ongoing treatment is shown in Figure 5. The median treatment duration for patients in this cohort was 9.2 months [95% CI: 8.3, 10.3] (280 days) (N=753).

Figure 5. Kaplan-Meier treatment duration plot (N=753)

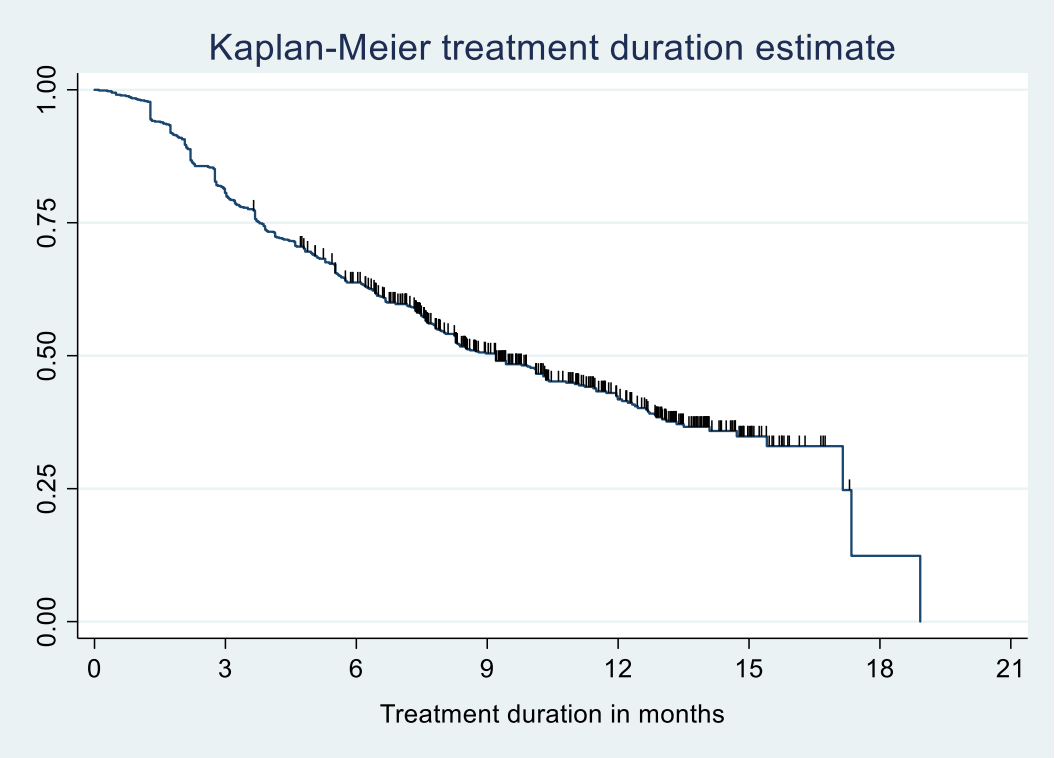


Table 17 and Table 18 show the number of patients at risk, the number of patients that were censored and the number of patients that ended treatment (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for all patients for treatment duration was 16.1 months (490 days).

Table 17. Includes the number of patients at risk, by quarterly breakpoints

Time intervals (months)	0-18	3-18	6-18	9-18	12-18	15-18	18
Number at risk	753	607	464	255	135	23	1

Table 18 shows that for all patients who received treatment, 339 were still on treatment (censored) at the date of follow-up and 414 had ended treatment (events).

Table 18. Number of patients at risk, by quarterly breakpoints split between patients that have ended treatment (events) and patients that are still on treatment (censored)

Time intervals (months)	0-18	3-18	6-18	9-18	12-18	15-18	18
Censored	339	339	322	199	115	19	0
Events	414	268	142	56	20	4	1

Overall survival (OS)

Sensitivity analyses was also carried out for OS on a cohort with at least six months follow-up in SACT. To identify the cohort, CDF applications were limited from 28 November 2019 to 30 January 2021.

Following the exclusions above, 1,080 patients (95%) were included in these analyses. The median follow-up time in SACT was 10.4 months (316 days). The median follow-up is the patients' median observed time from the start of their treatment to death or censored date.

Figure 6 provides the Kaplan-Meier curve for OS, censored at 30 July 2021. The median OS was not reached.

Figure 6. Kaplan-Meier survival plot (N=1,080)

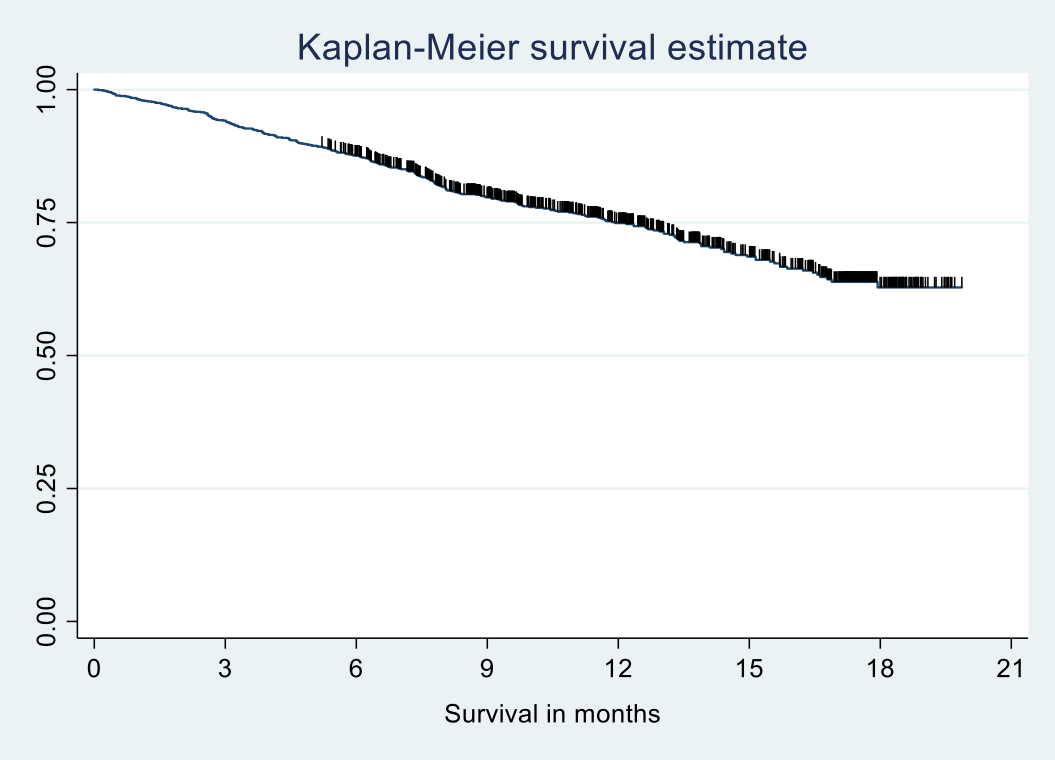


Table 19 and Table 20 show the number of patients at risk, the number of patients that were censored and the number of patients that died (events) from the time patients started treatment to the end of the follow-up period. The maximum follow-up period for survival was 20 months (608 days), all patients were traced on 30 July 2021.

Table 19. Includes the number of patients at risk, by quarterly breakpoints

Time intervals (months)	0-21	3-21	6-21	9-21	12-21	15-21	18-21
Number at risk	1,080	1,017	927	663	414	230	57

Table 20 shows that for all patients who received treatment, 797 were still alive (censored) at the date of follow-up and 283 had died (events).

Table 20. Number of patients at risk, those that have died (events) and those that are still alive (censored) by quarterly breakpoints

Time intervals (months)	0-21	3-21	6-21	9-21	12-21	15-21	18-21
Censored	797	797	778	589	373	216	57
Events	283	220	149	74	41	14	0

Table 21. Median treatment duration and OS, full cohort and sensitivity analysis

Metric	Standard analysis: Full cohort	Sensitivity analysis: 6 months follow-up cohort: treatment duration	Sensitivity analysis: 6 months follow-up cohort: OS
N	1,140	753	1,080
Median treatment duration	9.4 months [95% CI: 8.4, 10.8] (286 days)	9.2 months [95% CI: 8.3, 10.3] (280 days)	
OS	Not reached		Not reached

6. Conclusions

1,151 patients received palbociclib with fulvestrant for the treatment of hormone receptor-positive, HER2-negative, advanced breast cancer [TA619] through the CDF in the reporting period (28 November 2019 and 27 February 2021). 1,140 patients were reported to the SACT dataset, giving a SACT dataset ascertainment of 99%. An additional 27 patients with a CDF application did not receive treatment and 36 patients died before treatment. Not all were confirmed by the trust responsible for the CDF application by the team at NHSD.

Patient characteristics from the SACT dataset show that 99% (N=1,128) of patients that received palbociclib with fulvestrant for the treatment of hormone receptor-positive, HER2-negative, advanced breast cancer were female, 1% (N=12) of patients were male. Most of the cohort were aged 50 years and over (92%, N=1,045) and 81% (N=924) of patients had a performance status between 0 and 2 at the start of their regimen.

At data cut off, 43% (N=494) of patients were identified as no longer being on treatment. Of these 494 patients:

- 21% (N=104) of patients died not on treatment
- 19% (N=96) of patients stopped treatment due to progression
- 16% (N=77) of patients who received palliative treatment did not benefit
- 15% (N=75) of patients did not have a treatment record in SACT in at least three months and are assumed to have completed treatment
- 12% (N=61) of patients who received palliative treatment did benefit
- 9% (N=45) of patients died on treatment
- 4% (N=21) of patients stopped treatment due to acute toxicity
- 2% (N=10) of patients chose to end their treatment, and
- 1% (N=4) of patients stopped treatment due to COVID and less than 1% (N=1) of patients completed treatment as prescribed.

Median treatment duration was 9.4 months [95% CI: 8.4, 10.8] (286 days). 65% of patients were still receiving treatment at 6 months [95% CI: 62%,68%] and 43% of patients were still receiving treatment at 12 months [95% CI: 39%, 47%].

The median OS was not reached. OS at 6 months was 88% [95% CI: 86%, 89%], 12 months OS was 75% [95% CI: 72%, 78%], OS at 18 months was 63% [95% CI: 59%, 67%].

Sensitivity analysis was carried out on treatment duration and OS to evaluate a cohort for which all patients had a minimum follow-up of six months. Results for treatment duration showed a difference of 0.2 month (full cohort = 9.4 months; sensitivity analysis

cohort = 9.2 months). Results of OS showed no difference and the median OS was not reached.

7. References

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Palbociclib with fulvestrant for treating hormone receptor-positive, HER2-negative, advanced breast cancer (Review of TA619) [ID3779]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

NICE National Institute for Health and Care Excellence

1.Your name	Sukhi Kaur
2. Name of organisation	Breast Cancer Now
3. Job title or position	Senior Policy Officer
4a. Brief description of the organisation (including who funds it). How many members does it have?	From research to care, Breast Cancer Now has people affected by breast cancer at its heart – providing support for today and hope for the future. All of our funding comes from the public and our partners.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	Breast Cancer Now has received funding from a number of companies towards our support services, however, we do not receive any pharmaceutical funding for our Policy, Evidence and Influencing work, which includes our work on access to drugs. In the last 12 months (from 3 February 2021- 3 February 2022) we have received the following from the relevant pharmaceutical companies to this appraisal: • Pfizer – £107,747 sponsorship towards Breast Cancer Now's Service Pledge programme • AstraZeneca – £32,000 grant towards our Helpline • Lilly UK - £50,000 sponsorship towards Breast Cancer Now's Service Pledge programme • Novartis - £20,000 grant towards our Helpline and £4,002 towards our Living with Secondary Breast Cancer service

If so, please state the name of manufacturer, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	Breast Cancer Now was involved with the original NICE appraisal of palbociclib with fulvestrant acting as a patient expert, alongside a patient we found with direct experience of this treatment. As part of the reappraisal of this treatment, following its time on the Cancer Drugs Fund (CDF) we will utilise our various networks of supporters to gather information about patient experience, including people with experience of this treatment combination.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Secondary (also known as advanced, metastatic or stage 4) breast cancer is when cancer originating in the breast has spread to other parts of the body; most commonly the lungs, brain, bones or liver. There is no cure for secondary breast cancer, so treatment aims to control and slow down the spread of the cancer, relieve symptoms and give patients the best quality of life for as long as possible. A patient can be diagnosed with secondary cancer initially (de novo metastatic), or they can develop the condition years after treatment for their primary breast cancer has ended. The symptoms of secondary breast cancer can vary depending on where the cancer has spread to. For example, if it has spread to the bones the main symptoms can include pain in the bones or bone fractures. If breast cancer has spread to the lungs, someone may experience symptoms such as breathlessness or

	continuous pain and tightness in the chest. All breast cancer treatments can cause some side effects and although everyone reacts differently to drugs, for those people who experience more side effects than others, it can cause a significant impact on their day to day lives and health and wellbeing. Being diagnosed with secondary breast cancer is extremely difficult to come to terms with both for patients and their family and friends and it can affect patients in different ways. Many people may feel upset and shocked or anxious, as well as angry and alone. These common feelings can have a huge impact on people's mental health. As well as the huge emotional toll of living with secondary breast cancer, patients often have to cope with numerous practical concerns, such as managing their day-to-day activities, which may include working, household and parental responsibilities as well as travelling to and from regular hospital appointments. Patients are keen to find treatments that will halt progression and extend life for as long as possible. As patients' time is limited, people tell us that quality of life is just as important to take into account as length of life, as this enables them to spend quality time with their loved ones. Therefore, the type and severity of treatment side effects are also important for patients. A patient told us that living with this condition "*affects me mentally more than anything as at the moment I am lucky not to experience any pain. I am able to live a normal life on a daily basis but I did cut my work days from full time to three days a week to get a better work life balance. I have had to adjust my finances accordingly. Living with secondary breast cancer feels like you're on a rollercoaster as the treatment never stops and I have scans every three to four months so it is hard mentally. On the positive side, I appreciate my friends and family and don't stress over little things*."
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Before April 2019 and the first approval of a CDK 4/6 inhibitor in combination with fulvestrant, this patient group would have been offered hormone treatments including exemestane, everolimus in combination

	with exemestane, tamoxifen, or certain patients may receive chemotherapy. The introduction of CDK 4/6 inhibitors (palbociclib, ribociclib and abemaciclib) in combination with fulvestrant onto the Cancer Drugs Fund (CDF) throughout 2019 was hugely welcomed by the patient community, offering a new important treatment option. CDK 4/6 inhibitors with fulvestrant opened the door for thousands of women who had received prior endocrine therapy to benefit from the innovative CDK 4/6 inhibitors In 2021, both ribociclib and abemaciclib, in combination with fulvestrant were approved for routine use on the NHS, which were an important milestone to guarantee the treatments use on the NHS for future patients, providing patients with precious extra months before disease progression, offering the hope of life extension and delaying the use of chemotherapy. Abemaciclib and ribociclib also have different side effect profiles so having both available was important for improving patient choice and helping give them more control over their quality of life. Palbociclib's side effect profile is similar to ribociclib compared to abemaciclib but positively it does not require the ECG monitoring as ribociclib, therefore approving palbociclib for routine use on the NHS could improve treatment choices for those who may not be suitable to receive ribociclib due to certain cardiac disease
8. Is there an unmet need for patients with this condition?	Whilst abemaciclib with fulvestrant and ribociclib and fulvestrant are now recommended by NICE for routine use on the NHS which was hugely welcomed following their time on the CDF, palbociclib with fulvestrant does have a different side effect profile to abemaciclib which may be preferred by some patients and does not require the same ECG monitoring as ribociclib.

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	A key advantage of palbociclib with fulvestrant is the increase in progression free survival. The PALOMA-3 study demonstrated that palbociclib in combination with fulvestrant improves progression free survival (PFS) compared with fulvestrant alone, with a median PFS of 11.2 months compared to 4.6 months. We know patients value this extra time, as delaying disease progression means more quality time to spend with their relatives and friends. Maintaining a good quality of life for as long as possible is currently the best outcome for this patient group. Delaying progression can also have a positive impact on patients' emotional wellbeing and mental health, as it may mean that the patient can continue doing the activities they enjoy and leading a more or less normal daily life. Increasing the time until a patient's disease progresses is also likely to bring some comfort to their relatives and friends, as this is the best possible outcome for an incurable disease. This in turn could help to reduce any stress the patient is experiencing as a result of worrying about any burden on their friends and family. Importantly, similar to the other CDK 4/6 inhibitors, the use of this technology could also delay patients having to start on systemic (non-targeted) chemotherapy. Chemotherapy is traditionally associated with more severe and gruelling side effects which can result in a poorer quality of life for patients and people are often particularly fearful and anxious about starting chemotherapy treatment. This treatment option also has a different side effect profile to abemaciclib with fulvestrant which is now routinely available on the NHS following its time on the CDF and doesn't require the same ECG monitoring as ribociclib which has a small risk of the heart problem known as QT prolongation. Palbociclib is associated with an increased incidence of neutropenia, similar to ribociclib, whereas abemaciclib tends to increase the likelihood of diarrhoea. As mentioned, abemaciclib, and ribociclib in combination with fulvestrant are now recommended by NICE for routine use on the NHS.

	The latest data from the trial (presented at ASCO 2021) has shown that overall survival (OS) was longer in the palbociclib-fulvestrant combination compared to fulvestrant alone - 34.8 months versus 28 months. The 5-year OS rate was 23.3% with palbociclib and 16.8% with placebo. Benefits in OS were observed for multiple subgroups, including those who were sensitive to previous hormonal therapy, and those who did not receive prior chemotherapy. We look forward as part of this reappraisal to see the data collected on the NHS whilst the treatment combination has been available via the CDF. This would be extremely important for this patient group as there is no cure for secondary breast cancer so the aim of treatment is to extend the length of life, whilst providing a good quality of life. The ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with secondary breast cancer highlights that while there have been no head-to-head comparisons of the three CDK 4/6 inhibitors, the efficacy of these drugs in the secondary setting appear to be similar and that direct cross trial comparisons are not possible due to the heterogenous inclusion criteria of the individual trials. For example, patients we spoke to who have experience of palbociclib with fulvestrant have told us: "*The main advantage of this treatment is that it has worked – what more could you ask for?*" "*It is of paramount importance that these relatively easily tolerated and effective drugs should be offered to women with secondary breast cancer, especially if it gives them longer without having to turn to intravenous chemotherapy*"
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Palbociclib with fulvestrant is associated with some increased side effects, compared to fulvestrant alone. In the PALOMA-3 trial, neutropenia of all grades occurred more frequently in the palbociclib-fulvestrant arm compared to placebo-fulvestrant. Grade 3 neutropenia occurred in 58% of the palbociclib group and grade 4 occurred in 12% - no grade 4 adverse events were reported in the placebo arm. The other most common side effects include fatigue, nausea, infections and anaemia. Every treatment for breast cancer has some side effects and each patient's situation will be different, with side effects affecting some patients more than others. Patients' willingness to take treatments will vary,

	however, as long as all the side effects are clearly discussed with the patient, they will be able to make their own choice with the support of their clinician regarding treatment options. We generally hear from patients that palbociclib is well tolerated and that their day-to-day activities are not heavily impacted. Clinicians are also very familiar with the side effects associated with this treatment. OS was not observed in patients who received prior chemotherapy for advanced breast cancer or in those who were not sensitive to prior hormone therapy. A patient we spoke to told us: "*I didn't have many side effects. I was sometimes a bit weary or tired. But it's hard to say whether it was down to the treatment as I'm generally busy with 2 two daughters. I have had mouth ulcers at regular times in the drug cycle. But I can put up with that. I was also constipated on and off for the first month or so, but it got easier."* The patient went on to explain: *"in the first three to six months, my neutrophils were low at the end of the cycle. This meant starting the next cycle of treatment had to be delayed for a week. There is some monitoring required, but that's minor. I accept that as part of treatment*" "*I found the tablet easy to take in the morning. The buttock injection wasn't the most pleasant thing, but it's not excruciating pain, not even close. I actually don't like needles, but as it's in the buttock I couldn't see it. And any discomfort is minor in the grand scheme of everything*."

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	In the PALOMA-3 trial, patients were excluded if they had received any CDK 4/6 inhibitor, fulvestrant, everolimus or a PI3K inhibitor or had extensive symptomatic visceral metastasis. As mentioned, OS was not observed in patients who received prior chemotherapy for advanced breast cancer or in those who were not sensitive to prior hormone therapy. Analyses have suggested that those with endocrine-sensitive disease and those treated before chemotherapy could benefit most as reported at ASCO 2021.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	None that we are aware of.
Other issues	
13. Are there any other issues that you would like the committee to consider?	N/A.

Key messages
14. In up to 5 bullet points, please summarise the key messages of your submission: • In the PALOMA-3 trial, palbociclib in combination with fulvestrant improved progression-free survival compared to fulvestrant alone (with a median PFS of 11.2 months, versus 4.6 months respectively). This provided patients with an additional 6.6 months on average before their disease progressed. • Newer data from the ASCO study showed that overall survival was longer in the palbociclib-fulvestrant combination compared to fulvestrant alone - 34.8 months versus 28 months This enables patients to spend quality time with their friends and families as well as being able to continue with their daily activities, which can improve the emotional wellbeing of both patients and their families. • There are some increased side effects from palbociclib in combination with fulvestrant, compared to fulvestrant alone, however, not all patients will experience side effects. We hear from patients that they tolerate this treatment well and clinicians are very familiar with this treatment combination and the potential side effects. • Keeping this treatment as an option on the NHS for future patients would be welcome. It has a different side effect profile compared to abemaciclib with fulvestrant which been routinely available on the NHS since 2021 following its time on the CDF and whilst similar side effects to ribociclib, ribociclib is not suitable for certain patients with cardiac disease.

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NICE National Institute for Health and Care Excellence

Patient expert statement

Palbociclib with fulvestrant for treating hormone receptor-positive, HER2-negative, advanced breast cancer (Review of TA619) [ID3779]

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

About this Form
In **part 1** we are asking you to complete questions about living with or caring for a patient with the condition.
In **part 2** we are asking you to provide 5 summary sentences on the main points contained in this document.

If you have any questions or need help with completing this form please email the public involvement team via pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please return this form by **5pm** on **Monday 25 July 2022**

Completing this form
Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide.
You do not have to answer every question – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee. The text boxes will expand as you type.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable

- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 15 pages.

PART 1 – Living with or caring for a patient with this condition and current treatment options	
About you	
1.Your name	**Sukhi Kaur**
2. Are you (please tick all that apply):	☐ a patient with this condition? ☐ a patient with experience of the treatment being evaluated? ☐ a carer of a patient with this condition? ☒ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation.	Breast Cancer Now
4. Has your nominating organisation provided a submission? Please tick all options that apply.	☐ No, (please review all the questions below and provide answers where possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission

	☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☐ I am drawing from personal experience. ☒ I have other relevant knowledge/experience (e.g. I am drawing on others' experiences). Please specify what other experience: Breast Cancer Now has gathered insight from secondary breast cancer patients with experience of the treatment palbociclib with fulvestrant. ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☒ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
Living with the condition	
6. What is your experience of living with this condition? If you are a carer (for someone with this condition) please share your experience of caring for them.	Breast Cancer Now has already provided a patient organisation submission. Following our original submission, we have received insight from additional patients who wanted to share their experience to inform this drug appraisal, therefore, please accept this expert statement as supplementary evidence. All the patients we have spoken to are living with secondary breast cancer and have experience of the drug treatment palbociclib with fulvestrant. A patient with secondary breast cancer shares what it is like to live with this condition: "*Any advanced cancer diagnosis is devastating for the patient and their loved ones. Initially there are the symptoms of the cancer and physical symptoms of anxiety to deal with. As the weeks went on and I understood that there were many treatments*

	to help patients live as well as possible for as long as possible the panic died down but a lot of sadness remains. It is so hard to know that your position is hurting your loved ones so much. You can't help thinking of the things you will miss and how sad that will be for them too. I have a three year old grandson and we have a very special relationship. The thought that I won't be there for him as he grows up is so sad. I don't feel the need to travel or tick things off a list. I just want to be there for my family to love and support them and to enjoy them. I worry that I have made my family too reliant on me and I think about how my husband and children will cope when I am gone. *Due to my condition, I don't think I can commit to providing regular child care for my grandson anymore so there will be a financial impact on my daughter and son-in-law, who will have to make alternative childcare arrangements. There is also a financial impact on my husband. My husband and I are both retired and in our long-term planning we had assumed I would get state pension and draw my company pension for many years (my pension is greater than his). When I die the widowers pension will be quite significantly lower than my current pension with none of it tax free as my husband's allowance goes against his personal pension. Also there is no state widowers pension. As household costs remain pretty much the same, I am aware that my husband will be considerably worse off financially*."
Current treatment of the condition in the NHS	
7a. What do you think of the current treatments and care available for this condition on the NHS?	Please see Breast Cancer Now's original patient group submission.

7b. How do your views on these current treatments compare to those of other people that you may be aware of?	
8. If there are disadvantages for patients of **current NHS treatments** for this condition (for example how the treatment is given or taken, side effects of treatment etc) please describe these	Please see Breast Cancer Now's original patient group submission.
Advantages of this treatment	
9a. If there are advantages of this treatment over current treatments on the NHS please describe these. For example, the impact on your Quality of Life your ability to continue work, education, self-care, and care for others? 9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? 9c. Does this treatment help to overcome/address any of the listed disadvantages of current treatment	A number of patients with experience of palbociclib with fulvestrant have told us about the benefits of this drug treatment: "*The biggest benefit of palbociclib with fulvestrant for me at the moment is quality of life. I have recently started the treatment, and have found it very easy to tolerate and am already feeling the benefits. For the first time in many months I am not taking painkillers regularly. The absence of pain allows me to continue my daily life and even sometimes to forget that I have this condition for a few hours. This is a big help to my mood. So far I have experienced almost no side effects. A small discomfort around the injection site for a couple of days is the only thing I have noticed.* *I have no problems with swallowing the tablet, it is convenient that you don't have to worry about taking it with or without food. I appreciate the packaging with the days of the week shown. With previous treatments where there are no dates on the blister pack I have sometimes got confused as to whether I have taken it or not so I had to have a system of recording it on my calendar. I also have no problem with the fulvestrant injections. Just a small scratch and then no pain whilst the injection*

that you have described in question 8? If so, please describe these.	*went in. It is important to relax during administration which I was able to do and I think this helps a lot. Afterwards there was some very light soreness on the day and next day. After that I had no pain at the injection site at all.* *Everyone is very focussed on staying strong and positive for me and now I am on treatment we are all very much trying to carry on as normal. Knowing I am on a treatment that is very effective for many women allows me to carry on and enjoy my life in the present without focussing too much on the future. If I was aware that there was a good treatment out there that was denied to me I think I would struggle very much with that.* *I feel very fortunate and grateful that I have this treatment and the thought that it might be denied to other women is actually very upsetting for me. Breast cancer affects a lot of younger women who are still working and caring for children at the same time. It is of benefit to society that these women remain as well as possible for as long as possible. Also it is an important consideration for all patients that the treatment not only extends life but greatly improves quality of life."* Another secondary breast cancer patient with experience of palbociclib with fulvestrant shares their experience: "*I was first diagnosed with breast cancer in 2007. I had a mastectomy and was prescribed Tamoxifen for 5 years. In 2016 the cancer came back and had spread to lungs. I was prescribed Letrozole which worked for about two years then Exemestane which only worked for about 6 months. I started the drug treatment fulvestrant with palbociclib in March 2020. I am on 75mg of Palbociclib and don't find the side effects arduous. I have a monthly hospital appointment where they take bloods. I answer a questionnaire on side effects and the next day I come back for the tablets and injections.*

	The benefits of palbociclib with fulvestrant are that the treatment has put the breast cancer on hold, and it doesn't have the side effects of chemo, which I think was the other option for me. The administration method of the drug treatment is also fine, and I have had more painful injections in the past! *I think it's extremely important this treatment remains an option on the NHS and should be available for all women. It has certainly worked for me. We should all have this chance of a longer healthier life*."
Disadvantages of this treatment	
10. If there are disadvantages of this treatment over current treatments on the NHS please describe these? For example, are there any risks with this treatment? If you are concerned about any potential side affects you have heard about, please describe them and explain why.	A secondary breast cancer patient with experience of palbociclib with fulvestrant told us about some of the disadvantages of this treatment: *"My skin is very dry and so is my hair. After 3 weeks of taking the tablets, I do get bruising on my wrists, not sure if I knock myself they are quite ugly. I also feel my skin is thinner and I can cut myself more easily (gardening etc). I've not experienced any hair loss but my hair is thin. I do get more tired but I have to say I am 76 now so age is probably a factor. Lastly, I do feel more jittery"*
Patient population	
11. Are there any groups of patients who might benefit more from this treatment or any who may benefit less? If so, please describe them and explain why.	Please refer to Breast Cancer Now's original patient group submission.

Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme	Please refer to Breast Cancer Now's original patient group submission.

More general information about the Equality Act can and equalities issues can be found at https://www.gov.uk/government/publications/easy-read-the-equality-act-making-equality-real and https://www.gov.uk/discrimination-your-rights.	
Other issues	
13. Are there any other issues that you would like the committee to consider?	Please refer to Breast Cancer Now's original patient group submission.

PART 2 - Key messages
14. In up to 5 sentences, please summarise the key messages of your statement: Breast Cancer Now has provided key messages in its original patient group submission, please see below some additional key messages based on this expert statement. • Patients shared that it was extremely difficult being diagnosed with secondary breast cancer, for both them and their loved ones. In addition to the symptoms of breast cancer, patients experienced anxiety, but knowing that there are effective treatments available helped a considerable amount. • A key advantage of the drug treatment palbociclib with fulvestrant, cited by patients is that it is working for them and has improved their quality of life, which allows them to continue doing the activities they enjoy, for example spending quality time with loved ones, which in turn improves emotional wellbeing. • While some patients have tolerated the drug treatment well, experiencing very few side effects, other patients have reported some side effects, therefore if this drug treatment were to be routinely approved on the NHS following its time on the Cancer Drugs Fund it is

important that, as with all drugs, clinicians continue to discuss any potential side effects with patients so that patients can make an informed decision about their treatment.

- Patients remarked that they found the administration method of the drug treatment palbociclib with fulvestrant not particularly arduous.
- Patients currently taking palbociclib with fulvestrant have strongly expressed their view that they hope this drug treatment continues to remain an option on the NHS to allow future patients to experience the same benefits of the drug treatment as they have, including improved quality of life.

Thank you for your time.

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FINAL EAG FTA REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Palbociclib in combination with fulvestrant for treating advanced, hormone-receptor positive, HER2-negative breast cancer after endocrine therapy (review of TA619) [ID3779]

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 131913

Completed 1 June 2022

CONTAINS [redacted] AND [redacted] DATA

UNIVERSITY OF LIVERPOOL | LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Title: Palbociclib in combination with fulvestrant for treating advanced, hormone-receptor positive, HER2-negative breast cancer after endocrine therapy (review of TA619) [ID3779]

Produced by: Liverpool Reviews & Implementation Group (LR*i*G)

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Contributions of authors:

Rebecca Bresnahan	Project lead, critical appraisal of the clinical evidence and supervised the final report
Nigel Fleeman	Critical appraisal of the clinical evidence
James Mahon	Critical appraisal of the economic evidence
Marty Chaplin	Critical appraisal of the statistical evidence
Sarah Nevitt	Critical appraisal of the statistical evidence
Sophie Beale	Critical appraisal of the clinical and economic evidence, editorial input
Angela Boland	Critical appraisal of the clinical and economic evidence, editorial input
Rachel Houten	Critical appraisal of the economic model
Yenal Dundar	Critical appraisal of the company searches
Ashley Marsden	Critical appraisal of the company submission
Zafar Malik	Clinical advice and critical appraisal of the clinical evidence

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LIST OF ABBREVIATIONS

ABE+FUL	abemaciclib plus fulvestrant
AE	adverse event
AEOSI	adverse event of special interest
AI	aromatase inhibitor
CBR	clinical benefit response
CDF	Cancer Drugs Fund
CDK4/6	cyclin-dependent kinase 4 and 6
CI	confidence interval
DoR	duration of response
EAG	External Assessment Group
ECOG PS	Eastern Cooperative Oncology Group performance status
EORTC QLQ-BR23	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Breast cancer module
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EQ-5D	EurQol-5 Dimension
ET	endocrine therapy
EVE+EXE	everolimus plus exemestane
HER2	human epidermal growth factor receptor 2
HR	hazard ratio
HR	hormone receptor
HRQoL	health-related quality of life
ICER	incremental cost effectiveness ratio
IPD	individual patient data
ITC	indirect treatment comparison
MAIC	matching-adjusted indirect comparison
NICE	National Institute for Health and Care Excellence
ORR	objective response rate
OS	overall survival
PAL+FUL	palbociclib plus fulvestrant
PAS	Patient Access Scheme
PBO+FUL	placebo plus fulvestrant
PFS	progression-free survival
PH	proportional hazards
PHE	Public Health England
PRO	patient-reported outcomes
QALY	quality adjusted life year
QoL	quality of life
RCT	randomised controlled trial
RIB+FUL	ribociclib plus fulvestrant
RWE	real-world evidence
SACT	Systemic Anti-Cancer Therapy

1 SUMMARY OF THE EAG'S VIEW OF THE COMPANY'S COST COMPARISON CASE

The remit of the External Assessment Group (EAG) is to comment on the clinical and cost effectiveness evidence submitted to the National Institute for Health and Care Excellence (NICE) as part of the Fast Track Appraisal (FTA) process. Clinical and economic evidence has been submitted to NICE by the company (Pfizer UK) in support of the use of palbociclib plus fulvestrant (PAL+FUL) as a treatment option for patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer, who have received prior endocrine therapy (ET). This summary provides a brief overview of the key issues identified by the EAG as being potentially important for decision making.

1.1 Pharmacological, biological, and/or pharmacokinetic differences

Expert advice to the EAG is that palbociclib, abemaciclib and ribociclib all inhibit cyclin-dependent kinase 4 and 6 (CDK4/6) and share the same primary mechanism of action; however, there are some differences in potency, dosing schedules, serum concentration and toxicity.

1.2 Clinical effectiveness evidence

The EAG agrees with the company that the PALOMA-3 trial (palbociclib plus fulvestrant [PAL+FUL] versus placebo plus fulvestrant [PBO+FUL]) is a good quality trial with a low risk of bias. Clinical advice to the EAG is that PALOMA-3 trial patients appear to be more heavily pre-treated than patients currently treated in NHS clinical practice. Nevertheless, the EAG considers that PALOMA-3 trial results are still generalisable to NHS patients. However, the PALOMA-3 trial comparator is PBO+FUL; fulvestrant monotherapy is not a relevant comparator for NHS patients.

The company provided real-world data (Systemic Anti-Cancer Therapy [SACT]). There were several differences between the PALOMA-3 trial and SACT populations and the company considers that the SACT data may not be fully representative of PAL+FUL use in NHS clinical practice. Clinical advice to the EAG is that the patients included in the SACT dataset may be more representative of NHS patients than PALOMA-3 trial patients in terms of patient characteristics and types of subsequent treatments. In addition, a median overall survival (OS) follow-up period of 10 months is too short to form firm conclusions about effectiveness and subsequent treatments.

The EAG and the company consider that differences between the characteristics of the patients in the three pivotal trials (the PALOMA-3, MONARCH 2, MONALEESA-3 trials) could

lead to biased unadjusted indirect treatment comparison results; therefore, in addition to unadjusted Bucher indirect comparisons, the company appropriately conducted well-designed matching-adjusted indirect comparisons (MAICs) to account for the heterogeneity between trials.

The company Scenario A (the EAG's preferred scenario) progression-free survival (PFS) MAIC results for the comparison of PAL+FUL versus ribociclib plus fulvestrant (RIB+FUL) indicate that treatment with PAL+FUL is [redacted]. However, the [redacted] for all the other company OS and PFS MAIC scenarios presented in the company submission (CS) [redacted]. The company considers that these MAIC results confirm that, based on the best available evidence, PAL+FUL, abemaciclib plus fulvestrant (ABE+FUL) and RIB+FUL are clinically equivalent/similar. However, the EAG considers [redacted] cannot be interpreted as meaning that the comparative efficacy and/or safety of treatments is 'similar' or 'equivalent'.

The company has not performed any indirect comparisons to assess the comparative effect of different CDK4/6 inhibitors on health-related quality of life (HRQoL) or adverse events (AEs). After reviewing AE results presented in relevant Summary of Product Characteristic documents, the company identified that there were important differences between the three CDK4/6 inhibitors when comparing some AEs. Patients treated with ABE+FUL experienced higher levels of diarrhoea than patients treated with PAL+FUL or RIB+FUL. Clinical advice to the EAG is that diarrhoea is an important AE. Clinical evidence shows that discontinuations for patients treated with ABE+FUL were higher than discontinuations for patients treated with PAL+FUL and RIB+FUL.

1.3 Cost effectiveness evidence

If the efficacy of PAL+FUL is equal/similar to the efficacy of ABE+FUL and/or RIB+FUL, the EAG considers that the cost savings generated by the company base case analysis are reasonable. Palbociclib, abemaciclib and ribociclib are available to the NHS at confidential Patient Access Scheme (PAS) prices and the EAG has provided a confidential appendix showing results for the cost comparison of PAL+FUL versus ABE+FUL and PAL+FUL versus RIB+FUL using confidential prices for palbociclib, abemaciclib and ribociclib.

The EAG considers that there are no critical issues relating to the economic evidence/model submitted by the company and has not generated any alternative cost comparison results.

1.4 EAG conclusions

The EAG considers that the company has failed to establish that palbociclib, abemaciclib and/or ribociclib are clinically equivalent/similar (efficacy and safety). If treatment with PAL+FUL [redacted] and improved HRQoL (diarrhoea) versus ABE+FUL, then the EAG considers that the impact of these differences should be explored using a cost utility analysis over a patient's lifetime.

The EAG considers that this topic does not meet the NICE criteria for a cost comparison analysis.

2 INTRODUCTION

The focus of this appraisal is on palbociclib plus fulvestrant (PAL+FUL) as a treatment option for patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer, who have received prior endocrine therapy (ET). This critique includes the External Assessment Group (EAG) view on whether it is appropriate to appraise this topic via the National Institute for Health and Care Excellence (NICE) Fast Track Appraisal (FTA) process. In this EAG report, references to the company submission (CS) are to the company's Document B, which is the company's full evidence submission.

The company has provided a cost comparison submission. The company has chosen two comparators which it considers are clinically equivalent/similar to PAL+FUL for this appraisal:

- abemaciclib plus fulvestrant (ABE+FUL)
- ribociclib plus fulvestrant (RIB+FUL).

The company considers that all three drug combinations have equivalent/similar efficacy but not equivalent/similar toxicity.

2.1 Pharmacological, biological and pharmacokinetic comparison of palbociclib, abemaciclib and ribociclib

The company provided information about similarities and differences between palbociclib, abemaciclib and ribociclib in relation to their pharmacokinetic properties and mechanisms of action (company response to clarification letter, Question A1). In summary:

- palbociclib, abemaciclib and ribociclib are cyclin-dependent kinase (CDK) 4/6 inhibitors
- palbociclib and ribociclib are structurally similar to each other (but less similar to abemaciclib)
- despite structural differences, all three CDK4/6 inhibitors indirectly target the retinoblastoma tumour-suppressor protein (Rb) to prevent cell cycle progression
- in vitro studies have shown that palbociclib has similar potency against CDK4 and CDK6, whereas abemaciclib and ribociclib are more potent against CDK4 than CDK6. Abemaciclib also has some potency against CDK2, CDK5 and CDK9
- there are some differences in CDK4/6 inhibitor properties, including: maximum serum concentration [C_{max}], time taken to reach C_{max} [t_{max}]) and half-life ($t_{1/2}$).

All three CDK4/6 inhibitors are orally administered but, in line with slightly different inhibitor properties, the three drugs have different dose-delivery schedules in combination with fulvestrant (Table 1).

Table 1 Dose-delivery schedules (PAL+FUL, ABE+FUL and RIB+FUL)

	PAL+FUL	ABE+FUL	RIB+FUL
Administration	125mg palbociclib orally once daily for first 21 days of a 28-day cycle plus 500mg fulvestrant intramuscular injection on days 1, 15, 29 and once monthly thereafter Treatment is stopped on disease progression or if patients can no longer tolerate the combination	150mg abemaciclib orally twice daily on a continuous 28-day cycle plus 500mg fulvestrant intramuscular injection on days 1, 15, 29 and once monthly thereafter Treatment is stopped on disease progression or if patients can no longer tolerate the combination	600mg ribociclib orally once daily for first 21 days of a 28-day cycle plus 500mg fulvestrant intramuscular injection on days 1, 15, 29 and once monthly thereafter Treatment is stopped on disease progression or if patients can no longer tolerate the combination

ABE+FUL=abemaciclib plus fulvestrant; PAL+FUL=palbociclib plus fulvestrant; RIB+FUL=ribociclib plus fulvestrant; SmPC=summary of product characteristics
Source: SmPCs for palbociclib,[1] abemaciclib[2] and ribociclib[3]

Expert advice to the EAG is that palbociclib, abemaciclib and ribociclib all inhibit CDK4/6 and share the same primary mechanism of action; however, there are some differences in potency, dosing schedules, serum concentration and toxicity.

2.2 Marketing authorisations and NICE recommendations for palbociclib, abemaciclib and ribociclib

Palbociclib, abemaciclib and ribociclib all have similar marketing authorisations[1-3] in combination with an aromatase inhibitor (AI) or fulvestrant (Table 2). The company states (CS, p54) that treatment with palbociclib requires less intensive monitoring than treatment with either abemaciclib or ribociclib. Treatment with palbociclib only requires patients to have a full blood count, whereas treatment with abemaciclib and ribociclib require further monitoring tests (e.g., liver function test and electrocardiogram, respectively).

Table 2 European marketing authorisations for CDK4/6 inhibitors

	Palbociclib	Abemaciclib	Ribociclib
Marketing authorisation	Indicated for the treatment of HR-positive, HER2-negative locally advanced or metastatic breast cancer: • in combination with an AI • in combination with fulvestrant for women who have received prior ET For pre- or perimenopausal women, the ET should be combined with a LHRH agonist	Indicated for the treatment of HR-positive, HER2-negative locally advanced or metastatic breast cancer in combination with an AI or fulvestrant as initial endocrine-based therapy, or for women who have received prior ET For pre- or perimenopausal women, the ET should be combined with a LHRH agonist	Indicated for the treatment of HR-positive, HER2-negative locally advanced or metastatic breast cancer in combination with an AI or fulvestrant as initial endocrine-based therapy, or for women who have received prior ET For pre- or perimenopausal women, the ET should be combined with a LHRH agonist

AI=aromatase inhibitor; CDK=cyclin dependent kinases; ER=oestrogen receptor; ET=endocrine therapy; HER2=human epidermal growth factor receptor 2; HR=hormone receptor; LHRH=luteinising hormone-releasing hormone; SmPC=summary of product characteristics Source: SmPCs for palbociclib,[1] abemaciclib[2] and ribociclib[3]

NICE has recommended all three CDK4/6 inhibitors plus an AI[4-6] within their marketing authorisations[1-3] as options for treating patients with HR-positive, HER2-negative locally advanced or metastatic breast cancer. As shown in the CS (Figure 1), this can include patients who have completed ET in the (neo)adjuvant setting but progressed >12 months after completing this treatment, as well as patients who are treatment naïve. These patients are sometimes referred to as 'endocrine sensitive'[7] and are outside the scope of this appraisal.

All three CDK4/6 inhibitors plus fulvestrant were initially recommended[8-10] by NICE for use in the Cancer Drugs Fund (CDF) as treatment options for patients with HR-positive, HER2-negative locally advanced or metastatic breast cancer after ET. Recently, ABE+FUL and RIB+FUL received positive recommendations from NICE.[11,12] As shown in the CS (Figure 1), typically this group of patients will have progressed during, or <12 months after completing, ET in the (neo)adjuvant or advanced setting. These patients are sometimes referred to as 'endocrine resistant'.[9]

None of the CDK4/6 inhibitors have been directly compared with each other in pivotal trials (for references, see Section 2.3, Table 4) or indirectly via the NICE appraisal process. The pivotal trials for all three CDK4/6 inhibitors plus fulvestrant (see Table 4) were placebo controlled (placebo plus fulvestrant [PBO+FUL]). At the time of the previous appraisals,[8-10] the main comparator was everolimus plus exemestane (EVE+EXE); CDK4/6 inhibitors were only recommended by NICE for use in the CDF, and therefore were not relevant comparators (Table 3).

Table 3 Timeline of NICE recommendations for intervention and comparators

TA / drug(s)	Date of CS	Date guidance published	NICE recommendation
TA579 ABE+FUL[10]	2018 (Sep)	2019 (May)	Recommended for use within the CDF as an option for treating HR-positive, HER2-negative locally advanced or metastatic breast cancer in adults who have had previous ET only if: • EVE+EXE would be the most appropriate alternative to a CDK 4/6 inhibitor and • the conditions in the managed access agreement for ABE+FUL / RIB+FUL / PAL+FUL are followed
TA593 RIB+FUL[8]	2018 (Sep)	2019 (Aug)	
TA619 PAL+FUL[9]	**2019 (Apr)**	**2020 (Jan)**	
TA687 (CDF) RIB+FUL[13]	2020 (Sep)	2021 (Mar)	Recommended as an option for treating HR-positive, HER2-negative locally advanced or metastatic breast cancer in adults who have had previous ET only if: • EVE+EXE is the most appropriate alternative to a CDK 4/6 inhibitor, and • the company provides ribociclib / abemaciclib according to the commercial arrangement
TA725 (CDF) ABE+FUL[12]	2020 (Sep)	2021 (Sep)	

ABE+FUL=abemaciclib plus fulvestrant; CDF=Cancer Drugs Fund; CDK4/6=cyclin-dependent kinase 4 and 6; CS=company submission; ET=endocrine therapy; EVE+EXE=everolimus plus exemestane; HER2=human epidermal growth factor receptor 2; HR=hormone receptor; PAL+FUL=palbociclib plus fulvestrant; RIB+FUL=ribociclib plus fulvestrant; TA=technology appraisals

2.3 Main sources of clinical effectiveness evidence

The main source of clinical effectiveness evidence for the intervention (PAL+FUL) is the PALOMA-3 trial. This trial was a phase III, international, multicentre, double-blind, placebo-controlled randomised controlled trial (RCT) that compared PAL+FUL versus PBO+FUL for women with HR-positive, HER2-negative locally advanced or metastatic breast cancer after ET. The PALOMA-3 trial recruited the first patient on 7 October 2013 and the most recent publication (2018)[14] reported the final planned overall survival (OS) analysis results (median follow up of 44.8 months [April 2018]).

The main sources of clinical effectiveness data for the comparators, ABE+FUL and RIB+FUL, are the MONARCH 2 and MONALEESA-3 trials, respectively.

The MONARCH 2 trial was a phase III, international, multicentre, double-blind, placebo-controlled RCT that compared ABE+FUL versus PBO+FUL for patients with HR-positive, HER2-negative locally advanced or metastatic breast cancer after ET. The MONARCH 2 trial recruited the first patient on 7 August 2014 and the most recent publication (2020)[15] included the most recent OS analysis results (median follow up of 47.7 months [June 2019]).

The MONALEESA-3 trial was a phase III, international, multicentre, double-blind, placebo-controlled RCT that compared RIB+FUL versus PBO+FUL for patients with HR-positive, HER2-negative locally advanced or metastatic breast cancer after ET. The MONALEESA-3 trial recruited the first patient on 18 June 2015 and the most recent publication (2021)[16] included extended OS analysis results (median follow up 56.3 months [October 2020]).

A summary of the key publications for each trial is presented in Table 4.

Table 4 Key publications for the three pivotal trials

Trial / comparison	Key paper	Outcomes included*	Median follow up (date)
PALOMA-3 PAL+FUL vs PBO+FUL	Turner et al 2015[17]	PFS (interim) AEs >10% by grade	5.6 months (Dec 2014)
	Cristofanilli et al 2016[18]	PFS (primary) ORR CBR All AEs by grade Discontinuations due to AEs	8.9 months (Mar 2015)
	Harbeck et al 2016[19]	Disease specific HRQoL	8.9 months (Mar 2015)
	Loibl et al 2016[20] poster	EQ-5D-3L	15.3 months (Oct 2015)
	Turner et al 2018[21]	OS (final planned analysis) TEAEs (updated) by grade Discontinuations due to AEs	44.8 months (Apr 2018)
MONARCH-2 ABE+FUL vs PBO+FUL	Sledge et al 2017[22]	PFS (primary) ORR CBR DoR AEs ≥10% by grade Discontinuations due to AEs	19.5 months (Feb 2017)
	Kaufman et al 2020[23]	Disease specific HRQoL	19.5 months (Feb 2017)
	Sledge et al 2020[15]	OS (interim) PFS (updated) TEAEs ≥10% by grade	47.7 months (Jun 2019)
MONALEESA-3 RIB+FUL vs PBO+FUL	Slamon et al 2018[24]	PFS (primary) OS (interim) ORR CBR AEs ≥15% by grade	20.4 months (Nov 2017)
	Fasching-2020[25]	Disease specific HRQoL EQ-5D-5L	20.4 months (Nov 2017)
	Slamon et al 2020[26]	OS (final) PFS (updated) AEOSIs	39.4 months (Jun 2019)
	Slamon et al 2021[16]	OS (extended) AEOSIs Discontinuations due to AEs	56.3 months (Oct 2020)

* Not an exhaustive list of outcomes but those most relevant to the final scope[27] issued by NICE for this appraisal (ID3779) and which have informed subsequent sections of this EAG report

ABE+FUL=abemaciclib plus fulvestrant; AE=adverse event; AEOSI=adverse event of special interest; CBR=clinical benefit response; CS=company submission; DoR=duration of response; EQ-5D-3L=EuroQol-5 Dimensions-3 Levels; EQ-5D-5L=EurQol-5 Dimension-5 Levels; HRQoL=health-related quality of life; NICE=National Institute for Health and Care Excellence; ORR=objective response rate; OS=overall survival; PAL+FUL=palbociclib plus fulvestrant; PBO+FUL=placebo plus fulvestrant; PFS=progression-free survival; RIB+FUL=ribociclib plus fulvestrant; TEAE=treatment-emergent adverse event

3 EAG CRITIQUE OF THE DECISION PROBLEM IN THE COMPANY SUBMISSION

The company has developed a decision problem based on the final scope[27] issued by NICE. A discussion of the extent to which the company decision problem meets the final scope[27] is presented in Section 3.1 to 3.5.

3.1 Population

In line with the final scope[27] issued by NICE, the company has presented clinical effectiveness evidence for PAL+FUL for patients with HR-positive, HER2-negative locally advanced or metastatic breast cancer who have received prior ET. Specifically, the company has appropriately presented evidence for PAL+FUL for patients who:

- progressed on ET or <12 months post completion in the (neo)adjuvant setting

or

- progressed on ET or post completion in the advanced setting.

The population considered by the company represents patients who are 'endocrine resistant' and is identical to the population that was considered relevant to NHS clinical practice in two recent NICE appraisals:

- TA725[12] (Abemaciclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy)
- TA687[11] (Ribociclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy).

3.2 Comparators

The company considered that ABE+FUL and RIB+FUL were the relevant comparators to PAL+FUL because both treatments had been recommended by NICE for patients with HR-positive, HER2-negative locally advanced or metastatic breast cancer who had received prior ET.[11,12] Clinical advice to the EAG is that ABE+FUL and RIB+FUL represent standard of care for patients in NHS clinical practice with HR-positive, HER2-negative locally advanced or metastatic breast cancer who have received prior ET. In the absence of direct evidence, the company carried out unadjusted Bucher[28] indirect comparisons and anchored matching-adjusted indirect comparisons (MAIC) for OS and progression-free survival (PFS) using PALOMA-3 trial individual patient data (IPD) and aggregate data from the MONARCH 2 and MONALEESA-3 trials.

EVE+EXE was listed as a comparator in the final scope[27] issued by NICE. However, the company has not presented evidence for the comparison of PAL+FUL versus EVE+EXE.

3.3 Outcomes

Results from the PALOMA-3 trial for PAL+FUL versus PBO+FUL are presented in the CS (Table 12) for all outcomes included in the final scope[27] issued by NICE, with the exception of response rate. However, objective response rate (ORR) and clinical benefit rate (CBR) results are available for PAL+FUL versus PBO+FUL in the publication by Cristofanilli 2016[18] (and are summarised by the EAG in Table 6 for completeness).

PALOMA-3 trial results presented in the CS are stratified by the presence/absence of visceral metastases and sensitivity to prior ET (defined as a documented clinical benefit from treatment with ≥1 previous ET in the metastatic setting or treatment with ≥24 months of adjuvant therapy before disease recurrence). Clinical advice to the EAG is that the outcomes listed in the final scope[27] issued by NICE are the most relevant outcomes for this appraisal.

The company's case to support a conclusion of clinical equivalence/similarity relies on results from indirect treatment comparisons (ITCs), specifically MAIC results. Overall, the EAG does not consider that results from the company's MAICs provide conclusive evidence of the clinical equivalence/similarity of PAL+FUL versus ABE+FUL and/or PAL+FUL versus RIB+FUL. Further, the company states that important differences between the three CDK4/6 inhibitors can be seen when comparing some AEs (CS, p51).

3.4 Economic analysis

The company has presented a cost comparison analysis.

3.5 Subgroups to be considered

In the final scope[27] issued by NICE, no subgroups were specified.

4 SUMMARY OF THE EAG CRITIQUE OF CLINICAL EFFECTIVENESS EVIDENCE

4.1 Systematic literature review

4.1.1 Searches

The search strategies used to identify RCTs reporting efficacy and safety of relevant treatments for patients with HR-positive, HER2-negative locally advanced or metastatic breast cancer who have received prior ET were reported in the CS (Appendix D). The EAG is satisfied that the company's search strategies were appropriate.

The EAG conducted its own searches to identify any potentially relevant studies not identified by the company. The EAG did not identify any relevant studies in addition to those identified by the company.

4.1.2 Included studies

Trials identified and included in the company systematic literature review

The company systematic literature review (SLR) identified five potentially relevant RCTs:

- PALOMA-3 trial (PAL+FUL versus PBO+FUL)
- MONARCH 2 trial (ABE+FUL versus PBO+FUL)
- MONALEESA-3 trial (RIB+FUL versus PBO+FUL)
- FLIPPER[7] trial (PAL+FUL versus PBO+FUL)
- MONARCHplus[29] trial (ABE+AI versus PBO+AI and ABE+FUL versus PBO+FUL).

The company only presented evidence from three pivotal trials (PALOMA-3, MONARCH 2 and MONALEESA trials) in the CS; the company did not include evidence from the FLIPPER trial[7] or MONARCHplus[29] trial. A list of the publications for each of the three included trials is provided in Table 4.

A complete list of excluded studies with reasons for exclusion is provided in the CS (Appendix D).

4.2 Direct clinical effectiveness evidence

Only the PALOMA-3 trial provided PAL+FUL (versus PBO+FUL) clinical effectiveness evidence.

4.2.1 Quality of the PALOMA-3 trial

The company quality assessment of the PALOMA-3 trial is presented in the CS (Table 11). The EAG considers that the PALOMA-3 trial was well designed and well conducted.

4.2.2 PALOMA-3 trial: statistical approach

Information relevant to the statistical approach taken by the company to analyse the PALOMA-3 trial data is provided in the CS, the trial statistical analysis plan (TSAP)[30] and PALOMA-3 trial protocol.[30] A summary of the EAG checks of the pre-planned statistical approach used to analyse PALOMA-3 trial data is provided in Appendix 1 (Section 8.1). The EAG considers that appropriate statistical methods were used to analyse PALOMA-3 trial data.

4.2.3 PALOMA-3 trial: efficacy results

PALOMA-3 trial PFS results (data cut-off date: 13 April 2018) and OS results (data cut-off date: 17 August 2020) are provided in Section 4.4.5, Table 6. These results show that patients treated with PAL+FUL had improved PFS, OS, ORR and CBR compared with patients treated with PBO+FUL.

4.2.4 EAG assessment of PALOMA-3 trial

The PALOMA-3 trial is a well-designed, good quality trial and an appropriate and pre-defined statistical approach was used to analyse efficacy, patient reported outcome and safety data. Clinical advice to the EAG is that the PALOMA-3 trial patients appear to be more heavily pre-treated than patients currently treated in NHS clinical practice. Nevertheless, the EAG considers that PALOMA-3 trial results are still generalisable to NHS patients.

4.3 Real-world data

The company has presented results from a report produced by Public Health England (PHE) using linked NHS Blueteq, Systemic Anti-Cancer Therapy (SACT) and Personal Demographic Service (PDS) data (CS, Section 3.9.2). The PHE report includes data from 1140 patients who had a treatment record in the SACT dataset and had received PAL+FUL via the CDF. Data were collected between 28 November 2019 and 27 February 2021. A summary of the baseline characteristics of patients in the SACT database is presented in the CS (Appendix D1.9).

4.3.1 SACT: overall survival

Median OS had not been reached in the SACT dataset (median OS follow-up time=10 months). A summary of OS rates is presented in Table 5.

Table 5 SACT data: overall survival results

Time point	Patients alive, % (95% CI)
6 months	88% (86% to 89%)
12 months	75% (72% to 78%)
18 months	63% (59% to 67%)

CI=confidence interval
Source: CS, p36

4.3.2 SACT: treatment discontinuation

Records in the SACT dataset allowing assessment of treatment duration had a median follow-up time of 5.5 months (maximum follow-up time was 16.1 months). At the latest follow-up date (31 March 2021), 494/1140 patients (43%) had discontinued treatment. The company presented the reasons for treatment discontinuation in the CS (Table 14). Approximately a fifth of patients (96/494, 19.4%) discontinued treatment due to disease progression and 9.1% (45/494) of patients died on treatment. Median treatment duration was 9.4 months (95% CI: 8.4 months to 10.8 months).

4.3.3 SACT: subsequent therapies

The company reported that 240/1140 (21.1%) patients received subsequent therapies after discontinuing PAL+FUL. The median time from discontinuation of PAL+FUL to first subsequent therapy was 40.5 days. Most patients received chemotherapy as their first subsequent treatment after discontinuing PAL+FUL, with almost half of patients receiving capecitabine (119/240, 49.6%) and approximately a fifth of patients receiving paclitaxel (52/240, 21.7%). A small proportion of patients (17/240, 7.1%) switched to another CDK4/6 inhibitor in combination with fulvestrant (14/240, 5.8%) or as a monotherapy (3/240, 1.3%). Only 8/240 (3.3%) patients received EVE+EXE (4/240, 1.7%) as their first subsequent treatment (CS, Appendix D1.9, Table 45).

4.3.4 SACT: comparison of the PALOMA-3 trial and real-world patient populations

The company noted that SACT dataset median OS had not been reached (median follow-up of 10 months) and that SACT dataset OS rates (CS, p36) were consistently lower than PALOMA-3 trial PAL+FUL and PBO+FUL treatment arm OS rates. The OS differences may be due to the heterogeneity in baseline characteristics of the SACT and PALOMA-3 trial patient populations.

The main differences between the SACT and PALOMA-3 trial populations are that:

- the SACT population included a larger proportion of patients (787/1140, 69.0%) who were aged >60 years compared to the PALOMA-3 trial, which included much younger patients (392/521, 75.2% were aged <65 years)
- 9.5% of patients (108/1140) in the SACT population were assessed as having an Eastern Cooperative Oncology Group performance status (ECOG PS) ≥2, and 19% (217/1140) of patients had indeterminate ECOG PS. In contrast, the PALOMA-3 trial only included patients with an ECOG PS ≤1
- the Blueteq form did not list prior chemotherapy as an exclusion criterion, whereas the PALOMA-3 trial excluded patients who had received >1 line of chemotherapy for advanced disease. Patients in the SACT dataset may therefore have received more prior treatments than patients in the PALOMA-3 trial; however, information on the

proportion of patients who received prior chemotherapy in the real-world setting is not reported in the CS.

Other real-world data

SACT data were available for ABE+FUL (n=876) and RIB+FUL (n=187). The company highlighted (CS, p40) that the OS rates at 6 months and 12 months were identical for PAL+FUL and ABE+FUL, and duration of treatment was similar for the three CDK4/6 inhibitors (CS, Table 15). Baseline characteristics of patients in the ABE+FUL SACT dataset were similar to the baseline characteristics of patients in the PAL+FUL SACT dataset.

SACT dataset OS was not estimable for RIB+FUL.

4.3.5 SACT data: EAG conclusions

The company considered (CS, p40) that the SACT data may not be representative of PAL+FUL use in NHS clinical practice. Clinical advice to the EAG is that the patients included in the SACT dataset may be more representative of NHS patients than PALOMA-3 trial patients in terms of patient characteristics and type of subsequent treatments. In addition, a median OS follow-up period of 10 months is too short to form firm conclusions about effectiveness and patient subsequent treatment experience.

4.4 Evidence to demonstrate equivalence (indirect evidence)

In the absence of head-to-head comparisons of the efficacy and safety of PAL+FUL versus ABE+FUL and PAL+FUL versus RIB+FUL, the company carried out ITCs (unadjusted Bucher ITCs and MAICs) for PFS and OS.

During the clarification process, the company also provided results from meta-analyses[31,32] which the company considered showed that the clinical efficacy of palbociclib and abemaciclib, and palbociclib and ribociclib, were equivalent/similar (company response to clarification letter, Question A2). The studies in these meta-analyses[31,32] included comparisons of CDK4/6 inhibitors plus ET versus placebo plus ET (ET could consist of an AI or fulvestrant). The EAG does not consider that the results from the meta-analyses[31,32] support the company claim of equivalence/similarity. Rather, the results[31,32] show that the combinations of CDK4/6 inhibitors plus ET consistently improve PFS and OS versus placebo plus ET. The EAG has therefore not considered these additional results further in this report.

4.4.1 Trials excluded from the company ITCs

The company did not include data from the FLIPPER[7] trial and MONARCHplus[29] trial in any indirect comparisons due to differences in population characteristics between these two trials and the PALOMA-3, MONARCH 2 and MONALEESA-3 trials. In particular, the FLIPPER trial

was a phase II trial that only included patients with 'endocrine sensitive' disease. Also, the MONARCHplus[29] trial was a four arm trial and the comparison of ABE+FUL versus PBO+FUL was not powered for statistical tests. The EAG also notes OS data were immature in this trial. Details of the company's rationale for excluding these two studies is provided in the CS (Appendix D.1.4). The EAG agrees with the company decision.

4.4.2 Assessment of trial heterogeneity

Comparisons of the PALOMA-3, MONARCH 2 and MONALEESA-3 trial methodologies, eligibility criteria and patient baseline characteristics are presented in the CS (Table 8 and Table 9). The company performed an assessment of heterogeneity which considered baseline patient characteristics, interventions, prior endocrine and chemotherapy treatment, HR-positive and HER2-negative status, blinding of studies and treatment crossover in the three trials (CS, Appendix D, Section 1.5).

The company highlighted the following differences between the trials:

- a higher proportion of Asian patients was recruited to the MONARCH 2 trial (214/669, 32%) compared to the PALOMA-3 trial (105/521, 20%) and the MONALEESA-3 trial (63/726, 9%)
- approximately a third of PALOMA-3 trial patients (177/521, 34%) had received prior chemotherapy in the advanced setting, whereas no patients in the MONARCH 2 trial or the MONALEESA-3 trial had received prior chemotherapy in the advanced setting
- the proportion of patients who had previously received ET in the advanced setting was lower in the MONALEESA-3 trial (150/726, 21%) than in the MONARCH 2 trial (256/669, 38%) and much lower than in the PALOMA-3 trial (387/521, 74%)
- the proportion of patients who had previously received prior AI was lower in the MONALEESA-3 trial (375/726, 52%) than in the MONARCH 2 trial (465/669, 70%) and much lower than in the PALOMA-3 trial (447/521, 86%).

In addition, the EAG has identified the following differences between the trials:

- only patients who had received prior ET were included in the PALOMA-3 and MONARCH 2 trials (CS, Table 8 and Table 9). However, the MONALEESA-3 trial included a proportion of patients (145/726, 20%) who had received no prior ET and who represent patients who are 'endocrine sensitive' (Section 2.2)
- approximately a third of PALOMA-3 trial patients (182/521, 35%) had received >2 lines of therapy for metastatic breast cancer, whereas more than half the MONALEESA-3 trial (367/726, 52%) and MONARCH 2 (396/669, 61%) trial patients had not received any therapy in the metastatic setting (CS, Table 9)
- the MONALEESA-3 trial only included patients who were post-menopausal (CS, Table 8 and Table 9). However, approximately a fifth of PALOMA-3 trial (108/521, 21%) and MONARCH 2 trial (114/669, 17%) patients were pre- or peri-menopausal
- the PALOMA-3 and MONARCH 2 trials included higher proportions of patients aged <65 years (392/521, 75% and 424/669, 63% respectively) than the MONALEESA-3 trial (387/726, 53%).

The EAG and the company (CS, p43) consider that the differences between the trial patient characteristics could lead to biased unadjusted ITC results. In addition to unadjusted Bucher indirect comparisons, the company therefore, appropriately, conducted MAICs to account for the heterogeneity between trials (see 4.4.7).

The EAG highlights that during TA619,[9] NICE considered that the aim of treatment with a CDK4/6 inhibitor plus fulvestrant was to avoid or delay chemotherapy, a CDK4/6 inhibitor plus fulvestrant therefore would be used as a treatment option earlier in the treatment pathway before chemotherapy in the advanced setting. Clinical advice to the EAG is that all three trials are broadly representative of NHS patients and treatment pathways. However, PALOMA-3 trial patients were more heavily pre-treated with chemotherapy in the metastatic setting than patients in the other two trials; 387/521 (74%) of PALOMA-3 trial patients had received prior ET in the advanced setting and 182/521 (35%) patients had received >2 lines of therapy for metastatic breast cancer. Conversely, the MONALEESA-3 trial included 145/726 (20%) patients who had received no prior ET in any setting. Clinical advice to the EAG is that patients who are the most representative of patients in current NHS clinical practice are those who:

- have received prior ET in any setting
- are chemotherapy-naïve in the advanced setting
- have received <2 lines of therapy for metastatic breast cancer in the advanced setting.

4.4.3 Assessment of proportional hazards

The EAG agrees with the company PALOMA-3 trial proportional hazards (PH) assessment, i.e., that the PH assumption holds for OS but may not hold for PFS. The EAG assessed the validity of the PH assumption for PFS and OS in the MONARCH 2 and MONALEESA-3 trials by inspecting Schoenfeld residuals plots and accompanying tests (see Appendix 3, Section 8.3). The EAG concluded that there was evidence to suggest that PH is violated for OS in the MONARCH 2 trial. Therefore, OS HRs and 95% CIs estimated from the Bucher ITCs including the MONARCH 2 trial cannot be meaningfully interpreted and should not be used to infer statistically significant differences (or lack of statistically significant differences) for PAL+FUL versus ABE+FUL. For PFS in the MONARCH 2 trial, and OS and PFS in the MONALEESA-3, the PH assumption appeared to hold.

The EAG notes that the validity of the PH assumption for PFS and OS in the PALOMA-3 trial following population matching (with or without adjustment for effect modifiers) is unknown. Therefore, it is unknown whether the estimated HRs from the Bucher ITCs or the MAICs accurately represent the true treatment effect of PAL+FUL versus ABE+FUL and PAL+FUL versus RIB+FUL over time.

4.4.4 Quality assessment of included trials

The company quality assessments of the PALOMA-3 trial, the MONARCH 2 trial and the MONALEESA-3 trial are presented in the CS (Table 11 and Appendix D, Table 41). The EAG agrees with the company assessments and considers that the three trials are of good quality and have a low risk of selection bias, performance bias, attrition bias and detection bias. The EAG has some minor concerns regarding reporting bias as not all outcomes specified in the study protocols (available as online supplementary files to the trial publications)[30,33,34] were reported in the trial publications (see Table 4). However, clinical advice to the EAG is that PFS, OS, ORR, CBR, duration of response (DoR) and HRQoL are the most important outcomes and all these outcomes, except for DoR, were reported for all three trials.

4.4.5 Naïve comparison of efficacy results

A summary of PALOMA-3, MONARCH 2 and MONALEESA-3 trial PFS, OS, ORR and CBR results is provided in Table 6.

The results show that patients treated with a CDK4/6 inhibitor plus fulvestrant had improved PFS, OS, ORR and CBR compared with patients treated with PBO+FUL, but there were noticeable differences in median PFS, OS and ORR in the treatment arms across the trials. These differences may be due to differences in trial baseline characteristics (see Section 4.4.2 and CS, Table 9). Nonetheless, all PFS and OS HRs and ORR odds ratios were similar. However, the EAG agrees with the company conclusion that the assumption of PHs may be violated for PALOMA-3 trial PFS data and EAG analyses show that the PH assumption was violated for MONARCH 2 trial OS data. Where the PH assumption is violated, HRs cannot be meaningfully interpreted and should not be used to infer statistically significant differences (or lack of statistically significant differences).

Table 6 Summary of PALOMA-3, MONARCH 2 and MONALEESA-3 trial efficacy outcomes

		PALOMA-3 (ITT)		MONARCH 2 (ITT)		MONALEESA-3 (ITT)		MONALEESA-3 (Subpop B)*	
		PAL+FUL (n=347)	PBO+FUL (n=174)	ABE+FUL (n=446)	PBO+FUL (n=223)	RIB+FUL (n=484)	PBO+FUL (n=242)	RIB+FUL (n=237)	PBO+FUL (n=109)
PFS									
Median follow-up (date of data-cut)		44.8 months (Apr 2018)		47.7 months (June 2019)		39.4 months (June 2019)		39.4 months (June 2019)	
Median PFS, months (95% CI)		11.2 (9.5 to 12.9)	4.6 (3.5 to 5.6)	16.9 (NR)	9.3 (NR)	20.5 (18.5 to 23.5)	12.8 (10.9 to 16.3)	14.6 (12.5 to 18.5)	9.1 (6.1 to 11.1)
HR (95% CI)		0.50 (0.40 to 0.62)		0.54 (0.45 to 0.65)		0.59 (0.48 to 0.73)		0.57 (0.43 to 0.74)	
OS									
Median follow-up (date of data-cut)		73.3 months (Aug 2020)		47.7 months (June 2019)		56.3 months (October 2020)		39.4 months (June 2019)	
Median OS, months (95% CI)		34.8 (28.8 to 39.9)	28.0 (23.5 to 33.8)	46.7 (NR)	37.3 (NR)	53.7 (46.9 to NR)	41.5 (37.4 to 49.0)	40.2 (37.4 to NE)	32.5 (27.8 to 40.0)
HR (95% CI)		0.81 (0.65 to 0.99)		0.76 (0.61 to 0.95)		0.73 (0.59 to 0.90)		0.73 (0.53 to 1.00)	
ORR									
Median follow-up (date of data-cut)		8.9 months (Mar 2015)		19.5 months (Feb 2017)		20.4 months (Nov 2017)		NA	
Best tumour response, n (%)	CR	0 (0)	4 (2)	14 (3)	1 (0.4)	8 (2)	0 (0)	NR	NR
	PR	66 (19)	11 (6)	143 (32)	35 (16)	149 (31)	52 (21)	NR	NR
	SD	213 (61)	94 (54)	213 (48)	133 (60)	161 (33)	83 (34)	NR	NR
	PD	58 (17)	57 (33)	40 (9)	45 (20)	48 (10)	40 (17)	NR	NR
	Indeterminate	10 (3)	8 (5)	36 (8)	9 (4)	30 (6)	13 (5)	NR	NR
ORR (95% CI)		19 (15.0 to 23.6)	9 (4.9 to 13.8)	35.2 (30.8 to 39.6)	16.1 (11.3 to 21.0)	32.4 (28.3 to 36.6)	21.5 (16.3 to 26.7)	NR	NR
OR (95% CI); p-value		2.47 (1.36 to 4.91); p=0.0019		2.82 (NR); p<0.001)		NR; p<0.001		NR	
CBR (95% CI)		67 (61.3 to 71.5)	40 (32.3 to 47.3)	72.2 (68.0 to 76.4)	56.1 (49.5 to 62.6)	70.2 (66.2 to 74.3)	62.8 (56.7 to 68.9)	NR	NR
OR (95% CI); p-value		3.05 (2.07 to 4.61); p<0.0001		2.04 (NR); p<0.001		NR; p=0.003		NR	

*Subpopulation B included patients who had: (i) relapsed ≤12 months after completing (neo)adjuvant ET with no treatment for aBC, (ii) newly diagnosed aBC that progressed after one line and (iii) relapsed >12 months after completing adjuvant ET and then progressed after one line of ET for aBC. Subpopulation B represents patients who are 'endocrine resistant'

aBC=advanced breast cancer; ABE+FUL=abemaciclib plus fulvestrant; CI=confidence interval; CBR=clinical benefit response; CR=complete response; CS=company submission; ET=endocrine therapy; HR=hazard ratio; ITT=intention to treat; NA=not applicable; NE=not estimable; NR=not reported; OR=odds ratio; ORR=objective response rate; OS=overall survival; PAL+FUL=palbociclib plus fulvestrant; PBO+FUL=placebo plus fulvestrant; PD=progressive disease; PFS=progression-free survival; PR=partial response; RIB+FUL=ribociclib plus fulvestrant; SD=stable disease

Source: CS, Table 12 and p41, Cristofanilli 2016,[18] Turner 2018,[21] Slamon 2018,[24] Slamon 2021,[16] Sledge 2017,[22] Sledge 2020,[15] TA687 Committee papers[13]

4.4.6 Subsequent treatments

OS may also be affected by the subsequent therapies received following disease progression. Data on subsequent therapies are available from the PALOMA-3 trial and the MONALEESA-3 trial and are summarised in Table 7. The EAG highlights that:

The EAG highlights that:

- approximately [redacted] of patients in [redacted] received subsequent therapies after discontinuing the study drug
- a [redacted] proportion of patients received a subsequent CDK4/6 inhibitor in the MONALEESA-3 trial than in the PALOMA-3 trial
- the proportion of patients who received ET (alone or in combination with another drug) as their first subsequent therapy was [redacted]; this may include EVE+EXE
- [redacted] patients received chemotherapy (alone or in combination with another drug) as their first subsequent therapy in the PALOMA-3 trial than in the MONALEESA-3 trial.

Table 7 Summary of subsequent therapy received in PALOMA-3 and MONALEESA-3 trials

	PALOMA-3 trial, n (%)			MONALEESA-3 trial, n (%)		
	PAL+FUL (n=347)	**PBO+FUL (n=174)**	**Total (n=521)**	**RIB+FUL (n=484)**	**PBO+FUL (n=242)**	**Total (n=726)**
Patients who received subsequent therapy, n (%)						
Any	[redacted]	[redacted]	[redacted]	340 (70.2)	190 (78.5)	530 (73.0)
CDK4/6 inhibitor	[redacted]	[redacted]	[redacted]	58 (14.0)	66 (30.0)	124 (17.1)
- Palbociclib	[redacted]	[redacted]	[redacted]	36 (10.6)	52 (27.4)	88 (16.6)
- Abemaciclib	[redacted]	[redacted]	[redacted]	10 (2.9)	5 (2.6)	15 (2.8)
- Ribociclib	[redacted]	[redacted]	[redacted]	14 (4.1)	11 (5.8)	25 (4.7)
First subsequent therapy n (%)*						
Chemotherapy	[redacted]	[redacted]	[redacted]	132 (38.8)	73 (38.4)	205 (38.7)
ET	[redacted]	[redacted]	[redacted]	151 (44.4)	76 (40.0)	227 (42.8)
Everolimus	[redacted]	[redacted]	[redacted]	NR	NR	NR
CDK4/6 inhibitor	[redacted]	[redacted]	[redacted]	NR	NR	NR

* Either alone or in combination
CDK4/6=cyclin-dependent kinase 4/6; ET=endocrine therapy; NR=not reported; PAL+FUL=palbociclib plus fulvestrant; PBO+FUL=placebo plus fulvestrant; RIB+FUL=ribociclib plus fulvestrant
Source: Company response to clarification letter, Question A4, Slamon 2021[16]

The EAG highlights that patients in the intervention arms of both trials subsequently received CDK4/6 inhibitors. Clinical advice to the EAG is that in current NHS practice, patients would not receive a CDK4/6 inhibitor after previously progressing on CDK4/6 inhibitor (and would never receive the same CDK4/6 inhibitor).

4.4.7 Methodological approach to the company ITCs

The company carried out PFS (per investigator assessment) and OS unmatched and unadjusted Bucher ITCs, matched and unadjusted Bucher ITCs, and MAICs. Comparisons of the clinical effectiveness of PAL+FUL versus ABE+FUL and versus RIB+FUL were carried out separately, using the following networks:

- PALOMA-3 trial and the MONARCH 2 trial
- PALOMA-3 trial and the MONALEESA-3 trial.

Matching trial data

The process the company used to match trial data prior to carrying out adjusted ITCs is summarised in Table 8.

Table 8 Company ITCs: aligning populations

ITC	Summary
Unmatched and unadjusted Bucher ITCs	Using ITT population data from each trial
Matched and unadjusted Bucher ITCs and MAICs	Matching trial eligibility criteria, i.e., PALOMA-3 trial patients who did not meet the MONARCH 2 or MONALEESA-3 trial eligibility criteria were excluded. No adjustments for imbalances between potential treatment effect modifiers were implemented. For the MAICs including data from the PALOMA-3 and the MONARCH 2 trials, the following patients were excluded from the PALOMA-3 trial: • patients who had ≥2 prior lines of ET for mBC • patients who had prior chemotherapy for mBC For the MAICs including data from the PALOMA-3 and MONALEESA-3 trials, the following patients were excluded from the PALOMA-3 trial: • patients who were pre/perimenopausal • patients who had ≥2 prior lines of ET for mBC • patients who had prior chemotherapy for mBC
Anchored MAICs	Matching trial eligibility criteria (as described for matched and unadjusted) and adjustment for imbalances between potential treatment effect modifiers

ET=endocrine therapy; ITC=indirect treatment comparison; ITT=intention-to-treat; MAIC=matching-adjusted indirect comparison; mBC=metastatic breast cancer
Source: CS, p47 and CS, Appendix D, p115

The EAG considers that the company approach of excluding some patients from the ITCs was appropriate. However, it was not possible to exclude, match or adjust for patients who were 'endocrine sensitive' (including those who were ET naïve or had progressed >12 months post completion of ET) in the MONALEESA-3 trial; these patients would not receive a CDK4/6+FUL in current NHS clinical practice.

Accounting for imbalances between potential treatment effect modifiers

The company identified potential treatment effect modifiers by reviewing the literature, consulting with clinicians and examining PALOMA-3 trial IPD. Prior to performing analyses, the company produced a rank-ordered list of treatment effect modifiers for each of the comparisons (i.e., PAL+FUL versus ABE+FUL and PAL+FUL versus RIB+FUL). Treatment effect modifiers that varied substantially across the included trials and have a large impact on treatment effect were considered to be the most important. The rank-ordered list of the most important treatment effect modifiers for each comparison is provided in Table 9.

For each MAIC, the company initially included all treatment effect modifiers for each comparison (see Table 9). The company refers to this analysis as "Scenario A". This scenario includes adjustments for all relevant treatment effect modifiers (where possible), which is the EAG's preferred approach. Additional analyses were performed removing the least important treatment effect modifier one at a time (Scenario B to Scenario L for the MAICs including data from the PALOMA-3 and MONARCH 2 trials; Scenario B to Scenario H for the MAICs including data from the PALOMA-3 and MONALEESA-3 trials).

Table 9 Rank-ordered list of treatment effect modifiers for each comparison

MAIC approach	PAL+FUL vs ABE+FUL	PAL+FUL vs RIB+FUL*
Included trials	PALOMA-3 and MONARCH 2	PALOMA-3 and MONALEESA-3
Rank-ordered list of treatment effect modifiers	A. Race B. Previous lines of therapy for mBC C. Organs involved D. Region E. Metastatic site F. Age group (65-year cut-point) G. Prior chemotherapy H. Sensitivity to prior ET I. Measurable disease J. ECOG PS K. Prior AI L. Menopausal status	A. Prior ET setting B. Region C. Organs involved D. Prior chemotherapy E. ER status F. Race G. Disease-free interval H. Metastatic site Additional provided during clarification: 1. Measurable disease 2. Prior tamoxifen 3. Age group (65-year cut-point) 4. ECOG PS 5. ER status

* The company was unable to adjust for two treatment effect modifiers (previous lines of therapy for mBC and prior AI)
ABE+FUL=abemaciclib plus fulvestrant; AI=aromatase inhibitor; ECOG PS=Eastern Cooperative Oncology Group performance status; ER=oestrogen receptor; ET=endocrine therapy; MAIC=matching-adjusted indirect comparison; mBC=metastatic breast cancer; PAL+FUL=palbociclib plus fulvestrant; RIB+FUL=ribociclib plus fulvestrant
Source: CS, Appendix D, p114 and company response to clarification letter, Question A6

In addition, the company initially considered the following additional treatment effect modifiers for the PALOMA-3 trial and MONALEESA-3 trial MAICs: measurable disease, prior tamoxifen, age group, ECOG performance status and ER status. However, the company stated that these treatment effect modifiers were ranked as the least important and were excluded at the analysis stage to ensure that the effective sample size of the PALOMA-3 trial following

adjustments was not excessively reduced. The EAG requested the results from these additional treatment effect modifiers during the clarification process, which the company provided.

A detailed summary and EAG critique of the statistical approaches used to undertake the company ITCs is provided in Appendix 2 (Section 8.2, Table 20). In brief, the EAG considers that the company's statistical approach was appropriate.

4.4.8 Results from the company ITCs

The company presented ITC results for the comparison of PAL+FUL versus ABE+FUL and PAL+FUL versus RIB+FUL in Table 10 and Table 11, respectively. The additional results provided by the company during clarification are presented in Table 12. The EAG highlights the following limitations cast doubt on the reliability of the MAIC results:

- small ESS for some of the anchored MAICs (e.g., the sample used to generate Scenario A results (the EAG preferred scenario) for PAL+FUL versus ABE+FUL and PAL+FUL versus RIB+FUL only include approximately [redacted] and [redacted] of PALOMA-3 trial PAL+FUL arm patients respectively)
- the validity of the PH assumption for PFS and OS in the PALOMA-3 trial following population matching (with or without adjustment for effect modifiers) is unknown
- PAL+FUL versus RIB+FUL: the PALOMA-3 trial only included patients who had received prior ET; however, 20% (145/726) of MONALEESA-3 trial patients had not received prior ET. It was not possible for the company to adjust for this difference as MONALEESA-3 trial baseline characteristics were not available for the subgroup of patients who had received prior ET.

Table 10 Results from the ITCs including the PALOMA-3 and MONARCH 2 trials

ITC	ESS	PAL+FUL versus ABE+FUL	
		OS HR (95% CI)*	PFS HR (95% CI)*
Unadjusted Bucher			
Unmatched and unadjusted	516	[redacted]	[redacted]
Matched and unadjusted	[redacted]	[redacted]	[redacted]
Anchored MAICs **			
Scenario A: (1) to (12)	[redacted]	[redacted]	[redacted]
Scenario B: (1) to (11)	[redacted]	[redacted]	[redacted]
Scenario C: (1) to (10)	[redacted]	[redacted]	[redacted]
Scenario D: (1) to (9)	[redacted]	[redacted]	[redacted]
Scenario E: (1) to (8)	[redacted]	[redacted]	[redacted]
Scenario F: (1) to (7)	[redacted]	[redacted]	[redacted]
Scenario G: (1) to (6)	[redacted]	[redacted]	[redacted]
Scenario H: (1) to (5)	[redacted]	[redacted]	[redacted]
Scenario I: (1) to (4)	[redacted]	[redacted]	[redacted]
Scenario J: (1) to (3)	[redacted]	[redacted]	[redacted]
Scenario K: (1) to (2)	[redacted]	[redacted]	[redacted]
Scenario L: (1)	[redacted]	[redacted]	[redacted]

* The MONARCH 2 trial OS proportional hazards assumption is violated, and the PALOMA-3 trial PFS PH assumption may be violated

** The treatment effect modifiers matched and adjusted for consisted of: (1) race, (2) previous lines of therapy for mBC, (3) number of organs involved, (4) region, (5) metastatic site, (6) age group (65-year cut-point), (7) prior chemotherapy, (8) sensitivity to prior ET, (9) measurable disease, (10) ECOG PS, (11) Prior AI and (12) menopausal status

ABE+FUL=abemaciclib plus fulvestrant; AI=aromatase inhibitor; CI=confidence interval; ECOG PS=Eastern Cooperative Oncology Group performance status; ESS=effective sample size; ET=endocrine therapy; HR=hazard ratio; ITC=indirect treatment comparison; MAIC=matching-adjusted indirect comparison; mBC=metastatic breast cancer; OS=overall survival; PAL+FUL=palbociclib plus fulvestrant; PFS=progression-free survival

Source: CS, Table 20, Table 21 and Appendix D (Table 47)

Results presented in Table 10 show that [redacted].

Table 11 Results from the ITCs including the PALOMA-3 and MONALEESA-3 trials

ITC	ESS	PAL+FUL versus RIB+FUL	
		OS HR (95% CI)	PFS HR (95% CI)*
Unadjusted Bucher			
Unmatched and unadjusted	492	[redacted]	[redacted]
Matched and unadjusted	[redacted]	[redacted]	[redacted]
Anchored MAICs **			
Scenario A: (1) to (8)	[redacted]	[redacted]	[redacted]
Scenario B: (1) to (7)	[redacted]	[redacted]	[redacted]
Scenario C: (1) to (6)	[redacted]	[redacted]	[redacted]
Scenario D: (1) to (5)	[redacted]	[redacted]	[redacted]
Scenario E: (1) to (4)	[redacted]	[redacted]	[redacted]
Scenario F: (1) to (3)	[redacted]	[redacted]	[redacted]
Scenario G: (1) to (2)	[redacted]	[redacted]	[redacted]
Scenario H: (1)	[redacted]	[redacted]	[redacted]

* The PALOMA-3 trial PFS PH assumption may be violated
** The treatment effect modifiers matched and adjusted for consisted of: (1) prior ET setting, (2) region, (3) organs involved, (4) prior chemotherapy, (5) ER status, (6) race, (7) disease-free interval and (8) metastatic site
CI=confidence interval; ER=oestrogen receptor; ESS=effective sample size; ET=endocrine therapy; HR=hazard ratio; ITC=indirect treatment comparison; MAIC=matching-adjusted indirect comparison; OS=overall survival; PAL+FUL=palbociclib plus fulvestrant; PFS=progression-free survival; RIB+FUL=ribociclib plus fulvestrant
Source: CS, Table 18, Table 19 and Appendix D (Table 48)

Table 12 Results from the ITCs with additional treatment modifiers including the PALOMA-3 and MONALEESA-3 trials

ITC	ESS	PAL+FUL versus RIB+FUL	
		OS HR (95% CI)	PFS HR (95% CI) *
Anchored MAICs **			
Scenario 1: (1) to (13)	[redacted]	[redacted]	[redacted]
Scenario 2: (1) to (12)	[redacted]	[redacted]	[redacted]
Scenario 3: (1) to (11)	[redacted]	[redacted]	[redacted]
Scenario 4: (1) to (10)	[redacted]	[redacted]	[redacted]
Scenario 5: (1) to (9)	[redacted]	[redacted]	[redacted]

* The PALOMA-3 trial PFS PH assumption may be violated
** The treatment effect modifiers matched and adjusted for consisted of: (1) prior ET setting, (2) region, (3) organs involved, (4) prior chemotherapy, (5) ER status, (6) race, (7) disease-free interval, (8) metastatic site, (9) measurable disease, (10) prior tamoxifen, (11) age group, (12) ECOG PS and (13) ER status. Treatment effect modifiers (1) to (8) are included in Scenario A presented by the company for PAL+FUL versus RIB+FUL in the CS (see Table 11)
CI=confidence interval; ECOG PS=Eastern Cooperative Oncology Group performance status; ESS=effective sample size; HR=hazard ratio; ITC=indirect treatment comparison; MAIC=matching-adjusted indirect comparison; OS=overall survival; PAL+FUL=palbociclib plus fulvestrant; PFS=progression-free survival; PR=progesterone; RIB+FUL=ribociclib plus fulvestrant
Source: company response to clarification letter, Question A6

Results presented in Table 11 show that company PFS MAIC [redacted]. The EAG highlights that Scenario A includes all eight treatment effect modifiers adjusted for in the CS.

[redacted]

[redacted]. The company states that the ESS (effective sample size) has been reduced considerably in the additional scenarios and therefore results should be interpreted with caution (company response to clarification letter, Question A6).

4.4.9 Company and EAG interpretation of the company ITC results

The company considers that OS and PFS MAIC results for the comparisons of PAL+FUL versus ABE+FUL and PAL+FUL versus RIB+FUL [redacted] confirm that, based on the best available evidence, PAL+FUL, ABE+FUL and RIB+FUL are clinically equivalent/similar (CS, p53).

The EAG considers [redacted] cannot be interpreted as meaning that the comparative efficacy and/or safety of treatments is 'similar' or 'equivalent'. Uncertainty is high in cases where 95% CIs are wide; in these cases, it is particularly unclear which of the two treatments has the better efficacy. Therefore, the EAG does not consider that results from the MAICs provide conclusive evidence of the clinical equivalence/similarity of PAL+FUL versus ABE+FUL and/or PAL+FUL versus RIB+FUL.

4.5 Health-related quality of life

The company has provided a summary of key HRQoL data from the PALOMA-3, MONARCH-2 and MONALEESA-3 trials (CS, Table 12, Table 13 and pp31-32). The instruments and scales used to collect HRQoL data in the three key trials are presented in Table 13; statistically significant results (CDK4/6 versus PBO+FUL) are highlighted.

Three of the four statistically significant effect differences between PALOMA-3 trial arms (EQ-5D-3L, global QoL and pain) favoured PAL+FUL versus PBO+FUL (Table 13). The statistically significant difference for 'upset by hair loss' favoured PBO+FUL.

In the MONARCH 2 trial, pain was statistically significantly decreased for patients treated with ABE+FUL versus PBO+FUL, all other statistically significant effect differences favoured PBO+FUL. The EAG highlights that the statistically significant difference in diarrhoea score favoured PBO+FUL over ABE+FUL and was considered clinically meaningful (≥10 points difference); diarrhoea is a very common AE (any grade and Grade ≥3) for patients treated with ABE+FUL (see Section 4.6).

There were no statistically significant differences reported between RIB+FUL and PBO+FUL in the MONALEESA-3 trial.

The company has not performed any indirect comparisons to assess the comparative effect of different CDK4/6 inhibitors on HRQoL. However, the company cites the recent MAICs carried out by Law 2022[35] which compared PAL+FUL (the PALOMA-3 trial) versus ABE+FUL (the MONARCH 2 trial); the MAICs were performed for the QLQ-C30 and QLQ-BR23 scales. The MAIC results were based on an adjustment of 11/12 of the treatment-effect modifiers used by the company; the exception was measurable disease, which Law 2022[35] considered had a strong negative linear correlation with metastatic site. Statistically significantly different changes from baseline favouring PAL+FUL over ABE+FUL were observed for global QoL, emotional functioning, nausea/vomiting, appetite loss, diarrhoea and systemic therapy side effects. Based on published evidence-based guidelines,[36] the differences in global QoL, nausea/vomiting, appetite loss and diarrhoea can be considered to be clinically meaningful.

There are no published HRQoL MAICs for the comparison of PAL+FUL versus RIB+FUL.

Table 13 Instruments used for measuring HRQoL in the key trials of CDK4/6 inhibitors plus fulvestrant

Instrument/ scale	PALOMA-3 PAL+FUL vs PBO+FUL	MONARCH 2 ABE+FUL vs PBO+FUL	MONALEESA-3 RIB+FUL vs PBO+FUL
EQ-5D [a]	**EQ-5D-3L index** [x] EQ-5D-3L VAS	EQ-5D-5L index EQ-5D-5L VAS	EQ-5D-5L index [b] EQ-5D-5L VAS [b]
QLQ-C30 [a]	***Global QoL*** [x] Multi-item functional subscales: 1. Physical 2. Role **3. Emotional** [x] 4. Cognitive 5. Social functioning Multi-item symptom scales: 1. Fatigue **2. Nausea/vomiting** [x] ***3. Pain*** [x] Single item symptom scales: 1. Dyspnoea 2. Sleep disturbance 3. Appetite loss 4. Constipation 5. Diarrhoea 6. Financial impact of cancer	Global QoL Multi-item functional subscales: 1. Physical 2. Role 3. Emotional 4. Cognitive 5. Social functioning Multi-item symptom scales: 1. Fatigue **2. Nausea/vomiting** [y] ***3. Pain*** [x] Single item symptom scales: 1. Dyspnoea 2. Sleep disturbance **3. Appetite loss** [y] 4. Constipation ***5. Diarrhoea*** [y] 6. Financial impact of cancer	Global QoL Multi-item functional subscales: 1. Physical 2. Emotional 3. Social functioning Multi-item symptom scales: 1. Fatigue 2. Nausea/vomiting 3. Pain
QLQ-BR23 [a]	Functional scales: 1. Body image 2. Sexual functioning 3. Sexual enjoyment 4. Future perspective Symptom scales: 1. Systemic side effects 2. Breast symptoms 3. Arm symptoms **4. Upset by hair loss** [x]	Functional scales: 1. Body image 2. Sexual functioning 3. Sexual enjoyment [c] 4. Future perspective Symptom scales: **1. Systemic side effects** [y] 2. Breast symptoms 3. Arm symptoms 4. Upset by hair loss [c]	
BPI-sf [a, d]	N/A	***Pain*** [x] **Pain and analgesic use** [x]	Pain
Time to deterioration	Time to deterioration only measured for: Global QoL Pain	Time to deterioration measured for all outcomes above (except EQ-5D-5L) Time to sustained deterioration also measured for the same outcomes	Time to definitive deterioration measured for all outcomes above (except EQ-5D-5L)

[a] Results are presented as change from baseline for each intervention versus PBO+FUL
[b] The EAG is not aware of any published MONARCH 2 trial EQ-5D-5L data but notes that the manufacturer of ribociclib (Novartis) stated there were no statistically significant differences between the RIB+FUL and PBO+FUL arms in TA593[8]
[c] Not analysed because of small sample size
[d] Modified BPI-SF used in MONARCH 2 trial
[x, y] Text in **bold** denotes study results showing a statistically significant difference favouring **x** (the intervention) or **y** (PBO+FUL)
Text in ***bold italics*** denotes results for time to deterioration and/or time to sustained deterioration also statistically significant.
ABE+FUL=abemaciclib plus fulvestrant; BPI-SF=Brief Pain Inventory-Short Form; EQ-5D-3L=EuroQoL-5-dimension-3-levels; HRQoL=health-related quality of life; PAL+FUL=palbociclib plus fulvestrant; PBO+FUL=placebo plus fulvestrant; PRO=patient reported outcome; QLQ-BR23=23-item breast cancer module quality of life questionnaire; QLQ-C30=30-item quality of life questionnaire; RIB+FUL=ribociclib plus fulvestrant; VAS=visual analogue scale
Sources: PALOMA-3 trial HRQoL publication (disease-specific outcomes)[19] and conference poster (EQ-5D),[20] MONARCH 2 HRQoL publication (disease-specific outcomes)[23] and MONALEESA-3 HRQoL publication(disease-specific outcomes) and EQ-5D)[25]

4.6 Safety and tolerability results

The company was not able to perform AE MAICs due mainly to differences in the way that trial AEs were reported; instead, the company presented frequencies of Grade ≥3 AEs reported in the most recent trial publications (CS, Table 22). A summary of common Grade ≥3 AEs (i.e., those reported by ≥1% of patients in any of the trial arms) from the PALOMA-3, MONARCH 2 and MONALEESA-3 trials, as well as MONALEESA-3 trial AEs of special interest (AEOSIs), are presented in Table 14.

The company also presented a summary of the AEs which were tabulated in the summary of product characteristics (SmPC) documents for palbociclib,[1] abemaciclib[2] and ribociclib[3] (CS, Appendix F, Table 49). The SmPC data also include AEs reported for patients treated with CDK4/6 inhibitors in combination with AIs.

The frequencies of the most common Grade ≥3 AEs resulting from treatment with CDK4/6 inhibitors are broadly similar, with haematological AEs being particularly common. However, the company states that important differences can be seen when comparing some AEs (CS, p51):

- abemaciclib tends to induce less frequent and lower-grade neutropenia than palbociclib or ribociclib. In the three key trials, the EAG notes that any grade and Grade ≥3 neutropenia at the most recent data-cut off were as follows:
- PAL+FUL 84.1% and 69.6%, respectively
- ABE+FUL 49.7% and 29.7%, respectively
- RIB+FUL 72.0 and 58.2%, respectively (recorded as an AEOSI)
- diarrhoea was more common for patients treated with abemaciclib than for patients treated with palbociclib or ribociclib. In the three key trials, the EAG notes that any grade and Grade ≥3 diarrhoea were as follows:
- PAL+FUL 27.2% and 0%, respectively (most recent data-cut)
- ABE+FUL 87.1% and 14.5%, respectively (most recent data-cut)
- RIB+FUL 29.0% and 0.6%, respectively (primary data-cut).

The EAG highlights a few additional differences between the CDK4/6 inhibitors:

- the proportion of patients with Grade ≥3 abdominal pain, dyspnoea, rash and fatigue was higher with ABE+FUL than with PAL+FUL or RIB+FUL
- the proportion of patients with abnormal level of Grade ≥3 liver function (ALT increased and AST increased) was notably highest with RIB+FUL
- there were five types of Grade ≥3 AEOSIs (hepatobiliary toxicity, QT interval prolongation, pulmonary embolism, pulmonary toxicity and renal toxicity) identified for patients treated with RIB+FUL which were not reported for PAL+FUL or ABE+FUL.

Table 14 Summary of published Grade ≥3 AE frequency (%) from pivotal trials of CDK4/6 inhibitors plus fulvestrant occurring in ≥1% of patients in any intervention arm*

Type of AE	PALOMA-3 AEs ≥10%[21]		MONARCH 2 TEAEs ≥10%[15]		MONALEESA-3 AEs ≥15%[24]**		MONALEESA-3 AEOSIs[16]	
	PAL+ FUL (n=345)	PBO+ FUL (n=172)	ABE+ FUL (n=441)	PBO+ FUL (n=223)	RIB+ FUL (n=483)	PBO+ FUL (n=241)	RIB+ FUL (n=483)	PBO+ FUL (n=241)
Median follow-up (date of data-cut)	44.8 months (April 2018)		47.7 months (June 2019)		20.4 months (November 2017)		56.3 months (October 2020)	
Haematological AEs (myelosuppression)								
Neutropenia	69.6	0.0	29.7	0.9	53.4	0.0	58.2	0.4
Febrile neutropenia	1.0	0.0	0.9	0.0	1.0	0.0	NR	NR
Leukopenia	38.3	0.3	11.1	0.0	14.1	0.0	17.0	0.0
Anaemia	4.4	1.2	9.1	0.7	3.1	1.0	3.9	1.5
Thrombocytopenia	2.9	0.0	3.4	0.2	N/A	N/A	1.2	0.0
Lymphopenia	N/A	N/A	4.1	0.1	N/A	N/A	NR	NR
Non-haematological AEs								
Infections	5.2	1.7	N/A	N/A	N/A	N/A	8.1	2.1
Decreased appetite	1.2	0.3	1.1	0.2	0.2	0.0	NR	NR
ILD/pneumonitis	N/A	N/A	N/A	N/A	N/A	N/A	0.4	0.0
Pulmonary embolism	N/A	N/A	N/A	N/A	N/A	N/A	2.9	1.9
Pulmonary toxicity	N/A	N/A	N/A	N/A	N/A	N/A	2.5	1.7
Abdominal pain	N/A	N/A	3.2	0.5	N/A	N/A	NR	NR
Diarrhoea	0.0	0.6	14.5	0.2	0.6	0.4	NR	NR
Dyspnoea	0.6	0.6	2.7	0.7	N/A	N/A	NR	NR
Nausea	0.6	0.3	2.7	1.1	1.5	0.4	NR	NR
Vomiting	0.6	0.3	0.9	1.1	1.5	0.0	NR	NR
Hepatobiliary toxicity	N/A	N/A	N/A	N/A	N/A	N/A	13.9	3.1
Rash	0.9	0.0	3.2	0.0	0.4	0.4	NR	NR
Back pain	1.5	0.9	0.7	0.7	1.7	0.4	NR	NR
Muscular weakness	N/A	N/A	1.4	0.0	N/A	N/A	NR	NR
Fatigue	2.6	0.6	4.1	0.5	1.7	0.2	NR	NR
Pyrexia	0.3	0.0	1.1	0.2	N/A	N/A	NR	NR
ALT increased	N/A	N/A	4.5	0.9	8.5	0.2	NR	NR
AST increased	3.2	1.2	2.7	1.6	6.0	0.4	NR	NR
QT interval prolongation	N/A	N/A	N/A	N/A	N/A	N/A	3.1	0.6
Renal toxicity	N/A	N/A	N/A	N/A	N/A	N/A	1.7	0.0

* Criteria for where there are applicable data available are as follows:
≥10% of AEs of any grade or any cause in the PAL+FUL arm (PALOMA-3 trial)
≥10% any grade TEAEs in the ABE+FUL arm (MONARCH 2 trial)
≥15% of any grade AEs in the RIB+FUL arm (MONALEESA-3 trial) and AEOSIs (MONALEESA-3 trial)
AEs that do not meet these criteria are classified as N/A
** It was necessary to use an earlier data-cut to make comparisons for AEs reported in a similar manner to the other trials
In all trials, AEs were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0
ABE+FUL=abemaciclib plus fulvestrant; AE=adverse event; AEOSI=adverse event of special interest; ALT=alanine aminotransferase; AST=aspartate aminotransferases; ILD=interstitial lung disease; N/A=not applicable; NR=not reported to be an AEOSI; PAL+FUL=palbociclib plus fulvestrant; PBO+FUL=placebo plus fulvestrant; RIB+FUL=ribociclib plus fulvestrant; TEAE=treatment emergent adverse event; UTI=urinary tract infection
Source CS, Table 22, with additional data added from trial publications[15,16,21,24]

Discontinuations and deaths due to AEs were not reported in the CS. The EAG considers that these outcomes provide important information regarding safety and tolerability and has extracted this information from the most recent data sources where these data were available (Table 15). For ABE+FUL (MONARCH 2 trial), the data were available over a much shorter follow-up period (19.5 months) compared to the other two trials (44.8 months [PALOMA 3 trial] and 56.3 months [MONALEESA-3 trial]). It is noticeable that nearly two- to three-times as many patients discontinued ABE+FUL than either PAL+FUL or RIB+FUL, despite the much shorter follow-up for this outcome in the MONARCH 2 trial.

Table 15 Treatment discontinuations and deaths due to adverse events

Discontinued treatment or died due to AEs	**PALOMA-3[21]**		**MONARCH 2[22]**		**MONALEESA-3[24]**	
	PAL+FUL (n=345)	**PBO+FUL (n=172)**	**ABE+FUL (n=441)**	**PBO+FUL (n=223)**	**RIB+FUL (n=483)**	**PBO+FUL (n=241)**
Median follow-up (date of data-cut)	44.8 months (April 2018)		19.5 months (February 2017)		56.3 months (October 2020)	
Discontinued, n (%)	19 (5.5)	6 (3.5)	70 (15.9)	7 (3.1)	43 (8.9)	9 (3.7)
Deaths, n (%)	0	0	0	0	0	0

ABE+FUL=abemaciclib plus fulvestrant; AE=adverse event; PAL+FUL=palbociclib plus fulvestrant; PBO+FUL=placebo plus fulvestrant; RIB+FUL=ribociclib plus fulvestrant
Source: trial publications[16,21,22]

5 SUMMARY OF THE EAG CRITIQUE OF COST EFFECTIVENESS EVIDENCE

5.1 Company cost comparison

The company considers that PAL+FUL, ABE+FUL and RIB+FUL generate similar health benefits for patients with HR-positive, HER2-negative advanced breast cancer that has become resistant to previous ET. The company has, therefore, carried out a cost comparison analysis.

5.1.1 Summary of costs and assumptions

The company cost comparison analysis considered PAL+FUL, ABE+FUL and RIB+FUL. The key inputs and assumptions in the company cost comparison base case and sensitivity analyses are shown in Table 16 and Table 17 respectively. In summary, excluding drug costs, the company has assumed that the only differences between treatment with PAL+FUL, ABE+FUL and RIB+FUL are the frequency and type of AEs, and drug monitoring costs (drug monitoring costs are a model output [CS, Table 27 and Table 28]).

Table 16 Company cost comparison analysis: key inputs

Input name	Base case value	Source
Palbociclib cost (21-day supply, PAS price)	[redacted]	Pfizer UK
Abemaciclib (14-day supply, list price)	£1,475.00	MIMS, BNF
Ribociclib (21-day supply, list price)	£983.33	MIMS, BNF
Cost per fulvestrant administration (all treatments)	£130.31	PSSRU 2021; NHS Reference Costs (2019/2020)
AE management cost per patient: PAL+FUL	£147.77	PALOMA-3; PSSRU 2021; NHS Reference Costs (2019/2020)
AE management cost per patient: ABE+FUL	£284.83	MONALEESA-3; PSSRU 2021; NHS Reference Costs (2019/2020)
AE management cost per patient: RIB+FUL	£589.13	MONARCH 2; PSSRU 2021; NHS Reference Costs (2019/2020)

ABE+FUL=abemaciclib plus fulvestrant; AE=adverse event; BNF=British National Formulary; MIMS=Monthly Index of Medical Specialties; PAL+FUL=palbociclib plus fulvestrant; PAS=Patient Access Scheme; PSSRU=Personal Social Services Research Unit; RIB+FUL=ribociclib plus fulvestrant
Source: CS, Table 24 to Table 28, Table 30

Table 17 Company cost comparison analysis: key assumptions

Assumption	Rationale for assumption	Relevant sensitivity analysis
Time horizon of the analysis is 40 years	This is long enough to capture all treatment-related costs based on extrapolation of K-M curves	None undertaken
Treatment duration is based on PFS and assumed equal for all treatments	PFS provides the most pragmatic endpoints to assess treatment duration. The company considers that the evidence they have presented suggests that PFS is the same for all treatments considered in the model	Alternative PFS parametric models were considered but as PFS was assumed to be identical for all treatments, choice of model did not alter the cost effectiveness results
No discounting was applied to costs	According to NICE fast-track appraisal guidelines[37]	None undertaken

K-M=Kaplan–Meier; PFS=progression-free survival
Source: CS, Section B.4.2

5.1.2 Company cost comparison results

The company base case results are shown in Table 18. Using the proposed (confidential) list price for palbociclib and the list prices for abemaciclib, ribociclib and fulvestrant. The company estimated treatment over 40 years with PAL+FUL would cost [redacted] less than treatment with ABE+FUL and would cost [redacted] less than treatment with RIB+FUL.

Table 18 Company base case results (total per person costs over a 40-year time horizon)

Treatment	PAL+FUL	ABE+FUL	RIB+FUL
Acquisition	£75,212 [redacted]*	£75,212	£75,211
Administration	£2,920	£2,920	£2,920
Monitoring	£24	£35	£300
Adverse events	£148	£284	£589
List price total cost	£78,304	£78,451	£79,021
PAS price total cost	[redacted]	-	-
Incremental cost (PAL+FUL versus comparator) List price versus list price	-	-£148	-£717
Incremental cost (PAL+FUL versus comparator) PAS price versus list price	-	[redacted]	[redacted]

* PAS price for palbociclib
ABE+FUL=abemaciclib plus fulvestrant; PAL+FUL=palbociclib plus fulvestrant; PAS=Patient Access Scheme; RIB+FUL=ribociclib plus fulvestrant
Source: CS, Table 30

Full results of the company (list price and PAS) one-way sensitivity analyses are presented in the CS (Table 31 to Table 34). The finding that PAL+FUL was cost saving versus ABE+FUL and versus RIB+FUL held regardless of changes in AE management costs, AE incidence, monitoring test frequencies, monitoring test costs, and choice of PFS parametric model.

5.2 EAG critique of company cost comparison

If the NICE Appraisal Committee considers that PAL+FUL, ABE+FUL and RIB+FUL are sufficiently equivalent/similar and any differences in patient outcomes can be ignored for decision making purposes, then the EAG considers that, at list prices, the company cost comparison provides robust estimates of the likely cost savings over 40-years for patients treated with PAL+FUL compared to patients treated with ABE+FUL or RIB+FUL.

The EAG considers that the AE analysis undertaken by the company (a naïve between trials analysis) is too simplistic; however, any AE differences included in the company cost comparison analysis have no material impact on results.

The EAG considers that the clinical effectiveness evidence presented by the company does not support the assumption that treatment with PAL+FUL is equivalent/sufficiently similar to ABE+FUL and/or RIB+FUL to ignore any potential differences in clinical outcomes. The EAG highlights that [redacted]. This balance of additional costs and QALYs should be explored using a cost utility analysis over a patient's lifetime.

5.3 EAG cost comparison results

As the EAG is satisfied with the company cost comparison analysis methods, the EAG has not generated alternative cost comparison results.

6 SUMMARY OF EAG'S COMMENTARY ON THE ROBUSTNESS OF EVIDENCE SUBMITTED BY THE COMPANY

6.1 Submitted effectiveness data

Expert advice to the EAG is that palbociclib, abemaciclib and ribociclib all inhibit CDK4/6 and share the same primary mechanism of action; however, there are some differences in potency, dosing schedules, serum concentration and toxicity.

The PALOMA-3 trial (PAL+FUL versus PBO+FUL) is a high quality phase III double-blind RCT that was well designed and well conducted. However, the comparator is not relevant to NHS patients and, therefore, direct trial results cannot be used to inform this appraisal.

The company presented SACT data; however, these data may not be representative of PAL+FUL use in NHS clinical practice. Clinical advice to the EAG is that the patients included in the SACT dataset may be more representative of NHS patients than PALOMA-3 trial patients in terms of patient characteristics and types of subsequent treatments. However, a median OS follow-up period of 10 months is too short to form firm conclusions about effectiveness and subsequent treatments.

The EAG and the company consider that differences between the trial patient characteristics could lead to biased unadjusted Bucher ITC results; therefore, the company also appropriately conducted well-designed MAICs to account for the heterogeneity between trials. However, [redacted]. CIs describe the uncertainty inherent in the point estimate and indicate the range of values within which the reader can be reasonably sure that the true effect lies. [redacted]. The EAG, therefore, considers that results from the company MAICs have failed to establish that the effectiveness of palbociclib, abemaciclib and ribociclib are equal or non-inferior.

The company has not performed any indirect comparisons to assess the comparative effect of different CDK4/6 inhibitors on health-related quality of life (HRQoL) or adverse events (AEs). After reviewing AE results presented in relevant Summary of Product Characteristic documents, the company identified that there were important differences between the three CDK4/6 inhibitors when comparing some AEs. Clinical advice to the EAG is that diarrhoea is an important AE and that patients treated with ABE+FUL experience higher levels of diarrhoea than patients treated with PAL+FUL or RIB+FUL. Treatment discontinuations for patients

treated with ABE+FUL are much higher than discontinuations for patients treated with PAL+FUL and RIB+FUL.

6.2 Submitted economic data

The EAG considers that whilst the methods employed by the company to undertake a cost comparison analysis are appropriate, the clinical effectiveness evidence for PAL+FUL versus ABE+FUL and/or PAL+FUL versus RIB+FUL suggest that a cost comparison analysis is not appropriate.

6.3 EAG concluding remarks

The EAG considers that the company has failed to establish that palbociclib, abemaciclib and/or ribociclib are clinically equivalent/similar (efficacy and safety). If treatment with PAL+FUL [redacted] and improved HRQoL (diarrhoea) versus ABE+FUL then the EAG considers that the impact of these differences should be explored using a cost utility analysis over a patient's lifetime.

The EAG considers that this topic does not meet the NICE criteria for a cost comparison analysis.

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8 APPENDICES

8.1 Appendix 1 EAG assessment of statistical approach used in the PALOMA-3 trial

Table 19 EAG assessment of the statistical approach used to analyse data from the PALOMA-3 trial

Item	EAG assessment	Statistical approach with EAG comments
Were all analysis populations clearly defined and pre-specified?	Yes	The analysis populations are reported in the CSR (pp98-99). The EAG is satisfied that these analysis populations (ITT, as-treated [safety] and PRO) were clearly defined and pre-specified in the PALOMA-3 TSAP version 2.1 (pp13-14)
Was an appropriate sample size calculation pre-specified?	Yes	The sample size calculation of the PALOMA-3 trial relating to PFS is reported in the Appendix D to the CS (Table 42). The EAG is satisfied that this sample size calculation is appropriate and was pre-specified in the PALOMA-3 TSAP version 2.1 (p12). The EAG also notes that this sample size calculation for PFS allows for assessment of the difference in OS (PALOMA-3 TSAP version 2.1, p12)
Were all protocol amendments made prior to analysis?	No	The original protocol of the PALOMA-3 trial, plus three amended protocols with a list of all amendments made and the rationale for these amendments was available in the supplementary materials to the trial publication by Turner et al 2018.[21] Most amendments were administrative or related to minor language changes (for example, to clarify inclusion and exclusion criteria). The largest amendment within protocol amendment 3 related to the changes to efficacy and safety analyses following interim analysis of PFS (05 December 2014) and additional analyses of safety conducted to comply with Health Authorities requirements. The EAG is satisfied with the rationale for all amendments and notes that amendments made to the first two amended versions were made before the data cut-off date used for interim analysis (05 December 2014) and therefore not driven by any results. The EAG acknowledges that the third amendment of the protocol was related to results of the interim analysis of PFS, but notes that this amendment was made upon the request of a data monitoring committee and based on Health Authorities requirements and that the general definitions and statistical analysis approach of the efficacy and safety outcomes remained the same in protocol amendment 3. Therefore, the EAG does not consider that the analyses conducted at the subsequent data cuts of 16 March 2015, 23 October 2015, 13 April 2018, 17 August 2020 for efficacy outcomes and 31 July 2015 and 12 April 2018 for safety outcomes are likely to have been influenced by the third amendment
Were all primary and secondary efficacy outcomes pre-defined and analysed appropriately?	Yes	The primary (PFS) and secondary efficacy outcomes (OR, CBR, DoR, OS) outcomes are defined in the CSR (p99, pp102-103). The statistical analysis approach for the primary and secondary efficacy outcomes is reported in Appendix D to the CS (Table 42 and Table 43). A hierarchical testing strategy was employed to protect the family-wise error rate at the one-sided 0.025 level. OS was tested for significance at the time of PFS analyses, provided the primary PFS endpoint was statistically significant at the interim and/or final PFS analyses (CSR, p102). The EAG is satisfied that the primary and secondary efficacy outcome definitions and analysis approaches were pre-defined in the PALOMA-3 TSAP version 2.1 (pp14-16 and pp25-26) and that the definitions and analysis approaches are appropriate

Item	EAG assessment	Statistical approach with EAG comments
Was the analysis approach for PROs appropriate and pre-specified?	Yes	PROs included EORTC QLQ-C30, EORTC QLQ-BR23, EQ-5D and time to deterioration in pain score VAS (CS, Table 8). The EAG is satisfied that the analysis approaches for PROs were pre-defined in the PALOMA-3 TSAP version 2.1 (pp41-42) and that the analysis approaches are appropriate
Was the analysis approach for AEs appropriate and pre-specified?	Yes	Table 22 of the CS summarises AEs in the PALOMA-3 trial. AEs occurring with 10% or higher frequency in either arm of the PALOMA-3 trial are reported, as well as any AEs which were reported in the MONALEESA-3 and MONARCH 2 trials, even if their relative frequency in the PALOMA-3 study was less than 10%. The EAG is satisfied that the analysis approach for AEs was pre-specified in the PALOMA-3 TSAP version 2.1 (pp39-41) and that the analysis approaches are appropriate
Were modelling assumptions (e.g. proportional hazards) assessed?	Yes	It was pre-specified in the PALOMA-3 TSAP version 2.1 (p25) that PFS and OS would be analysed using a Cox PH model. In TA619, the company assessed the validity of the PH assumption by inspection of log cumulative hazard plots, Schoenfeld residuals plots and the accompanying Schoenfeld residuals tests (company response to clarification letter, Question A3). The company concluded that the PH assumption may not hold for PFS data from the PALOMA-3 trial, but that the PH assumption does appear to hold for OS data. The EAG acknowledges the importance of employing pre-specified statistical analysis methods to ensure the validity of clinical trial results. However, it should be noted that a HR estimated from a Cox PH model cannot be meaningfully interpreted and should not be used to infer statistically significant differences (or lack of statistically significant differences) when the PH assumption is violated
Was a suitable approach employed for handling missing data?	Yes	The company's approach to handling missing data for dates of any efficacy or safety assessments, tumour assessments, PFS derivation and PROs is described in the CSR (pp109-111). The EAG is satisfied that the approach to handling missing data was pre-defined in the PALOMA-3 TSAP version 2.1 (Section 7, pp23-24) and that all approaches are suitable
Were all subgroup and sensitivity analyses pre-specified?	Yes	The EAG is satisfied that the subgroup analyses of OS presented in Figure 5 of the CS were pre-specified in the PALOMA-3 TSAP version 2.1 (Section 8.2.3, p25). No sensitivity analyses are presented within the CS

AE=adverse event; CBR=clinical benefit response; CS=company submission; CSR=clinical study report; DoR=duration of response; EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer quality of life questionnaire; EORTC QLQ-BR23=European Organisation for Research and Treatment of Cancer quality of life questionnaire breast cancer module; EQ-5D=EuroQoL five dimensions score; EAG=External Assessment Group; HR=hazard ratio; ITT=intention to treat; OR=objective response; OS=overall survival; PFS=progression-free survival; PH=proportional hazards; PRO=patient reported outcome; TA=technology appraisal; TSAP=trial statistical analysis plan; VAS=visual analogue scale
Source: CS, CSR,[38] PALOMA-3 trial protocol,[30] TSAP,[30] company response to clarification letter question A3 and EAG comment

8.2 Appendix 2 EAG assessment of statistical approach used for ITCs

Table 20 EAG summary and critique of the ITC statistical approaches used by the company

Item	EAG assessment	Statistical approach	EAG comments
Were ITCs conducted for all relevant outcomes?	No	The company presents ITCs for PFS (per investigator assessment) and OS	No indirect evidence is presented for response rates, AEs or HRQoL in the CS. However, the company reference Law et al 2022[35] which provided indirect evidence for HRQoL outcomes for PAL+FUL (PALOMA-3 trial) versus ABE+FUL (MONARCH 2)
Were the networks of comparators appropriate?	Yes	In their SLR, the company identified three RCTs[18,22,26] for inclusion in their ITCs of PAL+FUL vs ABE+FUL and PAL+FUL vs RIB+FUL. For the ITCs of PAL+FUL versus ABE+FUL, the network consisted of the PALOMA-3 trial and the MONARCH 2 trial. For the ITCs of PAL+FUL versus RIB+FUL, the network consisted of the PALOMA-3 trial and the MONALEESA-3 trial	The EAG considers that the company networks for the ITCs are appropriate
Were ITC methods appropriate?	Yes	The company performed a series of ITCs to explore the impact of aligning the eligibility criteria of the included trials and accounting for imbalances between potential treatment effect modifiers (see Table 8 of this EAG report). All ITCs were performed using the Bucher method.[28] As part of this series of ITCs, the company conducted anchored MAICs to adjust for potential treatment effect modifiers that were imbalanced across trials at baseline. The anchored MAICs were conducted according to the methods outlined in DSU TSD 18.[39] Robust standard errors were calculated for the MAIC HRs using a sandwich estimator	The EAG considers that the company has described their statistical approach to the ITCs comprehensively and clearly. The company's anchored MAICs appear to have been correctly implemented using the methods described in DSU TSD 18[39]
Were all relevant effect modifiers identified appropriately?	Yes	An anchored MAIC is valid if all effect modifiers are known and adjusted for. The company process for identifying treatment effect modifiers is outlined in Appendix D to the CS (pp114-115) and the company response to the clarification letter (Question A3). Potential treatment effect modifiers were identified by reviewing the literature, consulting clinicians and examining IPD available from the PALOMA-3 trial	The EAG considers that the company approach to identifying treatment effect modifiers was comprehensive and appropriate. Clinical advice to the EAG is that all important treatment effect modifiers for which data were available have been identified

Item	EAG assessment	Statistical approach	EAG comments
Was the PH assumption appropriately assessed within the ITCs of PFS and OS?	Yes	The company assessed the PH assumption for PFS and OS in the PALOMA-3 trial by inspecting Schoenfeld residuals plots and accompanying tests (company response to the clarification letter (Question A3). Based on these assessments, the company considers that over the observed periods of the trials, the PH assumption may not hold for PFS but does hold for OS	The EAG assessed the validity of the PH assumption for PFS and OS in the MONARCH 2 and MONALEESA-3 trials by inspecting Schoenfeld residuals plots and accompanying tests (see Appendix 8.3). The EAG concluded that there was evidence to suggest that PH is violated for OS in the MONARCH 2 trial. Therefore, OS HRs and 95% CIs estimated from the Bucher ITCs including the MONARCH 2 trial do not have a meaningful interpretation and should not be used to infer statistically significant differences (or lack of statistically significant differences) for PAL+FUL vs ABE+FUL. For PFS in the MONARCH 2 trial, and OS and PFS in the MONALEESA-3, the PH assumption appeared to hold. The EAG agrees with the company PALOMA-3 trial PH assessments. However, the validity of the PH assumption for PFS and OS in the PALOMA-3 trial following population matching (with or without adjustment for effect modifiers) is unknown. Therefore, it is unknown whether the estimated HRs from the Bucher ITCs or the MAICs accurately represent the true treatment effect of PAL+FUL vs ABE+FUL and PAL+FUL vs RIB+FUL over time
Was the presentation of ITC results appropriate?	Yes	The company present ITC results as HR and 95% CIs for PFS and OS (CS, pp47-51)	The presentation of ITC results for all outcomes is appropriate

ABE+FUL=abemaciclib plus fulvestrant; AE=adverse event; CI=confidence interval; CS=company submission; DSU=decision support unit; EAG=External Assessment Group; HR=hazard ratio; HRQoL=health-related quality of life; IPD=individual patient data; ITC=indirect treatment comparison; MAIC=matching-adjusted indirect comparison; OS=overall survival; PAL+FUL=palbociclib plus fulvestrant; PFS=progression-free survival; PH=proportional hazards; RCT= randomised controlled trial; RIB+FUL=ribociclib plus fulvestrant; SLR=systematic literature review; TSD=technical support document

Source: CS, pp43-51; CS, Appendix D, pp114-115; company response to clarification letter, Question A3; EAG comment

8.3 Appendix 3 EAG assessment of proportional hazards for the MONARCH 2 and MONALEESA-3 trials

The EAG assessed the validity of the PH assumption for PFS and OS data from the MONARCH 2 and MONALEESA-3 trials. The EAG digitised Kaplan-Meier curves presented in the trial publications[15,16,24] and in the Cancer Drugs Fund review of TA579,[40] and used this data to produce Schoenfeld residuals plots and to perform the Grambsch-Therneau test[41] of Schoenfeld residuals.

Results of the tests of Schoenfeld residuals are presented in Table 21. Plots of Schoenfeld residuals against time for PFS and OS in the MONARCH 2 and MONALEESA-3 trials are presented in Figure 1 to Figure 4.

Table 21 Results of the tests of Schoenfeld residuals for PFS and OS data from the MONARCH 2 and MONALEESA-3 trials

Trial	p-values of Schoenfeld residuals test	
	PFS	OS
MONARCH 2	0.0985	0.0104
MONALEESA-3	0.7658	0.1866

EAG=External Assessment Group; K-M=Kaplan–Meier; OS=overall survival; PFS=progression-free survival
Source: EAG testing of digitised K-M data extracted from the trial publications[15,16,24] and the Cancer Drugs Fund review of TA579[40]

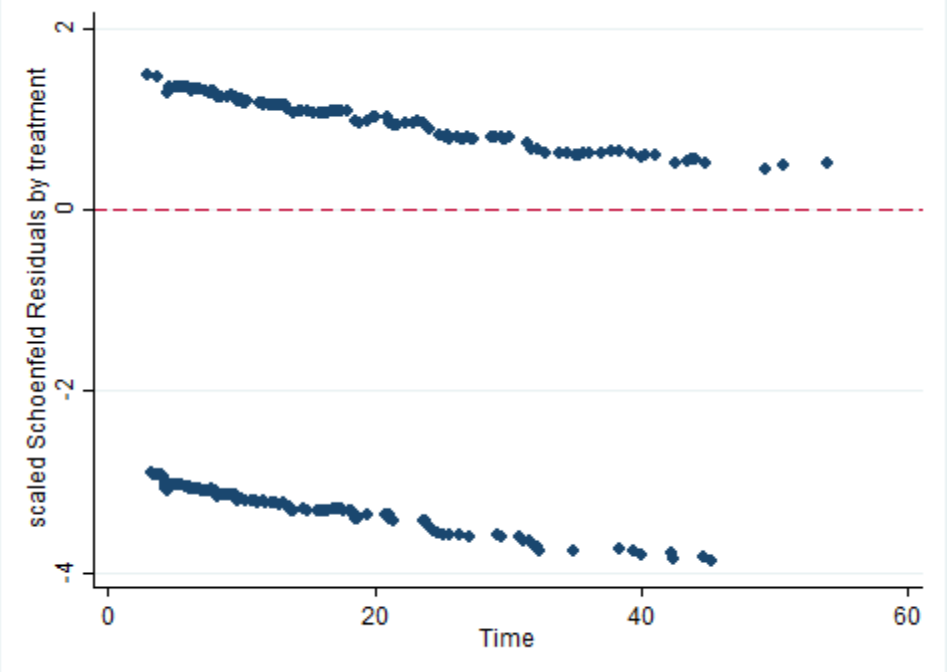

Figure 1 Schoenfeld residuals plot for PFS data from the MONARCH 2 trial

PFS=progression-free survival

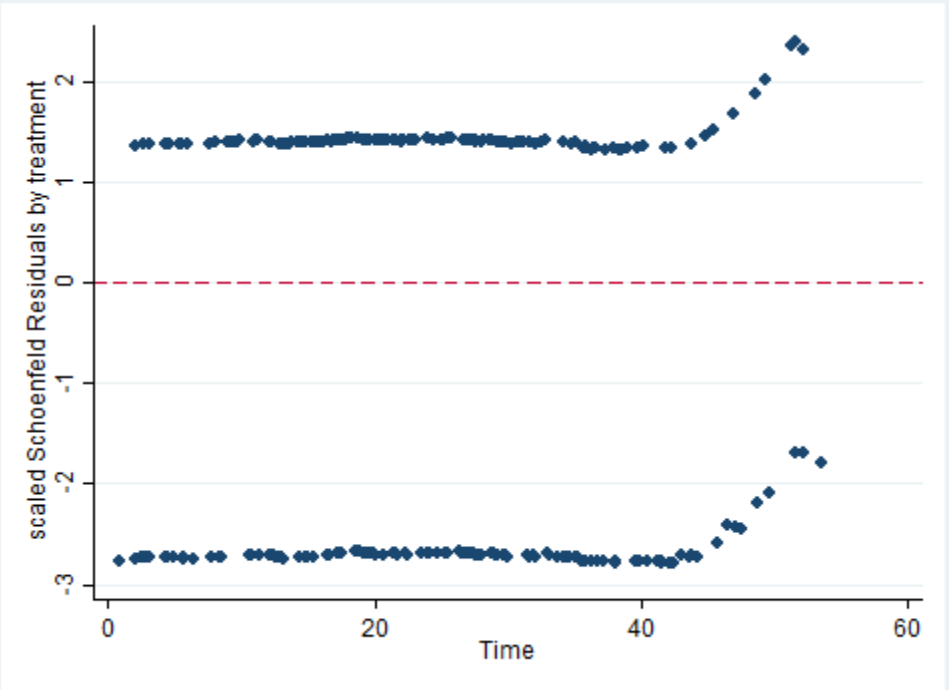

Figure 2 Schoenfeld residuals plot for OS data from the MONARCH 2 trial

OS=overall survival

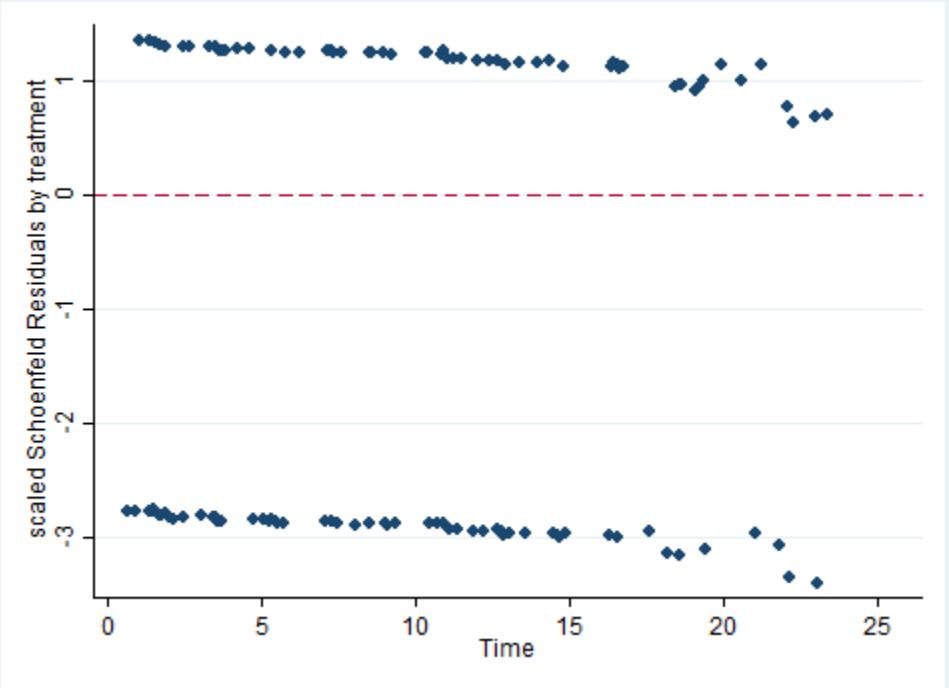

Figure 3 Schoenfeld residuals plot for PFS data from the MONALEESA-3 trial

PFS=progression-free survival

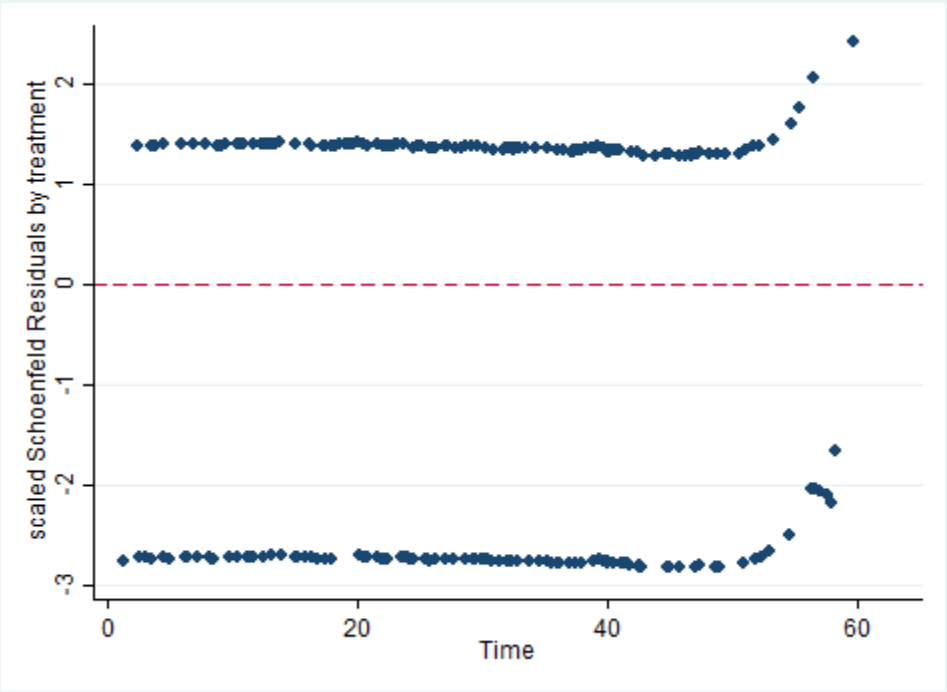

Figure 4 Schoenfeld residuals plot for OS data from the MONALEESA-3 trial

OS=overall survival