Palbociclib in combination with fulvestrant for treating advanced, hormone-receptor positive, HER2-negative breast cancer after endocrine therapy (a cost comparison using TA619 with post CDF update)

For Public – confidential information has been redacted

Technology appraisal committee A [09 August 2022]

Chair: Jane Adam

Evidence assessment group: LRiG

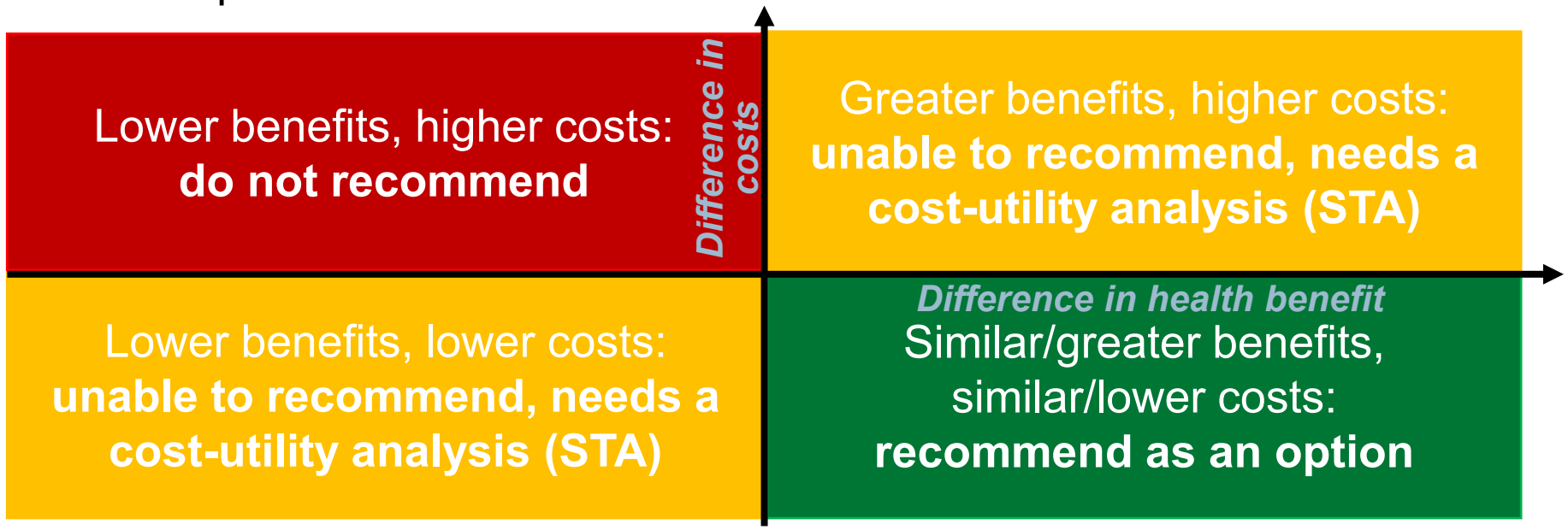
Technical team: Catherine Spanswick, Sana Khan, Rufaro Kausi, Janet Robertson

Company: Pfizer

NICE

Cost comparison appraisal

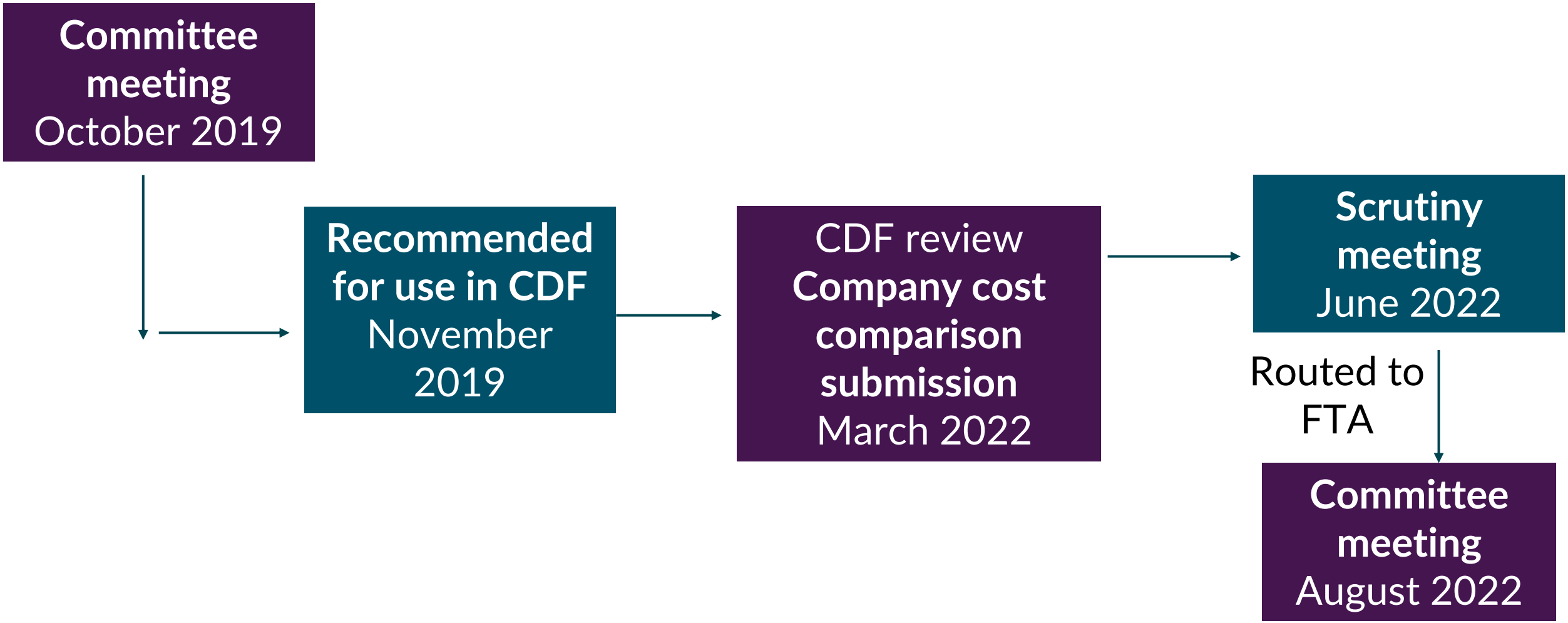
- Cost comparison appraisals are considered if the technology provides similar or greater benefits at a similar or lower cost to a NICE recommended comparator
- There are three possible recommendations



- If a technology is recommended through cost comparison, guidance states:
  "if patients and their clinicians consider both the technology and comparator/s to be suitable treatment, the least costly should be used"

Abbreviations: STA, single technology assessment

History of ID3779



Current appraisal: FTA (cost comparison) using updated data following time in the CDF

Abbreviations: CDF, cancer drugs fund; FTA, fast-track appraisal

Scrutiny panel report summary

Key: Low | Unclear | High

Questions to panel:	Perceived risk level
Is the technology pharmacologically similar to the comparator(s)?	Low
Has the company made a comparison to a relevant NICE-recommended comparator?	Low
Has the company presented evidence using the same outcome measures as those used in the cost-effectiveness model for the NICE-recommended comparator?	Low
Does the technology have similar (or improved) efficacy to the comparator? How robust is the evidence?	Low
Is the adverse event profile of the technology similar to that of the comparator? How robust is the evidence?	Unclear
Overall, is the treatment likely to offer similar or improved health benefits compared with the comparator?	Low
Is the claim for clinical similarity supported by comments received during the scoping consultation, and in any professional/patient organisation/expert submissions for this appraisal?	High
Are the healthcare resource costs associated with the technology likely to be similar to/lower than the respective costs for the NICE recommended comparator?	Low
Is the technology likely to affect the downstream costs of managing the condition (for example, subsequent treatments) and has this been accounted for?	Unclear
Are the overall costs for the technology similar to/lower than the comparator?	Low
Has the company used the same data sources for resource costs as the comparator?	Low
Has the company provided sufficient information to make a scrutiny recommendation?	Low

Scrutiny panel conclusions on clinical effectiveness compared with abemaciclib plus fulvestrant and ribociclib plus fulvestrant

- Is the claim for clinical similarity supported by comments received during the scoping consultation, and in any professional/patient organisation/expert submissions for this appraisal?
- Considered HIGH risk because comments from patient organisation highlighted differences in adverse events profile between the 3 CDK 4/6 treatments noting that palbociclib and ribociclib have more similar profile compared to abemaciclib (more severe)
- ERG: Adverse event profile of palbociclib differs slightly for low grade events from comparators

- Quality of evidence: EAG note that the company has not provided any additional evidence to assess the comparative effect of different CDK 4/6 inhibitors
- Overall, the results of the MAICs comparing palbociclib plus fulvestrant versus abemaciclib plus fulvestrant and ribociclib plus fulvestrant (for OS and PFS) suggest similar or improved health outcomes with palbociclib
  - *Quality of evidence:* EAG note that the company appropriately conducted well-designed MAICs to account for the heterogeneity between trials

Abbreviations: CDK, cyclin-dependent kinase; MAIC, matching-adjusted indirect comparisons; OS, overall survival; PAL, palbociclib; PFS, progression-free survival

Treatment pathway: are the effectiveness and costs similar enough to the relevant comparators to recommend palbociclib with fulvestrant as an option?

People with advanced, hormone-receptor positive, HER2-negative breast cancer that has:
- progressed on or <12 months after ET in (neo)adjuvant setting (1st line endocrine resistant), or
- progressed on or after ET in advanced setting (2nd line endocrine resistant)

Palbociclib + fulvestrant	Abemaciclib + fulvestrant	Ribociclib + fulvestrant	Everolimus + exemestane
Recommended for use in CDF [TA619]	Recommended [TA725]	Recommended [TA687]	Recommended [TA421]

CDK 4/6 inhibitors + fulvestrant

EAG's clinical advisors: abemaciclib plus fulvestrant and ribociclib plus fulvestrant are current standard of care in NHS

Abbreviations: CDF, cancer drugs fund; CDK, cyclin-dependent kinase; ET, endocrine therapy; HER-2, human epidermal growth factor receptor-2

Patient and carer perspectives

- Diagnosis of incurable metastatic breast cancer difficult. Has huge impact on mental and physical health, and quality of life
- Patients value knowing there are effective treatments. Main advantages of this treatment:
    - improved patient choice; increased PFS; could delay starting systemic chemotherapy; 1 pill a day; 21 day cycle
- Disadvantages include:
    - Fulvestrant administered by injection requiring hospital/ GP visits
    - Side effects (neutropenia, fatigue, nausea, infections & anaemia)
    - "my skin is very dry and so is my hair… I do get bruising on my wrists"
- OS longer with palbociclib plus fulvestrant than fulvestrant alone, so patients can spend more quality time with friends and families and continue daily activities = better emotional wellbeing
- Side effect profile of palbociclib is more similar to ribociclib than abemaciclib, but it does not require same ECG monitoring as ribociclib

"The main advantage of this treatment is that it has worked – what more could you ask for?"

"[I] have found it very easy to tolerate and am already feeling the benefits… Knowing I am on a treatment that is very effective for many women allows me to carry on and enjoy my life"

No clinical expert submissions received

Palbociclib (Ibrance, Pfizer)

Marketing authorisation **November 2016**	…is indicated for the treatment of hormone receptor-positive, HER2-negative locally advanced or metastatic breast cancer: • in combination with an aromatase inhibitor *already appraised and recommended* • **in combination with fulvestrant in women who have received prior endocrine therapy** (part of MA covered in this appraisal)
Mechanism of action	Selective cyclin-dependent-kinase 4 and 6 inhibitor. When these are activated, can cause the cancer cells to grow and divide too quickly
Administration	**Palbociclib:** 125 mg oral tablet once daily for 21 consecutive days then 7 day break **Fulvestrant:** 500 mg intramuscular injections monthly (with an additional dose on day 15 of cycle 1 only)
List price	**Palbociclib:** £2,950 per pack of 21 tablets (covers one 28-day cycle) **Fulvestrant:** £261.21 per month (but double dosed during the first month) Combined £3,211 per course (£3,472 in first course due to fulvestrant's double dose)

Abbreviations: HER-2, human epidermal growth factor receptor 2

CDF recommendations of TA619

Committee agreed there were several uncertainties, including:

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

Some of these uncertainties could be resolved by collecting further data:

1. PALOMA-3 clinical trial
2. SACT data on overall survival

Abbreviations: CFD, cancer drugs fund

Clinical trial evidence: PALOMA-3 study design

- Updated OS analysis (and final planned PFS analysis) used for company cost-comparison
- Trial compared palbociclib plus fulvestrant with placebo plus fulvestrant:

	Palbociclib: PALOMA-3
Design	Phase III, multicentre, double-blinded RCT
Locations	17 countries (including UK)
Population	Adult women with HR-positive, HER2-negative unresectable or metastatic advanced breast cancer
Intervention	PAL+FUL (n=347)
Comparator(s)	placebo+FUL (n=174)
Primary outcome	Investigator-assessed PFS (RECIST v1.1)
Follow up for CDF review	Further treatment-effectiveness data presented.

- Comparators for this appraisal, abemaciclib plus fulvestrant and ribociclib plus fulvestrant, were also compared with placebo plus fulvestrant in their clinical trials

Abbreviations: CDF, cancer drugs fund; FUL, fulvestrant; HER-2, human epidermal growth factor receptor 2; HR, hormone receptor; OS, overall survival; PAL, palbociclib; PFS, progression-free survival; RCT, randomised controlled trial

PALOMA-3 clinical trial: updated OS data

- Additional 28 mths of OS data (median follow up 73.3 mths)
- OS prolonged by 6.8 months with palbociclib plus fulvestrant:

[redacted]

ITT population	PAL+FUL (n=347)	placebo+FUL (n=174)
Events, n (%)	393/521 (75)	
Median OS, mths (95% CI)	34.8 (28.8 to 39.9)	28.0 (23.5 to 33.8)
Hazard ratio (95% CI) p-value	0.81 (0.65 to 0.99) p=0.022	

EAG

- Well-designed, good quality trial
- Participants may be more heavily pre-treated than in NHS clinical practice, but results are generalisable to NHS
- People treated with PAL+FUL had improved PFS, OS, ORR and CBR vs people treated with placebo+FUL

Abbreviations: CBR, clinical benefit rate; CI, confidence interval; FUL, fulvestrant; HR, hazard ratio; ORR, objective response rate; OS, overall survival; PAL, palbociclib; PFS, progression-free survival

Public Health England SACT data on overall survival

Palbociclib with fulvestrant:

- Data from 28 November 2019 to 27 February 2021:
- 1140 people received palbociclib with fulvestrant in CDF
- Median treatment duration 9.4 months (95% CI 8.4 to 10.8)
- 92% aged 50 years and over
- 81% had PS of 0 to 2 at start of treatment

- ***Median OS not reached*** (median follow-up 10 months)

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

- Sensitivity analysis in people with ≥6 months follow up = similar result

Abemaciclib with fulvestrant:
Same OS rate as palbociclib with fulvestrant at 6 and 12 months, over similar treatment duration (*RIB+FUL not estimable*)

Abbreviations: CDF, cancer drugs fund; CI, confidence interval; FUL, fulvestrant; OS, overall survival; PAL, palbociclib; PS, performance status; RIB, ribociclib; SACT, systematic anti-cancer therapy

Clinical effectiveness data used for cost-comparison

Covers:

- Palbociclib and comparators – the technologies and study designs
- Palbociclib and comparators – trial outcomes

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Palbociclib and comparator technologies

	Palbociclib	Abemaciclib	Ribociclib
Mechanism of action	All CDK 4/6 inhibitors which are structurally and functionally similar		
Marketing authorisation	Treatment of HR-positive, HER2-negative locally advanced or metastatic breast cancer in combination with fulvestrant *for women who have received prior ET*	Treatment of HR-positive, HER2-negative locally advanced or metastatic breast cancer in combination with fulvestrant *for women who have received prior ET*	
Administration and dose	125mg palbociclib orally once daily (21 days of 28-day cycle) plus 500mg fulvestrant intramuscular injection 2x first month then monthly	150mg abemaciclib orally twice daily (continuous) plus 500mg fulvestrant intramuscular injection 2x first month then monthly	600mg ribociclib orally once daily (21 days of 28-day cycle) plus 500mg fulvestrant intramuscular injection 2x first month then monthly

EAG's clinical advisors
The technologies all inhibit CDK 4/6 and share the same primary mechanism; however, there are some differences in *in vitro* potency against CDK 4 and 6 individually, and in dosing schedules, serum concentration and toxicity

Abbreviations: CDK, cyclin-dependent kinase; ET, endocrine therapy; HER-2, human epidermal growth factor receptor 2; HR, hormone receptor

Palbociclib and comparator clinical trial design and outcomes

- Three pivotal trials:

	Palbociclib: PALOMA-3	Abemaciclib: MONARCH 2	Ribociclib: MONALEESA-3
Design	Phase III, multicentre, double-blinded RCT		
No.	521	669	726
Menopause status*	Pre, peri or post	Pre, peri or post	Post
Progression	On or after endocrine therapy in (neo)adjuvant or metastatic setting		Not required
Intervention	PAL+FUL (n=347)	ABE+FUL (n=446)	RIB+FUL (n=484)
Comparator(s)	placebo+FUL (n=174)	placebo+FUL (n=223)	placebo+FUL (n=242)
Primary outcome	Investigator-assessed PFS (RECIST v1.1)		
Locations	17 countries (including UK)	19 countries (including Europe but not UK)	31 countries (including UK)

*In pre- and peri-menopausal women, prior endocrine therapy was combined with luteinizing hormone-releasing hormone agonist, to render these patients post-menopausal

Abbreviations: ABE, abemaciclib; FUL, fulvestrant; PAL, palbociclib; PFS, progression-free survival; RCT, randomised controlled trial; RECIST, Response Evaluation Criteria in Solid Tumours; RIB, ribociclib

Palbociclib and comparator studies: baseline characteristics

Characteristic	Palbociclib: PALOMA-3 (N=521)	Abemaciclib: MONARCH 2 (N=669)	Ribociclib: MONALEESA-3 (N=726)
Age group, %			
<65 years	75	63	53
>65 years	25	37	47
ECOG PS, %			
0	62	60	65
1	38	40	35
Prior chemotherapy, %			
(Neo)adjuvant	41	60	56
Metastatic	34	0	0
None	25	40	44

Abbreviations: ECOG, eastern cooperative oncology group; PS, performance status

Summary of PALOMA-3 and comparator trial outcomes

Outcome	Palbociclib: PALOMA-3		Abemaciclib: MONARCH 2		Ribociclib: MONALEESA-3	
	PAL+FUL	placebo+FUL	ABE+FUL	placebo+FUL	RIB+FUL	placebo+FUL
PFS, mths (95% CI)						
Median	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)
Hazard ratio	0.50 (0.40 to 0.62)		0.54 (0.45 to 0.65)		0.59 (0.48 to 0.73)	
Median follow-up	44.8 mths (April 2018)		47.7 mths (June 2019)		39.4 mths (June 2019)	
OS, mths (95% CI)						
Median	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)
Hazard ratio	0.81 (0.65 to 0.99)		0.76 (0.61 to 0.95)		0.73 (0.59 to 0.90)	
Median follow-up	73.3 mths (August 2020)		47.7 mths (June 2019)		56.3 mths (October 2020)	

Company

- PALOMA-3: proportional hazards assumption may be violated for PFS data but holds for OS data

EAG

- All PFS and OS hazard ratios are similar
- Proportional hazards assumption also violated for OS data in MONARCH 2
- Where proportional hazards assumption violated, hazard ratios cannot be meaningfully interpreted and should not be used to infer statistically significant differences (or lack of statistically significant differences)

Abbreviations: ABE, abemaciclib; CI, confidence interval; FUL, fulvestrant; NR, not reported; OS, overall survival; PAL, palbociclib; PFS, progression-free survival; RIB, ribociclib

Subsequent therapies in palbociclib and comparator studies

People who received subsequent therapy	Palbociclib: PALOMA-3		Ribociclib: MONALEESA-3	
	PAL+FUL (n=347)	placebo+FUL (n=174)	RIB+FUL (n=484)	placebo+FUL (n=242)
Any, %	[redacted]	[redacted]	70.2	78.5
CDK 4/6 inhibitor, %	[redacted]	[redacted]	14.0	30.0
Palbociclib	[redacted]	[redacted]	10.6	27.4
Abemaciclib	[redacted]	[redacted]	2.9	2.6
Ribociclib	[redacted]	[redacted]	4.1	5.8

Note: Data not collected in MONARCH 2 study of abemaciclib with fulvestrant

EAG

- Most patients received subsequent therapies; these can affect OS
- [redacted] had subsequent therapy after discontinuing study drug
- [redacted] had a subsequent CDK 4/6 inhibitor in MONALEESA-3 than PALOMA-3 – not NHS practice
- [redacted] had endocrine therapy as 1st subsequent therapy
- [redacted] had chemotherapy as 1st subsequent therapy in PALOMA-3 than MONALEESA-3

NICE Abbreviations: CDK, cyclin-dependent kinase; FUL, fulvestrant; OS, overall survival; PAL, palbociclib; RIB, ribociclib

Adverse events

Company

- CDK 4/6 inhibitors have broadly similar profile of Grade ≥3 AEs, however, important differences in some low grade AEs between CDK 4/6 inhibitors:

Type of AE	Palbociclib: PALOMA-3	Abemaciclib: MONARCH 2	Ribociclib: MONALEESA-3
	PAL+FUL (n=345)	ABE+FUL (n=441)	RIB+FUL (n=483)
Neutropenia, %			AEOSI:
Any grade	84.1	49.7	72.0
Grade ≥3	69.6	29.7	58.2
Diarrhoea, %			
Any grade	27.2	87.1	29.0
Grade ≥3	0	14.5	0.6

Neutropenia less common/ lower grade with ABE+FUL

Diarrhoea more common with ABE+FUL

EAG

- Grade ≥3 abdominal pain, dyspnoea, rash and fatigue more common with ABE+FUL than PAL+FUL or RIB+FUL
- Grade ≥3 liver function (ALT increased and AST increased) notably highest with RIB+FUL
- 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
- Lower rate of diarrhoea seen with PAL+FUL than ABE+FUL has potential impact on HRQoL

Abbreviations: ABE, abemaciclib; AE, adverse event; AEOSI, adverse event of special interest; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CDK, cyclin-dependent kinase; FUL, fulvestrant; HRQoL, health-related quality of life; MAIC, matching-adjusted indirect comparisons; PAL, palbociclib; RIB, ribociclib

Indirect treatment comparisons (ITCs)

Covers:

- Methodology of MAICs and Bucher ITC
- ITC results for OS and PFS:
  - versus abemaciclib plus fulvestrant
  - versus ribociclib plus fulvestrant
- Scrutiny panel conclusions on clinical effectiveness

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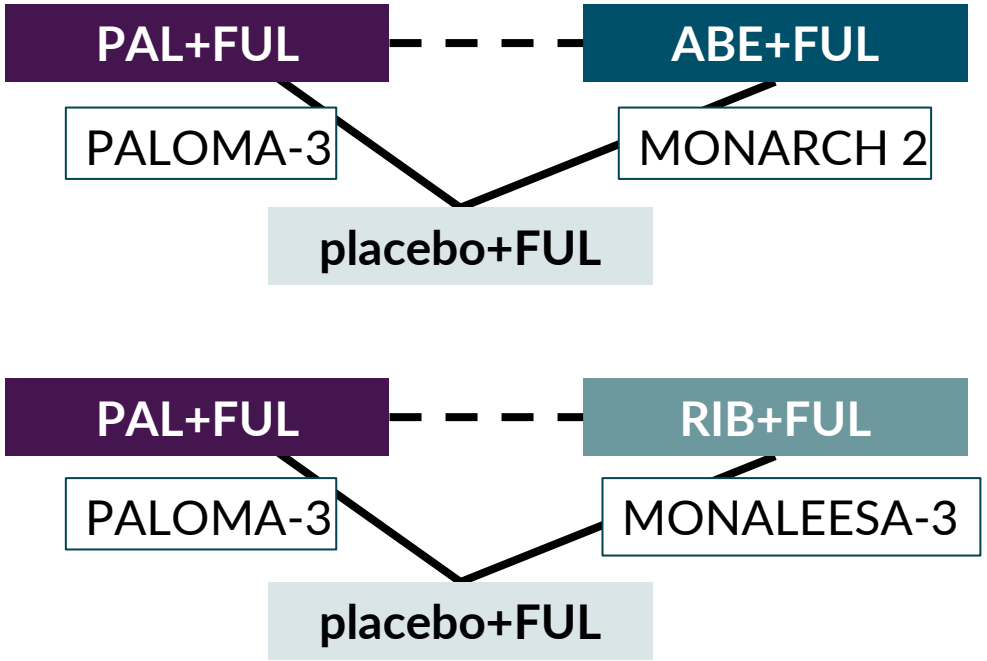
ITC methodology: MAIC and Bucher

Background

- In the MAICs, PALOMA-3 population was statistically adjusted to resemble MONARCH 2 and MONALEESA-3 populations, to predict treatment effect if PAL+FUL had been evaluated in these populations
- In addition to base-case analysis considering all effect modifiers, scenarios assessing impact of removing these in decreasing order of importance were implemented
- Bucher ITCs also done – assume 3 trials equivalent
- ITCs of efficacy outcomes only (OS and PFS)



EAG

- Differences between populations of 3 pivotal trials could lead to biased unadjusted ITC results
- Agrees with company approach to conducted well-designed MAICs to account for trial heterogeneity

Abbreviations: ABE, abemaciclib; FUL, fulvestrant; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; OS, overall survival; PAL, palbociclib; PFS, progression-free survival; RIB, ribociclib

ITC versus abemaciclib plus fulvestrant

Company - MAIC

- OS and PFS results [redacted]
- [redacted]

EAG

- [redacted]

Effect modifiers:

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
12) menopausal status

ITCs of PAL+FUL vs ABE+FUL	Sample size	OS HR (95% CI)	PFS HR (95% CI)
Anchored MAIC, **adjusted for all 12 effect modifiers**	[redacted]	[redacted]	[redacted]
Unadjusted Bucher	516	[redacted]	[redacted]

Abbreviations: ABE, abemaciclib; AI, aromatase inhibitor; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; ET, endocrine therapy; FUL, fulvestrant; HR, hazard ratio; ITC, indirect treatment comparison; MAIC, matched adjusted indirect comparison; mBC, metastatic breast cancer; OS, overall survival; PAL, palbociclib; PFS, progression-free survival; PS, performance status

ITC versus ribociclib plus fulvestrant

Company - MAIC

- OS [redacted]
- PFS:
  - Considering first 8 effect modifiers = [redacted]
  - Remaining scenarios (effect modifiers 1 to 7) = [redacted]
- Sample size reduced considerably with all 13 effect modifiers (requested by EAG)

EAG

- [redacted] for PAL+FUL versus RIB+FUL
- [redacted]

Effect modifiers:

1) prior ET setting
2) region
3) organs involved
4) prior chemotherapy
5) ER status
6) race
7) disease-free interval
8) metastatic site

Added at clarification…

9) measurable disease
10) prior tamoxifen
11) age group
12) ECOG PS
13) PR status

ITCs of PAL+FUL vs RIB+FUL	Sample size	OS HR (95% CI)	PFS HR (95% CI)
Anchored MAIC, **adjusted for first 8 effect modifiers**	[redacted]	[redacted]	[redacted]
Anchored MAIC, **adjusted for 13 effect modifiers**	[redacted]	[redacted]	[redacted]
Unadjusted Bucher	492	[redacted]	[redacted]

Company

EAG

Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; ER, oestrogen receptor; ET, endocrine therapy; FUL, fulvestrant; HR, hazard ratio; ITC, indirect treatment comparison; MAIC, matched adjusted indirect comparison; OS, overall survival; PAL, palbociclib; PFS, progression-free survival; PR, progesterone receptor; PS, performance status; RIB, ribociclib

Cost-comparison

Covers:

- Costs and assumptions
- Scrutiny panel conclusions on costs and panel outcome

Results presented in Part 2

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Costs and assumptions

Company
Drug acquisition, administration, monitoring and AEs were included in the cost comparison

Assumptions:
- Administration costs for fulvestrant only (33% in primary care, 67% as outpatient)
- No discounting
- No drug wastage; subsequent treatment costs excluded
- AE rates from most up-to-date publicly available data; vary by treatment
- Unit costs per grade 3/4 AE same for each treatment
- Monitoring differs by treatment:
  - palbociclib – full blood count
  - abemaciclib – full blood count, AST and ALT
  - ribociclib – full blood count, ECG, serum electrolytes and liver function test

EAG: Company's cost-comparison approach is reasonable

 Abbreviations: AE, adverse events; AST, aspartate transferase; ALT, alanine aminotransferase; ECG, electrocardiogram

Scrutiny panel conclusions on costs and panel outcome

- The list price acquisition costs of the 3 CDK 4/6 inhibitors are different, but they lead to the same average cost of a course of treatment
  - *EAG note:* [redacted]
- Drug monitoring and adverse event management costs differ across the 3 trials, but these are small proportion of total costs and sensitivity analyses show that they do not affect the conclusions from base case results
- Downstream costs of managing the condition unaffected
- Overall, costs for patients with palbociclib plus fulvestrant are lower than those for the comparators plus fulvestrant
  - The company has chosen appropriate resource use data sources

Outcome communicated with stakeholders:
"NICE has considered this topic in line with the selection criteria for a Fast Track Appraisal (FTA) and can confirm that the selection criteria are met, and that the appraisal can proceed as an FTA"

Abbreviations: CDK, cyclin-dependent kinase; PFS, progression-free survival

Issues for consideration by the Committee

- Is it satisfied that the 3 CDK 4/6 inhibitors with fulvestrant are sufficiently similar in terms of clinical effectiveness, to consider them clinically interchangeable?

- Is it satisfied that a cost comparison approach is appropriate and has been conducted appropriately by the company?

For Part 2 – where results with confidential PAS discounts will be presented

- Is it satisfied that palbociclib plus fulvestrant is associated with similar or lower costs than the comparators?

- Can palbociclib plus fulvestrant be recommended for use in routine commissioning through this Fast Track Appraisal?

Abbreviations: PAS, patient access scheme

Cost-comparison results including PAS discounts are reported in PART 2 slides because they confidential

Abbreviations: PAS, patient access scheme

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Thank you.