Alpelisib in combination with fulvestrant for treating advanced hormone-receptor positive, HER2-negative, PIK3CA-mutated breast cancer

Redacted

Technology appraisal committee A, 10 May 2022

Chair: Brian Shine

Lead team: Peter Baker, Michael V Holmes

Evidence assessment group: Sheffield

Technical team: Jane Adam, Catherine Spanswick, Michelle Green, Henry Edwards

Company: Novartis

NICE

Alpelisib with fulvestrant not recommended

Cannot be recommended for routine use or for use in Cancer Drugs Fund

Clinical effectiveness

- No direct evidence comparing alpelisib plus fulvestrant (A+F) with everolimus plus exemestane (Ev+Ex)
- Clinical trial evidence either did not compare A+F with other treatments, or only included a small number of people who would be eligible for A+F in clinical practice
- Indirect comparisons suggest A+F may be more effective than Ev+Ex, but analyses highly uncertain

Cost effectiveness

- Results of the economic model show A+F is not a cost-effective use of NHS resources
- Limitations in clinical evidence mean results very uncertain

Cancer Drugs Fund

- Issues with clinical evidence would not be resolved by ongoing studies
- Company's base case was not plausibly cost effective, and the committee's preferred assumptions would likely further increase the ICER

Abbreviations: A, alpelisib; Ev, everolimus; Ex, exemestane; F, fulvestrant; ICER, incremental cost-effectiveness ratio.

Recap from 1st meeting

NICE National Institute for Health and Care Excellence

Alpelisib (Piqray, Novartis)

Table 1 Technology details

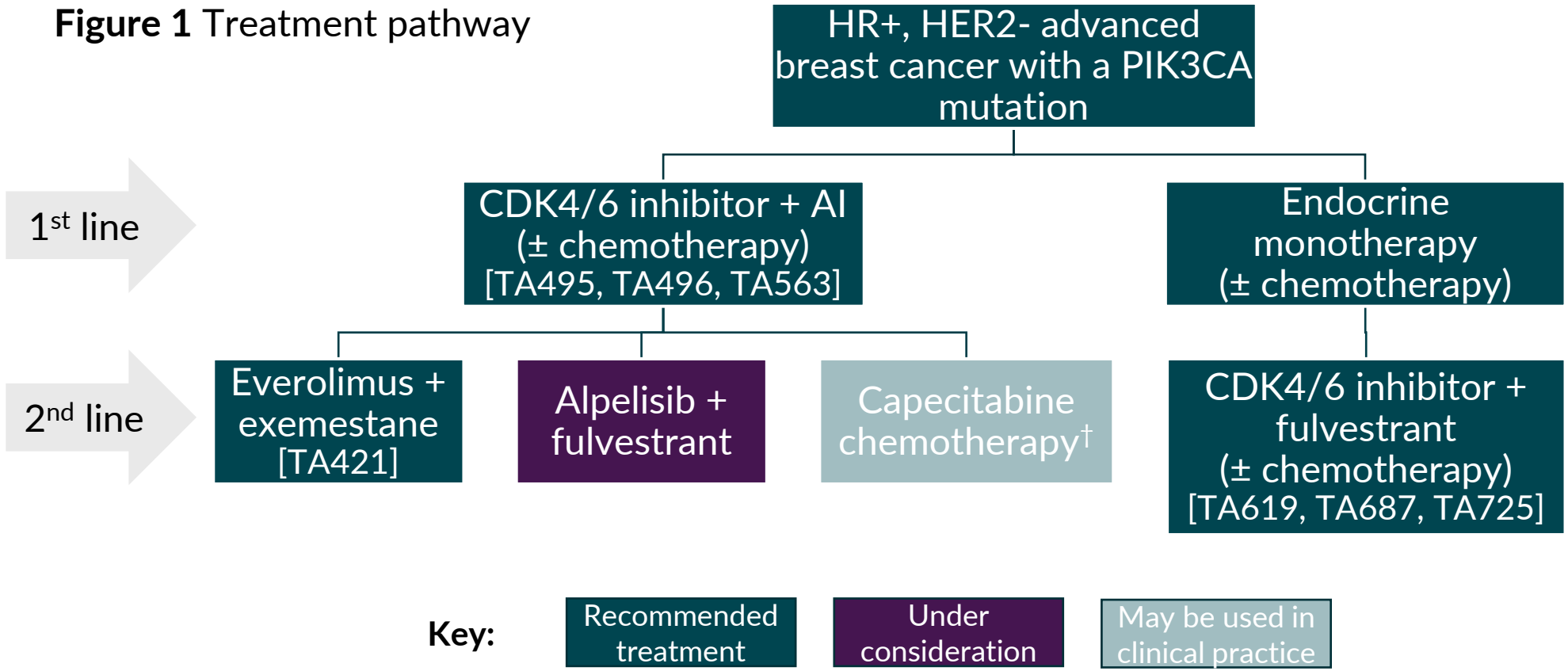
Marketing authorisation	• Indicated in combination with fulvestrant for the treatment of postmenopausal women, and men, with hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer with a PIK3CA mutation after disease progression following endocrine-based therapy • MHRA • Granted (2020), variation approved December 2021 • **Note**: company submission is narrower than licence, focusing on: People with HR+, HER2-negative advanced breast cancer with a PIK3CA mutation after disease progression following *a CDK4/6 inhibitor*
Mechanism of action	• Alpelisib is an oral tyrosine kinase inhibitor highly selective for the catalytic subunit alpha of PI3K
Administration	• Oral
Price	• Alpelisib: 150 mg film-coated tablets; pack 56 tablets £4,082.14 (1 cycle) • Alpelisib + fulvestrant at list price: £6,170.70 for loading dose and £5,126.42 for subsequent cycles (each 28 days); total for 12 months £67,687.74 • PAS for alpelisib (and fulvestrant) approved by NHS England • **Company improved its PAS in response to Appraisal Consultation Document (ACD)**

Abbreviations: HER2, human epidermal growth factor receptor 2; HR, hormone receptor; MHRA, Medicines and Healthcare products Regulatory Agency; PAS, patient access scheme; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

Treatment pathway

In postmenopausal women, and men, including pre- and peri-menopausal women who have ovarian suppression as 1st line treatment*

Figure 1 Treatment pathway



*Wording of any recommendation may be made in 'people' rather than by gender in line with NICE's commitment to promoting equality in all aspects of our work

†Because of tolerability issues with Ev+Ex, some people have oral capecitabine chemotherapy instead

Abbreviations: AI, aromatase inhibitor; CDK4/6, cyclin-dependent kinase; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

Clinical evidence

A+F investigated in 2 studies, populations in submission had confirmed PIK3CA mutation

Table 2 Study designs

	BYLieve cohort A (N=127)	SOLAR-1 PIK3CA-mutated cohort (N=341) (n=20 CDK4/6 inhibitor pre-treated)
Study design	Non-randomised, open-label, phase 2 study	Randomised, double-blind, phase 3 trial
Population	• Pre-, peri- and post-menopausal women, or men • HR+, HER2– ABC • Prior CDK4/6 inhibitor + AI	• Post-menopausal women, or men • HR+, HER2– ABC • Prior AI
Intervention	A+F	
Comparator	None	Placebo + F
1° endpoint	PFS at 6 months (locally assessed)	PFS (locally assessed)
2° and other endpoints	• OS, PFS, objective response rate, clinical benefit rate, duration of response • Safety	• OS, objective response rate, clinical benefit rate, time to response, duration of response • Safety
Quality of life	-	EQ-5D-5L

Abbreviations: A, alpelisib; ABC, advanced breast cancer; AI, aromatase inhibitor; CDK4/6, cyclin-dependent kinase; EQ-5D, EuroQol-5d; F, fulvestrant; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; OS, overall survival; PFS, progression-free survival.

Results of BYLieve and SOLAR-1 of alpelisib + fulvestrant

Used in Bucher indirect treatment comparison to compare with Ev+Ex

Clinical effectiveness in 2nd-line population of BYLieve – A+F after CDK4/6 inhibitor + AI

- Median duration of follow-up 11.7 months
- Results used in economic model (for A+F OS, PFS and TTD):

Table 3 PFS in 2nd-line population

	A+F
N events/N patients	[redacted]/[redacted]
Median PFS (95% CI), months	[redacted]

Table 4 OS in 2nd-line population

	A+F
N events/N patients	[redacted]/[redacted]
Median OS (95% CI), months	[redacted]

Clinical effectiveness in PIK3CA-mutated cohort of SOLAR-1 – A+F after AI

- Median duration of follow-up 42.4 months
- Results used in economic model (as part of Bucher ITC to estimate Ev+Ex OS and PFS):

Table 5 PFS in 2nd-line population (n=[redacted])

	A+F	Placebo+F
Median PFS, months	[redacted]	[redacted]
Hazard ratio (95% CI)	[redacted]	

Table 6 OS in 2nd-line population (n=[redacted])

	A+F	Placebo+F
Median OS, months	[redacted]	[redacted]
Hazard ratio (95% CI)	[redacted]	

Abbreviations: A, alpelisib; AI, aromatase inhibitor; CDK, cyclin-dependent kinase; CI, confidence interval; Ev, everolimus; Ex, exemestane; F, fulvestrant; OS, overall survival; PFS, progression-free survival; N, number; NR, not reached.

Bucher indirect treatment comparison used in company base case
No direct clinical evidence for A+F vs Ev+Ex

- Indirect analysis in proxy 2nd line treatment setting: A+F in SOLAR-1 vs Ev+Ex

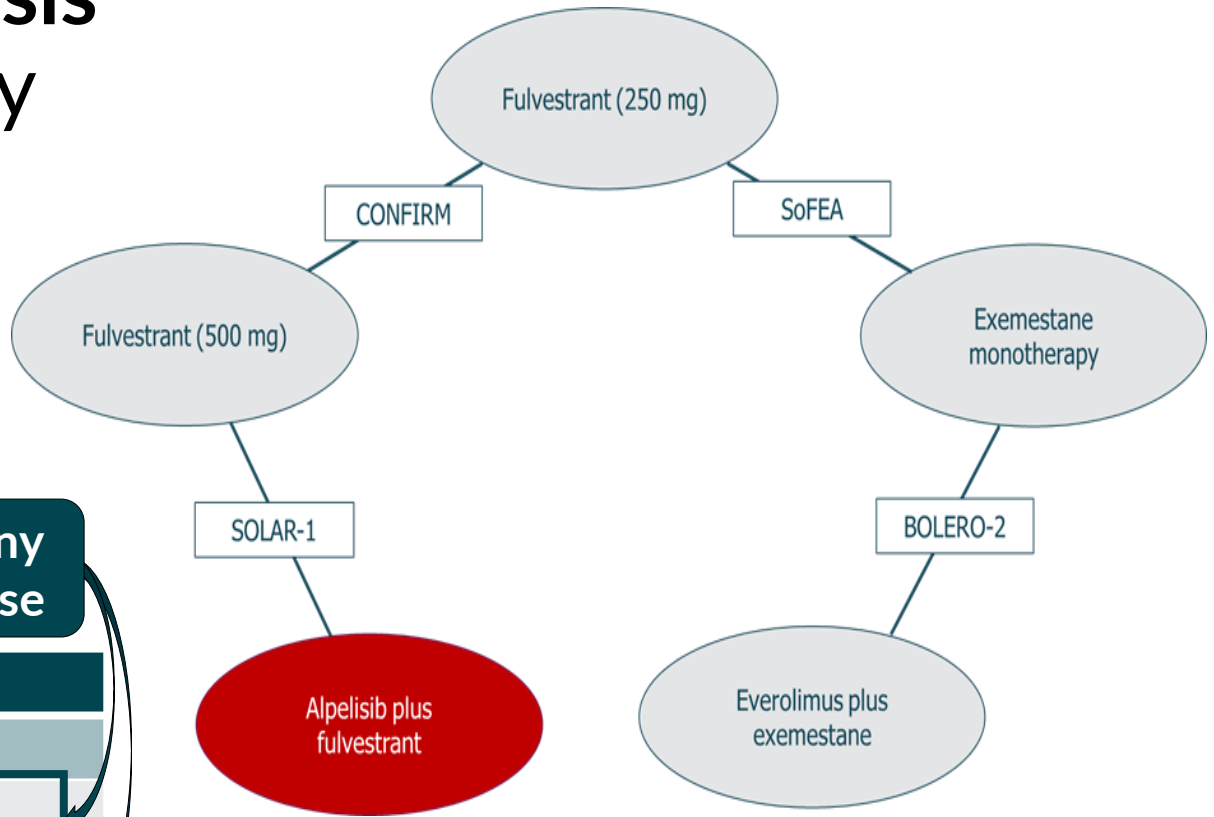
Table 7 Additional trials used in Bucher indirect analysis

	BOLERO-2 (N=724)	SoFEA (N=723)	CONFIRM (N=736)
Study design	Randomised, double-blind, placebo-controlled, phase 3 trial	Randomised, double-blind, controlled, phase 3 trial	Randomised, double-blind, placebo-controlled, phase 3 trial
Population	• Post-menopausal • HR+, HER2– ABC • Progressed on endocrine therapy	• Post-menopausal • HR+, HER2– or HER2+ (or unknown) ABC • Progressed on non-steroidal AI	• Post-menopausal • HR+, HER2- or HER2+ ABC • Progressed on endocrine therapy
Treatments	Ev+Ex, vs placebo + Ex	Ex vs F (250 mg) + placebo*	F (250 mg) + placebo, vs F (500 mg)
1° endpoint	PFS (locally assessed)	PFS	PFS
2° endpoints	• OS • Objective response rate, clinical benefit rate • Adverse events	• OS • Objective response rate, clinical benefit rate, duration of response • Adverse events	• OS • Objective response rate, clinical benefit rate, duration of response • Adverse events
Quality of life	EORTC QLQ-C30	-	FACT-B

*Also vs F + anastrozole

Abbreviations: A, alpelisib; ABC, advanced breast cancer; AI, aromatase inhibitor; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire-C30; Ev, everolimus; Ex, exemestane; F, fulvestrant; FACT-B, Functional Assessment of Cancer Therapy–Breast; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; OS, overall survival; PFS, progression-free survival.

Results of Bucher indirect analysis
2nd-line population used as proxy



Background:

- Reverse Bucher method, using hazard ratios for A+F to determine those for comparator Ev+Ex
- Wide confidence intervals of hazard ratios

Results:

Table 8 HR (95%CI) of Ev+Ex versus:

	Placebo+F	A+F
Progression-free survival		
Hazard ratio (95% CI)	[redacted]	[redacted]
Overall survival		
Hazard ratio (95% CI)	[redacted]	[redacted]

Company base case

ACD (3.9):

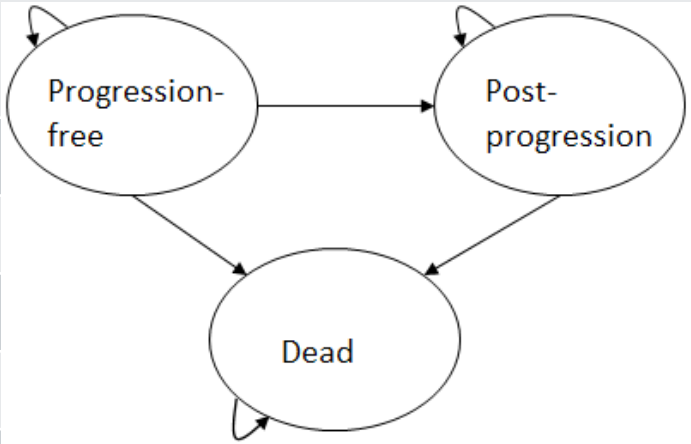
- Committee questioned internal validity of Bucher results as when comparing placebo+F with Ev+Ex, 1 treatment was favoured for progression-free survival and the other was favoured for overall survival

Abbreviations: A, alpelisib; AI, aromatase inhibitor; CI, confidence interval; Ev, everolimus; Ex, exemestane; F, fulvestrant; HR, hazard ratio.

Company's model

Table 9 Model description

Model type	Partitioned survival model (progression-free, post-progression, dead)
Population	Adult women with endocrine resistant HR+, HER2- advanced mutation, who have received prior CDK4/6 inhibitor therapy
Intervention	A+F
Comparator	Ev+Ex
Time horizon	40 years (lifetime)
Model cycle	28 days (half-cycle correction applied)
Discount rates	3.5% for both health and cost outcomes
Utility values	SOLAR-1 trial EQ-5D-5L, mapped to EQ-5D-3L, and published literature; adjusted for older-age decrease in health related quality of life
Costs	- BNF costs 2020 - NHS Reference Costs 2019/2020 - Confidential discounts available for modelled drugs. Discussed in part 2 only
Perspective	NHS and Personal Social Services



Abbreviations: A, alpelisib; BNF, British National Formulary; CDK, cyclin-dependent kinase; EQ-5D, EuroQol-5d; Ev, everolimus; Ex, exemestane; F, fulvestrant; HER2, human epidermal growth factor receptor 2; HR, hormone receptor.

Appraisal consultation document
Conclusions and uncertainties (1/3)

Table 10 ACD conclusions and uncertainties

	Committee conclusion	Discuss?	ACD
Treatment pathway	Company's positioning of A+F as second line after disease progression on a CDK4/6 inhibitor + AI appropriate	No	3.3
Comparators	Ev+Ex is most relevant comparator for this appraisal	No	3.4
Effectiveness in relevant population	Population of BYLieve generalisable to the NHS BYLieve suggests A+F may be clinically effective, but highly uncertain due to lack of comparative data	No *Uncertainty*	3.5, 3.6
Comparative effectiveness	SOLAR-1 limited because it only included 20 people relevant to appraisal	No	3.7
Adverse events	A+F associated with grade 3 or higher adverse events that need additional monitoring	No	3.8

Abbreviations: A, alpelisib; AI, aromatase inhibitor; CDK, cyclin-dependent kinase; Ev, everolimus; Ex, exemestane; F, fulvestrant.

Appraisal consultation document
Conclusions and uncertainties (2/3)

Table 10 ACD conclusions and uncertainties *continued*

	Committee conclusion	Discuss?	ACD
Indirect treatment comparison	Results of Bucher analysis highly uncertain for several reasons	Yes *Uncertainty*	3.9, 3.10
	A+F may be more effective than Ev+Ex, but results highly uncertain	Yes *Uncertainty*	3.11
Economic model	Company's economic model suitable for decision making	No	3.12
Modelled outcomes	Overall survival and progression-free survival estimates highly uncertain	No *Uncertainty*	3.13
Modelled treatment effect	Relative treatment effect of A+F compared with Ev+Ex highly uncertain	Yes *Uncertainty*	3.14
Duration of treatment effect	Assumption of indefinite treatment effect is optimistic	Yes - **updated**	3.15

Abbreviations: A, alpelisib; AI, aromatase inhibitor; Ev, everolimus; Ex, exemestane; F, fulvestrant

Appraisal consultation document
Conclusions and uncertainties (3/3)

Table 10 ACD conclusions and uncertainties *continued*

	Committee conclusion	Discuss?	ACD
Utilities	Reasonable to assume equal utilities for both treatments	No	3.16
Post-progression utility	Appropriate utility value after disease progression is uncertain and may be overestimated by company	Yes *Uncertainty*	3.17
Post-progression treatment costs	Treatment costs after disease progression are reasonable but uncertain	No *Uncertainty*	3.18
End of life	Whether A+F meets end of life criteria has not been robustly shown by evidence presented	Yes *Uncertainty*	3.19
Cost-effectiveness results	Committee preferred probabilistic model because this took account of uncertainty in modelling; would take both deterministic and probabilistic ICERs into account in decision making	Yes – **updated**	3.20
Other	A+F is not innovative	No	3.23

Abbreviations: A, alpelisib; F, fulvestrant; ICER, incremental-cost effectiveness ratio

Consultation responses

NICE National Institute for Health and Care Excellence

ACD consultation responses

Received from

- **Company:** Novartis
- **2 patient organisations:**
  - METUP UK, including a patient testimony
  - Breast Cancer Now, including a patient testimony (also submitted directly by patient)
- **1 clinical expert:** [redacted]

METUP UK perspectives on ACD

Difficult to comment on modelling and interpretations of evidence
In era of personalised medicine, alpelisib should be recommended

Problems with information accessibility and transparency:

- Discussion of models inaccessible to lay people, so looked an ESMO guidelines recognising these do not take into account value for healthcare systems
    - *ESMO guidelines: A+F is a treatment option for patients with PIK3CA-mutant tumours…*
- Can't comment on evidence interpretation due to redaction of trial data and treatment / comparator costs

NICE recommendations not a sound basis for NHS guidance:

- Successive health secretaries have lauded genomics as the future for cancer care. Government published *Genome UK: the future of healthcare (2020)* hails NHS use of personalised medicine and pharmacogenomics
- Genomic testing for PIK3CA mutation being rolled out in NHS from April 2022
- Not recommending a blow for patients who know they have a mutation when there is a targeted treatment
- Alpelisib is the first treatment available which targets the PIK3CA mutation = innovative
- Patient advocate with PIK3CA mutation:
    - *'NICE… have taken this opportunity and thus my hope for the future away' …*
    - *'What is the point in telling patients they have this mutation and then not allowing us to access the drugs?'*
    - *'ESMO recommendation for A+F indicates that this treatment is being used in many European countries'*

Abbreviations: A, alpelisib; ESMO, European Society for Medical Oncology; F, fulvestrant

Breast Cancer Now perspectives on ACD

Disappointed A+F not recommended – would improve options and is first targeted treatment for PIK3CA-mutated advanced breast cancer

- Difficult to understand why Cancer Drugs Fund (CDF) not being considered… Whilst there may not be a suitable clinical trial ongoing that will resolve the uncertainties that exist, … data collection can include SACT and population-based datasets… welcome clarity on reasons why the CDF is not being explored
- Following progression on CDK 4/6 inhibitor + AI there are limited effective treatment options – with Ev+Ex generally having poor uptake due to side effect profile and therefore in some instances single agent capecitabine being preferred. A+F could provide an important new option, especially as PIK3CA mutations can be associated with a poorer prognosis and increased resistance to treatments
- Urge flexibility regarding end of life criteria given the uncertainties that have been highlighted and given that it is possible that alpelisib with fulvestrant does meet end of life criteria
- Surprised A not recognised as an innovative treatment, given role PIK3CA may play in progression and that the treatment specifically targets this and could provide a new option
- Urge the company, Novartis, and NICE to work together to consider every possible solution

Abbreviations: AI, aromatase inhibitor; CDF, Cancer Drugs Fund; SACT, Systemic Anti-Cancer Therapy.

Patient perspectives on ACD

Testimony of patient (NHS neurologist) with recurrence of ER-positive breast cancer after CDK4/6 inhibitor + AI– non-resectable and expressing PIK3CA

- Endocrine resistance
  - PIK3CA mutation… directly contributed to endocrine resistance, resulting in my recurrence and my current prognosis
- PIK3CA and recurrence
  - My risk of developing more visceral disease without targeted treatment for PIK3CA is very high… Options are crucially important for patients in my position
- Targeted treatment
  - It is important to me as patient that I can access a drug which targets a mutation I know that I have
- High unmet need
  - …high unmet need .. I am one of 40% of women who develop this mutation as a cause for their recurrence and I now have incurable breast cancer
- Caring responsibilities
  - Without this treatment my options for survival to look after my children (aged 12 and 16) are significantly reduced
- Progression-free survival
  - Progression free survival means the world to me as it means I can spend more vital time with my family

Abbreviations: AI, aromatase inhibitor; ER, oestrogen receptor

Clinical expert perspectives on ACD

Comments on consideration of comparator treatment(s)

- Current treatment – *not 'usually only everolimus with exemestane', it may also be chemotherapy*
- Clinical trial evidence – *there is also no clinical trial evidence for the use of everolimus + exemestane compared to chemotherapy. Inconsistent to allow a 'legacy regimen', an expensive treatment option with no evidence, but not a new targeted treatment for a smaller population*
- '…most people have everolimus plus exemestane in NHS practice' – *how has this figure been arrived at? What about the number receiving single agent chemotherapy?*

Company ACD response summary

Model driver
Unknown impact
Small/Moderate impact

Table 11 Company ACD responses

Issue	Committee preferences	Company updated base case?	ERG critique	Impact on ICER
Bucher indirect analysis	Notes company restricted BOLERO-2 dataset to 2nd line and PIK3CA mutation identified in tumour tissue	No – restricted	Notes uncertainty	
	Notes high uncertainty – potential of HER2 status to be an effect modifier in population of SoFEA	No – full population	Sensitivity analysis HER2-subgroup	
Post-progression utility values	Appropriate utility value after disease progression is uncertain and may be overestimated by company	No – uses Mitra 0.69	Explores: 0.51, 0.69, [redacted]	
Duration of treatment effect	Assumption of indefinite treatment effect is optimistic	**Yes** – 5 year duration	Explores: 3 and 5 years	
Cost-effectiveness results	Probabilistic model, to take account of uncertainty; would take both models into account in decision	**Yes** – PSA constraint added	Disagrees – no PSA constraint	
End of life	Concluded that it was possible that A+F met end of life criteria, but this was not shown robustly enough by the evidence so far presented	Criteria met	Criteria not always met	N/A

Abbreviations: ICER, incremental-cost effectiveness ratio; PSA, probabilistic sensitivity analysis

Bucher indirect analysis: PIK3CA mutation identification

ACD 3.9

NICE National Institute for Health and Care Excellence

Key issue: Method of PIK3CA mutation identification in ITC

ACD

- ...company restricted the dataset of BOLERO-2 to the second-line population with a PIK3CA mutation based on tumour tissue sample. This led to 92% of patients [with plasma sampling] being excluded

Company response

- Tumour sampling of PIK3CA mutation status used in SOLAR-1 and BYLieve – data from tumour sampling used in BOLERO-2 for consistency and to avoid potential bias through different sampling methods
- In BOLERO-2, hazard ratios for progression-free survival differed depending on sampling method (Table 12)

ERG comments

- Hazard ratio for BOLERO-2 subgroup in ITC less favourable to Ev+Ex (0.61) than HRs for wider populations:

Table 12 BOLERO-2 results by subgroup

Subgroup	N (%)	PFS HR for Ev+Ex vs Ex (95% CI)	Source
Mutation in tumour tissue, 2nd line (ITC)	57	0.61 (0.33 to 1.14)	Company submission
Mutation in tumour tissue	143	0.51 (0.34 to 0.77)	Hortobagyi 2016
Mutation in plasma-derived cell-free DNA	238	0.37 (0.27 to 0.51)	Moynahan 2017

- ERG understands company's rationale for restricting BOLERO-2 population but notes it increases uncertainty in Bucher ITC

Is committee happy with restricting the BOLERO-2 population to those with PIK3CA mutation identified in tumour tissue?

NICE Abbreviations: CI, confidence interval; Ev, everolimus; Ex, exemestane; HR, hazard ratio; ITC, indirect treatment comparison

Bucher indirect analysis: population of SoFEA

ACD 3.10

NICE National Institute for Health and Care Excellence

Key issue: Population of SoFEA in Bucher indirect analysis

ACD

- Bucher analysis highly uncertain for several reasons… potential for HER2 status to be an effect modifier

Company response

- NICE appraisals of CDK4/6i+F in HER2-negative disease use overall population of CONFIRM and SoFEA
- Insufficient data to conclude that HER2 status is a treatment effect modifier
- HER2 status unknown for ~35% of SoFEA, restricting to known HER2 status may lead to information bias
- Use of the full population of SoFEA in line with CONFIRM (where results by HER2 status not available)
- Hazard ratios predict Ex more effective than F for HER2-negative subgroup of SoFEA – lacks face validity

ERG comments

- In all 3 appraisals of CDK4/6i+F, committee papers note SoFEA is not restricted to HER2-negative patients and that this is a source of heterogeneity and/or may impact on outcomes
- Treatment effect modifier?
  - Company Submission* notes HER2 status may be important treatment effect modifier in SoFEA
  - ERG's clinical advisors stated HER2 status may be an important treatment effect modifier
  - ERG considers that most relevant data (HER2-negative subgroup) should be used where available
- Information bias unlikely, unless HER2-negative patients with unknown HER2 status expected to have different outcomes to HER2-negative patients with known HER2 status
  - 60% (n=283) of SoFEA were HER2-negative – a reasonably sized subgroup

*Company submission, Appendix D, looking at SoFEA subgroup analysis

Abbreviations: A, alpelisib; CDK, cyclin-dependent kinase; Ev, everolimus; Ex, exemestane; F, fulvestrant; HER2, human epidermal growth factor receptor 2

Key issue: Population of SoFEA in Bucher indirect analysis

ERG comments *continued*

- Although CONFIRM did not report results by HER2 status, other trials in network (SOLAR-1 and BOLERO-2) were restricted to HER2-negative populations. Ideally, data from CONFIRM would also be restricted to HER2-negative patients, but this is not possible
  - Influence on ITC results is unclear – *uncertainty*
- Unclear why company considers results for HER2-negative subgroup lack face validity
  - HRs for HER2-negative subgroup numerically similar to those for all patients, with neither showing a statistically significant treatment effect; HRs for OS numerically favour Ex over F (Table 13):

Table 13 SoFEA results: overall and by HER2 subgroup

Subgroup	N (%)	PFS HR for F vs Ex (95% CI)	OS HR for F vs Ex (95% CI)
All patients	480 (100)	0.95 (0.79 to 1.14)	1.05 (0.84 to 1.29)
HER2-negative	283 (60)	1.06 (0·83 to 1·34)	1.26 (0.95 to 1.66)
HER2 unknown	166 (35)	0.93 (0·68 to 1·27)	0.99 (0.69 to 1.41)
HER2-positive	31 (6)	0.20 (0·08 to 0·51)	0.30 (0.10 to 0.84)

- Reasonable to consider the impact of using only the HER2-negative subgroup of SoFEA in ITC and economic model – **provided a sensitivity analysis using ITC results based on HER2-negative subgroup**

Is committee satisfied with use of the full population of SoFEA in the base case?

Abbreviations: Ex, exemestane; F, fulvestrant; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; ITC, indirect treatment comparison; OS, overall survival; PFS, progression-free survival

Post-progression utility values

ACD 3.17

NICE National Institute for Health and Care Excellence

Key issue: Most appropriate post-progression utility value

ACD

- Appropriate utility value after disease progression is uncertain and may be overestimated by the company

Company response: *continues to prefer 0.69 value from Mitra et al*

- Changes to treatment landscape in advanced breast cancer over last 15 years since 0.51 value of Lloyd et al.
- Mitra et al. methodologically preferable – used EQ-5D to measure HRQL in people with breast cancer
- Interviews with 4 clinical experts at technical engagement* used to validate approach: all said patients in 3rd line setting would have a utility reflecting Mitra value, noting this was similar to [redacted] in SOLAR-1
- In TA725†, Mitra value noted as possibly too high considering patient experience during all subsequent treatments, including chemotherapy, but was accepted as a basis for decision making
- ERG's base-case used 'arbitrary' and 'pessimistic' value of [redacted]

ERG comments

- No new evidence from company – ERG concerned utility values of Mitra and SOLAR-1 implausibly high
- All 3 sources considered (Lloyd, Mitra, SOLAR-1) have limitations (see ERG's technical engagement response)
- Exploratory analysis used [redacted] informed by clinical advisors – 1 said midway between Lloyd and Mitra ([redacted]), 1 said [redacted] to [redacted] in 3rd line setting. May have greater face validity than available empirical estimates
- Company asked experts about plausibility of utility values in 3rd line setting. However, modelled health state relates to entire duration of survival after disease progression on 2nd line therapy, including all subsequent treatment lines and supportive care

What is committee's view on most appropriate post-progression utility estimate to use in the model?

*Inaccuracy in ACD about interview timing to be amended in subsequent guidance documents. †TA725: Abemaciclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy. Abbreviations: EQ-5D, EuroQol-5d; HRQL, health-related quality of life

Treatment effect waning assumptions

ACD 3.15

NICE National Institute for Health and Care Excellence

Key issue: Assumption of treatment effect waning at 5 years

ACD

- Model assumes an indefinite treatment effect which is optimistic

Company response

- Uncertainty in longevity of treatment effect for A+F vs Ev+Ex given an absence of long-term data
- ERG sensitivity analyses explored treatment effect duration of 3 or 5 years, but overly pessimistic to assume waning after 3 years
- Follow-up data beyond 3 years from SOLAR-1 (final OS analysis at 42.4 months) available for A+F:
  - [redacted] reduction in risk of disease progression or death vs placebo+F
  - 14% reduction in risk of death vs placebo+F*
- SoFEA / BOLERO-2 / CONFIRM in Bucher indirect analysis had 36 / 48 / 80 months' follow up
- **Provided updated base case assuming treatment waning at 5 years where modelled hazards of PFS and OS for A+F switch to those for Ev+Ex**

ERG comments:

- ACD does not specify Committee's preferred assumption about duration of relative treatment effect
- **ERG has presented updated scenario analyses with treatment waning at 3 years and 5 years using same approach as company**

Is committee satisfied with the company's revised assumption of waning of treatment effect for A+F versus Ev+Ex at 5 years?

*SOLAR-1 results for OS not cross the pre-specified O-Brien Fleming stopping boundary (one-sided p≤0.0161)

Abbreviations: A, alpelisib; Ev, everolimus; Ex, exemestane; F, fulvestrant; OS, overall survival; PFS, progression-free survival

Probabilistic sensitivity analyses

ACD 3.20

NICE National Institute for Health and Care Excellence

Key issue: Use of probabilistic analyses in decision-making

ACD

- Committee noted that probabilistic methods are generally considered most appropriate for decision making because they allow for full expression of the uncertainty in model parameters
- Company's probabilistic estimate of the ICER is substantially higher (around £10,000 per QALY gained) than its deterministic estimate, which was highly unusual
- Committee concluded that on balance it preferred to use the probabilistic model. Although it was skewed by some unrealistic values, it overall better accounted for uncertainty than the deterministic ICER. However, it would take both ICERs into account in its decision making

Company response

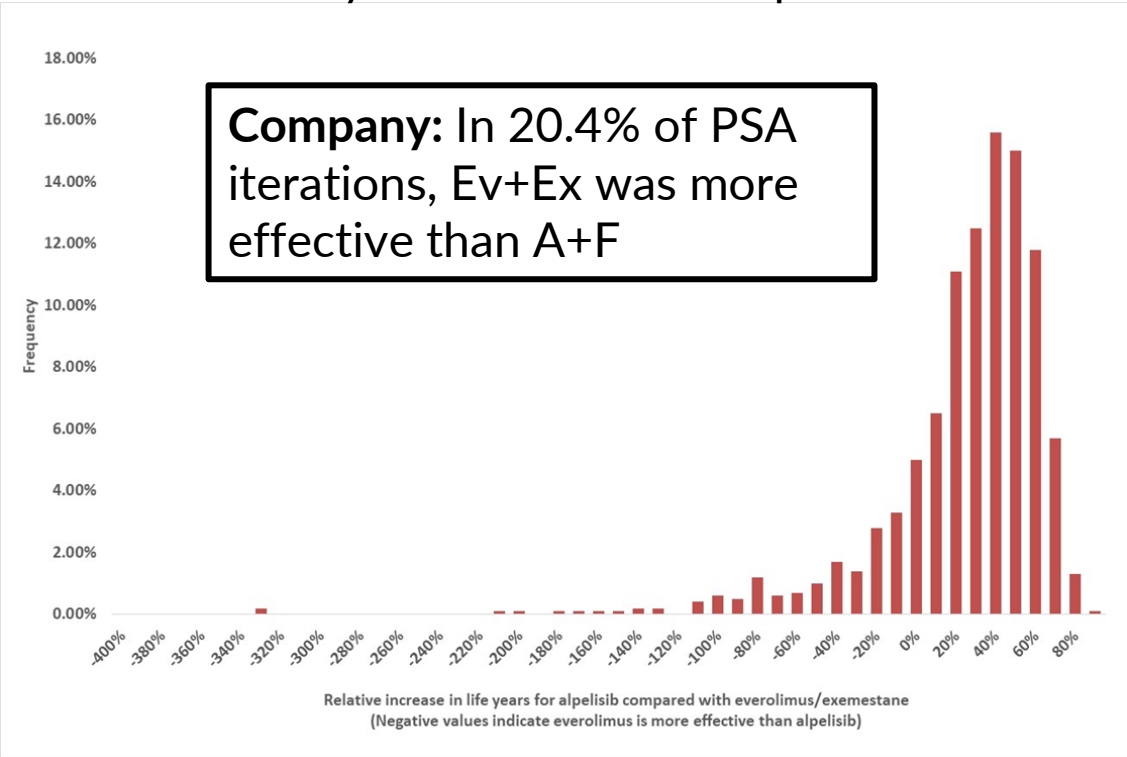
- Deterministic results more appropriate to inform the cost-effectiveness of A+F
- Results from PSA not suitable in current form – scope to introduce biases into interpretation of results
- While NICE methods guide (2013) applicable to this appraisal, updated guide (2022) provides clarity in how to handle uncertainty when analyses are clinically implausible
  - Consider expert elicitation to identify a plausible distribution of values
- Sought clinical opinion from 4 experts to identify extent of increase in life years for Ev+Ex vs A+F deemed clinically implausible (Figure 2 on next slide)
  - PSA constrained to exclude iterations with survival benefit of >10% for Ev+Ex vs A+F

Abbreviations: A, alpelisib; Ev, everolimus; Ex, exemestane; F, fulvestrant; ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life years

Key issue: Use of probabilistic analyses in decision-making

Company response *continued*

Figure 2 Original company base case: relative increase in life years for Ev+Ex compared with A+F



- **Provided updated probabilistic base case with PSA constraint**

ERG comments:

- Interpretation of deterministic ICERs problematic because of use of median, not mean, hazard ratios
- Interpretation of probabilistic ICERs problematic due to implausible samples and non-linear response of model to extreme hazard ratios
- Constraint to PSA not appropriate – resulting distribution of expected incremental QALYs no longer reflects CIs estimated from ITCs
  - Arbitrarily impacts mean incremental QALYs and costs
- Agrees with Appraisal Committee that both deterministic and probabilistic models should be taken into account
- **ERG excludes company's PSA constraint from its additional exploratory analyses**

Does the committee accept company's constrained PSA in probabilistic base case?

Abbreviations: A, alpelisib; CI, confidence interval; Ev, everolimus; Ex, exemestane; F, fulvestrant; ICER, incremental cost-effectiveness ratio; ITC, indirect treatment comparison; PSA, probabilistic sensitivity analysis

Resolved issue: Use of 'reverse' Bucher method (ACD 3.10)

ACD

- Notes uncertainties around the relative treatment effect estimates for A+F versus Ev+Ex, including that… "*A reverse Bucher was done, deriving comparator hazard ratios from those known for alpelisib plus fulvestrant*"

Company response

- Evaluation was based on survival data for A+F from single-arm BYLieve study… necessary to estimate PFS and OS curves for Ev+Ex by applying estimates of the HRs for PFS and OS for Ev+Ex versus A+F to the estimated PFS and OS curves for A+F
- Unclear why the method employed would introduce any more uncertainty; no rationale outlined in ACD
- Conclusion that company approach introduces uncertainty is overstated, and rather the approach taken is simply an alternative approach based on available data.

ERG comments:

- Agrees with the company that inversion of HRs is necessary within economic model given inclusion of data from BYLIEVE as a baseline
- ERG believes use of inverse HRs, together with the very wide 95% CIs generated from the Bucher ITCs, contributes to the problems regarding implausible samples in the PSA (see PSA issue)
- Not a standalone issue – **statement in ACD (above) can be removed from subsequent guidance documents**

Is committee happy that the reverse Bucher ITC in itself is not an issue, but may contribute to implausible PSA samples?

Abbreviations: A, alpelisib; CI, confidence interval; Ev, everolimus; Ex, exemestane; F, fulvestrant; HR, hazard ratio; ITC, indirect treatment comparison; OS, overall survival; PFS, progression-free survival; PSA, probabilistic sensitivity analysis

End-of-life criteria

ACD 3.19

NICE National Institute for Health and Care Excellence

Key issue: Whether A+F meets end-of-life criteria

ACD: *Short life expectancy criteria met, but extension of life unclear*

- Committee concluded that it was possible that A+F met end of life criteria, but this was not shown robustly enough by the evidence so far presented
- Clinical experts considered that people with hormone receptor-positive, HER2-negative, PIK3CA mutated advanced breast cancer whose disease had progressed on a CDK4/6 inhibitor with an aromatase inhibitor:
  - are unlikely to live longer than 24 months
  - it was less certain whether A+F extended life by 3 months or more
- Treatment effect estimates for A+F from the indirect analyses are highly uncertain
- Committee noted that to meet end of life criteria, it needed to be satisfied that estimates are robust and it was not satisfied that they were

Company response

- Due consideration must be applied to the totality of evidence available, and the social value judgments underpinning the decision modifier, when assessing whether a drug meets the short life expectancy criterion
- Evidence further suggests that A+F is able to extend life expectancy by >3 months:
  - Despite uncertainties in treatment effect due to the single arm nature of BYLieve, deterministic model predictions demonstrate that A+F increases life expectancy compared with Ev+Ex by >3 months
  - This criterion is not met only in an extreme and unrealistic scenario due to outliers in the PSA
  - In SOLAR-1, median overall survival gain with A+F versus placebo+F was 7.9 months*

*All lines of treatment

Abbreviations: A, alpelisib; CDK, cyclin-dependent kinase; F, fulvestrant; HER2, human epidermal growth factor receptor-2; PSA, probabilistic sensitivity analysis

Key issue: Whether A+F meets end-of-life criteria

ERG comments:

- Criteria not met using HER2-negative subgroup of SoFEA in Bucher ITC = mean OS is >2 years with Ev+Ex
- Criteria not met using probabilistic model (irrespective of SoFEA population used in Bucher ITC)
- ERG's clinical advisors noted predicted OS and PFS in deterministic model were plausible

Table 14 Model results – ERG critique (undiscounted LYGs)

Key: **EOL criteria met**

Base case results	Deterministic		Probabilistic	
	LYs with Ev/Ex	Additional LYGs, A+F vs Ev/Ex	LYs with Ev/Ex	Additional LYGs, A+F vs Ev/Ex
With 5-yr treatment waning assumption	**1.81 (<24 mo)**	**0.59 (>3 mo)**	2.17 (>24 mo)	**0.38 (>3 mo)**
With 3-yr treatment waning assumption	**1.81 (<24 mo)**	**0.46 (>3 mo)**	2.17 (>24 mo)	**0.29 (>3 mo)**
With 5-yr treatment waning assumption + HER2-negative subgroup in SoFEA	2.19 (>24 mo)	**0.30 (>3 mo)**	2.68 (>24 mo)	-0.03 (<3 mo)
With 5-yr treatment waning assumption + constraint in PSA	-	-	**1.73 (<24 mo)**	**0.70 (>3 mo)**

Has the committee seen sufficient evidence to consider end of life criteria are met?

Abbreviations: A, alpelisib; Ev, everolimus; Ex, exemestane; F, fulvestrant; LY, life years; LYG, life-years gained; mo, months; OS, overall survival; PFS, progression-free survival; PSA, probabilistic sensitivity analysis

Summary of key issues

- Is restriction of BOLERO-2 population to those with PIK3CA mutation identified in tumour tissue in Bucher indirect analysis appropriate?
- Is use of the full population of SoFEA acceptable in the Bucher indirect analysis? Should the population of SoFEA be restricted to those with HER2-negative disease?
- What is the most appropriate post-progression utility estimate to use in the model? Is the company's assumption based on Mitra (0.69) acceptable?
- Is the company's revised assumption of waning of treatment effect for A+F versus Ev+Ex at 5 years reasonable?
- Is use of a constrained PSA acceptable in the company's updated probabilistic base case?
    - Is committee happy that the reverse Bucher ITC in itself is not an issue, but may contribute to implausible PSA samples?
- Has committee been presented with evidence that is robust enough to support end of life criteria being met?

Abbreviations: A, alpelisib; AI, aromatase inhibitor; Ev, everolimus; Ex, exemestane; F, fulvestrant; HER2, human epidermal growth factor receptor-2; PSA, probabilistic sensitivity analysis

Equalities and innovation

Recap – company submission

Equalities:

- Use of A+F not expected to raise any equality issues

Innovation:

- Alpelisib is 1st licensed alpha-selective PI3K inhibitor (EMA, FDA)
- It is 1st targeted treatment for endocrine resistant HR+, HER2- advanced breast cancer with PIK3CA mutation – personalised treatment option

ACD

Equalities: [No comments]

Innovation:

- The committee concluded that A+F was not innovative

Consultation comments

Equalities: [No comments]

Innovation:

- *Breast Cancer Now:* surprised alpelisib not recognised as an innovative treatment, given the role PIK3CA may play in progression and that the treatment specifically targets this mutation
- *METUPUK*: alpelisib is first treatment available which targets the PIK3CA mutation in HR+, HER2- metastatic breast cancer, so we believe it is innovative

Abbreviations: A, alpelisib; F, fulvestrant; HER2, human epidermal growth factor receptor-2; HR, hormone receptor

Cost-effectiveness results

All ICERs are reported in PART 2 slides because they include confidential PAS discounts

Abbreviations: ICER, incremental-cost effectiveness ratio; PAS, patient access scheme