Confidential until published

Alpelisib in combination with fulvestrant for treating advanced hormone receptor positive, HER2-negative, *PIK3CA*-mutated breast cancer: A Single Technology Appraisal

Produced by	The School of Health and Related Research (ScHARR), The University of Sheffield
Authors	Aline Navega Biz, Research Associate, ScHARR, University of Sheffield, Sheffield, UK Katy Cooper, Senior Research Fellow, ScHARR, University of Sheffield, Sheffield, UK Kate (Shijie) Ren, Senior Research Fellow, ScHARR, University of Sheffield, Sheffield, UK Paul Tappenden, Professor of Health Economic Modelling, ScHARR, University of Sheffield, Sheffield, UK Mark Clowes, Information Specialist, ScHARR, University of Sheffield, Sheffield, UK
Correspondence Author	Aline Navega Biz, Research Associate, ScHARR, University of Sheffield, Sheffield, UK
Date completed	12th October 2021 (version includes amendments following the factual accuracy check)

Source of funding: This report was commissioned by the NIHR HTA Programme as project number NIHR134413.

Declared competing interests of the authors

None of the authors have any conflicts of interest to declare.

Acknowledgements

We would like to thank Uzma Asghar, Royal Marsden Hospital NHS Trust, London, Dr Ciara S O'Brien, The Christie Hospital NHS Foundation Trust, Manchester, and Janet Brown, Weston Park Hospital, Sheffield, for clinical advice throughout the course of the project. We would also like to thank Matt Stevenson, ScHARR, for providing comments on the draft report and Andrea Shippam, Programme Manager, ScHARR, for providing administrative support and in preparing and formatting the report.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

Navega Biz A, Cooper K, Ren S, Tappenden P, Clowes M. Alpelisib in combination with fulvestrant for treating advanced hormone receptor positive, HER2-negative, *PIK3CA*-mutated breast cancer: A Single Technology Appraisal. School of Health and Related Research (ScHARR), University of Sheffield; 2021.

Contributions of authors

Mark Clowes critiqued the company's search strategy. Katy Cooper summarised and critiqued the clinical effectiveness evidence reported within the company's submission. Kate Ren summarised and critiqued the statistical aspects of the submission. Aline Navega Biz and Paul Tappenden critiqued the health economic analysis submitted by the company and undertook additional exploratory analyses. All authors were involved in drafting and commenting on the final report.

CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF BOXES

ABBREVIATIONS

Abem	Abemaciclib
Abem/Fulv	Abemaciclib plus fulvestrant
Alp	Alpelisib
Alp/Fulv	Alpelisib plus fulvestrant
ABC	Advanced breast cancer
AE	Adverse event
AESI	Adverse event of special interest
AFT	Accelerated failure time
AI	Aromatase inhibitor
AIC	Akaike Information Criterion
AICc	AIC with correction
ASA	Additional sensitivity analysis
ATT	Average treatment effect among the treated
BC	Breast cancer
BIC	Bayesian Information Criterion
BNF	British National Formulary
BPI-SF	Brief Pain Inventory - Short Form
BSA	Body surface area
CBC	Complete blood count
CBR	Clinical benefit rate
CDF	Cancer Drugs Fund
CDK	Cyclin-dependent kinase
CDK4/6i	Cyclin-dependent kinase 4/6 inhibitor
CEAC	Cost-effectiveness acceptability curve
CG	Clinical Guideline
CGDB	US Flatiron Clinicogenomics Database
CI	Confidence interval
CMU	Commercial Medicines Unit
CNS	Central nervous system
CPI	Consumer Price Index
CR	Complete response
CRD	Centre for Reviews and Dissemination
CS	Company's submission
CT	Computerised tomography
DoR	Duration of response
DSA	Deterministic sensitivity analysis
EA	Exploratory analysis
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
eMIT	Electronic Market Information Tool
EoL	End-of-life
EORTC	European Organisation for Research and Treatment of Cancer
EORTC QLQ-C30	EORTC Quality of Life Questionnaire-C30
EQ-5D (3L/5L)	Euroqol 5-Dimensions (3-level / 5-level)
ER	Oestrogen receptor
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
ESS	Effective sample size
ET	Endocrine therapy
Eve	Everolimus
Eve/Exe	Everolimus plus exemestane
Exe	Exemestane
Fulv	Fulvestrant

FAS	Full analysis set
FE	Fixed effect
FPG	Fasting plasma glucose
GEE	Generalised estimating equation
GGT	Gamma-glutamyl transpeptidase
GI	Gastrointestinal
GP	General practitioner
HbA1c	Haemoglobin A1c
HER2	Human epidermal growth factor receptor 2
HER2-	Human epidermal growth factor receptor 2 negative
HR	Hazard ratio
HR+	Hormone receptor positive
HRQoL	Health-related quality of life
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
ICTRP	International Clinical Trials Registry Platform
IM	Intramuscular
INAHTA	International Network of Agencies for Health Technology Assessment
Inc.	Incremental
IPD	Individual patient data
IPTW	Inverse probability of treatment weighting
ITC	Indirect treatment comparison
Kg	Kilogram
LYG	Life year gained
m	Metre
MeSH	Medical Subject Heading
mFAS	Modified full analysis set
Mg	Milligram
MHRA	Medicines and Healthcare products Regulation Agency
mL	Millilitre
N	Number
N/A	Not applicable
NCCN	National Comprehensive Cancer Network
NHS	National Health Service
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NR	Not reported
ONS	Office for National Statistics
ORR	Overall response rate
OS	Overall survival
PAIC	Patient-adjusted indirect comparison
Palb	Palbociclib
Palb/Fulv	Palbociclib plus fulvestrant
PAS	Patient Access Scheme
Pbo	Placebo
Pbo/Fulv	Placebo plus fulvestrant
PD	Progressive disease
PF	Progression-free
PFS	Progression-free survival
PFS2	Progression on next line therapy
PH	Proportional hazards
PI3K	Phosphatidylinositol 3-kinase
PIK3CA	Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha
PP	Post-progression

PPS	Post-progression survival
PR	Partial response
PRO	Patient-reported outcome
PS	Performance status
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
QoL	Quality of life
RCS	Restricted cubic spline
RCT	Randomised controlled trial
RDI	Relative dose intensity
Ribo	Ribociclib
Ribo/Fulv	Ribociclib plus fulvestrant
SAE	Serious adverse event
SD	Standard deviation
SG	Standard gamble
SIGN	Scottish Intercollegiate Guidelines Network
SLR	Systematic literature review
SMD	Standardised mean difference
SmPC	Summary of Product Characteristics
TA	Technology Appraisal
Tam	Tamoxifen
TTD	Time to treatment discontinuation
Tx	Treatment
UK	United Kingdom
WTP	Willingness-to-pay
YHEC	York Health Economics Consortium

1 SUMMARY

This ERG report assesses alpelisib in combination with fulvestrant (Alp/Fulv) for treating advanced hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-), phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (*PIK3CA*) mutated breast cancer. This summary provides a brief overview of the key issues identified by the Evidence Review Group (ERG) as being potentially important for decision-making. It also includes the ERG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.5 explain the key issues in more detail. The results of the ERG's preferred analysis are summarised in Section 1.6. Background information on the condition, technology and evidence and information on non-key issues are detailed in the main ERG report.

All issues identified represent the ERG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the ERG's key issues

Table 1: Summary of the ERG's key issues

ID3929	Summary of issue	Report sections
Issue 1	Uncertainty surrounding the relevance of the evidence to the target population	3.1 and 5.3.4
Issue 2	Restrictions of the evidence used to inform the model - comparison against a single comparator (Eve/Exe) in the second-line population	5.3.4
Issue 3	Uncertainty surrounding relative treatment effects for Alp/Fulv versus Eve/Exe	4.8, 4.9 and 5.3.4
Issue 4	Concerns regarding company's HRQoL assumptions	5.3.4
Issue 5	Discrepancy between deterministic and probabilistic model results	5.3.4

Alp - alpelisib; Eve - everolimus; Exe - exemestane; Fulv - fulvestrant; HRQoL - health-related quality of life

The key difference between the company's base case model and the ERG's preferred analysis relates to the utility value applied in the post-progression health state (Issue 4). In addition, the company believes that the ICER is more likely to align with the results of the deterministic model, rather than the probabilistic model (Issue 5). In this case, the ERG is unsure whether the deterministic or probabilistic results should be preferred, as both are subject to problems.

1.2 Overview of key model outcomes

NICE technology appraisals (TAs) compare how much a new technology improves length of life (overall survival) and health-related quality of life (HRQoL) in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Increasing the amount of time that patients spend alive and progression-free (progression-free survival [PFS])
- Increasing the amount of time that patients spend alive (overall survival [OS]).

Overall, the technology is assumed to affect costs by:

- Increasing up-front drug acquisition costs due to the higher acquisition costs of Alp/Fulv compared with everolimus plus exemestane (Eve/Exe)
- Requiring testing in order to identify patients with *PIK3CA* mutations who may be eligible for treatment with Alp/Fulv
- Increasing follow-up and monitoring costs (due to extended PFS)
- Increasing the costs of chemotherapies used after disease progression (due to extended OS).

The modelling assumptions that have the greatest effect on the ICER are:

- The parametric survival model used for OS
- The duration over which relative treatment effects are assumed to apply
- Whether the Bucher indirect treatment comparison (ITC) is restricted to data relating to the HER2- subgroup in the SoFEA trial
- The utility value applied in the post-progression utility state
- Whether the ICER is based on the deterministic model or the probabilistic model.

1.3 The decision problem: Summary of the ERG's key issues

The decision problem addressed in the company's submission (CS) is generally in line with the final NICE scope. The target population in the CS is people with people with HR+, HER2− advanced breast cancer (ABC) with a *PIK3CA* mutation, who have progressed following an endocrine-based regimen (in the neo/adjuvant or advanced setting) and who have previously received treatment with a cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) in combination with an aromatase inhibitor (AI), and would subsequently receive Alp/Fulv for the first-, second-, third- or fourth-line treatment of ABC. This is a subset of the population defined in the NICE scope. However, the population reflected in the company's economic model is not in line with the current European Medicines Agency (EMA) licence for Alp/Fulv, which relates to people whose disease has progressed *"following endocrine therapy as monotherapy"*. The company has applied to the Medicines and Healthcare products Regulation Agency (MHRA) for a Type II variation to the current marketing authorisation. The wording of the revised marketing authorisation relates to patients with [redacted]. This variation has not yet been granted. The final NICE scope lists four comparators: (i) CDK4/6 inhibitors plus Fulv; (ii) Eve/Exe; (ii) tamoxifen (Tam) and (iv) Exe. The company's economic analysis includes Eve/Exe as the sole comparator.

Issue 1: Uncertainty surrounding the relevance of the economic analysis to the target population

Report section	3.1 and 5.3.4
Description of issue and why the ERG has identified it as important	The final NICE scope specifies the relevant population as people with advanced HR+, HER2- *PIK3CA*-mutated breast cancer that has progressed after prior endocrine therapy (in the neo/adjuvant or advanced setting). The wording of the current EMA licence for Alp/Fulv relates specifically to patients whose disease has progressed *"following endocrine therapy as monotherapy."* The company has applied to the MHRA for a Type II variation that is broader than the existing licence, and which is anticipated to relate to patients whose disease has progressed [redacted] The company's economic analysis is mostly based on data from a subset of [redacted] patients from the Cohort A of BYLieve study population who received prior CDK4/6i+AI treatment as first-line therapy in the advanced setting. The relevance of the company's economic analysis is dependent on the MHRA granting the Type II variation to the current EMA licence. If this variation is not granted, the implication is that patients recruited into BYLieve Cohort A would not have been eligible for treatment with Alp/Fulv under its marketing authorisation.
What alternative approach has the ERG suggested?	None
What is the expected effect on the cost-effectiveness estimates?	If the Type II variation is not granted by the MHRA, the company's economic analysis will not be relevant to this appraisal.
What additional evidence or analyses might help to resolve this key issue?	None

Issue 2: Restrictions of the evidence used to inform the model - comparison against a single comparator (Eve/Exe) in the second-line population

Report section	3.1 and 5.3.4
Description of issue and why the ERG has identified it as important	The company is seeking a positive recommendation for Alp/Fulv for CDK4/6i+AI-experienced endocrine-resistant patients in the second- and subsequent-line settings, and as first-line treatment for advanced disease after receiving a CDK4/6 inhibitor in the neo/adjuvant setting. However, the Alp/Fulv group of the company's economic model is based on a subset of data from Cohort A of BYLieve in the second-line setting only (n=[redacted]), with outcomes for Eve/Exe based on indirect comparisons using the Bucher method (see Issue 3). All patients included in the modelled BYLieve cohort are female. The company's economic analysis is narrower than their intended target population. Specifically, no economic analysis has been provided for Alp/Fulv for patients in the first-, third- or subsequent-line settings, or in men with ABC. The ERG's clinical advisors agreed that Eve/Exe is the main comparator for Alp/Fulv. The advisors commented that Exe monotherapy is not often used and that they would be unlikely to re-challenge patients who have progressed on a CDK4/6i with another CDK4/6i. However, they also commented that Tam and Fulv are sometimes used in older/unfit patients, and that chemotherapy may be offered to patients who are at high risk of visceral crisis. These comparators

	are not included in the company's economic analysis as they are not used widely in UK clinical practice, and their use is usually reserved for frail patients who would not be expected to receive Alp/Fulv.
What alternative approach has the ERG suggested?	None
What is the expected effect on the cost-effectiveness estimates?	The cost-effectiveness of Alp/Fulv in the populations not represented within the model remains unknown.
What additional evidence or analyses might help to resolve this key issue?	This issue largely relates to the patient population for whom a NICE recommendation will be made. Given the limitations of the clinical and economic analyses, which are restricted to patients in the second-line setting who would otherwise have received Eve/Exe, it may be appropriate to consider this in any future recommendation for Alp/Fulv.

1.4 The clinical effectiveness evidence: Summary of the evidence and the ERG's key issues

Effectiveness and safety of Alp/Fulv: The CS presents data from one randomised controlled trial (RCT) of Alp/Fulv vs. placebo (Pbo)/Fulv in a mostly CDK4/6i-naïve population (SOLAR-1) and one non-comparative study of Alp/Fulv in a post-CDK4/6i population (BYLieve Cohort A). A further RCT (EPIK-B5) of Alp/Fulv in the post-CDK4/6i population is planned to start in [redacted] with first results expected in [redacted]. The comparator for this trial is unclear.

PFS in SOLAR-1 was significantly improved for Alp/Fulv versus Pbo/Fulv in the full population (n=341, hazard ratio (HR) [redacted], 95% confidence interval (CI): [redacted]) as well as in the second-line endocrine-resistant population used in the Bucher ITC (n=[redacted], HR [redacted], 95% CI: [redacted]), while in the small post-CDK4/6i subgroup (n=20) the HR for PFS was [redacted](95% CI: [redacted]). In BYLieve Cohort A, median PFS was 7.3 months for the full population (n=121) and [redacted]months for second-line patients used in the economic model (n=[redacted]). OS in SOLAR-1 showed a non-significant trend favouring Alp/Fulv in the full population (HR 0.86, 95% CI: 0.64, 1.15) and in the second-line endocrine-resistant population (n=[redacted], HR [redacted], 95% CI: [redacted]), while in the small post-CDK4/6i subgroup (n=20) the HR for OS was [redacted](95% CI: [redacted]). In BYLieve Cohort A, median OS was 17.3 months for the full population (n=121) and [redacted]months for second-line patients used in the economic model (n=[redacted]).

The most common adverse events (AEs) in the Alp/Fulv arm of SOLAR-1 (vs. Pbo/Fulv) were: hyperglycaemia (65%vs. 9%); diarrhoea (60% vs. 16%); nausea (47% vs. 23%); decreased appetite (36% vs. 11%), and rash (36% vs. 7%). In the Alp/Fulv arm, 25% discontinued Alp due to AEs and 75% experienced dose reductions or interruptions.

Indirect treatment comparisons: The company conducted ITCs using three different approaches: (a) a matching/weighted analysis in a post-CDK4/6i population using data from BYLieve Cohort A and the US Flatiron Clinicogenomics Database (CGDB); (b) a Bucher ITC which indirectly compared Alp/Fulv (SOLAR-1) versus Eve/Exe (BOLERO-2) via a network involving two additional trials (CONFIRM and SoFEA), and (c) an unanchored patient-adjusted indirect comparison (PAIC) which compared second-line data from the Alp/Fulv arm from SOLAR-1 and the Eve/Exe arm from BOLERO-2. The Bucher ITC, which is included in the company's base case economic model, [redacted]Alp/Fulv for PFS (Eve/Exe versus Alp/Fulv: HR=[redacted], 95% CI [redacted]) and OS (Eve/Exe versus Alp/Fulv: HR=[redacted], 95% CI [redacted]). The results [redacted]when using the HER2-subgroup from SoFEA. The matching/weighted analysis and the PAIC both suggested [redacted]; these analyses were not included in the company's base case. The ERG's key concerns around the clinical evidence for Alp/Fulv and the ITCs are discussed in the context of the economic analysis (see Section 1.5)

1.5 The cost-effectiveness evidence: Summary of the evidence and the ERG's key issues

The company's economic model compares Alp/Fulv versus Exe/Eve in adult women with HR+, HER2− ABC with a *PIK3CA* mutation, who have received prior treatment with CDK4/6i+AI therapy. The model adopts a partitioned survival approach, and includes three health states: (i) progression-free; (ii) post-progression and (iii) dead. Health outcomes and costs are evaluated from the perspective of the NHS and Personal Social Services (PSS) over a lifetime horizon. OS, PFS and time to treatment discontinuation (TTD) for Alp/Fulv are based on data for second-line patients in BYLieve Cohort A whilst OS and PFS for Eve/Exe are estimated by applying the constant HRs derived from the Bucher second-line ITCs to the Alp/Fulv OS and PFS models as a baseline. TTD for Eve/Exe is informed by data on PFS and TTD from BOLERO-2. Health utilities for both treatment groups were estimated using a generalised estimating equation (GEE) model fitted to Euroqol 5-Dimensions-5 Level (EQ-5D-5L) data collected in SOLAR-1 (mapped to the 3L version). A utility decrement is applied to the progression-free state for the Eve/Exe group, based on European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire-C30 (EORTC QLQ-C30) data collected in BOLERO-2 (mapped to the EQ-5D-3L). Resource use estimates were derived from SOLAR-1, BOLERO-2, previous NICE TAs, standard costing sources and additional assumptions.

The company has proposed a Patient Access Scheme (PAS) for Alp which takes the form of a simple price discount of [redacted]). As the company also manufactures everolimus (Eve), the PAS price for this drug is also known ([redacted]). All results presented within this report include these discounts. The deterministic analysis of the company's base case model suggests that Alp/Fulv generates an additional [redacted]QALYs at an additional cost of [redacted]per patient compared

with Eve/Exe; the corresponding ICER is £60,462 per QALY gained. The probabilistic version of the model suggests a higher ICER of £68,880 per QALY gained.

The ERG's key issues regarding the company's economic analyses are summarised below.

Issue 3: Uncertainty surrounding the relative effectiveness of Alp/Fulv versus Eve/Exe

Report section	4.8
Description of issue and why the ERG has identified it as important	There is no direct head-to-head RCT evidence for Alp/Fulv versus Eve/Exe. The company's economic model estimates PFS and OS for the Alp/Fulv group using data for second-line patients in BYLieve Cohort A (n= [redacted]). HRs for PFS and OS for Eve/Exe versus Alp/Fulv were estimated from the Bucher ITCs. The ERG identified a number of issues relating to these ITCs: • None of the studies included in the network relate to the post-CDK4/6i population. Second-line treatment is assumed to be a proxy for CDK4/6i exposure. BYLieve, in which all patients who previously received a CDK4/6i+AI regimen, is not included in the network because it not a comparative study. • The data from SOLAR-1 and BOLERO-2 were restricted to second-line patients only; for CONFIRM and SoFEA separate data were not available by treatment line • SoFEA and CONFIRM did not test for *PIK3CA* mutations • The BOLERO-2 dataset was restricted to second-line patients with *PIK3CA* mutations based on tumour tissue samples, which led to a large proportion of patients being excluded from the analysis (57 of 724 randomised patients were included [8%]) • SOLAR-1 and BOLERO-2 restricted to HER2- patients, whilst CONFIRM did not evaluate HER2 status, and SoFEA enrolled 60% HER2-, 7% HER2+ and 33% with unknown HER2 status. The company's original Bucher ITC uses the full population of SoFEA, regardless of HER2 status. HER2 status may be an important treatment effect modifier. A revised ITC which includes only HER2- patients from SoFEA was provided in the company's clarification response. • Treatment effects may be biased by an imbalance in treatment effect modifiers • The assumption of proportional hazards (PH) in the second-line population is questionable • The Bucher method is equivalent to a fixed effect (FE) network meta-analysis (NMA). The use of FE models which assume zero between-study heterogeneity is not appropriate and uncertainty is underestimated. The ERG considers the company's estimates of relative treatment effects for Alp/Fulv versus Eve/Exe, and the resulting QALY estimates generated by the economic model, to be highly uncertain.
What alternative approach has the ERG suggested?	In the absence of head-to-head studies comparing Alp/Fulv versus Eve/Exe in a relevant population, the results of the company's ITCs and economic analyses should be considered highly uncertain.
What is the expected effect on the cost-effectiveness estimates?	The inclusion of the HER2- subgroup from SoFEA increases the ERG's preferred deterministic ICER from £78,538 to £119,303 per QALY gained. The inclusion of an assumption that relative treatment effects are lost at 3- or 5-years increases the deterministic ICER to £92,195 and £83,640 per QALY gained, respectively.

What additional evidence or analyses might help to resolve this key issue?	The company's clarification response indicates that a future trial of Alp/Fulv in a post-CDK4/6i cohort is planned to be initiated in [redacted]. The comparator for this trial is not clearly stated in the company's clarification response; hence, it is unclear whether this would reduce uncertainty around the relative clinical effectiveness of Alp/Fulv versus Eve/Exe.

Issue 4: Concerns regarding the health state utility values used in the company's model

Report section	5.3.4
Description of issue and why the ERG has identified it as important	The ERG has several concerns regarding the utility values applied in the company's model: • The data used to estimate utility values in the model do not reflect a CDK4/6i-experienced population • The utility value for patients receiving Alp/Fulv is higher than that for patients receiving Eve/Exe. It is possible that this is a consequence of patient heterogeneity and/or the use of different utility instruments and mapping algorithms. Given their respective toxicity profiles, the ERG's clinical advisors considered it reasonable to expect that health-related quality of life (HRQoL) would be similar for Alp/Fulv and Eve/Exe. • The CS notes that EQ-5D-5L data in SOLAR-1 *"were largely missing after progression"*. The ERG believes that the post-progression utility value of [redacted] appears high and may be a consequence of informative censoring. The majority of recent NICE appraisals in ABC have applied post-progression utility values from a published standard gamble study reported by Lloyd *et al*.
What alternative approach has the ERG suggested?	The ERG's preferred analysis: (i) applies the same utility value for patients who are progression-free and on treatment in both treatment groups and (ii) applies the utility value for progressed disease from Lloyd *et al.* (utility value = 0.51).
What is the expected effect on the cost-effectiveness estimates?	Applying the same utility value to the progression-free on-treatment state in both groups of the ERG's error-corrected model increases the deterministic ICER from £60,554 to £62,424 per QALY gained. Applying the utility value of 0.51 from Lloyd *et al.* in the ERG's error-corrected model increases the ICER to £74,665 per QALY gained.
What additional evidence or analyses might help to resolve this key issue?	Given the absence of preference-based estimates of HRQoL for Alp/Fulv in the CDK4/6i-experienced population, further clinical input may help to resolve uncertainty around the most appropriate utility values to apply in the model.

Issue 5: Discrepancy between the results of the deterministic and probabilistic versions of the economic model

Report section	5.3.4
Description of issue and why the ERG has identified it as important	The company's probabilistic ICER is around £8,400 higher than the deterministic estimate. The ERG believes that the key driver of this discrepancy relates to the uncertainty around the HR for OS. The company's model inappropriately uses median HRs for PFS and OS. However, applying the mean HR in the deterministic model increases the discrepancy between the deterministic and probabilistic ICERs. The ERG fully replicated the company's probabilistic sampling of OS for both treatment groups and obtained almost identical results. No errors were found and the ERG concludes that the probabilistic sampling has been

	implemented correctly. The ERG also implemented the company's Bucher ITCs using FE NMAs and obtained posterior distributions which were very similar to the log-normal samples used in the company's model. The ERG notes that a proportion of these samples suggest substantial OS losses for Alp/Fulv versus Eve/Exe which do not appear to be clinically plausible. Overall, the ERG believes that the interpretation of the results of the company's deterministic model is problematic because of the use of median HRs rather than mean HRs. However, there is a discrepancy in the results produced when using the mean of the HR in the deterministic model (whereby the ICER is decreased) and the use of the probabilistic samples of the HRs (whereby the expected ICER is increased) due to the non-linear response to extreme HRs. Given these problems, the ERG is unsure whether it is more appropriate to rely on the results of the deterministic or probabilistic model.
What alternative approach has the ERG suggested?	The results of the ERG's exploratory analyses are presented using both the deterministic and probabilistic analyses.
What is the expected effect on the cost-effectiveness estimates?	The deterministic version of the ERG's preferred analysis results in an ICER of £78,538 per QALY gained. The probabilistic version of the ERG-preferred model results in an ICER of £90,261 per QALY gained. This issue may also influence whether NICE's End-of-Life (EoL) criteria are considered to be met, as the probabilistic model suggests comparatively higher mean OS for Eve/Exe compared with the deterministic model.
What additional evidence or analyses might help to resolve this key issue?	A judgement is required by the Appraisal Committee regarding which analyses should be preferred.

1.6 Summary of ERG's preferred assumptions and resulting ICER

The results of the ERG's exploratory analyses are summarised in Table 2. Each analysis reflects individual model amendments relative to the ERG-corrected version of the model (Exploratory Analysis 1 [EA1]). The ERG's preferred analysis leads to a deterministic ICER for Alp/Fulv versus Exe/Eve of £78,538 per QALY gained and a probabilistic ICER of £90,261 per QALY gained. These ICERs are higher than the company's base case results. The ICER for Alp/Fulv is sensitive to: alternative assumptions regarding treatment benefit duration; the parametric survival distribution for OS; subsequent treatment costs and the inclusion of the HER2-subgroup in SoFEA in the ITC.

Table 2: Summary of results of ERG exploratory analyses, deterministic (unless otherwise stated)

Scenario	Incremental QALYs	Incremental cost	ICER (change from company base case)
Company's base case	[redacted]	[redacted]	**£60,462**
ERG's preferred analyses			
EA1: Correction of errors	[redacted]	[redacted]	£60,554 (+92)
EA2: Equal utility for the progression-free on-treatment state in both groups	[redacted]	[redacted]	£62,424 (+1,962)
EA3: Post-progression utility based on Lloyd *et al.*	[redacted]	[redacted]	£74,665 (+14,203)
EA4: Drug wastage	[redacted]	[redacted]	£61,342 (+880)
EA5: ERG-preferred analysis (EA1-4), deterministic	[redacted]	[redacted]	**£78,538 (+18,076)**
EA5: ERG-preferred analysis (EA1-4), probabilistic	[redacted]	[redacted]	**£90,261 (+£29,799)**
ERG's additional sensitivity analyses (using EA5)			
ASA1a: 3-year treatment effect duration	[redacted]	[redacted]	£92,195 (+31,733)
ASA1b: 5-year treatment effect duration	[redacted]	[redacted]	£83,640 (+23,178)
ASA2a: Subsequent treatment costs = £750	[redacted]	[redacted]	£67,529 (+7,067)
ASA2b: Subsequent treatment costs = £2,250	[redacted]	[redacted]	£89,548 (+29,026)
ASA3: Use of HRs from Bucher ITC using SoFEA HER2- subgroup	[redacted]	[redacted]	£119,303 (+58,841)
ASA4: Use of alternative OS models	[redacted]	[redacted]	£70,462 to £145,760 (£10,000 to £85,298)
ASA5: Use of alternative PFS models	[redacted]	[redacted]	£58,094 to £83,841 (-£2,368 to 23,379)

ASA - additional sensitivity analysis; EA - exploratory analysis; HR - hazard ratio; ICER - incremental cost-effectiveness ratio; ITC - indirect treatment comparison; PFS - progression-free survival; OS - overall survival; QALY - quality-adjusted life year.

The ERG's full critique of the company's economic analyses and the ERG's exploratory analyses can be found in the main ERG report (Sections 5.3 and 5.4, respectively).

2 BACKGROUND

This chapter presents a brief critique of the company's description of the disease (Section 2.1), the company's description of the current treatment pathway in England (Section 2.2) and the positioning and target population for alpelisib plus fulvestrant (Alp/Fulv) (Section 2.3).

2.1 Company's description of the underlying health problem

2.1.1 HR+, HER2- advanced breast cancer with PIK3CA mutation

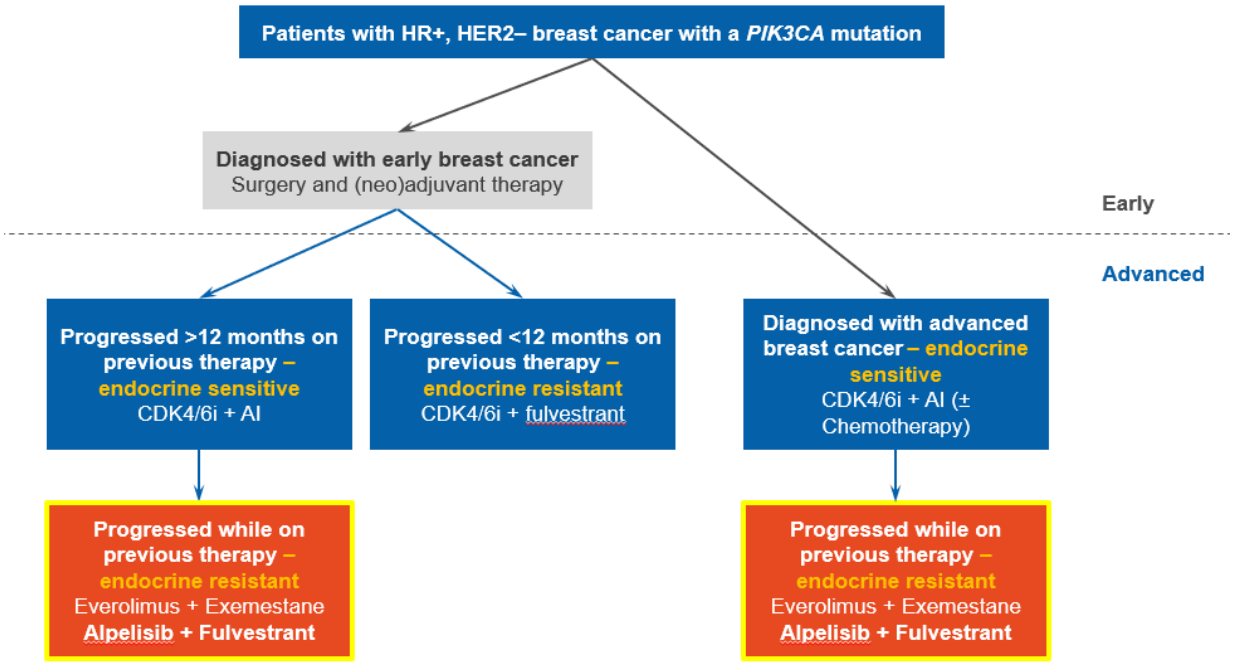
Advanced breast cancer (ABC) includes both unresectable locally advanced disease and metastatic disease. Although the disease is much more common in women, it can also affect men. The company's submission (CS)[1] (Section B.1.3.1) states that approximately 5-6% of women with breast cancer in the UK have metastatic disease at diagnosis (Stage IV), whilst approximately 35% of patients with a primary diagnosis of non-metastatic breast cancer go on to develop metastases within ten years following diagnosis. Breast cancer which is both hormone receptor positive (HR+) and human epidermal growth factor receptor 2 negative (HER2-) accounts for approximately 56-73% of cases. Approximately 30-40% of patients with HR+, HER2- ABC also have activating mutations in the phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (*PIK3CA*) gene.[1] Section B.1.3.1 of the CS states that patients with a *PIK3CA* mutation have demonstrated a shorter progression-free survival (PFS) and overall survival (OS) compared with patients with wild-type *PIK3CA*, and refers to pooled data across 11 studies in which patients with *PIK3CA*-mutated tumours had statistically significantly shorter PFS than those with *PIK3CA* wild-type tumours.

2.2 Critique of the company's overview of current service provision

2.2.1 Company's treatment pathway: Evidence sources

An overview of the treatment pathway (Figure 1) is provided in Section B.1.3.2 of the CS,[1] based on information from National Institute for Health and Care Excellence (NICE) Clinical Guideline CG81[2] (Advanced Breast Cancer: Diagnosis and Treatment), NICE Guideline NG101[3] (early and locally advanced ABC: Diagnosis and Treatment) and the NICE management pathway for HR+, HER2– ABC,[4] as well as international guidance from the European Society for Medical Oncology (ESMO)[5] on the treatment of HR+, HER2– ABC and the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines: Breast Cancer (2020).[6]

Figure 1: Anticipated positioning of alpelisib plus fulvestrant in the treatment pathway for HR+, HER2– ABC with a *PIK3CA* mutation in the UK (reproduced from CS, Figure 1)



Notes: Arrows in blue represent progression, and orange boxes represent the proposed positioning of Alp/Fulv, within the anticipated marketing authorisation from the Medicines and Healthcare products Regulation Agency (MHRA). The figure presented in the CS includes detailed footnotes regarding the relevance of cyclin-dependent kinase 4/6 inhibitors, everolimus plus exemestane, exemestane and tamofixen as comparators; this information not reproduced here but is included in the company's description of the decision problem in Table 3.
AI - aromatase inhibitor; CDK 4/6i - cyclin-dependent kinase 4/6 inhibitor; ET - endocrine therapy; HER2 - human epidermal growth factor receptor 2; HR+ - hormone receptor positive; PIK3CA - phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha

2.2.2 Endocrine therapy and other key therapies used in advanced breast cancer

This section briefly outlines the types of endocrine therapy (ET) and other key therapies used in management of ABC (as described in Section B.1.3.2 of the CS[1]). ET is used in both early and advanced breast cancer, as monotherapy and combination therapy. ETs include non-steroidal aromatase inhibitors (AIs; anastrozole and letrozole), steroidal AIs (exemestane [Exe]), as well as tamoxifen (Tam) and fulvestrant (Fulv). The cyclin-dependent kinase inhibitors (CDK4/6i) include ribociclib (Ribo), abemaciclib (Abem) and palbociclib (Palb). CDK4/6is can be used in combination with an AI (CDK4/6i+AI) or with Fulv (CDK4/6i+Fulv). In addition, everolimus (Eve) is a kinase inhibitor used in combination with exemestane (Exe).

2.2.3 Endocrine sensitivity and resistance

The CS[1] (Section B.1.3) states that patients with HR+, HER2– ABC can be further categorised as either endocrine-sensitive or endocrine-resistant. Endocrine-sensitive patients are those who are eligible for ET; in the advanced setting this includes patients who relapsed or progressed more than 12 months after completion of neo/adjuvant ET or were diagnosed with advanced disease (CS[1] Section B.1.3.2.2 and

Figure 1). Endocrine-resistant ABC patients are those who are not currently eligible for ET; this includes patients who relapsed or progressed whilst on or within 12 months of ET (in either the neo/adjuvant or advanced setting). The CS[1] (Section B.1.3) states that the population of interest to this appraisal is people with endocrine-resistant HR+, HER2− ABC with a *PIK3CA* mutation.

2.2.4 Treatment of endocrine-sensitive HR+, HER2- ABC

The CS[1] (Section B.1.3.2.2) states that standard of care for most patients requiring first-line treatment of endocrine-sensitive ABC would be a CDK4/6i+AI (see Figure 1). Prior to the use of a CDK4/6i+AI, standard treatment for this population was AI alone (CS,[1] Section B.1.3.2.2).

2.2.5 Treatment of endocrine-resistant HR+, HER2- ABC

According to the CS[1] (Section B.1.3.2.2), the mainstay of treatment in UK clinical practice for patients with endocrine-resistant disease depends on therapies previously received. In terms of CDK4/6i + Fulv combination therapy, Ribo/Fulv and Abem/Fulv after previous ET have received positive NICE recommendations for routine commissioning following their exit from the Cancer Drugs Fund (CDF), whilst Palb/Fulv is available for use only through the CDF. These regimens are recommended by NICE as treatment options in patients for whom everolimus plus exemestane (Eve/Exe) would have been the most appropriate alternative (TA725,[7] TA689[8] and TA619).[9] Further details of eligibility criteria for Palb/Fulv are available from the NHS England CDF drugs list.[10] The CS notes that if patients with HR+, HER2– ABC receive a CDK4/6i+AI for the first-line treatment for advanced disease in clinical practice, they are unlikely to receive a CDK4/6i+Fulv in subsequent lines. Therefore, in Figure 1, CDK4/6i+Fulv is shown as an option for first-line endocrine-resistant ABC only.

As shown in Figure 1, patients who progress following first-line CDK4/6i+AI treatment in the advanced setting are then considered endocrine-resistant. The current treatment option for these patients according to Figure 1 is Eve/Exe; this is recommended by NICE for postmenopausal women with HR+, HER2– ABC without symptomatic visceral disease that has recurred or progressed after a non-steroidal AI (anastrozole or letrozole) (TA421).[11]

2.2.6 ERG's critique of the company's treatment pathway

The Evidence Review Group (ERG) believes that the description of the treatment pathway provided within the CS[1] is broadly consistent with the NICE pathway[4] and the final NICE scope.[12] However, the ERG notes that the NICE scope[12] also lists Exe and Tam monotherapy as comparators, but these options are not included in the CS.[1] The CS[1] states that Exe and Tam monotherapy *"may also be options for patients in this setting, however their use is not widespread in UK clinical practice*" (CS,[1] Section B.1.3.2.2., page 30). The ERG's clinical advisors stated that whilst Eve/Exe is commonly used for endocrine-resistant patients who have received prior CDK4/6i+AI therapy, Tam monotherapy is

sometimes offered to patients who are unlikely to be able to tolerate the toxicity associated with Eve. One clinical advisor mentioned as factors to consider: age, fitness, comorbidities or compromise of liver or bone function. The clinical advisors agreed that Exe monotherapy is not commonly used. The advisors also mentioned Fulv monotherapy as a treatment option and noted that some patients might be offered chemotherapies such as paclitaxel or capecitabine (for those at risk of visceral crisis), although endocrine options would usually be offered first. These additional treatment options are not included as comparators in the NICE scope.

2.3 Positioning and target population for Alp/Fulv

2.3.1 Licensed indication for Alp/Fulv

The CS[1] (Foreword) states that Alp/Fulv has received a marketing authorisation from the European Medicines Agency (EMA) for the treatment of postmenopausal women, and men, with HR+, HER2–, locally advanced or metastatic breast cancer with a *PIK3CA* mutation after disease progression following ET as monotherapy. This potentially includes both endocrine-sensitive and endocrine-resistant patients. Since the approval of CDK4/6i+AI treatment for endocrine-sensitive patients at first-line in the metastatic setting (which has become the standard of care in this indication), the company suggests there is an unmet need for patients whose disease has progressed and who are endocrine-resistant after treatment with a CDK4/6i+AI regimen. However, these patients would not be eligible for treatment with Alp/Fulv under the current marketing authorisation issued by EMA as this is restricted to patients who have previously received endocrine monotherapy (see Section 3.1).[13] The company has applied to the Medicines and Healthcare products Regulatory Agency (MHRA) for a Type II variation to the existing EMA licence. The anticipated wording of the revised MHRA marketing authorisation for Alp/Fulv is [redacted]. This is broader than the existing marketing authorisation.

2.3.2 Population of interest for Alp/Fulv in the company submission

The CS[1] (Foreword and Section B.1.3) states that the population of interest for this appraisal corresponds to people with endocrine-resistant HR+, HER2− ABC with a *PIK3CA* mutation after disease progression following treatment with a CDK4/6i+AI regimen. This represents a subset of the anticipated MHRA licence. The company's proposed positioning of Alp/Fulv is shown in Figure 1. The ERG notes that, according to Figure 1, the population of interest relates to patients who were endocrine-sensitive prior to first-line treatment for ABC and became endocrine-resistant after receiving treatment with a CDK4/6i+AI regimen, so now require second- and subsequent-line treatment. The clinical advisors to the ERG were satisfied that these definitions generally reflect the relevant patient population who would be eligible for treatment with Alp/Fulv in England if the Type 2 MHRA licence variation is granted.

The ERG notes that the CS[1] is unclear with respect to whether the company is seeking a positive recommendation in the second-line ABC setting only, or whether the anticipated target population also includes: (a) patients in subsequent metastatic settings and (b) the first-line ABC setting where patients received a CDK4/6i as adjuvant/neo-adjuvant treatment. In response to a request for clarification from the ERG (question B1),[14] the company stated that they are seeking a positive recommendation in second- and subsequent lines of therapy post-CDK4/6i. However, the selection of patients for the indirect treatment comparison (ITC) and the Alp/Fulv group of the economic model is restricted to second-line patients and excludes third- and subsequent-line patients (see Sections 4.4 and 5.2). The company's clarification response also states that under current practice, patients receive CDK4/6i therapy mainly in the first-line advanced setting, but if the neo/adjuvant use of CDK4/6i therapies is implemented in the future, the company anticipates that Alp/Fulv would also be an option for patients who progress on this earlier CDK4/6i therapy.[14]

3 CRITIQUE OF COMPANY'S DEFINITION OF THE DECISION PROBLEM

This chapter presents a summary and critique of the decision problem addressed by the CS.[1] A summary of the decision problem as outlined in the final scope[12] issued by NICE and addressed in the CS is presented in Table 3. The ERG's critique of the decision problem addressed within the CS is presented in the subsequent sections.

Table 3: The decision problem (reproduced from CS Table 1, with minor amendments and comments from the ERG)

	Final NICE scope[12]	Decision problem addressed in the CS[1]	Company's rationale if different from the final NICE scope	ERG comments
Population	People with HR+, HER2−ABC with a *PIK3CA* mutation after disease progression following an endocrine-based regimen (in the neo/adjuvant or advanced setting)	People with HR+, HER2− ABC with a *PIK3CA* mutation after disease progression following a CDK4/6i	As described in the Foreword, this submission focusses on a subset of the anticipated licensed indication for alpelisib plus fulvestrant i.e. patients with HR+, HER2–, locally advanced or metastatic breast cancer with a *PIK3CA* mutation after disease progression following a CDK4/6i. This population represents patients with a substantial unmet need due to limited treatment options after CDK4/6is, and where the mainstay of treatment offers limited survival benefit. Patients post-CDK4/6i have limited treatment options (Section B.1.3.2) and prognosis is extremely poor; these patients meet NICE's End-of-Life criteria of a short life expectancy of <24 months (see Section B.2.11.3). The post-CDK4/6i population is aligned with the population assessed within Cohort A of the BYLieve clinical trial, a small number of patients from the SOLAR-1 clinical trial, and the patient populations anticipated to be treated with alpelisib plus fulvestrant in UK clinical practice.	The modelled population reflects patients with endocrine-resistant HR+, HER2− ABC with a *PIK3CA* mutation after disease progression following a CDK4/6i+ AI in the first-line setting. The current EMA licence for Alp (in combination with Fulv) relates to people who have experienced disease progression *"following endocrine therapy as monotherapy."* As such, the modelled population reflects a subset of the population described in the final NICE scope, which is not in line with the current EMA licence. The relevance of the company's economic analysis is reliant on the MHRA granting a Type II variation to the current marketing authorisation. The ERG notes that the company's Bucher indirect comparison, which is used in the economic analysis, is based on data for patients who are mostly CDK4/6i-naïve.
Intervention	Alpelisib plus fulvestrant	Alpelisib plus fulvestrant	N/A – in line with final NICE scope	Consistent with the final NICE scope.

	Final NICE scope[12]	Decision problem addressed in the CS[1]	Company's rationale if different from the final NICE scope	ERG comments

Comparators	• CDK4/6i in combination with fulvestrant
	  ○ Ribociclib
	  ○ Abemaciclib (subject to ongoing NICE appraisal)
	  ○ Palbociclib (subject to ongoing NICE guidance)
	• Everolimus plus exemestane
	• Exemestane
	• Tamoxifen
		• Everolimus plus exemestane	This submission focusses on the post-CDK4/6i population. For patients who have received CDK4/6i + AI first-line in the advanced setting, another CDK4/6i is typically not used second-line in UK practice.[15] Likewise, the 5th ESMO Clinical Practice Guidelines for Advanced Breast Cancer recommend the use of CDK4/6i + fulvestrant only in patients who have not previously used CDK4/6i.[5] The NCCN also highlight that there are limited data to support the use of another CDK4/6i, following disease progression while on CDK4/6i.[6] CDK4/6is are thus not considered relevant comparators for the population of interest in this submission. In addition, palbociclib and abemaciclib are still on the CDF, and are thus not considered standard of care in UK practice.[16]
			Based on clinical expert feedback, exemestane monotherapy and tamoxifen are not relevant comparators as they are not widely used in UK clinical practice in this setting and are therefore not considered standard of care.[15] This approach with regards to comparators is consistent with that taken in other appraisals in HR+, HER2– ABC (TA579, TA619 or TA687/TA593).[8, 9, 16]
			Everolimus plus exemestane is therefore the only relevant comparator to alpelisib plus fulvestrant within the scope of this submission.
				Eve/Exe is a clinically relevant comparator.
				The CS does not include Exe or Tam monotherapy as comparators.
				The ERG agrees that it would be unlikely that CDK4/6is would be used again if previously received as first-line treatment.
				The ERG's clinical advisors also commented that Fulv and Tam are sometimes used as monotherapies and single-agent chemotherapy may be offered to patients who are at risk of visceral crisis, although endocrine options would usually be used first. Except for Tam, these other treatments are not listed in the final NICE scope.

	Final NICE scope[12]	Decision problem addressed in the CS[1]	Company's rationale if different from the final NICE scope	ERG comments
Outcomes	• Progression-free survival (PFS) • Overall survival (OS) • Response rate • Adverse effects of treatment • Health-related quality of life (HRQoL)	• PFS • OS • Overall response rate (ORR)/ clinical benefit rate (CBR) • AEs of treatment • HRQoL (EQ-5D-3L)	N/A – in line with final NICE scope.	Consistent with the NICE final scope.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost-comparison may be carried out. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any Patient Access Schemes for the comparator technologies will be taken into account. The use of alpelisib is conditional	The cost-effectiveness of the treatments evaluated in this appraisal is expressed in terms of incremental cost per QALY. A lifetime time horizon was adopted to capture all relevant costs and health-related utilities All costs and utilities were discounted at a rate of 3.5% per year in alignment with the NICE guide to the methods of technology appraisal Costs were considered from an NHS and PSS perspective Where known, any PAS discounts have been applied within the base case economic analyses. The cost of *PIK3CA* mutation testing has been included within the base case economic analysis, and a scenario analysis has been conducted without the cost of the diagnostic test.	The proposed PAS discount for alpelisib has been taken into account within the economic results. The PAS discount for everolimus is known to Novartis and has therefore also been taken into account within the economic results. As of January 2021, fulvestrant is now available as a generic medicine; therefore, an estimate of this generic price (based on the latest available information regarding the discount; from April 2021) will be considered in the base case economic analysis.	Generally consistent with the final NICE scope (see Section 5.3). At the request of NICE, the list price for Fulv has been included in this ERG report.

	Final NICE scope[12]	Decision problem addressed in the CS[1]	Company's rationale if different from the final NICE scope	ERG comments
	on the presence of *PIK3CA* mutation. The economic modelling should include the costs associated with diagnostic testing for *PIK3CA* HR+, HER2− negative breast cancer who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test.			
Other considerations	Guidance will only be issued in according with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	Alpelisib plus fulvestrant is positioned in line with a subset of its anticipated marketing authorisation, consistent with the patient population within the BYLieve trial i.e. patients with HR+, HER2–, locally advanced or metastatic breast cancer with a *PIK3CA* mutation after disease progression following a CDK4/6i.	N/A – in line with final NICE scope	Consistent with the final NICE scope. The population for which the company is seeking approval (HR+, HER2–, locally advanced or metastatic BC with a *PIK3CA* mutation after disease progression following a CDK4/6i), is generally in line with the patient population within Cohort A of the BYLieve study. However, as noted above, this is not in line with the current marketing authorisation for Alp/Fulv.

ABC - advanced breast cancer; AE - adverse event; BC - breast cancer; CBR - clinical benefit rate; CDF - Cancer Drugs Fund; CDK4/6i - cyclin-dependent kinase 4/6 inhibitor; EQ-5D-3L - EuroQol 5-Dimensions 3-Levels; ESMO - European Society for Medical Oncology; Eve/Exe - everolimus plus exemestane; Exe - exemestane; HER2 - human epidermal growth factor receptor 2; HR+ - hormone receptor positive; HRQoL - health-related quality of life; MHRA - Medicines and Healthcare products Regulatory Agency; NCCN - National Comprehensive Cancer Network; NHS - National Health Service; NICE - National Institute for Health and Care Excellence; ORR - overall response rate; OS - overall survival; PAS - Patient Access Scheme; PFS - progression-free survival; PIK3CA - phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; QALY - quality-adjusted life year; Tam - tamoxifen

3.1 Population

The final NICE scope[12] specifies the relevant population as people with advanced HR+, HER2- *PIK3CA*-mutated breast cancer that has progressed after prior ET (in the neo/adjuvant or advanced setting).

The main clinical evidence for Alp/Fulv included in the CS[1] relates to the patient population in Cohort A of the BYLieve non-comparative study,[17] which comprises people with HR+, HER2− ABC with a *PIK3CA* mutation, who have progressed following an endocrine-based regimen (in the neo/adjuvant or advanced setting) and who have previously received treatment with a CDK4/6i+AI regimen, and subsequently received Alp/Fulv for the first-, second-, third- or fourth-line treatment of ABC. However, the clinical data for Alp/Fulv included in the company's Bucher ITC used in the economic analysis are restricted to endocrine-resistant patients from the SOLAR-1[18] randomised controlled trial (RCT) who received Alp/Fulv as second-line treatment for ABC and who are mostly CDK4/6i-naive.

The current marketing authorisation issued by the EMA is as follows: *"Piqray is indicated in combination with fulvestrant for the treatment of postmenopausal women, and men, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with a PIK3CA mutation after disease progression following endocrine therapy as monotherapy."*[13]

The ERG notes that whilst the population included in Cohort A of BYLieve[17] reflects a subset of the population defined in the final NICE scope,[12] patients enrolled in BYLieve would not be eligible to receive Alp/Fulv under the current EMA licence because they had received prior endocrine combination therapy rather than endocrine monotherapy. The Foreword to the CS[1] states that the company has applied to the MHRA for a Type II variation to the existing EMA licence. The anticipated revision to the indication for alpelisib is [redacted] [1] The ERG notes that the relevance of the clinical evidence and economic analyses presented in the CS are reliant on the MHRA granting this variation in the marketing authorisation for Alp/Fulv.

The ERG further notes that the company's economic analysis relates specifically to patients in BYLieve who had received one prior line of therapy in the advanced setting (i.e. patients receiving Alp/Fulv as second-line treatment for ABC). Whilst the economic model excludes third- and subsequent-line patients in BYLieve, the company's clarification response[14] (question B1) states that the company is also seeking a positive recommendation for Alp/Fulv in these subsequent-line settings. In their response, the company states that very few patients have been evaluated in BYLieve beyond second-line ([redacted] in third-line and [redacted] in fourth-line), but *"a recommendation should not preclude such patients from receiving alpelisib plus fulvestrant in the future"*.[14] In response to the

ERG's question about Alp/Fulv in first-line (following receipt of a CDK4/6i in the adjuvant/neo-adjuvant setting), the company clarified that in current clinical practice patients receive CDK4/6i therapy mainly in the first-line advanced setting, but should the neo/adjuvant use of CDK4/6i therapies be implemented in future practice, *"it is anticipated that alpelisib plus fulvestrant would be an option for patients who progress on this earlier CDK4/6i therapy"*.[14]

The CS[1] states that prognosis is extremely poor for the post-CDK4/6i+AI population, and that NICE's End-of-Life (EoL) criterion of a short life expectancy of <24 months is met for these patients. Owing to its non-comparative design, BYLieve[19] does not provide evidence on relative treatment effects for Alp/Fulv versus any comparator; however, data for a subset of these patients are used to inform PFS and OS in the intervention group of the company's economic model (see Section 5.2). Evidence for relative treatment effects are based on an ITC which use data from a subset of mostly CDK4/6i-naive patients who received second-line treatment in the SOLAR-1[18] and BOLERO-2[20] studies (which evaluated Alp/Fulv and Eve/Exe, respectively), with additional RCTs CONFIRM[21] and SoFEA[22] being used to form a connected network (see Sections 4.3 and 4.4). The clinical advisors to the ERG commented that it was appropriate to focus on the endocrine-resistant population and that the population enrolled in BYLieve reflects patients seen in clinical practice in England in terms of baseline characteristics and co-morbidities. They also agreed that the prognosis is poor for these patients.

3.2 Intervention

The intervention described in the CS[1] is consistent with the final NICE scope.[12] The intervention under consideration is alpelisib (Piqray®) plus fulvestrant. Alpelisib is an oral α-specific phosphatidylinositol 3-kinase (PI3K) inhibitor, which inhibits the activation of the *PIK3CA* signalling pathway, resulting in the inhibition of tumour cell growth and survival, and may also help overcome ET resistance in *PIK3CA*-mutated breast cancer. Fulvestrant is an oestrogen receptor (ER) antagonist, which down-regulates and degrades the ER protein in human breast cancer cells (CS,[1] Section B.1.2).

As noted in Section 3.1, a full marketing authorisation was issued by the EMA in July 2020. A Type II variation to this authorisation by the MHRA is expected in [redacted].[1] According to the current Summary of Product Characteristics (SmPC) for alpelisib,[23] the recommended dose of Alp/Fulv is alpelisib (300mg [2 x 150mg film-coated tablets], taken orally, once daily) plus fulvestrant (500mg at intervals of one month, with an additional 500mg dose given two weeks after the initial dose, via intramuscular [IM] injection). The list price per pack of 56 x 150mg alpelisib tablets (28 days' supply) is [redacted]. The company has proposed a Patient Access Scheme (PAS) which takes the form of a simple price discount of [redacted]; the discounted cost per pack of Alp is [redacted]. The list price of Fulv 250mg per 5ml solution for injection pre-filled syringes (×2) is £522.41.[24] The company assumes a PAS discount of [redacted] for Fulv, which leads to a discounted cost per pack of

[redacted]; however, at the request of NICE, only the list price for Fulv has been included in this ERG report. The marketing authorisation for alpelisib does not include a formal stopping rule; it states that treatment with Alp/Fulv *"should continue as long as clinical benefit is observed or until unacceptable toxicity occurs."*[23] It also notes that dose modifications may be necessary to improve tolerability. In their clarification response (question A6),[14] the company stated that a change in this wording is not anticipated in the Type II variation from the MHRA.

The SmPC for Alp[23] states that patients with HR+, HER2− ABC should be selected for treatment with Alp/Fulv based on the presence of a *PIK3CA* mutation in tumour or plasma specimens, using a validated test. If a mutation is not detected in a plasma specimen, tumour tissue should be tested if available. To monitor patients for alpelisib-induced hyperglycaemia, fasting plasma glucose (FPG) should be measured at weeks 1, 2, 4, 6 and 8 after treatment start and monthly thereafter, and haemoglobin A1c (HbA1c) should be measured at baseline, four weeks of treatment and every three months thereafter.

3.3 Comparators

The NICE scope[12] lists four comparators: (i) CDK4/6i in combination with Fulv (Ribo/Fulv, Abem/Fulv or Palb/Fulv), (ii) Eve/Exe; (iii) Exe and (iv) Tam. The company's economic analysis only includes Eve/Exe as a comparator (see Section 5.2).

The CS[1] (Section B.1.3) states that, for patients with endocrine-resistant HR+, HER2− ABC with a *PIK3CA* mutation with previous treatment with a CDK4/6i+AI in the advanced setting, Eve/Exe represents the mainstay of treatment in the UK. The CS comments that this regimen is associated with a limited survival benefit and that it is not a targeted therapy. The ERG's clinical advisors agreed that Eve/Exe is the main comparator in the post-CDK4/6i+AI population.

The CS[1] notes that patients who receive a CDK4/6i+AI for the first-line treatment of advanced disease (as was the case in Cohort A of the BYLieve study) are unlikely to receive CDK4/6i+Fulv at a subsequent treatment line. The CS also states that two of the CDK4/6s+Fulv combinations listed in the final NICE scope[12] (Abem/Fulv and Palb/Fulv) are currently available through the CDF, and as such, they cannot be considered standard of care and are therefore not relevant comparators to Alp/Fulv in this appraisal. Ribo/Fulv and Abem/Fulv, are no longer funded through the CDF, but are now available through routine NHS commissioning; however, the ERG's clinical advisors agreed that they would be unlikely to re-challenge patients who have progressed on a CDK4/6i with another CDK4/6i.

The CS[1] states that Exe and Tam monotherapy *"may also be options for patients in this setting, however their use is not widespread in UK clinical practice"* and that Exe and Tam have not undergone NICE appraisals in the endocrine-resistant population; therefore, these regimens are not considered as relevant comparators.[1] The ERG's clinical advisors commented that some patients receive Tam or Fulv as

monotherapy, whilst Exe monotherapy is used less often. They also mentioned that some patients will be offered single-agent paclitaxel or capecitabine if they are at risk of visceral crisis, although endocrine options would usually be offered first. The ERG notes that NICE guidance for the three CDK4/6is (TA725,[7] TA687,[8] and TA619[9]) state that the main alternative treatment for this population is Eve/Exe. Given that Tam monotherapy is listed as a comparator in the final NICE scope,[12] the ERG believes that this treatment should have been considered in the CS and that it might have been appropriate to include Fulv in the scope. However, the ERG agrees that it is appropriate to exclude CDK4/6i+Fulv and Exe monotherapy as comparators.

3.4 Outcomes

The following outcomes are listed in the final NICE scope:[12]

- Overall survival (OS)
- Progression-free survival (PFS)
- Response rate (RR)
- Adverse effects of treatment
- Health-related quality of life (HRQoL).

The CS[1] considers all of these outcomes for BYLieve[17] except for HRQoL, as this was not measured in the study. The company's economic analyses include outcome data on PFS, OS, and adverse events (AEs) from Cohort A of BYLieve (see Section 5.2). The company's Bucher ITC used in the economic model is restricted to PFS and OS outcomes only, with relative treatment effects for Alp/Fulv based on mostly CDK4/6i-naïve second-line *PIK3CA*-mutated patients in SOLAR-1,[18] rather than BYLieve (due to its non-comparative design). The economic model uses data from SOLAR-1 and BOLERO-2 to inform health-related quality of life (HRQoL) parameters.

3.5 Other relevant factors

Section B.1.4 of the CS[1] states *"No equality issues related to the use of alpelisib in combination with fulvestrant are foreseen."*

The CS[1] argues that the use of Alp/Fulv meets NICE's EoL criteria for patients with HR+, HER2– ABC with a *PIK3CA* mutation and acquired endocrine resistance who have progressed following first-or subsequent-line treatment with a CDK4/6i+AI regimen.

4 CLINICAL EFFECTIVENESS

The clinical evidence submitted by the company comprises:

- A systematic literature review (SLR)
- ITCs of Alp/Fulv versus Eve/Exe and other treatments for ABC.

This section summarises evidence for the clinical effectiveness of Alp/Fulv from the CS[1] including the company's SLR and ITCs, and provides a critique of the methods used to identify and synthesise this evidence. Full details are presented in CS Appendix D.[23]

4.1 Critique of the methods of review

4.1.1 Searches

Appendix D of the CS[23] reports the process by which studies were identified for the SLR of clinical effectiveness. As stated in the PICOS framework (CS Appendix D1.1),[23] the population of interest is specifically *"adults with HR+, HER2−, PIK3CA-mutated advanced or metastatic breast cancer."* Given the variety of different forms of breast cancer and the volume of associated literature, the ERG accepts the company's decision to define the population in this way. RCTs assessing Alp or various other treatments for ABC (broader than the final NICE scope) were eligible for inclusion in the SLR (CS Appendices,[23] Section D.1.1, Table 1, page 9, with slight differences depending on whether the setting was first- or second-line). Non-RCT evidence was only included for Alp or other PI3K inhibitors (in any line of therapy).

Searches were initially performed in January 2019; these were updated in October 2019, August 2020 and April 2021. These searches are reproduced in full in CS Appendix D.[23] The searches were restricted to studies published in 2007 or later. Conference abstracts published since 2016 were also eligible for inclusion. Databases include Medline (plus Medline-in-Process and Epub ahead of print); EMBASE and the Cochrane databases (including those formerly part of Cochrane and now hosted by the York Centre for Reviews and Dissemination [CRD]). The list of databases searched is in line with all core sources recommended by NICE.

The ERG considers that the search strategies have been designed and executed to a high standard, using an appropriate combination of subject headings (e.g. Medical Subject Headings [MeSH]) and free text terms. Study filters are based on those developed by the Scottish Intercollegiate Guidelines Network (SIGN). Whilst these filters are not formally validated, the ERG agrees with the company that they are most likely fit for purpose. Supplementary search methods included checking reference lists of included systematic reviews for missing studies. During the clarification process (see clarification response,[14] question A1), the ERG queried whether reference lists of primary studies were also checked. The

company responded that this was not the case, but they believed their other hand-searching methods were sufficient to identify all relevant studies. The ClinicalTrials.gov register was searched for unpublished or ongoing RCTs; whilst Glanville *et al* (2014)[25] recommends that for optimal coverage, the International Clinical Trials Registry Platform (ICTRP) should also be searched, the ERG considers it unlikely that any eligible trials have been missed on this occasion.

4.1.2 Inclusion criteria for the SLR

The inclusion criteria for the company's SLR are broader than the decision problem set out in the final NICE scope.[12] These inclusion criteria are summarised in CS Appendix D[23] (Section D.2, Table 8). The company's SLR included RCTs of several treatments for HR+, HER2– ABC with a *PIK3CA* mutation in the first- and second-line settings. Treatments included in the company's SLR were: Alp or other PI3K inhibitors (as monotherapy or in combination), CDK4/6i (plus an AI or Fulv), Tam, Exe, Eve/Exe, Fulv, and chemotherapy. The SLR also included non-RCTs, but only for Alp and other PI3K inhibitors.

The study selection process is described as a two-stage sifting process with titles and abstracts followed by full texts being screened by two independent reviewers, with a third reviewer consulted as necessary (CS Appendix D,[23] Section D.2, page 30). The ERG considers this appropriate.

The inclusion criteria included a date limit of post-2007, the date when the test for HER2 status was standardised. The ERG undertook a very brief PubMed search for RCTs of Alp/Fulv and RCTs of the main comparator (Eve/Exe) and none were published prior to 2008; therefore, the ERG is satisfied that it is reasonable to exclude evidence prior to this date. The SLR also excluded non-English language studies; the ERG is satisfied that no relevant evidence would have been excluded by applying this criterion. The SLR included studies in both the first- and second-line settings (subsequent lines are not explicitly mentioned, including both endocrine-sensitive and endocrine-resistant patients).

Overall the ERG is satisfied that the inclusion criteria for the SLR were appropriate.

4.1.3 Inclusion criteria for the indirect comparisons

Section B.1.1 of the CS[1] (Table 1, Decision Problem) states that the only relevant comparator is Eve/Exe. Since no studies directly compared Alp/Fulv against Eve/Exe, the results of the clinical SLR were used to identify RCTs of Alp/Fulv and/or Eve/Exe in order to conduct ITCs. To connect the trials, the studies identified in the SLR were re-reviewed for any studies investigating either Eve/Exe, placebo plus Exe, placebo plus Fulv (Pbo/Fulv) or Alp/Fulv (CS Appendix D,[23] Section B.2.6). However, it was not clear to the ERG if the re-reviewing took place at the title and abstract sift or at the full paper sift of the systematic review process, and therefore whether any relevant trials could have been missed.

The inclusion criteria for the ITCs were reported in Section D.5.1 of CS Appendix D.[23] A number of amendments were made to the eligibility criteria for the studies to be included in the ITCs. The eligibility criterion for the study design was restricted to RCTs. Where data were not available for patients with *PIK3CA*-mutated breast cancer, trials reporting outcomes for patients regardless of *PIK3CA* mutation status were considered. The ERG considers these amendments were appropriate in order to identify evidence for the ITCs.

4.1.4 Critique of data extraction

The data extraction process is described in Section D.2.1 of CS Appendix D.[23] Data were extracted into a pre-specified data extraction grid by one reviewer, a second reviewer verified the extracted information, and a third reviewer was consulted as necessary. Section D.5.1 of CS Appendix D[23] reports that data from the studies included in the ITCs were extracted into the same grid, although the number of reviewers involved was not stated.

4.1.5 Quality assessment

The process used to assess the quality of the trials included in the SLR is described in CS Appendix D (Section D.4).[23] The quality of RCTs was assessed using the York CRD checklist for RCTs[26] and the quality of each non-RCT and RCTs for which only one arm was relevant was assessed using a version of the Downs and Black checklist,[27] which was adapted by removing any questions which were not applicable to the current review. The CS[1] reports that the quality of each study was assessed by one reviewer, with the conclusions confirmed independently by a second reviewer, and any discrepancies were discussed. If necessary, a third reviewer arbitrated the final decision. The ERG considers this approach to be appropriate.

4.1.6 Evidence synthesis

The CS[1] did not include a standard meta-analysis of the trials of interest. The ERG agrees that this would not be possible. The CS[1] includes ITCs of Alp/Fulv versus Eve/Exe and other treatments for ABC; these are detailed in Sections 4.6 to 4.10.

4.1.7 Overall ERG view on company's review methods

Overall, the ERG considers that the company's review methods were appropriate.

4.2 Characteristics of the SOLAR-1 and BYLieve studies of Alp/Fulv

4.2.1 Results of the company's SLR

Seventeen studies met the inclusion criteria of the company's broad-focus SLR, which covered a range of treatments for HR+, HER2– ABC (CS Appendix D,[23] Section D.3.3, Table 17). However, most of these studies were ultimately not of relevance to the appraisal.

The CS[1] (Section B.2.2) reports that three studies of Alp/Fulv initially met the inclusion criteria for the SLR. These consisted of one RCT (SOLAR-1)[28] and two non-RCTs (BYLieve[29] and Juric *et al*, 2018[30]). Juric *et al*. (2018)[30] was subsequently excluded. The company justified this exclusion on the basis that only nine patients with *PIK3CA*-mutated disease received the licensed dose of Alp (300mg once daily), and that the patient population differed from the population of interest to the CS[1] in that patients were heavily pre-treated (median 5 prior lines of therapy) and only 60% (52 patients) had *PIK3CA*-mutated disease. The ERG agrees that exclusion of Juric *et al*. (2018) from the CS[1] was reasonable.

Therefore, two relevant studies of Alp/Fulv were presented in the CS[1]: one RCT (SOLAR-1)[28] and one non-RCT (BYLieve).[29] These studies are described in the remainder of Section 4.2. The literature search was also used to identify studies for inclusion in the company's ITCs; these are described in Section 4.3.

4.2.2 Overview and relevance of SOLAR-1 and BYLieve

The population of interest in the CS[1] is patients who have progressed following treatment with a CDK4/6i. However, the majority of patients in SOLAR-1[28] received prior endocrine monotherapy, with only 20 patients having received prior CDK4/6i. This is because CDK4/6i was not standard treatment prior to enrolment into SOLAR-1 (discussed in CS[1] Section B.2.2.1). Conversely, all patients in Cohort A of BYLieve[31] had received prior CDK4/6i+AI therapy. Therefore, BYLieve Cohort A is most relevant to the population of interest in the CS,[1] and is presented as the key source of evidence in the CS[1] (Section B.2.3), while data from SOLAR-1 are presented as supplementary evidence (CS[1] Section B.2.4 and CS Appendix F[23]). SOLAR-1 is also used in the company's ITCs (CS[1] Section B.2.7). The design of SOLAR-1 and BYLieve Cohort A are summarised in Table 4, and are described in more detail in the subsequent sections.

Table 4: Design of SOLAR-1 and BYLieve (adapted from CS, Table 5)

Study	BYLieve Cohort A	SOLAR-1
Study design	Non-randomised, open-label, three-cohort, multicentre, non-comparative Phase II trial	RCT: randomised, double-blind, placebo-controlled, international, multicentre, Phase III trial
Population	• Premenopausal, perimenopausal and postmenopausal women, or men • HR+, HER2− ABC • *PIK3CA* mutation • Prior CDK4/6i plus AI therapy	• Postmenopausal women, or men • HR+, HER2− ABC • *PIK3CA* mutated cohort (reported in CS[1]) and non-mutated cohort (not in CS[1]) • Prior AI treatment in (neo)adjuvant setting or for advanced disease
Intervention(s)	Alpelisib 300mg orally once daily plus fulvestrant 500mg IM[a]	Alpelisib 300mg orally once daily plus fulvestrant 500mg IM[a]
Comparator(s)	NA	Placebo plus fulvestrant 500 mg IM[a]
Reported endpoints specified in the decision problem	Primary endpoint: • Proportion patients alive without disease progression at 6 months (by cohort, locally assessed) Secondary endpoints: • OS • PFS (locally assessed) • PFS on next-line treatment (PFS2) • ORR and CBR • DoR in patients with confirmed CR or PR • Safety	Primary endpoint: • PFS (locally assessed) Secondary endpoints: • OS • ORR/CBR • HRQoL (EQ-5D-3L) • Safety
All other reported endpoints	Exploratory endpoints: • Clinical response in patients with *PIK3CA* mutation status measured in ctDNA • Clinical response in patients with *ESR1* mutations • Biomarkers	Exploratory endpoints: • Time to response • DoR An exhaustive list of exploratory endpoints is presented in CS Appendix F.[23]

[a]*Fulv given on Day 1 and Day 15 of the first 28-day cycle, then Day 1 of the subsequent 28-day cycles.*
ABC - advanced breast cancer; AI - aromatase inhibitor; CBR - clinical benefit rate; CDK 4/6i - cyclin-dependent kinase 4/6 inhibitor; CR - complete response; CS - company's submission; ctDNA - circulating tumour deoxyribonucleic acid; DoR - duration of response; HER2 - human epidermal growth factor receptor 2; HR+ - hormone receptor positive; HRQoL - health-related quality of life; IM - intramuscular; NA - not applicable; ORR - overall response rate; OS - overall survival; PFS(2) - progression-free survival (after next line therapy); PIK3CA - phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PR - partial response; RCT - randomised controlled trial

4.2.3 Study design: BYLieve

Summary of all cohorts of BYLieve and rationale for use of Cohort A

BYLieve (NCT03056755)[29] is an ongoing, open-label, multicentre, three-cohort, non-comparative Phase II study in men and women (premenopausal, perimenopausal and postmenopausal) with HR+, HER2− locally advanced or metastatic breast cancer with a *PIK3CA* mutation. The three cohorts are:

- Cohort A: Patients receive Alp/Fulv following prior CDK4/6i+AI
- Cohort B: Patients receive Alp plus letrozole following CDK4/6i+Fulv

- Cohort C (enrolment ongoing): Patients receive Alp/Fulv following prior ET (as monotherapy or in combination with targeted therapy, to include letrozole, Fulv or CDK4/6i+Fulv but not CDK4/6i+AI) or systemic chemotherapy.

Data from Cohort A (n=127 patients) are currently the only data available for Alp/Fulv from the BYLieve study,[31] and only these data are included in the CS[1] (Section B.2.3.6). Only patients at second-line ([redacted]) from BYLieve Cohort A were used in the company's economic analyses (see Section 5.2.4). The CS[1] (Section B.2.3.1) states that Cohort B is not relevant as patients did not receive Alp/Fulv. The CS[1] also states that some of Cohort C may be relevant to the submission, but that these data will not be available until [redacted]; therefore, Cohort C is not considered further within the CS[1] (the CS[1] also notes that only a small number of patients in this cohort will likely have received a prior CDK4/6i). Therefore, only Cohort A is discussed further in the CS[1] and in this report.

Population in BYLieve Cohort A

Key inclusion criteria for BYLieve Cohort A[31] are reported in Table 7 of the CS[1] and summarised in Table 4. Key inclusion criteria were: premenopausal, perimenopausal and postmenopausal women, or men; ≥18 years of age; HR+, HER2− ABC with confirmed *PIK3CA* mutation; tumour progression on or after CDK4/6i+AI as immediate prior therapy; ≤2 prior anti-cancer therapies for ABC; ≤1 prior regimens of chemotherapy, and ECOG PS ≤2. Clinical advisors to the ERG agreed that eligible patients appear representative of those with endocrine-resistant ABC in clinical practice in England.

Intervention in BYLieve Cohort A

Patients in Cohort A of BYLieve[31] received Alp/Fulv following progression on a CDK4/6i+AI. Alp was given at a dose of 300mg orally once daily, and Fulv as 500mg intramuscular (IM) injections once per month (with an additional dose two weeks after the initial dose).

Outcomes in BYLieve Cohort A

The primary outcome was the proportion of patients who are alive without disease progression at 6 months based on local investigator assessment. Secondary endpoints include PFS, progression on next line therapy (PFS2), OS, overall response rate (ORR), clinical benefit rate (CBR), duration of response (DoR) and safety.

The statistical methods for the primary analysis of BYLieve[31] are presented in Table 10 of the CS.[1] The proportion of 30% of patients alive without progression after 6 months, which is used in the primary endpoint, was considered a clinically meaningful threshold for this cohort based on previous trials and steering committee discussions (see clarification response,[14] question A13). Therefore, it was planned

that the null hypothesis would be rejected if the lower bound of the 95% confidence interval (CI) for the observed PFS proportion at 6 months was greater than 30%.

Analysis populations in BYLieve Cohort A

The analysis populations for BYLieve[31] are detailed in Table 9 of the CS[1] and summarised below:

- Full analysis set (FAS; n=127): all randomised patients; population for analyses of baseline patient characteristics
- Modified FAS (mFAS; n=121): all patients with *PIK3CA* mutation confirmed by a Novartis-designated laboratory; primary population for efficacy analyses
- Safety set (n=127): all patients who received at least one dose of study treatment; population for safety analyses
- Second-line patients (n=[redacted]): used in company's economic model (see Section 5).

Quality assessment of BYLieve Cohort A

The company's quality assessment of the BYLieve study,[31] based on the Downs and Black checklist,[27] is presented in Table 11 of the CS.[1] A number of issues regarding the quality of the study were highlighted by the assessment, although these primarily related to the non-comparative design of the study and the absence of randomisation and blinding. The CS did not report an overall opinion on the quality of BYLieve, but suggested that the study provides valuable clinical data for a population with critical unmet need.

4.2.4 Study design: SOLAR-1

SOLAR-1 (NCT02437318)[28] is an international multicentre, randomised, double-blind, Phase III trial of the efficacy and safety of Alp/Fulv versus placebo plus fulvestrant (Pbo/Fulv) in patients with HR+, HER2−, ABC (described in the CS[1] Section B.2.4 and CS Appendix F[23]).

Population in SOLAR-1

Inclusion criteria for SOLAR-1[28] are reported in CS Appendix F[23] (Table 32). The key inclusion criteria were: postmenopausal women, or men, ≥18 years of age, with HR+, HER2- advanced or metastatic breast cancer, having relapsed or progressed during or after AI therapy in the (neo)adjuvant or advanced setting, and with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1. Cohorts with and without a *PIK3CA* mutation were included in the trial; however, only the *PIK3CA*-mutated cohort (n=341) is included in the CS[1] and in this report. The majority of patients were endocrine-resistant but a small number (n=39) were endocrine-sensitive (these patients were excluded from the ITCs). In addition, only 20 patients had received a prior CDK4/6i, making SOLAR-1 less relevant to the population of interest.

Clinical advisors to the ERG agreed that the inclusion criteria reflect the characteristics of patients treated for endocrine-resistant ABC in clinical practice in England, except that in current practice the majority of patients now receive CDK4/6i+AI in the first-line metastatic setting.

Intervention in SOLAR-1

Patients were randomised to Alp/Fulv or Pbo/Fulv, stratified by the presence of lung and/or liver metastases and prior treatment with a CDK4/6i. Alp was given at a dose of 300mg orally once daily, and Fulv as 500mg IM injections once per month (with an additional dose two weeks after the initial dose). No stopping rule was applied in the trial. Of the 341 patients in the *PIK3CA*-mutated cohort, 169 were randomised to receive Alp/Fulv and 172 to receive Pbo/Fulv.

Comparator in SOLAR-1

The comparator in SOLAR-1 was Pbo/Fulv. This comparator does not reflect standard of care in England; hence, an ITC was necessary.

Outcomes in SOLAR-1

The primary endpoint of SOLAR-1 was investigator-assessed PFS. Secondary endpoints included OS, ORR, CBR, ECOG PS, HRQoL and safety (CS Appendix F[23] Table 31).

Analysis populations in SOLAR-1

The analysis populations for SOLAR-1 (*PIK3CA*-mutated cohort) are detailed in CS Appendix F[23] (Table 34) and summarised below:

- FAS (n=341): all randomised patients; population for analyses of baseline characteristics and efficacy
- Safety set (n=340): all patients who received at least one dose of study treatment; population for safety analyses
- Post-CDK4/6i population (n=20): randomised patients who received prior CDK4/6i+AI; key focus of CS[1] (the company's response to clarification question A7 notes that all 20 patients were endocrine-resistant[14])
- Second-line endocrine-resistant patients (n=[redacted]): used in ITCs.

Quality assessment of SOLAR-1

The company's quality assessment of SOLAR-1 based on the York CRD checklist is presented in CS Appendix F[23] (Table 36). No issues relating to quality were presented in the CS.[1] The CS[1] reports that SOLAR-1 can be considered high quality. The ERG agrees with this assessment.

4.2.5 Baseline characteristics: BYLieve Cohort A and SOLAR-1

The baseline characteristics of BYLieve Cohort A[31] and SOLAR-1[28] are summarised in Table 5. Patients in BYLieve Cohort A were recruited from 21 European and 2 UK study centres (n=55 and n=3 patients, respectively). In the second-line population of BYLieve Cohort A (which reflects the population used in the intervention group of the economic model), [redacted] patients were recruited from Europe, including [redacted] from the UK (clarification response,[14] question A12). Patients in SOLAR-1 were recruited from 139 European and 6 UK study centres (n=[redacted] and [redacted] patients, respectively).

The median age was 58 years in BYLieve Cohort A[31] and 63 and 64 years across SOLAR-1 arms.[28] All patients were female in BYLieve Cohort A and only one male was enrolled in in SOLAR-1. All women in SOLAR-1 and 78% of patients in BYLieve Cohort A were postmenopausal. The majority of patients were white (64% in BYLieve Cohort A and 69% and 63% across SOLAR-1 arms). In both studies, the majority of patients had an ECOG PS of 0 (62% in BYLieve and 66% in SOLAR-1) or ECOG PS of 1 (32% in BYLieve and 34% in SOLAR-1). The percentage of patients with Stage IV (metastatic) disease at study entry was 98% in BYLieve Cohort A and [redacted] and [redacted] across SOLAR-1 arms.

Prior CDK4/6i therapy was received by all patients in BYLieve Cohort A,[31] and by 9 patients (5.3%) in the SOLAR-1 Alp/Fulv arm and 11 patients (6.4%) in the Pbo/Fulv arm.[28] In terms of line of therapy, in BYLieve Cohort A, 12% were receiving first-line therapy in the advanced setting, 70% second-line therapy, 17% third-line therapy and 2% fourth-line therapy. In SOLAR-1, 52% were receiving first-line therapy and 47% second-line therapy. In SOLAR-1, 11% were endocrine-sensitive and 86% were endocrine-resistant. In Cohort A of BYLieve, 0.8% of patients were endocrine-sensitive and 80% of patients were endocrine-resistant (percentages do not sum to 100% due to incomplete data).

The clinical advisors to the ERG considered the majority of the patient characteristics in both BYLieve Cohort A[31] and SOLAR-1[28] to be typical of patients with HR+/HER2- endocrine-resistant ABC within clinical practice in England. However, few patients in SOLAR-1 had previously received a CDK4/6i. The company's clarification response[14] (question A9) states that the key differences between second-line patients in BYLieve Cohort A and SOLAR-1 were the receipt of prior CDK4/6i in BYLieve and the fact that BYLieve included premenopausal women.

Table 5: Baseline characteristics in BYLieve Cohort A and SOLAR-1 (adapted from CS, Table 8 and CS Appendix F, Table 33)

Characteristics	BYLieve Cohort A: Alp/Fulv (n=127)	SOLAR-1: Alp/Fulv (n=169)	SOLAR-1: Pbo/Fulv (n=172)
Age (years)			
Mean (SD)	56.7 (10.7)	[redacted]	[redacted]
Median (range)	58.0 (33–83)	63.0 (25–87)	64.0 (38–92)
Sex and menopausal status			
Female (%)	127 (100)	168 (99.4)	172 (100)
Postmenopausal (%)	[redacted]	168 (99.4)	172 (100)
Race, n (%)			
Caucasian/White	81 (64)	117 (69.2)	109 (63.4)
ECOG PS, n (%)			
0	79 (62)	112 (66.3)	113 (65.7)
1	41 (32)	56 (33.1)	58 (33.7)
2	2 (1.6)	0	0
Missing	5 (3.9)	1 (0.6)	1 (0.6)
Stage at time of study entry, n (%)			
III	3 (2.4)	NR	NR
IV	124 (97.6)	[redacted]	[redacted]
Previous treatment, n (%)			
Any CDK4/6i	127 (100)	9 (5.3)	11 (6.4)
Chemotherapy	NR	101 (59.8)	107 (62.2)
Time since most recent recurrence/relapse (months)			
Mean (SD)	2.2 (2.5)	NR	NR
Median (range)	1.6 (0.1-16.1)	NR	NR
Line of treatment in advanced disease, n (%)			
First-line	15 (12)	88 (52.1)	89 (51.7)
Second-line	89 (70)	79 (46.7)	82 (47.7)
Third-line	21 (17)	0 (0)	0 (0)
Fourth-line	2 (2)	0 (0)	0 (0)
Line not specified in CS[1]	0	2 (1)	1 (0.6)
Sites of metastases, n (%)			
Breast	5 (4)	1 (0.6)	3 (1.7)
Bone	108 (85)		
Bone only	24 (19)	42 (24.9)	35 (20.3)
Visceral	85 (67)	93 (55.0)	100 (58.1)
Liver	59 (47)	49 (29.0)	54 (31.4)
Lung	43 (34)	57 (33.7)	68 (39.5)
Lung or liver	NR	84 (49.7)	86 (50.0)
Skin	4 (3)	NR	NR
Lymph nodes	37 (29)	NR	NR
CNS	2 (2)	NR	NR
Other	12 (9)	NR	NR
Endocrine status, n (%)			
Endocrine-sensitive	NR	20 (11.8)	19 (11.0)
Endocrine-resistant	NR	143 (84.6%)	149 (86.6)
Endocrine status not available	NR	6 (3.6%)	4 (2.3%)

Alp/Fulv - alpelisib plus fulvestrant; CDK4/6i - cyclin-dependent kinase 4/6 inhibitor; CNS – central nervous system; CS - company's submission; ECOG - Eastern Cooperative Oncology Group; Pbo/Fulv - placebo plus fulvestrant; PS - Performance status; SD - standard deviation

4.3 Effectiveness of alpelisib plus fulvestrant

Effectiveness data for BYLieve Cohort A[31] and SOLAR-1[28] for each outcome are presented alongside each other in the following sections to facilitate comparison of results across the studies.

4.3.1 Participant flow

BYLieve Cohort A: participant flow

As described in Table 9 of the CS,[1] 127 patients (the FAS) were enrolled in BYLieve Cohort A,[31] of which 121 (the mFAS) had a confirmed *PIK3CA* mutation and were included in the efficacy analyses. Data from the subgroup of second-line patients (n=[redacted]) were used in the company's economic model (see Section 5.2.4). Results are presented in the CS[1] (Section B.2.3.6) for the 17th December 2019 data cut-off. The median duration of follow-up was 11.7 months.

SOLAR-1: participant flow

As shown in Figure 7 of the CS,[1] 341 patients (the FAS) were enrolled in the *PIK3CA*-mutated cohort of SOLAR-1. [28] The CS[1] (Section B.2.4.2) presents the results for the FAS as well as for patients who received a prior CDK4/6i (n=20), which is the key population of interest in the CS.[1] Data from the subgroup of second-line endocrine-resistant patients (n=[redacted]) were used in the ITCs (Sections 4.8, 4.9 and 4.10 of this report). Results are presented for two data cut-offs: 12th June 2018 (the primary analysis) with a median duration of follow-up of 20.0 months, and 23rd April 2020 (the final OS analysis) with a median duration of follow-up of 42.4 months.

4.3.2 Proportion of patients alive with PD at 6 months

BYLieve Cohort A

BYLieve Cohort A met its primary endpoint; the proportion of patients who were alive without disease progression at 6 months was 50.4% (n=61/121) (95% CI: 41.2 to 59.6%), with the lower bound of the 95% CI exceeding 30% (the protocol-defined clinically meaningful threshold).[31]

4.3.3 Progression-free survival (PFS)

BYLieve Cohort A: PFS

As shown in Table 6 and Figure 2, median PFS for BYLieve Cohort A (mFAS population, n=121) was 7.3 months.[31] Median PFS for second-line patients used in the economic model (n=[redacted]) was [redacted] months (clarification response,[14] question A10).

SOLAR-1: PFS

As shown in Table 7 and Figure 3, within the FAS (n=341), median PFS in June 2018 was [redacted] months for Alp/Fulv versus 5.7 months for Pbo/Fulv (hazard ratio [HR] 0.65, 95% CI: 0.50, 0.85), while median PFS in April 2020 was [redacted] months for Alp/Fulv versus [redacted] months for Pbo/Fulv

(HR [redacted], 95% CI: [redacted]). In post-CDK4/6i patients (n=20), median PFS in April 2020 was [redacted]months for Alp/Fulv versus [redacted]months for Pbo/Fulv (HR [redacted], 95% CI: [redacted]). In second-line endocrine-resistant patients (n=[redacted], used in the ITCs), median PFS in April 2020 was [redacted]months for Alp/Fulv versus [redacted]months for Pbo/Fulv (HR [redacted], 95% CI: [redacted]).[1]

Table 6: PFS in BYLieve Cohort A

Analysis set	Data cut-off	Prior CDK4/6i	Treatment lines	N Alp/Fulv	Median PFS (95% CI), months Alp/Fulv	Reference in CS[1]
mFAS	Dec 2019	Post-CDK4/6i	All lines	121	7.3 (5.6, 8.3)	CS[1] Table 13
Second-line (used in model)	Dec 2019	Post-CDK4/6i	Second-line	[redacted]	[redacted]	Clarification response question A10

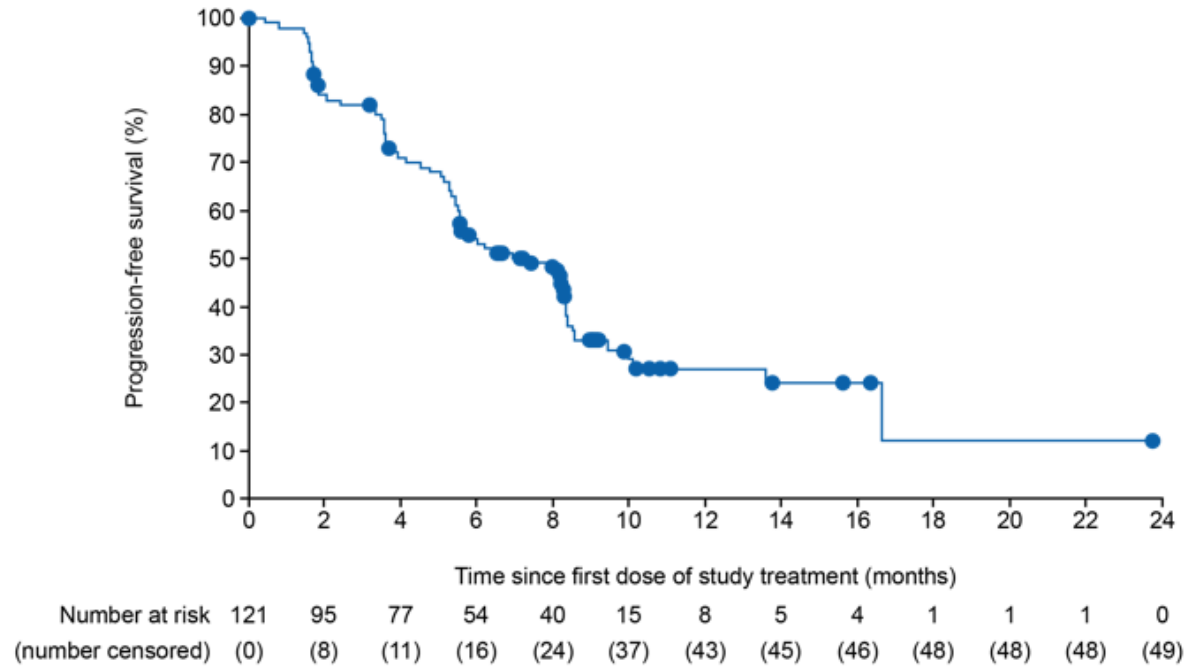
Alp - alpelisib; CDK4/6i - cyclin-dependent kinase 4/6 inhibitor; CI - confidence interval; CS - company's submission; Fulv - fulvestrant; mFAS - modified full analysis set; N - number; PFS - progression-free survival

Table 7: PFS in SOLAR-1

Analysis set	Data cut-off	Prior CDK4/6i	Treatment lines	N Alp/Fulv	N Pbo/Fulv	Median PFS, months		HR (95% CI)	Reference in CS[1]
						Alp/Fulv	Pbo/Fulv		
FAS	June 2018	Mostly CDK4/6i-naive	All lines	169	172	[redacted]	5.7	0.65 (0.50, 0.85)	CS Appendix F[23] Table 37
FAS	April 2020	Mostly CDK4/6i-naive	All lines	169	172	[redacted]	[redacted]	[redacted]	CS[1] Table 18
First-line endocrine-resistant	June 2018	Mostly CDK4/6i-naive	First-line	NR	NR	9.0	4.7	0.69 (0.46, 1.05)	CS Appendix F.3.1[23]
Second-line endocrine-resistant (used in ITC)	April 2020	Mostly CDK4/6i-naive	Second-line	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	CS Appendix D[23] Table 27
Post-CDK4/6i, endocrine-resistant (focus of CS[1])	April 2020	Post-CDK4/6i	All lines	9	11	[redacted]	[redacted]	[redacted]	CS[1] Table 18

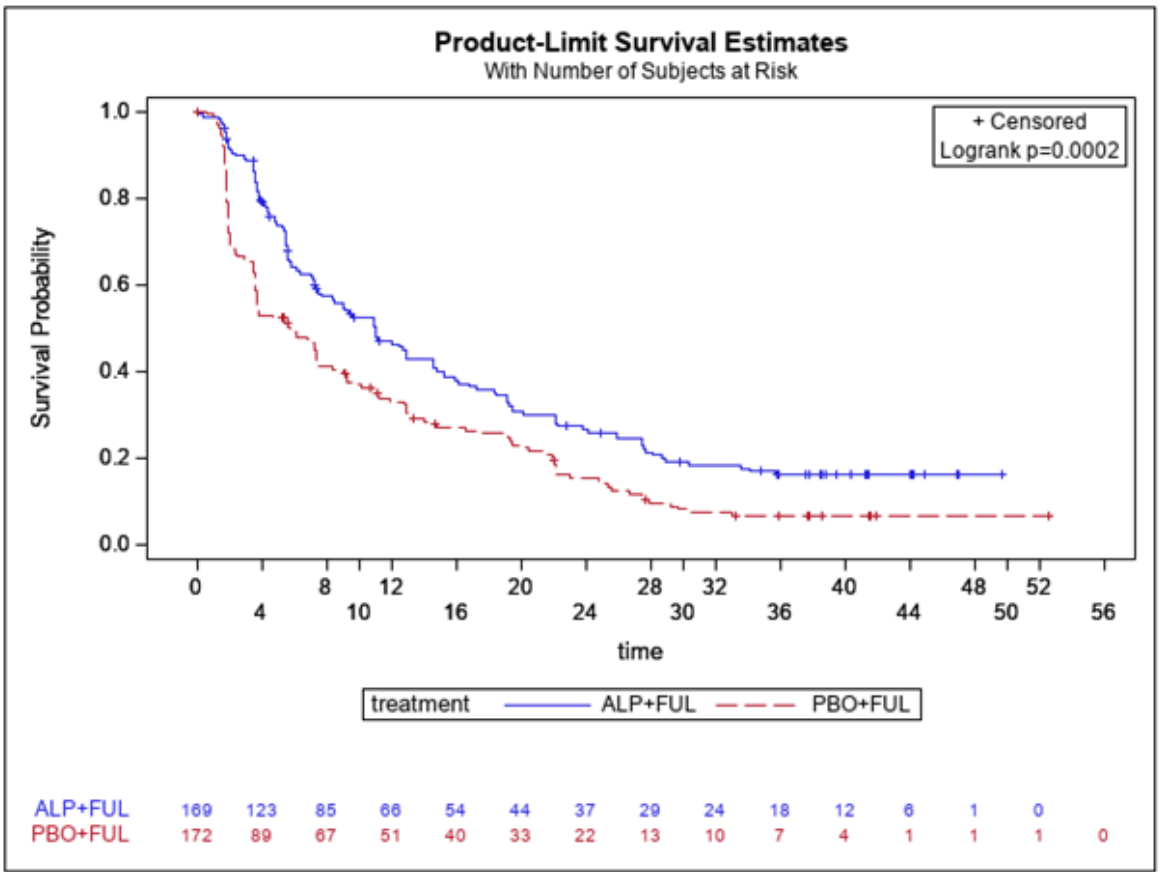
Alp - alpelisib; CDK4/6i - cyclin-dependent kinase 4/6 inhibitor; CI - confidence interval; CS - company submission; FAS - full analysis set; Fulv - fulvestrant; HR - hazard ratio; ITC - indirect treatment comparison; N - number; NR - not reported; Pbo - placebo; PFS - progression-free survival

Figure 2: Kaplan-Meier plot of PFS in BYLieve Cohort A, mFAS population (reproduced from CS, Figure 4)



mFAS - modified full analysis set; PFS - progression-free survival
Source: Rugo et al. (2021)

Figure 3: Kaplan-Meier plot of PFS in SOLAR-1 *PIK3CA*-mutated cohort (April 2020 data-cut, provided by the company)



Alp - alpelisib; Ful - fulvestrant; Pbo - placebo

4.3.4 Subgroup analyses for progression-free survival

BYLieve Cohort A: PFS subgrouped by duration of prior CDK4/6i therapy

A *post hoc* analysis of BYLieve (Cohort A) was conducted to explore the association of PFS with duration of prior CDK4/6i therapy (CS,[1] Section B.2.3.6.6). Patients were divided into two subgroups according to the duration of prior treatment: High (higher or longer than the median) and Low (lower or shorter than the median). Median (range) duration of prior CDK4/6i therapy was 380 days (1–1544) or ~12.5 months in Cohort A.

The CS[1] states that there was no significant difference in PFS between the High and Low subgroups, with a PFS of 7.3 months for all patients, 8.0 months for patients with longer prior CDK4/6i therapy versus 7.0 months for patients with shorter prior CDK4/6i therapy (p=0.927 across all three groups [High, Low and all patients], though no p-value is presented for the comparison of the High and Low subgroups alone). An analysis exploring the relationship between the proportion of patients alive without progression at 6 months and duration of prior CDK4/6i treatment (continuous scale) showed that there was little evidence that the duration of prior CDK4/6i impacts efficacy (p-value 0.252; 95% confidence band includes 0.5).

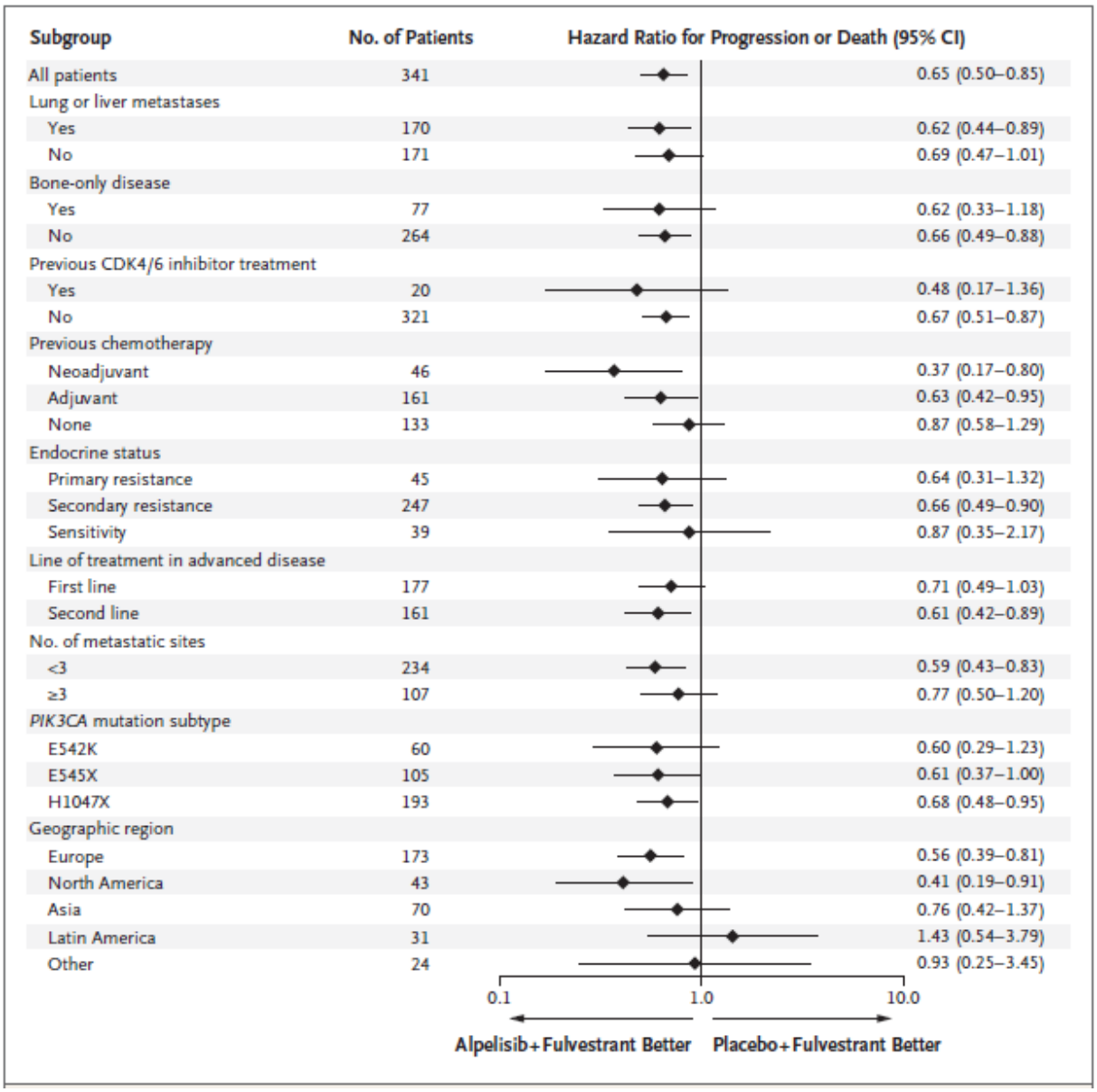
BYLieve Cohort A: PFS subgrouped by menopausal status

All patients were postmenopausal in SOLAR-1,[28] which is in line with the Alp licence. In BYLieve,[31] 22% of patients were premenopausal. The company's clarification response[14] (question A8) presents subgroup data by menopausal status for BYLieve Cohort A, which indicates that results for the primary endpoint (proportion of patients alive without disease progression at 6 months) and PFS were relatively similar between groups, but were numerically more favourable for the postmenopausal subgroup.

SOLAR-1: PFS subgrouped by various factors

Subgroup analyses for PFS in SOLAR-1[28] are presented in Figure 20 of CS Appendix F[23] and are shown in Figure 4 below. The treatment effect appears relatively consistent across subgroups, though it did not reach statistical significance in some subgroups, possibly due to small patient numbers.

Figure 4: Subgroup analysis of PFS from SOLAR-1 (FAS, *PIK3CA*-mutated cohort) (data cut-off 12th June 2018; reproduced from CS Appendix F, Figure 20)



Notes: CIs have not been adjusted for multiplicity. Inferences drawn from the CIs may not be reproducible. The previous chemotherapy subgroup was based on the last line of chemotherapy received. Patients may have received chemotherapy in the context of both neoadjuvant and adjuvant therapy. Patients may have had more than one PIK3CA mutation. E545X denotes mutations inclusive of E545A/D/G/K and H1047X denotes mutations inclusive of H1047L/R/Y
CDK - cyclin-dependent kinase; CI - confidence interval; FAS - full analysis set; PIK3CA - phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PFS - progression-free survival
Source: André et al. (2019)[18]

4.3.5 Overall survival (OS)

BYLieve Cohort A: OS

As shown in Table 8 and Figure 5, median OS for BYLieve Cohort A (mFAS population, n=121) was 17.3 months.[31] Median OS for second-line patients used in the economic model (n=[redacted]) was [redacted] months (clarification response,[14] question A10).

SOLAR-1: OS

As shown in Table 9 and Figure 6, within the FAS (n=341), median OS in April 2020 was 39.3 months for Alp/Fulv versus 31.4 months for Pbo/Fulv (HR 0.86, 95% CI: 0.64, 1.15). In post-CDK4/6i patients (n=20), median OS in April 2020 was [redacted] months for Alp/Fulv versus [redacted] months for Pbo/Fulv (HR [redacted], 95% CI: [redacted]). In second-line endocrine-resistant patients (n= [redacted], used in the ITCs), median OS in April 2020 was [redacted] months for Alp/Fulv versus [redacted] months for Pbo/Fulv (HR [redacted], 95% CI: [redacted]).

Table 8: OS in BYLieve Cohort A

Analysis set	Data cut-off	Prior CDK4/6i	Treatment lines	N Alp/Fulv	Median OS (95% CI), months Alp/Fulv	Reference in CS[1]
mFAS	Dec 2019	Post-CDK4/6i	All lines	121	17.3 (17.2, 20.7)	CS[1] Table 14
Second-line (used in model)	Dec 2019	Post-CDK4/6i	Second-line	[redacted]	[redacted]	Clarification response, question A10

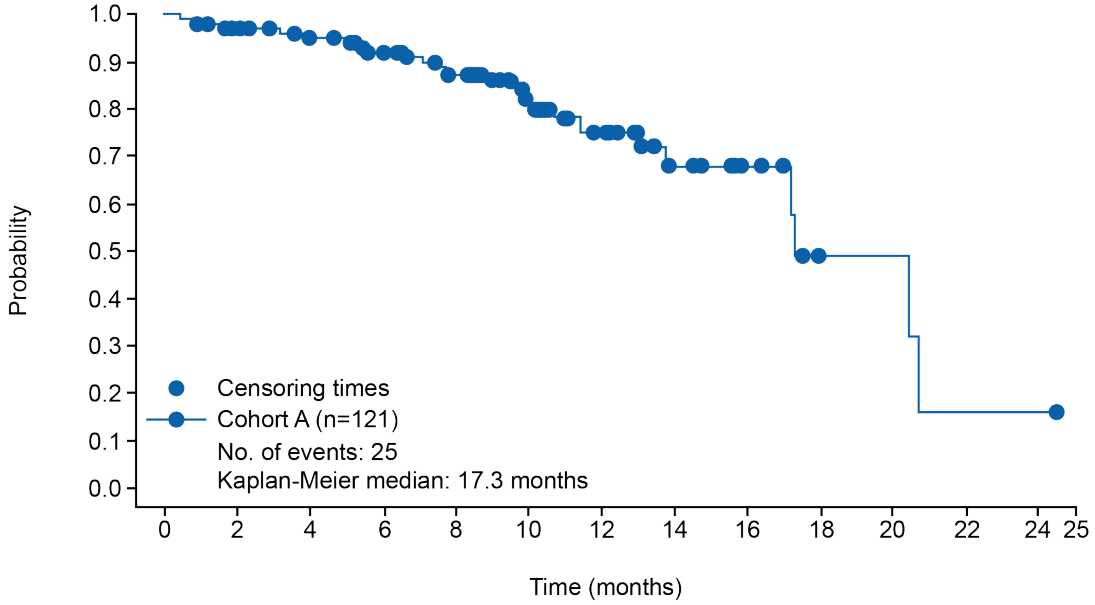
Alp - alpelisib; CDK-4/6i - cyclin-dependent kinase 4/6 inhibitor; CI - confidence interval; CS - company's submission; Fulv - fulvestrant; mFAS - modified full analysis set; N - number; OS - overall survival

Table 9: OS in SOLAR-1

Analysis set	Data cut-off	Prior CDK4/6i	Treatment lines	N Alp/Fulv	N Pbo/Fulv	Median OS, months		HR (95% CI)	Reference in CS[1]
						Alp/Fulv	Pbo/Fulv		
FAS	April 2020	Mostly CDK4/6i-naive	All lines	169	172	39.3	31.4	0.86 (0.64, 1.15)	CS[1] Table 19
Second-line endocrine-resistant (used in ITC)	April 2020	Mostly CDK4/6i-naive	Second-line	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	CS Appendix D[23] Table 28
Post-CDK4/6i, endocrine-resistant (focus of CS)	April 2020	Post-CDK4/6i	All lines	9	11	[redacted]	[redacted]	[redacted]	CS[1] Table 19

Alp - alpelisib; CDK-4/6i - cyclin-dependent kinase 4/6 inhibitor; CI - confidence interval; CS - company's submission; HR - hazard ratio; FAS - full analysis set; Fulv - fulvestrant; ITC - indirect treatment comparison; N - number; Pbo - placebo; OS - overall survival

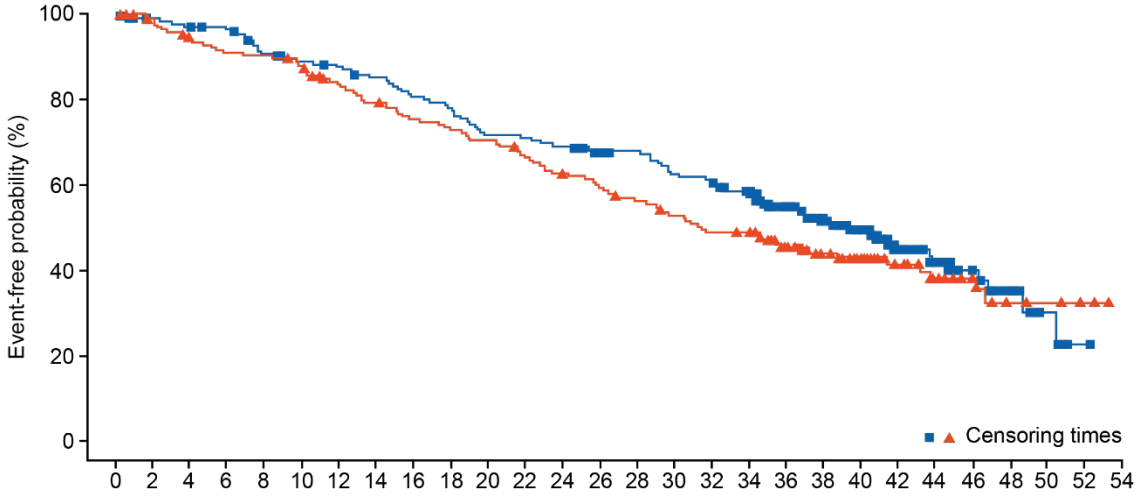
Figure 5: Kaplan-Meier plot of OS in BYLieve Cohort A, mFAS population (reproduced from CS, Figure 5)



Number at risk	121	110	101	92	73	41	29	17	11	3	3	1	1	0
(number censored)	(0)	(7)	(14)	(20)	(35)	(64)	(73)	(83)	(89)	(95)	(95)	(95)	(95)	(96)

mFAS - modified full analysis set; No. - number; OS - overall survival
Source: Rugo et al. 2021. Supplementary Appendix

Figure 6: Kaplan-Meier plot of OS in SOLAR-1 *PIK3CA*-mutated cohort (FAS, data cut-off 23rd April 2020; reproduced from CS Appendix F, Figure 17)



No. of patients at risk																									
Alpelisib + FUL	169	162	159	156	145	141	138	133	126	122	112	111	108	103	102	94	91	85	68	56	47	35	26	19	9	4	1	0
Placebo + FUL	172	164	155	150	149	143	133	126	119	115	111	104	98	92	86	80	74	73	60	49	42	29	20	13	7	6	3	0

FUL - fulvestrant; PIK3CA - phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; No. - number; OS - overall survival
Source: Andre et al. (2020)

4.3.6 Response rates

BYLieve Cohort A: response rates

In BYLieve Cohort A[31] (Table 10), ORR was 17.4%, partial response (PR) was 17.4% and complete response (CR) was 0%. The CBR was 45.5%. Median DoR was [redacted] months. Equivalent data for patients with measurable disease at baseline are presented in Table 10.

SOLAR-1: response rates

In SOLAR-1[28] (Table 11), ORR was 26.6% for Alp/Fulv vs. 12.8% for Pbo/Fulv, while CR was 0.6% for Alp/Fulv vs. 1.2% for Pbo/Fulv, and PR was 26.0% for Alp/Fulv vs. 11.6% for Pbo/Fulv. The CBR was 61.5% for Alp/Fulv vs. 45.3% for Pbo/Fulv. Median DoR was [redacted] months. In the 20 post-CDK4/6i patients, the CBR was [redacted]/9 ([redacted]%) for Alp/Fulv vs. [redacted]/11 ([redacted]%) for Pbo/Fulv. Equivalent data for patients with measurable disease at baseline are presented in Table 10.

Table 10: Response data for BYLieve Cohort A (Dec 2019 cut-off; based on CS, Table 15 and CS Appendix F, Table 30)

Response outcomes	BYLieve Cohort A	
	mFAS (n=121)	Measurable disease at baseline (n=100)
Response rates, n (%)		
CR	0	0
PR	21 (17.4)	21 (21.0)
Non-CR/Non-PD[a]	16 (13.2)	0
SD	55 (45.5)	55 (55.5)
PD[b]	14 (11.6)	11 (11.0)
Unknown	15 (12.4)	13 (13.0)
ORR (95% CI)	21 (17.4)	21 (21.0)
CBR (95% CI)	55 (45.5)	42 (42.0)
Duration of response, months		
DoR (95% CI)	[redacted]	NR

[a] Refers to presence of lesions not fulfilling criteria for target lesions at baseline or abnormal nodal lesions (i.e. ≥10 mm), unless there is unequivocal progression of the non-target lesions or it is not possible to determine progression unequivocally.
[b] Refers to neither sufficient shrinkage to qualify for PR or CR nor an increase in lesions that would qualify for PD.
CBR - clinical benefit rate; CI - confidence interval; CR - complete response; DoR - duration of response; mFAS - modified full analysis set; NR - not reported; ORR - overall response rate; PD - progressive disease; PR - partial response; SD - stable disease
Source: Rugo et al. (2021)

Table 11: Response data for SOLAR-1 (June 2018 cut-off; based on CS Appendix F, Sections F.3.3, F.3.4 and F.3.7)

Response outcomes	SOLAR-1: FAS			SOLAR-1: post-CDK4/6i			SOLAR-1: measurable disease at baseline		
	Alp/Fulv (n=169)	Pbo/Fulv (n=172)	*p*-value	Alp/Fulv (n=9)	Pbo/Fulv (n=11)	*p*-value	Alp/Fulv (n=126)	Pbo/Fulv (n=136)	*p*-value
Response rates, n (%)									
CR	1 (0.6%)	2 (1.2%)	NR	NR	NR	NR	1 (0.8%)	2 (1.5%)	NR
PR	44 (26.0%)	20 (11.6%)	NR	NR	NR	NR	44 (34.9%)	20 (14.7%)	NR
ORR (95% CI)	45 (26.6%)	22 (12.8%)	[redacted]	NR	NR	NR	45 (35.7%)	22 (16.2%)	[redacted]
CBR (95% CI)	NR (61.5%)	NR (45.3%)	[redacted]	[redacted]	[redacted]	NR	NR (57.1%)	NR (44.1%)	NR
Duration of response, months									
DoR (95% CI)	[redacted] (n= [redacted])	[redacted]	NR	NR	NR	NR	NR	NR	NR

Alp - alpelisib; CBR - clinical benefit rate; CDK-4/6i - cyclin-dependent kinase 4/6 inhibitor; CI - confidence interval; CR - complete response; CS - company's submission; DoR - duration of response; FAS - full analysis set; Fulv - fulvestrant; NR - not reported; ORR - overall response rate; Pbo - placebo; PR - partial response

4.3.7 Patient reported outcomes

BYLieve Cohort A: patient reported outcomes

No patient-reported outcomes (PROs) were measured in BYLieve.[31]

SOLAR-1: patient reported outcomes

PROs for SOLAR-1[28] are reported in CS Appendix F[23] (Section F.3.5). Data were collected using the following instruments: the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30, version 3.0), the EuroQoL 5-level instrument (EQ-5D-5L, tablet version), and the Brief Pain Inventory-Short Form (BPI-SF) questionnaire.

CS Appendix F[23] (Section F.3.5) states that the mean EORTC global health status/quality of life (QoL) scores were generally similar between treatment arms at baseline (69.7 [standard deviation (SD) = 21.0] in the Alp/Fulv arm and 68.0 [SD = 21.6] in the Pbo/Fulv arm). The change from baseline per arm in EORTC global health status/QoL was −3.50 (95% CI: −8.02, 1.02) in the Alp/Fulv arm and 0.27 (95% CI: −4.48, 5.02) in the Pbo/Fulv arm. However, the CS[1] states that these changes were not clinically meaningful based on the previous established minimally important difference for the instrument.

CS Appendix F[23] (Section F.3.5) also states that there was no difference in treatment arms with respect to time to 10% deterioration in global health/QoL status (HR: 1.03; 95% CI: 0.72, 1.49). There were [redacted] in the Alp/Fulv arm and [redacted] in the Pbo/Fulv arm who met the deterioration criteria.

4.3.8 Additional effectiveness outcomes

No further additional effectiveness outcomes were reported in the CS[1] or CS Appendices[23] for BYLieve. For SOLAR-1, CS Appendix F[23] reports the following outcomes: time to response (Section F.3.6), time to chemotherapy (Section F.3.8), concomitant medications (Section F.3.9), and PFS and OS for patients who achieved long-term disease control with Alp/Fulv. These are not reproduced here.

4.4 Safety of alpelisib plus fulvestrant

4.4.1 Safety: BYLieve

Safety cohort for BYLieve Cohort A

The safety population for BYLieve Cohort A included all patients who had received at least one dose of study treatment and was based on 127 patients who received Alp (of whom 126 patients also received Fulv).

Duration of exposure in BYLieve Cohort A

At the data cut-off (17th December 2019), treatment was ongoing in 33 patients (26%) and the median duration of exposure was 5.1 months for Alp and 6.5 months for Fulv.

Discontinuations and dose adjustments in BYLieve Cohort A

Discontinuations due to AEs occurred in 18/127 patients (14%). AEs leading to dose adjustments/interruptions occurred in 82/127 patients (65%).

Overview of AEs in BYLieve Cohort A

A summary of AEs in BYLieve Cohort A is presented in Table 12. AEs occurred in 99%; Grade ≥3 AEs in 67%; serious adverse event (SAEs) in 26%; AEs leading to discontinuation in 21%; AEs leading to dose adjustment/ interruption in 65%; AEs requiring additional therapy in 95%; and fatal SAEs in 0.8%.

Table 12: Overview of AEs in BYLieve Cohort A (reproduced from CS, Table 31)

Category	All grades, n (%)	Grade ≥3, n (%)
Adverse events	126 (99.2)	85 (66.9)
Treatment-related	126 (99.2)	79 (62.2)
SAEs	33 (26.0)	31 (24.4)
Treatment-related	20 (15.7)	18 (14.2)
Fatal SAEs	1 (0.8)	1 (0.8)
AEs leading to discontinuation	26 (20.5)	15 (11.8)
Treatment-related	23 (18.1)	13 (10.2)
AEs leading to dose adjustment/interruption	82 (64.6)	68 (53.5)
AEs requiring additional therapy	120 (94.5)	75 (59.1)

A patient with multiple severity grades for an AE is only counted under the maximum grade
AE - adverse event; SAE - serious adverse event
Source: Rugo et al. (2021)

Most common AEs in BYLieve Cohort A

The most common AEs in BYLieve Cohort A are shown in Table 13. The most frequent AEs were diarrhoea (60%); hyperglycaemia (58%); nausea (46%); fatigue (29%); decreased appetite (28%); rash (28%); stomatitis (27%) and vomiting (24%). The most common Grade ≥3 AEs were hyperglycaemia (28%); rash (9%); maculo-papular rash (9%) and diarrhoea (6%).

Table 13: Most common AEs (>10%) in BYLieve Cohort A (adapted from CS, Table 32)

Preferred term	All grades, n (%)	Grade ≥3, n (%)
At least one AE	126 (99.2)	85 (66.9)
Diarrhoea	76 (59.8)	7 (5.5)
Hyperglycaemia	74 (58.3)	36 (28.3)
Nausea	58 (45.7)	0
Fatigue	37 (29.1)	1 (0.8)
Decreased appetite	36 (28.3)	1 (0.8)
Rash	36 (28.3)	12 (9.4)
Stomatitis	34 (26.8)	2 (1.6)
Vomiting	30 (23.6)	2 (1.6)
Asthenia	25 (19.7)	1 (0.8)
Headache	24 (18.9)	1 (0.8)
Dry skin	20 (15.7)	1 (0.8)
Pruritus	20 (15.7)	2 (1.6)
Dyspnoea	19 (15.0)	3 (2.4)
Dysgeusia	18 (14.2)	0
Dyspepsia	18 (14.2)	0
Rash maculo-papular	18 (14.2)	12 (9.4)
Abdominal pain	17 (13.4)	2 (1.6)
Pyrexia	17 (13.4)	0
Alopecia	16 (12.6)	0
Weight decreased	16 (12.6)	2 (1.6)
Aspartate aminotransferase increased	15 (11.8)	4 (3.1)
Urinary tract infection	14 (11.0)	3 (2.4)
Abdominal pain upper	13 (10.2)	0
Alanine aminotransferase increased	13 (10.2)	4 (3.1)
Blood creatinine increased	13 (10.2)	1 (0.8)
Cough	13 (10.2)	1 (0.8)
Muscle spasms	13 (10.2)	0

A patient with multiple severity grades for an AE is only counted under the maximum grade
AE - adverse event
Source: Rugo et al. (2021). Supplementary Appendix; Novartis Data on File.

Serious AEs in BYLieve Cohort A

SAEs occurring in ≥1% of patients in BYLieve Cohort A regardless of study drug relationship are presented in Table 14. In total, SAEs occurred in 26%, and Grade ≥3 SAEs in 24%. SAEs included hyperglycaemia (6%); maculo-papular rash (3%); dyspnoea (2.4%); pleural effusion (2.4%); abdominal pain (1.6%) and haematemesis (1.6%).

Table 14: Serious AEs in BYLieve Cohort A (incidence ≥1% in either arm; reproduced from CS, Table 34)

Preferred term	All grades, n (%)	Grade ≥3, n (%)
Number of patients with at least one event	33 (26.0)	31 (24.4)
Hyperglycaemia	7 (5.5)	[redacted]
Rash maculo-papular	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]
Pleural effusion	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]
Haematemesis	[redacted]	[redacted]

A patient with multiple severity grades for an AE is only counted under the maximum grade.
AE - adverse event
Source: Rugo et al. (2021); Novartis Data on File.

AEs of special interest in BYLieve Cohort A

A summary of adverse events of special interest (AESIs) for Cohort A in BYLieve is presented in Table 15.

Table 15: Overview of AEs of special interest in BYLieve Cohort A (reproduced from CS, Table 37)

Safety topic	All grades, n (%)	Grade ≥3, n (%)
Number of patients with at least one event	124 (97.6)	67 (52.8)
GI toxicity (nausea/vomiting/diarrhoea)	95 (74.8)	9 (7.1)
Hyperglycaemia	77 (60.6)	36 (28.3)
Rash	58 (45.7)	26 (20.5)
Hypersensitivity and anaphylactic reaction	13 (10.2)	5 (3.9)
Pancreatitis	5 (3.9)	2 (1.6)
Pneumonitis	1 (0.8)	0
Severe cutaneous reactions	1 (0.8)	0

A patient with multiple severity grades for an AE is only counted under the maximum grade.
AE - adverse event; GI - gastrointestinal
Source: Rugo et al. (2021). Supplementary Appendix.

On-treatment deaths in BYLieve Cohort A

There were 7 (5.5%) on-treatment deaths in BYLieve Cohort A: four due to the study indication (breast cancer); one due to respiratory failure; one due to superior vena cava occlusion; and one unspecified.

4.4.2 Safety: SOLAR-1

Safety cohort for SOLAR-1

The safety data presented in the CS[1] for SOLAR-1 are based on the entire cohort including the *PIK3CA*-mutated cohort and *PIK3CA* wild-type cohort (571 patients; 284 in the Alp/Fulv arm and 287 in the Pbo/Fulv arm). The CS[1] states that the presence or absence of *PIK3CA* mutations was not expected to affect the occurrence of AEs, and that the safety data were generally consistent between patients in the *PIK3CA*-mutated cohort and the *PIK3CA* wild-type cohort. Data are presented in the CS[1] for both the June 2018 and April 2020 data cut-offs. This report includes a summary of key AE data, based on the

April 2020 cut-off where available. Additional AE data for SOLAR-1 are presented in the CS[1] (Section B.2.8.2) and CS Appendix F[23] (Sections F.4 and F.5).

Duration of exposure in SOLAR-1

Median duration of exposure in SOLAR-1 (at data cut-off June 2018) was 5.5 months for Alp and 8.2 months for Fulv in the Alp/Fulv arm, and 5.6 months for both Fulv and placebo in the Pbo/Fulv arm (durations for the April 2020 cut-off were very similar).

Discontinuations and dose adjustments in SOLAR-1

Discontinuations and dose adjustments in SOLAR-1 (at data cut-off June 2018) are shown in Table 16. Dose reductions occurred in 59% in the Alp/Fulv arm vs. 7% in the Pbo/Fulv arm, while dose interruptions occurred in 72% in the Alp/Fulv arm vs. 30% in the Pbo/Fulv arm. Discontinuations due to AEs occurred as follows: in the Alp/Fulv arm, 25% discontinued Alp and 5% discontinued Fulv due to AEs, while in the Pbo/Fulv arm, 4% discontinued placebo and 1% discontinued Fulv due to AEs.

Table 16: Dose adjustments and discontinuations of study drug in SOLAR-1 (cut-off June 2018; adapted from CS, Table 40)

	Alp/Fulv (n=284)		Pbo/Fulv (n=287)	
	Alpelisib	**Fulvestrant**	**Placebo**	**Fulvestrant**
Dose reductions and interruptions				
At least one dose reduction and/or interruption	213 (75.0)	14 (4.9)	89 (31.0)	4 (1.4)
At least one dose reduction	168 (59.2)	-	21 (7.3)	-
At least one dose interruption	205 (72.2)	14 (4.9)	86 (30.0)	4 (1.4)
Permanent discontinuation				
Permanent discontinuations – n (%)	244 (85.9)	231 (81.3)	249 (86.8)	242 (84.3)
Reason for permanent discontinuation				
Progressive disease	[redacted]	[redacted]	[redacted]	[redacted]
AE	71 (25.0)	14 (4.9)	12 (4.2)	3 (1.0)
Patient/guardian decision	[redacted]	[redacted]	[redacted]	[redacted]
Physician decision	[redacted]	[redacted]	[redacted]	[redacted]
Protocol deviation	[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]	[redacted]

AE - adverse event; Alp - alpelisib; Fulv - fulvestrant; Pbo - placebo; n - number

Overview of AEs in SOLAR-1

A summary of the AEs from SOLAR-1 (April 2020 cut-off) is presented in Table 17. AEs occurred as follows for Alp/Fulv vs. Pbo/Fulv: AEs (99% vs. 93%); Grade 3 or 4 AEs (78% vs. 37%); SAEs ([redacted]% vs. [redacted]%); AEs leading to discontinuation ([redacted]% vs. [redacted]%); AEs leading to dose adjustment/ interruption ([redacted]% vs. [redacted]%);

and fatal SAEs ([redacted] vs. [redacted]). There [redacted] ([redacted]%) treatment-related fatal SAE in the Alp/Fulv arm (fatal thrombotic microangiopathy).

Table 17: Overview of AEs in SOLAR-1 (cut-off April 2020; reproduced from CS, Table 42)

	Alp/Fulv (n=284)		Pbo/Fulv (n=287)	
	Any grade n (%)	**Grade 3/4 n (%)**	**Any grade n (%)**	**Grade 3/4 n (%)**
AEs	282 (99.3)	222 (78.2)	267 (93.0)	107 (37.3)
Treatment-related	[redacted]	[redacted]	[redacted]	[redacted]
SAEs	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-related	[redacted]	[redacted]	[redacted]	[redacted]
Fatal SAEs	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-related[a]	[redacted]	[redacted]	[redacted]	[redacted]
AEs leading to discontinuation	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-related	[redacted]	[redacted]	[redacted]	[redacted]
AEs leading to dose adjustment/ interruption	[redacted]	[redacted]	[redacted]	[redacted]
AEs requiring additional therapy	[redacted]	[redacted]	[redacted]	[redacted]

[a] This is patient C2301-1917007, who had a fatal SAE thrombotic microangiopathy reported with onset date within the on-treatment period, and who died >30 days after last dose of study drug.
A patient with multiple severity grades for an AE was only counted under the maximum grade.
AE - adverse event; Alp - alpelisib; Fulv - fulvestrant; Pbo - placebo; n - number; SAE - serious adverse event
Source: André et al. (2020); Novartis Data on File

Most common AEs in SOLAR-1

The most common AEs from SOLAR-1 (April 2020 cut-off), occurring in ≥20% of patients in either treatment arm, are presented in Table 18. The most common AEs in the Alp/Fulv arm were: hyperglycaemia (65% vs. 9%); diarrhoea (60% vs. 16%); nausea (47% vs. 23%); decreased appetite (36% vs. 11%); rash (36% vs. 7%); vomiting (29% vs. 10%); weight decrease (28% vs. 2%); fatigue (25% vs. 18%); stomatitis (25% vs. 7%); asthenia (23% vs. 14%) and alopecia (20% vs. 2%). The most common Grade 3 events in the Alp/Fulv arm were: hyperglycaemia (33% vs. 0.7%); diarrhoea (7% vs. 0.7%) and rash (10% vs. 0.3%). Treatment-related AEs occurring in ≥10% of either arm are presented in Table 39 of CS Appendix F.[23]

Table 18: Most common AEs (≥20% in either arm) in SOLAR-1 (cut-off April 2020; reproduced from CS, Table 44)

Preferred term	Alp/Fulv (n=284)[a]			Pbo/Fulv (n=287)[a]		
	Any grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Any grade n (%)	Grade 3 n (%)	Grade 4 n (%)
Total	282 (99.3)	187 (65.8)	35 (12.3)	267 (93.0)	90 (31.4)	17 (5.9)
Hyperglycaemia	184 (64.8)	94 (33.1)	11 (3.9)	27 (9.4)	2 (0.7)	1 (0.3)
Diarrhoea	169 (59.5)	20 (7.0)	0	47 (16.4)	2 (0.7)	0
Nausea	133 (46.8)	8 (2.8)	0	65 (22.6)	1 (0.3)	0
Decreased appetite	103 (36.3)	2 (0.7)	0	30 (10.5)	1 (0.3)	0
Rash	103 (36.3)	28 (9.9)	0	20 (7.0)	1 (0.3)	0
Vomiting	81 (28.5)	2 (0.7)	0	29 (10.1)	1 (0.3)	0
Weight decreased	79 (27.8)	15 (5.3)	0	7 (2.4)	0	0
Fatigue	72 (25.4)	10 (3.5)	0	51 (17.8)	3 (1.0)	0
Stomatitis	71 (25.0)	7 (2.5)	0	20 (7.0)	0	0
Asthenia	64 (22.5)	7 (2.5)	0	39 (13.6)	0	0
Alopecia	58 (20.4)	0	0	7 (2.4)	0	0

A patient with multiple severity grades for an AE was only counted under the maximum grade.
[a] AEs (any grade) leading to discontinuations of one or both treatments in the safety set occurred in 75 patients (26.4%) in the alpelisib plus fulvestrant arm and 16 patients (5.6%) in the placebo plus fulvestrant arm.
AE - adverse event; Alp – alpelisib; Fulv - fulvestrant; Pbo - placebo
Source: André et al. 2020.

SAEs in SOLAR-1

SAEs from SOLAR-1 (June 2018 cut-off), occurring in ≥1% of patients in either arm, are presented in Table 19. In total, SAEs occurred in 35% in the Alp/Fulv arm vs. 17% in the Pbo/Fulv arm, and Grade 3 or 4 SAEs occurred in 29% in the Alp/Fulv arm vs. 15% in the Pbo/Fulv arm. The most common SAEs in the Alp/Fulv arm were: hyperglycaemia (10% vs. 0%); diarrhoea (3% vs. 0%); abdominal pain (2% vs. 0.7%); acute kidney injury (2% vs. 0.3%); anaemia (2% vs. 0%); nausea (2% vs. 0.7%); Osteonecrosis of jaw (2% vs. 0.3%); rash (2% vs. 0%); and vomiting (2% vs. 1%).

Table 19: SAEs (≥1% in either arm) in SOLAR-1 (cut-off June 2018; reproduced from CS, Table 47)

Preferred term	Alp/Fulv (n=284)		Pbo/Fulv (n=287)	
	Any grade n (%)	Grade 3/4 n (%)	Any grade n (%)	Grade 3/4 n (%)
Total	99 (34.9)	82 (28.9)	48 (16.7)	43 (15.0)
Hyperglycaemia	28 (9.9)	26 (9.2)	0	0
Diarrhoea	8 (2.8)	4 (1.4)	0	0
Abdominal pain	6 (2.1)	4 (1.4)	2 (0.7)	1 (0.3)
Acute kidney injury	5 (1.8)	3 (1.1)	1 (0.3)	1 (0.3)
Anaemia	5 (1.8)	3 (1.1)	0	0
Nausea	5 (1.8)	4 (1.4)	2 (0.7)	1 (0.3)
Osteonecrosis of jaw	5 (1.8)	4 (1.4)	1 (0.3)	1 (0.3)
Rash	5 (1.8)	4 (1.4)	0	0
Vomiting	5 (1.8)	2 (0.7)	3 (1.0)	1 (0.3)
Pyrexia	4 (1.4)	0	0	0
Stomatitis	4 (1.4)	2 (0.7)	0	0
Dehydration	3 (1.1)	1 (0.4)	3 (1.0)	3 (1.0)
Erythema multiforme	3 (1.1)	2 (0.7)	0	0
Hypersensitivity	3 (1.1)	1 (0.4)	0	0
Hypokalaemia	3 (1.1)	3 (1.1)	1 (0.3)	0
Mucosal inflammation	3 (1.1)	3 (1.1)	0	0
Pleural effusion	3 (1.1)	3 (1.1)	5 (1.7)	4 (1.4)
Pneumonia	3 (1.1)	3 (1.1)	5 (1.7)	5 (1.7)
Rash maculo-papular	3 (1.1)	2 (0.7)	0	0
Dyspnoea	2 (0.7)	1 (0.4)	4 (1.4)	4 (1.4)
Pulmonary embolism	2 (0.7)	2 (0.7)	3 (1.0)	2 (0.7)
Urinary tract infection	2 (0.7)	1 (0.4)	3 (1.0)	3 (1.0)

A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
A patient with multiple AEs is counted only once in the total row.
Alp - alpelisib; Fulv - fulvestrant; Pbo - placebo; SAE - serious adverse event
Source: André et al. (2019) Supplementary Appendix

AEs of special interest in SOLAR-1

A summary of AEs of special interest in SOLAR-1 (data cut-off June 2018) is presented in Table 20. Management strategies are discussed in CS Appendix F[23] (Section F.5).

Table 20: AEs of special interest in SOLAR-1 (cut-off June 2018; reproduced from CS, Table 50)

Categories	Alp/Fulv (n=284)		Pbo/Fulv (n=287)	
	Any grade n (%)	Grade 3/4 n (%)	Any grade n (%)	Grade 3/4 n (%)
GI toxicity (nausea, vomiting, diarrhoea)	214 (75.4)	25 (8.8)	100 (34.8)	3 (1.0)
Hyperglycaemia	187 (65.8)	108 (38.0)	30 (10.5)	2 (0.7)
Rash	153 (53.9)	57 (20.1)	24 (8.4)	1 (0.3)
Hypersensitivity and anaphylactic reaction	47 (16.5)	5 (1.8)	12 (4.2)	0
Pancreatitis	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonitis	[redacted]	[redacted]	[redacted]	[redacted]
Severe cutaneous reactions	[redacted]	[redacted]	[redacted]	[redacted]

A patient with multiple severity grades for an AE is only counted under the maximum grade.
AE - adverse event; Alp - alpelisib; Fulv - fulvestrant; GI - gastrointestinal; Pbo - placebo
Source: SOLAR-1 CSR Table 12-13; André et al. (2019)

On-treatment deaths in SOLAR-1

Within the safety set, in the Alp/Fulv arm, [redacted] on-treatment deaths occurred; [redacted] due to the study indication, [redacted] due to cardiorespiratory arrest, and [redacted] due to a second primary malignancy. None were considered to be related to study treatment by the investigators. In the Pbo/Fulv arm, [redacted] on-treatment deaths occurred; [redacted] were due to the study indication, and the remaining [redacted] were due to gastrointestinal haemorrhage, pneumonia, septic shock and unknown cause respectively. None were considered to be related to study treatment by the investigators.

4.5 Ongoing studies

The following are ongoing studies of Alp/Fulv:

Additional BYLieve data

The CS[1] (Section B.2.9) states that BYLieve is ongoing and that the following data are anticipated within the next 12 months:

- Data from Cohort A – updated data are anticipated to be presented at the [redacted].
- Data from Cohort C – updated data are anticipated to be presented at [redacted]. These data would be considered within the licence for Alp/Fulv.

RCT of Alp/Fulv in post-CDK4/6i population

The company's clarification response[14] (question A4) states that the company are planning to conduct a Phase III, randomised, double-blind, placebo-controlled trial of Alp/Fulv for men and postmenopausal women with HR+ HER2– ABC with a *PIK3CA* mutation, who have progressed on or after a CDK4/6i+AI regimen. The comparator for this trial is not clear from the company's clarification response. This trial is referred to as EPIK-B5. The population of EPIK-B5 is expected to be comparable to Cohort A of BYLieve and to be consistent with the target population in the CS.[1] The company anticipates that the EPIK-B5 trial will be initiated in [redacted], with first results expected in [redacted]. Anticipated outcomes include PFS, OS and PROs using the EORTC QLQ-C30.

Registry data on frequency of PIK3CA mutations

The CS[1] (Section B.2.9) also states that [redacted].

4.6 Overview and relevance of company's indirect comparisons

4.6.1 Summary of indirect comparisons

In the absence of direct clinical evidence, the company undertook ITCs using three different approaches:

A. A matching/weighted analysis using data from BYLieve Cohort A in which patients received Alp/Fulv in the post-CDK4/6i setting, versus data from the US Flatiron Clinicogenomics Database (CGDB) for patients receiving a mix of standard treatments in the post-CDK4/6i setting. This analysis was conducted for PFS but not OS and is described in CS,[1] Section B.2.5. This analysis is not used in the company's economic model.
B. A Bucher ITC to indirectly estimate PFS and OS for the comparison of Alp/Fulv versus Eve/Exe, using one RCT of Alp/Fulv (SOLAR-1)[28] and one RCT of Eve/Exe (BOLERO-2),[20] as well as two further trials in order to form a connected network (CONFIRM[21] and SoFEA[22] This is described in CS,[1] Section B.2.7 and CS Appendix D,[23] Section D.5 to D.8. This analysis is used in the company's base case economic model.
C. A patient-adjusted indirect comparison (PAIC) to indirectly estimate PFS and OS for the comparison of Alp/Fulv versus Eve/Exe, using an unanchored comparison of the Alp/Fulv arm from SOLAR-1[28] and the Eve/Exe arm from BOLERO-2.[20] This is described in CS,[1] Section B.2.7 and CS Appendix D,[23] Section D.5 to D.8. This analysis is included as a sensitivity analysis in the company's economic model.

4.6.2 Relevance of indirect comparisons

Since the focus of the CS[1] is on the post-CDK4/6i population, the ERG notes that both the Bucher ITC and the PAIC have limited relevance as they use data from SOLAR-1[28] (mostly CDK4/6i-naïve). In the economic model, these HRs are applied to data from BYLieve, which are specific to the post-CDK4/6i population. Both the Bucher ITC and the PAIC analyses use data for the second-line population as a proxy for the post-CDK4/6i population (discussed below). The matching/weighted analysis uses data from BYLieve Cohort A[31] (post-CDK4/6i population), but does not compare against the relevant comparator (Eve/Exe).

The three indirect comparisons are summarised and critiqued in the subsequent sections.

4.7 Matching/weighted analysis of BYLieve versus Flatiron CGDB (post-CDK4/6i)

4.7.1 Studies included in matching/weighted analysis

The CS[1] (Section B.2.5) describes a matching/weighted analysis of PFS (but not OS), using data from 120 patients from BYLieve Cohort A (Alp/Fulv in the post-CDK4/6i setting) versus 95 patients from the US Flatiron CGDB for patients receiving a mix of standard treatments (but not Alp) in the post-CDK4/6i setting. Patients from the CGDB were eligible for inclusion if they met key inclusion criteria based on BYLieve (*PIK3CA* mutation; prior CDK4/6i plus ET; ≤2 prior lines of therapy for ABC; ≤1 prior line of chemotherapy for ABC). Table 21 shows the most common post-CDK4/6i regimens and components received in BYLieve Cohort A and the CGDB cohort (CS,[1] Section B.2.5).

Table 21: Most common post-CDK4/6i regimens and components in BYLieve and CGDB

Most common post-CDK4/6i regimens and components	BYLieve Cohort A (N=120)	Flatiron CGDB cohort (N=95)
Post-CDK4/6i regimens		
Alpelisib + fulvestrant	100%	
Capecitabine monotherapy		15%
Fulvestrant monotherapy		15%
Palbociclib + fulvestrant		14%
Everolimus + exemestane		12%
Palbociclib + fulvestrant + letrozole		5%
Post-CDK4/6i components		
Fulvestrant		45%
CDK4/6i		34%
Chemotherapy		32%
Everolimus		18%
Letrozole (AI)		16%

AI - aromatase inhibitor; CDK4/6i - cyclin-dependent kinase 4/6 inhibitor; CGDB - Clinicogenomics Database

4.7.2 Statistical analysis in the matching/weighted analysis of BYLieve and CGDB

Three matching/weighed approaches were used to adjust for the imbalance in baseline characteristics between patients from the two cohorts: (i) weighting by odds; (ii) propensity score matching, and (iii) exact matching (see CS[1] Section B.2.5 and CS[1] Table 21). The baseline covariates included in the matching/weighed models were: age; number of metastatic sites; bone lesions only; lung or liver metastases and time since initial diagnosis. The balance in the covariates between the two cohorts was assessed using standardised mean differences (SMD) with an SMD value of <25% being considered as balanced according to the study protocol.[19]

4.7.3 Results of the matching/weighted analysis of BYLieve and CGDB

In response to a request for clarification from the ERG[14] (question A24), the company states that the SMDs indicated that the patients' baseline covariates were balanced between the populations for each of the three matching/weighed approaches. The PFS medians and HRs for Alp/Fulv from BYLieve Cohort A compared to standard treatments from the CGDB cohort are summarised in Table 22. Section B.2.5 of the CS[1] states that, in a series of matching/weighted analyses, there was a consistent trend in the PFS HRs in favour of Alp/Fulv compared to standard treatments.

Table 22: PFS medians and HRs from the matching/weighted analysis of BYLieve and CGDB (reproduced from CS, Table 22)

Analysis method (BYLieve vs. CGDB)	Median PFS (months) (95% CI)		HR (95% CI)
	BYLieve Cohort A (Alp/Fulv)	CGDB (standard treatment)	
Unadjusted results (n=120, n=95)	7.3 (5.6, 8.3)	3.6 (3.1, 6.1)	[redacted]
Weighting by odds (n=120, n=116)	7.3 (5.3, 9.2)	3.7 (2.2, 5.3)	[redacted]
Propensity score matching (Greedy matching) (n=76, n=76)	8.0 (5.6, 8.6)	3.5 (3.0, 5.4)	[redacted]
Exact matching (n=61, n=61)	6.5 (5.3, 8.3)	3.4 (2.9, 3.9)	[redacted]

Alp - alpelisib; CI - confidence interval; CGDB - Clinicogenomics Database; Fulv - fulvestrant; HR - hazard ratio; PFS - progression-free survival
Source: Turner et al. (2021); Novartis Data on File.

4.7.4 Critique of the matching/weighted analysis of BYLieve and CGDB

Section B.2.5 of the CS[1] notes the following limitations: the CGDB data are derived from the US where standard treatment options differ from the UK; the sample sizes are relatively small, and matching can only account for measurable and feasible confounding factors, therefore potential selection bias and unmeasured and residual confounding cannot be ruled out. In addition, the ERG queried why an analysis of OS was not undertaken (clarification response,[14] question A24). In their response, the company states that an analysis of OS could not be performed because the CGDB dataset subsequently became unavailable after the analysis for the primary endpoint PFS.

As part of the clarification process, the ERG queried why a matching/weighted analysis was not conducted to compare BYLieve Cohort A[31] versus the Eve/Exe arm of BOLERO-2,[20] as this would have provided a comparison of Alp/Fulv versus Eve/Exe in the post-CDK4/6i population (see clarification response,[14] question A23c). In their response, the company states that there is a fundamental difference between the patient populations, in that a post-CDK4/6i population (such as BYLieve Cohort A) would be expected to have a poorer prognosis than a CDK4/6i-naïve population (such as BOLERO-2); hence, the two trial populations are not comparable. The ERG notes that, for patients receiving Alp/Fulv, median PFS is numerically worse in the post-CDK4/6i population from BYLieve Cohort A (7.3 months) [redacted] ([redacted] months) than in the CDK4/6i-naïve population in SOLAR-1 ([redacted]; see Table 6 and Table 7 in this report). Median OS also appears numerically worse in the post-CDK4/6i population (Table 8 and Table 9 in this report). Clinical advisors to the ERG agreed that prognosis is poor with few treatment options in the post-CDK4/6i population. The ERG therefore agrees that comparing BYLieve Cohort A and the Eve/Exe arm of BOLERO-2[20] directly without any adjustment would lead to biased results due to differences between the study populations. As all patients in BYLieve Cohort A[31] and no patients in BOLERO-2[20] had received a CDK4/6i, limited direct adjustments could be performed.

4.8 Bucher ITC of SOLAR-1 versus BOLERO-2: Critique of included studies

4.8.1 Studies included in Bucher ITC

The company undertook a Bucher ITC to indirectly estimate PFS and OS for the comparison of Alp/Fulv versus Eve/Exe (described further in the CS[1] Section B.2.7 and CS Appendix D,[23] Section D.5 to D.8). One RCT of Alp/Fulv vs. Fulv was available (SOLAR-1).[28] The clinical SLR was used to identify RCTs of Eve/Exe; one relevant RCT was identified (BOLERO-2),[20] which compared Eve/Exe vs. Exe. However, these two trials did not have a common comparator. Therefore, the clinical SLR was again used to identify additional RCTs to form a connected network for the ITC. Two such trials were identified: CONFIRM[21] (Fulv 500mg vs. Fulv 250mg) and SoFEA[22] (Fulv 250mg vs. Exe). The evidence network for PFS and OS is presented in Figure 7. The four trials included in the Bucher ITC are summarised in Table 23. The ERG believes that the CS[1] does not provide a particularly clear rationale regarding which trials were included in or excluded from the ITC; however, a very brief PubMed search by the ERG did not identify any other trials which could have been used in the network.

Figure 7: Evidence network for the Bucher ITC (reproduced from CS, Figure 11)

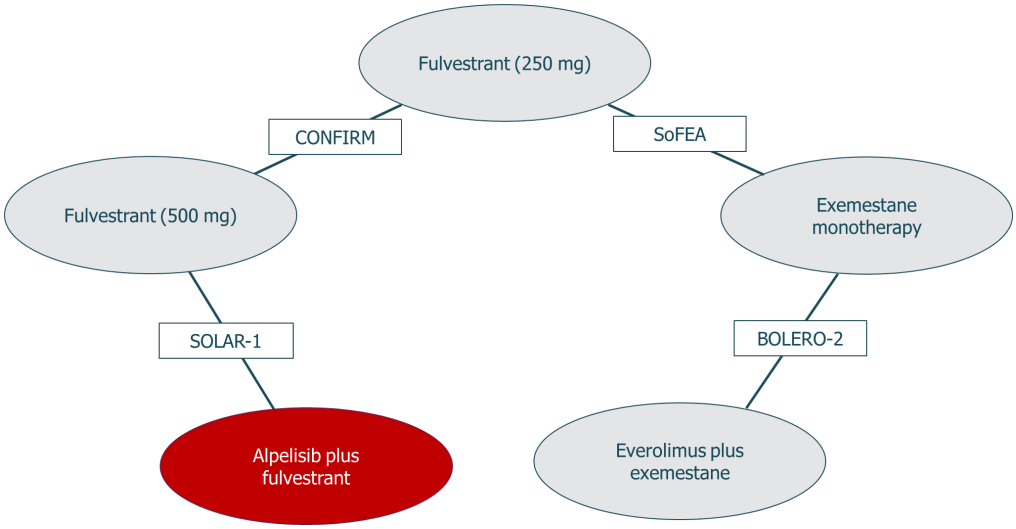


Table 23: Studies and cohorts included in ITC (adapted from CS, Table 23, CS Appendix D, Tables 27 and 28, and clarification response, question A22)

Study References	Intervention	Comparator	Sex & menopause status	*PIK3CA* status	HR status	HER2 status	Endocrine status	Line of therapy (advanced)	N trial or cohort	N analysed (per arm)	N excluded and reasons	Source of data
BOLERO-2 Yardley (2013)[20] Moynahan (2017)[32] Hortobagyi (2016)[33]	Eve/Exe	Exe	Post-menopausal women	*PIK3CA* mutant	HR+	HER2−	Endocrine-resistant	Second-line	N=724	N=57 (36, 21)	N=362 wildtype *PIK3CA* N=23 first-line N=282 third+ line	Cox PH regression of IPD
CONFIRM Di Leo (2010)[21] Di Leo (2014)[34]	Fulv500	Fulv250	Post-menopausal women	Not evaluated	HR+	Not evaluated	Endocrine-resistant	50% first-line; 50% second-line	N=736	N=736 (362, 374)	N/A	Di Leo (2010);[21] Di Leo (2014)[34]
SoFEA Johnston (2013)[22]	Fulv250[b]	Exe	Post-menopausal women	Not evaluated	HR+	60% HER2- 7% HER2+ 33% unknown	Resistant or sensitive (relapsed or progressed on ET)	20% first-line; 80% second-line	N=480	N=480 (231, 249)	N/A	Johnston (2013)[22]

SOLAR-1 Andre (2018)[28]	Alp/Fulv	Fulv	Post-menopausal women (plus 1 man)	*PIK3CA* mutant	HR+	HER2−	Endocrine-resistant (sensitive patients omitted)	Second-line	N= [redacted]	N= [redacted] ([redacted])	N= [redacted] wildtype *PIK3CA* N= [redacted] first-line N= [redacted] third+ line N= [redacted] endocrine-sensitive	Cox PH regression of IPD

[b]*SoFEA trial is a three-arm trial, and CS Table 23 mistakenly lists the fulvestrant plus anastrazole arm here, which has been corrected to fulvestrant alone*

Alp - alpelisib; ET - endocrine therapy; Eve - everolimus; Exe - exemestane; Fulv - fulvestrant; HER2 - human epidermal growth factor receptor 2; HR - hormone receptor; IPD - individual patient data; ITC - indirect treatment comparison; N/A - not applicable; PH - proportional hazards; PIK3CA - phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha

4.8.2 Restriction of Bucher ITC to the second-line population

The CS[1] (Section B.2.7.2) notes that there were no data for Eve/Exe in a post-CDK4/6i population. Therefore, as a proxy for the post-CDK4/6i setting, ITCs were conducted using a subset of trial data restricted to the second-line advanced setting (where available). The CS[1] states that clinical expert opinion suggested that it would be reasonable to assume that a treatment effect in the second-line ABC population would be applicable in the post-CDK4/6i setting. Data for the second-line population were generated by the company using individual patient data (IPD) for SOLAR-1[28] and BOLERO-2,[20] whereas for CONFIRM[21] and SoFEA[22] it was not possible to restrict the data to second-line patients. It is not clear to what extent the treatment effect in a second-line mostly-CDK4/6i-naïve population would reflect the treatment effect in a post-CDK4/6i population.

The use of IPD to restrict to second-line patients for SOLAR-1[28] and BOLERO-2,[20] as well as the restriction of BOLERO-2[20] data to patients with *PIK3CA* mutations based on tumour tissue rather than cell-free DNA (see below), meant that a large proportion of trial patients were excluded from the ITC. In total, the ITC included [redacted] of 341 (47%) patients from SOLAR-1[28] and 57 of 724 (8%) patients from BOLERO-2[20] (see Table 23). The ERG notes that the PFS HR for the restricted second-line BOLERO-2 population used in the ITC is less favourable to Eve/Exe than the HRs reported in publications for the wider BOLERO-2 population (for the ITC: HR 0.61; 95% CI: 0.33–1.14, based on 57 second-line patients with *PIK3CA* mutations from tumour tissue; while from publications: HR 0.51; 95% CI: 0.34 to 0.77, based on 143 patients from all lines with *PIK3CA* mutations from tumour tissue;[33] and HR 0.37; 95% CI: 0.27 to 0.51, based on 238 patients from all lines with *PIK3CA* mutations from plasma[32]).

4.8.3 Key differences between trials included in Bucher ITC

All four studies included in the ITC were Phase 3 RCTs. All were conducted in HR+ postmenopausal women (apart from one male patient in SOLAR-1)[28] who had progressed on prior ET. The median age of participants in the trials ranged from 56 to 66 years. However, there were a number of population differences between the trial subgroups included in the ITC, as summarised below and in Table 23.

Line of treatment: The ITC included only second-line patients for SOLAR-1[28] and BOLERO-2.[20] However, for CONFIRM[21] and SoFEA,[22] separate data were not available by treatment line. Patients in CONFIRM[21] were approximately 50% first-line and 50% second-line, while those in SoFEA[22] were approximately 20% first-line and 80% second-line. In response to ERG clarification question A16,[14] the company states that *"this would bias the comparison to the extent to which the treatment effects in SoFEA and CONFIRM were modified by presence of patients receiving first line treatment."* However, the direction of the effect modification from line of therapy is unclear as the results from SOLAR-1 and BOLERO-2 were inconsistent (CS, Appendix D[23]).

PIK3CA mutation status: For SOLAR-1[28] and BOLERO-2,[20] only patients with a *PIK3CA* mutation were included in the analysis, while CONFIRM[21] and SoFEA[22] did not test for *PIK3CA* status. In addition, the SOLAR-1 primary analysis was based on *PIK3CA* mutation status from tumour tissue samples; therefore, for consistency, the IPD analysis of BOLERO-2 was restricted to patients with *PIK3CA* mutations based on tumour tissue rather than cell-free DNA. As noted above, this led to exclusion of 92% of BOLERO-2 patients (see Table 23).

HER2 status: CS Appendix D[23] (Section D.5.3) indicates that HER2 status may be an important treatment effect modifier. SOLAR-1[28] and BOLERO-2[20] restricted to HER2- patients, while CONFIRM[21] did not evaluate HER2 status, and SoFEA[22] enrolled 60% HER2-, 7% HER2+ and 33% with unknown HER2 status. CS Appendix D[23] notes that HER2 status was a statistically significant treatment effect modifier in the SoFEA[22] trial, in which the treatment effect on PFS and OS (for Fulv over Exe) was statistically significantly greater in HER2+ patients than in HER2- patients (CS Appendix D,[23] Tables 24 and 25). The ERG queried why data for the full population of SoFEA[22] were used rather than the HER2- subgroup (see clarification response,[14] question A16). In their response, the company stated that they used the full population because excluding patients with unknown HER2 status (n=166) could lead to information bias, and the estimates for HER2+ patients may have been unreliable due to small sample size. The ERG notes that, because HER2 status may be an important treatment effect modifier, results of the ITC may be biased by the inclusion of HER2+ patients. In response to clarification question A20, the company conducted an additional ITC using PFS and OS data for the HER2- subgroup in SoFEA.[22]

Endocrine resistance: Patients in BOLERO-2[20] and CONFIRM[21] were endocrine-resistant, and only endocrine-resistant patients from SOLAR-1[28] were included in the ITC (see CS Appendix D,[23] Section D.5.3 page 110). All patients in SoFEA[22] had relapsed or progressed on prior ET but the timing was unclear, so it was unclear whether all patients were endocrine-resistant. Overall, it appears that the included populations from all trials were either all or mostly endocrine-resistant.

4.8.4 Quality assessment of trials included in ITC

A quality assessment of CONFIRM[21] and SoFEA[22] was not included in the CS[1] or its appendices.[23] A quality assessment of BOLERO-2[20] was reported in CS Appendix D[23] (Table 18); the ERG does not note any major quality issues. The ERG briefly assessed the quality of CONFIRM and SoFEA using the York CRD checklist[26] (not shown here) and both trials appeared to be at low risk of bias, except that in SoFEA,[22] participants and investigators were not blinded to use of Fulv or Exe.

4.8.5 Individual trial results for trials included in ITC

The PFS and OS data from each of the four trials used in the ITC are presented in Table 24 and Table 25, respectively (adapted from CS Appendix D,[23] Tables 27 and 28 and clarification response,[14] question A22). The company undertook analyses of IPD from the company-sponsored studies (SOLAR-1[28] and BOLERO-2[20]), whilst data for CONFIRM[21] and SoFEA[22] were taken from the trial publications.

Table 24: HRs for PFS for trials used in the ITC (adapted from CS Appendix D, Table 27 and clarification response question, A20 and A22)

Trial	Treatment	Control	*PIK3CA* mutant (%)	HER2 status	Line of therapy (analysed patients)	Endocrine status	N analysed (per arm)	Median PFS (months)		PFS HR (95% CI)
								Treatment	Control	
BOLERO-2[20, 32, 33]	Eve/Exe	Exe	100% *PIK3CA* mutant	HER2−	Second-line	Endocrine-resistant	N=57 (36, 21)	7.8	3.3	0.61 (0.33–1.14)
CONFIRM[21, 34]	Fulv500	Fulv250	NR	HER2− or HER2+	50% first-line; 50% second-line	Endocrine-resistant	N=736 (362,374)	6.5	5.5	0.80 (0.68–0.94)
SoFEA[22] (all patients)	Fulv250	Exe	NR	60% HER2- 7% HER2+ 33% unknown	20% first-line; 80% second-line	Resistant or sensitive	N=480 (231, 249)	4.8	3.4	0.95 (0.79–1.14)
SoFEA[22] (HER2-)	Fulv250	Exe	NR	HER2-	20% first-line; 80% second-line (approx.)	Resistant or sensitive	N=283 (NR)	NR	NR	1.06 (0.83–1.34)
SOLAR-1[28]	Alp/Fulv	Fulv	100% *PIK3CA* mutant	HER2−	Second-line	Endocrine-resistant	N=[redacted] ([redacted])	[redacted]	[redacted]	[redacted] ([redacted])

Alp - alpelisib; CI - confidence interval; Eve - everolimus; Exe - exemestane; Fulv - fulvestrant; HER2 - human epidermal growth factor receptor 2; HR - hazard ratio; ITC - indirect treatment comparison; NR - not reported; PIK3CA - phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PFS - progression-free survival.

Table 25: HRs for OS for trials used in the ITC (adapted from CS Appendix D, Table 28 and clarification response, question A20 and A22)

Trial	Treatment	Control	*PIK3CA* mutant (%)	HER2 status	Line of therapy for included patients	Endocrine status	N analysed (per arm)	Median OS (months)		OS HR (95% CI)
								Treatment	Control	
BOLERO-2[20, 32, 33]	Eve/Exe	Exe	100% *PIK3CA* mutant	HER2−	Second-line	Endocrine-resistant	N=57 (36, 21)	31.0	26.6	1.09 (0.58–2.03)
CONFIRM[21, 34]	Fulv500	Fulv250	NR	HER2− or HER2+	50% first-line; 50% second-line	Endocrine-resistant	N=736 (362, 374)	26.4	22.3	0.81 (0.69–0.96)
SoFEA[22]	Fulv250	Exe	NR	60% HER2- 7% HER2+ 33% unknown	20% first-line; 80% second-line	Resistant or sensitive	N=480 (231, 249)	19.4	21.6	1.05 (0.84–1.29)
SoFEA[22] (HER2-)	Fulv250	Exe	NR	HER2-	20% first-line; 80% second-line (approx.)	Resistant or sensitive	N=283 (NR)	NR	NR	1.26 (0.95–1.66)
SOLAR-1[28]	Alp/Fulv	Fulv	100% *PIK3CA* mutant	HER2−	Second-line	Endocrine-resistant	N=[redacted] ([redacted])	[redacted]	[redacted]	[redacted] ([redacted])

Alp - alpelisib; CI - confidence interval; Eve - everolimus; Exe - exemestane; Fulv - fulvestrant; HER2 - human epidermal growth factor receptor 2; HR - hazard ratio; ITC - indirect treatment comparison; NR - not reported; OS - overall survival; PIK3CA - phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

4.8.6 Summary of issues relating to trials included in the Bucher ITC

The ERG notes the following issues regarding the trials included in the ITC:

- None of the trials were conducted in a post-CDK4/6i population. It is not clear to what extent the treatment effect in a second-line mostly-CDK4/6i-naïve population would reflect the treatment effect in a post-CDK4/6i population.
- The ERG does not believe that the CS[1] provides a particularly clear rationale regarding which trials were included in or excluded from the ITC. However, a very brief PubMed search by the ERG did not identify any other trials which could have been used in the network.
- As CONFIRM[21] and SoFEA[22] did not measure *PIK3CA* status, it was not possible to restrict the population to *PIK3CA* mutant patients
- As HER2 status was not measured in CONFIRM,[21] it was not possible to restrict the population to HER2- patients in this study. HER2 status was measured in SoFEA;[22] however, only the results for the unselected population were included in the company's original Bucher ITCs. Clinical advisors to the ERG and subgroup analyses of the trials contributing to the ITC suggest that HER2 status may be an important treatment effect modifier. Following clarification, the company provided ITC results using the HER2- subgroup from SoFEA.[22]
- For SoFEA,[22] it was unclear whether all patients were endocrine-resistant
- The data from CONFIRM[21] and SoFEA[22] could not be restricted to the second-line population due to a lack of subgroup data by line of therapy for these trials
- For BOLERO-2,[20] the data in the ITC were based on only a small subgroup of trial patients, and excluded third- and subsequent-line patients and those with *PIK3CA* mutations based on plasma DNA (in order to align with the SOLAR-1 population[28]). Analysis of subgroups which were not stratified for during randomisation may introduce confounding. The resulting HRs were less favourable than those for the wider groups of patients with *PIK3CA* mutations in the trial publications.

4.9 Bucher ITC of SOLAR-1 versus BOLERO-2: Critique of statistical methods

4.9.1 Overall approach for Bucher ITC

The key trials identified by the company's SLR (SOLAR-1[28] and BOLERO-2[20]) form a disconnected network of evidence and the company chose to connect the network by widening the inclusion criteria for trials contributing to the ITC. This required the addition of two further trials (CONFIRM[21] and SoFEA[22]; see Figure 7).

4.9.2 Assessment of proportional hazards in Bucher ITC

The assessment of proportional hazards (PH) for the observed trial data was based on plots of Schoenfeld residuals and *p*-values for the test of linearity of the residuals were presented for each study

and population (CS Appendix D,[23] Section D.5). The test for non-PH was not found to be statistically significant for any contributing study. Based on this, the company performed ITC using the Bucher method[35] to synthesise HRs under the assumption of PH.

The ERG notes that the absence of evidence for non-PH does not guarantee that this assumption holds. The reduced sample size when considering the second-line population alone may contribute to the finding of a non-statistically significant *p*-value. The ERG asked the company to provide the graphs of the log(-log(survival)) versus the log of survival time for checking the PH assumption (see clarification response,[14] question A17). The plots provided show potential deviations from the PH assumption for both PFS and OS. Furthermore, the assessment of PH was based purely on the observed data. When asked to comment on the plausibility of this assumption for the extrapolated period, the company responded that "*this assumption was considered reasonable compared with potential limitations that may be introduced by conducting the more complex time-varying hazard NMA*" but no discussion of whether the assumption is likely to be valid was provided (see clarification response,[14] question A17). The ERG therefore considers that the appropriateness of the assumption of constant HRs is questionable.

4.9.3 Bucher ITC of SOLAR-1 versus BOLERO-2

The Bucher method[35] was used to provide indirect comparisons. The Bucher method is equivalent to performing a fixed effect (FE) network meta-analysis (NMA) and does not allow for between-study heterogeneity in treatment effects. When asked to comment on the validity of this assumption, the company replied that *"the use of a fixed or random effects approach would have yielded identical HRs and CIs and therefore only a fixed effects approach was conducted"* (clarification response,[14] question A17). The ERG notes that this statement is incorrect. Due to the sparsity of the network (with only one study informing each comparison), an informative prior would be required to inform the between-study heterogeneity: this would lead to more realistic estimates of the uncertainty. Assuming artificially precise estimates due to the lack of sample data to inform the between-study heterogeneity is not appropriate. The ERG considers that the assumption of zero between-study variation should be treated with caution given the identified differences between studies. Furthermore, in the presence of heterogeneity, the predictive distribution, rather than the distribution of the mean treatment effect, would better represent uncertainty about the treatment effect in a future study.[36]

4.9.4 Results of Bucher ITC of SOLAR-1 versus BOLERO-2

The results of the company's analysis for PFS and OS are presented in Table 26. The results also include the additional analysis requested by the ERG using the HER2- subgroup from SoFEA (clarification response,[14] question A20). The values highlighted in bold are used in the company's economic model. The results presented in Table 26 suggest that Eve/Exe has [redacted] for [redacted] PFS

[redacted] OS when compared with Alp/Fulv. When using HER2- subgroup of SoFEA, the results [redacted] for Eve/Exe vs. Alp/Fulv, but [redacted].

Table 26: Results of Bucher ITC (adapted from CS, Tables 25 and 26 and clarification response, question A20)

Comparator	HR (95% CI) of comparator versus:	
	Fulv	Alp/Fulv
Base case HRs based on all patients in SoFEA regardless of HER2 status		
PFS		
Alp/Fulv	[redacted]	[redacted]
Eve/Exe	[redacted]	[redacted]
Fulv	[redacted]	[redacted]
OS		
Alp/Fulv	[redacted]	[redacted]
Eve/Exe	[redacted]	[redacted]
Fulv	[redacted]	[redacted]
Revised HRs based on the HER2– subgroup of SoFEA		
PFS		
Alp/Fulv	[redacted]	[redacted]
Eve/Exe	[redacted]	[redacted]
Fulv	[redacted]	[redacted]
OS		
Alp/Fulv	[redacted]	[redacted]
Eve/Exe	[redacted]	[redacted]
Fulv	[redacted]	[redacted]

Values highlighted in bold are used in the company's economic model (see Section 5.2.4)
Alp - alpelisib; CI - confidence interval; Eve – everolimus; Exe - exemestane; Fulv - fulvestrant; HER2 - human epidermal growth factor receptor 2; HR - hazard ratio; ITC - indirect treatment comparison; N/A - not applicable; OS - overall survival; PFS - progression-free survival

4.9.5 Summary of issues relating to implementation of the Bucher ITC

The ERG believes that the results of the company's Bucher ITC should be interpreted with caution for several reasons:

- The overall approach of including additional studies (CONFIRM[21] and SoFEA[22]) to perform an anchored ITC was not well justified
- Treatment effects are potentially biased due to the imbalance in treatment effect modifiers
- The assumption of PH for the second-line population is questionable
- FE models were used. The assumption of zero between-study variation is not appropriate, hence uncertainty is underestimated
- The network involves a single chain of evidence (with no closed loops) and each comparison is informed by only one trial. It is not possible to assess consistency of evidence statistically.

4.10 PAIC of SOLAR-1 versus BOLERO-2

4.10.1 Studies included in the PAIC (SOLAR-1 versus BOLERO-2)

The CS[1] also describes a PAIC to indirectly estimate PFS and OS for the comparison of Alp/Fulv versus Eve/Exe, using an unanchored comparison of the Alp/Fulv arm from SOLAR-1[28] and the Eve/Exe arm from BOLERO-2[20] (described in CS,[1] Section B.2.7 and CS Appendix D,[23] Section D.5 to D.8).

The population comprised postmenopausal women with HR+, HER2– ABC with a *PIK3CA* mutation who had received no more than one prior treatment with an AI in the (neo)adjuvant or advanced/metastatic setting. For SOLAR-1,[28] this corresponds to patients receiving second-line treatment in the *PIK3CA*-mutant cohort, excluding those who were ET-sensitive (20 and 19 patients in the Alp/Fulv and Pbo/Fulv arms, respectively) and excluding the single male patient. For BOLERO-2,[20] this population corresponds to patients in the ITT population with *PIK3CA* mutation, excluding patients who had received more than one prior line of ET for advanced disease.

4.10.2 Statistical method used in the PAIC (SOLAR-1 versus BOLERO-2)

Patients in SOLAR-1[28] and BOLERO-2[20] were matched using inverse probability of treatment weighting (IPTW) methods.[37] Patients in the Alp/Fulv arm of SOLAR-1 were matched to the patients in the Eve/Exe arm of BOLERO-2, and patients in the Pbo/Fulv arm of SOLAR-1 were matched to the patients in the Pbo/Exe arm of BOLERO-2 (see clarification response,[14] question A23). For each patient, the probability of being in the trial in which the patient was enrolled (i.e. the propensity score) was estimated using a multivariable logistic regression model conditional on baseline demographic and clinical characteristics; covariates included in the analysis are presented in CS Appendix D,[23] Section D.6.2. Several logistic regression models with alternative selected covariates were performed for the 2019 data cut-off for SOLAR-1, and the best method was then carried forward for the analyses using the 2020 data cut-off.

Unanchored ITCs of PFS and OS were performed by comparing the two active arms of each trial without reference to the control arms. Further description of the assessment of distribution of IPTW, assessment of adequacy of matching, and calculation of HRs for PFS and OS are provided in CS Appendix D,[23] Section D.6.2.

4.10.3 Results of the PAIC (SOLAR-1 versus BOLERO-2)

The PAIC analysis included a total of [redacted] and [redacted] second-line patients receiving Alp/Fulv and Pbo/Fulv, respectively, from SOLAR-1[28] who met the inclusion criteria; and [redacted] and [redacted] second-line patients receiving Eve/Exe and Pbo/Exe, respectively, from BOLERO-2[20] who met the inclusion criteria. The effective sample size (ESS) after applying average treatment effect among the treated (ATT) weights was [redacted] and [redacted] for patients receiving Eve/Exe and Pbo/Fulv, respectively.

The results of Cox PH regressions for PFS and OS for second-line patients in SOLAR-1[28] versus BOLERO-2[20] are presented in Table 27. The company states that the results should be interpreted with caution given the small sample size and ESS from BOLERO-2.

Table 27: Results of Cox proportional hazards regressions for PFS and OS for second-line patients in SOLAR-1 versus BOLERO-2 (adapted from CS, Table 28)

Endpoint	Weighted	Arms		Cox regression		
		Active (N)	Comparator (N)	HR	95% CI	*p*-value
PFS	Yes	Alp/Fulv ([redacted])	Eve/Exe ([redacted])	[redacted]	[redacted]	[redacted]
OS	Yes	Alp/Fulv ([redacted])	Eve/Exe ([redacted])	[redacted]	[redacted]	[redacted]

Alp - alpelisib; CI - confidence interval; Eve – everolimus; Exe - exemestane; Fulv - fulvestrant; HR - hazard ratio; OS - overall survival; PFS - progression-free survival

4.10.4 Critique of the PAIC (SOLAR-1 versus BOLERO-2)

The selection of methods for estimating the propensity scores was based on the 2019 data cut-off. Based on the 2019 data cut-off results, the estimated HR of PFS ranged from [redacted] to [redacted] and the estimated HR of OS ranged from [redacted] to [redacted]. There is no description in the CS[1] regarding how the best method was selected. In response to clarification question A23,[14] the company provided results of Cox proportional hazards regressions for PFS and OS for second-line patients in SOLAR-1 versus BOLERO-2, using different model/variable selection methods, but provided no additional information on how the best method was selected. The company states that the results using the 2020 data cut-off were not qualitatively different from the results using the 2019 data cut-off. As unanchored ITCs of PFS and OS were performed by comparing the two active arms of each trial, it is unclear what the benefit would be of including the Pbo/Fulv from SOLAR-1[28] and Pbo/Exe from BOLERO-2[20] in the estimation of the propensity scores. It is also unclear whether the results would be different if only the two active arms were included in the IPTW. The ERG was not able to check the programming code used because it is proprietary and the company stated that it could not be shared (see CS Appendix D,[23] Section D.7). The ERG agrees with the company that the results of the unanchored ITCs need to be interpreted with caution because of the small sample sizes.

4.11 Additional work on clinical effectiveness undertaken by the ERG

The ERG did not undertake additional analyses of the clinical effectiveness data.

4.12 Conclusions of the clinical effectiveness section

Methods of systematic review: The ERG considers the company's systematic review methods to be of a good standard.

Clinical studies: The CS[1] presents data from two studies of Alp/Fulv: one RCT (SOLAR-1)[28] and one non-RCT (BYLieve Cohort A).[29] These are both of relevance to the decision problem set out in the final NICE scope,[12] and the ERG's clinical advisors were satisfied that the study populations were sufficiently similar to the population who would be treated with Alp/Fulv in England. However, the population of interest in the CS[1] is patients who have progressed following a CDK4/6i, while in SOLAR-1 only 20 patients received a prior CDK4/6i. Conversely, patients in BYLieve Cohort A received a prior CDK4/6i+AI, and are therefore most relevant to the population of interest in the CS.[1] Data from SOLAR-1 were used in the company's Bucher ITC against Eve/Exe; BYLieve did not contribute to the network due to its non-comparative design. Updated data from BYLieve Cohorts A and C are anticipated within the next 12 months. In addition, an RCT of Alp/Fulv in the post-CDK4/6i population (EPIK-B5) is planned to start in [redacted], with first results expected in [redacted]. The comparator for this trial is not clear from the company's clarification response.

Effectiveness and safety: SOLAR-1 results indicated that Alp/Fulv significantly improved PFS versus Pbo/Fulv in patients with HR+ HER2- *PIK3CA*-mutated ABC. There was a trend for improvement in OS in favour of Alp/Fulv, though this was not statistically significant. PFS and OS for the post-CDK4/6i subgroup of SOLAR-1 (n=20) also numerically favoured Alp/Fulv. The most common AEs in the Alp/Fulv arm of SOLAR-1 (vs. Pbo/Fulv) were: hyperglycaemia (65%vs. 9%); diarrhoea (60% vs. 16%); nausea (47% vs. 23%); decreased appetite (36% vs. 11%), and rash (36% vs. 7%). In the Alp/Fulv arm, 25% discontinued Alp due to AEs and 75% experienced dose reductions or interruptions.

Indirect treatment comparisons: The company conducted ITCs using three different approaches, as summarised below.

Matching/weighted analysis of BYLieve versus CGDB in post-CDK4/6i setting: The company conducted a matching/weighted analysis using data from BYLieve Cohort A (n=120; Alp/Fulv in the post-CDK4/6i setting) versus data from the US Flatiron CGDB (n=95; mix of standard treatments in the post-CDK4/6i setting; not Alp). Three matching/weighed approaches were used to adjust for the imbalance in baseline characteristics. The CS[1] states that there was a consistent trend in the HRs for PFS in favour of Alp/Fulv compared to standard treatments. OS was not analysed and there was no comparison against Eve/Exe. The results of this analysis are not used in the company's economic analysis.

Bucher ITC of SOLAR-1 versus BOLERO-2: The company conducted Bucher ITCs to compare Alp/Fulv and Eve/Exe for PFS and OS. The SOLAR-1[28] trial (Alp/Fulv versus Fulv) and the BOLERO-2[20] trial (Eve/Exe versus Exe) were connected via a network involving two additional trials (CONFIRM[21] and SoFEA[22]). For SOLAR-1[28] and BOLERO-2,[20] second-line data were used as a proxy

for the post-CDK4/6i population. The company's Bucher ITCs suggest that Alp/Fulv has [redacted] Eve/Exe on PFS (Eve/Exe versus Alp/Fulv: HR=[redacted], 95% CI [redacted]) [redacted] OS (Eve/Exe versus Alp/Fulv: HR=[redacted], 95% CI [redacted]). The ERG requested additional ITCs using only the HER2- subgroup of SoFEA from the company. The alternative ITC suggests [redacted] for Alp/Fulv versus Eve/Exe for PFS (Eve/Exe versus Alp/Fulv: PFS HR= [redacted], 95% CI [redacted]) [redacted] OS (Eve/Exe versus Alp/Fulv: HR=[redacted], 95% CI [redacted]). The results of the former analysis are used in the company's base case economic analysis.

The ERG has a number of concerns with the company's ITCs. The two connecting trials (CONFIRM[21] and SoFEA[22]) did not restrict to second-line, HER2- or *PIK3CA*-mutated patients. For BOLERO-2, the data used in the ITC were based on only a small proportion of trial patients (n=57), and excluded first-line, third-line and subsequent-line patients and those with *PIK3CA* mutations based on plasma DNA (in order to align with the SOLAR-1 population). The resulting HRs for Eve/Exe versus Exe were [redacted] those reported in the BOLERO-2 trial publications. For the SoFEA study, the (original) ITC used HRs for all patients rather than those for HER2- patients. As the ITC is formed from a single chain of evidence (with no closed loops) and contains trials with imbalances in treatment effect modifiers, the treatment effects estimated from the company's ITC is subject to an unquantified degree of bias. The Bucher method assumes zero between-study heterogeneity, thereby underestimating uncertainty. In addition, the PH assumption is questionable. The ERG also notes that the ITC does not provide comparative effectiveness estimates for Alp/Fulv in the post-CDK4/6i population. Given the small patient numbers post-CDK4/6i from SOLAR-1 (n=20 across both treatment arms in the *PIK3CA*-mutated cohort) and the fact that other RCTs (BOLERO-2, CONFIRM and SoFEA) have not assessed patients following the receipt of a prior CDK4/6i, this precludes a robust analysis from being conducted.

PAIC of SOLAR-1 versus BOLERO-2: The company also conducted a PAIC to indirectly estimate PFS and OS for the comparison of Alp/Fulv versus Eve/Exe, using an unanchored comparison of second-line data from the Alp/Fulv arm from SOLAR-1[28] and the Eve/Exe arm from BOLERO-2.[20] Patients in SOLAR-1[28] and BOLERO-2[20] were matched using IPTW methods. Unanchored ITCs of PFS and OS were performed by comparing the two active arms of each trial without reference to the control arms. The PAIC generated HRs for PFS and OS which [redacted] Alp/Fulv [redacted] Eve/Exe (PFS: HR [redacted]; 95% CI: [redacted]; and OS: HR [redacted]; 95% CI: [redacted]). The company states, and the ERG agrees, that the results should be interpreted with caution given the small sample size and ESS from BOLERO-2. The results of the PAIC are included as a sensitivity analysis of the company's economic model.

Overall, the ERG considers that there is a large degree of uncertainty in all three of the company's ITC approaches.

5 COST EFFECTIVENESS

This chapter presents a summary and critique of the company's health economic analyses of Alp/Fulv for the treatment of patients with endocrine-resistant HR+, HER2− ABC with a *PIK3CA* mutation. Section 5.1 describes and critiques the company's review of existing economic evaluations. Section 5.2 describes the company's economic model and summarises the company's results. Sections 5.3 and 5.4 present the ERG's critical appraisal of the company's model and the results of the ERG's exploratory analyses. Section 5.5 presents a discussion of the company's economic analysis.

5.1 Company's review of existing cost-effectiveness evidence

5.1.1 Summary and critique of the company's search strategy

The company undertook searches to identify economic evaluations, health utility studies and cost/resource use studies relevant to the decision problem; these are reported in CS Appendix G.[23] These searches were run together and are presented as a single SLR, though the results feature in Appendices G, H and I as well as throughout Section B.3 of the main CS.[1]

Initial searches were run on the 18th December 2018 and were updated on the 28th October 2019, 14th August 2020 and 16th April 2021. The searches covered Medline (including 'in process' and Epub ahead of print); EMBASE; and the NHS Economic Evaluations Database (NHS EED) and Health Technology Assessment (HTA) databases formerly hosted by Cochrane (now archived on the CRD website). The most recent searches (in April 2021) included the newly-launched International Network of Agencies for Health Technology Assessment (INAHTA) database, which is essentially an updated version of the CRD's HTA database. The searches are reproduced in full and have been designed and executed systematically. The 'population' terms are the same as those used for the clinical SLR. Appropriate subject headings are combined with free text terms and (in Medline and EMBASE) with search filters based on the work of SIGN and York Health Economics Consortium (YHEC), whose expertise in the field of information retrieval is widely acknowledged. Although to the best of our knowledge these filters have not been formally validated, the ERG accepts that given their origins, they are most likely suitable for their intended purpose. Database searches were augmented by complementary searching of international HTA websites; manual searches of relevant conference proceedings since 2016, and checking of reference lists for included review articles. ClinicalTrials.gov was used to access additional data about trials used as sources of utility data. Given the robust methods used in these searches, the ERG believes it is unlikely that any evidence relevant to the decision problem has been missed.

5.1.2 Summary of company's review findings

The company's searches did not identify any economic analyses of Alp/Fulv or any other PI3K inhibitor for the treatment of HR+, HER2- ABC. Further details of included and excluded studies are presented

in CS Appendix G.[23] The ERG considers that it may have been useful for the review inclusion criteria to have been broader (e.g. to include CDK4/6i therapy) in order to explore alternative model structures, assumptions and evidence sources used in models developed to inform recent appraisals of other classes of drug for patients with HR+, HER2- ABC. However, the CS[1] refers to evidence sources and assumptions employed in previous models of breast cancer therapies submitted to NICE.

5.2 Summary of the company's submitted economic evaluation

This section describes the company's original submitted model, as described in the CS.[1] Following the clarification round, the company submitted an updated base case model which included some minor amendments. These amendments are not detailed here, but are instead included as part of the ERG's exploratory analyses in Section 5.4.

5.2.1 Scope of the company's economic analysis

As part of their submission to NICE,[1] the company submitted a fully executable health economic model programmed in Microsoft Excel. The scope of the company's economic analyses is summarised in Table 28.

Table 28: Scope of the company's base case economic analyses

Population	Adult women with endocrine-resistant HR+, HER2− ABC with a *PIK3CA* mutation, who have received prior treatment with a CDK4/6i+AI in either the neo/adjuvant or advanced settings (including first- and subsequent-line)
Time horizon	40 years (lifetime)
Intervention	Alpelisib plus fulvestrant (Alp/Fulv)
Comparator	Everolimus plus exemestane (Eve/Exe)
Outcome	Incremental cost per QALY gained
Perspective	NHS and PSS
Discount rate	3.5% per annum
Price year	2019/2020

ABC - advanced breast cancer; HR - hormone receptor; HER2 - human epidermal growth factor receptor 2; PIK3CA - phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; CDK4/6i - cyclin-dependent kinase 4/6 inhibitor; AI - aromatase inhibitor; QALY - quality-adjusted life year; NHS - National Health Service; PSS - Personal Social Services

Whilst the company's base case analysis is intended to reflect the population of women who have documented disease progression following an endocrine-based regimen in the advanced setting who have previously received treatment with CDK4/6i+AI therapy, BYLieve[31] is a non-comparative study and does not contribute data to the ITCs used in the company's base case (described previously in Section 4.8). The estimates of relative treatment effects for Alp/Fulv versus Eve/Exe are instead derived from indirect comparisons using second-line patients recruited into SOLAR-1[28] and other RCTs included in the company's Bucher ITCs (BOLERO-2,[20] CONFIRM[21] AND SoFEA;[22]). The company's economic analyses use time-to-event data for Alp/Fulv on PFS and OS from women who received Alp/Fulv at second-line (n=[redacted]).

The economic analysis was undertaken from the perspective of the NHS and Personal Social Services (PSS) over a 40-year (lifetime) horizon. Cost-effectiveness is expressed in terms of the incremental cost per quality-adjusted life year (QALY) gained. Unit costs are valued at 2019/20 prices. Health outcomes and costs are discounted at a rate of 3.5% per annum.

Population

The company's intended target population relates to adult women with endocrine-resistant HR+, HER2− ABC with a *PIK3CA* mutation who have progressed following treatment with a CDK4/6i+AI regimen in the neo/adjuvant or advanced settings. This population represents a subset of the anticipated Type 2 variation in the MHRA marketing authorisation, and reflects patients who have previously received both a CDK4/6i and an AI (rather than an AI alone). The population reflected in the company's economic model is based on clinical data from the second-line patients in Cohort A of BYLieve.[31] As such, the company's intended target population is broader than the model and includes patients who received a CDK4/6i in the neo/adjuvant settings as well as patients who will receive Alp/Fulv beyond the second-line (see clarification response,[14] question B1).

As discussed in Section 3.1, the current marketing authorisation for Alp/Fulv granted by the EMA[38] relates specifically to patients whose disease has progressed following ET as monotherapy. If the Type II variation to the existing EMA licence is not granted by the MHRA, the population included in the economic model, and indeed the main clinical evidence for Alp/Fulv presented in the CS,[1] will not be in line with the marketing authorisation. The ERG also notes that the company's analyses do not provide economic evidence for: (i) patients with prior CDK4/6i+AI treatment in the (neo)adjuvant setting (first-line setting for advanced/metastatic disease), (ii) patients in the third- and subsequent-line settings, or (iii) men with ABC, who would be eligible for treatment according to the proposed marketing authorisation for Alp/Fulv.

Patients are assumed to have a mean age of 57 years at model entry and all patients are assumed to be female. The clinical advisors to the ERG agreed that the characteristics of the population of Cohort A in BYLieve appear reasonably consistent with the population who would be eligible for treatment in clinical practice in England.

Intervention

The intervention evaluated within the company's base case analyses is Alp/Fulv. Alp is assumed to be administered orally at a dose of 300mg daily during each 28-day dosing cycle, whilst Fulv is assumed to be administered via IM injection at a dose of 500mg (two 5mL injections) on days 1 and 15 in the first 28-day cycle, and on day 1 (±3) in each subsequent 28-day cycle. In line with the current SmPC

for Alp,[13] the model does not include a formal stopping rule; time on treatment is modelled using parametric survival functions fitted to data on time to treatment discontinuation (TTD).

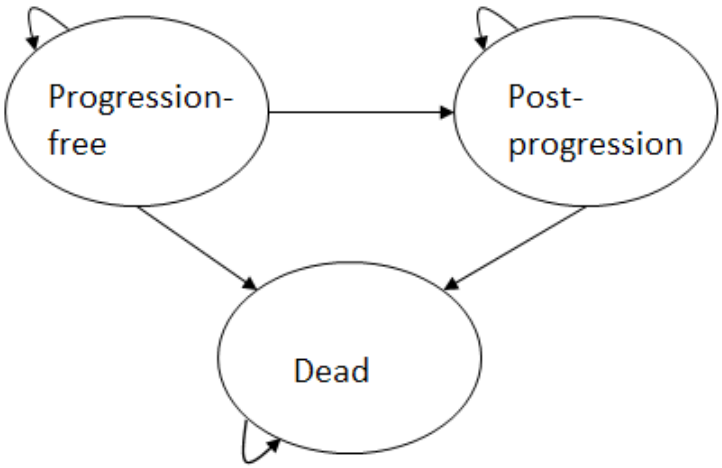
Comparators

The company's economic analyses include a single comparator: Eve/Exe. Within the model, both components of this treatment regimen are assumed to be administered orally once daily, with Eve given at a dose of 10mg in each 28-day dosing cycle and Exe given at a dose of 25mg in each 30-day dosing cycle. The final NICE scope[12] lists three further comparators: (i) CDK4/6i (ribociclib, abemaciclib or palbociclib) in combination with Fulv, (ii) Tam monotherapy and (iii) Exe monotherapy. According to the CS,[1] these other treatment options were excluded from the economic analyses as for "*patients who have received CDK4/6i + AI first-line in the advanced setting, another CDK4/6i is typically not used second-line in UK practice"* or they are not widely used in UK clinical practice (see Section 3.3).

5.2.2 Model structure and logic

The company's economic analysis adopts a partitioned survival model structure and is comprised of three health states: (i) progression-free; (ii) post-progression, and (iii) dead (see Figure 8).

Figure 8: Company's model structure



The model logic operates as follows. Patients enter the model in the progression-free state and receive treatment with either Alp/Fulv or Eve/Exe. All patients are assumed to receive these treatments in the second-line setting. For any time *t*, the probability of being alive and progression-free is given by the cumulative probability of PFS, the probability of being alive is given by the cumulative probability of OS, and the probability of being alive following disease progression is given by the cumulative probability of OS minus the cumulative probability of PFS. Within each treatment group, the model applies three sets of structural constraints: (i) that TTD must be less than or equal to PFS; (ii) that PFS must be less than or equal to OS, and (iii) that the PFS and OS risks for women with HR+, HER2− ABC with a *PIK3CA* mutation must be at least as high as the mortality risk of the age- and sex-matched

general population. The cumulative probabilities of OS, PFS and TTD in each time interval are modelled using different approaches between the two treatment groups. The survivor functions used in the company's base case and the evidence sources to derive these functions are summarised in Box 1 and Table 29, with further detail provided in Section 5.2.4.

HRQoL is assumed to be determined by the patient's progression status, treatment group, whether the patient is still receiving that treatment, their proximity to death and age. Health utilities used in the model are largely based on a generalised estimating equation (GEE) model fitted to EQ-5D-3L data (mapped from 5L data) from patients receiving second-line treatment in SOLAR-1.[28] The model assumes that HRQoL for patients who are progression-free and on-treatment is improved for the Alp/Fulv group compared with the Eve/Exe group, whilst the utility values for patients who have discontinued treatment and/or progressed are assumed to be the same for both treatment groups (see Section 5.2.4). The company's model does not explicitly include HRQoL losses associated with the incidence of Grade 3/4 AEs as these are assumed to be already captured in the treatment-specific utility values. The model applies a QALY loss, which was also derived from the GEE model, to reflect a lower level of HRQoL during the terminal phase of the disease. Utility estimates are age-adjusted.[39]

The model includes costs associated with: (i) drug acquisition; (ii) drug administration; (iii) disease management (follow-up and monitoring); (iv) treatments following progression; (v) *PIK3CA* mutation testing; (vi) the management of AEs, and (vii) end-of-life care. Drug acquisition and administration costs for each regimen are modelled as a function of the TTD survival functions for each regimen component, the planned treatment schedule, relative dose intensity (RDI) and unit costs. The analyses presented in the CS[1] include confidential price discounts for Alp, Eve and Fulv. [redacted]. At the request of NICE, the estimated discount for Fulv has been excluded from the results presented in this report. Disease management costs include those associated with clinical visits, examinations and tests. A fixed monthly cost associated with subsequent-line treatments (regimens not specified) is applied to all surviving patients in both treatment groups in all model cycles after disease progression. The cost of *PIK3CA* mutation testing is included as a once-only cost in the first model cycle for patients in the Alp/Fulv group. AE management costs and end-of-life care costs are applied as once-only costs in the first cycle and at the point of death, respectively. All cyclical costs are calculated using the half-cycle corrected model trace.

The incremental health gains, costs and cost-effectiveness for Alp/Fulv versus Eve/Exe are estimated over 40-year time horizon using 28-day cycles. No subgroup analyses are presented in the CS.[1]

5.2.3 Key assumptions employed in the company's model

The company's model employs the following key assumptions:

- All patients are assumed to be female
- Estimates of relative treatment effects on PFS and OS for Eve/Exe versus Alp/Fulv are based on the company's Bucher ITCs, which include SOLAR-1, but exclude BYLieve due to the single-arm design of this study (see Sections 4.8 and 4.9). The parametric survival distributions used for OS, PFS and TTD in each treatment group are summarised in Box 1 and Table 29, with further detail provided in Section 5.2.4.
- The company's survival analysis approach assumes that relative treatment effects for Alp/Fulv versus Eve/Exe persist over the patient's remaining lifetime.
- Within each treatment group, the model applies three constraints: (i) TTD must be less than or equal to PFS; (ii) PFS must be less than or equal to OS, and (iii) per-cycle PFS and OS risks for women with HR+, HER2− ABC with a *PIK3CA* mutation must be at least as high as the mortality risk for the age- and sex-matched general population. Aside from these constraints, the risks of progression and death are structurally unrelated.
- HRQoL is assumed to be dependent on health state, treatment group, whether the patient is still receiving that treatment, their proximity to death and age. HRQoL is assumed to be lower for Eve/Exe than Alp/Fulv whilst patients are progression-free and on-treatment.
- A QALY loss is applied at the point of death to reflect lower HRQoL during the last 84 days of life.
- Patients in the Alp/Fulv group who discontinue one component of the regimen may continue to receive the other component. Higher on-treatment utilities are assumed to apply even if the patient has discontinued part of the treatment regimen.
- No wastage is applied to drug acquisition costs.
- Costs associated with disease management, post-progression treatments and end-of-life care costs are assumed to be the same for both treatment groups.
- All patients who progress receive further treatment in all subsequent cycles. The mix of regimens received are not explicitly stated in the CS;[1] the monthly cost of these therapies is reported to be based on NICE TA593.[40]
- Only Grade 3-5 AEs occurring in ≥5% patients in one or both treatment groups in BYLieve or BOLERO-2 are included in the model. These AEs are assumed to lead to additional costs; impacts on HRQoL are assumed to be captured in the treatment-specific health utility values.
- *PIK3CA* mutation testing costs are applied to patients receiving Alp/Fulv, based on the assumption of a zero probability of an invalid test result.

5.2.4 Evidence used to inform the company's model parameters

Table 29 summarises the evidence sources used to inform the parameters of the company's base case model. These are discussed in detail in the subsequent sections.

Table 29: Summary of evidence used to inform the company's base case model

Parameter group	Alp/Fulv	Eve/Exe
Patient characteristics	Mean age is based on BYLieve Cohort A.[1] All patients are assumed to be female.	
OS	Log-logistic model fitted to observed OS data for second-line patients from Cohort A in BYLieve.[31]	Constant HR derived from Bucher ITC[1] (using second-line patients in SOLAR-1[28] BOLERO-2,[20] SoFEA[22] and CONFIRM[34] see Section 4.4) applied to Alp/Fulv OS model
General population mortality	National life tables for England 2017/2019[41]	
PFS	Log-normal model fitted to observed PFS data for second-line patients from Cohort A in BYLieve.[31]	Constant HR derived from Bucher ITC[1] (using second-line patients in SOLAR-1,[28, 42] BOLERO-2,[20] SoFEA[22] and CONFIRM[34] see Section 4.4) applied to Alp/Fulv PFS model.
TTD	Exponential models fitted to observed TTD data for second-line patients from Cohort A in BYLieve[31] (separate models were fitted for each regimen component).	HR for Eve/Exe TTD versus PFS from BOLERO-2[20] applied to Eve/Exe PFS model.
Health state utility values	GEE model fitted to EQ-5D data (5L mapped to 3L) from second-line population in SOLAR-1[28]	Same as Alp/Fulv group, but with progression-free on treatment utility decrement estimated using mapped EORTC QLQ-C30 data from BOLERO-2[20]
QALY loss terminal disease	Based on EQ-5D GEE model for second-line population of SOLAR-1[28]	
General population utility	Ara and Brazier[39]	
Drug acquisition and administration costs	CS[1] and BNF.[28] PAS for alpelisib proposed by company	BNF.[28] PAS for everolimus set by company
Dosing schedules and median RDIs	SOLAR-1[28] and BYLieve[43]	BOLERO-2[20]
Drug administration/ dispensing costs	PSSRU[44] and NHS Reference Costs 2019/20[45]	
Follow-up and monitoring costs	Various sources including NICE CG81[2], Alp draft SmPC[13] and Eve SmPC.[46] Unit costs from NHS Reference Costs 2019/20,[45] PSSRU,[44] Gillett *et al*,[47] and ONS CPI Annual Rate for Medical Services.[48]	
Post-progression treatment costs	Fixed cost per month applied to all patients in post-progression state, for both populations and both treatment groups; estimate based on data in NICE TA496[49]	
End-of-life costs	NICE CG81[2] (uplifted to 2020 using hospital health services index)	
PIK3CA test costs	Unit cost from Hamblin *et al*[50] (not uplifted to current prices); *PIK3CA* mutations prevalence from Mollon *et al*[51]	Not applicable
AEs costs	BYLieve Cohort A[31] and NHS Reference Costs 2019/20[45]	BOLERO-2[20] and NHS Reference Costs 2019/20[45]

Alp/Fulv - alpelisib plus fulvestrant; Eve/Exe - everolimus plus exemestane; PIK3CA - phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; OS - overall survival; PFS - progression-free survival; TTD - time to treatment discontinuation; BSA - body surface area; HR - hazard ratio; ITC - indirect treatment comparison; GEE - generalised estimating equation, EQ-5D - Euroqol 5-Dimensions; RCS restricted cubic spline ; eMIT - electronic Market Information Tool; RDI - relative dose intensity; PAS - Patient Access Scheme; PSSRU - Personal Social Services Research Unit; AE - adverse event; ONS - Office for National Statistics

Patient characteristics

At model entry, patients are assumed to have a mean age of 57 years, based on BYLieve.[31] All patients are assumed to be female.

Time-to-event model parameters

The company's overall approach to modelling OS, PFS and TTD in the model is summarised in Box 1. The approach used for each individual endpoint and each treatment group is described in further detail in the subsequent sections. Patients receiving Alp/Fulv as second-line therapy in Cohort A of BYLieve[31] (n=[redacted]) were used in each survival analysis for the intervention group. For the Eve/Exe comparator group, PFS and OS are derived by applying the inverse HRs from the company's Bucher ITCs (see Section 4.8) to the Alp/Fulv models as a baseline. For TTD in the Eve/Exe group, the ERG believes that all 54 patients in first-/second-line in BOLERO-2 were used to estimate the HR for TTD to PFS (data provided as part of the company's response during the earlier terminated appraisal of Alp).

Box 1: Summary of company's approach to modelling OS, PFS and TTD in the model

Alp/Fulv group

- OS: log-logistic model (second-line patients, BYLieve)
- PFS: log-normal model (second-line patients, BYLieve)
- TTD: exponential model (second-line patients, BYLieve)

Eve/Exe group

- OS: HR (derived from second-line Bucher ITC) applied to Alp/Fulv log-logistic OS model as baseline
- PFS: HR (derived from second-line Bucher ITC) applied to Alp/Fulv log-normal PFS model as baseline
- TTD: HR for TTD versus PFS (first- and second-line patients BOLERO-2*) applied to Eve/Exe PFS (log-normal) model as baseline

Alp/Fulv - alpelisib plus fulvestrant; Eve/Exe - everolimus plus exemestane; OS - overall survival; PFS - progression-free survival; TTD - time to treatment discontinuation; NMA - network meta-analysis; HR - hazard ratio.
**The ERG assumes that data on TTD for Eve/ Exe were based on first- and second-line patients in BOLERO-2 were used to estimate the HR for TTD versus PFS; however, this is not fully clear from the CS.[1]*

Overall survival

The cumulative probabilities of OS are modelled using different approaches for each treatment group. For the Alp/Fulv group, the company fitted a range of parametric survival models to the available IPD data for second-line patients from Cohort A of BYLieve (n=[redacted]).[31] These included exponential, Weibull, Gompertz, log-logistic, log-normal, generalised gamma, generalised F distributions and restricted cubic spline (RCS) models with one, two or three knots fitted on the log cumulative hazard, odds and inverse normal scale (referred to in the CS[1] as "Weibull" , "log-logistic" and "log-normal", respectively).

The Akaike Information Criteria (AIC), AIC with correction (AICc), and the Bayesian Information Criterion (BIC) statistics for each of the candidate models are presented in Figure 9. The Kaplan-Meier plot and modelled OS functions for the Alp/Fulv group are presented in Figure 10.

Figure 9: AIC, AICc and BIC statistics for OS, alpelisib plus fulvestrant (reproduced from CS, Figure 17)

AIC - Akaike Information Criterion; AICc - Akaike Information Criterion with correction; BIC - Bayesian information criterion; Gen - generalised; RCS - restricted cubic spline

Figure 10: Kaplan-Meier plot and modelled OS, alpelisib plus fulvestrant* (re-drawn by the ERG)

** Includes general population mortality constraint using life tables*
Base case (log-logistic) model shown in red.

The CS[1] states that the log-logistic model was selected for inclusion in the base case analysis on the basis of consideration of: relative goodness-of-fit statistics (the BIC criterion); visual inspection of the fitted distributions, an assumption that the projected OS would be equal to or higher than projected PFS (based on the view that the PFS data from BYLieve are more robust than the OS data); examination of hazard plots and validation by clinical expert opinion. The ERG notes that the log-logistic function was ranked third best in terms of AIC, AICc and BIC, and that the Gompertz and Weibull functions consistently provided a slightly better model fit than the log-logistic model. The six best-fitting OS models (log-logistic, Gompertz, Weibull, exponential, log-normal and RCS 1-knot "Weibull") were assessed in the company's sensitivity analyses (see CS,[1] Table 83).

For OS in the Eve/Exe group, the model applies a constant HR derived from the Bucher ITC (HR= [redacted], 95% CrI [redacted]), which was estimated using data on OS for second-line patients in SOLAR-1 and BOLERO-2, to the log-logistic OS model for the Alp/Fulv group. The CS[1] states that based on the test of linearity of Schoenfeld residuals the PH assumption was not violated in this population, therefore the Bucher method was considered appropriate. The Kaplan-Meier plot and modelled OS functions for the Alp/Fulv and Eve/Exe groups are presented in Figure 11. The ERG notes that the selected log-logistic model appears to over-estimate OS for the Alp/Fulv group after around 1.5 years, although very few events occur beyond this timepoint.

Figure 11: Kaplan-Meier plot and modelled OS, alpelisib and fulvestrant versus everolimus plus exemestane*† (re-drawn by the ERG)

** Includes general population mortality constraint using life tables*
†Kaplan-Meier plot for Eve/Exe group not available from company's model or CS

Progression-free survival

PFS for the Alp/Fulv group was modelled using the available IPD for second-line patients from Cohort A of BYLieve (n=).[31] The company fitted the same range of parametric survival models to the PFS data as for OS. The company selected the log-normal model for inclusion in their base case analysis through consideration of: relative goodness-of-fit statistics (AIC, AICc and BIC statistics, as presented in Figure 12, with BIC being used as the primary measure of statistical fit); visual inspection of the fitted distributions; hazard functions, time dependent HRs, diagnostic plots for treatment effects, and clinical plausibility.[1] The log-normal function had the lowest BIC and the fourth lowest AIC and AICc. The Kaplan-Meier plot and modelled PFS functions for Alp/Fulv are presented in Figure 13.

Figure 12: AIC, AICc and BIC statistics for PFS, fulvestrant plus alpelisib (reproduced from CS, Figure 12)

AIC - Akaike Information Criterion; AICc - Akaike Information Criterion with correction; BIC - Bayesian information criterion; Gen - generalised; RCS - restricted cubic spline

Figure 13: Kaplan-Meier plot and modelled PFS, alpelisib plus fulvestrant* (re-drawn by the ERG)

** Includes general population mortality constraint using life tables*

The six best-fitting PFS models (the log-normal, log-logistic, generalised gamma, RCS 3-knot log-normal, RCS 3-knot log-logistic, and RCS 3-knot Weibull) were assessed in the company's sensitivity analyses (see CS,[1] Table 82).

In keeping with the approach used to model OS, PFS for the Eve/Exe group was modelled by applying the HR from the Bucher ITC for PFS in second-line patients (HR=, 95% CrI) to the selected log-normal PFS model for the Alp/Fulv group as a baseline. The Kaplan-

Meier plot and modelled PFS functions for the Alp/Fulv and Eve/Exe groups are presented in Figure 14.

Figure 14: Observed Kaplan-Meier plot and modelled PFS, alpelisib plus fulvestrant versus everolimus plus exemestane* (drawn by the ERG)

** Includes general population mortality constraint using life tables*

Time to treatment discontinuation

TTD for patients receiving Alp/Fulv was modelled using observed time-to-event data from second-line patients from Cohort A in BYLieve[31] (n=). The company fitted the same range of parametric survival models to the available data separately for Alp and Fulv. The CS justifies estimating TTD separately for each regimen component on account of patients in BYLieve being allowed to discontinue Alp whilst permitted to continue receiving Fulv (CS,[1] page 122).

The AIC, AICc and BIC statistics for each of the candidate models for Alp and Fulv are presented in Figure 15 and Figure 16, respectively. The Kaplan-Meier plots and modelled TTD functions for Alp and Fulv are presented in Figure 17 and Figure 18, respectively.

Figure 15: AIC, AICc and BIC statistics for TTD, alpelisib (reproduced from CS, Figure 22)

AIC - Akaike Information Criterion; AICc - Akaike Information Criterion with correction; BIC - Bayesian information criterion; Gen - generalised; RCS - restricted cubic spline

Figure 16: AIC, AICc and BIC statistics for TTD, fulvestrant (reproduced from CS, Figure 26)

AIC - Akaike Information Criterion; AICc - Akaike Information Criterion with correction; BIC - Bayesian information criterion; Gen - generalised; RCS - restricted cubic spline

Figure 17: Observed Kaplan-Meier plot and modelled TTD, alpelisib* (re-drawn by the ERG)

** Includes general population mortality constraint using life tables*

Figure 18: Observed Kaplan-Meier plot and modelled TTD functions, fulvestrant* (re-drawn by the ERG)

** Includes general population mortality constraint using life tables*

The CS[1] (pages 126 and 130) states that the company selected the exponential model as their preferred TTD function for both Alp and Fulv through consideration of: the assumption that the probabilities of remaining on treatment should be lower than those for PFS; good visual fit, and relative goodness-of-fit statistics. The ERG notes that with respect to the Alp component of the regimen, the exponential is the third best-fitting model according to the BIC, but only the 13th best-fitting model according to the AIC. For Fulv, the exponential distribution is the second-best fitting model based on the BIC and the seventh best-fitting model based on the AIC.

The six best-fitting TTD models for each component (exponential, log-normal, log-logistic, Gompertz, generalised gamma and RCS 1-knot log-normal) were assessed in the company's sensitivity analyses (see CS,[1] Tables 84 and 85).

Within the Eve/Exe group, the company fitted a Cox PH model to the available IPD on TTD and PFS data from patients in BOLERO-2[20] to derive a constant HR (1.27; 95% CI 1.01 to 1.60) for PFS versus TTD for Eve/Exe. A single function was used to represent TTD for both regimen components as data for each individual drug were not available. The CS[1] notes that the approach used in the model was considered reasonable in avoiding overestimation of the costs for Eve/Exe, as the model includes separate RDI estimates in the calculation of drug acquisition costs for each regimen component. The ERG believes that all 54 patients in first-/second-line in BOLERO-2 were used to estimate the HR for TTD to PFS, although this is not fully clear from the CS.

TTD for the Eve/Exe group was estimated by applying this HR to the PFS model for Eve/Exe, which in turn, was estimated by applying the HR from the Bucher ITC to the Alp/Fulv log-normal PFS model. Hence, this approach combines two HRs applied to the log-normal PFS model function for Alp/Fulv (combined HR= [redacted]). The CS[1] (page 130) justifies this approach on the basis that it *"ensure[d] that the TTD was consistent with the PFS estimated based on the ITC of HRs for PFS."* The CS also states that the PH assumption was assessed through examination of Schoenfeld residuals, and that the assumption was not violated ($p>0.05$). Figure 19 presents the observed Kaplan-Meier plots and modelled TTD functions for Alp, Fulv, Eve and Exe.

Figure 19: Observed Kaplan-Meier plots and modelled TTD, alpelisib, fulvestrant, everolimus and exemestane* (re-drawn by the ERG)

** Includes general population mortality adjustment*
Dashed red line shows the time spent in PFS on treatment in which the PFS on-treatment utility is applied

Health-related quality of life

The BYLieve study[31] did not include the measurement of HRQoL, whilst SOLAR-1[28] included data collection using the EQ-5D-5L questionnaire. Within SOLAR-1, the EQ-5D-5L questionnaire was administered 1 to 28 days before randomisation (baseline), before any study drug administration at the visits indicated in every eight weeks after randomisation during the first 18 months, and every 12 weeks thereafter until disease progression, death, withdrawal of consent, loss to follow-up subject/guardian decision, and at the end of treatment assessment.[42]

The company's economic analyses use data from second-line only patients in SOLAR-1[28] as the main source of HRQoL data. The company mapped the EQ-5D-5L data to the EQ-5D-3L using the algorithm reported by Van Hout *et al*[52] and fitted six GEE regression models to the SOLAR-1 dataset.[28] The models included selected covariates including baseline utility, status of treatment (receipt of treatment whilst event-free) by treatment group, health state, and proximity to death, whilst accounting for repeated measures in the same patient. A forward selection process was used to select the final regression model. The final selected model, which was the most comprehensive of those considered, included all of the following terms: (i) an intercept; (ii) a covariate for baseline utility value; (iii) treatment-group specific covariates for being progression-free and on treatment; (iv) a covariate for the post-progression state, and (v) a covariate for assessments occurring within 84 days of death.

Utility values for the progression-free (on-treatment or post-discontinuation) and post-progression states were estimated, together with a disutility which reflects deterioration in HRQoL during the final 84 days before death. Utilities for the progression-free on-treatment state are assumed to differ between

the treatment groups, whilst utilities for the post-progression state and the terminal phase decrement are assumed to be independent of treatment group. For Eve/Exe, the company mapped EORTC QLQ-C30 data collected in BOLERO-2[20] to the EQ-5D-3L and estimated a relative utility decrement between Eve/Exe versus Exe. This disutility was then applied to the utility value for the Fulv group of SOLAR-1, based on the assumption that Exe and Fulv are equivalent.

The model does not include any further HRQoL decrements associated with Grade 3/4 AEs for Alp/Fulv or Eve/Exe. The CS[1] (page 134) states that such effects would already have been captured in the EQ-5D data collected from patients event-free and on treatment in SOLAR-1. The QALY loss associated with the terminal phase of the disease is applied in the model at the point of death.

The characteristics of the EQ-5D data from SOLAR-1[28] and the health utility values applied in the company's model are summarised in Table 30. Utility estimates were adjusted for age using absolute decrements derived from Ara and Brazier[39] based on the mean patient age at model entry (57 years).

Table 30: Numbers of patients and EQ-5D-3L assessments used in the GEE regressions using data from second-line patients in SOLAR-1 and utility values used in company's model (adapted from CS, Tables 61 and 63)

Health state	N patients		N assessments		Mean utility (95% CI)	
	Alp/Fulv	Pbo/Fulv	Alp/Fulv	Pbo/Fulv	Alp/Fulv	Eve/Exe
Progression-free, on treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progression-free, off treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Post-progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Terminal phase disutility	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Alp/Fulv - alpelisib plus fulvestrant; Eve/Exe - everolimus plus exemestane; Pbo/Fulv - placebo plus fulvestrant; CI - confidence interval
**Calculated by applying decrement between Eve/Exe and Exe in mapped BOLERO-2 data to GEE model estimate for Pbo/Fulv*

Resources and costs

The model includes costs associated with: (i) drug acquisition; (ii) drug administration (iii) disease management (follow-up and monitoring); (iv) treatments following progression; (v) *PIK3CA* mutation testing; (vi) management of AEs; and (vii) end-of-life care. Table 31 summarises the costs applied within the model.

Table 31: Summary of costs applied in the company's model (including PAS discounts for alpelisib and everolimus)

Cost parameter(s)	Alp/Fulv	Eve/Exe
Drug acquisition costs (per 28-day cycle)*	Alp: [redacted] Fulv: £1,044.82 (loading); £522.41 (ongoing)	Eve: [redacted] Exe: £5.21
Drug administration costs (per 28-day cycle)	Alp: £10.40 Fulv: £136.03 (loading); £83.46 (ongoing)	Eve: £53.50 Exe: £10.40
Disease management – progression-free on treatment, initial treatment (once-only)	£71.31	£2.58
Disease management – progression-free on treatment (per 28-day cycle)	£251.41	£229.95
Disease management – progression-free off treatment (per 28-day cycle)	£229.55	£229.55
Disease management – post-progression (per 28-day cycle)	£253.01	£253.01
Post-progression treatment costs (per 28-day cycle)	£1,379.88	£1,379.88
PIK3CA mutation testing (once-only)	£699.29	N/a
Grade 3+ AEs (once-only)	£254.54	£276.46
End-of-life care (once-only)	£6,143.77	£6,143.77

Alp/Fulv - alpelisib plus fulvestrant; Eve/Exe - everolimus plus exemestane; PAS - Patient Access Scheme; PIK3CA - Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; AE - adverse event
**Drug acquisition costs do not include RDI adjustments*

Drug acquisition costs

All drugs are costed according to a 28-day cycle length. Based on its list price, the cost per pack of 28 x 300mg Alp tablets (28 days' supply) is [redacted]. The company has proposed a PAS which takes the form of a simple price discount of [redacted]; the discounted cost per pack of Alp is [redacted]. Fulv is assumed to be administrated via two subcutaneous injections of 500mg each, twice in the first 28-days cycle (the "loading phase") and one injection in all subsequent cycles (the "ongoing phase"); drug prices were taken from the British National Formulary (BNF),[24] and an assumed price discount of [redacted] is applied for Fulv[1] (this discount is excluded from the results presented within this report). Within the company's model, the acquisition costs of Alp and Fulv are estimated separately as a function of the unit cost per pack, the planned treatment schedules from SOLAR-1, the amount of planned treatment received in BYLieve (Alp mean RDI=[redacted]; Fulv mean RDI=[redacted])[28] and TTD for each regimen component. Drug acquisition and administration costs for Eve and Exe are also calculated as a function of the unit cost per pack, the planned treatment schedules from BOLERO-2, the RDI for each regimen component (Eve mean RDI=0.79; Exe mean RDI=0.98)[20] and TTD for both regimen components combined. Drug prices for Eve and Exe were taken from the British National Formulary (BNF)[24] and the electronic Market Information Tool (eMIT)[53] published by the Commercial Medicine Unit (CMU). A price discount of [redacted] is included for Eve as part of the company's existing commercial access agreement. Wastage is not included for any of the four drugs included in the model.

Drug administration costs

Administration costs for Alp/Fulv and Eve/Exe were based on Curtis and Burns[44] and NHS Reference Costs 2019/20,[45] together with additional assumptions.[1] The administration costs for all oral drugs (Alp, Eve and Exe) were assumed to be subject to a dispensing fee, obtained by multiplying the average time spent per patient for dispensing treatment by the hourly rate of a hospital pharmacist.[44] Administration costs for Fulv are assumed to include an initial consultation with an oncologist from NHS Reference Costs 2018/19[45] (WF01B – consultant led non-admitted face-to-face; service code 370 - Medical Oncology) and assuming a cost of £83.46 thereafter. The model also assumes an additional visit for 25% of patients receiving Eve/Exe for the administration of intravenous bisphosphonates for the treatment of bone metastases.[1] As with the drug acquisition costs, administration costs are modelled as a function of the TTD for each treatment regimen component.

Medical resource use associated with treatment assignment

Disease management costs include visits to general practitioners (GPs), consultant oncologists, nurses and social workers; diagnostic imaging procedures (computerised tomography [CT]); and laboratory tests (complete blood counts [CBCs], FPG and HbA1c monitoring). The model includes three sets of costs:

(i) Once-only costs which correspond to procedures related to treatment initiation. These are applied in the first model cycle to all patients in the progression-free state and are assumed to differ between the treatment groups.

(ii) Disease management costs for patients in the progression-free state. These are applied in every cycle and include two subsets of resource costs: (a) the same type and frequency of clinical visits and CT scans, regardless of status of treatment (on or off treatment) and treatment group; and (b) additional tests received by patients whilst progression-free and on treatment which vary by treatment group.

(iii) Disease management costs for patients in the post-progression state. These are assumed to be the same for all patients, regardless of treatment group and include a fixed frequency of visits and procedures each month.

Resource use assumptions were based on NICE Clinical Guideline 81 (CG81),[2] previous NICE technology appraisals (TAs; not specified in the CS[1]) and the draft/published SmPCs for Alp[13] and Eve.[46] Unit costs were taken from NHS Reference Costs 2019/20,[45] Personal Social Services Research Unit (PSSRU) 2020,[44] and Gillett *et al*[47] (inflated using the Consumer Price Index [CPI], where appropriate). All disease management costs are estimated per 28 days of treatment. Resource use and cost assumptions by health state are summarised in Table 32.

Table 32: Summary of health state resource use and costs (monthly and per 28-day cycle)

Resource component	Resource use						Unit cost	Total Costs					
	Initial treatment (one-off)		PF on tx (per month)		PF off tx (per month)	PP (per month)		Initial treatment (one-off)		PF on tx (per month)		PF off tx (per month)	PP (per month)
	A+F	E+E	A+F	E+E				A+F	E+E	A+F	E+E	A+F and E+E	A+F and E+E
GP visits	0.00	0.00	0.30	0.30	0.30	0.30	£39.23	£0.00	£0.00	£11.77	£11.77	£11.77	£11.77
Oncology consultant	0.00	0.00	0.20	0.20	0.20	0.20	£153.55	£0.00	£0.00	£30.71	£30.71	£30.71	£30.71
Community nurse	0.00	0.00	0.30	0.30	0.30	0.30	£39.00	£0.00	£0.00	£11.70	£11.70	£11.70	£11.70
Clinical nurse specialist	0.00	0.00	1.00	1.00	1.00	1.00	£50.00	£0.00	£0.00	£50.00	£50.00	£50.00	£50.00
Social worker	0.00	0.00	0.00	0.00	0.00	0.50	£51.00	£0.00	£0.00	£0.00	£0.00	£0.00	£25.50
CT scan	0.00	0.00	1.00	1.00	1.00	1.00	£145.35	£0.00	£0.00	£145.35	£145.35	£145.35	£145.35
CBC	0.00	1.00	0.00	0.17	0.00	0.00	£2.58	£0.00	£2.58	£0.00	£0.44	£0.00	£0.00
FPG	3.00	0.00	1.00	0.00	0.00	0.00	£18.03	£54.10	£0.00	£18.03	£0.00	£0.00	£0.00
HbA1c monitoring	1.00	0.00	0.33	0.00	0.00	0.00	£17.20	£17.20	£0.00	£5.73	£0.00	£0.00	£0.00
Total (monthly)								**£71.31**	**£2.58**	**£273.30**	**£249.97**	**£249.53**	**£275.03**
Total (per 28-day cycle)								**£71.31**	**£2.58**	**£251.41**	**£229.95**	**£229.55**	**£253.01**

A+F - alpelisib plus fulvestrant; E+E - everolimus plus exemestane; PF - progression-free; PP - post-progression; tx - treatment; GP - general practitioner; CT - computer tomography; CBC complete blood count; FPG - fasting plasma glucose

Post-progression treatment costs

The costs associated with treatments received following disease progression are assumed to be £1,500 per month (£1,379.88 per 28-day cycle). This cost estimate was based on a value originally reported in NICE TA496[49] and is applied to all patients in all cycles following disease progression. The ERG notes that it is not clear which treatments and which resource components (e.g., administration, hospitalisations, other procedures) are included in this assumed cost.

PIK3CA mutation test costs

The unit cost per *PIK3CA* mutation test is assumed to be £261.42, based on Hamblin *et al.*,[50] uplifted to 2020 prices using the medical services CPI.[48] The model assumes a prevalence of *PIK3CA* mutations among breast cancer patients of 36.4%, based on Mollon *et al.*,[51] which implies that 2.75 breast cancer patients would need to be tested in order to identify one patient with a *PIK3CA* mutation. The model assumes that no tests would yield invalid results. This results in a *PIK3CA* test cost of £718.19 per treatment-eligible patient, which is applied as a once-only cost to all patients in Alp/Fulv group. The ERG notes that in the company's original model, a lower cost of £699.29 was applied, based on a unit cost of £254.54. As part of their clarification response (question B12),[14] the company submitted an updated version of the model using the correct higher value of £718.19. This amendment is included as part of the ERG's exploratory analyses (see Section 5.4).

AE costs

Costs related to the management of AEs are applied once-only during the first model cycle, based on the frequency of individual Grade 3/4 AEs in BYLieve[31] and BOLERO-2[20] and NHS Reference Costs 2019/20.[45] Only AEs with an incidence ≥5% in either treatment group were included, with an assumed duration of one month. The AE frequencies and costs used in the model are summarised in Table 33.

Table 33: Frequency of Grade 3/4 AEs and associated costs (taken from the company's model)

AE	AE incidence		Unit cost	Total costs	
	A+F	E+E		A+F	E+E
Anaemia	[redacted]	8.0%	£601.37	£0.00	£48.11
Diarrhoea		3.0%	£151.03	£8.32	£4.53
Dyspnoea		6.0%	£2,203.86	£52.06	£132.23
Fatigue		5.0%	£151.03	£1.19	£7.55
Hyperglycaemia		6.0%	£552.78	£156.69	£33.17
Increased GGT		7.0%	£151.03	£0.00	£10.57
Rash		1.0%	£151.03	£14.27	£1.51
Rash maculopapular		0.0%	£151.03	£14.27	£0.00
Stomatitis	[redacted]	8.0%	£484.89	£7.64	£38.79
Total				**£254.54**	**£276.46**

A+F - alpelisib plus fulvestrant; E+E - everolimus plus exemestane; GGT - gamma-glutamyl transpeptidase

End-of-life care costs

The cost of end-of-life care was assumed to be £6,143.77, based on NICE CG81,[2] (including inflation to 2020 prices based on the Office for National Statistics (ONS) Hospital Health Services Index[48]). This is applied as a once-only cost at the point of death.

5.2.5 Model evaluation methods

The CS[1] presents base case incremental cost-effectiveness ratios (ICERs) for Alp/Fulv versus Eve/Exe. Results are presented using both the deterministic and probabilistic versions of the model; the probabilistic ICERs are based on 1,000 Monte Carlo simulations. The results of the probabilistic sensitivity analysis (PSA) are also presented as cost-effectiveness planes and as cost-effectiveness acceptability curves (CEACs). The CS also reports a number of deterministic sensitivity analyses (DSAs) and scenario analyses exploring the use of alternative parametric models, alternative values for HRs used to estimate outcomes in the Eve/Exe group and alternative assumptions regarding costs, utilities, the time horizon and discount rates. The distributions used in the company's PSA are presented in CS Table 79; for the sake of brevity, this information is not reproduced here.

5.2.6 Company's model validation and face validity check

The CS[1] (pages 174 to 175) describes a number of measures taken by the company to verify the executable model. These include white-box testing (assessing the integrity of the underlying formulae and programming code) and black-box testing (assessing the behaviour of the model). The CS also describes the use of clinical input to inform assumptions relating to patient characteristics, the treatment pathway, survival modelling, resource use and cost assumptions and AEs.

5.2.7 Company's cost-effectiveness results

This section presents the results of the company's economic analyses. All results include the PAS for Alp and Eve; the cost of Fulv is based on the list price for this drug. The amendments applied in the company's updated model provided following the clarification round are not presented separately here as they are minor; instead, these are included as part of the ERG's exploratory analyses in Section 5.4.

Company's central estimates of cost-effectiveness

Table 34 presents the central estimates of cost-effectiveness generated using the company's model for the comparison of Alp/Fulv versus Eve/Exe. The probabilistic version of the company's model suggests that Alp/Fulv is expected to generate an additional [redacted] QALYs at an additional cost of [redacted] per patient compared with Eve/Exe; the corresponding ICER is £68,880 per QALY gained. The deterministic version of the model produces a lower ICER of £60,462 per QALY gained. As shown in Table 34, there is a marked difference in incremental life years gained (LYGs) between the probabilistic and deterministic versions of the model; this is discussed further in Section 5.3.4.

Table 34: Company's base case results – alpelisib plus fulvestrant versus everolimus plus exemestane, including PAS discounts for alpelisib and everolimus (generated by the ERG)

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. Costs	ICER
Probabilistic model							
Alp/Fulv	2.71	[redacted]	[redacted]	0.54	[redacted]	[redacted]	**£68,880**
Eve/Exe	2.17	1.35	[redacted]	-	-	-	-
Deterministic model							
Alp/Fulv	2.58	[redacted]	[redacted]	0.76	[redacted]	[redacted]	**£60,462**
Eve/Exe	1.81	1.21	[redacted]	-	-	-	

Alp/Fulv - alpelisib plus fulvestrant; Eve/Exe - everolimus plus exemestane; ICER - incremental cost-effectiveness ratio; Inc. - incremental; LYG - life year gained; QALY - quality-adjusted life year
** undiscounted*

Company's PSA results

Figure 20 presents CEACs for Alp/Fulv versus Eve/Exe generated by the ERG. Assuming willingness-to-pay (WTP) thresholds of £30,000 and £50,000 per QALY gained, the company's model suggests that the probability that Alp/Fulv generates more net benefit than Eve/Exe is 0.00 and 0.27, respectively.

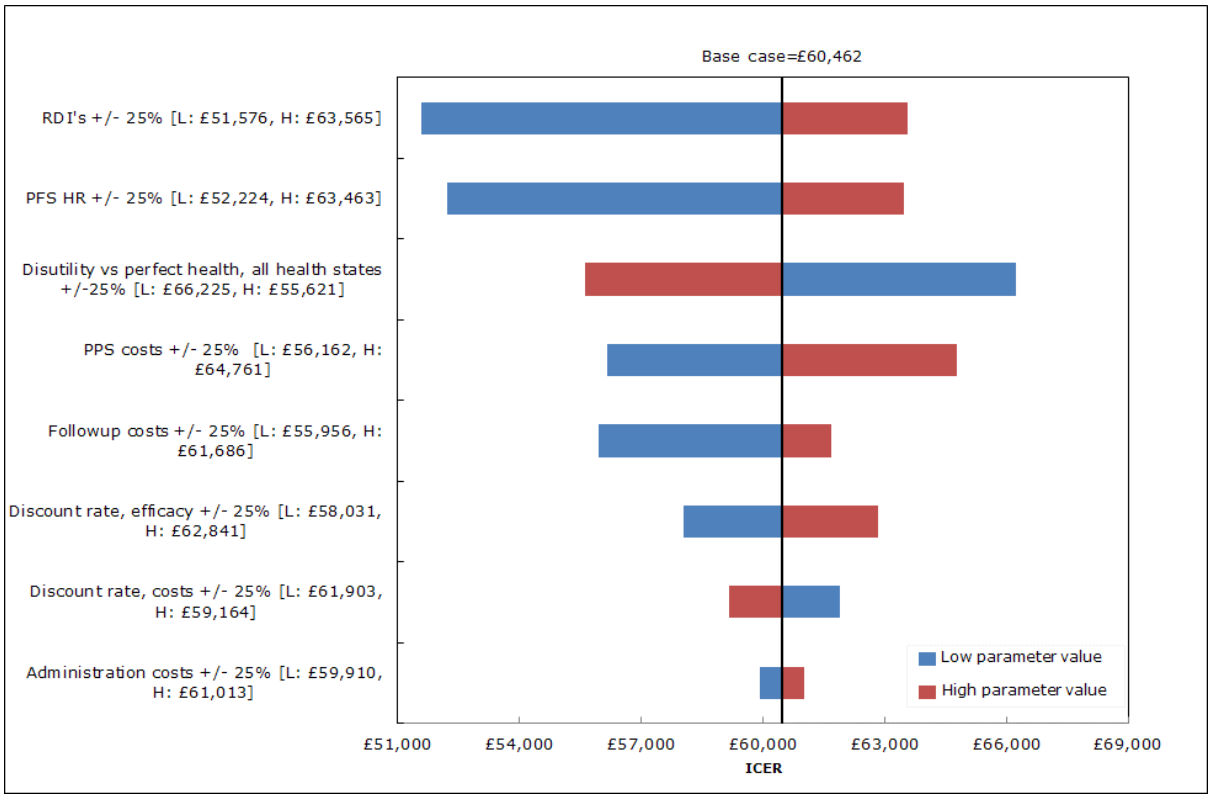
Figure 20: Company's PSA results – CEACs, alpelisib plus fulvestrant versus everolimus plus exemestane, including PAS discounts for alpelisib and everolimus (generated by the ERG)

Alp - alpelisib; Fulv - fulvestrant; Eve - everolimus; Exe - exemestane

Company's DSA results

The company's tornado plot is shown in Figure 21. The plot indicates that the HR for PFS, the RDIs for all regimen components, utility age-adjustments, post-progression drug costs and follow-up costs have a reasonably large impact on the ICER for Alp/Fulv versus Eve/Exe. The lowest ICER generated from the DSAs is £51,576 per QALY gained. The ERG notes that the HR for OS does not appear in the tornado plot – this is because the ranges used in the DSA are based on +/-25% of the point estimate. The ICERs generated using the 95% CI from the Bucher ITC of OS ([redacted]) result in ICERs ranging from dominated to £44,127 per QALY gained.

Figure 21: Company's DSA results – tornado plot, alpelisib plus fulvestrant versus everolimus plus exemestane, including PAS discounts for alpelisib and everolimus (generated by the ERG)



RDI - relative dose intensity; PPS - post-progression survival; HR - hazard ratio; L - low; H - high

Company's scenario analysis results

Table 35 presents a summary of the results of the company's scenario analyses. Across all of the scenarios assessed, the ICER for Alp/Fulv versus Eve/Exe ranged from £43,264 per QALY gained (post-progression treatment costs excluded) to £127,126 per QALY gained (Alp/Fulv OS modelled using Gompertz distribution).

Table 35: Summary of company's scenario analysis results - alpelisib plus fulvestrant versus everolimus plus exemestane, including PAS discounts for alpelisib and everolimus (generated by the ERG)

Scenario analysis set	Scenario description	ICER / range (per QALY gained)
-	Base case (deterministic)	£60,462 per QALY gained
1	Alp/Fulv - alternative PFS models (6 best-fitting models)	£49,825 per QALY gained (RCS 3-knot log-logistic) to £60,462 per QALY gained (log-normal)
2	Alp/Fulv - alternative OS models (6 best-fitting models)	£52,860 per QALY gained (log-normal) to £127,126 per QALY gained (Gompertz)
3	Alp/Fulv - alternative alpelisib TTD models (6 best-fitting models)	£60,462 QALY gained (exponential) to £66,476 per QALY gained (Gompertz)
4	Alp/Fulv - alternative fulvestrant TTD models (6 best-fitting models)	£60,462 per QALY gained (exponential) to £60,777 per QALY gained (log-logistic)
5	Eve/Exe - HRs for PFS, OS and TTD	£44,127 per QALY gained (upper bound of 95% CI for HR for OS) to £63,012 per QALY gained (upper bound of 95% CI for HR for TTD vs PFS)
6	Cost scenarios - excluding certain cost components from model	£43,264 per QALY gained (post-progression costs excluded) to £60,755 per QALY gained (terminal care costs excluded)
7	Utility scenarios - 95% CI limits for individual utility values	£58,528 per QALY gained (upper bound of 95% CI for PPS utility from SOLAR-1) to £74,552 per QALY gained (PPS utility values from Lloyd *et al*.[54])
8	Time horizon - 10, 20 or 40 years	£60,462 per QALY gained (40 years) to £64,346 per QALY gained (10 years)
9	Discount rates for health outcomes and costs (3.5%, 1.5% or 6%)	£58,044 per QALY gained (discount rate=1.5%) to £63,361 per QALY gained (discount rate=6%)

Alp - alpelisib; Fulv - fulvestrant; Eve - everolimus; Exe - exemestane; ICER - incremental cost-effectiveness ratio; QALY - quality-adjusted life year; PFS - progression-free survival; PPS - post-progression survival; RCS - restricted cubic spline; OS - overall survival; TTD - time to treatment discontinuation; HR - hazard ratio; CI - confidence interval

5.3 Critical appraisal of the company's health economic analysis

The ERG adopted a number of approaches to explore, interrogate and critically appraise the company's submitted economic analyses and the underlying health economic model upon which these were based. These included:

- Consideration of key items contained within published economic evaluation and health economic modelling checklists.[55, 56]
- Scrutiny of the company's model by health economic modellers and discussion of issues identified amongst the members of the ERG.
- Double-programming of the deterministic version of the company's model to fully assess the logic of the company's model structure, to draw out any unwritten assumptions and to identify any apparent errors in the implementation of the model.
- Double-programming of the company's PSA sampling for OS and PFS.

- Examination of the correspondence between the description of the model reported in the CS[1] and the company's executable model.
- Replication of the base case results, PSA, DSAs and scenario analyses reported in the CS.[1]
- Examination of certain parameter values used in the PSA.
- Where possible, checking of key parameter values used in the company's model against their original data sources.
- The use of expert clinical input to judge the credibility of the company's economic evaluation and the assumptions underpinning the model.

5.3.1 Model verification and replication of the company's health economic analyses

The ERG rebuilt the deterministic version of the company's base case in order to verify its implementation. As shown in Table 36, the ERG's results are almost identical to those generated using the company's submitted model. During the process of rebuilding the model, the ERG identified a small number of minor errors; these are discussed in further detail in Section 5.3.4. Overall, the ERG is satisfied that the company's model has been implemented without significant programming error.

Table 36: Comparison of company's base case results and ERG's rebuilt model results (excluding corrections of errors), includes alpelisib and everolimus PAS discounts

	Company's model			ERG's rebuilt model		
Outcome	**Alp/Fulv**	**Eve/Exe**	**Inc.**	**Alp/Fulv**	**Eve/Exe**	**Inc.**
LYGs*	2.58	1.81	0.76	2.58	1.81	0.76
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER	-	-	**£60,462**	-	-	**£60,498**

** Undiscounted*
Alp - alpelisib; Fulv - fulvestrant; Eve - everolimus; Exe - exemestane; ERG - Evidence Review Group; LYG - life year gained; QALY - quality-adjusted life year gained; Inc. - incremental; ICER - incremental cost-effectiveness ratio

5.3.2 Correspondence of the model inputs and the original sources of parameter values

Where possible, the ERG checked the company's model inputs against their original sources, although many of these were drawn from unpublished analyses of SOLAR-1[18] and BYLieve.[31] The ERG was able to check that the parametric survival models fitted to data from BYLieve and the GEE models for EQ-5D were implemented appropriately in the executable model, but did not have access to the IPD to check that the statistical models had been fitted appropriately. In addition, the ERG was unable to check some of the frequencies of tests and clinical visits used to calculate disease management costs with the original sources reported in the CS.[1]

The CS[1] states that the model assumes a monthly cost of post-progression treatments of £1,500 per month based on the cost accepted by the ERG in TA687,[8] which relates to the CDF guidance review of TA593 (ribociclib with fulvestrant for treating HR+ HER2- ABC after ET). The Committee papers for

TA687 do not mention directly this value and the original committee papers for TA593 are no longer publicly available from the NICE website. However, the ERG notes that the value of £1,500 is mentioned in TA496 (ribociclib with fulvestrant for treating HR+ HER2-negative ABC)[49] as the monthly cost of subsequent therapies used in the company's revised base-case. In TA496, the Appraisal Committee *"concluded that it would consider costs in the region of £1,140 to £1,200 in its decision making."* The impact of alternative post-progression treatment costs is assessed in the ERG's exploratory analyses (see Section 5.4).

The ERG also notes that it is unclear from the CS[1] how the ongoing administration costs for Fulv (£136.03 and £83.46) and the costs of the administration of intravenous bisphosphonates for the treatment of bone metastases for patients receiving Eve/Exe (£43.10) were derived from the NHS Reference Costs.[45]

The company's model assumes an RDI of [redacted] for Fulv, based on the First Interpretable Results report from BYLieve.[43] However, the relevant table in this report does not present any values for Fulv in Cohort A. The ERG is unclear regarding the source of this value.

5.3.3 Adherence of the company's model to the NICE Reference Case

The company's economic analysis is generally in line with the NICE Reference Case[57] (see Table 37). The most notable issues relate to the exclusion of CDK4/6 inhibitors plus Fulv, Exe and Tam as comparators and uncertainty regarding the relevance of the economic analysis if the Type II variation to the current licence is not granted by the MHRA.

Table 37: Adherence of the company's economic analyses to the NICE Reference Case

Element	Reference case	ERG comments
Defining the decision problem	The scope developed by NICE	With the exception of the comparators assessed, the company's economic analyses are generally in line with the final NICE scope.[12] The base case analysis reflects a subset of the patient population recruited into Cohort A of BYLieve[31] (second-line only, CDK4/6i+AI-experienced). As discussed in Section 5.3.4 (critical appraisal point [3]), BYLieve is not in line with the wording of the current EMA licence.[13] The relevance of the company's economic analysis is dependent on whether the MHRA grants a Type II variation to the current EMA licence.
Comparator(s)	As listed in the scope developed by NICE	The final NICE scope[12] lists four comparators: (i) CDK4/6 inhibitors (ribociclib, abemaciclib and palbociclib) plus Fulv (ii) Eve/Exe; (iii) Exe and (iv) Tam. The company's model includes only Eve/Exe as a comparator, based on the view that: (i) patients who have already received a CDK4/6i are not usually retreated with these therapies, and (ii) Tam and Exe monotherapy are not widely used in UK practice. The ERG believes that it is reasonable to exclude CDK4/6i+Fulv and Exe as comparators for the reasons given by the company, but notes that some patients are treated with Fulv or Tam as monotherapy. The ERG's clinical advisors noted that single-agent chemotherapy might be offered to patients at risk of visceral crisis, although endocrine options would usually be offered first.
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Health gains accrued by patients are valued in terms of QALYs gained. Impacts on caregivers are not included.
Perspective on costs	NHS and PSS	The analysis adopts an NHS and PSS perspective.
Type of economic evaluation	Cost-utility analysis with fully incremental analysis	The results of the company's base case analysis are presented in terms of the incremental cost per QALY gained for Alp/Fulv versus Eve/Exe.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The model adopts a 40-year time horizon. At this timepoint, virtually all patients in the model have died.
Synthesis of evidence on health effects	Based on systematic review	Relative treatment effects were estimated using Bucher ITCs using studies identified through the company's SLR.[20, 22, 28, 34] BYLieve[31] does not contribute to this evidence network: estimates of relative treatment effects for Alp are instead drawn from SOLAR-1.

Element	Reference case	ERG comments
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults.	Health state utility values are based on EQ-5D-5L data collected in SOLAR-1[28] (mapped to the 3L version) and EORTC QLQ-C30 data collected in BOLERO-2[20] (mapped to the EQ-5D-3L). Utilities were valued using the UK tariff.
Source of data for measurement of HRQoL	Reported directly by patients and/or carers	
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	No additional equity weighting is applied to estimated QALY gains.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Resource costs include those relevant to the NHS and PSS. Unit costs were valued at 2019/20 prices.
Discount rate	The same annual rate for both costs and health effects (currently 3.5%)	Costs and health effects are discounted at a rate of 3.5% per annum.

CDK4/6i - cyclin-dependent kinase 4/6 inhibitor; Eve/Exe - everolimus plus exemestane; Exe - exemestane; NHS - National Health Service; PSS - Personal Social Services; QALY - quality-adjusted life year; HRQoL - health-related quality of life; EQ-5D - Euroqol 5-Dimensions; EORTC QLQ-C30 - European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30

5.3.4 Main issues identified within the ERG's critical appraisal

The main issues identified from the ERG's critical appraisal are summarised in Box 2. These are discussed in further detail in the subsequent sections.

Box 2: Summary of main issues identified within the ERG's critical appraisal

(1) Model errors
(2) Relevant comparators excluded from economic analysis
(3) Uncertainty surrounding the relevance of the economic analysis to the target population
(4) Relevant subgroups excluded from economic analyses
(5) Uncertainty surrounding relative treatment effects for Alp/Fulv versus Eve/Exe
(6) Issues relating to survival modelling
(7) Concerns regarding company's HRQoL assumptions
(8) Concerns regarding company's cost assumptions
(9) Discrepancy between deterministic and probabilistic model results
(10) Limited model functionality

(1) Model errors

The ERG's double-programming exercise did not identify any major programming errors within the company's implemented model. However, during this process, the ERG identified three minor errors in the company's original submitted model relating to: (a) the use of median HRs; (b) the incorrect calculation of administration of Eve and (iii) the use of an incorrect cost estimate for *PIK3CA* testing.

(a) Use of median estimates of HRs

The HRs for PFS and OS used in the deterministic version of the model are based on the point estimates obtained from the Bucher ITCs. These are equivalent to median values, which ignore the skewness in the distribution. This contributes to the discrepancy between the results of the deterministic and probabilistic versions of the model (see Table 34). Usually, the ERG would suggest that it would be appropriate to add half the variance (σ^2) to the log of the HR (μ) and then to exponentiate this function to obtain an estimate of the mean HR. However, the interpretation of the HR differs depending on the comparison being made (Alp/Fulv versus Eve/Exe or Eve/Exe Alp/Fulv) as the distribution is positively skewed in both cases. Counterintuitively, using this approach to estimate the mean HRs for PFS and OS for Eve/Exe versus Alp/Fulv in the deterministic version of the model increases the discrepancy between the results of the deterministic and probabilistic versions of the model. Whilst the ERG believes that it is more appropriate to use mean estimates of the HR in economic models, this may lead to misleading results when applied to the deterministic model in this particular case. This issue is discussed further in critical appraisal point [9].

(b) Incorrect administration costs for Eve used

According to the CS[1] (Tables 65 and 66), Eve is available in packs of 30 tablets, but its dosage schedule is set as 28-days cycles in the model. In response to a request for clarification from the ERG (question B13),[14] the company confirmed that in the original submitted model, the administration and dispensing costs related to Eve were not adjusted to reflect the difference between the number of tablets in a pack and the cycle length in the model (30 tablets, 28 days per cycle). An updated version of the model was submitted following the clarification response, where this error was fixed. The impact of this error is small, increasing the ICER from £60,462 to £60,512 per QALY gained.

(c) Incorrect cost for PIK3CA test used

As discussed in Section 5.3.2, the executable model includes an expected cost of *PIK3CA* mutation testing per treatment-eligible patient of £699.29 (based on unit cost of £254.54), whilst the CS[1] states that the cost used is £718.19 (based on unit cost of £261.42). In response to clarification question B12,[14] the company confirmed that the original model had used an incorrect unit cost estimate, and corrected this in the updated version of the model. This error also has a minor impact on the results: the ICER from £60,462 to £60,503 per QALY gained.

These issues are addressed as part of the ERG's exploratory analyses in Section 5.4.

(2) Relevant comparators excluded from economic analysis

The final NICE scope[12] includes four comparators: (i) CDK4/6 inhibitors (ribociclib, abemaciclib and palbociclib) + Fulv (ii) Eve/Exe; (iii) Exe and (iv) Tam. However, the company's model includes only a single comparator - Eve/Exe. As discussed in Section 3.3, the CS states that Exe and Tam were not considered as relevant comparators as *"they are not widely used in UK clinical practice in this setting and are therefore not considered standard of care"* (CS,[1] Table 1, page 13). The ERG's clinical advisors agreed that Eve/Exe is the main relevant comparator for patients in the post-CDK4/6i+AI setting. However, the ERG's clinical advisors commented that Fulv and Tam are sometimes used as single agents in this setting, and that chemotherapy may be offered if the patient is at risk of visceral crisis, although endocrine options would usually be offered first. The ERG notes that Fulv and chemotherapy are not included in the final NICE scope. The company would need to expand their evidence network in order to consider any of these other therapies as comparators in the model.

As previously discussed in Sections 2.2.3 and 5.2.1, the company excluded CDK4/6is from the economic analyses on the basis that in UK clinical practice, if patients with endocrine resistant HR+, HER2– ABC have received a CDK4/6i+AI regimen as first-line treatment in the advanced setting, they are unlikely to receive another CDK4/6i in second-line. The ERG's clinical advisors agreed with this view. The CS[1] also notes that two of the three CDK4/6is currently available (Abem/Fulv and Palb/Fulv)

are only available through the CDF. However, Ribo/Fulv is recommended by NICE for use in the NHS after previous ET. Abem/Fulv has also recently exited the CDF and is now available through routine commissioning (since September 2021). Nevertheless, the ERG agrees that it is unlikely that currently in clinical practice patients would be re-treated with a CDK4/6i in the second- or subsequent line settings.

(3) Uncertainty surrounding the relevance of the economic analysis to the target population

The clinical advisors to the ERG indicated that most patients currently receive a CDK4/6i+AI regimen in the first-line setting, and that this group of treatments has become the standard of care in England. The available data from Cohort A of BYLieve[31] reflects expected outcomes for patients who received a CDK4/6i+AI prior to receiving treatment with Alp/Fulv; a subset of this study population – patients receiving Alp/Fulv as second-line therapy – is used in the company's economic analysis. As discussed in Section 3.1, the wording of the current EMA licence relates specifically to patients whose disease has progressed "*following endocrine therapy as monotherapy,"* which is more restrictive than the anticipated wording of the anticipated MHRA Type II variation, which relates to disease progression occurring [redacted] If the MHRA Type II variation requested by the company is not granted, and the current wording of the marketing authorisation remains in line with the current EMA licence, the implication is that patients recruited into BYLieve Cohort A would not be eligible for treatment with Alp/Fulv. As such, the relevance of the company's economic analysis is dependent on the MHRA granting the Type II variation to the current licence.

(4) Relevant subgroups excluded from economic analyses

As described in Section 5.2, the company's base case analysis uses a subset of data for Alp/Fulv from Cohort A of BYLieve, which relates to CDK4/6i+AI-experienced endocrine-resistant patients in the second-line setting, with ITCs which synthesise data for these patients from SOLAR-1,[28] CONFIRM,[21] SoFEA[22] and BOLERO-2.[20] The company's economic analysis does not include: (i) patients in BYLieve who were treated with Alp/Fulv in the third- and subsequent-line settings; (ii) people who received Alp/Fulv as first-line treatment for advanced disease after receiving a CDK4/6i in the neo/adjuvant setting, or (ii) men with ABC. As such, the cost-effectiveness of Alp/Fulv in these patients remains unknown. The company's clarification response (question B1)[14] confirms that the company is seeking a positive recommendation for Alp/Fulv beyond the second-line setting. The company's response comments that few patients in BYLieve received Alp/Fulv in these later lines of therapy and argues that *"a recommendation should not preclude such patients from receiving alpelisib plus fulvestrant in the future."* However, these patients were specifically excluded from the economic analysis.

(5) Uncertainty surrounding relative treatment effects for alpelisib plus fulvestrant versus everolimus plus exemestane

The company's model uses HRs obtained from the Bucher ITCs. The ERG identified several key areas of uncertainty regarding these ITC. These issues are described in detail in Section 4.9 and for the sake of brevity they are not repeated here. Overall, the ERG considers that the uncertainty around the relative treatment effects for Alp/Fulv versus Eve/Exe means that the resulting QALY estimates and ICERs generated by the company's model should be considered to be highly uncertain.

(6) Issues relating to survival modelling

The ERG has several concerns regarding the appropriateness of the company's survival analyses. These relate to the inappropriate use of HRs, the assumption of indefinite relative treatment effects and the limited consideration of clinical plausibility in the model selection process.

(a) Application of HRs to accelerated failure time models

Within their economic analysis, the company modelled outcomes for the Eve/Exe group by applying HRs derived from the Bucher ITCs to baseline models fitted to data for the Alp/Fulv group from Cohort A of BYLieve.[31] For PFS, the baseline model is assumed to follow a log-normal distribution, whilst for OS, the baseline model is a log-logistic distribution (see Section 5.2.4). These are both accelerated failure time (AFT) models which do not make the assumption of PH; as such, applying HRs to these models is not statistically appropriate. The ERG sought clarification from the company on this issue (see clarification response,[14] question B3). In their response, the company stated that applying an HR to a non-PH distribution will result in a distribution that is of a different form than the original, but argued that there is no obvious reason why this would be biased. The company also notes that this approach has been applied in several previous NICE TAs. The ERG agrees that this approach has been used in numerous previous appraisals, but reiterates that the results of this approach may not be meaningful and that precedents set in previous appraisals do not legitimise this approach.

(b) Assumption of lifetime relative treatment effects

Within the economic analysis, the company's model applies constant HRs to the PFS and OS models for Alp/Fulv over the entire 40-year time horizon. This approach therefore assumes that relative treatment effects apply indefinitely. The company has not presented any evidence to support this assumption, or scenarios in which treatment effects are reduced or lost over time. The ERG notes that less optimistic assumptions regarding the duration of treatment benefit would increase the ICER for Alp/Fulv.

(c) Concerns related to model selection and the use of clinical input

The ERG believes that the company's use of clinical opinion to inform the choice of models for PFS and OS in each treatment group is fairly weak. The CS[1] provides very little detail regarding the role of clinical expert judgement in selecting between the candidate PFS and OS models and/or in validating the final selected models. Additional information relating to the company's PFS and OS model selection/validation process is contained in the separate following documents: (i) the minutes of an advisory board meeting held by the company in May 2020,[58] and (ii) the brief description of a clinical validation meeting held by the company in June 2021,[59] which were shared by the company as part of the CS and clarification response reference packs, respectively. Table 38 summarises the information provided by the company regarding model selection/validation reported in the CS and in the minutes of the company's advisory board meetings.

Table 38: Summary of company's justification of PFS and OS model selection

Endpoint	Model selected	Justification given in CS[1]	Company's clinical expert's comments[58, 59]	Sensitivity analysis reported in CS[1]
PFS – Alp/Fulv	Log-normal	*"excellent visual fit and the best statistical goodness of fit"*	Clinician agreed that the log-normal curve was the most reasonable in estimating PFS, based on clinical plausibility of predicted survival rates	Alternative models considered in sensitivity analysis
PFS – Eve/Exe	HR applied to log-normal baseline model	N/a - PH assumption considered to hold, hence Bucher approach used	None documented in the minutes	Alternative Alp/Fulv baseline models and uncertainty around HR considered in sensitivity analysis
OS – Alp/Fulv	Log-logistic	OS must be higher than PFS *"excellent goodness of fit"* *"reasonable long-term projections of OS... validated by clinical expert opinion"*	Clinician agreed that the log-logistic curve was the most reasonable in estimating PFS, based on clinical plausibility of predicted survival rates	Alternative models considered in sensitivity analysis
OS – Eve/Exe	HR applied to log-logistic baseline model	N/a - PH assumption considered to hold, hence Bucher approach used	1 year OS: 50% 2 year OS: 33.33% 5-year OS: ~5%	Alternative Alp/Fulv baseline models and uncertainty around HR considered in sensitivity analysis

Alp - alpelisib; Fulv - fulvestrant; Eve - everolimus; Exe - exemestane; CS - company's submission; PFS - progression-free survival; OS - overall survival; HR - hazard ratio; PH - proportional hazards

With respect to the company's model selection and clinical validation approach, the ERG makes the following observations:

- For PFS in the Alp/Fulv group, the company selected the log-normal model. This model was selected on the basis of the absolute visual fit, relative statistical goodness-of-fit to the observed data and clinical plausibility. The clinical expert who attended the clinical validation meeting held by the company in June 2021 considered the selected log-normal PFS function to be the most reasonable based on the clinical plausibility of the predicted survival rates.[59] Sensitivity analyses assessing alternative PFS models are presented in the CS for this endpoint (see Table 35).
- PFS in the Eve/Exe group is modelled by applying an HR to the log-normal Alp/Fulv PFS model. Clinical plausibility of this model is not discussed in the CS,[1] the advisory board or clinical validation meeting minutes.[58, 59] However, sensitivity analyses assessing alternative (baseline) PFS models and uncertainty around the point estimate of the HR are presented in the CS (see Table 35).
- For OS in the Alp/Fulv group, the company selected the log-logistic model. This model was selected based on goodness-of-fit statistics and clinical plausibility. The minutes from the clinical validation meeting[59] mention that this model was validated by clinical expert opinion based on the clinical plausibility of predicted survival rates. Sensitivity analyses assessing alternative OS models are presented in the CS for this endpoint (see Table 35).
- OS in the Eve/Exe group is modelled by applying an HR to the log-logistic Alp/Fulv OS model as a baseline. This approach was adopted for consistency with the approach used to model PFS. The advisory board minutes indicate that the expert suggested survival estimates of 50%, 33.33% and ~5% at 1-, 2- and 5- years, respectively.[58] The company's model indicates survival estimates of approximately 65%, 30% and 4% at these timepoints. These discrepancies are not discussed in the CS.[1] However, the ERG notes that none of the parametric models fitted provide estimates of OS which are similar to the expert's estimates, and the company's selected model might be considered more reasonable than the other candidate models. Sensitivity analyses assessing alternative baseline OS models and uncertainty around the point estimate of the HR are presented in the CS for this endpoint (see Table 35).

Despite these issues, the ERG's clinical advisors considered the company's selected OS models to be plausible, but commented on the difficulties of making such judgements in the absence of direct comparisons from head-to-head RCTs in the target population. The ERG's clinical advisors also expressed some uncertainty with regard to the company's assumption that the relative treatment effect on OS for Alp/Fulv versus Eve/Exe persists indefinitely.

(7) Concerns regarding company's HRQoL assumptions

The utility values used in the company's model are summarised in Table 30. The ERG has a number of concerns regarding the company's approach to estimating HRQoL:

- No HRQoL data are available from BYLieve[31] (i.e. patients who have previously failed on a CDK4/6i). The utility values applied in the economic analysis of BYLieve are instead based on SOLAR-1 and BOLERO-2.[20, 28]
- There is no direct evidence to suggest that HRQoL is higher for patients receiving Alp/Fulv than for patients receiving Eve/Exe. It may be the case that the derived differences in utility values between treatment groups reflect the differential impact of AEs; however, it is also possible that these differences are a consequence of patient heterogeneity and/or the use of different utility instruments and mapping algorithms.
- As noted in a recent review paper by Vernieri *et al*,[60] the incidence of Grade 3/4 AEs was higher for Alp/Fulv in SOLAR-1 than for Eve/Exe in BOLERO-2 (76% versus 42%). Given its increased toxicity profile compared with Eve/Exe, it seems unlikely that HRQoL would be improved for Alp/Fulv (although this would depend on the severity and HRQoL impact of specific AEs). The clinical advisors to the ERG considered it more reasonable to expect that HRQoL would be similar for Alp/Fulv and Eve/Exe.
- The ERG considers the company's approach to estimating the utility value for the progression-free on-treatment state for patients on Eve/Exe to be convoluted and perhaps unnecessary. The company's response to clarification question B7 indicates that this approach was based on TA687/TA593.[8, 40] However, it is unclear why the company did not estimate the absolute utility value for the progression-free on-treatment state for the Eve/Exe group using the utility values from BOLERO-2[20] (mapped from the EORTC QLQ-C30 to the EQ-5D-3L). This approach would have used the available data for the treatment group under consideration and would not have required the company's additional assumptions of equivalence between Exe and Fulv in terms of HRQoL.
- The company fitted six alternative GEE models to the available data from SOLAR-1[18] and selected the model which included the greatest number of covariates. The ERG notes that the problems of fitting linear models to EQ-5D response data have been discussed in the literature.[61, 62] The ERG considers that a mixture model, rather than a linear model, would have been better able to reflect the underlying distribution of the EQ-5D data and may have produced more appropriate estimates of mean utility for each of the modelled health states.
- The CS[1] (page 133) notes that EQ-5D-5L data *"were largely missing after progression."* This raises the possibility of informative censoring, whereby sicker patients (in particular, those who have progressed) are not represented in the dataset. In their clarification response[14] (question B5), the company stated: *"Although Novartis acknowledges that this may therefore influence*

the utility estimates derived for this population, in the absence of suitable alternative data, utilising the EQ-5D data from SOLAR-1 was considered to be the most suitable approach (and one that aligns to the NICE reference case and the source for the other utility estimates in the model), despite there being some limitations in terms of small patient numbers." The ERG notes that the problem relates to potential informative censoring rather than imprecision caused by small sample sizes, and believes that it may be preferable to deviate from the NICE Reference Case if other less biased utility estimates are available.

- The company's executable model (worksheet "Utilities_AE") includes a list of disutility values associated with AEs which appear to be taken from a standard gamble (SG) study using members of the general public reported by Lloyd *et al*.[54]. These utility values are not included in the model calculations and are not discussed in the CS.[1] In response to clarification question B8,[14] the company commented that including additional disutilities may represent double-counting. The ERG agrees, but notes that the company's approach to estimating treatment-specific health utilities is subject to uncertainty. Nonetheless, the ERG agrees that including these additional health impacts over a short duration would likely have a minimal impact on the model results.
- The ERG notes potential issues regarding the face validity of the model-based estimates:
    - The utility values applied to the progression-free state in the model are [redacted] for Alp/Fulv and [redacted] for Eve/Exe, whereas the utility value for the progressed state is estimated to be [redacted]. As a consequence, the difference between the utility values for these states is small (utility decrement of [redacted] or less). Within the previous appraisals of CDK4/6 inhibitors and Eve,[9, 16, 40, 49, 63, 64] the utility value for the post-progression health state was assumed to be 0.56 or lower (based on the Lloyd *et al.* SG study;[54] see Table 39). This leads to a much larger decrement between the progression-free and post-progression states. Three previous appraisals (TA503,[65] TA639[66] and TA725[7]) have applied comparatively higher utility values in the post-progression state; however, these are also lower than the value used in the Alp model.
    - The utility decrement associated with the terminal phase (disutility [redacted]) is less than one might expect for patients who are very close to death. As shown in Table 30, few response data were available to inform this component of the GEE model.

Table 39: Comparison of utility values applied in the CS and estimates from other recent appraisals in ABC

Model / treatment group	Progression-free utility – value(s)	Progression-free utility – source	Post-progression utility – value(s)	Post-progression utility – source
NICE ID3929 (Alp/Fulv)[1]	Alp/Fulv PF on tx=[redacted]; PF off tx=[redacted] Eve/Exe PF on tx=[redacted]; PF off tx=[redacted]	SOLAR-1 (second-line)	PD=[redacted]	SOLAR-1 (second-line)
NICE TA495[63] (Palb+AI)	Values redacted in CS	PALOMA-2	PD=0.45	Lloyd *et al.*[54]
NICE TA496[49] (Eve/Exe)	PF1 redacted; PF2 on tx=0.77	MONALEESA-2; BOLERO-2	PD=0.51	Lloyd *et al.*[54]
NICE TA503[65] (Fulv)	PF=0.75	FALCON	PD=0.69	FALCON
NICE TA563[64] (Abem+ AI)	PF1 redacted; PF2=0.774 (endocrine+/-target therapies) or 0.661	MONARCH-3; TA496	PD=0.51	Lloyd *et al.*[54]
NICE TA579[16]/TA725[7] (Abem/Fulv)	Values redacted in CS	MONARCH-2	TA579 PD=0.51 TA725 PD = 0.67	TA579 Lloyd *et al.*[54] TA725 Mitra *et al.*[67]
NICE TA593[40]/TA687[8] (Ribo/Fulv)	Values redacted in CS	MONALEESA-3	PD=0.51	Lloyd *et al.*[54]
NICE TA619[9] (Palb/Fulv)	Palbociclib SD=0.74 Everolimus plus exemestane SD=0.69	PALOMA-3	PD=0.56	Lloyd *et al.*[54]
NICE TA639[66] (atezolizumab with nab-paclitaxel)*	Atezolizumab plus nab-paclitaxel, paclitaxel and docetaxel= 0.726	IMpassion130 (PD-L1 positive patients only)	PD= 0.653	IMpassion130 (PD-L1 positive patients only)
NICE TA704[68] (trastuzumab deruxtecan)	Trastuzumab deruxtecan PFS on tx= 0.750 Eribulin PFS on tx = 0.713 Capecitabine PFS on tx= 0.725 Vinorelbine PFS on tx = 0.717 Blended SoC PFS on tx = 0.713 PFS off treatment = 0.704	TA423 (eribulin, 3rd line metastatic BC, EMBRACE trial)	PD= 0.588	TA423 (eribulin, 3rd line metastatic BC, EMBRACE trial)

Alp - alpelisib; Fulv - fulvestrant; Eve - everolimus; Exe - exemestane; Palb – palbociclib; Abem – abemaciclib; Ribo – ribociclib; AI – aromatase inhibitor; BC - breast cancer; PF - progression-free; PD - progressed-disease; SD - stable disease; tx – treatment; TA - technology appraisal; CS - company's submission

(8) Concerns regarding company's cost assumptions

The ERG has two main concerns regarding the company's costing approach and related assumptions. These relate to: (a) the exclusion of costs associated with drug wastage and (b) the approach used to reflect post-progression treatment costs in the model.

(a) Drug wastage costs excluded from model

The company's model calculates drug acquisition costs in terms of the amount of each regimen component required per cycle, including adjustment for RDI, and applies this to the half-cycle corrected TTD in each interval. This approach ignores any costs associated with drug wastage. Whilst wastage is unlikely to be relevant for Fulv, as it is administered intramuscularly at a fixed dose which is equal to its vial size, it is a relevant concern for the oral drugs (Alp, Eve and Exe) which would likely be prescribed and dispensed on a 28 or 30-day basis (depending on pack size). As such, any patient who discontinues or dies during the cycle will generate some wastage. The ERG asked the company for clarification on this matter (see clarification response[14] question B11); the company's response does not acknowledge that additional costs for wastage should have been included in the economic analyses. The ERG's clinical advisors commented that some wastage would be expected for the oral drugs. The advisors noted that most oncologists are able to judge when their patient is not well enough to continue therapy and suggested that a total of 7 days or less wastage might represent a reasonable assumption for these therapies.

(b) Non-specific post-progression treatment regimens

The company's model assumes that following disease progression, patients will receive subsequent treatments at a cost of £1,500 per month, based on TA687[8] (although as discussed in Section 5.3.2, this value appears to be from TA496[49]). The model assumes that all patients receive post-progression therapy and that they will continue to do so until death. The clinical advisors to the ERG commented that these costs and the assumptions applied in the company's model are reasonable. However, the ERG believes that it would be more conventional to apply subsequent-line treatment costs based on observed post-progression treatments received in the clinical study, rather than applying simplistic assumptions. Such an approach would align the estimates of health benefits predicted by the model with the costs of resources required to generate those benefits. The CS[1] does not provide any information relating to the use of post-progression treatments used in BYLieve[31] or BOLERO-2.[20]

As part of the clarification process, the ERG requested further information on the treatments used following disease progression in the model (see clarification response,[14] question B10). The company's response does not provide the requested information on post-progression treatments, as they stated that they did not consider this approach to be necessary. The company also stated that *"a straightforward approach was taken whereby a monthly cost was applied, which encapsulated all future treatments*

patients will receive following second line treatment progression, and therefore all future treatment related costs a patient will experience (excluding terminal care associated costs).” The company further commented that this approach is consistent with TA593,[40] TA495,[63] TA496[49] and TA503,[65] and stated that *“Given the level of complexity required in deriving a specific treatment flow for the post-progression health state, it was considered that it would be reasonable to apply a simple fixed cost.”* In the absence of the requested information on post-progression treatments in the clinical studies, the ERG is unable to comment on whether it is reasonable to assume a mean cost £1,500 per month for post-progression treatments, or whether this is aligned with the experience of the studies used to inform the clinical parameters of the model. As noted in Section 5.3.2, in TA496[49] the Appraisal Committee accepted a lower cost estimate ranging from £1,140 to £1,200.

(9) Discrepancy between deterministic and probabilistic model results

There are marked differences between the results of the deterministic and probabilistic versions of the company’s model, which lead to the probabilistic ICER being around £8,400 higher than the deterministic estimate (see Table 40). There are also noticeable differences in LYGs, QALYs and costs between the deterministic and probabilistic estimates of OS.

Table 40: Comparison of deterministic and probabilistic model results

Treatment group	Deterministic model	Probabilistic model	Difference
Alp/Fulv LYGs*	2.58	2.71	0.13
Eve/Exe LYGs*	1.81	2.17	0.35
Incremental LYGs*	0.76	0.54	-0.22
Alp/Fulv QALYs	[redacted]	[redacted]	[redacted]
Eve/Exe QALYs			
Incremental QALYs gained			
Alp/Fulv costs			
Eve/Exe costs			
Incremental costs			
ICER	**£60,462**	**£68,808**	£8,419

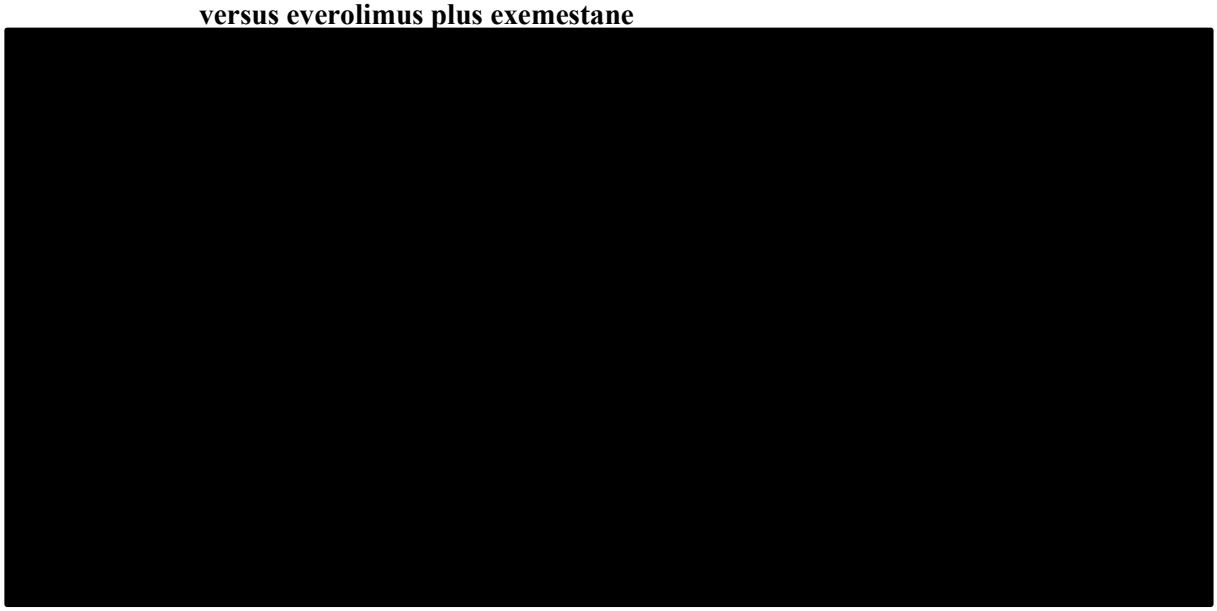
** Undiscounted*
Alp - alpelisib; Fulv - fulvestrant; Eve - everolimus; Exe - exemestane; LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio

In their clarification response[14] (question B16), the company stated that *“The larger ICERs obtained from the probabilistic analysis were due to the variation associated with the treatment effect, with the sampled treatment effect being less favourable towards alpelisib plus fulvestrant at times.”* The company’s response suggests that not all sampled values are clinically plausible, and the company suggests that a constraint could have been added to ensure that all sampled HRs favoured Alp/Fulv, but that for the sake of transparency this was not included. The company’s response also suggests that the probabilistic analyses are considered conservative and that the ICER is more likely to be aligned with the deterministic analysis (which produces a comparatively lower ICER).

The ERG fully replicated the company's probabilistic sampling of OS for both treatment groups and obtained almost identical results. No errors were found and the ERG concludes that the probabilistic sampling has been implemented correctly. In addition, the ERG replicated the company's Bucher ITCs for OS using an FE NMA; this resulted in posterior distributions for the HRs which were very similar to the company's sampled HRs. The ERG also re-ran the PSA using artificially smaller SEs around the HRs for PFS and OS; this broadly aligned the results of the deterministic and probabilistic models. A similar analysis was also presented in the company's clarification response (question B16). With respect to the company's comments on this issue, the ERG does not consider it appropriate to add a constraint to truncate the sampled HRs. However, the ERG agrees that the main driver of the discrepancy between the deterministic and probabilistic results is the very wide interval around the HR for OS ([redacted]). The company's probabilistic sampling of OS suggests that Alp/Fulv is less effective than Eve/Exe in more than 18% of samples (see Figure 22). In several samples, the incremental loss in survival for Alp/Fulv is substantial; this is unlikely to be plausible.

Overall, the ERG believes that the interpretation of the results of the company's deterministic model is problematic because of the use of median HRs rather than mean HRs. However, there is a discrepancy in the results produced when using the mean of the HR in the deterministic model (whereby the ICER is decreased) and the use of the probabilistic samples of the HRs (whereby the expected ICER is increased) due to the non-linear response to extreme HRs. Given these problems, the ERG is unsure whether it is more appropriate to rely on the results of the deterministic or probabilistic model.

Figure 22: Distribution of incremental OS from company's PSA, alpelisib plus fulvestrant versus everolimus plus exemestane



LYG - life year gained

(10) Limited model functionality

The ERG notes that the executable model includes the functionality to allow the user to select alternative PFS, OS and TTD models; however, bootstrap samples are included only for the company's selected base case survival models. Consequently, it was not possible for the ERG to run the PSA for any alternative parametric survival models other than those applied in the company's base case.

5.4 Exploratory analyses undertaken by the ERG

5.4.1 ERG exploratory analysis – methods

ERG preferred base case analysis

The ERG's preferred analysis is comprised of four sets of amendments to the company's model; these are detailed below. All exploratory analyses (EAs) were undertaken using the deterministic version of the model. The ERG's preferred analysis is also presented using the probabilistic model.

EA1: Correction of errors

The ERG applied the following corrections to the company's original model:

(a) *Administration costs for Eve.* The calculation of the administration costs for Eve were adjusted to reflect the 28-day cycle length applied in the model.

(b) *Costs of PIK3CA test.* The unit cost of a *PIK3CA* test was updated to 2020 values (£718.19 per patient).

The ERG notes that both corrections (a) and (b) correspond to the amendments included in the company's updated model submitted following the clarification round.[14]

All other exploratory analyses undertaken by the ERG are applied using the corrected version of the model.

EA2: Alternative utility assumptions for the progression-free on-treatment state

As noted in Section 5.3.4, the ERG has concerns regarding the assumption that HRQoL is better for Alp/Fulv than Eve/Exe whilst on treatment. Within this analysis, the utility value for patients who are progression-free and still receiving treatment was assumed to be the same for both treatment groups, based on the estimate for Alp/Fulv derived from the SOLAR-1 GEE model.

EA3: Alternative utility assumptions for post-progression state

The ERG considers that the utility value for the post-progression state appears to be unrealistically high, potentially as a consequence of informative censoring. Within this analysis, the utility for the post-progression state was assumed to be 0.51, based on Lloyd *et al.*[54] This is consistent with the source used to inform post-progression utility values in TA495, TA496, TA563, TA579, TA593 and TA687/TA619.

EA4: Drug wastage

The company's model does not account for drug wastage. Within this exploratory analysis, the company's model was amended to include 7 days' wastage for all oral drugs (Alp, Eve and Exe). Wastage costs were assumed not to apply to Fulv.

EA5: ERG preferred analysis

The ERG's preferred analysis incorporates EA1-4.

Additional sensitivity analyses

The ERG notes that there is uncertainty surrounding long-term PFS and OS outcomes for Alp/Fulv versus Eve/Exe, and subsequent treatment costs applied in the model. The ERG also believes that the company's assumption of a lifetime relative treatment benefit may be optimistic. Hence, three additional sets of additional sensitivity analyses (ASAs) were undertaken using the ERG's preferred analysis.

ASA1: Alternative treatment effect durations

Within this analysis, the relative treatment effect for Alp/Fulv versus Eve/Exe is assumed to persist for: (a) 3 years or (b) 5 years.

ASA2: Subsequent treatment costs

The ERG has concerns regarding the company's assumed cost of treatments received post-progression. Two alternative scenarios were explored: (a) post-progression treatments cost £750 per month (the company's estimate minus 50%), and (b) post-progression treatments cost £2,250 per month (the company's estimate plus 50%).

ASA3: Use of HRs from Bucher ITC using SoFEA HER2- subgroup

This analysis applies the HRs for the company's revised Bucher ITC including only HER2- patients in SoFEA provided in response to ERG clarification question A20[14] (HRs reported in Table 26).

ASA4: Use of alternative OS models

This sensitivity analysis explores the use of all fitted OS models within the ERG's preferred model.

ASA5: Use of alternative PFS models

This sensitivity analysis explores the use of all fitted PFS models within the ERG's preferred model.

5.4.2 ERG exploratory analysis – results

Table 41 presents the results of the ERG's exploratory analyses. The results show that correcting the errors in the company's model slightly increases the ICER for Alp/Fulv versus Eve/Exe from £60,462 to £60,554 per QALY gained (EA1). Based on the ERG-corrected model, the inclusion of drug wastage increases the ICER to £61,342 per QALY gained (EA4). Applying the same utility value for patients who are progression-free and on treatment in both groups increases the ICER to £62,424 per QALY gained (EA2), whilst applying the post-progression utility value from Lloyd *et al.*[54] in both groups has a greater impact, increasing the ICER to £74,665 per QALY gained (EA3). The ERG's preferred analysis, which includes all of these amendments, leads to a deterministic ICER for Alp/Fulv versus Eve/Exe is £78,538 per QALY gained (EA5). The probabilistic ICER for the ERG's preferred analysis is expected to be £90,261 per QALY gained.

Table 41: ERG exploratory analysis results, alpelisib plus fulvestrant versus everolimus plus exemestane, deterministic‡

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER
Company's base case							
Alp/Fulv	2.58	[redacted]	[redacted]	0.76	[redacted]	[redacted]	**£60,462**
Eve/Exe	1.81	[redacted]	[redacted]	-	-	-	-
EA1a: Correction of errors (admin costs)							
Alp/Fulv	2.58	[redacted]	[redacted]	0.76	[redacted]	[redacted]	**£60,512**
Eve/Exe	1.81	[redacted]	[redacted]	-	-	-	-
EA1b: Correction of errors (*PIK3CA* test cost)							
Alp/Fulv	2.58	[redacted]	[redacted]	0.76	[redacted]	[redacted]	**£60,503**
Eve/Exe	1.81	[redacted]	[redacted]	-	-	-	-
EA1: Correction of errors (all)							
Alp/Fulv	2.58	[redacted]	[redacted]	0.76	[redacted]	[redacted]	**£60,554**
Eve/Exe	1.81	[redacted]	[redacted]	-	-	-	-
EA2: Alternative PFS on tx utility assumption							
Alp/Fulv	2.58	[redacted]	[redacted]	0.76	[redacted]	[redacted]	**£62,424**
Eve/Exe	1.81	[redacted]	[redacted]	-	-	-	-
EA3: Alternative PPS utility value							
Alp/Fulv	2.58	[redacted]	[redacted]	0.76	[redacted]	[redacted]	**£74,665**
Eve/Exe	1.81	[redacted]	[redacted]	-	-	-	-
EA4: Drug wastage							
Alp/Fulv	2.58	[redacted]	[redacted]	0.76	[redacted]	[redacted]	**£61,342**
Eve/Exe	1.81	[redacted]	[redacted]	-	-	-	-
EA5: ERG preferred analysis (deterministic)							
Alp/Fulv	2.58	[redacted]	[redacted]	0.76	[redacted]	[redacted]	**£78,538**
Eve/Exe	1.81	[redacted]	[redacted]	-	-	-	-
EA5: ERG preferred analysis (probabilistic)							
Alp/Fulv	2.71	[redacted]	[redacted]	0.54	[redacted]	[redacted]	**£90,261**
Eve/Exe	2.17	[redacted]	[redacted]	-	-	-	-

**undiscounted; ‡ For ERG-preferred analysis both deterministic and probabilistic are presented.*
EA - exploratory analysis; Alp - alpelisib; Fulv - fulvestrant; Eve - everolimus; Exe - exemestane; LYG - life year gained; QALY - quality-adjusted life year; Inc. - incremental; ICER - incremental cost-effectiveness ratio

The results of the ERG's additional sensitivity analyses are shown in Table 42, Table 43 and Table 44. With the exception of ASA2a (lower post-progression treatment costs), all of ASAs 1-3 increase the ICER relative to the ERG's preferred analysis. Applying an assumption that the relative treatment effects on PFS and OS are lost at 3 years or 5 years increases the ICER to £92,195 per QALY gained and £83,640 per QALY gained, respectively (ASAs 1a and 1b). Increasing the monthly post-progression treatment cost by 50% increases the ICER to £89,548 per QALY gained, whilst decreasing this cost by 50% reduces the ICER to £67,529 per QALY gained (ASAs 2a and 2b). The application of the HRs from the company's Bucher ITC using only the HER2- subgroup of SoFEA substantially increases the ICER to £119,303 per QALY gained (ASA3). The application of alternative OS models (Table 43) leads to ICERs ranging from £70,462 per QALY gained (log-normal) to £145,760 per QALY gained (Gompertz). The application of alternative PFS models leads to ICERs ranging from £58,094 per QALY gained (RCS 3 log-logistic) and £83,841 per QALY gained (Weibull).

Table 42: ERG additional sensitivity analysis 1 to 3 results, alpelisib plus fulvestrant versus everolimus plus exemestane, deterministic

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER
EA5: ERG preferred analysis (deterministic)							
Alp/Fulv	2.58	[redacted]	[redacted]	0.76	[redacted]	[redacted]	**£78,538**
Eve/Exe	1.81	[redacted]	[redacted]	-	-	-	-
ASA1a: Treatment effect duration = 3 years							
Alp/Fulv	2.27	[redacted]	[redacted]	0.46	[redacted]	[redacted]	**£92,195**
Eve/Exe	1.81	[redacted]	[redacted]	-	-	-	-
ASA1b: Treatment effect duration = 5 years							
Alp/Fulv	2.40	[redacted]	[redacted]	0.59	[redacted]	[redacted]	**£83,640**
Eve/Exe	1.81	[redacted]	[redacted]	-	-	-	-
ASA2a: Post-progression treatment costs = £750 per month							
Alp/Fulv	2.58	[redacted]	[redacted]	0.76	[redacted]	[redacted]	**£67,529**
Eve/Exe	1.81	[redacted]	[redacted]	-	-	-	-
ASA2b: Post-progression treatment costs = £2,250 per month							
Alp/Fulv	2.58	[redacted]	[redacted]	0.76	[redacted]	[redacted]	**£89,548**
Eve/Exe	1.81	[redacted]	[redacted]	-	-	-	-
ASA3: Use of HRs from Bucher ITC using SoFEA HER2- subgroup							
Alp/Fulv	2.58	[redacted]	[redacted]	0.38	[redacted]	[redacted]	**£119,303**
Eve/Exe	2.19	[redacted]	[redacted]	-	-	-	-

**undiscounted*
ASA - additional sensitivity analysis; Alp - alpelisib; Fulv - fulvestrant; Eve - everolimus; Exe - exemestane; LYG - life year gained; QALY - quality-adjusted life year; Inc. - incremental; ICER - incremental cost-effectiveness ratio

Table 43: ERG additional sensitivity analysis 4 results, impact of alternative OS models on ERG-preferred analysis, alpelisib plus fulvestrant versus everolimus plus exemestane, deterministic

OS model	Comparator LYGs*	Inc. LYGs*	Inc. QALYs	Inc. Costs	ICER (per QALY gained)
Exponential	2.49	0.95	[redacted]	[redacted]	**£71,527**
Weibull	1.42	0.28	[redacted]	[redacted]	**£111,235**
Gompertz	1.28	0.17	[redacted]	[redacted]	**£145,760**
Log-normal	2.33	1.12	[redacted]	[redacted]	**£70,462**
Log-logistic (base case)	1.81	0.76	[redacted]	[redacted]	**£78,538**
Generalised gamma	1.31	0.18	[redacted]	[redacted]	**£139,620**
Generalised F	1.35	0.29	[redacted]	[redacted]	**£108,643**
RCS 1 Log-logistic	1.53	0.48	[redacted]	[redacted]	**£90,308**
RCS 1 Log-normal	1.54	0.43	[redacted]	[redacted]	**£92,670**
RCS 1 Weibull	1.34	0.23	[redacted]	[redacted]	**£123,308**
RCS 2 Log-logistic	1.47	0.42	[redacted]	[redacted]	**£94,524**
RCS 2 Log-normal	1.43	0.33	[redacted]	[redacted]	**£101,911**
RCS 2 Weibull	1.34	0.23	[redacted]	[redacted]	**£123,592**
RCS 3 Log-logistic	1.41	0.34	[redacted]	[redacted]	**£101,481**
RCS 3 Log-normal	1.39	0.29	[redacted]	[redacted]	**£107,783**
RCS 3 Weibull	1.32	0.21	[redacted]	[redacted]	**£129,851**

*LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; ITT - intention-to-treat; *undiscounted*

Table 44: ERG additional sensitivity analysis 5 results, impact of alternative PFS models on ERG-preferred analysis, alpelisib plus fulvestrant versus everolimus plus exemestane, deterministic

PFS model	Comparator LYGs*	Inc. LYGs*	Inc. QALYs	Inc. Costs	ICER (per QALY gained)
Exponential	1.81	0.76	[redacted]	[redacted]	**£79,720**
Weibull	1.81	0.76	[redacted]	[redacted]	**£83,841**
Gompertz	1.81	0.76	[redacted]	[redacted]	**£83,317**
Log-normal (base case)	1.81	0.76	[redacted]	[redacted]	**£78,538**
Log-logistic	1.81	0.76	[redacted]	[redacted]	**£73,965**
Generalised gamma	1.81	0.76	[redacted]	[redacted]	**£70,366**
Generalised F	1.81	0.76	[redacted]	[redacted]	**£70,192**
RCS 1 Log-logistic	1.81	0.76	[redacted]	[redacted]	**£68,580**
RCS 1 Log-normal	1.81	0.76	[redacted]	[redacted]	**£76,584**
RCS 1 Weibull	1.81	0.76	[redacted]	[redacted]	**£79,671**
RCS 2 Log-logistic	1.81	0.76	[redacted]	[redacted]	**£77,161**
RCS 2 Log-normal	1.81	0.76	[redacted]	[redacted]	**£80,497**
RCS 2 Weibull	1.81	0.76	[redacted]	[redacted]	**£80,816**
RCS 3 Log-logistic	1.81	0.76	[redacted]	[redacted]	**£58,094**
RCS 3 Log-normal	1.81	0.76	[redacted]	[redacted]	**£66,079**
RCS 3 Weibull	1.81	0.76	[redacted]	[redacted]	**£70,252**

*LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; ITT - intention-to-treat; *undiscounted*

5.5 Discussion

The company's searches did not identify any economic analyses of Alp/Fulv or any other PI3K inhibitor therapy for the treatment of HR+, HER2- ABC.

The CS[1] presents the methods and results of a *de novo* health economic model to assess the cost-effectiveness of Alp/Fulv versus Eve/Exe in patients with endocrine-resistant HR+, HER2− ABC with a *PIK3CA* mutation. Incremental health gains, costs and cost-effectiveness are evaluated over a 40-year time horizon from the perspective of the NHS and PSS, with health outcomes and costs discounted at a rate of 3.5%. The model includes a proposed PAS for Alp and an existing PAS for Eve, both of which take the form of simple price discounts. The CS also includes an assumed price discount for Fulv; this has not been included in the results presented in this ERG report.

The economic analysis is implemented as a partitioned survival model, based on three health states: (i) progression-free; (ii) post-progression and (iii) dead. OS, PFS and TTD for Alp/Fulv are based on data from BYLieve, OS and PFS for Eve/Exe are estimated by applying constant HRs derived from Bucher NMAs to the Alp/Fulv OS and PFS models, and TTD is informed by data on PFS and TTD from BOLERO-2. Relative treatment effects are assumed to apply over the patient's remaining lifetime. Health utilities for both treatment groups were estimated using a GEE model fitted to EQ-5D-5L data collected in SOLAR-1 which had been mapped to the 3L version. A utility decrement is applied to the progression-free state for the Eve/Exe group, based on EORTC QLQ-C30 data collected in BOLERO-2 which was mapped to the EQ-5D-3L. Resource use estimates were derived from SOLAR-1, BOLERO-2, previous TAs, standard costing sources and assumptions.

The probabilistic version of the company's base case model suggests that Alp/Fulv is expected to generate an additional [redacted] QALYs at an additional cost of [redacted] per patient compared with Eve/Exe; the corresponding ICER is £68,880 per QALY gained. The deterministic version of the model produces a lower ICER of £60,462 per QALY gained.

The ERG critically appraised the company's health economic analyses and double-programmed the deterministic version of the company's original model for both populations. The ERG's critical appraisal identified several issues relating to the company's model and the evidence used to inform its parameters. These included: (i) the identification of minor model errors; (ii) the exclusion of relevant comparators from the economic analysis; (iii) concerns regarding the relevance of the economic analysis given the current licence for Alp; (iv) uncertainty surrounding relative treatment effects for Alp/Fulv versus Eve/Exe; (v) questionable assumptions regarding HRQoL; (vi) questionable assumptions regarding costs and (vii) concerns regarding the discrepancy between the deterministic and probabilistic estimates.

The ERG undertook four sets of exploratory analyses, which taken together, comprise the ERG's preferred analysis. These included: correcting model errors; applying alternative utility assumptions and including costs of wastage for orally administered drugs. Additional sensitivity analyses were undertaken using the ERG's preferred model to explore the impact of alternative assumptions regarding the duration of relative treatment effects for Alp/Fulv, alternative post-progression costs, alternative treatment effect estimates and alternative survival distributions for PFS and OS.

The ERG's preferred analysis suggests that the probabilistic ICER for Alp/Fulv versus Eve/Exe is £90,261 per QALY gained. This is considerably higher than the company's base case probabilistic ICER for this population (company's probabilistic ICER=£68,880 per QALY gained). The ERG's preferred deterministic ICER is also higher than the company's estimate (£78,538 versus £60,462 per QALY gained). The main driver of the difference between the company's and the ERG's estimates relates to the utility value applied in the post-progression state. The ERG's additional sensitivity analysis which applies treatment effects from the Bucher ITC including the HER2- subgroup of SoFEA leads to a higher ICER of £119,303 per QALY gained. The model is also sensitive to the parametric survival model for OS, with ICERs ranging from £70,462 per QALY gained (log-normal) to £145,760 per QALY gained (Gompertz). These estimates may favour Alp/Fulv due to the assumption of an indefinite relative treatment effect.

6 END OF LIFE

NICE End of Life (EoL) supplementary advice should be applied in the following circumstances and when both the criteria referred to below are satisfied:

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months and;
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment.

The CS[1] makes the case that Alp/Fulv meets NICE's EoL criteria within the BYLieve population (second-line, CDK4/6i+AI-experienced). The CS states that within Cohort A of BYLieve, median OS was 17.3 months and given that the Bucher ITC suggests that Alp/Fulv extends OS relative to Eve/Exe, OS under standard care would be lower than this. The company's deterministic model suggests a mean OS for Eve/Exe of 1.81 years, whilst the incremental survival gain for Alp/Fulv is estimated to be 0.76 years. The CS also comments that the post-CDK4/6i-experienced patients in the Pbo/Fulv arm of SOLAR-1 had a median OS of [redacted] months, although patient numbers are small (n=11).

The company's base case model and the ERG's preferred analysis both suggest that both EoL criteria are met when using the deterministic version of the model (see Table 45). However, if the company's revised Bucher ITC including only HER2- patients in SoFEA is used, mean OS in the Eve/Exe group is greater than 2 years. The probabilistic version of the company's model suggests that the EoL criteria are not both met, irrespective of which Bucher ITC is used.

Table 45: Company's estimates of undiscounted survival for Eve/Exe and additional OS gains, deterministic model

Option	Deterministic model		Probabilistic model	
	LYGs - Eve/Exe	Additional LYGs - Alp/Fulv vs. Eve/Exe	LYGs - Eve/Exe	Additional LYGs - Alp/Fulv vs. Eve/Exe
Company's Bucher ITC (company's base case and ERG preferred analysis)	1.81	0.76	2.17	0.54
Company's revised Bucher ITC including only HER2- subgroup from SoFEA (ERG ASA3)	2.19	0.38	2.68	0.03

Alp - alpelisib; Fulv - fulvestrant; Eve - everolimus; Exe - exemestane; LYG - life year gained; ITC - indirect treatment comparison

7 OVERALL CONCLUSIONS

7.1 Clinical effectiveness conclusions

Effectiveness and safety: In the SOLAR-1 RCT, PFS was significantly improved for Alp/Fulv versus Pbo/Fulv in the full population (HR [redacted], 95% CI: [redacted]) and in the second-line population used in the Bucher ITC, while in the small post-CDK4/6i subgroup (n=20) the HR for PFS was [redacted](95% CI: [redacted]). In the BYLieve Cohort A non-comparative study, median PFS was 7.3 months. OS in SOLAR-1 non-significantly favoured Alp/Fulv in the full population (HR=0.86, 95% CI: 0.64, 1.15) and in the second-line population, while in the post-CDK4/6i subgroup the OS HR was [redacted](95% CI [redacted]). In BYLieve Cohort A, median OS was 17.3 months. Common AEs included hyperglycaemia, diarrhoea, nausea, decreased appetite and rash, while in SOLAR-1, 25% discontinued alpelisib due to AEs and 75% experienced dose reductions or interruptions. A further RCT (EPIK-B5) of Alp/Fulv in the post-CDK4/6i population is planned to start in [redacted].

Indirect treatment comparisons (ITCs): The company conducted ITCs using three different approaches: (a) a matching/weighted analysis in a post-CDK4/6i population using data from BYLieve Cohort A and the US Flatiron CGDB; (b) a Bucher ITC which indirectly compared Alp/Fulv (SOLAR-1) versus Eve/Exe (BOLERO-2) via a network involving two additional trials (CONFIRM and SoFEA), and (c) an unanchored PAIC compared second-line data from the Alp/Fulv arm from SOLAR-1 and the Eve/Exe arm from BOLERO-2. The Bucher ITC, which is included in the company's base case model, [redacted]Alp/Fulv for PFS (Eve/Exe versus Alp/Fulv: HR=[redacted], 95% CI [redacted]) and OS (Eve/Exe versus Alp/Fulv: HR=[redacted], 95% CI [redacted]), while results [redacted]when using the HER2- subgroup from SoFEA. The ERG has a number of concerns regarding the Bucher ITCs: none of the trials are in a post-CDK4/6i population; the two connecting trials did not restrict to second-line, HER2- or *PIK3CA*-mutated patients; BOLERO-2 data were based on a small proportion of randomised patients (57/724; 8%); there may be imbalances in treatment effect modifiers; the PH assumption is questionable, and the FE models assume zero between-study heterogeneity and may underestimate uncertainty. The matching/weighted analysis and the PAIC both suggested [redacted], but the results of these analyses were not included in the company's base case model.

7.2 Cost-effectiveness conclusions

The deterministic version of the company's original base case model suggests that the ICER for Alp/Fulv versus Eve/Exe is £60,462 per QALY gained. The probabilistic version of the model suggests a higher ICER of £68,880 per QALY gained.

The ERG's preferred analysis includes: (i) the corrections of minor errors; (ii) an assumption of equal health utility for all patients whilst progression-free and on treatment; (iii) the inclusion of a lower utility value of 0.51 in the post-progression state (from Lloyd *et al.*[54]) and (iv) the inclusion of 7 days' wastage for Alp, Eve and Exe. The ERG's preferred analysis, which includes all of these amendments, leads to a deterministic ICER for Alp/Fulv versus Eve/Exe is £78,538 per QALY gained and a probabilistic ICER of £90,261 per QALY gained. Whilst the ERG would usually consider ICERs generated using probabilistic models to be more appropriate than their deterministic counterparts, the very wide interval around the HR for OS results in some probabilistic samples which are unlikely to be clinically plausible. As such, the ERG is unsure which version of the model should be used to inform decision-making. The ERG's additional sensitivity analyses indicate that the ICER may be substantially higher if lifetime treatment effects are not assumed, or if the subgroup of HER2- patients in SoFEA is used to inform the Bucher ITCs.

It is unclear whether Alp/Fulv meets NICE's EoL criteria. The deterministic version of the company's base case model suggests that the EoL criteria are met. However, the criteria are not both met if the probabilistic model is used, or if the Bucher ITC includes only HER2- patients in SoFEA.

8 REFERENCES

1. Novartis AG. Company's submission: Alpelisib plus fulvestrant for treating HR+, HER2– advanced breast cancer with a PIK3CA mutation [ID3929]. London, UK; 2021.
2. National Institute for Health and Care Excellence. Clinical Guideline CG81: Advanced breast cancer: diagnosis and treatment. London; 2009.
3. National Institute for Health and Care Excellence. Early and locally advanced breast cancer: diagnosis and management. NICE Guideline NG101 London; 2018.
4. National Institute for Health and Care Excellence. NICE Pathway: Managing advanced breast cancer (https://pathways.nice.org.uk/pathways/advanced-breast-cancer). NICE: London; 2020.
5. Cardoso F, Paluch-Shimon S, Senkus E, Curigliano G, Aapro MS, André F, *et al.* 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). *Annals of Oncology* 2020;31:1623-49.
6. Gradishar Wj Anderson BO, et al. NCCN Clinical practice guidelines in oncology - breast cancer. Available at: www.nccn.org [Last accessed: 14 July 2021].
7. National Institute for Health and Care Excellence. Abemaciclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy. Technology Appraisal Guidance 725 NICEL London; 2021.
8. National Institute for Health and Care Excellence. Ribociclib with fulvestrant for treating hormone receptorpositive, HER2-negative advanced breast cancer after endocrine therapy: Technology Appraisal Guidance 687. NICE: London; 2021.
9. National Institute for Health and Care Excellence. Palbociclib with fulvestrant for treating hormone receptor-positive, HER2-negative, advanced breast cancer. NICE Technology Appraisal Guidance TA619. NICE: London; 2020.
10. NHS England. National Cancer Drugs Fund List (version 1.186). NHSE: London; 2021.
11. National Institute for Health and Care Excellence. Everolimus with exemestane for treating advanced breast cancer after endocrine therapy. NICE Technology Guidance TA421. NICE: London; 2016.
12. National Institute for Health and Care Excellence. Alpelisib in combination with fulvestrant for treating advanced hormone-receptor positive, HER2-negative, PIK3CA-mutated breast cancer. NICE Final Scope. NICE: London; 2021.
13. European Medicines Agency. Summary of Product Characteristics - alpelisib. EMA: London; 2020.
14. Novartis AG. Company's clarification response: Alpelisib in combination with fulvestrant for treating advanced hormone-receptor positive, HER2-negative, PIK3CA-positive breast cancer [ID3929]. Novartis: London, UK; 2021.
15. Novartis. Interview with UK Clinician (June 2021). Data on File. 2021.
16. National Institute for Health and Care Excellence. Abemaciclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy. NICE Technology Appraisal Guidance TA579. NICE: London; 2019.
17. Rugo HS, Lerebours F, Ciruelos E, Drullinsky P, Ruiz-Borrego M, Neven P, *et al.* Alpelisib plus fulvestrant in PIK3CA-mutated, hormone receptor-positive advanced breast cancer after a CDK4/6 inhibitor (BYLieve): One cohort of a phase 2, multicentre, open-label, non-comparative study. *Lancet Oncology* 2021;22:489-98.
18. André F, Ciruelos E, Rubovszky G, Campone M, Loibl S, Rugo HS, *et al.* Alpelisib for PIK3CA-mutated, hormone receptor–positive advanced breast cancer. *New England Journal of Medicine* 2019;380:1929-40.

19. Turner S, Chia S, Kanakamedala H, Hsu WC, Park J, Chandiwana D*, et al.* Effectiveness of alpelisib + fulvestrant compared with real-world standard treatment among patients with HR+, HER2-, PIK3CA-mutated breast cancer. *Oncologist* 2021;26:e1133-e42.

20. Yardley DA, Noguchi S, Pritchard KI, Burris HA, 3rd, Baselga J, Gnant M*, et al.* Everolimus plus exemestane in postmenopausal patients with HR(+) breast cancer: BOLERO-2 final progression-free survival analysis. *Advances in Therapy* 2013;30:870-84.

21. Di Leo A, Jerusalem G, Petruzelka L, Torres R, Bondarenko IN, Khasanov R*, et al.* Results of the CONFIRM phase III trial comparing fulvestrant 250 mg with fulvestrant 500 mg in postmenopausal women with estrogen receptor-positive advanced breast cancer. *Journal of Clinical Oncology* 2010;28:4594-600.

22. Johnston SR, Kilburn LS, Ellis P, Dodwell D, Cameron D, Hayward L*, et al.* Fulvestrant plus anastrozole or placebo versus exemestane alone after progression on non-steroidal aromatase inhibitors in postmenopausal patients with hormone-receptor-positive locally advanced or metastatic breast cancer (SoFEA): a composite, multicentre, phase 3 randomised trial. *Lancet Oncology* 2013;14:989-98.

23. Novartis AG. Appendices to company's submission: Alpelisib plus fulvestrant for treating HR+, HER2– advanced breast cancer with a PIK3CA mutation [ID3929]. Novartis: London, UK; 2021.

24. Joint Formulary Committee. British National Formulary (online). London; 2020.

25. Glanville JM, Duffy S, McCool R, Varley D. Searching ClinicalTrials.gov and the International Clinical Trials Registry Platform to inform systematic reviews: what are the optimal search approaches? *Journal of the Medical Library Association : JMLA* 2014;102:177-83.

26. Centre for Reviews and Dissemination. Systematic Reviews: CRD's gudance for undertaking reviews in healthcare. CRD: York; 2009.

27. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *Journal of Epidemiology and Community Health* 1998;52:377-84.

28. Andre F, Ciruelos E, Rubovszky G, Campone M, Loibl S, Rugo HS*, et al.* Alpelisib for PIK3CA-Mutated, Hormone Receptor-Positive Advanced Breast Cancer. *New England Journal of Medicine* 2019;380:1929-40.

29. Rugo HS, Bianchi GV, Chia SKL, Turner NC, Juric D, Jacot W*, et al.* BYLieve: A phase II study of alpelisib (ALP) with fulvestrant (FUL) or letrozole (LET) for treatment of PIK3CA mutant, hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2–) advanced breast cancer (aBC) progressing on/after cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) therapy. *Journal of Clinical Epidemiology* 2018;36:ACSO abstract.

30. Juric D, Rodon J, Tabernero J, Janku F, Burris HA, Schellens JHM*, et al.* Phosphatidylinositol 3-kinase alpha-selective inhibition with alpelisib (BYL719) in PIK3CA-altered solid tumors: Results from the first-in-human study. *Journal of Clinical Oncology* 2018;36:1291-9.

31. Rugo HS, Lerebours F, Ciruelos E, Drullinsky P, Ruiz-Borrego M, Neven P*, et al.* Alpelisib plus fulvestrant in PIK3CA-mutated, hormone receptor-positive advanced breast cancer after a CDK4/6 inhibitor (BYLieve): One cohort of a phase 2, multicentre, open-label, non-comparative study. *Lancet Oncology* 2021;22:489-98.

32. Moynahan ME, Chen D, He W, Sung P, Samoila A, You D*, et al.* Correlation between PIK3CA mutations in cell-free DNA and everolimus efficacy in HR(+), HER2(-) advanced breast cancer: results from BOLERO-2. *British Journal of Cancer* 2017;116:726-30.

33. Hortobagyi GN, Chen D, Piccart M, Rugo HS, Burris HA, 3rd, Pritchard KI*, et al.* Correlative analysis of genetic alterations and everolimus benefit in hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: Results from BOLERO-2. *Journal of Clinical Oncology* 2016;34:419-26.

34. Di Leo A, Jerusalem G, Petruzelka L, Torres R, Bondarenko IN, Khasanov R*, et al.* Final overall survival: fulvestrant 500 mg vs 250 mg in the randomized CONFIRM trial. *Journal of the National Cancer Institute* 2014;106:djt337.

35. Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect comparisons in meta-analysis of randomised controlled trials. *Journal of Clinical Epidemiology* 1997;50:683-91.

36. Dias S, Ades AE, Welton NJ, Jansen JP, Sutton AJ. Network meta-analysis for decision-making: John Wiley & Sons; 2018.

37. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. *Statistics in Medicine* 2015;34:3661-79.

38. European Medicines Agency (EMA). Committee for Medicinal Products for Human Use (CHMP) positive opinion for alpelisib (Piqray) for locally advanced or metastatic breast cancer with a PIK3CA mutation. EMA: London; 2020.

39. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. *Value in Health* 2010;13:509-18.

40. National Institute for Health and Care Excellence. Ribociclib with fulvestrant for treating hormone receptor-positive, HER2-negative, advanced breast cancer. NICE Technology Appraisal Guidance TA593. NICE: London; 2019.

41. Office for National Statistics. National life tables: England. ONS: London; 2020.

42. Novartis AG. A Phase III randomized double-blind, placebo controlled study of alpelisib in combination with fulvestrant for men and postmenopausal women with hormone receptor positive, HER2-negative advanced breast cancer which progressed on or after aromatase inhibitor treatment. SOLAR-1 Clinical Study Report. Novartis: London; 2018.

43. Yu-Ming S. BYLieve: A phase II, multicenter, open-label, three-cohort, non-comparative study to assess the efficacy and safety of alpelisib plus fulvestrant or letrozole in patients with PIK3CA mutant, hormone receptor (HR) positive, HER2- negative advanced breast cancer (aBC), who have progressed on or after prior treatments. First Interpretable Results (FIR) Primary Analysis for Cohort A / Second Interim Analysis. Novartis; London; 2020.

44. Curtis L, Burns A. Unit costs of health and social care 2019. PSSRU: Kent; 2019.

45. NHS Improvement. NHS Reference Costs 2019/20. NHS: London; 2021.

46. European Medicines Agency. Summary of Product Characteristics - everolimus. EMA: London; 2020.

47. Gillett M, Brennan A, Watson P, Khunti K, Davies M, Mostafa S*, et al.* The cost-effectiveness of testing strategies for type 2 diabetes: a modelling study. *Health Technology Assessment* 2016;19:1-80.

48. Office for National Statistics. CPI index - medical services. ONS: London; 2020.

49. National Institute for Health and Care Excellence. Ribociclib with an aromatase inhibitor for previously untreated, hormone receptor positive, HER2-negative, locally advanced or metastatic breast cancer. NICE Technology Guidance TA496. NICE: London; 2017.

50. Hamblin A, Wordsworth S, Fermont JM, Page S, Kaur K, Camps C*, et al.* Clinical applicability and cost of a 46-gene panel for genomic analysis of solid tumours: Retrospective validation and prospective audit in the UK National Health Service. *PLoS Medicine* 2017;14:e1002230.

51. Mollon L, Aguilar A, Anderson E, Dean J, Davis L, Warholak T*, et al.* A systematic literature review of the prevalence of PIK3CA mutations and mutation hotspots in HR+/HER2- metastatic breast cancer AACR Annual Meeting 2018; April 14-18, 2018; Chicago, IL, abstract no. 35.

52. Van Hout B, Janssen MF, Feng Y, Kohlmann T, Busschbach J, Golicki D*, et al.* Interim scoring for the EQ-5D-5L: Mapping the EQ-5D-5L to EQ-5D-3L value sets. . *Value in Health* 2012;15:708-15.

53. Commercial Medicines Unit (CMU). Drugs and pharmaceutical electronic market information tool (eMIT). CMU: London; 2020.

54. Lloyd A, Nafees B, Dewilde S, Watkins J. Health state utilities for metastatic breast cancer. *British Journal of Cancer* 2006;95:683-90.

55. Weinstein MC, O'Brien B, Hornberger J, Jackson J, Johannesson M, McCabe C*, et al.* Principles of good practice for decision analytic modeling in health-care evaluation: Report of the ISPOR Task Force on good research practices—modeling studies. *Value in Health* 2003;6:9-17.

56. Drummond MF, Sculpher MJ, Torrance GW, O'Brien B, Stoddart GL. Methods for the economic evaluation of health care programmes. . 4th edn. London: Oxford University Press: London; 2015.

57. National Institute for Health and Care Excellence. Guide to the methods of technology appraisal 2013. NICE: London; 2013.

58. Novartis AG. Alpelisib plus fulvestrant for the treatment of HR+, HER2– advanced breast cancer with a PIK3CA mutation. Clinical validation meeting: 4th May 2020 1:00pm–2:00pm. Novartis: London; 2020.

59. Novartis. NICE submission clinical validation meeting – 28th June 2021 (2–3pm). Novartis: London; 2021.

60. Vernieri C, Corti F, Nichetti F, Ligorio F, Manglaviti S, Zattarin E*, et al.* Everolimus versus alpelisib in advanced hormone receptor-positive HER2-negative breast cancer: targeting different nodes of the PI3K/AKT/mTORC1 pathway with different clinical implications. *Breast Cancer Research* 2020;22.

61. Hernández Alava M, Wailoo AJ. Fitting adjusted limited dependent variable mixture models to EQ-5D. *The Stata Journal* 2015;15:737-50.

62. Hernández Alava M, Wailoo AJ, Ara R. Tails from the peak district: adjusted limited dependent variable mixture models of EQ-5D questionnaire health state utility values. *Value in Health* 2012;15:550-61.

63. National Institute for Health and Care Excellence. Palbociclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer. NICE Technology Guidance TA495. NICE: London; 2017.

64. National Institute for Health and Care Excellence. Abemaciclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer. NICE Technology Appraisal Guidance TA563. NICE: London; 2019.

65. National Institute for Health and Care Excellence. Fulvestrant for untreated locally advanced or metastatic oestrogen-receptor positive breast cancer. Technology Appraisal Guidance TA503. NICE: London; 2018.

66. National Institute for Health and Care Excellence. Technology Appraisal Guidance 639: Atezolizumab with nab-paclitaxel for untreated PD-L1-positive, locally advanced or metastatic, triple-negative breast cancer. NICE: London, UK; 2021.

67. Mitra D, Wood R, De Courcy J, Iyer S. PCN222 - Patient reported health utility in HR+/HER2- advanced/metastatic breast cancer. *Value in Health* 2016;19.

68. National Institute for Health and Care Excellence. Trastuzumab deruxtecan for treating HER2-positive unresectable or metastatic breast cancer after 2 or more anti-HER2 therapies. Technology Appraisal Guidance 704. NICE: London, UK; 2021.

9 APPENDICES

Appendix 1: Implementation of the ERG's exploratory analyses

All economic analyses have been implemented using drop-down menus in a modified version of the company's original model. Please refer to the model uploaded to NICEDocs with filename "AlpelisibERGModel_220921.xls"