NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Alpelisib in combination with fulvestrant for treating advanced hormone-receptor positive, HER2-negative, PIK3CA-mutated breast cancer [ID3929]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Alpelisib in combination with fulvestrant for treating advanced hormone-receptor positive, HER2-negative, PIK3CA-mutated breast cancer [ID3929]

Contents:

The following documents are made available to consultees and commentators:

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

1. **Company submission summary** from Novartis
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3. **Patient group, professional group and NHS organisation submissions** from:
   a. Breast Cancer Now
   b. NCRI-ACP-RCP-RCR
4. **Evidence Review Group report** prepared by the School of Health and Related Research
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   a. Dr Catherine Harper-Wynne, Consultant Medical Oncologist – clinical expert, nominated by the NCRI-ACP-RCP-RCR
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Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Alpelisib plus fulvestrant for treating HR+, HER2– advanced breast cancer with a *PIK3CA* mutation [ID3929]

Document B

Company evidence submission

July 2021

File name	Version	Contains confidential information	Date
ID3929_Novartis_Alpelisib_Document B_200721_FINAL_Fully Redacted	FINAL	No	20th July 2021

Instructions for companies

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Please note that the information requirements for submissions are summarised in this template; full details of the requirements for pharmaceuticals and devices are in the user guide.

This submission must not be longer than 150 pages, excluding appendices and the pages covered by this template. If it is too long, it will not be accepted.

Companies making evidence submissions to NICE should also refer to the NICE guide to the methods of technology appraisal and the NICE guide to the processes of technology appraisal.

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Foreword

Alpelisib plus fulvestrant has received a marketing authorisation from the European Medicines Agency (EMA) for the treatment of postmenopausal women, and men, with hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2–), locally advanced or metastatic breast cancer with a phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (*PIK3CA*) mutation after disease progression following endocrine therapy (ET) as monotherapy.

However, following the National Institute of Health and Care Excellence (NICE) approval of ribociclib, abemaciclib and palbociclib in combination with an aromatase inhibitor (AI), cyclin-dependent kinase inhibitors (CDK4/6is) in combination with AIs (i.e. not endocrine monotherapy) are now considered the standard of care for patients at first line in the metastatic setting who are sensitive to endocrine therapy (see Figure 1).

Patients whose disease has progressed after treatment with a CDK4/6i in combination with AI, or for whom this combination is not well-tolerated, face a poor prognosis, and meet NICE's end-of-life criteria (Section B.2.11.3). There are also limited options for this population, as patients are not usually re-treated with CDK4/6is in UK practice. Therefore, everolimus plus exemestane would typically be the next treatment.

Recognising the lack of treatment options and poor prognosis for patients who have received CDK4/6i therapy, Novartis have applied to the Medicines and Healthcare products Regulatory Agency (MHRA) for a Type II variation to the existing EMA licence; the updated marketing authorisation is anticipated in [redacted]. The anticipated licensed wording for this variation is as follows:

[redacted]

Therefore, following a marketing authorisation from the MHRA, alpelisib plus fulvestrant is anticipated to be licensed in a broader population than the current EMA marketing authorisation, as the licence will include patients who have received ET combination therapy as a prior treatment, rather than only those patients who have received prior ET as monotherapy.

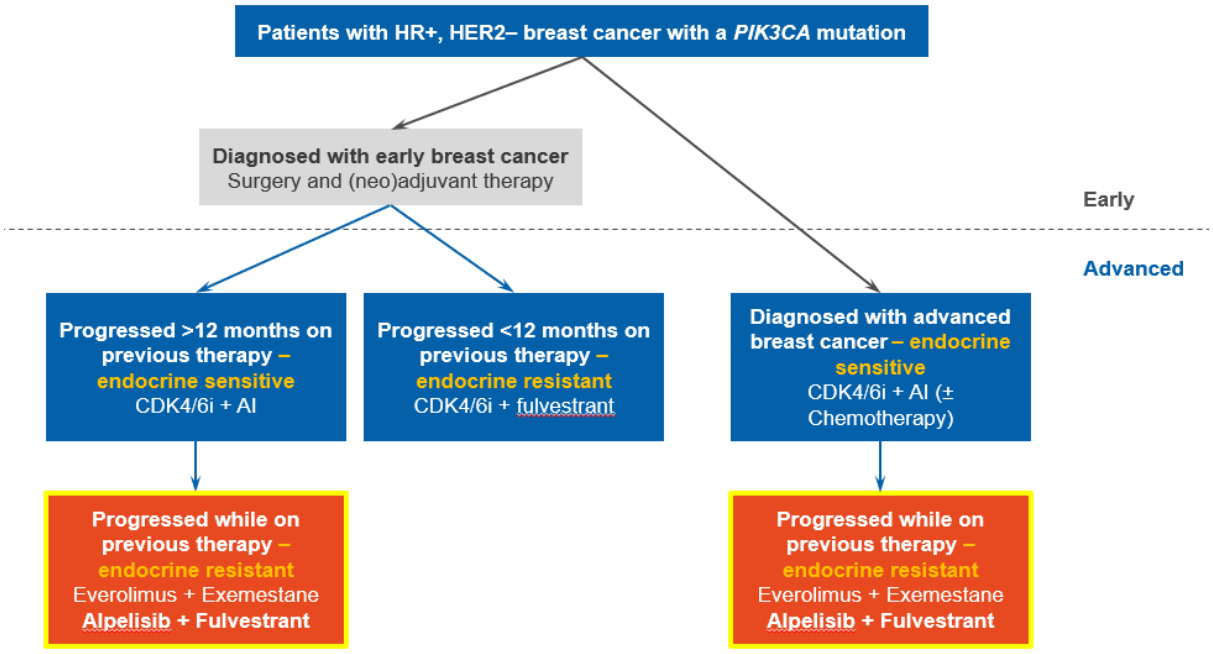
The population of specific interest for this submission is a subset of the newly licensed population, i.e., patients with HR+, HER2–, locally advanced or metastatic breast cancer with a *PIK3CA* mutation after disease progression following treatment with a CDK4/6i. Accordingly, alpelisib plus fulvestrant is anticipated to be positioned in the treatment pathway for advanced breast cancer (ABC) as per Figure 1.

The key evidence base for alpelisib plus fulvestrant in HR+, HER2–, locally advanced or metastatic breast cancer with a *PIK3CA* mutation after disease progression following treatment with a CDK4/6i comprises Cohort A of the BYLieve trial. This cohort of BYLieve enrolled patients who had received immediate prior CDK4/6i + AI therapy, and this cohort is thus considered the main source of evidence for the post-CDK4/6i population. Evidence is also available from a small number of patients from the pivotal SOLAR-1 randomised controlled trial (RCT), which enrolled 20 patients who had received prior CDK4/6i therapy (nine [5.3%] in the alpelisib plus fulvestrant

arm and 11 [6.5%] in the placebo plus fulvestrant arm). These numbers were relatively small due to the evolving treatment pathway for ABC and the speed of enrolment for SOLAR-1. CDK4/6i + AI is a relatively new addition to the treatment pathway – the first CDK4/6i was approved by the FDA in February 2015, while the SOLAR-1 enrolment period commenced in July 2015 and ran until July 2017. As patients typically received CDK4/6i + AI for a relatively long duration, enrolment for SOLAR-1 was largely complete by the time any patients who had received this combination had discontinued and subsequently progressed; only a small subgroup of subjects post-CDK4/6i therapy were thus enrolled in SOLAR-1. Data for the post-CDK4/6i population of SOLAR-1 are presented in Section B.2.3; data for the full SOLAR-1 population including patients who had not received prior CDK4/6i therapy are presented in Appendix F.

As described above, patients who have previously received a CDK4/6i and progress following first-line treatment for ABC (i.e. the population of interest for this submission) have an extremely poor prognosis, and these patients meet NICE's end-of-life criterion of a short life expectancy of <24 months. Everolimus plus exemestane is the only reimbursed treatment option available to delay the time to cytotoxic chemotherapy for these patients. Thus, this combination represents the relevant comparator within the scope of this submission.

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



Arrows in blue represent progression, and orange boxes represent the proposed positioning of alpelisib plus fulvestrant, within the anticipated marketing authorisation from the MHRA. Everolimus plus exemestane is the main comparator to alpelisib plus fulvestrant in this setting. Although outlined in the final scope, exemestane monotherapy, tamoxifen and CDK4/6i + fulvestrant are not relevant comparators. Exemestane monotherapy and tamoxifen are not widely used in UK clinical practice.[1] For patients who have received CDK4/6i + AI first-line in the advanced setting, another CDK4/6i would not be used second-line in UK clinical practice.[1] Likewise, the 5th European Society for Medical Oncology (ESMO) Clinical Practice Guidelines for Advanced Breast Cancer recommend the use of CDK4/6i + fulvestrant in patients who have not previously used CDK4/6i.[2] The National Comprehensive Cancer Network (NCCN) also highlight limited data to support an additional line of therapy with another CDK4/6i, following disease progression while on CDK4/6i.[3] CDK4/6i are thus not considered relevant comparators for the population of interest in this submission. In addition, only one of the CDK4/6is + fulvestrant is routinely funded by the National Health Service (NHS) (ribociclib: TA687),[4] while the other two are currently funded only via the Cancer Drugs Fund (CDF) and thus are not considered standard of care (palbociclib: TA619,

and abemaciclib: TA579).[5, 6]
Abbreviations: 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; *PIK3CA*: phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.
Source: NICE CG81;[7] NICE management pathway for HR+, HER2– ABC;[8] Novartis Data on File.[1, 9]

Within this submission, Novartis have considered prior comments from the Evidence Review Group (ERG) on the terminated 2020 appraisal (TA652) and the CDF exit submission for ribociclib plus fulvestrant (TA687).[4] These considerations have been incorporated throughout the submission, for example when updating the cost-effectiveness model, and through the provision of further supportive clinical and indirect treatment comparison analyses.

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

B.1.1 Decision problem

This submission presents the clinical and cost-effectiveness of alpelisib plus fulvestrant, in line with its anticipated marketing authorisation from the MHRA, for the treatment of [redacted]. Novartis have applied to the MHRA for a Type II variation to the EMA licence; the updated marketing authorisation is anticipated in [redacted]. This submission focusses on a subset of the proposed licence: those patients who have previously received a CDK4/6i.

The decision problem addressed within this submission aligns with the NICE final scope for this appraisal; any differences are highlighted in Table 1.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	• 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

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			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
Intervention	Alpelisib plus fulvestrant	Alpelisib plus fulvestrant	N/A – in line with final NICE scope
Comparator(s)	• 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.[1] Likewise, the 5th European Society for Medical Oncology (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.[2] The National Comprehensive Cancer Network (NCCN) also highlight that there are limited data to support the use of another CDK4/6i, following disease progression while on CDK4/6i.[3] 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.[5, 6] • 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.[1] This approach with regards to comparators is consistent with that taken in

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			other appraisals in HR+, HER2– ABC (TA579, TA619 or TA687/TA593)[4-6] • Everolimus plus exemestane is therefore the only relevant comparator to alpelisib plus fulvestrant within the scope of this submission
Outcomes	• Progression-free survival (PFS) • Overall survival (OS) • Response rate • Adverse events (AEs) 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
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	• 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	• 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

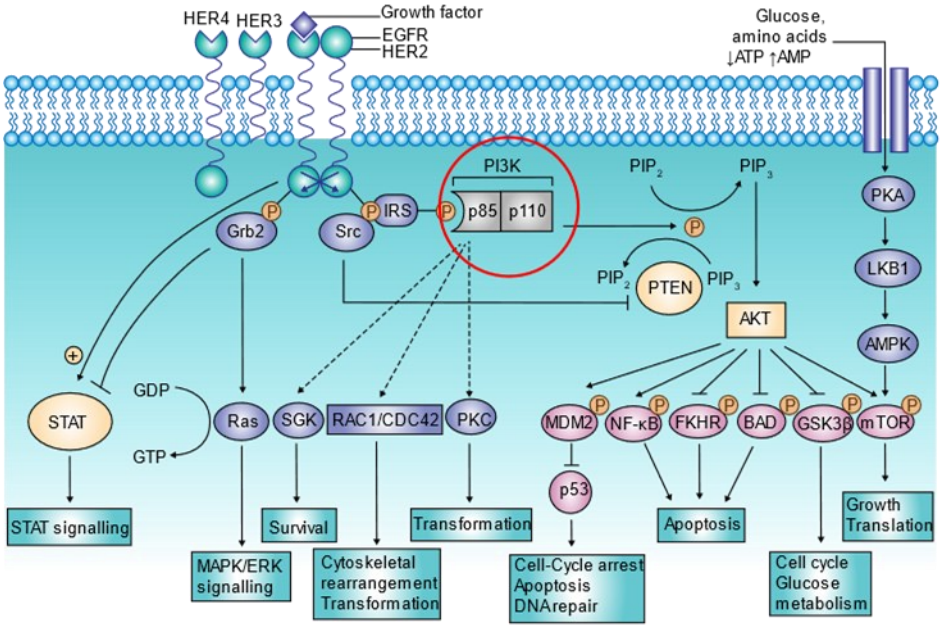
	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	perspective • The availability of any patient access schemes for the comparator technologies will be taken into account • The use of alpelisib is conditional on the presence 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	discounts have been applied within the base case economic analysis • 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	
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

Abbreviations: ABC: advanced breast cancer; AE: adverse event; CBR: clinical benefit rate; CDK4/6i: cyclin-dependent kinase 4/6 inhibitor; DoR: duration of response; EQ-5D-3L: EuroQol 5-Dimensions 3-Levels; ET: endocrine therapy; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; HRQoL: health-related quality of life; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; 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.
Source: NICE final scope for ID3929.[10]

B.1.2 Description of the technology being appraised

A summary of the mechanism of action, marketing authorisation status, costs and administration requirements associated with alpelisib plus fulvestrant in this indication is presented in Table 2.

Table 2: Technology being appraised

UK approved name and brand name	Alpelisib (Piqray®) plus fulvestrant
Mechanism of action	**Alpelisib** The phosphatidylinositol 3-kinase (PI3K) signalling pathway plays a critical role in vital cellular processes such as growth, proliferation, metabolism, survival and motility; specifically, the PI3K/AKT/mammalian target of rapamycin (mTOR) pathway has been implicated in the pathogenesis of various human cancers through its influence on cell cycle progression, angiogenesis and metastasis (Figure 2).[11] **Figure 2: The PI3K signalling pathway**  **Abbreviations:** AMP: adenosine monophosphate; AMPK: AMP-activated protein kinase; ATP: adenosine 5'-triphosphate; CDC42: cell division control protein 42 homolog; DNA: deoxyribonucleic acid; EGFR: epidermal growth factor receptor; ERK: extracellular-signal-regulated kinase; GDP: guanosine diphosphate; Grb2: growth factor receptor-bound protein 2; GSK3β: glycogen synthase kinase 3 beta; GTP: guanosine-5'-triphosphate; HTTP: guanosine triphosphate; HER2/3/4: human epidermal growth factor receptor 2/3/4; IRS: insulin receptor substrate; LKB1: liver kinase B1; MAPK: mitogen-activated protein kinase; MDM2: mouse double minute 2 homolog; mTOR: mammalian target of rapamycin; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; PI3K: phosphatidylinositol-3 kinase; PIP2: phosphatidylinositol 4,5-bisphosphate; PIP3: phosphatidylinositol 3,4,5-triphosphate; PKA: protein kinase A; PKC: protein kinase C; PTEN: phosphatase and tensin homolog; RAC1: ras-related C3 botulinum toxin substrate 1; SGK: serine/threonine-protein kinase; STAT: signal transducer of activation and transcription. **Source:** Adapted from Hennessy *et al.* (2005).[12]

	Approximately 30–40% of patients with HR+, HER2– ABC have a mutation in the *PIK3CA* gene, inducing hyperactivation of the α-isoform of PIK3CA.[13-21] This in turn promotes uncontrolled cell division, propagation of abnormal cells and the downregulation of autophagy.[22] *PIK3CA* mutations are also associated with resistance to endocrine, chemo-, radio-, and anti-HER2 therapies, tumour growth, and a poorer prognosis compared with patients who do not have the mutation.[23-28] Alpelisib is an orally bioavailable, small-molecule, α-specific PI3K inhibitor, which selectively inhibits p110α 50 times more strongly than other isoforms (β, δ, γ).[29] In this way, alpelisib 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.[24, 30, 31] **Alpelisib plus fulvestrant** HRs are key to cell proliferation and survival signalling pathways, with upregulation of the HR signalling pathway identified as a key driver of tumour development and progression.[32, 33] Approximately 75% of breast cancers in postmenopausal women are HR+ and around two-thirds are oestrogen receptor positive (ER+) specifically.[30, 34] Fulvestrant is an ER antagonist, which down-regulates and degrades the ER protein in human breast cancer cells (known as a selective ER degrader).[35] The combination of alpelisib plus fulvestrant has demonstrated synergistic anti-tumour activity as compared with either agent alone in *PIK3CA*-mutated, ER+ xenograft models.[29] Furthermore, in a Phase Ib trial, alpelisib plus fulvestrant led to a complete or partial response in 29% of patients with heavily pre-treated *PIK3CA*-mutated, HR+ ABC, compared with no complete or partial response in patients with *PIK3CA* wild-type tumours.[36]
Marketing authorisation/ CE mark status	On 24th May 2019, alpelisib plus fulvestrant received regulatory approval from the Food and Drug Administration (FDA) in the US for the treatment of postmenopausal women, and men, with HR+, HER2– advanced or metastatic breast cancer with a *PIK3CA* mutation following progression on or after an endocrine-based regimen.[37] Alpelisib in with fulvestrant received marketing authorisation from the EMA on 27th July 2020 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 endocrine therapy (ET) as monotherapy.[38] Novartis have applied to the MHRA for a Type II variation to the current EMA licence for alpelisib plus fulvestrant to include patients who have progressed following CDK4/6i-containing regimens, aligning the UK label with the authorisation granted by the FDA. The anticipated licence wording is: [redacted]. Marketing authorisation from the MHRA is anticipated in [redacted].
Indications and any restriction(s) as described in the summary of product	Alpelisib is anticipated to be licensed for: [redacted] It should be noted that alpelisib plus fulvestrant has not yet received a marketing authorisation from the MHRA and therefore the anticipated licence wording is yet to be confirmed.

characteristics (SmPC)	The SmPC and European public assessment report (EPAR) are aligned with the existing EMA licence, and is thus different from the intended MHRA licence wording.[38, 39] **Contraindications to alpelisib**[38] • Hypersensitivity to the active substance or to any of the excipients listed in Section 6.1 of the SmPC • Alpelisib is not indicated in women of child-bearing potential. It is not to be used in women who are, or may be, pregnant or breastfeeding (see Section 4.6 of the SmPC) **Contraindications to fulvestrant**[40] • Hypersensitivity to the active substance or to any of the excipients listed in Section 6.1 of the SmPC • Pregnancy and lactation • Severe hepatic impairment
Method of administration and dosage	The recommended dose of alpelisib plus fulvestrant is as follows: • Alpelisib*:* 300 mg (2 x 150 mg film-coated tablets), taken orally, once daily • Fulvestrant*:* 500 mg at intervals of one month, with an additional 500 mg dose given two weeks after the initial dose, via intramuscular (IM) injection.[29, 40]
Additional tests or investigations	Patients with HR+, HER2− ABC should be selected for treatment with alpelisib plus fulvestrant 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. The cost of mutation testing has been factored into the base case economic results of this submission. 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 HbA1c should be measured at baseline, four weeks and every three months thereafter.[41, 42]
List price and average cost of a course of treatment	• The list price of alpelisib for 150 mg × 56 tablets is [redacted] • The generic price of fulvestrant 250 mg per 5 mL solution for injection pre-filled syringes (×2) is assumed as [redacted], representing an [redacted] on the originator list price of Faslodex (£522.41).[43] [redacted] • Based on the base case economic analysis, the mean time on treatment is estimated to be [redacted] months for alpelisib and [redacted] months for fulvestrant, resulting in an average cost of a course of treatment with alpelisib plus fulvestrant of [redacted] (at list price) and [redacted] (with alpelisib at PAS price)
Patient access scheme (if applicable)	• A confidential PAS discount has been proposed for alpelisib of [redacted]. The proposed with-PAS price for alpelisib is [redacted] per 150 mg × 56 tablets.

Abbreviations: ABC: advanced breast cancer; EMA: European Medicines Agency; EPAR: European public assessment report; ER: oestrogen receptor; ET: endocrine therapy; EU: European Union; FDA: Food and Drug Administration; FPG: fasting plasma glucose; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; IM: intramuscular; NHS: National Health Service; PAS: patient access scheme; PI3K:

phosphatidylinositol 3-kinase; *PIK3CA*: phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; SmPC: Summary of Product Characteristics.

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

Disease overview

- Breast cancer arises when cells in the ducts or lobules of the breast divide uncontrollably to form a tumour. ABC refers to both unresectable locally advanced disease and metastatic disease.[2]
    - 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.[44-46]
    - Whilst treatable, metastatic breast cancer remains incurable and is associated with devastating effects on the physical and psychological health of both patients and caregivers.[2, 47-51]
- Breast cancers are classified according to the cell type from which the tumour arises.
    - HR+, HER2- disease is the most common form of breast cancer, accounting for approximately 56–73% of cases.[37, 52, 53,54]
    - Approximately 30–40% of patients with HR+, HER2− breast cancer also have activating mutations in the *PIK3CA* gene, inducing hyperactivation of the alpha isoform (p110α) of PI3K, which may be associated with a poor prognosis and the development of endocrine resistance.[13-18, 21, 23, 25-27, 55]
- Patients with HR+, HER2– ABC can be further categorised as either endocrine sensitive or endocrine resistant. The patient population of interest to this appraisal is people with *endocrine resistant* HR+, HER2− ABC with a *PIK3CA* mutation (see definitions in the Foreword), which aligns with the patient populations of the pivotal BYLieve and SOLAR-1 trials (endocrine sensitive patients were deemed ineligible for enrolment in the SOLAR-1 trial following a protocol amendment on 30th August 2016, to focus the trial on the endocrine resistant population).[29]

Clinical pathway of care

- International guidance on the treatment of HR+, HER2– ABC is available from the ESMO Clinical Practice Guidelines: Advanced Breast Cancer (2020) and NCCN Clinical Practice Guidelines: Breast Cancer (2020).[2, 3]
    - The ESMO 2020 Guidelines recommend alpelisib plus ET (e.g. fulvestrant) as a treatment option in patients with HR+, HER2– ABC with a *PIK3CA* mutation, and suggest that, based on data from the BYLieve trial, alpelisib plus ET could be used following CDK4/6i plus ET.[2]
    - Following FDA approval, the NCCN also already recommends alpelisib plus fulvestrant as a 'preferred regimen' for the treatment of HR+, HER2− ABC with a *PIK3CA* mutation.[3]

- Additionally, alpelisib is included in the ESMO online guidance for anti-cancer treatments, and received a score of 3 on the ESMO-Magnitude of Clinical Benefit Scale (ranging from 1–5), in which 5 indicates the greatest magnitude of clinical benefit.[56]

- Treatment decisions in UK clinical practice are largely guided by NICE guidance: NICE Clinical Guideline 81 (NG81 Advanced Breast Cancer: Diagnosis and Treatment [2009]) and the NICE management pathway for HR+, HER2– ABC (2019).[7, 8]
- For patients with HR+, HER2− ABC with a *PIK3CA* mutation who experience disease progression following treatment with a CDK4/6i, the mainstay of treatment in the UK comprises everolimus plus exemestane.[57] Everolimus plus exemestane has a limited survival benefit and there is no biomarker to determine who will benefit (or not) from treatment.[58-61]
    - According to the ESMO (2020) and NCCN (2020) guidelines, there are limited data to support the use of another CDK4/6i in patients who progress on a CDK4/6i.[2, 3]
- The evidence base for alpelisib plus fulvestrant comprises two trials: BYLieve and SOLAR-1. This submission focuses on a subset of the anticipated marketing authorisation, consistent with the patient population within the BYLieve trial (Cohort A) i.e. patients with HR+, HER2–, locally advanced or metastatic breast cancer with a *PIK3CA* mutation after disease progression following a CDK4/6i (see Foreword).

Unmet need

- Despite the availability of everolimus plus exemestane for patients with HR+, HER2– ABC, there is still a substantial unmet need for a therapy to specifically target the *PIK3CA* mutation.
    - Patients with HR+, HER2– ABC with a *PIK3CA* mutation have demonstrated a shorter PFS and OS versus patients with wild-type *PIK3CA,* yet there is currently a lack of treatment options that specifically address the effects of this mutation.[16, 18, 23, 26, 28, 42, 62-68]
    - There is also a lack of treatment options that are biomarker-driven and have a differential (improved) impact on patients with a *PIK3CA* mutation versus those without. Such a treatment would allow patients who are likely to benefit (or not) to be identified and would therefore lead to an efficient use of NHS resources.[21, 29]
    - For patients who have progressed following treatment with a CDK4/6i, prognosis is extremely poor, and these patients meet NICE's end-of-life criterion of a short life expectancy of <24 months. There is, therefore, a substantial unmet need in this patient population, particularly as these patients are unlikely to receive a CDK4/6i inhibitor again in the second-line setting. Thus, everolimus plus exemestane is the only reimbursed treatment option available to delay the time to cytotoxic chemotherapy for these patients.
- Alpelisib plus fulvestrant is the first alpha-selective PI3K inhibitor to be licensed by the FDA and EMA.[37, 38] This combination provides patients with HR+, HER2–, *PIK3CA*-mutated ABC with an effective treatment option that targets the *PIK3CA* mutation specifically, and that can

be sequenced to delay the onset of cytotoxic chemotherapy by increasing the time spent progression-free, allowing for the maintenance of patient HRQoL.[4, 50, 69, 70]

B.1.3.1 Disease overview

Breast cancer arises when cells in the ducts or lobules of the breast divide uncontrollably to form a tumour.[71] ABC refers to both unresectable locally advanced disease (where the cancer has grown directly into nearby tissues and is not amenable to curative treatment by surgery), and metastatic disease (where the cancer has spread to other parts of the body, most commonly the lymph nodes, bones, liver, lungs and brain).[2]

Tumour classification

Breast cancers are classified according to the cell type from which the tumour arises. Approximately 75% of breast cancers in postmenopausal women are HR+, meaning the cancer cells express receptors for oestrogen (ER) and/or progesterone (PgR), which promote their growth.[30, 33] Tumours can also be classified as HER2+ or HER2−, depending on whether the growth-promoting HER2 protein is expressed.[72] HR+, HER2− disease is the most common form of breast cancer, accounting for approximately 56–73% of cases in which the HR/HER2 status is known. [37, 52, 53,54]

Endocrine resistance

Patients with HR+, HER2– ABC can be further categorised as either endocrine sensitive or endocrine resistant. The ESMO Clinical Practice Guidelines: Advanced Breast Cancer (2020) provide definitions for resistance to ET.[a2]

In this submission, alpelisib plus fulvestrant is positioned in line with the patient population of the BYLieve clinical trial, with supporting evidence derived from the SOLAR-1 trial.

BYLieve considered endocrine resistant patients only. All patients in Cohort A had progressed following immediate prior CDK4/6i + AI therapy (either in the (neo)adjuvant or metastatic setting) and all patients in Cohort C were all required to have received an AI in either the (neo)adjuvant or metastatic setting (+/- additional lines of ET monotherapy or combination therapy in the two allowable prior lines of therapy in the metastatic setting). Full details of the Cohorts included in BYLieve are presented in Section B.2.3.[41, 73]

SOLAR-1 enrolled both primary and secondary resistant patients according to the ESMO definitions. ESMO-defined endocrine sensitive patients were initially eligible for enrolment in SOLAR-1; however, following a protocol amendment on 30th August 2016, all endocrine sensitive patients were

[a] ESMO endocrine resistance definitions: Primary endocrine resistance is defined as relapse while on the first two years of adjuvant ET, or disease progression within the first 6 months of first-line ET for advanced disease; Secondary endocrine resistance is defined as relapse while on adjuvant ET but after the first two years, relapse <12 months after completing adjuvant ET, or disease progression ≥6 months after initiating ET for advanced disease; Endocrine sensitivity is defined as relapse ≥12 months after completion of (neo)adjuvant ET, with no subsequent treatment for advanced disease.

excluded from enrolment in order to focus the trial on the endocrine resistant population.[29]

PIK3CA mutation

Of patients with HR+, HER2− ABC, approximately 30–40% have activating mutations in the *PIK3CA* gene, inducing hyperactivation of the alpha isoform (p110α) of PI3K.[13-18, 20, 21] *PIK3CA* is an oncogene; thus, a mutation may result in PI3K pathway hyperactivation, thereby promoting uncontrolled cell survival, propagation of abnormal cells and the downregulation of autophagy.[22] This in turn contributes to tumour growth, resistance to ET (a major challenge in the treatment of patients with endocrine resistant HR+, HER2– ABC)[29, 74] and a poor prognosis.[13-18, 21, 23, 25-27, 55]

In BYLieve, all patients had a *PIK3CA* mutation.[41, 75] However, it should be noted that in SOLAR-1, both patients with and without *PIK3CA*-mutated HR+, HER2− ABC underwent randomisation; *PIK3CA* wild-type patients were randomised as part of a proof-of-concept (PoC) analysis.[29] PoC criteria to conclude a treatment benefit with alpelisib plus fulvestrant with respect to PFS in the biomarker-negative control cohort were not met at the final efficacy analysis.[29] Sample size and power calculations for the primary analyses of SOLAR-1 were based on the population with *PIK3CA*-mutated tumours, so statistical interpretation of results in that group are unaffected (see Section Appendix F). Therefore, this submission focusses on patients with HR+, HER2– ABC with a *PIK3CA* mutation only, in line with the marketing authorisation for alpelisib plus fulvestrant from the EMA, and the anticipated marketing authorisation from the MHRA.

Several Phase III RCTs of endocrine resistant populations not previously exposed to CDK4/6i have revealed that patients with tumours harbouring *PIK3CA* mutations demonstrate a numerically shorter PFS and/or OS compared to wildtype patients (Table 3). Specifically, data from the placebo arms of BELLE-2[76] (buparlisib plus fulvestrant versus placebo plus fulvestrant), BELLE-3[18] (buparlisib plus fulvestrant versus placebo plus fulvestrant), BOLERO-2 (everolimus plus exemestane versus placebo plus exemestane),[62] FERGI (pictilisib plus fulvestrant versus placebo plus fulvestrant),[77] MONALEESA-2 (ribociclib plus letrozole versus placebo plus letrozole),[16, 63, 64] MONALEESA-3 (ribociclib plus fulvestrant versus placebo plus fulvestrant),[65] MONALEESA-7 (ribociclib plus a non-steroidal aromatase inhibitor [NSAI] versus placebo plus NSAI),[66] MONARCH-2 (abemaciclib plus fulvestrant versus placebo plus fulvestrant),[67] PALOMA-3 (palbociclib plus fulvestrant versus placebo plus fulvestrant)[68, 78] and SOLAR-1 (alpelisib plus fulvestrant versus placebo plus fulvestrant)[29, 42] reveal that median PFS and/or median OS (where these data have been reported to date) are numerically shorter for patients with tumours harbouring *PIK3CA* mutations, suggesting a poorer prognosis, and therefore a greater and distinct clinical unmet need (Table 3).

These findings are further supported by pooled evidence from 3,238 patients from 33 study cohorts across 11 studies, in which patients with tumours harbouring the *PIK3CA* mutation were found to be associated with a shorter PFS versus wild-type disease (difference −2.15 months; 95% CI: −4.14, −0.15), especially when ctDNA testing was used (difference −2.16 months; 95% CI: −3.65, −0.66]),[79] as well as a Phase II randomised trial (SAFIR02), which demonstrated that *PIK3CA* mutations are a negative prognostic factor for OS, PFS and disease-free survival (DFS).[23, 26, 28, 80] Additionally, patients with HR+, HER2− ABC with a *PIK3CA* mutation are less sensitive to chemotherapy and have a shorter breast cancer-specific survival and distant metastasis-free survival compared to patients with wild-type *PIK3CA*.[25, 27, 80]

Table 3: Prognosis of patients with tumours harbouring *PIK3CA* mutations compared to tumours with wild-type *PIK3CA* based on the control arms of Phase III RCTs

Study	Endpoint	Patient population (control arm)		Difference
		PIK3CA wildtype	*PIK3CA* mutation	
BELLE-2[a]	PFS	6.8 months	3.2 months	−3.6 months
	OS	36.8 months	24.8 months	−12.0 months
BELLE-3	PFS	1.7 months	1.4 months	−0.3 months
BOLERO-2	PFS	3.0 months	2.7 months	−0.3 months
	OS	29.7 months	22.7 months	−7.0 months
FERGI	PFS	3.6 months	5.1 months	1.5 months
MONALEESA-2	PFS	14.7 months	12.7 months	−2 months
MONALEESA-3	PFS	16.7 months	11.1 months	−5.6 months
MONALEESA-7	PFS	[redacted]	[redacted]	−1.7 months
MONARCH-2	PFS	12.7 months	5.7 months	−7 months
PALOMA-3	PFS	4.6 months	3.6 months	−1.0 months
	OS	33.0 months	22.2 months	−10.8 months
SOLAR-1	PFS	[redacted]	5.7 months	−[redacted]
	OS	[redacted]	31.4 months	−[redacted]

Comparison of the control arms has been presented to preclude the effects of confounding.
[a] Note: The safety profile of buparlisib plus fulvestrant did not support its further development in HR+/HER2– ABC on or after mTOR inhibition.[18]
Abbreviations: PFS: progression-free survival; *PIK3CA*: phosphatidlyinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; RCT: randomised controlled trial; OS: overall survival.
Source: BELLE-2, Baselga *et al.* (2017);[76] BELLE-3, Di Leo *et al.* (2018);[18] BOLERO-2, Moynahan *et al.* (2017);[21, 81] FERGI, Krop *et al.* (2016);[77] MONALEESA-2, Hortobagyi *et al.* (2017);[64] MONALEESA-3, Slamon *et al.* (2018);[65] MONALEESA-7, MONALEESA-7 CSR;[66] MONARCH-2, Sledge *et al.* (2017);[67] PALOMA-3, Cristofanilli *et al.* (2016);[68, 78] SOLAR-1, André *et al.* (2020);[82] Novartis Data on File.[29, 42]

B.1.3.1.1 Epidemiology

Breast cancer is the most common cancer in the UK, accounting for 15% of all new cancer cases (2016).[83] In 2016, there were ~54,500 new cases of breast cancer diagnosed in females and approximately 360 diagnoses in men.[83] Moreover, incidence rates are projected to rise by around 2% overall in the UK between 2014 and 2035, from 173 cases per 100,000 females in 2014 to 210 cases per 100,000 females by 2035.[83] The incidence of breast cancer is strongly age-dependent with >80% of cases occurring in women over the age of 50;[84] as such, a large proportion of breast cancer patients are postmenopausal women. In terms of prevalence, an estimated 600,000 people are alive in the UK after a diagnosis of breast cancer (2019).[84, 85] This is predicted to rise to 1.2 million in 2030.[84]

Approximately 5–6% of women with breast cancer in the UK have metastatic disease at diagnosis (stage IV),[86] while around 35% with a primary diagnosis of breast cancer go on to develop metastases in the 10 years following diagnosis.[44-46, 83, 86]

B.1.3.1.2 Morbidity and mortality

Breast cancer is the 4th most common cause of cancer death in the UK, accounting for 7% of all cancer deaths in 2016.[83, 87] Additionally, there are approximately 11,400 breast cancer deaths in the UK every year (based on data from 2014–2016).[83, 87]

Whilst treatable, metastatic breast cancer remains an incurable disease with a 5-year survival rate of only approximately 25% for patients with metastatic disease at diagnosis.[2, 48] Furthermore, data from various Phase III RCTs (Table 3), and retrospective and pooled analyses indicates that patients with HR+, HER2– ABC with a *PIK3CA* mutation have a poorer prognosis than patients with wild-type *PIK3CA* disease.[18, 23, 25-28, 59, 65, 68, 88] For patients who have progressed following first-line treatment for ABC with a CDK4/6i, prognosis is extremely poor and these patients meet NICE's end-of-life criterion of a short life expectancy of <24 months (see Section B.2.11.3).

Progression to ABC is associated with debilitating physical symptoms including pain, fatigue, nausea, reduced appetite and trouble sleeping, as well as anxiety and depression.[50, 51, 89] Additional symptoms vary according to the metastatic site, but can include breathlessness, weakness, confusion and irritability.[90] Progression can also have a detrimental effect on a patient's HRQoL, impacting their ability to work and carry out daily activities.[50, 58] Caregivers may also experience a significant burden, including anxiety, stress and depression, as well as impairments to work productivity, which also negatively impacts their HRQoL.[51]

B.1.3.1.3 Unmet need

ABC is a life-limiting disease that has a substantial impact on both patient and caregiver quality of life, negatively affecting both physical and psychological health.[50, 58] Specifically, patients with endocrine resistant HR+, HER2– ABC with a *PIK3CA* mutation have a particularly poor prognosis, with a shorter OS and PFS, and reduced sensitivity to chemotherapy compared with patients with wild-type *PIK3CA* disease.[18, 23, 25-28, 59, 65, 67, 68, 79, 80] This is substantiated by several Phase III RCTs, in which patients with tumours harbouring *PIK3CA* mutations have consistently demonstrated a numerically lower median PFS and/or OS (where these data have been reported to date) compared with wild type patients (see Table 3 above),[23, 27, 28] which is thought to result from PI3K pathway hyperactivation contributing to endocrine resistance.[91, 92]

This is further supported by pooled evidence from 3,238 patients across 11 studies, in which patients with tumours harbouring the *PIK3CA* mutation were found to be associated with a shorter PFS versus wild-type disease (difference −2.15 months; 95% CI: −4.14, −0.15), especially when ctDNA testing was used (difference −2.16 months; 95% CI: −3.65, −0.66).[79] Finally, these findings are corroborated by feedback from UK clinical experts, who consider the *PIK3CA* mutation to be clinically meaningful in terms of altering prognosis for patients with endocrine resistant HR+, HER2– ABC.[93] Despite this, there are currently no recommended therapies that specifically inhibit *PIK3CA* for UK patients with endocrine resistant HR+, HER2– ABC with a *PIK3CA* mutation. Further, current treatments may not have a differential effect in patients with versus those without the *PIK3CA* mutation.[21, 29] Moreover, there is a lack of treatment options that are biomarker-driven, whereby patients who are likely to benefit (or not) from a particular treatment can be identified; such treatments would lead to an efficient use of NHS resources.

There also remains an unmet need for more treatment options to utilise in sequence, in order to delay the introduction of cytotoxic chemotherapy that is associated with short- and long-term side effects such as diarrhoea, vomiting, weight gain and cardiac dysfunction.[4, 9, 94, 95] The priority for these patients is to prolong PFS and maintain HRQoL for as long as possible.[4]

UK clinicians report that improvements in PFS and therefore delays to the initiation of cytotoxic chemotherapy (via increased time remaining progression-free), are a positive outcome in the ABC treatment landscape.[50, 69, 96] Novel treatments that improve PFS and provide more treatment options for sequencing are therefore of immense benefit for clinicians, patients and their caregivers in meeting a high unmet need.[9]

Lastly, breast cancer, and ABC in particular, is also associated with a substantial economic burden, both via direct treatment and drug development costs and indirect costs such as absenteeism and reduced productivity for both patients and their caregivers.[51, 97] Whilst these indirect aspects are not considered within the economic analysis presented within this submission, it remains relevant to consider the potential and broader positive implications that novel and effective therapies for ABC will provide.

B.1.3.2 Clinical pathway of care

Alpelisib plus fulvestrant is expected to be positioned in line with its anticipated marketing authorisation for the treatment of postmenopausal women, and men, with [redacted].

In UK clinical practice, alpelisib plus fulvestrant is anticipated to be used mainly in the post-CDK4/6i population, which has limited treatment options and poorer prognosis (see Section B.1.3.2.2 section below).

International guidance on the treatment of HR+, HER2– ABC is available in the ESMO Clinical Practice Guidelines: Advanced Breast Cancer (2020) and NCCN Clinical Practice Guidelines: Breast Cancer (2020).[2, 3] The ESMO 2020 Guidelines recommend alpelisib plus ET (e.g. fulvestrant) as a treatment option in patients with HR+, HER2– ABC with a *PIK3CA* mutation, and suggest that, based on data from the BYLieve trial, alpelisib plus ET could also be used following CDK4/6i plus ET.[2] Alpelisib is included in the ESMO online guidance to anti-cancer treatments, and received a score of 3 on the ESMO-Magnitude of Clinical Benefit Scale (ranging from 1–5), in which 5 indicates the greatest magnitude of clinical benefit.[56] Additionally, following FDA approval, the NCCN recommended alpelisib plus fulvestrant as a 'preferred regimen' for the treatment of HR+, HER2− ABC with a *PIK3CA* mutation.[3]

Treatment decisions in UK clinical practice specifically are largely guided by NICE clinical guidance including NICE Clinical Guideline 81 (NG81 Advanced Breast Cancer: Diagnosis and Treatment [2009]) and the NICE management pathway for HR+, HER2– ABC (2019).[7, 8] Treatment decisions are also shaped by whether patients are considered to be endocrine sensitive or endocrine resistant (Figure 1 in the Foreword).

A summary of clinical guideline recommendations is presented in Table 4.

Table 4: Summary of clinical guidelines for the management of ABC

Clinical guideline	Clinical guideline recommendations
5th ESMO Clinical Practice Guidelines: Advanced Breast Cancer (2020)[2]	• ET is the preferred option for HR+ ABC, even in the presence of visceral disease, unless there is visceral crisis or concern/proof of endocrine resistance • The preferred first-line ET depends on the type and duration of adjuvant ET as well as the time elapsed from the end of adjuvant ET; it can be an AI, tamoxifen or fulvestrant • The addition of a CDK4/6i to an AI, in patients naïve or pre-exposed to ET, is a preferred treatment option (although patients relapsing <12 months from the end of adjuvant AI are not included in published studies and so may not be suitable) • The addition of a CDK4/6i to fulvestrant, in patients previously exposed to ET is a preferred treatment option, if a CDK4/6i was not previously used • Based on the data from the BYLieve trial, alpelisib plus ET may be used following CDK4/6i plus ET in patients with PIK3CA-mutated tumours • The addition of everolimus to an AI is a valid option for some patients previously exposed to ET; however, toxicity must be taken into account • CDK4/6i plus ET is the standard of care for patients with HR+, HER2– ABC. The CDK4/6i can be combined with an AI or with fulvestrant, in de novo or recurrent ABC, in first- or second-line and in cases of primary or secondary resistance • It remains unclear if CDK4/6i should be preferably administered in the first- or second-line setting
NICE management pathway for HR+, HER2– ABC (2019)[8]	• ET alone (an AI) is recommended for the first-line treatment of postmenopausal women with HR+ ABC (with either no prior history of ET or if previously treated with tamoxifen) • Abemaciclib, palbociclib and ribociclib in combination with an AI are recommended as initial treatments • Abemaciclib, palbociclib and ribociclib in combination with fulvestrant are recommended for those who have received previous ETb • Everolimus is recommended in combination with exemestane for those who with disease that has recurred or progressed after treatment with a non-steroidal AI • Systemic sequential chemotherapy should be offered to treat patients with ABC for whom a greater probability of response is important and who understand, and are likely to tolerate the additional toxicity
NCCN Clinical Practice Guidelines in Oncology: Breast Cancer (2020)[3]	• ET alone is recommended as first-line treatment for patients with recurrent or metastatic HR+ disease • Abemaciclib, palbociclib and ribociclib in combination with an AI, or fulvestrant, are also recommended as first-line treatment • ET alone is also recommended as second-line treatment • Abemaciclib, palbociclib and ribociclib in combination fulvestrant, are also recommended as second-line treatment for those patients

Clinical guideline	Clinical guideline recommendations
	who have not received prior treatment with CDK4/6is • If there is disease progression while on a CDK4/6i therapy, there are limited data to support an additional line of therapy with another CDK4/6i-containing regimen • Everolimus in combination with ET (exemestane, fulvestrant or tamoxifen) is recommended as second-line treatment • Alpelisib in combination with fulvestrant is recommended as preferred second-line treatment

[a] The ESMO guidelines included here apply to both men and postmenopausal women, as per the proposed licensed indication for alpelisib.
[b] Note that abemaciclib and palbociclib in combination with fulvestrant are recommended on the CDF in the UK.[5, 6]
Abbreviations: ABC: advanced breast cancer; AI: aromatase inhibitor; CDF: Cancer Drugs Fund; CDK4/6i: cyclin-dependent kinase 4/6 inhibitor; ESMO: European Society for Medical Oncology; ET: endocrine therapy; HR: hormone receptor; NICE: National Institute for Health and Care Excellence; NCCN: National Comprehensive Cancer Network.

B.1.3.2.1 Treatment of early and locally advanced breast cancer

NICE Clinical Guideline 101 (NG101 Early and Locally Advanced Breast Cancer: Diagnosis and Treatment [2018]) recommends that patients with early breast cancer undergo surgery and receive appropriate (neo)adjuvant therapy, unless significant comorbidity precludes surgery.[98]

The mainstay of treatment for HR+ breast cancer comprises therapies that regulate oestrogen signalling, collectively referred to as ET.[98] There are two broad types of ET: therapies that target oestrogen receptors, such as selective oestrogen receptor modulators (SERMs; e.g. tamoxifen) or selective oestrogen receptor down-regulators (SERD; e.g. fulvestrant), and those that reduce the production of oestrogen through the inhibition of enzymatic activity required for the production of oestrogens, termed AIs (e.g. anastrozole and letrozole [non-steroidal], and exemestane [steroidal]). Most HR+ breast cancer patients will receive (neo)adjuvant ET.[99] NICE guidance states that postmenopausal women should be offered an AI if they are at medium or high risk of disease recurrence, or tamoxifen if they are at low risk, or if AIs are not tolerated or are contraindicated. Tamoxifen is also offered as initial adjuvant ET for men and premenopausal women with HR+, invasive breast cancer.[98]

B.1.3.2.2 Treatment of HR+, HER2– ABC

Endocrine sensitive HR+, HER2– ABC

Patients who progress to HR+, HER2– ABC >12 months following completion of (neo)adjuvant ET, or patients who are diagnosed with *de novo* HR+, HER2– ABC and have not received prior ET are termed endocrine sensitive. Alpelisib plus fulvestrant will not be used in this population, given that endocrine sensitive patients were subsequently excluded from SOLAR-1 following a protocol amendment and there were no endocrine sensitive patients in BYLieve. The treatment pathway for these patients has been described below to provide information on the treatment sequence for patients who ultimately become endocrine resistant.

For endocrine sensitive patients, the NICE management pathway for HR+, HER2– ABC states that ET alone (an AI) is recommended for the first-line treatment of postmenopausal women with HR+ ABC (with either no prior history of ET, or if previously treated with tamoxifen).[8] The CDK4/6is, abemaciclib, palbociclib and ribociclib (all in combination with an AI), are also recommended by NICE as first-line treatment for previously untreated HR+, HER2– ABC, and are considered the standard of care for most patients.[100-102] Finally, according to the NICE management pathway for HR+, HER2– ABC, tamoxifen should be offered to men as a first-line treatment with HR+ ABC.[8] This is the only guidance included for the treatment of male ABC patients within these NICE guidelines.[8] Male breast cancer is rare, with approximately 390 diagnoses each year in the UK compared to ~54,800 new cases in women, and therefore treatment guidelines for men with ABC are sparse.[103]

Endocrine resistant HR+, HER2– ABC

Treatment for patients with endocrine resistant HR+, HER2– ABC depends on therapies previously received. Ribociclib in combination with fulvestrant is recommended by NICE for those who have progressed on ET.[4] Other CDK4/6is (abemaciclib and palbociclib, both in combination with fulvestrant) have also been recommended for reimbursement by NICE on the Cancer Drugs Fund (CDF) for the same population (TA579 and TA619). Abemaciclib is currently undergoing CDF exit reappraisal; and a reassessment of palbociclib will be conducted after the conclusion of the ongoing PALOMA-3 clinical study.[6, 104] However, it is important to note that if patients receive

a CDK4/6i + AI for the first-line treatment for advanced disease, they are unlikely to receive another CDK4/6i in the second-line, based on UK clinical practice and in line with the ESMO 2020 and NCCN 2020 guidelines.[1, 2] These CDK4/6is have also not been assessed by NICE in the post-CDK4/6i population.

In patients with endocrine resistant HR+, HER2– ABC (in UK clinical practice) that have received a prior CDK4/6i, the mainstay of treatment is everolimus plus exemestane, which 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 (TA421).[57] However, this combination can be associated with limited survival benefit.[58-61] Additionally, there is currently a lack of adequate biomarkers for predicting which patients will likely benefit (or not) from everolimus plus exemestane, preventing the efficient use of NHS resources to treat only those patients who are likely to derive the most benefit.[61]

Exemestane monotherapy and tamoxifen may also be options for patients in this setting, however their use is not widespread in UK clinical practice.[4, 9] Moreover, exemestane monotherapy and tamoxifen have not undergone NICE appraisal in the endocrine resistant population.[8] These therapies are therefore not considered comparators in this submission.

For patients who have progressed following first-line treatment for HR+, HER2– ABC with a CDK4/6i, prognosis is extremely poor and these patients meet NICE's end-of-life criterion of a short life expectancy of <24 months (see Section B.2.11.3). There is, therefore, a high unmet need in this patient population, particularly as these patients are unlikely to receive a CDK4/6i again in the second-line setting. Thus, everolimus plus exemestane is the only reimbursed treatment option available to delay the time to cytotoxic chemotherapy for these patients.

B.1.3.2.3 Positioning of alpelisib plus fulvestrant in the treatment pathway

In this submission, alpelisib plus fulvestrant is positioned in line with its anticipated marketing authorisation for the treatment of postmenopausal women, and men, with [redacted]. More specifically, this submission focuses on a subset of the 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 (see Foreword).The methodology and results of BYLieve and SOLAR-1, the pivotal trials supporting the use of alpelisib plus fulvestrant in this setting are described in detail in Section B.2 and Appendix F.

As patients with a prior CDK4/6i are unlikely to receive another CDK4/6i,[1-3] the mainstay of treatment in the UK for patients with HR+, HER2– ABC with a *PIK3CA* mutation after disease progression following treatment with a CDK4/6i comprises everolimus plus exemestane,[57] which therefore represents the most relevant comparator to alpelisib plus fulvestrant in the context of this submission. Despite the availability of everolimus plus exemestane for patients with endocrine resistant HR+, HER2– ABC, there remains a substantial unmet need (see Section B.1.3.1.3). Prognosis is also extremely poor in patients who progress following the first line of treatment containing CDK4/6i (see Section B.2.11.3). Alpelisib plus fulvestrant is therefore anticipated to provide patients with an effective, tolerable therapy that is personalised to specifically target tumours harbouring the *PIK3CA* mutation that are associated with a worse prognosis compared with wild-type disease.

B.1.4 Equality considerations

No equality issues related to the use of alpelisib in combination with fulvestrant are foreseen.

B.2 Clinical effectiveness

Summary of clinical effectiveness

- The efficacy and safety of alpelisib plus fulvestrant as a treatment for patients with endocrine resistant HR+, HER2– ABC with a *PIK3CA* mutation who have progressed following prior CDK4/6i therapy has been demonstrated in the ongoing, phase II, international multicentre trial, BYLieve,[41, 75] and the Phase III international, multicentre RCT, SOLAR-1.[29]

BYLieve

- In Cohort A of BYLieve, 127 patients with HR+, HER2–, *PIK3CA*-mutated ABC were enrolled to receive alpelisib plus fulvestrant post-progression on a CDK4/6i plus AI.[75]
    - Data for Cohort C of BYLieve (where patients receive alpelisib plus fulvestrant following prior ET monotherapy, ET plus targeted therapy [e.g. everolimus, or CDK4/6i plus fulvestrant once Cohort B has closed]) are not yet available; however the patient population evaluated therein is relevant within the context of the anticipated licence for alpelisib plus fulvestrant.
- At the primary analysis for Cohort A (17th December 2019), the study met its primary endpoint; the proportion of patients who were alive without disease progression at 6 months was 50.4% (95% CI: 41.2, 59.6), with the lower bound of the 95% CI exceeding 30% (the protocol-defined clinically meaningful threshold).[75]
- Median PFS for Cohort A was 7.3 months (95% CI: 5.6, 8.3) and median OS was 17.3 months (95% CI: 17.2, 20.7).[75]
- In terms of response rates, ORR for Cohort A was 17.4% (95% CI: 11.1, 25.3) and CBR was 45.5% (95% CI: 36.4, 54.8).[75]

SOLAR-1

- In SOLAR-1, 341 patients with HR+, HER2– ABC with a *PIK3CA* mutation who had progressed on or after treatment with AI therapy (in the neo/adjuvant or advanced setting) were randomised 1:1 to receive either alpelisib plus fulvestrant or placebo plus fulvestrant. 20 patients had received prior CDK4/6i therapy (nine [5.3%] in the alpelisib plus fulvestrant arm, and 11 [6.5%] in the placebo plus fulvestrant arm).[29]
- At the final OS analysis (23rd April 2020), PFS results for the overall population (i.e. including patients with and without prior CDK4/6i therapy) showed longer-term benefit and a [redacted] risk reduction in disease progression or death in favour of the alpelisib plus fulvestrant arm ([redacted]). Median PFS was prolonged by a clinically meaningful [redacted] months in favour of the alpelisib plus fulvestrant arm, from [redacted] months (95% CI: 3.7, 7.4) in the placebo plus fulvestrant arm to [redacted] months (95% CI: [redacted]) in the alpelisib plus fulvestrant arm; this was consistent with median PFS from the primary analysis (12th June 2018 data cut-off).[105]
- PFS results for patients with prior CDK4/6i showed a positive trend consistent with that observed in the overall population. A clinically meaningful [redacted] in disease progression or death was observed among patients with prior CDK4/6 inhibitor use in the

alpelisib plus fulvestrant arm (n=9) compared to the placebo plus fulvestrant arm (n=11) ([redacted]).[105]

- At the final OS analysis (23rd April 2020), OS results for the overall population (i.e. including patients with and without prior CDK4/6i therapy) demonstrated an approximate 14% reduction in the risk of death in the alpelisib plus fulvestrant arm compared with the placebo plus fulvestrant arm (HR: 0.86; 95% CI: 0.64, 1.15; p=0.15). These results did not cross the pre-specified O-Brien Fleming stopping boundary (one-sided p≤0.0161). Median OS was 39.3 months (95% CI: 34.1, 44.9) in the alpelisib plus fulvestrant arm and 31.4 months (95% CI: 26.8, 41.3) in the placebo plus fulvestrant arm, representing a positive trend with an increase of 7.9 months in median OS in favour of alpelisib plus fulvestrant.[82]
- For patients with prior CDK4/6i, median OS was prolonged by [redacted] in the alpelisib plus fulvestrant arm, from [redacted] in the placebo plus fulvestrant arm to [redacted].[105] While patient numbers are relatively small, this provides supportive evidence that the post-CDK4/6i population fulfils the end-of-life criteria (see Section B.2.11.3).

Matching/weighted analysis of BYLieve and real-world standard of care

- A series of weighted/matched analyses comparing BYLieve to patients in the real-world setting who had received prior CDK4/6i therapy has demonstrated a consistent trend in the PFS HRs in favour of alpelisib plus fulvestrant compared to standard treatment.[106]
- A full description of the trial design and methodology is available in Section B.2.5.1.
- The unadjusted median PFS was 7.3 months (95% CI, 5.6, 8.3) in the BYLieve cohort compared with a median real-world PFS of 3.6 months (95% CI, 3.1, 6.1). After weighting by odds, median PFS for patients in the BYLieve cohort was 7.3 months (95% CI, 5.3, 9.2) versus 3.7 months (95% CI: 2.2, 5.3) in the real-world cohort.[106]

Summary of safety

- Alpelisib plus fulvestrant has a well-characterised safety profile; key AEs include hyperglycaemia, rash and gastrointestinal (GI) toxicity.[29, 75, 107, 108] These AEs are typically manageable with medical therapies and/or dose modifications or interruptions, and are generally reversible.[29, 75, 107, 108] Furthermore, robust management guidelines for key AEs have been developed and refined over the course of SOLAR-1 and BYLieve.

Summary of the results from the indirect treatment comparison (ITC)

- In the absence of a head-to-head trial between alpelisib plus fulvestrant and everolimus plus exemestane, the relevant comparator for this submission, an ITC was conducted to estimate the relative efficacy between alpelisib plus fulvestrant and everolimus plus exemestane in terms of PFS and OS in patients with endocrine resistant HR+, HER2– ABC with a *PIK3CA* mutation.
- One RCT providing evidence for the efficacy of everolimus plus exemestane in patients with endocrine resistant HR+, HER2– ABC with a *PIK3CA* mutation was identified via a clinical SLR: BOLERO-2.[62] As BYLieve is a single-arm trial, data from the second-line population of SOLAR-1 were used in the indirect comparison.

- In order to connect the two trials (SOLAR-1 and BOLERO-2), two additional trials were required to create a network: SoFEA and CONFIRM.[109, 110]
- Based on the available data, ITCs for PFS and OS were conducted using data for patients in second-line ABC. A Bucher ITC was conducted, based on the assumption of proportional hazards; the test for proportional hazards was not violated for any study in the network.
- The results of the Bucher ITC in the second-line population demonstrate everolimus plus exemestane to be associated with HRs of [redacted] and [redacted] for PFS and OS, respectively, versus alpelisib plus fulvestrant.

Summary

- The efficacy and safety of alpelisib plus fulvestrant has been demonstrated in patients with endocrine resistant HR+, HER2– ABC with a *PIK3CA* mutation, in both the SOLAR-1 and BYLieve clinical trials. The ITC conducted in second-line ABC demonstrates alpelisib plus fulvestrant to be associated with superior efficacy in terms of both PFS and OS versus the only relevant comparator to this appraisal: everolimus plus exemestane. This extension of 'progression-free' time and prolongation of time to disease progression delays the use of cytotoxic chemotherapy and maintains patients HRQoL for a longer duration.[50, 69]

B.2.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted to identify relevant clinical evidence for the efficacy and safety of alpelisib plus fulvestrant (RCTs and non-RCTs) and the relevant comparator (RCTs only) for the treatment of endocrine resistant HR+, HER2– ABC with a *PIK3CA* mutation. The SLR took a broad approach and therefore did not search specifically for studies investigating treatments in patients that had previously received a CDK4/6i.

The SLR was conducted according to a pre-specified protocol and performed in accordance with the methodological principles of conduct for systematic reviews as detailed in the York Centre for Reviews and Dissemination (CRD) Handbook recommended by NICE.[111, 112] The SLR was conducted in January 2019 and three updates have since been performed (October 2019, August 2020 and April 2021). These updates were conducted to identify any additional evidence published since the original SLR was conducted.

In total the SLR identified 17 unique studies (reported in 235 records) that met the inclusion criteria of the review. Of these, one RCT (SOLAR-1; reported in 26 records) and two non-RCTs (Juric *et al.* 2018 and BYLieve; reported in three and eight records, respectively) were identified for alpelisib plus fulvestrant, and one RCT (BOLERO-2, reported in 24 records) was identified for everolimus plus exemestane. (Note: studies for other interventions were also eligible for inclusion in the review as the SLR was conducted from a Global perspective i.e. trials of therapies that are not comparators to this submission).

Full details of the SLR search strategy, study selection process and results are presented in Appendix D.

B.2.2 List of relevant clinical effectiveness evidence

As described above and in Appendix D, the SLR identified one RCT (SOLAR-1; reported in 26 records) and two non-RCTs (Juric *et al.* [2018] and BYLieve; reported in three and eight records, respectively) that provide evidence for the clinical efficacy and safety of alpelisib plus fulvestrant in patients with HR+, HER2– ABC with a *PIK3CA* mutation.

SOLAR-1

SOLAR-1 (NCT02437318) is a Phase III randomised, double-blind, international, multicentre, clinical trial investigating the efficacy and safety of alpelisib plus fulvestrant versus placebo plus fulvestrant in postmenopausal women, and men, with HR+, HER2– ABC with known *PIK3CA* mutation status, who progressed on or after AI treatment (i.e. ET).[29] The methodology and results of SOLAR-1 are presented in Section B.2.4 and Appendix F. A small number of patients received prior CDK4/6i and are thus relevant to the scope of this submission. Importantly, as a randomised trial with a comparator arm, SOLAR-1 is required to provide treatment effect data as part of the indirect treatment network constructed (see Section B.2.7).

BYLieve

BYLieve (NCT03056755) is an ongoing, open-label, multicentre, three-cohort, non-comparative Phase II trial in men and women (premenopausal, perimenopausal and postmenopausal) with HR+, HER2– locally advanced or metastatic breast cancer with a *PIK3CA* mutation.[73, 75] Data from Cohort A of BYLieve are currently the only data available for alpelisib plus fulvestrant from the BYLieve trial and have therefore been included in this submission. The methodology of BYLieve and the results of Cohort A are presented in Section B.2.3.2 onwards.

Data from Cohort B (where patients receive alpelisib plus letrozole following CDK4/6i plus fulvestrant therapy) have been published, however are not relevant to the decision problem addressed within this submission as patients did not receive alpelisib plus fulvestrant.[113] Whilst a small number of patients from Cohort C (where patients receive alpelisib plus fulvestrant following prior ET monotherapy, ET plus targeted therapy [e.g. everolimus, or CDK4/6i plus fulvestrant once Cohort B has closed]) would have received prior treatment with a CDK4/6i and would go on to receive alpelisib plus fulvestrant, data for this cohort are not anticipated to be available until Q4 2021, and it is anticipated that only a small number of patients would be post-CDK4/6i. Therefore, data from Cohort C will not form a pivotal evidence source for the post-CDK4/6i population, the population of focus for this submission. However, it should be noted that when the results of Cohort C become available, these data would be considered within the anticipated licence for alpelisib plus fulvestrant.

Finally, Juric *et al.* (2018) was an open-label, single-arm, Phase Ib study designed to assess the maximum tolerated dose of alpelisib plus fulvestrant in patients with HR+, HER2– ABC.[36] Overall, 87 patients were included in this study, of whom only nine patients with *PIK3CA*-mutated disease received the licensed dose of alpelisib (300 mg once daily).[36] The patient population differed further from the population of interest to this submission in that patients were heavily pre-treated (median 5 prior lines of therapy) and only 60% (52 patients) had *PIK3CA*-mutated disease. Given the identification of the larger, more robust Phase III RCT SOLAR-1 and as Juric *et al.* (2018) did not include any patients post-CDK4/6i, the study is not discussed further within this submission.

Table 5: Clinical effectiveness evidence from SOLAR-1 and BYLieve

Study	SOLAR-1 (NCT02437318)			BYLieve (NCT03056755)		
Study design	Randomised, double-blind, placebo-controlled, international, multicentre, Phase III trial			Non-randomised, open-label, three-cohort, multicentre, non-comparative Phase II trial		
Population	Postmenopausal women, or men, with HR+, HER2− ABC who were receiving or had received AI treatment in the context of neoadjuvant or adjuvant therapy, or for advanced disease			Premenopausal, perimenopausal[a] **and postmenopausal women, or men with HR+, HER2− locally advanced or metastatic breast cancer with a *PIK3CA* mutation and:** **Cohort A: prior CDK4/6i plus AI therapy** **Cohort B:** prior CDK4/6i plus fulvestrant therapy **Cohort C:** prior ET (as monotherapy or in combination with targeted therapy, except CDK4/6i plus AI), or systemic chemotherapy. This cohort includes patients from Cohort B, once enrolment for Cohort B is complete		
Intervention(s)	Alpelisib 300 mg PO QD plus fulvestrant 500 mg IM[b]			**Cohort A: alpelisib 300 mg PO QD plus fulvestrant 500 mg IM[b]** **Cohort B:** alpelisib 300 mg PO QD plus letrozole 2.5 mg PO QD[c] **Cohort C:** alpelisib 300 mg PO QD plus fulvestrant 500 mg IM[b]		
Comparator(s)	Placebo plus fulvestrant 500 mg IM[b]			NA		
Indicate if trial supports application for marketing authorisation	Yes	**Indicate if trial used in the economic model**	Yes	Yes	**Indicate if trial used in the economic model**	Yes
Rationale for use/non-use in the model	BYLieve is a single-arm trial and utility data were not collected; therefore, data from SOLAR-1 are required to supplement BYLieve data in the cost-effectiveness model in terms of utility values and estimates of relative efficacy			Data from Cohort A of BYLieve provide evidence of the efficacy and safety of alpelisib plus fulvestrant for patients who have previously received a CDK4/6i		
Reported endpoints specified in the decision problem[d,e]	Primary endpoint: • **PFS** (locally assessed) Secondary endpoints: • OS • Overall response rate (ORR)/clinical benefit rate (CBR) • HRQoL (EQ-5D-3L) • Safety			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 complete response (CR) or partial response (PR) • Safety
All other reported endpoints	Exploratory endpoints: • Time to response • Duration of response (DoR) • An exhaustive list of exploratory endpoints captured in SOLAR-1 is presented in Appendix F.	Exploratory endpoints: • Clinical response in patients with *PIK3CA* mutation status measured in ctDNA • Clinical response in patients with *ESR1* mutations • Biomarkers

[a] In BYLieve, perimenopausal and premenopausal status was grouped together and referred to as 'premenopausal'.[41] [b] Fulvestrant given on Day 1 and Day 15 of the first 28-day cycle, then Day 1 of the subsequent 28-day cycles. [c] Goserelin or leuprolide given every 28 days only in men and premenopausal women in Cohort B. [d] Endpoints are reported for the *PIK3CA*-mutated cohort unless specified otherwise. [e] Endpoints included in the model are presented in bold.
Abbreviations: ABC: advanced breast cancer; CBR: clinical benefit rate; ctDNA: circulating tumour deoxyribonucleic acid; DoR: duration of response; ECOG: Eastern Cooperative Oncology Group; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; 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; PK: pharmacokinetics; PO: by mouth; PS: performance status; QD: once daily.
Source: André *et al.* (2019);[29] BYLieve Protocol (Amendment 4).[41]

B.2.2.1 Relevance of SOLAR-1 and BYLieve within the decision problem

As mentioned above, SOLAR-1 and BYLieve comprise the two main sources of evidence for alpelisib plus fulvestrant in patients with HR+, HER2– ABC with a *PIK3CA* mutation.

Alpelisib plus fulvestrant received marketing application approval the EMA in 2020; this approval was supported primarily by evidence from the pivotal phase III RCT SOLAR-1.[114] In 2015, when the design and protocol for SOLAR-1 was written, the only published CDK4/6i data available were from a Phase II study with palbociclib. Recognising that CDK4/6i could be considered as part of the future treatment landscape, prior CDK4/6i use was included as a randomisation stratification factor, to ensure treatment group balance for this subgroup of patients. The first CDK4/6i was approved in the US in February 2015, while the SOLAR-1 enrolment period commenced in July 2015 and ran until July 2017.[114] As patients typically receive CDK4/6i + AI for a relatively long duration, few patients would have received this combination, discontinued, and progressed before enrolling in SOLAR-1. As a result, only a small number of patients – nine (5.3%) in the alpelisib plus fulvestrant arm and 11 (6.5%) in the placebo plus fulvestrant arm – had received prior CDK4/6i therapy and were enrolled. Hence, data from SOLAR-1 is skewed towards patients who were CDK4/6i-naïve.[29]

As mentioned in the Foreword, this submission focusses on a subset within the anticipated MHRA marketing authorisation licence, i.e. patients with HR+, HER2– ABC with a *PIK3CA* mutation who have progressed following CDK4/6i therapy. The post-CDK4/6i population faces a particularly high unmet need, with limited therapeutic options besides everolimus plus exemestane (See Section B.1.3); these patients also meet NICE's end-of life-criterion of a short life expectancy of <24 months (See Section B.2.11.3).

Despite being a well-designed, high quality RCT, evidence from SOLAR-1 does not represent the full value of alpelisib plus fulvestrant in the post-CDK4/6i population, as SOLAR-1 was designed

and initiated before CDK4/6is became standard of care in HR+, HER2– ABC, and therefore included only a small number of patients post-CDK4/6i. Given the high unmet need in the post-CDK4/6i population, the non-comparative BYLieve trial was initiated in 2017 to evaluate alpelisib plus ET in the post-CDK4/6i setting. As illustrated in Table 5 above, patients in Cohort A are similar to SOLAR-1 besides the requirement to have received prior CDK4/6i plus and AI as immediate prior treatment.[114]

Thus, in this submission, data from Cohort A of BYLieve represents the key source of evidence for alpelisib plus fulvestrant in the post-CDK4/6i population and is presented before SOLAR-1. While SOLAR-1 assessed the efficacy of alpelisib plus fulvestrant in a large number of patients (341 patients in the *PIK3CA*-mutated cohort and 231 patients in the proof-of-concept *PIK3CA* wildtype cohort), only the above-mentioned 20 patients who had received prior CDK4/6i therapy are relevant to the decision problem addressed within this submission. As such, the trial methodology and design, as well as baseline characteristics of the full SOLAR-1 population (including both CDK4/6i naïve and post-CDK4/6i patients) are summarised briefly in this section and are presented fully in Appendix F.2. Likewise, in the section discussing the clinical effectiveness evidence of SOLAR-1 (Section B.2.4.2), data specifically from the post-CDK4/6i subgroup have been presented. An overview of the key efficacy results for the overall population are presented in Section B.2.4.2 for context; full results are available in Appendix F.3. As prior receipt of CDK4/6i therapy is not anticipated to influence the safety profile of alpelisib plus fulvestrant, safety data for the SOLAR-1 RCT is presented before BYLieve in Section B.2.8.

B.2.3 BYLieve

B.2.3.1 Trial design

A key source of evidence for the use of alpelisib plus fulvestrant in the post-CDK4/6i population derives from the ongoing, open-label, multicentre, three-cohort, non-comparative Phase II BYLieve trial (NCT03056755), in men and women (premenopausal, perimenopausal and postmenopausal) with HR+, HER2− locally advanced or metastatic breast cancer with a *PIK3CA* mutation.[73]

Patients were eligible for enrolment in BYLieve if they had documented evidence of tumour progression on or after:[41]

- CDK4/6i plus ET (AI or fulvestrant) treatment as immediate prior therapy
- AI treatment (in the adjuvant or metastatic setting) and ET (monotherapy or combination, except CDK4/6i plus AI) or systemic chemotherapy as immediate prior therapy
- ≤2 prior anti-cancer therapies for ABC
- ≤1 prior regimen of chemotherapy for the treatment of ABC

Additionally, patients must have adequate tumour tissue for central analysis of *PIK3CA* mutational status or a pathology report confirming *PIK3CA* mutational status by a certified laboratory using a validated *PIK3CA* mutation assay (either from tissue or blood).[41]

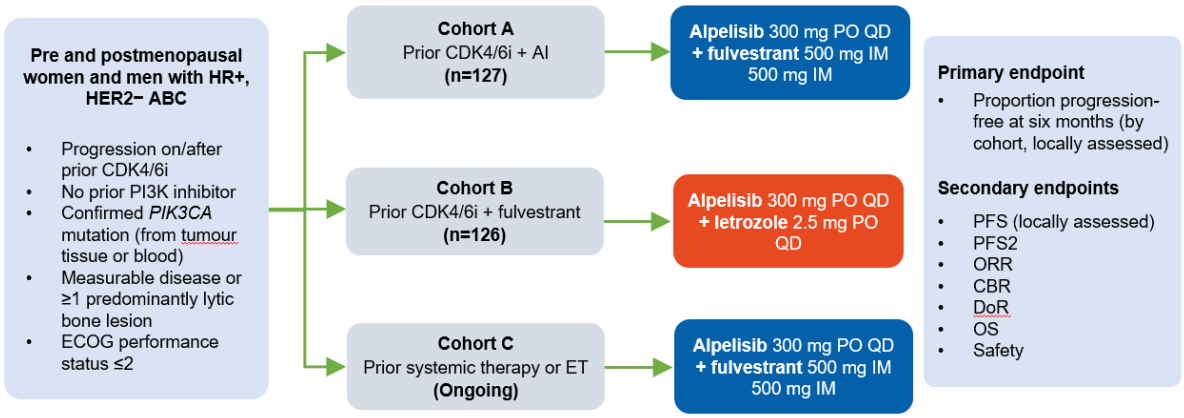
After confirmation of the eligibility criteria, patients are assigned to one of three cohorts based on previous therapy, as indicated below:[41, 73]

- Cohort A: Patients receive alpelisib plus fulvestrant following prior CDK4/6i plus AI therapy
- Cohort B: Patients receive alpelisib plus letrozole following CDK4/6i plus fulvestrant therapy
- Cohort C (ongoing): Patients receive alpelisib plus fulvestrant following prior ET (as monotherapy or in combination with targeted therapy, except a CDK4/6i plus an AI) or systemic chemotherapy. ET includes letrozole, fulvestrant and CDK4/6i plus fulvestrant.

A summary of the trial design of BYLieve is presented in Figure 3. Treatment crossover between cohorts is not permitted.

Data from Cohort A of BYLieve are currently the only data available for alpelisib plus fulvestrant from the BYLieve trial and have therefore been included in this submission. The methodology of BYLieve and the results of Cohort A are presented in Section B.2.3.2 onwards. Patients in Cohort B received alpelisib plus letrozole; this is beyond the approved marketing authorisation and hence is not considered within this submission. While Cohort C may be relevant to this submission given some patients will have received prior CDK4/6i therapy, data will not be available until Q4 2021 and are therefore not considered further within this submission. Though an exact estimate of patient numbers cannot be provided at this stage, it is anticipated that the number of patients that will have received prior CDK4/6i will be small. However, it should be noted that when the results of Cohort C become available, these data would be considered within the anticipated licence for alpelisib plus fulvestrant.

Figure 3: BYLieve trial design



Note: premenopausal women, and men in Cohort B also received goserelin (3.6 mg SC every 28 days) or leuprolide (7.5 mg IM every 28 days) to achieve adequate hormonal suppression.
Abbreviations: ABC: advanced breast cancer; AI: aromatase inhibitor; CBR: clinical benefit rate; CDK: cyclin dependent kinase; DoR: duration of response; ECOG: Eastern Cooperative Oncology Group; ET: endocrine therapy; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; IM: intramuscular; PFS: progression-free survival; PFS2: progression on next line therapy; *PIK3CA*: phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; ORR: overall response rate; OS: overall survival; PO: by mouth; QD: once daily; SC: subcutaneously.
Source: CT.gov BYLieve;[115] Rugo *et al.* (2020);[116] Rugo, *et al.* (2021).[75]

Definitions of the primary and secondary endpoints assessed in BYLieve are provided in Table 6.

Table 6: Endpoint definitions in BYLieve

Endpoint	Definition
Primary endpoint	

Proportion progression-free at 6 months	• Proportion of patients who are alive without disease progression at 6 months based on local Investigator assessment using RECIST v1.1 in each cohort
Secondary endpoints	
PFS	• Time from the start date of treatment to the date of the first documented progression or death due to any cause, based on local Investigator assessment using RECIST v1.1
PFS2	• Time from the date of first dose of study medication to the date of first documented progression on next-line therapy or death from any cause
OS	• Time from start of treatment to date of death or lost to follow-up
ORR	• Proportion of patients with best overall response of complete response or confirmed partial response based on local Investigator's assessment according to RECIST 1.1 criteria
DoR	• Duration between the date of first document response (CR or PR) to the date of first documented progression or death
Safety	• Determined by type, frequency and severity of adverse events and laboratory toxicities per CTCAE v4.03

Abbreviations: CR: complete response; CTCAE v4.03: Common Terminology Criteria for Adverse Events version 4.03; DoR: duration of response; ORR: overall response rate; OS: overall survival; PFS2: progression-free survival after next-line therapy; PR: partial response; RECIST: Response Evaluation Criteria in Solid Tumours.
Source: BYLieve Protocol.[41]

B.2.3.2 Trial methodology

A summary of the methodology of BYLieve is presented in Table 7. Further details of the methodology of BYLieve, including the full eligibility criteria are reported in Section 5.2 of the BYLieve protocol.[41]

Table 7: Summary of BYLieve study methodology

Trial name	BYLieve (NCT03056755)
Location	International: 118 sites in 19 countries in Europe (including 5 sites in the United Kingdom), the Middle East, Africa, Japan, Argentina, Brazil, North America, Latin America, Latin America, the Caribbean and Canada
Trial design	International, multicentre, open-label, three-cohort, non-comparative, Phase II study
Eligibility criteria for participants	**Key inclusion criteria** • Premenopausal, perimenopausal[a] and postmenopausal women, or men, ≥18 years of age • Advanced (locoregionally recurrent, not amenable to curative therapy) or metastatic breast cancer • Histologically and/or cytologically confirmed diagnosis of ER+ and/or PgR+ (i.e. HR+) breast cancer • Confirmed HER2− ABC, defined as a negative in situ hybridisation test or an immunohistochemistry status of 0, 1+ or 2+ • *PIK3CA* mutation confirmed, in which adequate formalin-fixed paraffin-embedded tissue sections with >10% tumour tissues must be provided, or a pathology report confirming *PIK3CA* mutation status by a certified laboratory • Documented evidence of tumour progression on or after: ○ CDK4/6i plus ET as immediate prior therapy

	○ AI (in adjuvant or metastatic setting) and ET (monotherapy or combination with targeted therapy, except CDK4/6i plus AI) or systemic chemotherapy, as immediate prior therapy ○ ≤2 prior anti-cancer therapies for ABC ○ ≤1 prior regimens of chemotherapy ○ Recovered to Grade 1 or better from any AE related to previous anti-cancer therapy prior to study entry • Either measurable disease (at least one measurable lesion according to the RECIST version 1.1) or one or more predominantly lytic bone lesions • ECOG performance-status score ≤2 • Adequate organ and bone marrow function **Key exclusion criteria** • Known hypersensitivity to alpelisib, fulvestrant, letrozole, goserelin or leuprolide or their respective excipients • Prior treatment with any PI3K inhibitor • CNS involvement unless they meet all of the following criteria: ○ ≤4 weeks from prior therapy completion (including radiation and/or surgery) to starting the study treatment ○ Clinically stable CNS tumour at the time of screening or without evidence of progressions for at least 4 weeks after treatment as determined by clinical examination and brain imaging (MRI or CT) during screening period and stable low dose of steroids for 2 weeks prior to initiating study treatment • Established diagnosis of diabetes mellitus type I or uncontrolled type II • Concurrent cancer or cancer within three years before randomisation (except for adequately treated basal-cell or squamous-cell carcinoma, non-melanomatous skin cancer, or curatively resected cervical cancer) • Prior radiotherapy ≤4 weeks or limited field radiation for palliation ≤2 weeks prior to enrolment, and who had not recovered to Grade 1 or better from related side effects • Receiving or had received systemic corticosteroids ≤2 weeks prior to starting treatment with alpelisib, or had not fully recovered from side effects of such treatment • History of HIV seropositivity • History of GI disease, pneumonitis/interstitial lung disease which is active and requiring treatment or severe liver impairment A full list of the inclusion and exclusion criteria is presented in Section 5.2 and 5.3 of the BYLieve protocol, respectively.[41]
Intervention	• After confirmation of the eligibility criteria, patients were assigned to one of three cohorts based on previous prior treatment; patients whose prior treatment was CDK4/6i plus fulvestrant were enrolled in Cohort B until enrolment closed, and then in Cohort C ○ **Cohort A** (n=127): Patients receive alpelisib plus fulvestrant following prior CDK4/6i plus AI therapy ○ **Cohort B** (n=126): Patients receive alpelisib plus letrozole following CDK4/6i plus fulvestrant therapy ○ **Cohort C** (ongoing): Patients receive alpelisib plus fulvestrant following prior ET (± targeted therapy) or systemic chemotherapy • Premenopausal women, and men in Cohort B, also received goserelin or leuprolide • Patients received treatment until disease progression (radiologically

	documented according to RECIST v1.1) or until discontinuation of study treatment due to any other reason
Method of study drug administration	**Alpelisib** • 300 mg PO QD continuously • Patients received alpelisib/placebo on an outpatient basis, and were provided with an adequate supply for self-administration at home • Patients were instructed to take alpelisib/placebo at approximately the same time each day after a meal (preferably breakfast) except on days where blood collection was scheduled at the clinic, when the doses were taken in clinic at a later time **Fulvestrant** • 500 mg at intervals of one month, with an additional 500 mg dose given two weeks after the initial dose, via IM injection • Fulvestrant was dispensed according to the local prescribing information and practice **Letrozole** • 2.5 mg PO QD continuously • Letrozole was dispensed according to the local prescribing information and practice **Goserelin** • Premenopausal women, and men in Cohort B, received goserelin as an injectable subcutaneous implant at a dose of 3.6 mg every 28 days • For patients already receiving goserelin before Cycle 1 Day 1, a 28-day schedule was maintained based on the pre-existing dosing schedule • Goserelin was dispensed according to the local prescribing information and practice **Leuprolide** • Men in Cohort B and premenopausal women received leuprolide an intramuscular injection at a dose of 7.5 mg every 28 days • For patients already receiving leuprolide before Cycle 1 Day 1, a 28-day schedule was maintained based on the pre-existing dosing schedule • Leuprolide was dispensed according to the local prescribing information and practice
Permitted and disallowed concomitant medication	The following medications were permitted during the study: • Medications required to treat AEs, to manage cancer symptoms or concurrent diseases, and supportive care agents (such as pain medications, anti-emetics, and anti-diarrhoeals) • Oral anti-diabetics • Gastric protection agents • Corticosteroids • Palliative radiotherapy The following uses of corticosteroids were permitted: single doses, topical applications (e.g. for rash), inhaled sprays (for obstructive airways disease), eye drops or local injections (e.g. intra-articular), stable CNS tumour on consistent low dose of steroids. Permitted concomitant therapies requiring caution and/or action are listed in Section 6.4.2 of the BYLieve protocol.[41]

	The following medications were prohibited during the study: • Strong inducers of CYP3A4 • Inhibitors of Breast Cancer Resistance Protein (BCRP) efflux transporter • Other investigational and antineoplastic therapies • Herbal preparations/medications and dietary supplements (except for vitamins) Further prohibited medications are listed in Section 6.4.4 of the BYLieve protocol.[41]
Primary endpoints	Proportion of patients who are alive without disease progression at 6 months based on local Investigator assessment per RECIST v1.1 in each cohort
Secondary and exploratory endpoints	**Secondary endpoints** • PFS (locally assessed) • PFS2 • ORR • CBR • DoR • OS • Safety and tolerability These endpoints are defined in Table 6. **Exploratory endpoints** • Molecular analysis of ctDNA at baseline and correlation with PFS • Molecular analysis of ctDNA and tumour tissue • Molecular and protein-based analysis of tumour tissue and ctDNA (baseline, during treatment and EOT)
Pre-planned subgroups	N/A. There were no pre-planned subgroups.
Discontinuation of study treatment and premature patient withdrawal	Study treatment was discontinued under the following circumstances: • AE or laboratory abnormality, as indicated in Section 6.3 of the BYLieve protocol[41] • Pregnancy • Lost to follow-up • Physician decision • Patient/guardian decision • Death • Progressive disease • Protocol deviation • Study termination by sponsor • Technical problems • Patients could also voluntarily withdraw from the study for any reason at any time. A patient was considered withdrawn if they withdrew consent, failed to return for visits, or were lost to follow-up for any other reason • The Investigator discontinued study treatment for a given patient if they believed that continuation would be detrimental to the patient's well-being • For patients who discontinued treatment for reasons other than documented disease progression, death, loss to follow-up, or withdrawal of consent, tumour assessments were performed every 12 weeks until documented disease progression, death, loss to follow-up, or withdrawal of consent • Patients who permanently discontinued study treatment were scheduled for

	an EOT visit followed by a 30-day safety follow-up. At EOT, tumour assessments were performed if the previous scan was older than 30 days

Duration of study and follow-up	• The study was initiated on 14th August 2017 and is ongoing
	  ○ Data for Cohort A are presented from the 17th December 2019 data cut-off
	  ○ The study completion date is anticipated to be 15th July 2022 (see Section B.2.9)
	• Imaging (computerised tomography, magnetic resonance imaging, or both) was performed at screening within 21 of treatment start (Day −21 to Day −1 prior to Cycle 1 Day 1), and then every 12 weeks until disease progression or withdrawal for any other reason. Vital signs, performance status, ECG, cardiac imaging, haematological and biochemical laboratory tests, including glucose monitoring, were performed at every visit
	• **Efficacy follow-up:** patients who discontinued study treatment for reasons other than disease progression or withdrawal of consent were followed every 12 weeks until disease progression, death, withdrawal of consent or loss to follow-up
	• **Safety follow-up:** patients were followed weekly for 30 days after discontinuation of study treatment or resolution of the AE to ≤Grade 1, whichever occurred first
	• **Survival follow-up:** All patients were followed for survival (after progression) every 12 weeks regardless of treatment discontinuation reason (except for withdrawal of consent, death or loss to follow-up) until death, loss to follow-up or withdrawal of consent for survival follow-up or end of study. Survival information could be obtained via phone. At the 17th December 2019 data cut-off, survival follow-up was ongoing in [redacted] patient in Cohort A[108]

[a] In BYLieve, perimenopausal and premenopausal status was grouped together and referred to as 'premenopausal'.[41]
Abbreviations: ABC: advanced breast cancer; AE: adverse event; AI: aromatase inhibitor; BCRP: Breast Cancer Resistance Protein; CBR: clinical benefit rate; CDK4/6: cyclin-dependent kinase 4/6; CNS: central nervous system; CT: computerised tomography; ctDNA: circulating tumour deoxyribonucleic acid; CYP3A4: cytochrome P450 3A4; DoR: duration of response; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EOT: end of treatment; ER: (o)estrogen receptor; ET: endocrine therapy; GI: gastrointestinal; HER2: human epidermal growth factor receptor 2; HIV: human immunodeficiency virus; HR: hormone receptor; IM: intramuscular; MRI: magnetic resonance imaging; N/A: not applicable; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; PFS2: progression on next line therapy; *PIK3CA*: phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PI3K: phosphatidylinositol 3-kinase; PK: pharmacokinetic; PO: by mouth; PgR: progesterone receptor; QD: once daily; RECIST: Response Evaluation Criteria in Solid Tumours.
Source: Rugo *et al.* (2019);[73] BYLieve protocol;[41] ClinicalTrials.gov.[115]

B.2.3.3 Baseline characteristics

BYLieve recruited patients from 21 European (n=55) and two UK (n=3) study centres in Cohort A.[75] The patient population can be considered largely generalisable to the eligible population for alpelisib plus fulvestrant in UK clinical practice, based on the input from expert clinicians.[93, 115]

Baseline demographics and disease characteristics of patients included in BYLieve are presented in Table 8. Note these are presented for Cohort A only, as this cohort received alpelisib plus fulvestrant. At the time of writing this submission, no data were available from Cohort C.[117]

Table 8: Baseline characteristics of patients in Cohort A of BYLieve (FAS)

Characteristics	Cohort A (N=127) n (%)
Age (years)	
Mean (SD)	56.7 (10.7)
Median	58.0
Min–Max	33–83
Age category (years) – n (%)	
<50	39 (30.7)
≥50 to <65	56 (44.1)
≥65	32 (25.2)
Sex – n (%)	
Female	127 (100)
Race, n (%)	
Asian	12 (9.4)
Black	6 (4.7)
Caucasian	81 (63.8)
Missing	1 (0.8)
Other	3 (2.4)
Pacific Islander	1 (0.8)
Unknown	23 (18.1)
Ethnicity, n (%)	
East Asian	7 (5.5)
Hispanic or Latino	20 (15.7)
Mixed ethnicity	1 (0.8)
NR	32 (25.2)
Other	42 (33.1)
Russian	0
South Asian	3 (2.4)
Southeast Asian	3 (2.4)
Unknown	19 (15.0)
Body mass index (BMI) (kg/m^2)	
n	117
Mean (SD)	26.1 (5.5)
Median	25.34
Min–Max	16.1–46.6
Child-bearing status, n (%)	
Able to bear children	[redacted]
Postmenopausal	[redacted]
Sterile – of child-bearing age	[redacted]
ECOG performance status, n (%)	

Characteristics	Cohort A (N=127) n (%)
0	79 (62.2)
1	41 (32.3)
2	2 (1.6)
Missing	5 (3.9)
Lines of prior medication therapy in the metastatic setting	
0	15 (11.8)
1	89 (70.1)
2	21 (16.5)
3	2 (1.6)
Lines of prior ET in the metastatic setting	
0	15 (11.8)
1	98 (77.2)
2	14 (11.0)
Previous exposure as first-line treatment in the metastatic setting	
Fulvestrant	0
Chemotherapy	8 (6.3)
Endocrine status at study entry[a]	
Primary endocrine resistance	26 (20.5)
Secondary endocrine resistance	76 (59.8)
Endocrine sensitivity	1 (0.8)
Primary site of cancer, n (%)	
Breast	127 (100)
Details of tumour histology/cytology, n (%)	
Adenocarcinoma	[redacted]
Invasive ductal carcinoma	[redacted]
Invasive lobular carcinoma	[redacted]
Lobular carcinoma in situ	[redacted]
Squamous cell carcinoma	[redacted]
Undifferentiated carcinoma	[redacted]
Not applicable	[redacted]
Other	[redacted]
Histologic grade, n (%)	
Well differentiated	[redacted]
Moderately differentiated	[redacted]
Poorly differentiated	[redacted]
Undifferentiated	[redacted]
Unknown	[redacted]
Time since most recent recurrence/relapse (months)	
n	127

Characteristics	Cohort A (N=127) n (%)
Mean (SD)	2.2 (2.5)
Median	1.6
Min–Max	0.1–16.1
Stage at time of study entry, n (%)	
III	3 (2.4)
IV	124 (97.6)
Types of lesions at baseline, n (%)	
Target-only	2 (1.6)
Non-target only	2 (1.6)
Both target and non-target	123 (96.9)
Current extent of disease, n (%) (metastatic sites)	
Sites of metastases, n (%)	
Breast	5 (4)
Bone	108 (85)
Bone only	24 (19)
Visceral	85 (67)
Liver	59 (47)
Lung	43 (34)
Other	8 (6)
Skin	4 (3)
Lymph nodes	37 (29)
CNS	2 (2)
Other	12 (9)

[a] Endocrine status was defined as in SOLAR-1.
Abbreviations: CNS: central nervous system; ECOG: Eastern Cooperative Oncology Group; FAS: full analysis set; SD: standard deviation.
Source: Rugo *et al.* (2021); Rugo *et al.* (2021). Supplementary Appendix;[75] Novartis Data on File.[108]

B.2.3.4 Statistical analysis and definition of study arms in the relevant clinical effectiveness evidence

The definitions of the BYLieve study populations in Cohort A are presented in Table 9.

Table 9: Trial populations used for the analysis of endpoints in Cohort A of BYLieve

Analysis set	Definition
Full analysis set (FAS; n=127)	• All patients randomised to study treatment • The FAS was the primary population for analyses of patient baseline characteristics
Modified full analysis set (mFAS; n=121)	• All patients of the FAS population who have a *PIK3CA* mutation confirmed by a Novartis designated laboratory • The mFAS was the primary population for the efficacy analyses
Safety set (n=127)	• All patients who received at least one dose of study treatment

	○ Treatment received is defined as the randomised treatment (if the patient took at least one dose of that treatment)
Per-protocol set (PPS; n=[redacted])	• The subset of patients in the mFAS without any protocol deviations • Sensitivity analyses were performed using the PPS for the primary efficacy endpoint[a]

[a] The results of sensitivity analyses conducted for the PPS are not yet available.
Abbreviations: *PIK3CA*: phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; (m)FAS: (modified) full analysis set; PPS: per protocol set.
Source: Rugo *et al.* (2021);[75] BYLieve protocol.[41]

The statistical analyses used to analyse the primary endpoint (proportion of patients alive without disease progression at 6 months), alongside sample size calculations and methods for handling missing data, are presented in Table 10.

Table 10: Statistical methods for the primary analysis of BYLieve

Trial name	BYLieve
Hypothesis objective	• The primary objective of BYLieve was to determine the proportion of patients who are alive without disease progression at 6 months based on local Investigator assessment using RECIST v1.1 • A proportion of 30% of patients alive without progression after 6 months was considered a clinically meaningful threshold for all cohorts in this study. Therefore, evidence of treatment effect was tested using the following: Null hypothesis: H_0: p≤0.30 Alternative hypothesis: H_1: p>0.30 Where p is the proportion of patients who are alive without progression at 6 months • The null hypothesis was rejected (demonstrating evidence of a treatment effect) if the lower bound of the 95% CI for the observed proportion at 6 months was greater than 30% ○ To reject the null hypothesis (p≤0.30) at least 44 patients needed to be alive without progression at 6 months out of 112 in each cohort
Statistical analysis	• The Kaplan-Meier estimate of the PFS survival function was estimated and the resulting median PFS time was given with 95% CIs, as well as 25th and 75th percentiles
Sample size, power calculation	• A proportion of 30% of patients alive without progression after 6 months was considered a clinically meaningful threshold and was used for sample size calculation • The sample size was based on an exact Binomial test for single proportion to test the null hypothesis H_0: p≤0.30, where p was the proportion of patients alive without progression at 6 months. With a one-sided 2.5% level of significance (two-sided 95% CI), a total sample size of 112 patients in each cohort was required in order to have a power of at least 90% when the true p≤0.45
Data management, patient withdrawals	• For the primary endpoint analysis, patients who progressed, died, or discontinued study treatment before 6 months were counted as a "failure". Six months was defined in this study as 24 weeks ± 1 week. Therefore, tumour assessments between week 23 and 25 were considered for the primary analysis • The end of the study for a given patient was defined as 19 months after last patient first treatment (LPFT); which included 18 months follow-up plus 1-

	month safety follow-up

Abbreviations: CI: confidence interval; LPFT: last patient first treatment; RECIST: Response Evaluation Criteria in Solid Tumours.
Source: BYLieve protocol.[41]

B.2.3.4.1 Participant flow in the relevant randomised controlled trials

Between 14th August 2017 and 17th December 2019, a total of 127 patients were enrolled into Cohort A of BYLieve.[75] As of the latest data cut-off (17th December 2019), study treatment was still being received by [redacted] patients [redacted].[41, 108]

Full details of the participant flow (CONSORT) diagram for BYLieve are reported in Appendix D.

B.2.3.5 Quality assessment of the relevant clinical effectiveness evidence

A quality assessment of the BYLieve trial is presented in Table 11, based on the information presented in the Rugo *et al.* (2021).[75] The quality assessment was performed based on the abbreviated Downs and Black checklist (for non-RCTs).[112, 118]

Table 11: Quality assessment of BYLieve using an abbreviated Downs and Black checklist

Study ID and publications	BYLieve (NCT03056755)
Is the hypothesis/aim/objective of the study clearly described?	Yes
Are the main outcomes to be measured clearly described in the Introduction or Methods section?	Yes
Are the characteristics of the patients included in the study clearly described?	Yes
Are the interventions of interest clearly described?	Yes – Clear description provided
Are the distributions of principal confounders in each group of patients to be compared clearly described?	NA
Are the main findings of the study clearly described?	Partially – Cohort A is reported in detail, cohort B only reported PFS, cohort C not reported separately to date. Limited results available for full study population
Does the study provide estimates of the random variability in the data for the main outcomes?	No
Have all important adverse events that may be a consequence of the intervention been reported?	Partially – Adverse events are only reported for cohort A and B. Adverse events reported for the full study population is limited
Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?	No
Was an attempt made to blind study patients to the intervention they have received?	No – Open-label
Was an attempt made to blind those measuring the main outcomes of the intervention?	No – Open-label
If any of the results of the study were based on "data dredging", was this made clear?	Unclear – No evidence of data dredging

In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?	Unclear – Analyses are time to event and response rate; unclear if all patients have been followed up until disease progression or data cut-off in the interim analysis
Were the statistical tests used to assess the main outcomes appropriate?	Yes – Clopper and Pearson exact method was used for each cohort separately for the primary endpoint
Was compliance with the intervention(s) reliable?	Unclear – Compliance not reported
Were losses of patients to follow-up taken into account?	Partially – Loss to follow-up was only reported for cohort A

Abbreviations: AE: adverse event; N/A: not applicable; ORR: overall response rate.
Source: BYLieve protocol.[112]

B.2.3.6 Clinical effectiveness results of BYLieve

Results from BYLieve in this submission are presented for Cohort A only from the 17th December 2019 data cut-off. The median duration of follow-up was 11.7 months. These data have been published by Rugo *et al.* (2019) (first interim results);[119] Rugo *et al.* (2020) (ASCO; oral presentation abstract 1006);[117] and Rugo *et al.* (2021).[75] Additional data are also available as Data on File.[108]

B.2.3.6.1 Primary endpoint: Proportion of patients alive without PD at 6 months

The study met its primary endpoint at the primary analysis; the proportion of patients who were alive without disease progression at 6 months was 50.4% (95% CI: 41.2, 59.6), with the lower bound of the 95% CI exceeding 30%. A summary of the primary analysis is presented in Table 12.

Table 12: Proportion of patients alive without disease progression at 6 months as per local Investigator assessment in Cohort A of BYLieve (mFAS)

Cohort	Alive without PD, n	Proportion, n (95% CI)
Cohort A	61/121	50.4 (41.2, 59.6)

95% CI was calculated using Clopper and Pearson (1934) exact method.
Abbreviations: CI: confidence interval; mFAS: modified full analysis set.
Source: Rugo *et al.* 2021.[75]

B.2.3.6.2 Secondary endpoint: PFS

At the primary efficacy analysis, median PFS for Cohort A was 7.3 months (95% CI: 5.6–8.3).[75] A summary of the PFS results are presented in Table 13 and Figure 4.

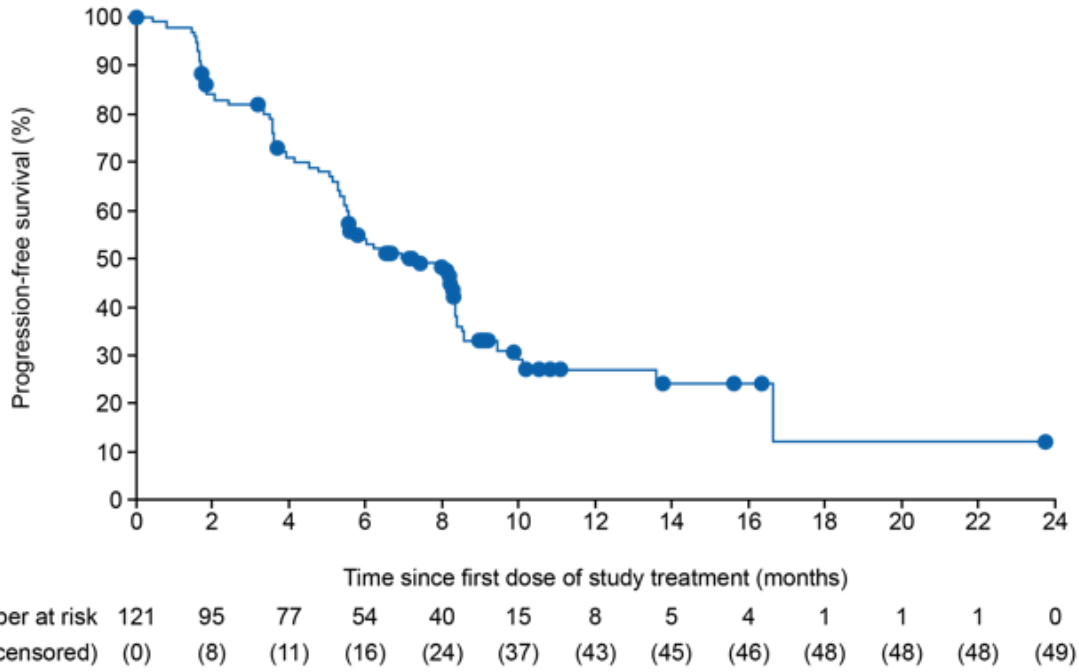
Table 13: PFS as per local Investigator assessment in Cohort A of BYLieve (mFAS)

Cohort	Alive without disease progression, n
n/N (%)	61/121 (50.4)
Percentiles (95% CI):[a]	
25th	[redacted]
50th	7.3 (5.6, 8.3)
75th	[redacted]
% Event-free probability estimates (95% CI)[b]	

6 months	53.9 (44.4, 62.5)
12 months	[redacted]

[a] Percentiles with 95% CIs are calculated using the Brookmeyer and Crowley (1982) method.
[b] Percentage event-free probability estimate is the estimated probability that a patient will remain event-free up to the specified time point. Percentage event-free probability estimates were obtained from the Kaplan-Meier survival estimates for all treatment groups; Greenwood formula is used for CIs of Kaplan-Meier estimates.
n: Total number of events included in the analysis; N: Total number of patients included in the analysis.
Abbreviations: CI: confidence interval; mFAS: modified full analysis set; NE: not estimable; PFS: progression-free survival.
Source: Rugo *et al.* 2021;[75] Rugo *et al.* (2021). Supplementary Appendix;[75] Novartis Data on File.[108]

Figure 4: Kaplan-Meier plot of PFS as per local Investigator assessment in Cohort A of BYLieve (mFAS)



Abbreviations: mFAS: modified full analysis set; PFS: progression-free survival.
Source: Rugo *et al.* 2021.[75]

B.2.3.6.3 Secondary endpoint: OS

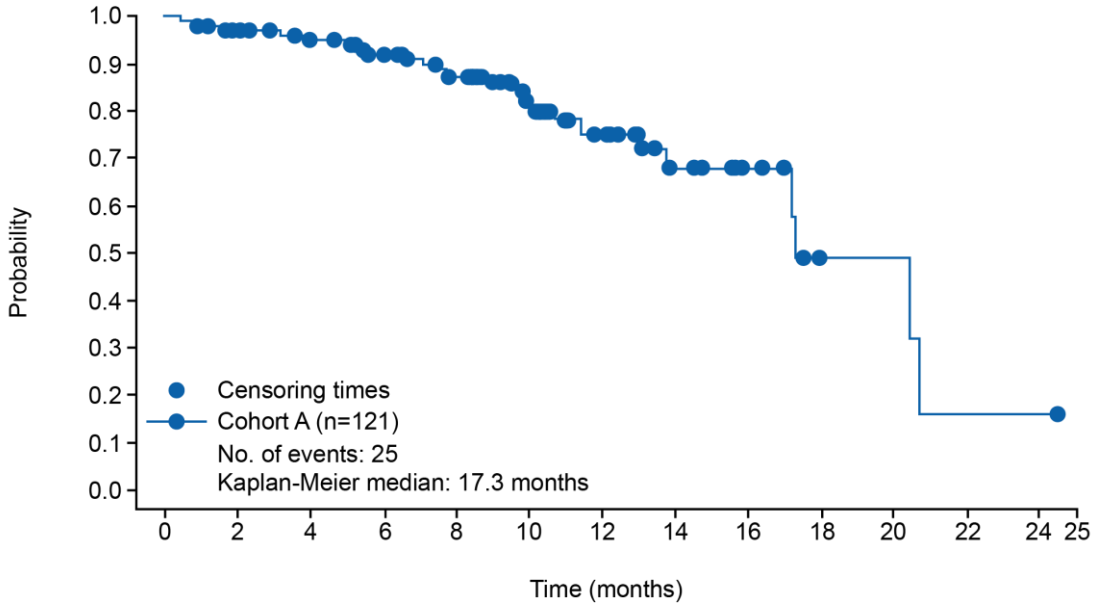
At the primary analysis, median OS for Cohort A was 17.3 months (95% CI: 17.2, 20.7).[75] A summary of the OS data is presented in Table 14 and Figure 5.

Table 14: Summary of OS in Cohort A of BYLieve (mFAS)

Cohort	Months
n/N (%)	25/121 (20.7)
Percentiles (95% CI):[a]	
25th	[redacted]
50th	17.3 (17.2, 20.7)
75th	[redacted]
% Event-free probability estimates (95% CI)[b]	
6 months	[redacted]
12 months	[redacted]

[a] Percentiles with 95% CIs are calculated using the Brookmeyer and Crowley (1982) method.
[b] Percentage event-free probability estimate is the estimated probability that a patient will remain event-free up to the specified time point. Percentage event-free probability estimates were obtained from the Kaplan-Meier survival estimates for all treatment groups; Greenwood formula is used for CIs of Kaplan-Meier estimates.
n: Total number of events included in the analysis; N: Total number of patients included in the analysis.
Abbreviations: CI: confidence interval; mFAS: modified full analysis set; NE: not estimable.
Source: Rugo *et al.* 2021;[75] Novartis Data on File.[108]

Figure 5: Kaplan-Meier plot of time to OS in Cohort A of BYLieve (mFAS)



Abbreviations: mFAS: modified full analysis set; OS: overall survival.
Source: Rugo *et al.* 2021. Supplementary Appendix.[75]

B.2.3.6.4 Secondary endpoint: Overall response

A summary of best overall response data for Cohort A of BYLieve is presented in Table 15.

Table 15: Best overall response as per local Investigator assessment in Cohort A of BYLieve (mFAS)

Response rates, n (%)	All patients with centrally confirmed *PIK3CA* mutation (n=121)	Patients with measurable disease at baseline (n=100)
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[c] (12.4)	13 (13.0)
ORR (95% CI)	21 (17.4) (11.1, 25.3)[c]	21 (21.0) (13.5, 30.3)[c]
CBR (95% CI)	55 (45.5) (36.4, 54.8)[c]	42 (42.0) (32.2, 52.3)[c]

[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. [c] 95% CI was calculated using Clopper and Pearson (1934) exact method.
Abbreviations: CBR: clinical benefit rate; CR: complete response; ORR: overall response rate; PD: progressive disease; PR: partial response,
Source: Rugo *et al.* 2021.[75]

B.2.3.6.5 Secondary endpoint: DoR

DoR data for Cohort A of BYLieve are presented in Appendix F.

B.2.3.6.6 Subgroup analysis: duration of prior CDK4/6i therapy

A post-hoc analysis of BYLieve (Cohort A and B) was conducted to explore the association of PFS with duration of prior CDK4/6i therapy.[120] 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.

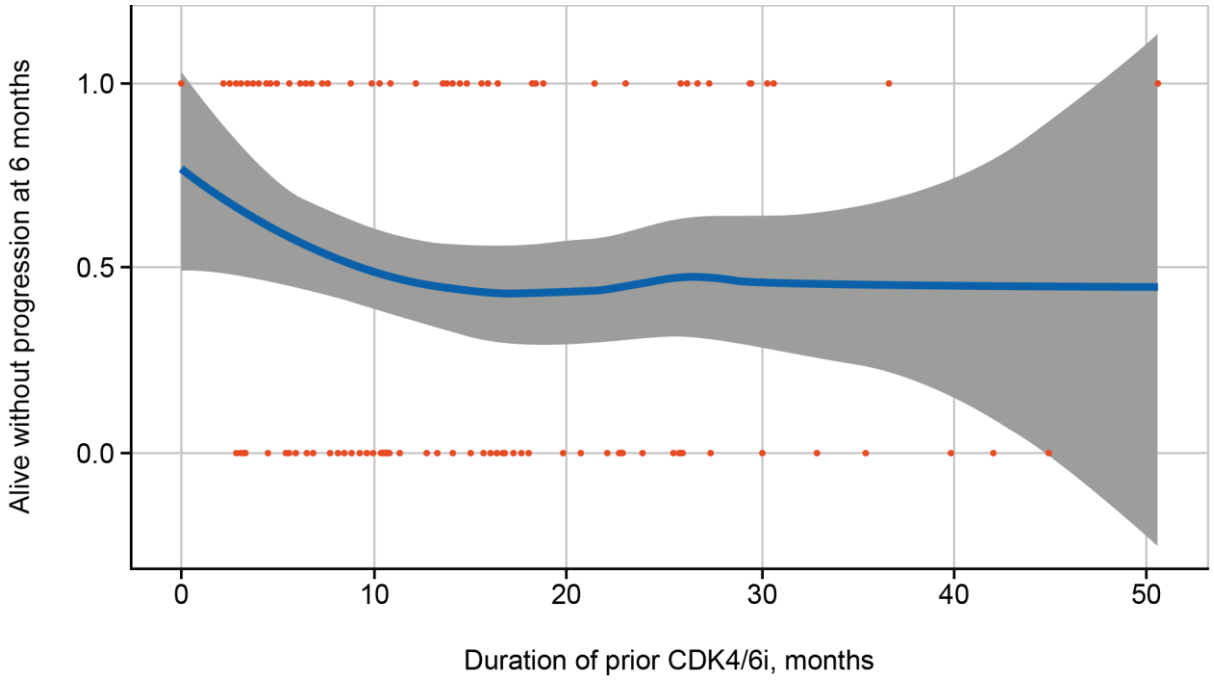
There was no significant difference in PFS between the High and Low subgroups (Table 16). An analysis exploring the relationship between proportion of patients alive without progression at 6 months and duration of prior CDK4/6i (continuous scale) showed that there was little evidence that the duration of prior CDK4/6i impacts efficacy (p value 0.252; 95% confidence band includes 0.5) (Figure 6).

Table 16: PFS for all patients and by duration of prior CDK4/6i therapy in High/Low subgroups (mFAS) in Cohort A of BYLieve

	Event/N (%)	Stratified log-rank test		Cox model
		Median time (95% CI), months	p value	HR* (95% CI)
All patients	61/121 (50.4)	7.3 (5.55, 8.34)	0.927	1.03 (0.64, 1.64)
High (≥380 days)	34/60 (56.7)	8.0 (5.39, 8.34)		
Low (<380 days)	37/60 (61.7)	7.0 (5.36, 9.99)		

[a] Hazard ratio was obtained by using Low subgroup as reference, and p value was based on the 2-tailed hypothesis test.
Abbreviations: CDK4/6i: cyclin dependent kinase 4/6 inhibitor; CI: confidence interval; HR: hazard ratio; mFAS: modified full analysis set; PFS: progression-free survival.
Source: Chia *et al* (2021).[120]

Figure 6: Proportion of patients alive without disease progression at 6 months by duration of prior CDK4/6i exposure (subpopulation treatment effect pattern plot – continuous scale) in Cohort A of BYLieve (mFAS)



Abbreviations: CDK4/6i: cyclin dependent kinase 4/6 inhibitor; mFAS: modified full analysis set.
Source: Chia *et al* (2021).[120]

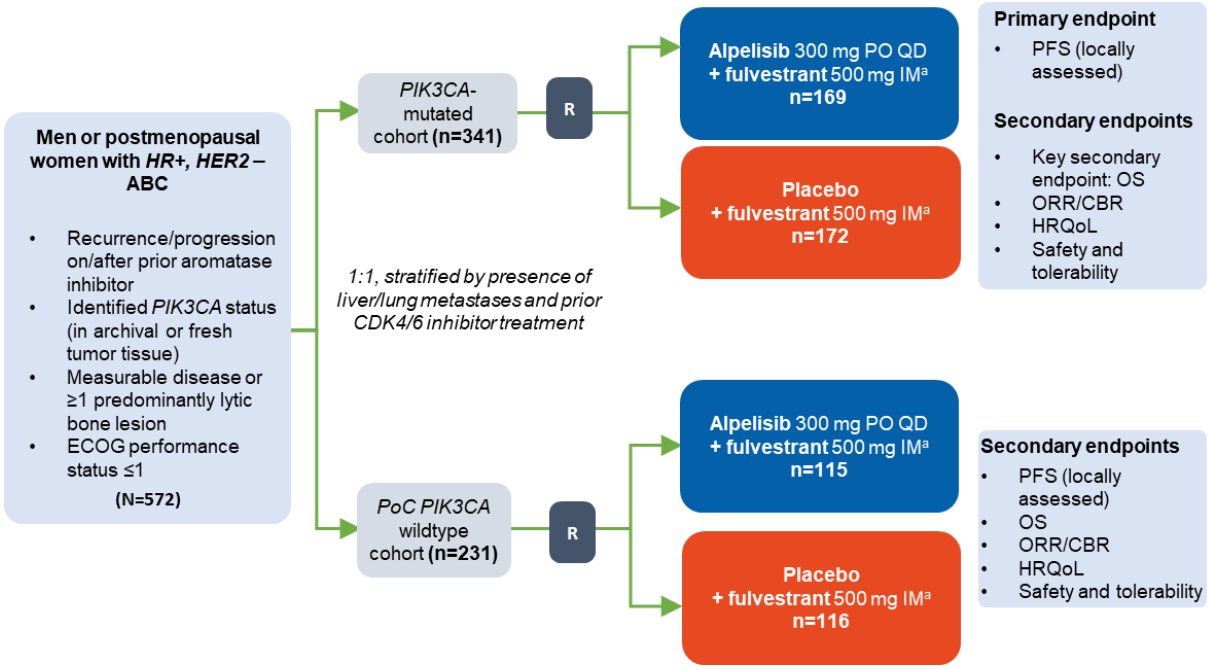
B.2.4 SOLAR-1

As described in Section B.2.2.1, the majority of patients in SOLAR-1 were CDK4/6i-naïve, and only 20 patients had received prior CDK4/6i therapy. Although BYLieve (Cohort A) represents the key source of evidence for alpelisib plus fulvestrant in the post CDK4/6i population, data from the relevant subgroup of patients from SOLAR-1 are presented here as supportive evidence.

B.2.4.1 Trial design and baseline characteristics in SOLAR-1

Full details of the SOLAR-1 trial design and methodology are detailed in Appendix F.2.1 and F.2.2. In brief, SOLAR-1 enrolled postmenopausal women and men with HR+, HER2− ABC, with a *PIK3CA* mutation. They were eligible to receive further ET after relapse or progression on or after prior AI treatment (in the [neo]adjuvant, or metastatic setting).[29] Patients were randomised to receive alpelisib plus fulvestrant, or placebo plus fulvestrant (Figure 7).

Figure 7: SOLAR-1 trial design



[a] Given on Cycle 1 Day 1 and Day 15 and then Day 1 of each subsequent cycle thereafter.
Abbreviations: ABC: advanced breast cancer; CBR: clinical benefit rate; CDK: cyclin dependent kinase; ECOG: Eastern Cooperative Oncology Group; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; IM: intramuscular; PFS: progression-free survival; *PIK3CA*: phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; ORR: overall response rate; OS: overall survival; PO: by mouth; QD: once daily; R: randomised.
Source: André *et al.* (2019).[29]

Definitions of the primary and key secondary endpoints with data available for the post-CDK4/6i population are provided in Table 17. Definitions of additional endpoints such as ORR that are available for the overall SOLAR-1 population are presented in the Appendix.

Table 17: Endpoint definitions in SOLAR-1

Endpoint	Definition
Primary endpoint	
PFS	• Time from the date of randomisation to the date of the first documented progression or death due to any cause
Secondary endpoints	
OS	• Time from randomisation to date of death due to any cause
CBR	• Proportion of patients with a best overall response of CR or PR or SD or Non-CR/Non-PD lasting 24 weeks or more based on local Investigator assessment according to RECIST 1.1 criteria

Abbreviations: CBR: clinical benefit rate; CR: complete response; OS: overall survival; PR: partial response; RECIST: Response Evaluation Criteria in Solid Tumours; SD: stable disease.
Source: André *et al.* (2019);[29] SOLAR-1 CSR Section 10.4-10.5.[121]

Overall, baseline demographics were well-balanced between the alpelisib plus fulvestrant (alpelisib) arm (n=169) and the placebo plus fulvestrant (placebo) arm (n=172). The median age was 63 years (range: 25–87) in the alpelisib plus fulvestrant arm and 64 in the placebo plus fulvestrant arm (range: 38–92), and 99.4% and 100% of patients were female, respectively (only

one male patient was enrolled).[29] The majority of patients were white (69.2% of patients in the alpelisib plus fulvestrant arm and 63.4% of patients in the placebo plus fulvestrant arm).[122]

Furthermore, baseline disease characteristics were also well-balanced between the two treatment arms with regards to the extent and location of disease. In the alpelisib plus fulvestrant and placebo plus fulvestrant arms respectively, [redacted] and [redacted] of patients had stage IV (metastatic) disease at study entry.[121] The median time from initial diagnosis of the primary site was [redacted] in the alpelisib plus fulvestrant arm and [redacted] in the placebo plus fulvestrant arm.[121]

In the alpelisib plus fulvestrant arm, nine patients (5.3%) had received prior CDK4/6i therapy and 143 (84.6%) had endocrine resistant disease.[29] In the placebo plus fulvestrant arm, 11 patients (6.5%) had previously received CDK4/6i therapy and 149 (86.6%) had endocrine resistant disease.[29] As mentioned in the Foreword and Section B.2.2.1, these numbers were relatively small due to the evolving treatment pathway for ABC and the speed of enrolment for SOLAR-1. CDK4/6 + AI is a relatively new addition to the treatment pathway, and as patients typically received CDK4/6i + AI for a relatively long duration, enrolment for SOLAR-1 was largely complete by the time any patients who had received this combination had discontinued and subsequently progressed.

Full baseline characteristics of the SOLAR-1 population is available in Appendix F.2.3.

B.2.4.2 Clinical effectiveness results of SOLAR-1

Results from the SOLAR-1 trial (i.e., including the majority of patients who had not received prior CDK4/6i therapy) from the primary analysis (12th June 2018) and final OS analysis (23rd April 2020) where available are presented in the following sections and Appendix F.3.

To provide context with which to assess the results for the post-CDK4/6i population, the following text summarises the results from the full SOLAR-1 population; complete results from this population are presented in Appendix F:

- In the *PIK3CA*-mutated cohort of the full population in SOLAR-1, the median duration of follow-up from randomisation to data cut-off was 20.0 months (range: 10.7–33.3) for the primary analysis (12th June 2018),[29] and 42.4 months (range: 33.1–55.7) for the final OS analysis (23rd April 2020).[82]
- At the primary analysis (12th June 2018), the study met its primary endpoint, demonstrating a statistically significant improvement in PFS by Investigator assessment for patients receiving alpelisib plus fulvestrant versus placebo plus fulvestrant. Median PFS was 11.0 months (95% CI: 7.5, 14.5) for alpelisib plus fulvestrant versus 5.7 months (95% CI: 3.7, 7.4) for placebo plus fulvestrant (HR: 0.65; 95% CI: 0.50, 0.85; one-sided p=0.00065).[29, 123] Therefore, alpelisib plus fulvestrant prolonged PFS by 5.3 months.[29]
- At the final OS analysis (23rd April 2020), median OS was 39.3 months (95% CI: 34.1, 44.9) in the alpelisib plus fulvestrant arm and 31.4 months (95% CI: 26.8, 41.3) in the placebo plus fulvestrant arm, representing a positive trend with an increase of 7.9 months in median OS in favour of alpelisib plus fulvestrant.[82] There was an approximate 14% reduction in the risk of death in the alpelisib plus fulvestrant arm compared with the placebo plus fulvestrant arm

(HR: 0.86; 95% CI: 0.64, 1.15; p=0.15). These results did not cross the pre-specified O-Brien Fleming stopping boundary (one-sided p≤0.0161).

- At the final OS analysis (23rd April 2020), median PFS was consistent with the primary analysis (12th June 2018). Median PFS was prolonged by a clinically meaningful [redacted] months in favour of the alpelisib plus fulvestrant arm, from [redacted] months (95% CI [redacted]) in the placebo plus fulvestrant arm to [redacted] months (95% CI [redacted]) in the alpelisib plus fulvestrant arm.[105] Alpelisib plus fulvestrant showed longer-term benefit and a [redacted] risk reduction in disease progression or death over placebo plus fulvestrant ([redacted]).[105]

As this submission focusses on the post-CDK4/6i population, results for the subpopulation of 20 patients with prior CDK4/6i therapy from SOLAR-1 are presented in the subsequent sections. These results are consistent with that of the full population, and likewise highlight the value of alpelisib plus fulvestrant in patients with HR+, HER2– ABC.

B.2.4.2.1 Primary endpoint: PFS (post-CDK4/6i population)

PFS results at the time of the final OS analysis (23rd April 2020) in subjects with prior CDK4/6i use showed a positive trend consistent with that observed in the overall population (Section F.3.1 in Appendix F), supporting that prior CDK4/6i treatment is not a treatment effect modifier. While a statistically significant result was not expected for the limited sample size for this subgroup (n = 20), a clinically meaningful [redacted] in disease progression or death was observed among patients with prior CDK4/6i use in the alpelisib plus fulvestrant arm (n=9) compared to the placebo plus fulvestrant arm (n=11) ([redacted]) (Table 18).[105] The treatment effect, as measured by the PFS hazard ratio, was consistent with that observed in the overall population using the latest available data cut-off date ([redacted]% risk reduction; [redacted]).[105]

Table 18: Descriptive PFS update in the *PIK3CA*-mutated cohort with prior CDK4/6i use in SOLAR-1, compared with FAS (data cut-off 23rd April 2020)

Post-CDK4/6i population	Alpelisib plus fulvestrant (n=9)	Placebo plus fulvestrant (n=11)
Number of PFS events, n (%)	[redacted]	[redacted]
Median PFS (95% CI)	[redacted]	[redacted]
HR (95% CI)	[redacted]	
FAS (descriptive update; for comparison)	**Alpelisib plus fulvestrant (n=169)**	**Placebo plus fulvestrant (n=172)**
Median PFS (95% CI)	[redacted]	[redacted]
HR (95% CI)	[redacted]	

Abbreviations: CDK4/6i: cyclin dependent kinase 4/6 inhibitor; CI: confidence interval; HR: hazard ratio; FAS: full analysis set; PFS: progression-free survival; *PIK3CA*: phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.
Source: Novartis Data on File.[105]

B.2.4.2.2 Key secondary endpoint: OS (post-CDK4/6i population)

Results at the final OS analysis (23rd April 2020) in subjects with prior CDK4/6 inhibitor use also showed a positive trend ([redacted]) (Table 19). Median OS was prolonged by [redacted] in the alpelisib plus fulvestrant arm from [redacted] in the placebo plus fulvestrant arm to [redacted].[105] Note that these results should be interpreted with caution given that the final OS analysis did not cross the pre-specified efficacy boundary and

due to this subgroup analysis being based on a small number of events. While patient numbers are relatively small, this provides supportive evidence that the post-CDK4/6i population fulfils the end-of-life criteria (see Section B.2.11.3).

Table 19: Final OS analysis in the *PIK3CA*-mutated cohort with prior CDK4/6i use in SOLAR-1, compared with FAS (data cut-off 23rd April 2020)

Post-CDK4/6i population	Alpelisib plus fulvestrant (n=9)	Placebo plus fulvestrant (n=11)
Number of OS events, n (%)	[redacted]	[redacted]
Median OS (95% CI)	[redacted]	[redacted]
HR (95% CI)	[redacted]	
FAS (for comparison)	**Alpelisib plus fulvestrant (n=169)**	**Placebo plus fulvestrant (n=172)**
Median OS (95% CI)	39.3 (34.1, 44.9)	31.4 (26.8, 41.3)
HR (95% CI)	0.86 (0.64, 1.15)	

Abbreviations: CDK4/6i: cyclin dependent kinase 4/6 inhibitor; CI: confidence interval; FAS: full analysis set; HR: hazard ratio; *PIK3CA*: phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; OS: overall survival.
Source: André *et al.* (2020);[82] Novartis Data on File.[105]

B.2.4.2.3 Secondary endpoint: CBR (post-CDK4/6i population)

At the primary data cut-off (12th June 2018), in patients with prior CDK4/6i use in the *PIK3CA*-mutated cohort, the CBR was [redacted] in the alpelisib plus fulvestrant arm compared with [redacted] in the placebo plus fulvestrant arm.[121] CBR results for the overall SOLAR-1 population are reported in Section F.3.4 of Appendix F.

Updated CBR data are not available from the final OS analysis.

B.2.4.2.4 Additional secondary and exploratory endpoints: ORR, PROs, time to response and DoR

Data on additional secondary endpoints (ORR and PROs), exploratory endpoints (time to response and DoR), concomitant medications and subgroup analysis for PFS from SOLAR-1 (data cut-off 12th June 2018) are presented in Appendix F.

In brief, ORR and time to response were in favour of the alpelisib plus fulvestrant arm; DoR was determined in too few patients in the placebo plus fulvestrant arm for an adequate treatment comparison.[121] Treatment with alpelisib plus fulvestrant did not impact the patients' HRQoL, suggesting that any treatment-associated AEs do not incur additional burden to the HRQoL of patients in this setting.[124]

B.2.5 Additional efficacy data in the post-CDK4/6i population

B.2.5.1 Matching/weighted analysis of BYLieve and real-world standard of care

B.2.5.1.1 Trial design and methodology

As BYLieve does not include a comparator arm, an additional analysis was performed to compare PFS results for Cohort A of BYLieve with a similar group of patients in the real-world setting, derived from the Flatiron Clinicogenomics Database (CGDB) in the United States. The

matching/weighted analysis of BYLieve and real-world standard of care (henceforth referred to as 'matching/weighted analysis') was a non-interventional, retrospective, observational 2-cohort study comparing clinical outcomes among patients treated with alpelisib combined with fulvestrant in the BYLieve trial with those among patients treated with standard treatments in the real world.[106] Novartis have also presented results from this analysis to the MHRA as supportive data in the licensing application.[105]

Subjects who received alpelisib plus fulvestrant in Cohort A of the BYLieve trial and eligible patients from the Flatiron CGDB who satisfied relevant entry criteria for the BYLieve trial were considered. The eligibility criteria below was applied; full eligibility criteria can be found in Turner *et al.* (2021)[106] and Novartis data on file.[105]

Patients were eligible to be included in the CGDB cohort if they met key inclusion criteria from BYLieve (Section B.2.3.2) that were feasible to apply to the CGDB:

- Women and men with confirmed ABC, age ≥18 years with a confirmed *PIK3CA* mutation
- Received a line of therapy after CDK4/6i plus ET
- ≤2 prior lines of therapy for ABC, and ≤1 prior line of chemotherapy for ABC
- Aligned with standard real-world analytic procedures, subjects who had a documented death event within 14 days of treatment initiation were excluded, as these events may not be directly associated with the real-world effectiveness of therapy. For consistency, this was also applied to the BYLieve cohort. As such, one subject from Cohort A of the BYLieve trial who died within 14 days of enrolment was excluded.

Key exclusion criteria included:

- >2 lines of anti-cancer therapy in the advanced setting and/or >1 line of chemotherapy in the locoregional or metastatic setting prior to index date
- No prior CDK4/6i therapy
- Treatment with alpelisib, HER2-directed therapy, or a clinical trial drug
- Receipt of HER2+-specific treatment (proxy for HER2+ status)

Full details of the CGDB cohort selection are reported in Table 1 of the full publication.[106] The primary endpoint, real-world PFS, was defined as observed progression or death events >14 days after index date (the start date of the next line of therapy after CDK 4/6i).[106]

B.2.5.1.2 Baseline characteristics

Pre-matching patient characteristics and baseline disposition of the real-world study arm and BYLieve cohort in the matching/weighted analysis are presented in Table 20. Post-matching patient characteristics and baseline disposition are reported in the full publication.[106]

Table 20: Baseline characteristics of patients in the real-world (CGDB) and BYLieve arm in the matching/weighted analysis

Characteristics	CGDB (N=95) n (%)	BYLieve (N=120) N (%)
Sex, n (%)		

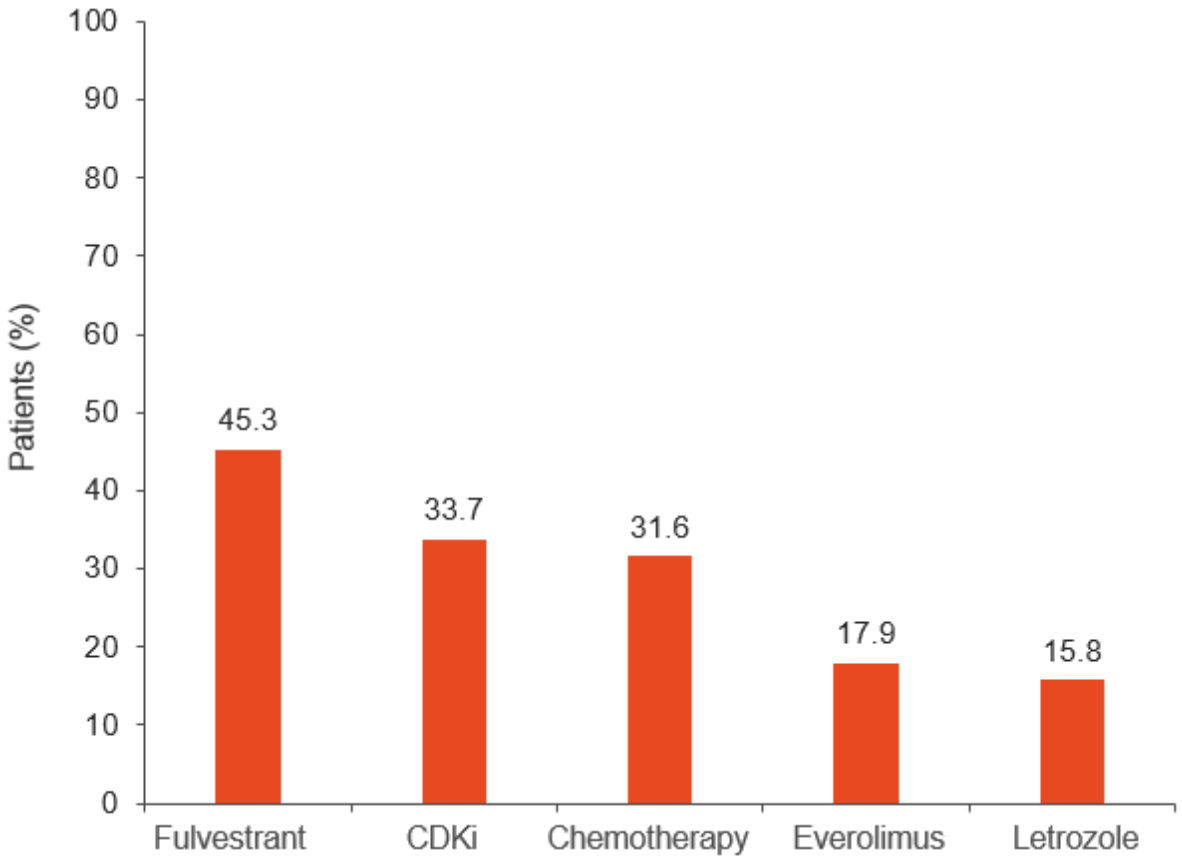
Characteristics	CGDB (N=95) n (%)	BYLieve (N=120) N (%)
Female	[redacted]	[redacted]
Male	[redacted]	[redacted]
Age at indexing (years)		
Mean (SD)	[redacted]	[redacted]
Median (Min–max)	[redacted]	[redacted]
Age category at index, n (%)		
<50	13 (13.7)	35 (29.2)
50 to < 65	49 (51.6)	54 (45.0)
≥65	33 (34.7)	31 (25.8)
Race, n (%)		
White	[redacted]	[redacted]
Non-white	[redacted]	[redacted]
ECOG at baseline, n (%)		
0	[redacted]	[redacted]
1	[redacted]	[redacted]
2	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Stage at initial diagnosis, n (%)		
0/I	[redacted]	[redacted]
II	[redacted]	[redacted]
III	[redacted]	[redacted]
IV	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Stage at index, n (%)		
III	[redacted]	[redacted]
IV	[redacted]	[redacted]
Pooled number of metastatic sites		
<3	57 (60.0)	84 (70.0)
≥3	38 (40.0)	36 (30.0)
Sites of metastases		
Bone only	20 (21.1)	22 (18.3)
Lung/liver	56 (59.0)	80 (66.7)
Time from initial diagnosis to index date, months		
Mean (SD)	[redacted]	[redacted]
Median (Min–max)	[redacted]	[redacted]
Time from initial diagnosis to index date in months, n (%)		
<27	22 (23.2)	31 (25.8)
27 to <60	24 (25.3)	30 (25.0)
60 to <128	24 (25.3)	31 (25.8)
≥128	25 (26.3)	28 (23.3)

Abbreviations: CGDB: Clinicogenomics Database.

Source: Turner *et al.* (2021);[106] Novartis Data on File.[105]

The treatments received by patients in the CGDB cohort are presented in Figure 8 below. The most frequently used components of post-CDK4/6i treatment regimens included fulvestrant (45.3%, n=43), CDK4/6i (33.7%, n=32), chemotherapy (31.6%, n=30), everolimus (17.9%, n=17), and letrozole (15.8%, n=15), as displayed below. The most frequent treatment regimens were capecitabine monotherapy (14.7%, n=14), fulvestrant monotherapy (14.7%, n=14), palbociclib combined with fulvestrant (13.7%, n=13), everolimus combined with exemestane (11.6%, n=11), and palbociclib combined with fulvestrant and letrozole (5.3%, n=5).[106]

Figure 8: Treatments received post-CDK4/6i in the CGDB cohort



Abbreviations: CDK(4/6)i: cyclin-dependent kinase (4/6) inhibitor; CGDB: Clinicogenomics Database.
Source: Turner *et al.* (2021).[106]

B.2.5.1.3 Statistical analysis and definition of study arms in the relevant clinical effectiveness evidence

To mitigate differences in baseline characteristics that may be related to the study endpoints, subjects were matched/weighted using three distinct approaches: weighting by odds, propensity score matching, and exact matching, as described in Table 21.

Table 21: Methodology for weighting/matching approaches

Approach	Description
Weighting by odds	Weighting by odds is utilised to account for differences between the cohorts at baseline and to estimate the average treatment effect of the treated (ATT)

	subjects. Each subject is assigned a weight that represents their odds of being in the BYLieve cohort, conditional on their observed baseline covariates. Assigning each BYLieve cohort subject a weight of one maintains the composition of the BYLieve cohort subjects.
Propensity score matching (Greedy matching)	The propensity score is defined as the probability of a subject belonging in the BYLieve cohort, conditional on their observed baseline covariates. Logistic regression is used to derive propensity scores from baseline covariates selected as potentially clinically relevant for exposure and outcome differences between cohorts. Each subject from the BYLieve cohort will be randomly matched with a subject from the CGDB cohort with similar propensity scores, using the Greedy matching technique and a caliper value of 0.2.
Exact matching	Each subject from the BYLieve cohort will be matched to one subject from the CGDB cohort based on an exact match of relevant baseline covariates.

Abbreviations: CGDB: Clinicogenomics Database.
Source: Novartis Data on File.[105]

Standardised mean differences (SMD) between the two cohorts were assessed. Success of the matching process was evaluated by comparing the SMD; an SMD value of <25% for a particular variable was considered balanced. For the weighting by odds approach, SMD was calculated using the corresponding weights. For exact matching, the covariate values within each subclass were guaranteed to be the same.[105]

The following baseline covariates are available for all subjects in BYLieve and the matching/weighted analysis and were selected to be included in the weighting/matching models based on their clinical relevance:[105]

- Age category: <50, 50 to <65, ≥65 years old
- Number of metastatic sites: <3, ≥3
- Bone lesions only: yes, no
- Lung or liver metastases: present, absent
- Time since initial diagnosis: <27, 27 to <60, 60 to <128, ≥128 months

B.2.5.1.4 Clinical effectiveness results of the matching/weighted analysis

Table 22 summarises median PFS and HRs for alpelisib plus fulvestrant from the BYLieve cohort compared to standard treatments from the CGDB cohort. In a series of weighted/matched analyses, there was a consistent trend in the PFS HRs in favour of alpelisib plus fulvestrant compared to standard treatments. This validates the observations from SOLAR-1, and supporting alpelisib plus fulvestrant treatment efficacy in the post-CDK4/6i population in HR+, HER2– ABC patients with a *PIK3CA* mutation.

Table 22: Summary of Kaplan-Meier estimates and hazard ratios of PFS from the weighting and matching approaches (matching/weighted analysis)

Analysis method (BYLieve vs. CGDB arm)	Median PFS (months) (95% CI)		HR (95% CI)
	Alpelisib plus fulvestrant (BYLieve)	Standard treatment (CGDB)	
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]

Abbreviations: CI: confidence interval; CGDB: Clinicogenomics Database; HR: hazard ratio; PFS: progression-free survival.
Source: Turner *et al.* (2021);[106] Novartis Data on File.[105]

B.2.5.1.5 Limitations of the matching/weighted analysis

As mentioned above, the main limitation of this analysis is the fact that real-world data for standard treatment in the post-CDK4/6i setting is derived from the United States, where alternative treatment options to those in the UK are considered in this population. However, this study still provides important supportive evidence for the benefits of alpelisib plus fulvestrant following treatment with a CDK4/6i.

In addition, this analysis relies on a relatively small sample size, and as matching approaches were implemented to balance on observable prognostic factors in the absence of a RCT, it should be acknowledged that such approaches can only account for measurable and feasible confounders that can be included in the model. Potential selection bias and unmeasured and residual confounding cannot therefore be ruled out.[106]

B.2.6 Meta-analysis

No meta-analysis was conducted as part of this appraisal.

B.2.7 Indirect and mixed treatment comparisons

There is no head-to-head clinical trial evidence comparing alpelisib plus fulvestrant versus everolimus plus exemestane, the relevant comparator in this submission. Thus, the results of the clinical SLR described in Section B.2.1 were used to identify relevant evidence (in the form of RCTs) of the efficacy and safety of everolimus plus exemestane for the purposes of conducting ITCs to estimate the relative efficacy between alpelisib plus fulvestrant versus everolimus plus exemestane in patients with endocrine resistant HR+, HER2– ABC with a *PIK3CA* mutation. A network meta-analysis (NMA) using the Bucher ITC method, as well as a supportive patient-adjusted indirect comparison (PAIC) were conducted to compare alpelisib plus fulvestrant versus everolimus plus exemestane.

B.2.7.1 Trials identified in the SLR

The SLR identified 1 RCT for alpelisib plus fulvestrant (SOLAR-1) and 1 RCT for everolimus plus exemestane (BOLERO-2). SOLAR-1 investigated the efficacy of alpelisib plus fulvestrant versus placebo plus fulvestrant.[29] BOLERO-2 investigated the efficacy of everolimus plus exemestane versus placebo plus exemestane;[62] as such a connected network could not be created between the two trials.

In order to connect the two trials (SOLAR-1 and BOLERO-2), the studies identified in the SLR were re-reviewed for any studies investigating either everolimus plus exemestane, placebo plus exemestane (exemestane monotherapy), placebo plus fulvestrant (fulvestrant monotherapy) and alpelisib plus fulvestrant. Where data were not available for patients with *PIK3CA*-mutated breast cancer, trials reporting outcomes for patients regardless of *PIK3CA* mutation status were considered in order to be able to create a network.

Two relevant trials were identified: SoFEA and CONFIRM.[109, 110] Whilst CONFIRM did not separately report results for HER2− patients and therefore did not meet the eligibility criteria to be included in the SLRs, it was included in the Bucher ITC on the basis that no other trials of fulvestrant 500 mg versus fulvestrant 250 mg were identified that reported results for HER2− patients.[110]

An overview of the trials included in the ITCs are provided in Table 23 and full details of the feasibility assessment for the ITCs are provided in Appendix D.

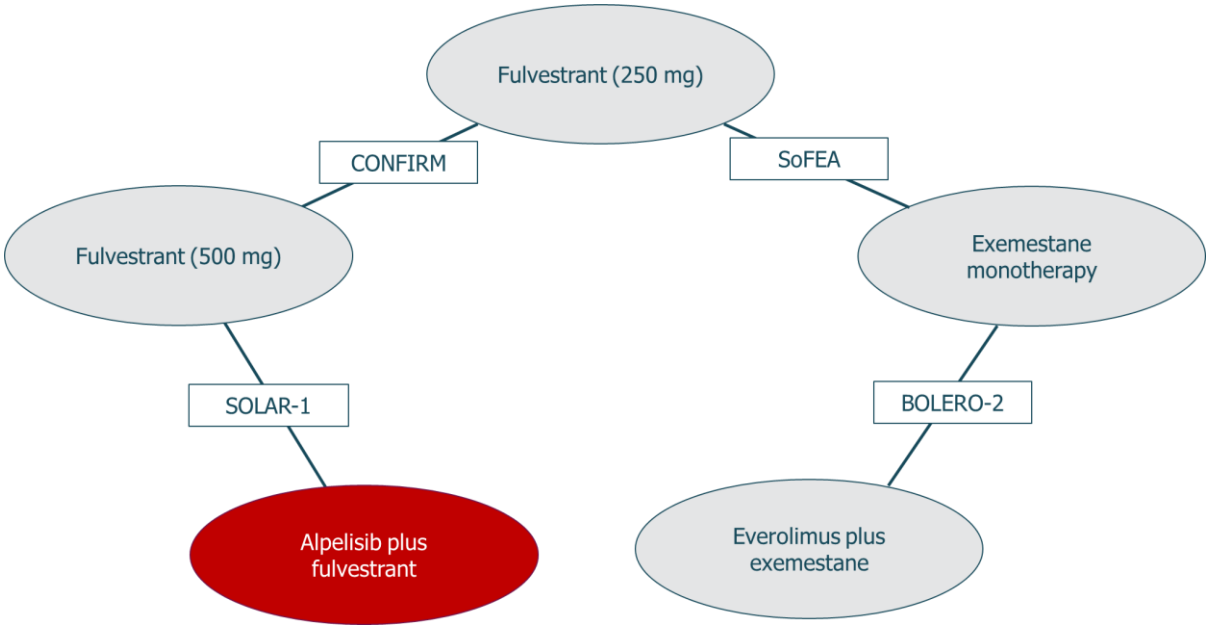
Table 23: Studies included in the ITCs

Study	Author, year	Intervention	Comparator	Patients (N)	Patient population					
					HR status	HER2 status	Menopause status	*PIK3CA* mutation data available	Prior treatment in (neo) adjuvant setting	Prior treatment for advanced disease
BOLERO-2	Yardley *et al.* (2013)[62]	Everolimus plus exemestane	Placebo plus exemestane	724	HR+	HER2–	Postmenopausal	Yes	Resistant	Progressed on ET
CONFIRM	Di Leo *et al.* (2010)[110]	Fulvestrant 500 mg	Fulvestrant 250 mg	736	HR+	HER2– or HER2+	Postmenopausal	No	Resistant	Progressed on ET
SoFEA	Johnston *et al.* (2013)[109]	Fulvestrant plus anastrazole	Placebo plus exemestane	723	HR+	HER2– or HER2+	Postmenopausal	No	Resistant or sensitive	Progressed on ET
SOLAR-1	André *et al.* (2018)[29]	Alpelisib plus fulvestrant	Placebo plus fulvestrant	341	HR+	HER2–	Postmenopausal	Yes	Resistant or sensitive[a]	Progressed on ET

[a]Protocol was amended to exclude ET-sensitive first-line patients; Resistant: relapsed ≤12 months from completion of (neo)adjuvant ET and no treatment for metastatic disease; Sensitive: relapsed >12 months from completion of (neo)adjuvant ET and no treatment for metastatic disease.
Abbreviations: ET: endocrine therapy; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; N/A: not available; *PIK3CA*: phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

The evidence network for both PFS and OS is presented in Figure 9.

Figure 9: Evidence network for the Bucher ITC



Abbreviations: ITC: indirect treatment comparison; OS: overall survival; PFS: progression-free survival; *PIK3CA*: phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

B.2.7.2 Bucher ITC

B.2.7.2.1 Methodology of the Bucher ITC

It should be noted that due to there being no data available for everolimus plus exemestane in a post-CDK4/6i population, it was not possible to conduct ITCs in the post-CDK4/6i population specifically. As a proxy for the post-CDK4/6i setting, based on the available data, ITCs for PFS and OS were conducted using data for patients in second-line ABC. This approach was validated by clinical expert opinion, which suggested that, in the absence of direct evidence comparing alpelisib plus fulvestrant to everolimus plus exemestane in the post-CDK4/6i population, it would be reasonable to assume that a treatment effect in the second-line population would be applicable in the post-CDK4/6i setting.[93]

The ITCs were conducted using the Bucher method, which relies on the assumption of proportional hazards. Full details of the methodology of this approach are presented in Appendix D.

Proportional hazards assumption

Full details of the assessment of proportional hazards are presented in Appendix D. Results of the assessment of the proportionality assumption for PFS and OS based on the test of the linearity of the Schoenfeld residuals for each of the trials is summarised in Table 24.

The test for proportional hazards was not violated for any study in the network, and therefore the Bucher method approach was considered appropriate to estimate the relative efficacy of alpelisib plus fulvestrant versus everolimus plus exemestane. This methodology has been utilised in previous NICE submissions in ABC.[4]

Table 24: Results of assessment of proportional hazards assumption for PFS and OS based on test of linearity of Schoenfeld residuals

Trial	p-value for test of proportional hazards assumption	
	PFS	OS
Second-line population		
SOLAR-1[a]	[redacted]	[redacted]
BOLERO-2[a]	[redacted]	[redacted]
Line of therapy not available		
CONFIRM	[redacted]	[redacted]
SoFEA	[redacted]	[redacted]

[a] *PIK3CA*-mutated ABC.
Abbreviations: OS: overall survival; PFS: progression-free survival.

B.2.7.2.2 Results of the Bucher ITC

PFS

Results of the ITC between alpelisib plus fulvestrant and everolimus plus exemestane of PFS based on the Bucher method are shown in Table 25.

Table 25: Results for HRs for PFS from the ITC using the Bucher method

Comparator	HR (95%CI) of comparator versus:	
	Fulvestrant	Alpelisib plus fulvestrant
Alpelisib plus fulvestrant	[redacted]	[redacted]
Everolimus plus exemestane	[redacted]	[redacted]
Fulvestrant	[redacted]	[redacted]

Abbreviations: CI: confidence interval; HR: hazard ratio; ITC: indirect treatment comparison; N/A: not available; PFS: progression-free survival.

OS

Results of the ITC between alpelisib plus fulvestrant and everolimus plus exemestane of OS based on the Bucher method are shown in Table 26.

Table 26: Results for HRs for OS from the ITC using the Bucher method

Comparator	HR (95%CI) of comparator versus:	
	Fulvestrant	Alpelisib plus fulvestrant
Alpelisib plus fulvestrant	[redacted]	[redacted]
Everolimus plus exemestane	[redacted]	[redacted]
Fulvestrant	[redacted]	[redacted]

Abbreviations: CI: confidence interval; HR: hazard ratio; ITC: indirect treatment comparison; N/A: not available; OS: overall survival.

B.2.7.3 PAIC: SOLAR-1 versus BOLERO-2

B.2.7.3.1 Methodology of the PAIC

A PAIC of alpelisib plus fulvestrant versus everolimus plus exemestane in postmenopausal women with HR+, HER2- ABC and *PIK3CA* mutation was conducted based on data from the SOLAR-1 and BOLERO-2 trials.[62, 82] Data from SOLAR-1 were from the final OS analysis (23rd

April 2020 data cut-off); data from BOLERO-2 were from the 15th December 2011 data cut-off.

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, 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 alpelisib plus fulvestrant and placebo plus fulvestrant arms, respectively). For BOLERO-2, 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. The single male patient from SOLAR-1 was excluded.

Outcomes included investigator-assessed PFS and OS which were analysed using Kaplan-Meier methods, Cox proportional hazards regression, and using parametric survival distributions. Patients in SOLAR-1 and BOLERO-2 were matched using inverse probability of treatment weighting (IPTW) methods.[125] For each patient, the probability of being in the trial in which the patient was enrolled (i.e. 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 Appendix D.6.2.

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 Appendix D.6.2.

B.2.7.3.2 Results of the PAIC

Patient attrition

A summary of patient attrition for the comparison of alpelisib plus fulvestrant versus everolimus plus exemestane based on data from SOLAR-1 and BOLERO-2 is presented in Table 27. A total of [redacted] and [redacted] second-line patients receiving alpelisib plus fulvestrant and placebo plus fulvestrant, respectively, from SOLAR-1 met the inclusion criteria for this analysis. For BOLERO-2, [redacted] and [redacted] patients receiving everolimus plus exemestane and placebo plus fulvestrant, respectively, met inclusion criteria. The effective sample size (ESS) after applying average treatment effect among the treated (ATT) weights was [redacted] and [redacted] for patients receiving everolimus plus exemestane and placebo plus fulvestrant, respectively.

Given the small number of patients in the BOLERO-2 trial who met inclusion criteria and the small ESSs, the results of this analysis should be interpreted with caution. Patient characteristics for the second-line patients in SOLAR-1 and BOLERO-2, as well as the plots of SMDs and IPTWs are detailed in Appendix D.9.1.

Table 27: Patient attrition for comparison of alpelisib plus fulvestrant versus everolimus plus exemestane

Inclusion / exclusion criteria	SOLAR-1				BOLERO-2			
	Alpelisib plus fulvestrant		Placebo plus fulvestrant		Everolimus plus exemestane		Placebo plus exemestane	
	N	%	N	%	N	%	N	%

Full analysis set	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exclude ≥2 prior lines	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PIK3CA mutation (tissue)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exclude ET sensitive patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Second-line	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ET: endocrine therapy; *PIK3CA*: phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

Analysis of PFS and OS

Kaplan-Meier estimates for PFS and OS are presented in Appendix D.6.2.

Results of Cox proportional hazards regressions for PFS and OS for second-line patients in SOLAR-1 versus BOLERO-2 are shown below in Table 30. The HRs for PFS and OS for alpelisib plus fulvestrant versus everolimus plus fulvestrant are [redacted] and [redacted], respectively.

Table 28: Results of Cox proportional hazards regressions for PFS and OS for second-line patients in SOLAR-1 versus BOLERO-2

Endpoint	Weighted	Arms		Cox regression		
		Active (N)	Comparator (N)	HR	95% CI	p value
PFS	Yes	Alpelisib plus fulvestrant ([redacted])	Everolimus plus exemestane ([redacted])	[redacted]	[redacted]	[redacted]
OS	Yes	Alpelisib plus fulvestrant ([redacted])	Everolimus plus exemestane ([redacted])	[redacted]	[redacted]	[redacted]

Abbreviations: CI: confidence interval; OS: overall survival; PFS: progression-free survival.

B.2.7.4 Uncertainties in the indirect and mixed treatment comparisons

In the absence of a head-to-head trial, the objective of these analyses was to estimate the relative efficacy between alpelisib plus fulvestrant and everolimus plus exemestane. Given SOLAR-1 compared alpelisib plus fulvestrant to fulvestrant alone, and BYLieve was a non-comparative, open label study, ITCs were required to estimate the relative efficacy between alpelisib plus fulvestrant and everolimus plus exemestane.

The SLR identified one RCT for alpelisib plus fulvestrant (SOLAR-1), and one RCT for everolimus plus exemestane (BOLERO-2).[21, 126-147] In order to connect the two trials (SOLAR-1 and BOLERO-2), two additional trials were added to the network: SoFEA and CONFIRM.[109, 110] Whilst CONFIRM did not separately report results for HER2− patients and therefore did not meet the eligibility criteria to be included in the SLRs, it was included in the ITC on the basis that no other trials of fulvestrant 500 mg versus fulvestrant 250 mg were identified that reported results for HER2− patients.[110]

Whilst data for patients with tumours harbouring a *PIK3CA* mutation were available from SOLAR-1 and BOLERO-2, these ITCs relied on a network being created between SOLAR-1 and BOLERO-2 with the SoFEA and CONFIRM trials.[109, 148] A potential limitation of this analysis is that data from these additional trials were not available for patients with tumours harbouring a *PIK3CA* mutation. However, it is not anticipated that the treatment effect of a specific therapy

(that does not target the PI3K pathway such as everolimus plus exemestane, exemestane monotherapy or fulvestrant monotherapy) would differ depending on *PIK3CA* mutation. This assumption is supported by pre-clinical and clinical data (including data from the placebo and fulvestrant arm of SOLAR-1),[21, 29] as well as the tests for treatment effect modifiers conducted as part of the feasibility assessment for this ITC (see Appendix D).

No data are available for everolimus plus exemestane in a post-CDK4/6i population, and as a single-arm trial, it was not possible to incorporate data for alpelisib plus fulvestrant from BYLieve into an ITC. In the absence of an alternative approach to estimate the relative efficacy between alpelisib plus fulvestrant and everolimus plus exemestane in the post-CDK4/6i population, ITCs were conducted via a network that included data from SOLAR-1 and BOLERO-2 in the second-line setting, and this ITC was used to inform the economic analysis (see Section B.3.3.1.1). Additionally, the SoFEA[109] and CONFIRM[148] trials enrolled patients receiving first- and second- or subsequent line treatment for ABC and HRs for PFS and OS were not available by line of therapy. Similarly, in the absence of alternative available data, these trials were required to create a network to estimate the relative efficacy of alpelisib plus fulvestrant versus everolimus plus exemestane and were incorporated within the ITC.

It is acknowledged that these analyses may be subject to potential limitations stemming from differences in patient populations across RCTs; full details of the feasibility assessment performed prior to conducting the ITCs are presented in Appendix D. However, the results of the assessment for treatment effect modification demonstrated that HER2 status was the only factor for which effect modification on PFS or OS was found to be statistically significant ($p<0.05$) in one trial. The effect of fulvestrant 250 mg versus exemestane was favourable in patients with HER2+ tumours but unfavourable among those with HER2– tumours. This only affects the CONFIRM trial of fulvestrant 500 mg versus fulvestrant 250 mg, which was the only trial which included patients with HER2+ tumours; the distribution of patients HER2 status was not reported and outcomes by HER2 status were not evaluated in this trial. In the absence of alternative data, the use of the SoFEA and CONFIRM trials allowed for the connection of trials to estimate the relative efficacy of alpelisib plus fulvestrant versus everolimus plus exemestane. The results of this analysis therefore represent the best estimates of relative efficacy between alpelisib plus fulvestrant and everolimus plus exemestane for the purposes of this submission.

PAIC

As described above, the PAIC estimated PFS and OS for alpelisib plus fulvestrant versus everolimus plus exemestane in patients with HR+/HER2- ABC with *PIK3CA* mutation based on data from the SOLAR-1 and BOLERO-2 trials. Patients in BOLERO-2 were selected to match the inclusion criteria of the SOLAR-1 trial and weighted using IPTW to match baseline demographic and clinical characteristics of patients in SOLAR-1. Unanchored comparisons were performed, which is a limitation of the analysis and therefore is potentially confounded by unobserved characteristics that may have differed across the trials. Also, the numbers of subjects and ESSs were relatively small, and there is an inherent assumption that all effect modifiers and prognostic factors are accounted for. In spite of these limitations, the results of the PAIC may be useful as they suggest that alpelisib plus fulvestrant may yield improved survival compared to everolimus plus exemestane in patients with HR+/HER2- ABC with *PIK3CA* mutation receiving second-line treatment. However, this analysis has been presented as supporting evidence to the Bucher ITC, given the potential limitations associated with this PAIC approach.

The conclusions of the Bucher ITC and PAIC also directionally support the matching/weighted analysis reported in Section B.2.5, which also supports a PFS benefit with alpelisib plus fulvestrant versus current treatment options in a post-CDK4/6i population specifically. Therefore, in the absence of a more robust indirect analysis in the post-CDK4/6i population, the Bucher ITC is considered a reasonable proxy for the relative efficacy of alpelisib plus fulvestrant in the post-CDK4/6i population to inform the base case economic analysis, with the PAIC providing supportive evidence (and as part of a scenario analysis for the cost-effectiveness model).

B.2.8 Adverse reactions

- The tolerability of alpelisib plus fulvestrant has been demonstrated in both BYLieve and SOLAR-1; safety data have been shown to be consistent across both patient populations and therefore evidence from both trials can be used to support that alpelisib plus fulvestrant has a well-characterised and manageable safety profile.[29, 75]

BYLieve

- The overall safety and tolerability profile observed in BYLieve was consistent with the prior known safety profile of alpelisib.[75, 108]
    - In total, 127 patients were included in the safety set for Cohort A.[75]
- The median duration of exposure to fulvestrant (6.5 months) was longer than for alpelisib (5.1 months).[75]
- The most common AEs (≥20%) were diarrhoea (59.8%), hyperglycaemia (58.3%), nausea (45.7%), fatigue (29.1%), decreased appetite (28.3%), rash (28.3%), stomatitis (26.8%) and vomiting (23.6%).[75]
- The most common AEs leading to discontinuation were rash (3.9%), colitis (1.6%), hyperglycaemia (1.6%), urticaria (1.6%) and vomiting (1.6%).[75]
    - AE data from BYLieve support the conclusion that experience from SOLAR-1 has led to a decrease in the incidence and proportion patients discontinuing treatment due to key AEs such as hyperglycaemia.[75]
- Overall, 25 deaths (19.7%) occurred up to the date of data cut-off (17th December 2019), with 7 (5.5%) classified as on-treatment deaths (i.e. up to 30 days after end of treatment).[75]
    - The causes of on-treatment deaths (n=7) were study indication (breast cancer) (3.1%), respiratory failure (0.8%), superior vena cava occlusion (0.8%) and death due to unspecified reason (0.8%).[75]
- Treatment discontinuations were reported for 94 (74%) of patients, the primary reasons for which were progressive disease (50%) and AEs (14%).[75]

SOLAR-1

- The overall safety and tolerability profile observed in SOLAR-1 was consistent with the prior known safety profile of alpelisib.[29, 107]
    - In total (*PIK3CA*-mutated cohort and *PIK3CA* wildtype cohort), 284 patients and 287 patients were included in the safety set for the alpelisib plus fulvestrant and placebo plus fulvestrant arms, respectively.[29]
    - Safety data were generally consistent between patients in the *PIK3CA*-mutated cohort and *PIK3CA* wildtype cohort, and therefore the following conclusions are summarised for all patients (i.e. the overall safety population combines both cohorts regardless of *PIK3CA* status).[29]
- At the final OS analysis (23rd April 2020), the most common AEs (at any Grade; regardless of study drug relationship) reported in the alpelisib plus fulvestrant arm were hyperglycaemia (64.8%), diarrhoea (59.5%) and nausea (46.8%). The same AEs

occurred in 9.4%, 16.4% and 22.6% of patients, respectively in the placebo plus fulvestrant arm.[82]

- At the final OS analysis (23rd April 2020), median duration of exposure to study drug in the *PIK3CA*-mutated cohort was 5.5 (0–51.4) months for alpelisib and 8.3 (0.4–51.4) months for fulvestrant in the alpelisib plus fulvestrant arm, and 4.6 (0–52.5) months for placebo and 5.5 (0.5–52.5) months for fulvestrant in the placebo plus fulvestrant arm.[82]
- The incidence of AEs was higher in the alpelisib plus fulvestrant arm, but the AEs were generally manageable using concomitant medications and/or dose modifications.[29] Dose interruptions (72.2%) and dose reductions (59.2%) were more frequent in patients treated with alpelisib plus fulvestrant and were primarily due to AEs.[107] The majority of events were resolved by the 12th June 2018 data cut-off.[121]
- Grade 3/4 AEs were generally reported in ≤5% of patients in the alpelisib plus fulvestrant arm, with the exception of hyperglycaemia (37.0%) and diarrhoea (7.0%) (cut-off date 23rd April 2020).[82]
- Overall, at the final OS analysis (23rd April 2020), 87 deaths (51.5%) and 94 deaths (54.7%) occurred in the alpelisib plus fulvestrant and placebo plus fulvestrant arms, respectively.[82]
- Serious adverse events (AEs) were reported more frequently in the alpelisib plus fulvestrant arm compared to placebo plus fulvestrant (34.9% versus 16.7%).[29] In the alpelisib plus fulvestrant arm, with the exception of hyperglycaemia (9.9%), all SAEs occurred in <3% of patients (cut-off date 12th June 2018).[122]
- Discontinuation of either study drug due to AEs was more frequent in the alpelisib plus fulvestrant arm compared to the placebo plus fulvestrant arm (25.0% versus 4.5%) (cut-off date 12th June 2018).[122]
- Improvements in the management of AEs over time in SOLAR-1 were evident via a decrease in treatment discontinuations due to any AE and ≥Grade 3 AEs for patients in the alpelisib plus fulvestrant arm when comparing the first 50% of patients randomised to the second 50%; discontinuations due to any Grade AE decreased from 29.2% to 20.7% and Grade 3/4 AEs decreased from 18.1% to 7.9% (cut-off date 12th June 2018).[107]

Summary

- Alpelisib plus fulvestrant has a well-characterised safety profile with AEs that are associated with PI3K pathway inhibition, such as hyperglycaemia, rash and gastrointestinal (GI) toxicity as the key AEs of special interest (AESIs).[29, 75, 107]
- Robust AE management guidelines, which include medical therapies and/or dose modifications, have been developed and refined throughout SOLAR-1 and BYLieve, and are specified in the SmPC for alpelisib.[38]

As of the 13th May 2019, a total of [redacted] patients (including cancer patients, hepatic impaired patients, and healthy volunteers) had been exposed to alpelisib across [redacted] Novartis sponsored studies with alpelisib as a single agent or in combination with targeted agents (everolimus, everolimus plus exemestane, MEK162, LGX818, LJM716, ribociclib, imatinib, trastuzumab emtansine [T-DM1], olaparib), endocrine therapy (e.g. fulvestrant, letrozole) or chemotherapy (e.g. paclitaxel, nab-paclitaxel). [redacted] studies have been completed, including [redacted] clinical pharmacology studies in healthy volunteers and [redacted] hepatic impairment study. [redacted] clinical studies are currently ongoing.[149] Over the course of these investigations, the safety profile of alpelisib has been well-characterised, and robust management strategies have been developed and refined for key AEs.

The safety and tolerability of alpelisib plus fulvestrant in patients with endocrine resistant HR+, HER2– ABC with a *PIK3CA* mutation was evaluated as a secondary endpoint in SOLAR-1, reported in André *et al.* 2019,[29, 122] Juric *et al.* SABCS 2018; oral presentation GS3-08,[123] André *et al.* 2020,[82] and the SOLAR-1 CSR,[121] with additional safety analyses presented at ESMO 2019 (Rugo *et al.*; poster 324P).[107] Safety and tolerability were also assessed as a secondary endpoint in BYLieve and have been reported by Rugo *et al.* (ASCO 2020; oral presentation abstract 1006), and Rugo *et al.* 2021,[75] and are also available on file.[108]

Given the safety profile of alpelisib plus fulvestrant is not anticipated to be influenced by the receipt of prior CDK4/6i therapy, full safety results have been presented for both BYLieve and SOLAR-1 below.

B.2.8.1 BYLieve

The safety and tolerability of alpelisib plus fulvestrant in patients with endocrine resistant HR+, HER2– ABC with a *PIK3CA* mutation was evaluated as a secondary endpoint in BYLieve and have been reported by Rugo *et al.* (ASCO 2020; oral presentation abstract 1006) and Rugo *et al.* 2021,[75] and are also available on file.[108]The safety population for Cohort A in BYLieve included all patients who had received at least one dose of study treatment and was based on 127 patients who received alpelisib (of whom 126 patients also received fulvestrant).[75]

B.2.8.1.1 Treatment duration and dosage

Drug exposure

At the time of data cut-off at 17th December 2019, treatment was ongoing in 33 patients (26%) in Cohort A.[75] The median duration of exposure to study treatment in the overall safety population was longer with fulvestrant (6.5 months) compared to alpelisib (5.1 months) (see Table 29).[75]

Table 29: Duration of exposure to study treatment in Cohort A of BYLieve (safety set)

	Alpelisib (n=127)	Fulvestrant (n=126)	Overall (N=127)
Duration of exposure (months)			
Mean (SD)	5.8 (4.7)	6.7 (4.7)	7.0 (4.6)
Median	5.1	6.5	7.4
Q1-Q3	1.8–8.6	2.3–9.0	2.8–9.2
Min-Max	0–25	0–25	0–25
Duration of exposure categories, n (%)			

<2 months	[redacted]	[redacted]	[redacted]
2–<4 months	[redacted]	[redacted]	[redacted]
4–<6 months	[redacted]	[redacted]	[redacted]
6–<8 months	[redacted]	[redacted]	[redacted]
8–<10 months	[redacted]	[redacted]	[redacted]
10–<12 months	[redacted]	[redacted]	[redacted]
12–<14 months	[redacted]	[redacted]	[redacted]
14–<16 months	[redacted]	[redacted]	[redacted]
16–<18 months	[redacted]	[redacted]	[redacted]
≥18 months	[redacted]	[redacted]	[redacted]

Duration of exposure (days) = (date of last administration of study treatment) – (date of first non-zero dose administration of study treatment) + 1 day
Abbreviations: SD: standard deviation.
Source: Rugo *et al.* (2021);[75] Rugo *et al.* (2021). Supplementary Appendix;[75] Novartis Data on File.[108]

Dose adjustments and discontinuation

A summary of reasons for discontinuation from Cohort A in BYLieve is presented in Table 30. Further information on AEs leading to study drug discontinuation are presented in the BYLieve protocol.[41]

Table 30: Discontinuation of study drug in Cohort A of BYLieve (FAS)

	n (%)
Discontinued from treatment	94 (74.0)
Reason for discontinuation	
Progressive disease	64 (50.4)
Adverse event	18 (14.2)
Physician decision	4 (3.1)
Death	3 (2.4)
Patient/guardian decision	3 (2.4)
Protocol deviation	1 (0.8)
Technical problems	1 (0.8)

Abbreviations: FAS: full analysis set.
Source: Rugo *et al.* (2021).[75]

B.2.8.1.2 Adverse events

In BYLieve, AEs were assessed according to the National Cancer Institute Common Terminology Criteria, version 4.03) and were recorded continuously until 30 days after the last dose of trial treatment.[41] A summary of the AEs from BYLieve for the safety population is presented in Table 31.

Table 31: Overview of AEs in BYLieve (safety set)

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.
Abbreviations: AE: adverse event; SAE: serious adverse event.
Source: Rugo *et al.* (2021).[75]

AEs regardless of study drug relationship

A summary of AEs occurring in >5% of patients regardless of study treatment relationship for the safety set from BYLieve is presented in Table 32.

Table 32: AEs (>5%) regardless of study treatment relationship in BYLieve, by preferred term (safety set)

Preferred term	All grades, n (%)	Grade ≥3, n (%)
Number of patients with at least one event	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)

Preferred term	All grades, n (%)	Grade ≥3, n (%)
Blood creatinine increased	13 (10.2)	1 (0.8)
Cough	13 (10.2)	1 (0.8)
Muscle spasms	13 (10.2)	0
Musculoskeletal pain	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]
Constipation	[redacted]	[redacted]
Dry mouth	[redacted]	[redacted]
Hypokalaemia	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Myalgia	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]
Oedema peripheral	[redacted]	[redacted]
Vision blurred	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]
Erythema	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]
Hyponatraemia	[redacted]	[redacted]
Palmar-plantar erythrodysaesthesia syndrome	[redacted]	[redacted]
Back pain	[redacted]	[redacted]
Gamma-glutamyltransferase increased	[redacted]	[redacted]

A patient with multiple severity grades for an AE is only counted under the maximum grade.
Abbreviations: AE: adverse event.
Source: Rugo *et al.* (2021). Supplementary Appendix;[75] Novartis Data on File.[108]

Deaths

Details of patients for the safety set from BYLieve who died while on-treatment are presented in Table 33.

Table 33: On-treatment deaths in BYLieve (Safety set)

Safety topic	n (%)
On-treatment deaths	7 (5.5)
Primary reason: Study indication	4 (3.1)
Breast cancer	4 (3.1)
Primary reason: Other	3 (2.4)
Unspecified death	1 (0.8)
Hepatic failure	0
Respiratory failure	1 (0.8)
Superior vena cava occlusion	1 (0.8)

Source: Rugo *et al.* (2021). Supplementary Appendix.[75]

SAEs regardless of study drug relationship

SAEs in ≥1% of patients in Cohort A regardless of study drug relationship are presented in Table

34.

Table 34: Serious AEs irrespective of relationship to study drug in BYLieve, by preferred term and grade (incidence ≥1% in either arm) (safety set)

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.
Abbreviations: AE: adverse event.
Source: Rugo *et al.* (2021);[75] Novartis Data on File.[108]

AEs leading to study drug discontinuation

AEs leading to discontinuation in >1% of patients in Cohort A regardless of study drug relationship are presented in Table 35.

Table 35: AEs leading to treatment discontinuation irrespective of study treatment relationship in BYLieve, by preferred term (safety set)

Preferred term	All grades, n (%)	Grade ≥3, n (%)
Number of patients with at least one event	26 (20.5)	15 (11.8)
Rash	5 (3.9)	3 (2.4)
Colitis	2 (1.6)	1 (0.8)
Hyperglycaemia	2 (1.6)	2 (1.6)
Urticaria	2 (1.6)	2 (1.6)
Vomiting	2 (1.6)	1 (0.8)

A patient with multiple severity grades for an AE is only counted under the maximum grade.
Abbreviations: AE: adverse event.
Source: Rugo *et al.* (2021).[75]

AEs requiring dose adjustment or study treatment interruption

A summary of AEs requiring dose adjustment and/or interruption in ≥3 patients in either treatment arm is presented in Table 36.

Table 36: AEs requiring dose adjustment and/or interruption in BYLieve, by preferred term and maximum grade (in ≥3 patients in either arm) (safety set)

Preferred term	All grades, n (%)	Grade ≥3, n (%)
Number of patients with at least one event	82 (64.6)	68 (53.5)
Hyperglycaemia	37 (29.1)	32 (25.2)
Rash	16 (12.6)	10 (7.9)
Rash maculo-papular	12 (9.4)	11 (8.7)
Diarrhoea	10 (7.9)	6 (4.7)
Vomiting	5 (3.9)	1 (0.8)

Asthenia	4 (3.1)	1 (0.8)
Pruritus	4 (3.1)	2 (1.6)
Stomatitis	4 (3.1)	2 (1.6)
Hypokalaemia	3 (2.4)	3 (2.4)
Pyrexia	3 (2.4)	0
Weight decreased	3 (2.4)	1 (0.8)

A patient with multiple severity grades for an AE is only counted under the maximum grade.
Abbreviations: AE: adverse event.
Source: Rugo *et al.* (2021).[75]

AEs of special interest (AESIs)

A summary of AESIs for Cohort A in BYLieve is presented in Table 37.

Table 37: Overview of AESIs in BYLieve (safety set)

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.
Abbreviations: AESI: adverse event of special interest; GI: gastrointestinal.
Source: Rugo *et al.* (2021). Supplementary Appendix.[75]

Subgroup analysis of AEs by duration of prior CDK4/6i therapy

As described in Section B.2.3.6.6, a subgroup analysis was conducted to explore the association of PFS with duration of prior CDK4/6i therapy in Cohort A of BYLieve. Grade ≥3 AEs were experienced by 66.9% of all patients and 66.7%/68.3% in the High/Low subgroups, respectively (Table 38).

Table 38: AEs (≥20% by preferred term) by duration of prior CDK4/6i therapy in Cohort A (safety set)

	High (n=63)		Low (n=63)		All patients (n=127)	
	All grades, n (%)	Grade 3/4, n (%)	All grades, n (%)	Grade 3/4, n (%)	All grades, n (%)	Grade 3/4, n (%)
Total	62 (98.4)	42 (66.7)	63 (100)	43 (68.3)	126 (99.2)	85 (66.9)
Hyperglycaemia	36 (57.1)	16 (25.4)	38 (60.3)	20 (31.7)	74 (58.3)	36 (28.3)
Diarrhoea	42 (66.7)	5 (7.9)	33 (52.4)	2 (3.2)	76 (59.8)	7 (5.5)
Nausea	29 (46.0)	0	30 (47.6)	0	59 (46.5)	0
Rash[a]	13 (20.6)	4 (6.3)	23 (36.5)	8 (12.7)	36 (28.3)	12 (9.4)
Fatigue	20 (31.7)	1 (1.6)	17 (27.0)	0	37 (29.1)	1 (0.8)

Decreased appetite	18 (28.6)	0	19 (30.2)	1 (1.6)	37 (29.1)	1 (0.8)
Stomatitis	16 (25.4)	1 (1.6)	18 (28.6)	1 (1.6)	34 (26.8)	2 (1.6)
Asthenia	9 (14.3)	0	17 (27.0)	1 (1.6)	26 (20.5)	1 (0.8)
Vomiting	16 (25.4)	2 (3.2)	14 (22.2)	0	30 (23.6)	2 (1.6)
Headache	15 (23.8)	0	9 (14.3)	1 (1.6)	24 (18.9)	1 (0.8)
Pruritus	7 (11.1)	1 (1.6)	13 (20.6)	2 (3.2)	20 (15.7)	3 (2.4)

[a] All-grade rash maculo-papular (preferred terms) was reported in 10 (15.9%), 8 (12.7%), and 18 (14.2%) in High, Low, and All patient subgroups, respectively; grade 3/4 was reported in 6 (9.5%) in both High and Low subgroups, and 12 (9.4%) in All patients.
Abbreviations: AE: adverse event; CDK4/6i: cyclin dependent kinase 4/6 inhibitor.
Source: Chia *et al.* (2021)[120]

B.2.8.2 SOLAR-1

The safety population in SOLAR-1 included all patients who had received at least one dose of study treatment (n=571).[29] Therefore, the total safety population included 284 patients who received alpelisib plus fulvestrant (169 in the *PIK3CA*-mutated cohort and 115 in the wild type *PIK3CA* cohort) and 287 who received placebo plus fulvestrant (171 patients in the *PIK3CA*-mutated cohort and 116 in the wild type *PIK3CA* cohort).[29]

The presence or absence of *PIK3CA* mutations was not expected to affect the occurrence of AEs. The incidence of AEs, SAEs, and AESIs was generally consistent between the mutated and wildtype *PIK3CA* cohorts, and therefore safety data from both cohorts were combined to present the safety profile of alpelisib from a larger number of patients.[121] Further details on adverse reactions are presented in Appendix F.

B.2.8.2.1 Treatment duration and dosage

Drug exposure

Data cut-off: 12th June 2018

In the alpelisib plus fulvestrant arm, exposure to fulvestrant was longer than alpelisib (median 8.2 versus 5.5 months), reflecting a population of patients who discontinued alpelisib for reasons other than disease progression and continued treatment with fulvestrant (see Table 39).[107] In the placebo plus fulvestrant arm, the duration of exposure to both study drugs was the same (with a median of 5.6 months for both placebo and fulvestrant).[107]

In the *PIK3CA*-mutated cohort, the median duration of exposure to study treatment in the alpelisib plus fulvestrant arm was 5.5 months (0.0–29.0), and 4.6 months (0.0–30.1) in the placebo plus fulvestrant arm.[29]

Table 39: Duration of exposure to study drug in SOLAR-1 (safety set) (data cut-off 12th June 2018)

	Alpelisib plus fulvestrant (n=284)			Placebo plus fulvestrant (n=287)		
	Alpelisib	Fulvestrant	Overall	Placebo	Fulvestrant	Overall
Total number of patients exposed – n (%)	283 (99.6)	284 (100.0)	284 (100.0)	286 (99.7)	287(100.0)	287 (100.0)

	Alpelisib plus fulvestrant (n=284)			Placebo plus fulvestrant (n=287)		
	Alpelisib	Fulvestrant	Overall	Placebo	Fulvestrant	Overall
Duration of exposure (months)						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	5.5	8.2	8.2	5.6	5.6	5.6
Q1-Q3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min-Max	0.0[a]–30.8	0.4–30.8	0.4–30.8	0.0*–30.1	0.5–30.1	0.5–30.1
Duration of exposure categories, n (%)						
<1 month	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥1 month	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥2 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥3 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥4 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥18 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Overall: Corresponds to duration of study treatment.
[a]One patient in the alpelisib plus fulvestrant arm and one patient in the placebo plus fulvestrant arm received a single injection of fulvestrant but did not start alpelisib/placebo treatment.
Abbreviations: Q: quartile; SD: standard deviations.
Source: Rugo *et al.* (2019);[107] SOLAR-1 CSR.[121]

Data cut-off: 23rd April 2020

Treatment was still being received by 21 patients (12.4%) in the alpelisib plus fulvestrant arm and 7 (4.1%) patients in the placebo plus fulvestrant arm at the time of the data cut-off.[82] In the *PIK3CA*-mutated cohort, the median duration of exposure to study treatment was 5.5 months for alpelisib (range: 0.0–51.4) and 8.3 months for fulvestrant (range: 0.4–51.4) in the alpelisib plus fulvestrant arm, and 4.6 months for placebo (range: 0.0–52.5) and 5.5 months for fulvestrant (range: 0.5–52.5) in the placebo plus fulvestrant arm.[82]

Dose adjustments and discontinuation

Data cut-off: 12th June 2018

In the *PIK3CA*-mutated cohort, the proportion of patients who had at least one dose reduction was 63.9% in the alpelisib plus fulvestrant arm and 8.8% in the placebo plus fulvestrant arm.[29] The proportion of patients with at least one dose interruption was 74.0% in the alpelisib plus fulvestrant arm and 32.2% in the placebo plus fulvestrant arm.[29] Similar results were seen in the overall population (supporting that safety results for the overall population and *PIK3CA*-mutated cohort are similar); 59.2% of patients requiring at least one dose reduction in the alpelisib plus fulvestrant group compared with 7.3% of patients in the placebo plus fulvestrant group.[107] In addition, 72.2% of patients required at least one dose interruption in the alpelisib plus fulvestrant group compared with 30.0% in the placebo plus fulvestrant group.[107]

A summary of dose adjustments and discontinuation of study drug from the overall population in SOLAR-1 is presented in Table 40 (data cut-off 12th June 2018). Further information on AEs

leading to study drug discontinuation are presented in Table 40.

Table 40: Dose adjustments and discontinuation of study drug in SOLAR-1 (safety set) (data cut-off 12th June 2018)

	Alpelisib plus fulvestrant (n=284)		Placebo plus fulvestrant (n=287)	
	Alpelisib	**Fulvestrant**	**Placebo**	**Fulvestrant**
With no dose reduction and/or interruption	[redacted]	[redacted]	[redacted]	[redacted]
With at least one dose reduction and/or interruption	213 (75.0)	14 (4.9)	89 (31.0)	4 (1.4)
Dose reductions				
With no dose reduction	[redacted]	-	[redacted]	-
With at least one dose reduction	168 (59.2)	-	21 (7.3)	-
Only one dose reduction	[redacted]	-	[redacted]	-
Two dose reductions	[redacted]	-	[redacted]	-
More than two dose reductions	[redacted]	-	[redacted]	-
Number of patients with at least one dose reduction by reason – n (%)				
AE	[redacted]	-	[redacted]	-
Physician decision	[redacted]	-	[redacted]	-
Dosing error	[redacted]	-	[redacted]	-
Missing	[redacted]	-	[redacted]	-
Dispensing error	[redacted]	-	[redacted]	-
Dose interruptions				
With no dose interruption	[redacted]	[redacted]	[redacted]	[redacted]
With at least one dose interruption	205 (72.2)	14 (4.9)	86 (30.0)	4 (1.4)
Only one dose interruption	[redacted]	[redacted]	[redacted]	[redacted]
Two dose interruption	[redacted]	[redacted]	[redacted]	[redacted]
More than two dose interruption	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients with at least one dose interruption by reason – n (%)				
AE	[redacted]	[redacted]	[redacted]	[redacted]
Dosing error	[redacted]	[redacted]	[redacted]	[redacted]
Physician decision	[redacted]	[redacted]	[redacted]	[redacted]
Technical problems	[redacted]	[redacted]	[redacted]	[redacted]
Dispensing error	[redacted]	[redacted]	[redacted]	[redacted]
Permanent discontinuation				

	Alpelisib plus fulvestrant (n=284)		Placebo plus fulvestrant (n=287)	
	Alpelisib	Fulvestrant	Placebo	Fulvestrant
Number of patients – 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]

Abbreviations: AE: adverse event.
Source: SOLAR-1 CSR;[121] Rugo *et al.* (2019).[107]

B.2.8.2.2 AEs

In SOLAR-1, AEs were assessed according to the National Cancer Institute Common Terminology Criteria, version 4.03) and were recorded continuously until 30 days after the last dose of trial treatment.[29]

Data cut-off: 12th June 2018

A summary of the AEs from SOLAR-1 for the safety population at the primary data cut-off is presented in Table 41. The incidence of AEs, SAEs, and AESIs were generally consistent between the *PIK3CA*-mutated and wild type cohorts.

Management of AEs improved over the course of SOLAR-1; there was a decrease in discontinuations due to any AE and ≥Grade 3 AEs for patients in the alpelisib plus fulvestrant arm when comparing the first 50% of patients randomised to the second 50%. Furthermore, discontinuations due to any Grade AE decreased from 29.2% to 20.7%, and discontinuations due to Grade 3/4 AEs decreased from 18.1% to 7.9%.[107]

Table 41: Overview of AEs in SOLAR-1 (safety set) (data cut-off 12th June 2018)

	Alpelisib plus fulvestrant (n=284)		Placebo plus fulvestrant (n=287)	
	Any grade n (%)	Grade 3/4 n (%)	Any grade n (%)	Grade 3/4 n (%)
AEs	282 (99.3)	216 (76.1)	264 (92.0)	102 (35.5)
Treatment-related	[redacted]	[redacted]	[redacted]	[redacted]
SAEs	99 (34.9)	82 (28.9)	48 (16.7)	43 (15.0)
Treatment-related	[redacted]	[redacted]	[redacted]	[redacted]
Fatal SAEs	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-related[a]	[redacted]	[redacted]	[redacted]	[redacted]

	Alpelisib plus fulvestrant (n=284)		Placebo plus fulvestrant (n=287)	
	Any grade n (%)	Grade 3/4 n (%)	Any grade n (%)	Grade 3/4 n (%)
AEs leading to discontinuation	71 (25.0)	37 (13.0)	13 (4.5)	11 (3.8)
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.
Abbreviations: AE: adverse event; SAE: serious adverse event.
Source: SOLAR-1 CSR;[121] André *et al.* (2019);[29] André *et al.* (2019) Supplementary Appendix.[122]

Data cut-off: 23rd April 2020

A summary of the AEs from SOLAR-1 for the safety population at the final OS analysis is presented in Table 42.

Table 42: Overview of AEs in SOLAR-1 (safety set) (data cut-off 23rd April 2020)

	Alpelisib plus fulvestrant (n=284)		Placebo plus fulvestrant (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.
Abbreviations: AE: adverse event; SAE: serious adverse event.
Source: André *et al.* (2020);[82] Novartis Data on File.[150]

AEs regardless of study drug relationship

Data cut-off: 12th June 2018

A summary of AEs occurring in ≥10% of patients in either treatment arm regardless of study drug relationship is presented in Table 43. A summary of treatment-related AEs occurring in ≥10% of patients in either treatment arm is presented in Appendix F.

Table 43: AEs by preferred term and maximum grade (≥10% in either treatment arm) in SOLAR-1 (safety set) (data cut-off 12th June 2018)

Preferred term	Alpelisib plus fulvestrant (n=284)		Placebo plus fulvestrant (n=287)	
	Any grade n (%)	Grade 3/4 n (%)	Any grade n (%)	Grade 3/4 n (%)
Total	282 (99.3)	216 (76.1)	264 (92.0)	102 (35.5)
Hyperglycaemia	181 (63.7)	104 (36.6)	28 (9.8)	2 (0.7)
Diarrhoea	164 (57.7)	19 (6.7)	45 (15.7)	1 (0.3)
Nausea	127 (44.7)	7 (2.5)	64 (22.3)	1 (0.3)
Decreased appetite	101 (35.6)	2 (0.7)	30 (10.5)	1 (0.3)
Rash	101 (35.6)	28 (9.9)	17 (5.9)	1 (0.3)
Vomiting	77 (27.1)	2 (0.7)	28 (9.8)	1 (0.3)
Weight decreased	76 (26.8)	11 (3.9)	6 (2.1)	0
Stomatitis	70 (24.6)	7 (2.5)	18 (6.3)	0
Fatigue	69 (24.3)	10 (3.5)	49 (17.1)	3 (1.0)
Asthenia	58 (20.4)	5 (1.8)	37 (12.9)	0
Alopecia	56 (19.7)	0	7 (2.4)	0
Mucosal inflammation	52 (18.3)	6 (2.1)	3 (1.0)	0
Pruritus	51 (18.0)	2 (0.7)	16 (5.6)	0
Headache	50 (17.6)	2 (0.7)	38 (13.2)	0
Dysgeusia	47 (16.5)	0	10 (3.5)	0
Dry skin	[redacted]	[redacted]	[redacted]	[redacted]
Oedema peripheral	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]
Rash maculopapular	[redacted]	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia	32 (11.3)	1 (0.4)	47 (16.4)	3 (1.0)
Dyspepsia	[redacted]	[redacted]	[redacted]	[redacted]
Blood creatinine increased	[redacted]	[redacted]	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	[redacted]	[redacted]

A patient with multiple severity grades for an AE was only counted under the maximum grade.
Source: SOLAR-1 CSR;[121] André *et al.* (2019).[29]

Data cut-off: 23rd April 2020

A summary of AEs occurring in ≥20% of patients in either treatment arm regardless of study drug relationship for the safety set from SOLAR-1 is presented in Table 44 below.

Table 44: AEs by preferred term and maximum grade (≥20% in either treatment arm) in SOLAR-1 (safety set) (data cut-off 23rd April 2020)

Preferred term	Alpelisib plus fulvestrant (n=284)[a]			Placebo plus fulvestrant (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.
Source: André *et al.* 2020.[82]

Deaths

Data cut-off: 12th June 2018

The overall incidence of deaths at any time during the study was higher in the placebo plus fulvestrant arm; out of 571 patients in the safety set, a total of [redacted] in the alpelisib plus fulvestrant arm and [redacted] in the placebo plus fulvestrant arm had died by the time of the data cut-off.[29, 121] Most deaths were due to the study indication.[121] In the *PIK3CA*-mutated cohort, death was reported for [redacted] versus [redacted] (alpelisib plus fulvestrant versus placebo plus fulvestrant, respectively), with disease progression as the primary cause in most of these cases [redacted].[121]

In the alpelisib plus fulvestrant arm, seven (2.5%) on-treatment deaths occurred; five (1.8%) due to the study indication, one (0.4%) due to cardiorespiratory arrest, and one (0.4%) due to a second primary malignancy.[29, 122] None were considered to be related to study treatment by the Investigators. In the placebo plus fulvestrant arm, 12 (4.2%) on-treatment deaths occurred; eight (2.8%) were due to the study indication, and the remaining four (1.4%) were due to

gastrointestinal haemorrhage, pneumonia, septic shock and unknown cause respectively.[121] None were considered to be related to study treatment by the Investigators. In the *PIK3CA*-mutated cohort, on-treatment death was reported for [redacted] in the alpelisib plus fulvestrant arm and [redacted] in the placebo plus fulvestrant arm.[121]

Details of patients for the safety set from SOLAR-1 who died while on-treatment are presented in Table 45.

Table 45: On-treatment deaths in SOLAR-1 (safety set) (data cut-off 12th June 2018)

	Alpelisib plus fulvestrant (n=284) n (%)	Placebo plus fulvestrant (n=287) n (%)
Number of patients who died	7 (2.5)	12 (4.2)
Primary reason: Study indication	5 (1.8)	8 (2.8)
Primary reason: Other	2 (0.7)	[redacted]
Cardio-respiratory arrest	1 (0.4)	[redacted]
Death	0	[redacted]
Gastrointestinal haemorrhage	0	[redacted]
Pneumonia	0	[redacted]
Second primary malignancy	1 (0.4)	[redacted]
Septic shock	0	[redacted]

Source: SOLAR-1 CSR Table 12-8;[121] André *et al.* (2019).[29]

Data cut-off: 23rd April 2020

OS data for the 23rd April 2020 data cut-off for SOLAR-1 are also presented in Section B.2.4.2 above for the *PIK3CA*-mutated cohort. At the time of the data cut-off there were 181 deaths, 87 (51.5%) in the alpelisib plus fulvestrant arm and 94 (54.7%) in the placebo plus fulvestrant arm.[82]

In the alpelisib plus fulvestrant 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.[29, 122] None were considered to be related to study treatment by the Investigators. In the placebo plus fulvestrant 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.[150] None were considered to be related to study treatment by the Investigators.

Table 46: On-treatment deaths in SOLAR-1 (safety set) (data cut-off 23rd April 2020)

	Alpelisib plus fulvestrant (n=284) n (%)	Placebo plus fulvestrant (n=287) n (%)
Number of patients who died	[redacted]	[redacted]
Primary reason: Study indication	[redacted]	[redacted]
Primary reason: Other	[redacted]	[redacted]
Cardio-respiratory arrest	[redacted]	[redacted]
Gastrointestinal haemorrhage	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]

Second primary malignancy	[redacted]	[redacted]
Septic shock	[redacted]	[redacted]

Source: Novartis Data on File.[150]

SAEs regardless of study drug relationship

Data cut-off: 12th June 2018

SAEs from SOLAR-1 that occurred in ≥1% of patients in either treatment arm regardless of study drug relationship are presented in Table 47.

Table 47: SAEs irrespective of relationship to study drug, by preferred term and grade (incidence ≥1% in either arm) in SOLAR-1 (safety set) (data cut-off 12th June 2018)

Preferred term	Alpelisib plus fulvestrant (n=284)		Placebo plus fulvestrant (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.
Abbreviations: AE: adverse event; SAE: serious adverse event.
Source: André *et al.* (2019) Supplementary Appendix.[122]

AEs leading to study drug discontinuation

Data cut-off: 12th June 2018

A summary of AEs leading to study drug discontinuation in >3 patients in either treatment arm, by preferred term and maximum grade is presented in Table 48.

Table 48: AEs leading to study drug discontinuation by preferred term and maximum grade (in >2 patients in either arm) in SOLAR-1 (safety set) (data cut-off 12th June 2018)

Preferred term	Alpelisib plus fulvestrant (n=284)		Placebo plus fulvestrant (n=287)	
	Any grade n (%)	Grade 3/4 n (%)	Any grade n (%)	Grade 3/4 n (%)
Total	71 (25.0)	37 (13.0)	13 (4.5)	11 (3.8)
Hyperglycaemia	18 (6.3)	12 (4.2)	0	0
Rash	9 (3.2)	3 (1.1)	0	0
Diarrhoea	8 (2.8)	1 (0.4)	0	0
Fatigue	6 (2.1)	3 (1.1)	0	0
Nausea	5 (1.8)	1 (0.4)	0	0
Decreased appetite	4 (1.4)	0	0	0
Stomatitis	4 (1.4)	1 (0.4)	1 (0.3)	0
Hypersensitivity	3 (1.1)	2 (0.7)	0	0
Lipase increased	3 (1.1)	1 (0.4)	4 (1.4)	4 (1.4)
Pneumonitis	3 (1.1)	1 (0.4)	0	0
Rash maculo-papular	3 (1.1)	1 (0.4)	0	0
Vomiting	3 (1.1)	0	0	0
Dry mouth	2 (0.7)	1 (0.4)	0	0
Erythema	2 (0.7)	2 (0.7)	0	0
Erythema multiforme	2 (0.7)	0	0	0
Mucosal inflammation	2 (0.7)	1 (0.4)	0	0
Weight decreased	2 (0.7)	0	0	0
Spinal cord compression	0	0	2 (0.7)	1 (0.3)

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.
Abbreviations: AE: adverse event.
Source: André *et al.* (2019) Supplementary Appendix.[122]

AEs requiring dose adjustment or study treatment interruption

Data cut-off: 12th June 2018

A summary of AEs requiring dose adjustment and/or interruption in ≥3 patients in either treatment arm is presented in Table 49.

Table 49: AEs requiring dose adjustment and/or interruption by preferred term and maximum grade (in ≥3 patients in either arm) in SOLAR-1 (safety set) (data cut-off 12th June 2018)

Preferred term	Alpelisib plus fulvestrant (n=284)		Placebo plus fulvestrant (n=287)	
	Any grade n (%)	Grade 3/4 n (%)	Any grade n (%)	Grade 3/4 n (%)
Total	[redacted]	[redacted]	[redacted]	[redacted]
Hyperglycaemia	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Rash maculo-papular	[redacted]	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]	[redacted]
Stomatitis	[redacted]	[redacted]	[redacted]	[redacted]
Mucosal inflammation	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]
Lipase increased	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]	[redacted]	[redacted]
Hypokalaemia	[redacted]	[redacted]	[redacted]	[redacted]
Blood creatinine increased	[redacted]	[redacted]	[redacted]	[redacted]
Hyponatraemia	[redacted]	[redacted]	[redacted]	[redacted]
Acute kidney injury	[redacted]	[redacted]	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]	[redacted]	[redacted]
Dysgeusia	[redacted]	[redacted]	[redacted]	[redacted]
Weight decreased	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
Rash generalised	[redacted]	[redacted]	[redacted]	[redacted]

Preferred term	Alpelisib plus fulvestrant (n=284)		Placebo plus fulvestrant (n=287)	
	Any grade n (%)	Grade 3/4 n (%)	Any grade n (%)	Grade 3/4 n (%)
Amylase increased	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]
Dehydration	[redacted]	[redacted]	[redacted]	[redacted]
Dyspepsia	[redacted]	[redacted]	[redacted]	[redacted]
Erythema	[redacted]	[redacted]	[redacted]	[redacted]
Gamma-glutamyltransferase increased	[redacted]	[redacted]	[redacted]	[redacted]
Rash macular	[redacted]	[redacted]	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac failure	[redacted]	[redacted]	[redacted]	[redacted]
Hyperkalaemia	[redacted]	[redacted]	[redacted]	[redacted]

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.
Abbreviations: AE: adverse event.
Source: SOLAR-1 CSR Table 12-12.[121]

AEs of special interest (AESIs)

Data cut-off: 12th June 2018

AESIs were defined as events (serious or non-serious) of scientific and medical concern specific to alpelisib plus fulvestrant, for which ongoing monitoring and rapid communication by the Investigator was considered appropriate.[121] A summary of AESIs for each treatment arm in SOLAR-1 is presented in Table 50.

Table 50: Overview of AESIs in SOLAR-1 (safety set) (data cut-off 12th June 2018)

Categories	Alpelisib plus fulvestrant (n=284)		Placebo plus fulvestrant (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.
Abbreviations: GI: gastrointestinal.
Source: SOLAR-1 CSR Table 12-13;[121] André *et al.* (2019).[29]

Hyperglycaemia

Hyperglycaemia refers to elevated blood glucose levels and is an on-target effect of PI3K inhibition. Alpelisib-induced hyperglycaemia typically occurs within the first month of treatment and is an easily identifiable AE. Additionally, increased blood sugar levels are generally well-managed and reversible with lifestyle and dietary changes, dose interruptions, and/or dose modifications or anti-hyperglycaemic agents like metformin and insulin sensitisers. Occasionally, insulin might also be needed for a short period of time to successfully control the increased blood sugar levels induced by alpelisib (for further information on the management of hyperglycaemia, refer to the treatment algorithm in Appendix F).

Hyperglycaemia events were more frequently reported in patients in the alpelisib plus fulvestrant arm than in the placebo plus fulvestrant arm (65.8% versus 10.5%), with the majority of the hyperglycaemia events suspected to be treatment-related by the Investigator ([redacted] versus [redacted]).[29, 121] Of those who had a ≥Grade 3 hyperglycaemia event in the alpelisib plus fulvestrant arm, the median time to onset was [redacted], with a median time to improvement for ≥Grade 1 events of [redacted].[107] The median duration of exposure to alpelisib was very similar for patients who experienced hyperglycaemia versus the whole patient population [redacted].[121]

Overall, 163 patients (57.4%) patients in the alpelisib plus fulvestrant arm were treated for hyperglycaemia; 87.1% of these patients received metformin, alone or in combination (some patients required more than one anti-hyperglycaemic medication).[107] Only 6.3% of patients discontinued treatment with alpelisib due to hyperglycaemia and there was no sustained induction of diabetic metabolism observed after discontinuation of alpelisib treatment, suggesting that patients are not rendered diabetic in the long-term.[107]

Management of hyperglycaemia was also seen to improve over the course of SOLAR-1, due optimisation of strategies to address this AE. Specifically, the proportion of patients discontinuing due to both any Grade and Grade 3/4 hyperglycaemia decreased from the first 50% patients randomised in SOLAR-1 compared to the second [redacted].[121] Further, safety data from BYLieve support that the management of hyperglycaemia has improved with increased experience (see Section B.2.8.1.2).

The incidence of hyperglycaemia events in SOLAR-1 is presented in Table 51. Management strategies for hyperglycaemia are also described in Appendix F.

Table 51: Incidence of hyperglycaemia events in SOLAR-1 (safety set) (data cut-off 12th June 2018)

	Alpelisib plus fulvestrant (n=284) n (%) 95% CI	Placebo plus fulvestrant (n=287) n (%) 95% CI
Number of patients with at least one event	187 (65.8) [redacted]	30 (10.5) [redacted]
Maximum grade		
Grade 2 AEs	[redacted]	[redacted]
Grade 3 AEs	[redacted]	[redacted]
Grade 4 AEs	[redacted]	[redacted]
Treatment-related AEs	[redacted]	[redacted]
SAEs	[redacted]	[redacted]
Action taken		
Permanently discontinued	[redacted]	[redacted]
Dose adjusted	[redacted]	[redacted]
Temporarily interrupted	[redacted]	[redacted]
None/NA/Unknown	[redacted]	[redacted]
Medication or therapy taken	[redacted]	[redacted]
AE outcome		
Recovered/resolved	[redacted]	[redacted]
Recovering/resolving	[redacted]	[redacted]
Not recovered/not resolved	[redacted]	[redacted]
Recovered/resolved with sequelae	[redacted]	[redacted]
Unknown	[redacted]	[redacted]
Missing	[redacted]	[redacted]

A patient may be counted in several rows for action taken.
Abbreviations: AE: adverse event; CI: confidence interval; SAE: serious adverse event.
Source: SOLAR-1 CSR Table12-15;[121] André *et al.* (2019).[29]

GI toxicities

GI toxicity events (nausea, vomiting and diarrhoea) were more frequently reported in the alpelisib plus fulvestrant arm compared to the placebo plus fulvestrant arm (75.4% versus 34.8%), with most events considered treatment-related by the Investigator ([redacted] versus [redacted]).[29, 121] The most common (all grade) preferred terms (PTs) in the alpelisib plus fulvestrant arm were diarrhoea (57.7%), nausea (44.7%), and vomiting (27.1%).[29] These events were low grade, mostly Grade 1 or 2; no Grade 4 events were reported. SAEs were not frequent ([redacted] in the alpelisib plus fulvestrant arm versus [redacted] in the placebo plus fulvestrant arm) and few AEs led to treatment discontinuation (only [redacted] of patients in the alpelisib plus fulvestrant arm permanently discontinued due to GI toxicities).[121]

In addition, concomitant treatment with metformin (to manage hyperglycaemia) did not increase the incidence or severity of diarrhoea in SOLAR-1; 49.3% of patients receiving alpelisib plus fulvestrant in addition to metformin experienced diarrhoea at any Grade, which was a very similar proportion to the patients receiving alpelisib plus fulvestrant without metformin (50.4% at any

Grade).[151] A similar pattern was also observed for Grade 3/4 diarrhoea, although with a much lower incidence (3.4% of patients receiving alpelisib plus fulvestrant and metformin versus 8.8% receiving alpelisib plus fulvestrant and no metformin).[151]

A summary of GI toxicities in SOLAR-1 is presented in Appendix F. Management strategies for GI toxicities are also described in Appendix F.

Rash

Rash events were more frequently reported in patients in the alpelisib versus the placebo plus fulvestrant arm (53.9% versus 8.4%, respectively) with the majority of AEs suspected to be treatment-related by the Investigator ([redacted] versus [redacted]).[29, 121] The majority of these events were low grade and [redacted] were Grade 4.[121] Of rash events, the most common AEs in the alpelisib plus fulvestrant arm were rash (35.6%) and rash maculo-papular (14.1%).[29] Among patients who experienced rash, at least one of the events was managed with medication in [redacted] of patients, with dose interruption in [redacted], and with dose adjustment in [redacted].[121]

Importantly though, and consistent with other key AEs, knowledge of alpelisib-induced toxicity from prior clinical trial experiences has led to the development of refined treatment protocols for the robust management of key AEs such as rash.[41] In SOLAR-1, patients in the alpelisib plus fulvestrant arm who received anti-rash medication without first developing rash (i.e. prophylactically, such as anti-histamines), experienced a lower incidence of rash than those who did not (26.7% versus 64.1%, respectively).[107] Consequently, prophylactic anti-histamine use is recommended in the SmPC for alpelisib.[38] Given the ability to successfully manage rash events, only 3.2% of patients in the alpelisib plus fulvestrant arm discontinued treatment due to rash in SOLAR-1, whilst a total of [redacted] of patients had at least one rash event that resolved.[107, 121] In the alpelisib plus fulvestrant arm, the median duration of exposure to alpelisib among patients who developed rash during the study was [redacted], which was the same as in the overall study population.[121]

Data cut-off: 23rd April 2020

Rash AESIs, comprising the preferred terms of rash, rash maculopapular, rash macular, dermatitis, dermatitis acneiform, rash papular, rash pruritic, drug eruption, genital rash, and rash pustular, were observed in 54% of patients in the alpelisib plus fulvestrant arm versus 9% of patients in the placebo plus fulvestrant arm. However, most of these events were low grade (Grade 1 or Grade 2).[82]

A summary of rash events in SOLAR-1 is presented in Appendix F. Management strategies for rash are also described in Appendix F.

Severe cutaneous reactions

Severe cutaneous reactions occurred in [redacted] in the alpelisib plus fulvestrant arm ([redacted] considered treatment-related by the Investigator) and [redacted] in the placebo plus fulvestrant arm.[121] The PTs were erythema multiforme in [redacted] and Stevens-Johnson syndrome (SJS) in [redacted]; [redacted] of these events were Grade 2 or 3 ([redacted] were Grade 4) and [redacted] were reported at Japanese sites.[121] Permanent treatment discontinuations occurred in [redacted], and in [redacted], study treatment was temporarily interrupted.[121] All [redacted] of the events resolved.[121]

A summary of severe cutaneous reactions in SOLAR-1 is presented in Appendix F.

Hypersensitivity and anaphylactic reaction events

Hypersensitivity events (including allergic dermatitis) were more frequently reported in patients in the alpelisib plus fulvestrant arm than in the placebo plus fulvestrant arm (16.5% versus 4.2%).[29] These events were considered to be treatment-related by the Investigator in [redacted] in the alpelisib plus fulvestrant arm compared with [redacted] in the placebo plus fulvestrant arm.[121] Only [redacted] patients had a maximum severity of Grade 3 hypersensitivity; [redacted] anaphylactic reaction was reported.[121] The most common hypersensitivity and anaphylactic AEs were hypersensitivity [redacted], face oedema [redacted], and swelling face [redacted].[121]

Among the patients with a hypersensitivity event, at least one of the events was managed with concomitant medication in [redacted] of patients, with dose interruption in [redacted] and with dose adjustment in [redacted].[121] Only [redacted] patients discontinued treatment due to a hypersensitivity event and [redacted] of patients had at least one hypersensitivity event that resolved by the time of data cut-off (12th June 2018).[121]

A summary of hypersensitivity events in SOLAR-1 is presented in Appendix F.

Pancreatitis

[redacted] of pancreatitis was reported and the event resolved with permanent discontinuation of alpelisib.[121] Pancreatitis events were uncommon and occurred in [redacted] of patients in the alpelisib plus fulvestrant arm and [redacted] of patients in the placebo plus fulvestrant arm.[121] Pancreatitis events primarily consisted of increased lipase [redacted] and an increased amylase [redacted].[121] SAEs and discontinuations due to these events were infrequent; only [redacted] were reported as SAEs and [redacted] discontinued treatment in the alpelisib plus fulvestrant arm.[121]

In the alpelisib plus fulvestrant arm, dose adjustments and interruptions were reported for [redacted] and [redacted] of patients, respectively.[121] Permanent discontinuation of study treatment occurred in [redacted]. Additionally, at least one pancreatitis event was resolved in [redacted] patients.[121]

A summary of pancreatitis events in SOLAR-1 is presented in Appendix F.

Pneumonitis

Pneumonitis was infrequent, occurring in [redacted] of patients in the alpelisib plus fulvestrant arm and in [redacted] in the placebo plus fulvestrant arm; nearly all of these events were considered treatment-related by the Investigator.[121] [redacted] had a Grade 3 event in the alpelisib plus fulvestrant arm; there were [redacted] Grade 4 events.[121] Treatment with alpelisib was discontinued in [redacted] patients where pneumonitis was considered treatment-related by the Investigator.[121]

A summary of pneumonitis events in SOLAR-1 is presented in Appendix F.

B.2.9 Ongoing studies

Overall, information provided below has been reported as accurately as possible, based on the information available at the current time; however, circumstances such as COVID-19 may lead to a delay in timelines beyond Novartis' control.

The following data from SOLAR-1 are anticipated within the next 12 months:

- SOLAR-1 post-progression treatment sequencing ([redacted])
- Baseline EOT matched biomarkers ([redacted])
- Additional PRO data ([redacted])
- ctDNA levels, genomic profiling and clinical outcomes ([redacted])

BYLieve is still ongoing. The following data from BYLieve are anticipated within the next 12 months:

- Data from Cohort A – updated data are anticipated to be presented at the San Antonio Breast Cancer Symposium (SABCS) in December 2021.
- Data from Cohort C – updated data are anticipated to be presented at SABCS in December 2021. Note these data would be considered within the licence for alpelisib plus fulvestrant.

Data from a *PIK3CA* testing registry, which aims to describe the frequency of *PIK3CA* mutations in men and women with HR+, HER2− ABC across ~20 participating countries (Europe, Asia, the Middle East and America) are anticipated in Q1/Q2 2022.

B.2.10 Innovation

Alpelisib is the first alpha-selective PI3K inhibitor to be licensed by the FDA and EMA, and represents an important addition to the treatment pathway in the management of patients with endocrine resistant HR+, HER2– ABC with a *PIK3CA* mutation as the first licensed therapy to directly target this mutation.[70]

ABC has a substantial impact on both patient and caregiver HRQoL, negatively affecting both physical and psychological health.[50, 58, 89] Approximately 30–40% of patients with HR+, HER2– ABC have a tumour that harbours a mutation in *PIK3CA*, and these patients face a worse prognosis compared to patients without this mutation, as supported by subgroup PFS and OS data from Phase III RCTs comparing patients with and without this mutation.[18, 23, 25-28, 59, 65, 67, 68, 79] This is further supported by pooled evidence from 3,238 patients across 11 studies, in which patients with tumours harbouring the *PIK3CA* mutation were found to be associated with a shorter PFS than wild-type disease (difference −2.15 months; 95% CI: −4.14, −0.15), especially when ctDNA testing was used (difference −2.16 months; 95% CI: −3.65, −0.66).[79] These findings are corroborated by feedback from UK clinical experts, who consider the *PIK3CA* mutation to be clinically meaningful in terms of altering prognosis for patients with endocrine resistant HR+, HER2– ABC.[93] PI3K pathway hyperactivation due to *PIK3CA* mutations can also contribute to resistance to endocrine therapy and chemotherapy in HR+, HER2– ABC, which is a major challenge in the treatment of such patients.[25, 80, 91]

For patients with endocrine resistant HR+, HER2– ABC with a *PIK3CA* mutation who have progressed following a CDK4/6i + AI as first-line treatment, current treatment options are limited to everolimus plus exemestane, which can be associated with a limited survival benefit.[58-61] Prognosis is extremely poor for the post-CDK4/6i population, and these patients meet NICE's end-of-life criterion of a short life expectancy of <24 months (see Section B.2.11.3). Further, there is a limited ability to identify patients who are likely to benefit the most (or not benefit) from treatment with everolimus plus exemestane via an identifiable biomarker.[59] Finally,

chemotherapy is reserved for high-risk patients in visceral crisis in earlier lines or reserved for later lines of therapy. There is therefore also a need to delay the onset of cytotoxic chemotherapy through prolonged PFS and maintain patient HRQoL for a longer period of time ideally through use of a targeted therapy.[8, 9, 50, 69]

By specifically targeting the α-isoform of PI3K, alpelisib has demonstrated relevant anti-tumour activity in a number of preclinical breast cancer models, Phase I studies (in combination with endocrine therapy in AI-resistant HR+, HER2– ABC) and in Phase II and III studies (BYLieve and SOLAR-1, respectively).[29, 36, 75, 108] This treatment may also be associated with alleviation of caregiver burden and improved productivity that will not be reflected in the cost-effectiveness model results. The addition of alpelisib (plus fulvestrant) represents an important addition to the treatment pathway for ABC in the UK, moving towards a system where patients can be tested for specific mutations (such as *PIK3CA*) and then treated accordingly. This aligns with the aims of the NHS to be world-leading in its use of cutting-edge genomic technologies to predict and diagnose disease, and to subsequently treat in a personalised manner. Genomic testing for *PIK3CA* within the NHS would enable the prediction of patients most likely to benefit (or not benefit) from treatment with alpelisib plus fulvestrant, thus enabling an efficient use of NHS resources.[152] Further, alpelisib plus fulvestrant has been shown to have a differential effect in patients with the *PIK3CA* mutation versus those without; other treatments in this setting have not shown such an effect.[21, 29] Furthermore, the availability of alpelisib plus fulvestrant is particularly important in the context of the post-CDK4/6i population, as these patients have limited treatment options currently, leading to a high unmet need.

B.2.11 Interpretation of clinical effectiveness and safety evidence

B.2.11.1 Principal findings from the clinical evidence base

Evidence for the efficacy of alpelisib plus fulvestrant as a treatment for endocrine resistant HR+, HER2– ABC with a *PIK3CA* mutation derives from the Phase II BYLieve trial (Cohort A),[75, 108] and the Phase III RCT, SOLAR-1.[29, 82, 121]

BYLieve

BYLieve is a Phase II, multicentre, open-label, three-cohort, non-comparative study, which aimed to assess the efficacy and safety of alpelisib plus endocrine therapy (either fulvestrant or letrozole) in HR+, HER2–, ABC with a *PIK3CA* mutation. At the time of submission, only data for Cohort A of BYLieve are available, in which patients who had received immediate prior CDK4/6i plus an AI and were assigned to receive alpelisib plus fulvestrant. This cohort therefore currently represents the most relevant cohort to the decision problem. Data from Cohort C (where patients receive alpelisib plus fulvestrant following prior ET monotherapy, ET plus targeted therapy [e.g. everolimus, or CDK4/6i plus fulvestrant once Cohort B has closed], or systemic chemotherapy) are not anticipated to be available until Q4 2021; however, it should be noted that when the results of Cohort C become available, these data would be considered within the licence for alpelisib plus fulvestrant.

Data from BYLieve Cohort A have demonstrated that alpelisib plus fulvestrant provides a clinically meaningful PFS in patients who have previously received a CDK4/6i + AI. As of the data cut-off date (17th December 2019), the primary objective for Cohort A was met, and the proportion of patients who were alive and without disease progression at 6 months was 50.4% (95% CI: 41.2, 59.6), with the lower bound of the CI greater than the pre-specified 30% threshold

defining a clinically meaningful result.[75] Median PFS was 7.3 months (95% CI: 5.6, 8.3).[75] In terms of OS, data from BYLieve demonstrate a median OS for patients enrolled in Cohort A of 17.3 months (95% CI: 17.2, 20.7).[75]

SOLAR-1

The SOLAR-1 trial is a randomised, double-blind, international, multicentre, Phase III clinical trial investigating the efficacy and safety of alpelisib plus fulvestrant in patients with HR+, HER2−, ABC with a *PIK3CA* mutation and who are endocrine resistant.[29, 121]

Data from the entire cohort with a *PIK3CA* mutation in SOLAR-1 (i.e. comprising patients with and without prior CDK4/6i therapy) demonstrated the efficacy of alpelisib plus fulvestrant in patients with HR+, HER2– ABC. At the final OS analysis (23rd April 2020), alpelisib plus fulvestrant showed longer-term benefit and a [redacted] risk reduction in disease progression or death over placebo plus fulvestrant ([redacted]); median PFS was prolonged by a clinically meaningful [redacted] months, from [redacted] months (95% CI: 3.7, 7.4) in the placebo plus fulvestrant arm to [redacted] months (95% CI: [redacted]) in the alpelisib plus fulvestrant arm; this was consistent with median PFS for the primary analysis (12th June 2018).[105] Additionally, there was an approximate 14% reduction in the risk of death in the alpelisib plus fulvestrant arm compared with the placebo plus fulvestrant arm (HR: 0.86; 95% CI: 0.64, 1.15; p=0.15). Median OS was 39.3 months (95% CI: 34.1, 44.9) in the alpelisib plus fulvestrant arm and 31.4 months (95% CI: 26.8, 41.3) in the placebo plus fulvestrant arm, representing a positive trend with an increase of 7.9 months in median OS in favour of alpelisib plus fulvestrant.[82]

Additionally, the efficacy of alpelisib plus fulvestrant is evident from data for the subgroup of patients in SOLAR-1 who have received prior CDK4/6i therapy. Based on data from the 23rd April 2020 data cut-off, a clinically meaningful [redacted] in disease progression or death was observed among patients with prior CDK4/6i use in the alpelisib plus fulvestrant arm (n=9) compared to the placebo plus fulvestrant arm (n=11) ([redacted]).[105] The treatment effect, as measured by the PFS hazard ratio, was consistent with that observed in the overall population using the latest available data cut-off date ([redacted]).[105] Results at the final OS analysis in subjects with prior CDK4/6 inhibitor use also showed a positive trend ([redacted]). Median OS was prolonged by [redacted] in the alpelisib plus fulvestrant arm from [redacted] in the placebo plus fulvestrant arm to [redacted].[105] The data support the use of alpelisib plus fulvestrant in patients with HR+, HER2– ABC who have progressed on prior CDK4/6i therapy.

Bucher ITC, PAIC and matching/weighted analysis of BYLieve

As BYLieve was a single-arm trial, data from the second-line setting of SOLAR-1 have been used as a proxy to determine the relative efficacy of alpelisib plus fulvestrant compared to everolimus plus exemestane via a Bucher ITC (i.e. comparing SOLAR-1 and BOLERO-2). The results of the Bucher ITC demonstrate everolimus plus exemestane to be associated with HRs of [redacted] and [redacted] for PFS and OS, respectively, versus alpelisib plus fulvestrant. Whilst the 95% CIs are relatively wide, these results demonstrate everolimus plus exemestane to be associated with an increased hazard of progression and death versus alpelisib plus fulvestrant. The results of a PAIC also support that alpelisib plus fulvestrant may yield improved survival versus everolimus plus exemestane in patients with HR+/HER2- ABC with *PIK3CA* mutation receiving second-line treatment.

Furthermore, data from a matching/weighted analysis comparing BYLieve with the real-world setting further supports the clinical benefit of alpelisib with fulvestrant for treatment of HR+, HER2– ABC with a *PIK3CA* mutation post-CDK4/6i.[106, 120]

Overall, these indirect analyses support a benefit with alpelisib plus fulvestrant versus everolimus plus exemestane in the indication of interest. In particular, and as validated by clinical opinion, the use of a treatment effect from second-line ABC appears to be a reasonable proxy for the post-CDK4/6i population specifically, in the absence of data for everolimus plus exemestane in this population.

In summary, alpelisib plus fulvestrant has demonstrated an extension in both PFS and OS versus everolimus plus exemestane. This extension of 'progression-free' time and prolongation of time to disease progression delays the use of cytotoxic chemotherapy, and maintains patients HRQoL for a longer duration.[50, 69] In turn, this helps to reduce the emotional and psychological impact associated with each progression, by prolonging the time to receiving the news of progressed disease.[153]

Safety

The safety profile of alpelisib has been demonstrated to be consistent across both SOLAR-1 and BYLieve. As of 23rd May 2021, a total of [redacted] patients (including cancer patients, hepatic impaired patients, and healthy volunteers) had been exposed across [redacted] Novartis-sponsored studies to alpelisib as a single agent or in combination (including fulvestrant).[149] Of these patients, 284 were treated with alpelisib plus fulvestrant in SOLAR-1 and 127 in Cohort A of BYLieve, and the overall safety and tolerability profile observed was consistent with the known safety profile of alpelisib from prior studies, with no new or unexpected safety signals reported.[29, 75, 107, 108, 121] In summary, alpelisib has a well-characterised and consistent safety profile.

In SOLAR-1, hyperglycaemia, diarrhoea, nausea, decreased appetite, rash, vomiting and weight decreased were the most common AEs (>25% of patients) reported in the alpelisib plus fulvestrant arm, with hyperglycaemia, rash and diarrhoea as the most common ≥Grade 3 AEs.[29] Despite this, only 6.3%, 3.2% and 2.8% of patients discontinued treatment due to each of these AEs, respectively.[107] Specifically, hyperglycaemia was generally reversible, and manageable with lifestyle changes, the use of oral anti-hyperglycaemic agents (such as metformin), and dose modifications as needed during alpelisib treatment.[107, 123] Importantly, metformin was not associated with an increase in incidence or severity of diarrhoea, which as mostly low grade (with no Grade 4 events reported).[107] Even so, diarrhoea is a common AE associated with oncology drugs, and clinicians are therefore well versed in its management.[154] The prophylactic use of anti-rash medication such as anti-histamines, decreased the incidence and severity of rash.[29] This is supported by a retrospective analysis from a single centre where dermatological improvement of rash was evident with anti-histamines, topical and/or systemic corticosteroids and most patients were able to continue oncologic treatment at a maintained or reduced dose upon re-challenge.[155] Furthermore, additional safety analyses (comparing the first 50% of patients randomised in SOLAR-1 to the second 50%) have indicated that improvements in management strategies over time have led to decreases in discontinuations due to key AEs such as hyperglycaemia and rash.[107] Therefore, the early and effective management of these AEs in clinical practice, according to updated management guidelines, will allow for the continuation of treatment with alpelisib plus fulvestrant in a tolerable manner.[38, 41]

With longer follow-up, as assessed at the latest data cut-off (23rd April 2020), no new safety signals or cumulative toxicity for any AE were observed. The incidence of hyperglycaemia did not increase with increased time on treatment. Observed AEs continued to be manageable with close monitoring, administration of concomitant medication, and dose modifications when necessary.[82]

Further, data from BYLieve are in line with the safety profile characterised in SOLAR-1. Diarrhoea, hyperglycaemia, nausea were the most commonly reported AEs, occurring in 59.8%, 58.3% and 45.7% patients, respectively, whilst hyperglycaemia, rash and rash maculo-papular were the most common AEs at ≥Grade 3.[117] Importantly though, safety data from Cohort A of BYLieve support a continuing trend of improvements in the AE profile of alpelisib plus fulvestrant with increased experience (as seen over time in SOLAR-1).[107] For example, in BYLieve both the incidence of hyperglycaemia (as an AE, AE at ≥Grade 3, SAE and SAE at ≥Grade 3) and discontinuations due to this AE were decreased, evidencing that management strategies for key AEs have been effective.[117]

B.2.11.2 Strengths and limitations of the clinical evidence base

Evidence for the efficacy of alpelisib plus fulvestrant as a treatment for endocrine resistant HR+, HER2– ABC with a *PIK3CA* mutation derives from the Phase II BYLieve trial (Cohort A),[75, 108] and the Phase III RCT, SOLAR-1.[29, 82, 121]

By applying inclusion criteria requiring the receipt of prior CDK4/6i therapy, BYLieve provides valuable clinical data within a patient population with a critical unmet need. However, it is an open-label study that lacks a comparator arm. Therefore, data from SOLAR-1 can be used to add to the evidence base in the post-CDK4/6i population. SOLAR-1 is a large international, multicentre RCT, and thus provides robust evidence for the efficacy and safety of alpelisib plus fulvestrant for the treatment of patients with endocrine resistant HR+, HER2–, ABC with a *PIK3CA* mutation.[29] As mentioned in Section B.2.2.1, alpelisib has been approved by 21 health authorities, including the FDA in 2019 and the EMA in 2020; marketing authorisation decisions were supported primarily by data from SOLAR-1.[114] Additionally SOLAR-1 can be considered high quality (as discussed in Appendix F.2.5); it was conducted in a large number of patients (including at six UK centres) and evaluated a patient population deemed by clinical experts to be generalisable to patients with endocrine resistant HR+, HER2–, ABC with a *PIK3CA* mutation in the UK.[9, 93] Notably, a small number of post-CDK4/6i patients were enrolled in SOLAR-1, providing an important source of supportive evidence for the post-CDK4/6i population.

The endpoints assessed in both SOLAR-1 and BYLieve are clinically relevant for evaluating alpelisib plus fulvestrant in this indication. Both trials were designed to capture the endpoints most relevant to ABC patients and clinicians alike, as well as healthcare providers, measuring both clinical efficacy (via PFS, OS, ORR and CBR) but also safety endpoints (exposure and AEs) consistent with other studies of ABC therapies.[29, 41, 62, 65, 67, 68] Specifically, the primary endpoint of PFS is a true measure of patient benefit, given that increased time in the progression-free state maintains HRQoL for a longer period of time and delays time to cytotoxic chemotherapy (which is meaningful to clinicians, patients and caregivers).[9, 50, 69, 156] In addition, PFS is a widely used endpoint across clinical trials in ABC.[62, 65, 67, 68] SOLAR-1 also measured patients' HRQoL, which is a very important consideration (in addition to both efficacy and safety) when determining the most beneficial treatment options in a patient-centric manner. Treatment with alpelisib plus fulvestrant did not impact the patients' HRQoL, suggesting that any treatment-related AEs do not

incur additional burden to the HRQoL of patients in this setting.[124] PROs from SOLAR-1 are presented in Appendix F.[121]

A limitation of the evidence base is the lack of direct evidence assessing alpelisib plus fulvestrant versus everolimus plus exemestane (the standard of care for these patients), to inform relative efficacy estimates. SOLAR-1 compared alpelisib plus fulvestrant to fulvestrant alone,[29] and BYLieve was a non-comparative and open label study.[41]

No data are available for everolimus plus exemestane in the post-CDK4/6i population, and as a single-arm trial, it was not possible to incorporate data for alpelisib plus fulvestrant from BYLieve into an ITC. In the absence of an alternative approach to estimate the relative efficacy between alpelisib plus fulvestrant and everolimus plus exemestane in this population, ITCs were conducted for PFS and OS using data from SOLAR-1 and BOLERO-2 in the second-line setting, and this ITC was used to inform the economic analysis. A PAIC has also been conducted, whereby an ITPW approach was used to match patients from SOLAR-1 and BOLERO-2 in order to compare PFS and OS outcomes.

It is acknowledged that the Bucher ITC may be subject to potential limitations stemming from differences in patient populations across RCTs. Data for patients with tumours harbouring a *PIK3CA* mutation were available from SOLAR-1 and BOLERO-2, and these ITCs relied on a network being created between SOLAR-1 and BOLERO-2 with the SoFEA and CONFIRM trials.[109, 110] A potential limitation of this analysis is that data from these additional trials were not available for patients with tumours harbouring a *PIK3CA* mutation. However, it is not anticipated that the treatment effect of a specific therapy (that does not target the PI3K pathway such as everolimus plus exemestane, everolimus monotherapy or fulvestrant monotherapy) would differ depending on *PIK3CA* mutation. This assumption is supported by pre-clinical and clinical data (including data from the placebo and fulvestrant arm of SOLAR-1), as well as the tests for treatment effect modifiers conducted as part of the feasibility assessment for this ITC (see Appendix D).[21, 29] The results of the assessment for treatment effect modification demonstrated that HER2 status was the only factor for which effect modification on PFS or OS was found to be statistically significant ($P<0.05$) in one trial, and this impacts the CONFIRM trial only.

In the absence of alternative available data, the SoFEA and CONFIRM trials were required to create a network to estimate the relative efficacy of alpelisib plus fulvestrant versus everolimus plus exemestane. Moreover, the approaches adopted in previous appraisals in this area were also reviewed and considered a similar ITC approach given the limited evidence available. The results of these analyses therefore represent the best estimates of relative efficacy between alpelisib plus fulvestrant and everolimus plus exemestane for the purposes of this submission.

Although the PAIC was also associated with limitations, most importantly the unanchored nature of the analysis, it nevertheless provides useful supportive evidence of a potential benefit of alpelisib plus fulvestrant versus everolimus plus exemestane.

Estimates derived from both the Bucher ITC and PAIC were also directionally consistent with results from the matching/weighted analysis of BYLieve and Flatiron in the post-CDK4/6i population specifically, suggesting that alpelisib plus fulvestrant can provide benefit versus relevant comparators in second-line ABC, and in the post-CDK4/6i population specifically.

B.2.11.3 End-of-life criteria

For patients who have progressed following first-line treatment for ABC with a CDK4/6i + AI, prognosis is extremely poor, and these patients meet NICE's end-of-life criterion of a short life expectancy of <24 months. There is, therefore, a greater unmet need in this patient population, particularly as these patients are unlikely to receive a CDK4/6i again in the second-line setting (see Section B.1.3.2). Thus, everolimus plus exemestane is the only reimbursed treatment option to delay the time to chemotherapy.

The data supporting alpelisib plus fulvestrant meeting the NICE end-of life criteria are summarised in Table 52, demonstrating that in this population, alpelisib plus fulvestrant should be assessed according to the higher willingness-to-pay threshold of £50,000/QALY gained.

Table 52: End-of-life criteria

Criterion	Data available	Reference in submission (section and page number)
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Based on data from Cohort A of BYLieve, the median OS was 17.3 months (95% CI: 17.2, 20.7) following treatment with alpelisib plus fulvestrant;[75] thus, as treatment with alpelisib plus fulvestrant has been shown to extend OS versus everolimus plus exemestane (as per the Bucher ITC presented within this submission), it is estimated that median OS with everolimus plus exemestane in this patient population would be <17.3 months and therefore <24 months. In addition, in the base case analysis for the cost-effectiveness model (see Section B.3.7), the estimated LYG (undiscounted) for everolimus plus exemestane was 1.81 LYs (21.7 months). This estimate is based on HRs for PFS and OS (derived from a Bucher ITC for second-line data of SOLAR-1 and BOLERO-2) between everolimus plus exemestane and alpelisib plus fulvestrant, applied to the PFS and OS curves of the second-line population in the BYLieve trial. In the final OS analysis of the post-CDK4/6i population in SOLAR-1, median OS was [redacted] in the placebo plus fulvestrant arm and therefore <24 months. Median OS was extended by [redacted] in the alpelisib plus fulvestrant arm to [redacted].[105]	Section B.2.3.6.3 and Section B.3.7
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at	In the base case analysis (see Section B.3.7), alpelisib plus fulvestrant was associated with a gain of 2.58 LYG (undiscounted) versus 1.81 for everolimus plus exemestane, representing an increase of	Section B.3.7

least an additional 3 months, compared with current NHS treatment	0.76 LYG (9.1 months), which exceeds NICE's criterion for end-of-life medicines, whereby an extension to life of 3 months versus standard of care.	

Abbreviations: AI: aromatase inhibitor; CDK4/6i: cyclin-independent kinase 4/6 inhibitor; ITC: indirect treatment comparison; LYG: life years gained; NICE: National Institute of Health and Care Excellence; PFS: progression-free survival; OS: overall survival.

B.3 Cost effectiveness

Summary

- A *de novo* cost-utility model was developed to determine the cost-effectiveness of alpelisib plus fulvestrant versus everolimus plus exemestane for patients with endocrine resistant HR+, HER2– ABC with a *PIK3CA* mutation after disease progression following a CDK4/6i. This patient population has an immense unmet need; patients have a poor prognosis and meet NICE's end-of-life criterion of a short life expectancy of <24 months (see Section B.2.11.3).
- The analysis was conducted from an UK NHS/PSS perspective, with a lifetime time horizon and with costs and outcomes discounted at 3.5% per annum.
- Costs included: drug acquisition and administration, *PIK3CA* testing, management of AEs, monitoring and follow-up, and end-of-life care.
- Efficacy and safety data for alpelisib plus fulvestrant were derived from the BYLieve trial; for everolimus plus exemestane, a HR was applied for PFS and OS derived from a Bucher ITC of second-line data for alpelisib plus fulvestrant and everolimus plus exemestane that included SOLAR-1 and BOLERO-2 (as described in Section B.2.7.2). A scenario analysis using the HR for PFS and OS derived from the PAIC (as described in Section B.2.7.3) was also explored.
- As EQ-5D data were not collected in BYLieve, health-state utility values were estimated from EQ-5D-5L data collected in SOLAR-1, which were subsequently mapped to EQ-5D-3L in line with the NICE preferred methodology.[157]
- In the base case analysis for this population, alpelisib plus fulvestrant (when alpelisib is provided with the confidential PAS discount, applying the known PAS discount of everolimus and with an assumed discount of [redacted] for fulvestrant) was associated with higher costs but also higher quality-adjusted life years (QALYs) than everolimus plus exemestane, resulting in an incremental cost-effectiveness ratio (ICER) of £49,907 per QALY gained.
- Moreover, alpelisib plus fulvestrant was associated with a gain of 2.58 life years (LYG; undiscounted) versus 1.81 for everolimus plus exemestane, representing an increase of 0.76 LYG (9.1 months), which exceeds NICE's criterion for end-of-life medicines.
- As such, considering a willingness-to-pay threshold of £50,000 per QALY gained, alpelisib plus fulvestrant represents a cost-effective use of NHS resources in this BYLieve population with a critical unmet need.

Sensitivity analyses

- Probabilistic sensitivity analyses (PSA) and deterministic sensitivity analyses (DSA) were conducted to assess the extent of uncertainty in the base case economic analysis; both sensitivity analyses demonstrated the base case cost-effectiveness results to be robust to the variation explored (see Section B.3.8).
- The DSA showed the base case economic analyses results to be most sensitive to relative dose intensities (RDIs) and the HR for PFS (see Section B.3.8.2).

- A range of scenario analyses were also conducted, with the results generally robust to most parameters and structural assumptions of the base case economic analyses (see Section B.3.8.3).

Summary

- The base case ICER for alpelisib plus fulvestrant versus everolimus plus exemestane was £49,907. Alpelisib plus fulvestrant therefore represents a cost-effective use of NHS resources at a £50,000 per QALY gained willingness-to-pay threshold.

B.3.1 Published cost-effectiveness studies

An SLR was conducted to identify any relevant economic evaluations previously published for alpelisib plus fulvestrant in patients with HR+, HER2− ABC. The SLR was originally conducted in December 2018 with updates conducted in October 2019, August 2020 and April 2021 using the same methodology, in order to identify any additional evidence published since the original SLR was conducted. Full details of the SLR search strategy, study selection process and results are reported in Appendix G.

No economic evaluations of alpelisib plus fulvestrant (or any other PI3K inhibitors) were identified in the SLR. As such, a *de novo* cost-effectiveness model was constructed for the purposes of this appraisal.

B.3.2 Economic analysis

The objective of the economic analysis was to assess the cost-effectiveness of alpelisib plus fulvestrant versus everolimus plus exemestane for people with endocrine resistant HR+, HER2− ABC with a *PIK3CA* mutation who have received prior CDK4/6i therapy. In line with the NICE reference case, the economic analysis was conducted from the perspective of the NHS and PSS and included direct medical costs only.[158]

B.3.2.1 Patient population

The patient population evaluated in the base case economic analysis was patients with endocrine resistant HR+, HER2− ABC with a *PIK3CA* mutation who have received prior CDK4/6i therapy. This is consistent with the population of interest in this submission and is a subset of the anticipated licensed indication for alpelisib plus fulvestrant from the MHRA. Evaluating the cost-effectiveness of alpelisib plus fulvestrant in the post-CDK4/6i population is particularly important given the substantial unmet need (Section B.1.3.1.3) and short life expectancy (Section B.2.11.3) in this population.

The population was based on patients in Cohort A of the BYLieve trial. There were [redacted] patients receiving alpelisib plus fulvestrant following disease progression on or after treatment with a CDK4/6i plus AI as the immediate prior therapy; [redacted] patient was excluded from the original mFAS (n=121) as this patient experienced a progression event within 14 days of the index date. Among this mFAS, n=[redacted] patients were receiving first-line therapy, n=[redacted] patients were receiving second-line therapy, n=[redacted] patients were receiving third-line therapy, and n=[redacted] patient received fourth-line therapy. The [redacted] patients in BYLieve Cohort A at first-line in the advanced setting received CDK4/6i + AI therapy as adjuvant therapy.

Within the *de novo* cost-effectiveness model, only a subset of the above patients receiving alpelisib plus fulvestrant as second-line therapy (n=[redacted]) are considered as these patients are those most relevant to the decision problem. The second-line population was considered most relevant as a proxy for patients in the post-CDK4/6i population, as the majority of patients in UK would typically receive a CDK4/6i plus AI as first-line treatment for ABC. Given this, and the fact that there are small patient numbers in BYLieve beyond second-line, it was not considered appropriate to conduct any analyses using BYLieve data from these subsequent treatment lines. Thus, patients in BYLieve Cohort A receiving alpelisib plus fulvestrant at other lines of therapy ([redacted] patients in first line, [redacted] patients in third line and [redacted] patient in fourth line) were excluded from the economic analysis.

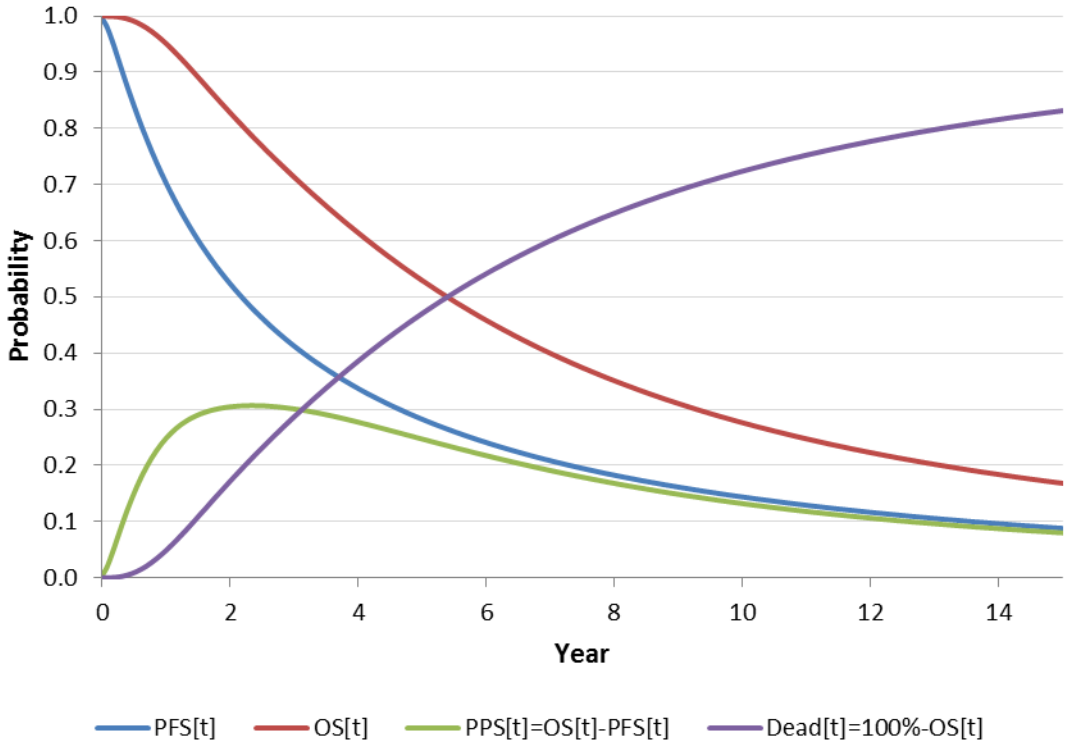
B.3.2.2 Model structure

The *de novo* cost-effectiveness model was a partitioned survival (PSM) model. A PSM model was used for the following reasons:

- The model needed to link PFS and OS via an ITC
- Data from BYLieve are relative mature, and therefore fitting a curve directly to the OS data was considered to be appropriate
- The use of a PSM has been adopted in multiple advanced oncology appraisals to date

The PSM approach included three health states for PFS, PPS, and dead. Patients who were alive were “partitioned” according to progression status (i.e., progression-free or post-progression) under the assumption that progression had implications on quality of life and costs. Membership of the three states over time was determined by efficacy parameters – in the form of survival curves – for PFS and OS. The survival curve for PFS provided the proportion of patients remaining in the PFS state over time. In the model, the survival curve for OS acted as a ceiling for PFS, meaning that the model assumed PFS at any point in time could not exceed OS. Membership of the ‘Dead’ state was calculated as the complement of the OS survival curve over time. Membership of the PPS state was calculated as the difference between PFS and OS over time. The process of deriving membership of the PFS state and the dead state (PFS[t] and Dead[t], respectively) is illustrated in Figure 10 below.

Figure 10: Membership of health states in the cost-effectiveness model



Abbreviations: OS: overall survival; PFS: progression-free survival; PPS: post-progression survival.

This approach did not include explicit states for "on" and "off" treatment. Hence, probabilities of PFS were not conditioned on whether patients were on or off therapy. However, costs and utilities were dependent on whether patients were on therapy in the PFS state based on estimated distributions of time to discontinuation (TTD). Expected costs and QALYs were therefore calculated by combining information on TTD by time in each state with cost and utility values conditioned on whether patients were on or off therapy.

Assuming a mean age at model entry of 57 years (derived from the mean age of patients enrolled in Cohort A of BYLieve and considered generalisable to the UK patient population)[93] and that virtually all patients will die before reaching 100 years of age, a modelling time horizon of 40 years was used in the base case. This corresponds to a lifetime time horizon and is consistent with recommended good practices for cost-effectiveness analysis.[159, 160] Scenario analyses were undertaken using alternative time horizons (see Section B.3.8.3). The model employed a 28-day cycle length (approximately monthly) and a half-cycle correction was employed. The cycle length was considered short enough to capture any differences in outcomes between treatment arms. Finally, costs and effects were discounted at a rate of 3.5% per annum in line with the NICE reference case.[158] Scenario analyses were undertaken using alternative discount rates (see Section B.3.8.3).

An overview of the key features of the economic analysis is presented in Table 53. The approach in the current appraisal is compared to that undertaken in TA421 (everolimus with exemestane for treating advanced breast cancer after endocrine therapy). Whilst some inputs and approaches utilised within the *de novo* model are derived from TA687 (ribociclib with fulvestrant for treating hormone receptor-positive, HER2-negative, advanced breast cancer; previously TA593), a full comparison to this previous appraisal is not provided given that ribociclib plus

fulvestrant is not a relevant comparator within the scope of this submission.

Table 53: Features of the economic analysis

Factor	Previous appraisals	Current appraisal	
	TA421[57]	Chosen values	Justification
Time horizon	15 years	Lifetime (assumed to be 40 years)	• In line with the NICE reference case[158] • Sufficient to capture all meaningful differences in technologies compared • Sensitivity analyses were undertaken using alternative time horizons
Cycle length	1 month	28-days (approximately one month)	Short enough to capture any differences in clinical outcomes between treatments
Discount rate	3.5%	3.5% discount per annum applied for both costs and benefits	In line with the NICE reference case[158]
Perspective	NHS	NHS/PSS	• In line with the NICE reference case[158] • Direct non-medical costs (e.g. transportation to medical appointments) were not included as these costs were not considered likely to be material
Source of utilities	• Utility values were derived from Lloyd *et al.* (2006) for stable and progressed disease • Utility values were adjusted for age and the degree of response to treatment, based on CBR from BOLERO-2 (the latter was only applied for the 'stable disease' health state) • In revised modelling after consultation, the manufacturer	• Utility values were estimated from EQ-5D-5L data from the SOLAR-1 trial (using the UK tariff), mapped onto the EQ-5D-3L • Utility values were adjusted for the decrease in HRQoL associated with older age	• Utility values based on the EQ-5D-3L were included in line with the NICE reference case[158] • As EQ-5D data were not collected in BYLieve, health-state utility values were estimated from EQ-5D-5L data collected in SOLAR-1 (in the second-line population as a proxy for the post-CDK4/6i population)

	included a utility value for the 'progressed disease' health state from Launois *et al.* (1997)		
Source of costs	• Resource use inputs were derived from NHS reference costs, NICE CG81 and PSSRU, Unit Costs of Health and Social Care • Drug costs were derived from the BNF	• Resource use inputs were derived from NHS reference costs 2019–2020 and NICE TA687/TA593 where applicable • Drug costs were derived from the BNF and eMIT[43, 161]	In line with the NICE reference case[158]

Abbreviations: BNF: British National Formulary; EQ-5D-3L: EuroQol 5-dimensions 3-levels; EQ-5D-5L: EuroQol 5-dimensions 5-levels; eMIT: Drugs and Pharmaceutical Electronic Market Information; HRQoL: health-related quality of life; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; PSS: Personal Social Service; PSSRU: Personal Social Services Research Unit.

B.3.2.3 Intervention technology and comparators

Intervention

The intervention of interest is alpelisib at a dose of 300 mg, administered orally once daily, in combination with fulvestrant at a dose of 500 mg (as two 5 mL injections), administered intramuscularly, on Days 1 and 15 of Cycle 1 and on Day 1 ± 3 days of a 28-day cycle thereafter. Treatment was assumed to continue until disease progression or unacceptable toxicity. This is in line with the regimen used in BYLieve (Cohort A), SOLAR-1 and the SmPC for alpelisib.[29, 38, 75]

Comparator

As discussed in Section B.1.3.2, everolimus plus exemestane is the only treatment routinely available for patients with HR+, HER2− ABC who have received prior CDK4/6i therapy in the UK, and is therefore the only relevant comparator to alpelisib plus fulvestrant within the context of the economic analysis conducted for this appraisal.

According to their respective SmPCs, everolimus is administered orally at a dose of 10 mg once daily at the same time every day, consistently either with or without food, and exemestane is administered orally at a dose of 25 mg once daily after food.[162, 163]

B.3.3 Clinical parameters and variables

As described in Section B.2.7, a Bucher ITC and PAIC have been conducted to assess the relative efficacy of alpelisib plus fulvestrant in patients with HR+, HER2– ABC with a *PIK3CA* mutation; however, given there are no data for everolimus plus exemestane in a post-CDK4/6i population, HRs from these indirect analyses are assumed to apply to the post-CDK4/6i population within the economic analysis. This assumption has been supported by clinical expert opinion, and by the matching/weighted analysis of BYLieve versus Flatiron which was conducted in the post-CDK4/6i population specifically. Therefore, it is considered reasonable to apply a HR derived from second-line ABC to the post-CDK4/6i population in the absence of alternative options.

B.3.3.1 PFS

Alpelisib plus fulvestrant

The PFS distributions for alpelisib plus fulvestrant were derived from parametric survival curves fitted to patient-level data for the second-line population of BYLieve.

Estimation of parametric survival distributions using the individual patient failure time data from BYLieve (Cohort A) was performed using Flexsurv, an R package for fully-parametric modelling of survival data. The following parametric distributions were considered:

- Exponential;
- Weibull;
- Log-logistic;
- Lognormal;
- Gompertz;
- Generalised gamma;
- Generalised F; and
- Restricted cubic spline (RCS) distributions.

For RCS distributions, Weibull, log-logistic and lognormal distributions were estimated. RCS distributions were estimated using 1-, 2- and 3-knot spline (plus the two boundary knots which are always included). The boundary knots were based on the minimum and maximum failure times. The non-boundary knot was based on the median of the failure times. Because patients with HR+/HER2– ABC are unlikely to be cured by treatment, mixture and non-mixture cure models were not considered.

The distributions used in the model were selected based on fit statistics, visual inspection of survival distributions, hazard functions, time dependent HRs, and diagnostic plots for treatment effects, as well as clinical plausibility. Measures of statistical fit included the Akaike Information Criteria (AIC), AIC with Correction (AICc), and Bayesian Information Criteria (BIC). The AIC is commonly used as a means for comparing the quality of a model relative to other models that have been fit to the same data. AICc includes an additional term based on the number of parameters in the model and therefore penalises models with a greater number of parameters. Similarly compared with AIC and AICc, BIC penalises models with more parameters. The BIC was used as the primary measure of statistical fit, as this statistic places a relatively high penalty on the number of parameters included in the distribution and hence avoids placing undue influence on the tail of the distribution which can have a large effect on long term survival projections.

Kaplan-Meier survival and hazard rates for alpelisib plus fulvestrant in the second-line subgroup of BYLieve are reported in Figure 11. The hazard rate for alpelisib plus fulvestrant has a slight increasing pattern just after Month 3 until approximately Month 7, after which point the hazard rate is constant.

Figure 11: PFS for the second-line population of BYLieve

Abbreviations: PFS: progression-free survival.

A ranking of parametric distributions fit to PFS by the BIC fit statistic is presented in Figure 12. The top five distributions, according to BIC statistic were as follows:

- Lognormal;
- Log-logistic;
- RCS 3 lognormal;
- RCS 3 log-logistic; and
- Generalised gamma

The top five best fitting distributions based on the AIC and AICc are similar to those based on the BIC except the log-logistic distribution is not among the top five according to the AIC and AICc, and the RCS 3 Weibull is not among the top five according to the BIC.

Figure 12: Fit statistics for parametric distributions fit to PFS for the second-line population of BYLieve

Abbreviations: BIC: Bayesian information criterion; Gen: generalised; PFS: progression-free survival; RCS: restricted cubic spline.

Parametric survival distributions for PFS during the trial period for the six best fitting distributions plus the best fitting distribution with a proportional hazards treatment effect based on BIC are shown in Figure 13. The visual fit of the parametric distributions to the Kaplan-Meier curves are all reasonably good, with very little differentiation except at the maximum follow-up time (approximately 24 months).

Figure 13: Parametric survival distributions fit to PFS for the second-line population of BYLieve

Best fitting distributions based on BIC. Distributions are ranked by BIC (left to right, top to bottom).
Abbreviations: BIC: Bayesian information criterion; Gen: generalised; PFS: progression-free survival; RCS: restricted cubic spline.

Hazard rates for PFS during the trial follow-up for the top six best fitting parametric survival distributions based on BIC are compared with non-parametric hazards in Figure 14. The lognormal, log-logistic, and generalised gamma yield hazard rates that increase initially, reach a peak around months 3 to 6, and then decrease over time, which is generally consistent with the non-parametric hazards, though the latter two distributions underestimate the non-parametric hazards by the end of follow-up. The RCS 3 lognormal, RCS 3 log-logistic and RCS 3 Weibull distributions increase sharply in Month 2, then again in Month 6, which is not reflected in the non-parametric hazards.

Figure 14: Hazard rates for parametric survival distributions fit to PFS from BYLieve

Best fitting distributions based on BIC. Distributions are ranked by BIC (left to right, top to bottom).
Abbreviations: BIC: Bayesian information criterion; Gen: generalised; PFS: progression-free survival; RCS: restricted cubic spline.

Long-term projections of PFS (out to 15 years) for these distributions are shown in Figure 15. These parametric distributions all yield similar projections for PFS during the follow-up period with an initially rapidly decreasing slope between months 0 to 18. Most of the distributions yield similar long-term projections of PFS as well. The RCS 3 Weibull distribution yields the most optimistic projections of PFS reaching zero at approximately 108 months (nine years). It should be noted that these projections do not incorporate non-ABC mortality, which is captured separately in the model.

Figure 15: Long-term projections of PFS based on parametric survival distributions fit to PFS for the second-line population of BYLieve

Best fitting distributions based on BIC. Distributions are ranked by BIC (left to right, top to bottom).
Abbreviations: BIC: Bayesian information criterion; Gen: generalised; PFS: progression-free survival; RCS: restricted cubic spline.

The lognormal distribution was selected based on clinical plausibility, excellent visual fit and the best statistical goodness of fit; the choice of lognormal distribution was also validated by a clinical expert during a one-to-one teleconference call between the clinician and Novartis.[93] A range of alternative distributions were adopted within scenario analyses to explore the impact of the choice of distribution on the cost-effectiveness results (see Section B.3.8.3).

Everolimus plus exemestane

In the absence of published data for everolimus plus exemestane in the post-CDK4/6i population, estimates of relative efficacy in terms of PFS and OS between alpelisib plus fulvestrant and everolimus plus exemestane were derived from an ITC of second-line data from the SOLAR-1 and BOLERO-2 trials.

As described in Section B.2.7, the proportional hazards assumption held within the second-line populations of SOLAR-1 and BOLERO-2. Therefore, a frequentist approach (Bucher approach) was used to derive a HR for PFS for everolimus plus exemestane versus alpelisib plus fulvestrant in the second-line setting. This HR was then applied to the BYLieve curve in order to generate a PFS curve for everolimus plus exemestane using the formula below:

$$S[t]_{Comp} = S[t]_{Alp+\ Fulv}^{\ HR_{Comp\ v\ Alp+\ Fulv}}$$

In summary, PFS for everolimus plus exemestane was estimated by applying a HR for PFS between everolimus plus exemestane versus alpelisib plus fulvestrant (derived from the Bucher method ITC using second-line SOLAR-1 and BOLERO-2 data) to the estimated PFS curve for alpelisib plus fulvestrant from the second-line population of BYLieve. The estimated HRs for PFS from the ITC (Bucher method) are presented in Table 54 below. While data were largely utilised from patients who have not received prior CDK4/6i therapy (SOLAR-1 and BOLERO-2), this HR estimate appears reasonable when considering the clinical effectiveness results of the matching/weighted analysis favouring alpelisib plus fulvestrant (see Section B.2.5.1.4).

Table 54: Results for HRs for PFS from the ITC of second-line treatments using the Bucher method

Comparator	HR (95% CI) of comparator versus	
	Fulvestrant	Alpelisib plus fulvestrant
Everolimus plus exemestane	[redacted]	[redacted]

Abbreviations: CI: confidence interval; HR: hazard ratio; ITC: indirect treatment comparison; PFS: progression-free survival.

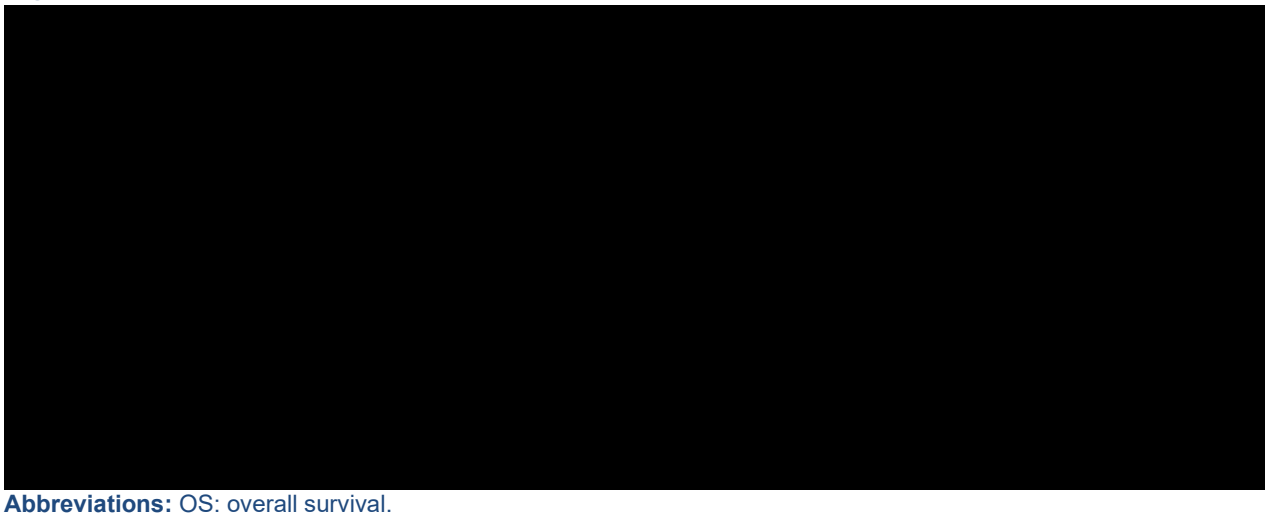
Scenario analyses have been conducted to explore the impact of any uncertainty in this HR, whereby the upper limit of the 95% CI for the HR is applied in the cost-effectiveness model (see Section B.3.8.3). An additional scenario has been conducted using the HRs obtained from the PAIC of SOLAR-1 versus BOLERO-2. For PFS, a HR of [redacted] (exemestane + everolimus versus alpelisib plus fulvestrant) is used in the scenario (see Section B.2.7.3.2). Novartis acknowledge the limitations associated with this PAIC approach (as described in B.2.7.4), hence why the Bucher ITC was utilised in the base case. However, the PAIC provides supportive evidence for a potentially beneficial effect of alpelisib plus fulvestrant versus everolimus plus exemestane using an alternative methodology, and investigation of this approach is in line with ERG feedback from the terminated NICE appraisal for alpelisib plus fulvestrant in 2020.

B.3.3.2 OS

Alpelisib plus fulvestrant

Kaplan-Meier survival and hazard rates for the second-line population of BYLieve are reported in Figure 16. The plots of the hazard rates during shows an increasing pattern until 12 months, after which point the hazards are constant.

Figure 16: OS for the second-line population of BYLieve



Abbreviations: OS: overall survival.

A ranking of parametric distributions fit to OS by the fit statistics are shown in Figure 17. The top five distributions, according to BIC statistic were as follows:

- Gompertz;
- Weibull;
- Log-logistic;
- Exponential; and
- Lognormal

The best fitting distributions based on the AIC and AICc are generally consistent with those based on the BIC, except the BIC includes the exponential and lognormal distributions and the AIC and AICc include the RCS 1 Weibull and generalised gamma distributions.

Figure 17: Fit statistics for parametric distributions fit to OS for the second-line population of BYLieve

Abbreviations: BIC: Bayesian information criterion; Gen: generalised; OS: overall survival; RCS: restricted cubic spline.

Projections of OS during the trial period for the best fitting distributions based on BIC are shown in Figure 18. Most of the distributions shown had good visual fit to the Kaplan-Meier estimated OS, although the Gompertz, Weibull, and RCS 1 Weibull distributions appear to be heavily weighted at the tail end of the Kaplan-Meier OS. In contrast, the log-logistic, exponential, and lognormal distributions diverge from the Kaplan-Meier OS at the end of follow-up. This finding is reflected by a single event occurring at approximately 20 months, with two patients remaining at risk. While this event had a relatively large impact on the Kaplan-Meier OS, it was relatively uninformative in the estimation of the OS extrapolations.

Figure 18: Parametric survival distributions fit to OS for patients in the second-line population of BYLieve

Best fitting distributions based on BIC. Distributions are ranked by BIC (left to right, top to bottom).
Abbreviations: BIC: Bayesian information criterion; Gen: generalised; OS: overall survival; RCS: restricted cubic spline.

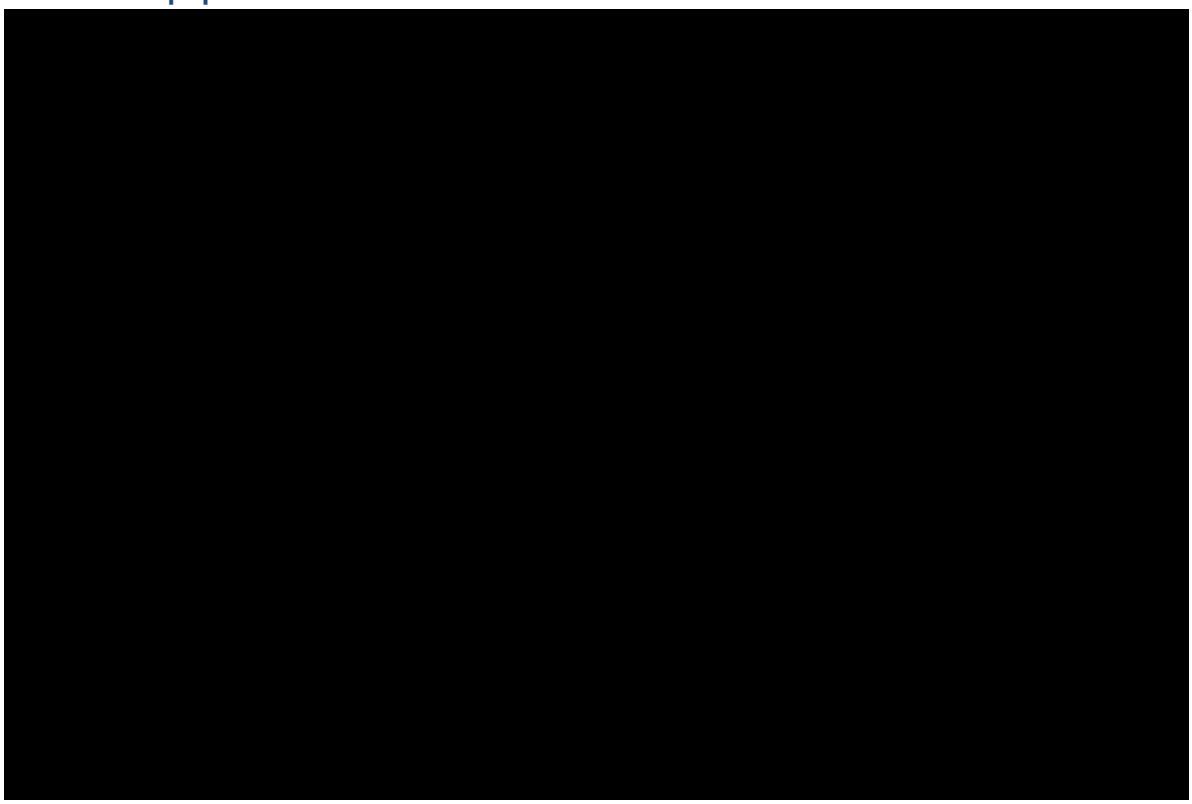
Projected hazard rates for OS are shown in Figure 19. Projected hazards for the Gompertz, Weibull, and RCS 1 Weibull are constantly increasing, which is inconsistent with the observed hazard rates. It should be noted that after 12 months, the visual fit to the Kaplan-Meier curve becomes less important due to the smaller number of events. The log-logistic yields projected hazards that are most consistent with the non-parametric hazards, though the lognormal and exponential are relatively consistent as well.

Figure 19: Hazard rates for parametric survival distributions fit to OS for patients in the second-line population of BYLieve

Best fitting distributions based on BIC. Distributions are ranked by BIC (left to right, top to bottom).
Abbreviations: BIC: Bayesian information criterion; Gen: generalised; OS: overall survival; RCS: restricted cubic spline.

Long-term projections of OS based on the best-fitting distributions are shown in Figure 20. The lognormal distribution yields the most optimistic projections of OS with estimations not yet reaching zero at 180 months (15 years). On the other hand, the Gompertz distribution illustrates the most pessimistic projections of OS reaching zero just before 36 months (three years). Both the Gompertz and Weibull yield projected OS that is less than projected PFS by five years. Projected OS with the log-logistic distribution appears to be intermediate among the other best fitting models.

Figure 20: Long-term projections based on parametric distributions fit to OS for the second-line population of BYLieve



Best fitting distributions based on BIC. Distributions are ranked by BIC (left to right, top to bottom).
Abbreviations: BIC: Bayesian information criterion; Gen: generalised; OS: overall survival; RCS: restricted cubic spline.

In selecting the parametric distribution fit to OS, it was assumed that projected OS for alpelisib plus fulvestrant would be at least as much as projected PFS. This was based on the assumption that data on PFS from BYLieve are more robust than data on OS. The log-logistic distribution fit to OS was therefore selected. While this distribution ranked third according to the BIC, the two better performing distributions according to the BIC (Gompertz and Weibull) had a projected OS that was less than the projected PFS before five years. The Gompertz and Weibull distributions are therefore not clinically plausible, and are influenced by the small number of patients at risk of event after 12 months. Additionally, the log-logistic distribution has excellent visual fit to the observed Kaplan-Meier OS and reasonable long-term projections of OS, which were validated by clinical expert opinion.[93] A range of alternative distributions were adopted within scenario analyses to explore the impact of the choice of distribution on the cost-effectiveness results (see Section B.3.8.3).

Everolimus plus exemestane

As described above, the proportional hazards assumption held within the second-line populations of SOLAR-1 and BOLERO-2 (see Section B.2.7). Therefore, a frequentist approach (Bucher approach) was used to derive a HR for OS for everolimus plus exemestane versus alpelisib plus fulvestrant (using second-line SOLAR-1 and BOLERO-2 data) to apply to the second-line BYLieve curve.

Estimated HRs for OS from the ITC (Bucher method) are presented in Table 55.

Table 55: Results for HRs for OS from the ITC of second-line treatments using the Bucher method

Comparator	HR (95% CI) of comparator versus	
	Fulvestrant	Alpelisib plus fulvestrant
Everolimus plus exemestane	[redacted]	[redacted]

Abbreviations: CI: confidence interval; HR: hazard ratio; ITC: indirect treatment comparison; OS: overall survival.

Survival projections for everolimus plus exemestane in the post-CDK4/6i population were also validated by UK clinical feedback that indicated that approximately 5% patients receiving everolimus plus exemestane (following receipt of CDK4/6i +AI) would be alive at five years.[93]

Scenario analyses have been conducted to explore the impact of any uncertainty in this HR, whereby the upper limit of the 95% CI for the HR was utilised in the cost-effectiveness model (see Section B.3.8.3). An additional scenario is conducted using the HRs obtained from the PAIC of SOLAR-1 versus BOLERO-2. For OS, a HR of [redacted] (exemestane + everolimus versus alpelisib plus fulvestrant) is used in the scenario (see Section B.2.7.3.2). As described above, Novartis acknowledge the limitations associated with this PAIC approach (as described in B.2.7.4), hence why the Bucher ITC was utilised in the base case. However, the PAIC provides supportive evidence for a potentially beneficial effect of alpelisib plus fulvestrant versus everolimus plus exemestane using an alternative methodology, and investigation of this approach is in line with ERG feedback from the terminated NICE appraisal for alpelisib plus fulvestrant in 2020.

B.3.3.3 TTD

Probabilities of remaining on treatment (and the complemental probabilities of discontinuation) for patients receiving alpelisib plus fulvestrant were estimated using individual patient failure time data from BYLieve. Since patients in BYLieve could discontinue alpelisib or fulvestrant independently, and those who discontinued alpelisib were permitted to continue receiving fulvestrant, TTD of alpelisib and TTD of fulvestrant were estimated separately.

TTD was defined as time from treatment start to discontinuation of medication or death, whichever occurred first, with patients who did not discontinue or die censored at censoring time for OS. In the base case, it is assumed that TTD for alpelisib or fulvestrant cannot exceed the PFS (i.e., PFS is used as a ceiling for TTD).

Alpelisib

Kaplan-Meier survival probabilities and hazard rates for TTD for alpelisib among patents in the second-line subgroup of BYLieve are reported in Figure 21. The hazard rates for TTD for alpelisib generally decline over the trial follow-up.

Figure 21: TTD of alpelisib in the second-line population of BYLieve

Abbreviations: TTD: time to discontinuation.

A ranking of parametric distributions fit to TTD for alpelisib by BIC is shown in Figure 22. The top five distributions, according to BIC statistic were as follows:

- Lognormal;
- Log-logistic;
- Exponential;
- Gompertz; and
- Generalised gamma

The best fitting distributions according to AIC and AICc are generally consistent with the best fitting distributions according to BIC, except that the exponential and Gompertz distributions are not among the top five distributions based on the AIC and AICc, and the RCS 1 lognormal and RCS 1 Weibull are not among the top five according to the BIC.

Figure 22: BIC for parametric distributions fit to TTD for alpelisib in the second-line population of BYLieve

Abbreviations: BIC: Bayesian information criterion; Gen: generalised; RCS: restricted cubic spline; TTD: time to discontinuation.

Parametric survival distributions for TTD for alpelisib during the trial follow-up period are shown in Figure 23. All of the top six distributions by BIC have excellent visual fit to the Kaplan-Meier curve throughout the trial period.

Figure 23: Parametric survival distributions fit to TTD for alpelisib in the second-line population of BYLieve

Top six best fitting distributions based on BIC are shown. Distributions are ranked by BIC (left to right, top to bottom).
Abbreviations: BIC: Bayesian information criterion; Gen: generalised; RCS: restricted cubic spline; TTD: time to discontinuation.

Hazard rates during trial follow-up for the best fitting parametric survival distributions for TTD for alpelisib are shown in Figure 24. The exponential distribution is characterised by constant hazard rates, which closely aligns with the nonparametric hazards. The remaining best fitting distributions according to the BIC illustrate a slightly decreasing hazard rate, which also aligns with the observed hazard rate.

Figure 24: Hazard rates for parametric distributions fit to TTD for alpelisib in the second-line population of BYLieve

Top six best fitting distributions based on BIC are shown. Distributions are ranked by BIC (left to right, top to bottom).
Abbreviations: BIC: Bayesian information criterion; Gen: generalised; RCS: restricted cubic spline; TTD: time to discontinuation.

In selecting the parametric distribution fit to TTD, it was assumed that projected TTD for alpelisib plus fulvestrant would be less than projected PFS. Based on this assessment, the exponential distribution was employed. This model had excellent visual, good statistical fit, and yields projected TTD that did not exceed PFS. A range of alternative distributions were adopted within scenario analyses to explore the impact of the choice of distribution on the cost-effectiveness results (see Section B.3.8.3).

Fulvestrant

Kaplan-Meier survival probabilities and hazard rates for TTD of fulvestrant in the second-line population of BYLieve are reported in Figure 25. The hazard rates for TTD of fulvestrant are relatively stable over the trial follow-up.

Figure 25: TTD for fulvestrant for the second-line population of BYLieve

Abbreviations: TTD: time to discontinuation.

A ranking of parametric distributions fit to TTD for fulvestrant by BIC is shown in Figure 26. The top five distributions, according to BIC, were as follows:

- Lognormal;
- Exponential;
- Log-logistic;
- Generalised gamma; and
- RCS 1 lognormal

The best fitting distributions according to AIC and AICc are generally consistent with the best fitting distributions according to BIC, except that the exponential distribution is not among the top five distributions according to the AIC and AICc.

Figure 26: BIC for parametric distributions fit to TTD for fulvestrant for the second-line population of BYLieve

Abbreviations: BIC: Bayesian information criterion; Gen: generalised; RCS: restricted cubic spline TTD: time to discontinuation.

Projections for TTD for fulvestrant during the trial period for these distributions are shown in Figure 27. All of the top performing distributions based on the BIC have excellent visual fits.

Figure 27: Parametric survival distributions fit to TTD for fulvestrant for the second-line population of BYLieve

Top six best fitting distributions based on BIC are shown. Distributions are ranks by BIC (left to right, top to bottom).
Abbreviations: Gen: generalised; RCS: restricted cubic spline; TTD: time to discontinuation.

Hazard rates during the trial follow-up for the top six best fitting parametric survival distributions for TTD for fulvestrant are shown in Figure 28. The exponential distribution yields a constant projection that is most similar to the observed hazard rates for the entire follow-up period. The remaining top distributions by BIC have hazard rates that declined steadily during follow-up, which is inconsistent with the observed nonparametric hazards.

Figure 28: Hazard rates for parametric survival distributions fit to TTD for fulvestrant for the second-line population of BYLieve

Top six best fitting distributions based on BIC are shown. Distributions are ranks by BIC (left to right, top to bottom).
Abbreviations: BIC: Bayesian information criterion; Gen: generalised; RCS: restricted cubic spline; TTD: time to discontinuation.

The exponential distribution was utilised because it had an excellent statistical fit, and was the best visual match compared with the Kaplan-Meier TTD among the top performing distributions. A range of alternative distributions were adopted within scenario analyses to explore the impact of the choice of distribution on the cost-effectiveness results (see Section B.3.8.3).

Everolimus plus exemestane

TTD for everolimus plus exemestane was estimated by applying a HR for TTD versus PFS (derived from TTD and PFS data from the BOLERO-2 trial) to the PFS curve for everolimus plus exemestane. This approach was employed to ensure that the TTD was consistent with the PFS estimated based on the ITC of HRs for PFS.

TTD in BOLERO-2 was estimated using available individual patient-level data with TTD defined as the time from randomisation to discontinuation of medication or death, whichever occurred first. Patients who did not discontinue or die were censored at the censoring time for OS. Since data on discontinuation were not available for the individual drug components of everolimus plus exemestane in BOLERO-2, it was assumed that TTD was the same for both components of the regimen. Given separate relative dose intensities (RDIs) for each of everolimus and exemestane were included in the model, which take into account that everolimus may be associated with a lower RDI due to tolerability issues (see Section B.3.5.1.2),[62] this approach was considered reasonable in avoiding overestimation of the costs for everolimus plus exemestane.[62] The HR for TTD versus PFS for everolimus plus exemestane in BOLERO-2 was estimated using Cox

proportional hazards regression.

The proportional hazards assumption for TTD versus PFS in BOLERO-2 was tested by examination of Schoenfeld residuals. The HR for TTD versus PFS for the everolimus plus exemestane arm did not violate the proportional hazards assumption (p>0.05) for everolimus plus exemestane or exemestane alone in BOLERO-2. The estimated HR for TTD versus PFS for everolimus plus exemestane is shown in Table 56. This HR was applied to the estimated PFS curve for everolimus plus exemestane in this population.

Table 56: HR for TTD versus PFS from BOLERO-2

Comparator	HR for TTD versus PFS (95% CI)	Proportional hazards test p-value	Source trial
Everolimus plus exemestane	1.27 (1.01, 1.60)	0.88	BOLERO-2

Abbreviations: CI: confidence interval; HR: hazard ratio; PFS: progression-free survival; TTD: time to discontinuation.

Scenario analyses have been conducted to explore the impact of any uncertainty in this HR, whereby the upper and lower limits of the 95% CIs for the HR were utilised in the cost-effectiveness model (see Section B.3.8.3).

Base case model projections of TTD for everolimus plus exemestane versus corresponding PFS distributions are shown in Figure 29.

Figure 29: Model projections of TTD versus PFS for everolimus plus exemestane from BOLERO-2

Abbreviations: PFS: progression-free survival; TTD: time to discontinuation.

B.3.3.4 AEs

AEs considered in the model were all-cause ≥Grade 3 AEs with an incidence ≥5% for either alpelisib plus fulvestrant or everolimus plus exemestane (Table 57). Grade 1 or 2 AEs were not considered because they are generally self-limiting and are therefore not likely to be associated with substantial treatment costs or reductions in HRQoL. Data from Cohort A of BYLieve and SOLAR-1 were used to estimate the incidence of all-cause ≥Grade 3 AEs for alpelisib plus fulvestrant for the BYLieve and SOLAR-1 populations, respectively. The incidence of all-cause ≥Grade 3 AEs for everolimus plus exemestane were based on the BOLERO-2 trial.

Table 57: Incidence of ≥Grade 3 AEs included in the model

≥Grade 3 AE	Alpelisib plus fulvestrant	Everolimus plus exemestane
Anaemia	0%	8%
Diarrhoea	6%	3%
Dyspnoea	2%	6%
Fatigue	1%	5%
Hyperglycaemia	28%	6%
Increased GGT	0%	7%
Rash	9%	1%
Rash maculopapular	9%	0%
Stomatitis	2%	8%

Grade 4 AEs reported in Yardley *et al.* (2013) were sometimes reported as occurring in '<1%'patients. In this instance, within the cost-effectiveness model, the AE has been assumed to have an incidence of 1% at Grade 4.[62]
Abbreviations: AE: adverse event; GGT: gamma-glutamyl transpeptidase.
Source: Rugo *et al.* (2021);[75] Yardley *et al.* (2013).[62]

B.3.3.5 General population mortality

The probability of death in any given model cycle was assumed to not be lower than the age and sex-matched mortality probabilities for the general population. These probabilities were based on England life tables from the Office for National Statistics,[164] assuming a mean starting age of 57 years (derived from the mean age of patients enrolled in Cohort A of the BYLieve trial) and that 100% of patients are female at entry into the model.[75]

B.3.4 Measurement and valuation of health effects

B.3.4.1 Health-related quality-of-life data from clinical trials

EQ-5D data were not collected from BYLieve; therefore, utility values for alpelisib plus fulvestrant were derived from those estimated for alpelisib plus fulvestrant in the second-line population of SOLAR-1 (23rd April 2020 data cut-off).

As described in Section F.1.5 in Appendix F, HRQoL was assessed in SOLAR-1 via the EQ-5D-5L (23rd April 2020 data cut-off).[29] Per study protocol, EQ-5D assessments were scheduled to occur every 8 weeks, starting at baseline, during the first 18 months and every 12 weeks thereafter until disease progression, death, withdrawal of consent, loss to follow-up, or end of treatment. Following discontinuation of study treatment, if the patient failed to return for their

assessment, the investigator was required to make every reasonable effort to contact the patient. Nevertheless, EQ-5D-5L data were largely missing after progression.

Analysis of the EQ-5D-5L data from SOLAR-1 showed a trend for a [redacted] in the index score in the placebo plus fulvestrant arm, while it seemed to be [redacted] in the alpelisib plus fulvestrant arm.[121] The difference between treatment groups [redacted] based on the previously established minimum important difference (MID) for the instrument.[121]

B.3.4.2 Mapping

Based on the NICE position statement released in August 2017 and updated in October 2019, the EQ-5D-3L should be used for reference-case analyses until further research is undertaken to better understand the impact of adopting the EQ-5D-5L.[157] Therefore, EQ-5D-3L utility values were estimated using patient item responses to the EQ-5D-5L and the response mapping algorithm developed by van Hout *et al.* (2012).[165] Mapped EQ-5D-3L values were based on UK tariffs estimated using the crosswalk from the EQ-5D-5L responses to the EQ-5D-3L available on the EuroQol website.[166]

B.3.4.3 Health-related quality-of-life studies

An SLR was conducted to identify relevant HRQoL data in patients with HR+, HER2− ABC. Notably, the SLR included a wider patient population (not limited to patients with *PIK3CA* mutations, nor those who had progressed following a CDK4/6i therapy) than that addressed in the decision problem, in order to identify all potentially relevant evidence. The SLR was originally conducted in December 2018 with updates conducted in October 2019, August 2020 and April 2021 using the same methodology, in order to identify any additional evidence published since the original SLR was conducted. Full details of the SLR search strategy, study selection process and results are reported in Appendix H.

In total, the SLR identified 15 publications reporting on seven studies containing EQ-5D data (Table 58). All seven studies specifically investigated patients with HR+, HER2− breast cancer,[167-173] six of which reported EQ-5D values,[167-172] and one study presented the least squares mean of EQ-5D VAS at the end of treatment.[173] EQ-5D values were reported for numerous disease states including first-line treatment, second or subsequent treatment lines,[170, 171] for progression-free or progressive disease,[167, 171] for disease stage,[172] and by various treatments at baseline, on treatment or at the end of treatment.[168, 169, 172]

Table 58: Publications reporting EQ-5D data included in the SLR

	Author, year	Citation
1	Lambert-Obry *et al.* (2018)	Lambert-Obry V, Gouault-Laliberté A, Castonguay A, et al. Real-world patient-and caregiver-reported outcomes in advanced breast cancer. Current Oncology 2018;25:e282.
2	Hettle *et al.* (2017)	Hettle R, Suri G, Mistry R, et al. Cost-Effectiveness of Ribociclib Plus Letrozole Versus Palbociclib Plus Letrozole for Postmenopausal Women with Hormone Receptor-Positive (HR+), Human Epidermal Growth Factor Receptor 2-Negative (HER2−) Advanced/Metastatic Breast Cancer from A UK National Health Service Perspective. Value in Health 2017;20:A433.

	Author, year	Citation
3	MONARCH-2 ClinicalTrials.gov	ClinicalTrials.gov. A Study of Abemaciclib (LY2835219) Combined With Fulvestrant in Women With Hormone Receptor Positive HER2 Negative Breast Cancer (MONARCH 2) [Available from: https://clinicaltrials.gov/ct2/show/NCT02107703].
4	Ou *et al.* (2019)	Ou H-T, Chung W-P, Su P-F, et al. Health-related quality of life associated with different cancer treatments in Chinese breast cancer survivors in Taiwan. European Journal of Cancer Care 2019;28:e13069.
5	Rugo *et al.* (2018)	Rugo HS, Dieras V, Gelmon KA, et al. Impact of palbociclib plus letrozole on patient-reported health-related quality of life: results from the PALOMA-2 trial. Ann Oncol 2018;29:888-894.
6	Loibl *et al.* (2016)	Loibl S, Demichele A, Turner N, et al. Impact of palbociclib plus fulvestrant on patient reported general health status compared with fulvestrant alone in HR+, HER2- metastatic breast cancer. Annals of Oncology 2016;27.
7	Wood *et al.* (2017)	Wood R, Mitra D, de Courcy J, et al. Patient-reported pain severity, pain interference and health status in HR+/HER2- advanced/metastatic breast cancer. ESMO Open 2017;2:e000227.

Abbreviations: HRQoL: health-related quality of life; SLR: systematic literature review.

B.3.4.4 Adverse reactions

As discussed in Section B.2.8, alpelisib plus fulvestrant has a well-characterised safety profile with AEs that are associated with PI3K pathway inhibition such as hyperglycaemia, rash and GI toxicity.[29] These AEs are typically manageable with medical therapies and/or dose modifications or interruptions, and are generally reversible.[29, 122]

AEs considered in the model were all-cause ≥Grade 3 AEs with an incidence of ≥5% for any of the comparators of interest. Grade 1–2 events were not considered because they are generally self-limiting and are therefore not likely to be associated with substantial treatment costs or reductions in HRQoL. Data from Cohort A of BYLieve and SOLAR-1 were used to estimate the incidence of all-cause ≥Grade 3 AEs for alpelisib plus fulvestrant. The incidence of all-cause ≥Grade 3 AEs for everolimus plus exemestane were based on the BOLERO-2 trial.

Since the health state utility values in the model are estimated from the SOLAR-1 and BOLERO-2 trials, respectively, the impact of AEs on HRQoL associated with alpelisib plus fulvestrant and everolimus plus exemestane has already been accounted for.[121] This approach is considered to avoid double counting, and is aligned with the NICE appraisal for ribociclib plus fulvestrant for treating hormone receptor-positive, HER2-negative, advanced breast cancer (TA687/TA593). In that submission, Novartis did not incorporate additional disutilities based on the assumption that any disutility resulting from AEs would have been captured in the utilities elicited from patients in the MONALEESA-3 trial. This was not considered a key concern for the ERG and it is not anticipated that the inclusion of additional disutilities would have a large impact on the base case results of the economic analysis.[4] This is also supported by evidence that in oncology, the inclusion of AE costs and disutilities could be considered negligible compared to the costs of treatment and severity of the disease.[174]

B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

As described above, EQ-5D data were not collected from BYLieve; therefore, utility values for

alpelisib plus fulvestrant in the base case were derived from SOLAR-1.

Scenario analyses were conducted varying the health state utility values according to their upper and lower 95% CIs to explore the impact on the ICER (see Section B.3.8.3).

B.3.4.5.1 Alpelisib plus fulvestrant

Mapped EQ-5D-3L utility values from SOLAR-1 were analysed using generalised estimating equations (GEEs) regression (an extension of generalised linear model [GLM] regression for analysing data with correlation of the dependent variable across observations) to estimate utility values for the following mutually exclusive health states controlling for baseline EQ-5D utility values:

- PFS on treatment (alpelisib and fulvestrant);
- PFS on treatment (placebo and fulvestrant);
- PFS off treatment; and
- Post-progression survival (PPS).

The model also included a covariate to indicate whether the patient was in the terminal or "near death" phase, which was defined as within 84 days of death. GEE regression models were explored that included a covariate for a terminal phase (defined as assessments within 84 days of the recorded date of death) as well as models that did not include this covariate. An alternative time period of 28 days was also explored, but there were very few assessments during this time period. Exploration of the time period of 84 days found that for the second-line population of SOLAR-1, the p-value for the terminal phase covariate was statistically significant in each of the models where the covariate was included. This suggested that patients' HRQoL was adversely affected in the 84 days preceding the date of death, and as such, HRQoL was assumed to diminish during this period within the economic analysis.

Patients could contribute multiple observations to the analysis. To be included in the analysis, patients must have had a baseline assessment and at least one post-baseline assessment.

GEE regressions were conducted using an identity link function, normal error term distribution, and exchangeable correlation structure with the following covariates for baseline EQ-5D-3L utility value and health state at assessment. PFS off treatment was used as the reference state for the variable coding disease state (note that the choice of the reference level of the covariate has no impact on the predicted utility values). GEE regression was conducted using the SAS PROC GENMOD procedure with the REPEATED statement.

Six different regression models were considered, each with different combinations of the covariates described above. All models included an intercept term and a covariate for baseline utility value, as well as a covariate for assessment in the PPS state. Models 2, 4, and 6 also included a covariate for assessments occurring within 28 days of death. Models 1 and 2 included only a single additional covariate for assessments in the PFS state, therefore, in these Models, utility values during the PFS state were assumed to be independent of treatment group and whether patients were on or off treatment. In Models 3 and 4, an additional covariate was included to differentiate PFS on- versus off-treatment, therefore, in these Models, utility values were assumed to potentially differ for patients who were on versus off therapy but were otherwise independent of treatment. Finally, Models 5 and 6 included separate covariates for on therapy in

the alpelisib plus fulvestrant group and on therapy in the placebo plus fulvestrant group. In these final regression models, the effect of on versus off treatment was assumed to potentially differ by treatment group.

Table 59: Alternative regression models for analysing utility values in SOLAR-1

Model	Intercept	Baseline utility	PFS	PFS off treatment	PFS on treatment	PFS on treatment (alpelisib plus fulvestrant)	PFS on treatment (placebo plus fulvestrant)	PPS	Terminal phase (within 84 days of death)
1	X	X	Reference					X	
2	X	X	Reference					X	X
3	X	X		Reference	X			X	
4	X	X		Reference	X			X	X
5	X	X		Reference		X	X	X	
6	X	X		Reference		X	X	X	X

Abbreviations: PFS: progression-free survival; PPS: post-progression survival.

Mean (SD) EQ-5D-3L utility values (by treatment arm) for second-line patients in SOLAR-1 (which were used for the base case population), estimated using the mapping developed by van Hout *et al.* (2012), are summarised in Table 60 below.

Table 60: Mean (SD) EQ-5D-3L utility values at baseline and follow-up assessments by treatment arm (based on second-line population of SOLAR-1)

Timepoint	Alpelisib plus fulvestrant (N=140)		Placebo plus fulvestrant (N=148)	
	N	Mean (SD)	N	Mean (SD)
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 1	-	-	[redacted]	[redacted]
Cycle 3	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 4	[redacted]	[redacted]	-	-
Cycle 5	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 6	[redacted]	[redacted]	-	-
Cycle 7	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 8	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 9	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 11	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 12	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 13	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 15	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 16	[redacted]	[redacted]	-	-
Cycle 17	[redacted]	[redacted]	[redacted]	[redacted]

Cycle 19	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 21	-	-	[redacted]	[redacted]
Cycle 22	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 25	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 28	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 31	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 34	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 37	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 40	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 43	[redacted]	[redacted]	-	-
Cycle 46	[redacted]	[redacted]	-	-
Cycle 49	[redacted]	[redacted]	-	-
Cycle 52	[redacted]	[redacted]	-	-
End of Treatment	[redacted]	[redacted]	[redacted]	[redacted]
Efficacy Follow Up 1	[redacted]	[redacted]	-	-
Efficacy Follow Up 2	[redacted]	[redacted]	-	-
Efficacy Follow Up 3	[redacted]	[redacted]	-	-
Efficacy Follow Up 4	[redacted]	[redacted]	-	-
Efficacy Follow Up 5	[redacted]	[redacted]	-	-
Efficacy Follow Up 6	[redacted]	[redacted]	-	-
Efficacy Follow Up 7	[redacted]	[redacted]	-	-

Abbreviations: EuroQol 5-dimensions 3-levels; SD: standard deviation.
Source: Novartis data on file.

Numbers of patients and EQ-5D-3L assessments by treatment group and health state for second-line patients in SOLAR-1 are shown in Table 61 below.

Table 61: Numbers of patients and EQ-5D-3L assessments contributing to GEE regression analyses of EQ-5D-3L assessments (based on second-line population of SOLAR-1)

Outcome	Alpelisib plus fulvestrant	Placebo plus fulvestrant	Total
Patients			
Baseline	[redacted]	[redacted]	[redacted]
PFS on treatment (alpelisib plus fulvestrant)	[redacted]	-	[redacted]
PFS on treatment (placebo plus fulvestrant)	-	[redacted]	[redacted]
PFS off treatment	[redacted]	[redacted]	[redacted]
PPS	[redacted]	[redacted]	[redacted]
Terminal phase	[redacted]	[redacted]	[redacted]
Assessments			
Baseline	[redacted]	[redacted]	[redacted]
PFS on treatment (alpelisib plus fulvestrant)	[redacted]	-	[redacted]

PFS on treatment (placebo plus fulvestrant)	-	[redacted]	[redacted]
PFS off treatment	[redacted]	[redacted]	[redacted]
PPS	[redacted]	[redacted]	[redacted]
Terminal phase	[redacted]	[redacted]	[redacted]

Abbreviations: EQ-5D-3L: EuroQol 5-Dimensions 3-Level; ET: endocrine therapy; GEE: generalised estimation equation.
Source: Novartis data on file.

The six different GEE regression models for predictive utility values are shown in Appendix L. Predicted mean utility values by state using the regression equations, and the mean baseline EQ-5D-3L score for second-line patients in SOLAR-1 ([redacted], SE=[redacted]) to control for differences in baseline utility values between arms, are also shown in Appendix L.

Model 6 was chosen for the base case analysis, given this model includes a covariate for baseline utility, treatment-group specific covariates for PFS on treatment, a covariate for PPS, and a covariate for the 84 days prior to death. Baseline utility values were significant predictors of follow-up utility values in all regressions. Utility assessments during the 84 days prior to death were not statistically significant predictor of utility values in any of the regression models in which this covariate was included. However, the coefficient is consistent with expectations that utility would be lower in the period preceding death. As expected, utility values were lower for PPS than PFS off treatment (coefficient estimate [redacted]) though this was not statistically significant.

Results of the regression using Model 6 are detailed in Table 62 below.

Table 62: Results of GEE regression model predicting EQ-5D-3L at follow-up assessments for the BYLieve population (based on second-line population of SOLAR-1)

Variable	Parameter estimate	95% CI	p-value
Intercept	[redacted]	[redacted]	[redacted]
Baseline EQ-5D-3L	[redacted]	[redacted]	[redacted]
PFS on treatment (alpelisib plus fulvestrant)	[redacted]	[redacted]	[redacted]
PFS on treatment (placebo plus fulvestrant)	[redacted]	[redacted]	[redacted]
PPS	[redacted]	[redacted]	[redacted]
Terminal phase	[redacted]	[redacted]	[redacted]

Abbreviations: CI: confidence interval; EQ-5D-3L: EuroQol 5-Dimensions 3-Levels; GEE: generalised estimation equation; PFS: progression-free survival; PPS: post-progression survival.

Utility values adopted in the base case

Using the regression equation above, and the mean baseline EQ-5D-3L score for second-line patients in SOLAR-1 ([redacted], SE=[redacted]) to control for differences in baseline utility values between arms, the predicted mean utility value for PFS on treatment (alpelisib plus fulvestrant) and not terminal phase was estimated to be [redacted]. The corresponding value for PFS on treatment (placebo plus fulvestrant) and not terminal phase was [redacted]. The predicted mean utility values for PFS off treatment and not terminal phase was estimated to be [redacted]. Predicted mean utility value for PPS not terminal phase was estimated to be [redacted]; the mean disutility value for patients who were terminal phase was estimated to be [redacted] (Table 63). As there are various

treatment options for patients following progression from second-line treatment in the advanced setting (hence why post-progression costs have been included within the cost-effectiveness model [See Section B.3.5.2.1]), a utility value of [redacted] was considered a reasonable estimate of utility for patients in the PPS state (i.e. that utility would not decrease a substantial amount from the PFS to PPS state). This was validated by clinical expert opinion.[93]

Table 63: Utility values adopted in the base case

Health state	Utility	95% CI	SE
PFS on treatment (alpelisib plus fulvestrant)	[redacted]	[redacted]	[redacted]
PFS on treatment (placebo plus fulvestrant)	[redacted]	[redacted]	[redacted]
PFS off treatment	[redacted]	[redacted]	[redacted]
PPS	[redacted]	[redacted]	[redacted]
Terminal phase (disutility)	[redacted]	[redacted]	[redacted]

Abbreviations: CI: confidence interval; GEE: generalised estimation equation; PFS: progression-free survival; PPS: post-progression survival; SE: standard error.

As raised by the ERG during the prior review, a scenario is conducted using the PPS utility estimate of 0.505 from Lloyd *et al.* (2006).[94] Considering that clinical expert opinion has validated the base case assumption of [redacted], this scenario is not considered to be an accurate estimate of utility in this health state for this population.

B.3.4.5.2 Everolimus plus exemestane

For everolimus plus exemestane, the impact of treatment on utility values (PFS [on treatment] health state) was based on data from the BOLERO-2 trial on utility values obtained by mapping from the EORTC QLC-C30 to the EQ-5D.

The utility values from BOLERO-2 (presented in Appendix L) were used to estimate a utility decrement for everolimus plus exemestane versus exemestane alone. It was then assumed that the utility value for exemestane would be equal to that for fulvestrant. This approach is based on the NICE submission for ribociclib plus fulvestrant for treating hormone receptor-positive, HER2-negative, advanced breast cancer (TA687/TA593).[4] The estimation of the health state utility for everolimus plus exemestane may be considered an indirect treatment comparison approach under the assumption that the utility value for fulvestrant is equal to that for exemestane alone. Under this assumption, the utility value for everolimus plus exemestane was estimated by adding the estimated difference in utility between everolimus plus exemestane versus exemestane alone (fulvestrant) to the utility value for fulvestrant from SOLAR-1. Novartis is not aware of any other evidence besides the data from BOLERO-2, which suggest there is a difference in utility for everolimus plus exemestane versus exemestane.

The mean utility value at baseline was [redacted] for patients in the everolimus plus exemestane arm and [redacted] among those in the placebo plus exemestane arm (difference [redacted]). The weighted average utility value during follow-up was [redacted] for patients in the everolimus plus exemestane arm and [redacted] among those in the placebo plus exemestane arm (difference [redacted]). It was therefore estimated that the difference in mean utility value for everolimus plus exemestane versus alpelisib plus fulvestrant was [redacted], based on the mean difference in utility during follow-up ([redacted]) and the net of the difference in mean utility at baseline ([redacted]).

Overall, the utility value for PFS (on treatment) for everolimus plus exemestane in the model was then calculated as the difference between the estimated utility for fulvestrant and the disutility for everolimus plus exemestane versus exemestane. This led to utility values for the PFS (on treatment) health state for everolimus plus exemestane of [redacted].

General population utility values

Age- and gender-matched general population utilities were used to adjust utility values for age-related declines in HRQoL. These utilities were based on published UK population norms for the EQ-5D as reported by Ara and Brazier,[175] who report the following formula for calculating age and sex-specific utility values:

$$\text{Utility} = 0.9508566 + 0.0212126 \times \text{male} - 0.0002587 \times \text{age\_years} - 0.0000332 \times \text{age\_years}^2$$

Age-specific declines in utility were applied by subtracting the difference in utility for current age versus the age at entry into the model from the state- and comparator/treatment-specific utilities.

B.3.5 Cost and healthcare resource use identification, measurement and valuation

An SLR was conducted to identify any relevant cost or resource use data that could be incorporated into the model. The SLR was originally conducted in December 2018 with updates conducted in October 2019, August 2020 and April 2021 using the same methodology, in order to identify any additional evidence published since the original SLR was conducted. Full details of the SLR search strategy, study selection process and results are presented in Appendix I.

In total, the SLR identified 67 publications reporting cost or resource use data from 57 studies in patients with HR+, HER2− breast cancer (Table 64). Of these, four studies were conducted in the UK and applicable to UK practice,[176-179] with the remaining 53 studies reporting cost and resource use data elsewhere in Europe, the US, Canada, India, Taiwan, Mexico, Korea, China or internationally. Of the four UK studies, two studies investigated palbociclib,[177, 179] one ribociclib[176] and one abemaciclib,[178] and the relevant reported outcomes included medication use, length of hospital stay and drug price.[176-179] The 53 non-UK studies additionally reported outcomes such as treatment setting, therapy duration, dose reductions and use of tests.

Table 64: Publications reporting healthcare resource use data included in the SLR

	Author, year	Citation
1	Battisti *et al.* (2018)	Battisti N, Kingston B, King J, et al. Palbociclib and endocrine therapy in fourth line and beyond for hormone receptor-positive HER2- negative advanced breast cancer: the UK compassionate access program experience. 2019.
2	Blum *et al.* (2018)	Blum J, McCune S, Salkeni M, et al. 344P First report of real-world patient characteristics and treatment patterns from POLARIS: Palbociclib in hormone receptor-positive (HR+) advanced breast cancer: A prospective, multicenter, noninterventional study. Annals of Oncology 2018;29:mdy272. 334.
3	Caldeira and Scazafave (2016)	Caldeira R, Scazafave M. Real-world treatment patterns for hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer in Europe and the United States. Oncology and therapy 2016;4:189-197.

	Author, year	Citation
4	Chandler. (2020)	Chandler, A. Adherence to and patient satisfaction with the combination therapy of exemestane andeverolimus in postmenopausal women with HR+ HER2-advanced breast cancer: Results from the IPSOC-mamma study Cancer Research Conference 2020.
5	Dalal *et al.* (2018)	Dalal AA, Gauthier G, Gagnon-Sanschagrin P, et al. Treatment and Monitoring Patterns Among Premenopausal Women with HR+/HER2− Advanced Breast Cancer. Advances in therapy 2018;35:1356-1367.
6	Darden *et al.* (2018)	Darden C, Mitra D, McSorley D, et al. Patient-Reported Treatment Satisfaction Among Women Receiving Palbociclib Combination Therapies for HR+/HER2– Advanced or Metastatic Breast Cancer in the United States. Presented at the 35th Annual Miami Breast Cancer Conference (MBCC); March 8–11, 2018; Miami Beach, FL, USA. 2018.
7	Dent *et al.* (2017)	Dent S, Califaretti N, Doyle C, et al. Abstract P3-15-02: Treat ER+ ight Canadian prospective observational study in HR+ advanced breast cancer: 2nd interim analysis: SABC 2017.
8	Doyle *et al.* (2020)	Doyle C, Vandenberg TA, Ferrario C, et al. Exploratory analysis of TreatER+ight: A Canadian prospective real-world observational study in HR+ advanced breast cancer. Annals of Oncology 2020.
9	Lardy-Cleaud *et al.* (2017)	Lardy-Cleaud A, Cottu P, Frank S, et al. 266PUse of everolimus in advanced hormone receptor positive metastatic breast cancer in a multicenter national observational study. Annals of Oncology 2017;28.
10	Eziokwu *et al.* (2019)	Eziokwu AS, Varella L, Kruse ML, et al. Real-world evidence evaluating continuation of CDK4/6 inhibitors beyond first progression in hormone receptor-positive (HR+) metastatic breast cancer: American Society of Clinical Oncology, 2019.
11	Fabi et al. (2019)	Fabi A, Russilo M, Ciccarese M, et al. P5-11-18 Real-world evidence of efficacy and activity of palbociclib plus endocrine therapy and post-progression treatments in HR+/HER2- metastatic breast cancer patients: The PALPract study. Cancer Res, 2019.
12	Feinberg *et al.* (2019)	Feinberg B, Kish J, Dokubo I, et al. PCN325 Real-world data describing the role of chemotherapy in the treatment of HR+/HER2 MBC patients – Divergence from evidence-based medicine. ISPOR Europe, 2019
13	Fountzilas *et al.* (2019)	Fountzilas E, Koliou GA, Rapti V, et al. 334P Clinical outcome and toxicity data in patients with advanced breast cancer treated with cyclin-dependent kinase 4/6 (CDK4/6) inhibitors combined with endocrine therapy in a real-world clinical setting. Annals of Oncology 2019. Annals of Oncology30 2019;Supplement 5:v118
14	Fountzilas *et al.* (2020)	Fountzilas E, Koliou GA, Vozikis A, et al. Real-world clinical outcome and toxicity data and economic aspects in patients with advanced breast cancer treated with cyclin-dependent kinase 4/6 (CDK4/6) inhibitors combined with endocrine therapy: the experience of the Hellenic Cooperative Oncology Group. Esmo Open 2020.
15	Galve-Calvo *et al.* (2018)	Galve-Calvo E, González-Haba E, Gostkorzewicz J, et al. Cost-effectiveness analysis of ribociclib versus palbociclib in the first-line treatment of HR+/HER2− advanced or metastatic breast cancer in Spain. ClinicoEconomics and outcomes research: CEOR 2018;10:773.
16	Giuliani & Bonetti (2020)	Guiliani J, Bonetti A. The introduction of a third CDK4/6 inhibitor does not change the cost-effectiveness profile in first and subsequent-lines after progression or relapse during previous endocrine therapy in patients with hormone receptor positive (HR+)/human epidermal receptor-2 negative (HER-2) advanced or metastatic breast cancer. Journal of Oncology Pharmacy Practice 2020.

	Author, year	Citation
17	Guérin *et al.* (2018)	Guérin A, Goldschmidt D, Small T, et al. Monitoring of Hematologic, Cardiac, and Hepatic Function in Post-Menopausal Women with HR+/HER2− Metastatic Breast Cancer. Advances in therapy 2018;35:1251-1264.
18	Gupta *et al.* (2014)	Gupta S, Zhang J, Jerusalem G. The association of chemotherapy versus hormonal therapy and health outcomes among patients with hormone receptor-positive, HER2- negative metastatic breast cancer: experience from the patient perspective. Expert Rev Pharmacoecon Outcomes Res 2014;14:929-40
19	Joy *et al.* (2017)	Joy AA, Verma S, Provencher L, et al. Safety results of the Canadian Expanded Access Program (EAP) of palbociclib (PAL) plus letrozole (L) in postmenopausal patients (pts) with hormone receptor-positive (HR+)/human epidermal growth factor receptor 2-negative (HER2-) advanced breast cancer (ABC) deemed appropriate candidates for first-line (1L) endocrine therapy (ET) with L: American Society of Clinical Oncology, 2017.
20	Kourlaba *et al.* (2018)	Kourlaba G, Rapti V, Alexopoulos A, et al. Everolimus plus exemestane versus bevacizumab-based chemotherapy for second-line treatment of hormone receptor-positive metastatic breast cancer in Greece: An economic evaluation study. BMC health services research 2015;15:307.
21	Lambert-Obry *et al.* (2018)	Lambert-Obry V, Gouault-Laliberté A, Castonguay A, et al. Real-world patient-and caregiver-reported outcomes in advanced breast cancer. Current Oncology 2018;25:e282.
22	Lankford *et al.* (2018)	Lankford ML BS BA, Scharf M, Tiscione B, Willey JP. Evolving treatment patterns in hormone receptor-positive, HER2- negative metastatic breast cancer. San Antonio Breast Cancer Symposium 2018.
23	Lewis *et al.* (2020)	Lewis K, Kurosky S, Last M, et al. First-line treatment patterns in HR+/HER2- locally advanced or metastatic breast cancer in Europe. Annals of Oncology 2020.
24	Lupichuk *et al.* (2019)	Lupichuk S, Recaldin B, Nixon N, et al. Real-world experience using exemestane and everolimus in patients with hormone receptor positive/HER2 negative breast cancer with and without prior CDK4/6 inhibitor exposure, In Ccancer Research, Amer Assic Cancer Research 2019.
25	Luhn *et al.* (2018)	Luhn P OHC TT, Sanglier T, Hsieh A, Oliveri D, Chuo J, Xiao Y, Emens L. Time to treatment discontinuation of second-line fulvestrant monotherapy for HR+/HER2− metastatic breast cancer in the real-world setting. San Antonio Breast Cancer Symposium 2018. San Antonio Breast Cancer Symposium 2018.
26	Lux *et al.* (2019)	Lux MP, Lewis K, Rider A, et al. Abstract P2-15-02: BRCA1/2 status, treatment patterns, and safety outcomes in HER2- advanced breast cancer (ABC): Results from the European component of a multi-country real-world study. Cancer Res 2020.
27	Mahtani *et al.* (2020)	Mahtani R, Niyazov A, Lewis K, et al. Real-world multi-country study of treatment trends among patients (pts) with HER2- BRCA1/2 mutated (BRCA1/2mut) advanced breast cancer (ABC). Annals of Oncology 2020.
28	Meade *et al.* (2019)	Meade D, Hensley Alford S, Mahatma S, et al. Abstract P4-09-06: Analyzing the changes in the HR+/HER2- metastatic breast cancer (mBC) landscape since the arrival of CDK4/6 inhibitors with machine learning and visual analytics. Cancer Research 2019;79:P4-09-06-P4-09-06.

	Author, year	Citation
29	Misty *et al.* (2018)	Mistry R, Suri G, Young K, et al. Budget impact of including ribociclib in combination with letrozole on US payer formulary: first-line treatment of post-menopausal women with HR+/HER2− advanced or metastatic breast cancer. Current medical research and opinion 2018;34:2143-2150.
30	Mitra *et al.* (2018)	Mitra D, Taylor-Stokes G, Waller G, et al. Real World Treatment Clinical Outcomes Associated with Palbociclib Combination Therapy in the United States: Results from the IRIS Study. Presented at the 35th Annual Miami Breast Cancer Conference (MBCC); March 8–11, 2018; Miami Beach, FL, USA. 2018.
31	Musicco *et al.* (2019)	Musicco F, Abrate P, Lasala R, et al. Real-world clinical outcomes in metastatic breast cancer patients treated with Palbociclib. Journal of Oncology Pharmacy Practice 2019.
32	NICE GID-TA10262	NICE. Abemaciclib with an aromatase inhibitor for untreated advanced hormone-receptor positive, HER2- negative breast cancer (GID-TA10262) [Accessed at https://www.nice.org.uk/guidance/TA563 on 3rd March 2020]. 2018.
33	NICE TA495	National Institute for Health and Care Excellence (NICE): TA495. Palbociclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2- negative, locally advanced or metastatic breast cancer. 2017. Available at: https://www.nice.org.uk/guidance/ta495. [Last Accessed 29 Aug 2019].
34	NICE TA496	National Institute for Health and Care Excellence (NICE): TA496. Ribociclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2- negative, locally advanced or metastatic breast cancer. 2017. Available at: https://www.nice.org.uk/guidance/ta496. [Last Accessed 29 Aug 2019].
35	Olufade *et al.* (2017)	Olufade T HA, Shenolikar R, et al. Health resource utilization and costs in BRCA-positive metastatic breast cancer patients treated in the community oncology setting. Journal of Managed Care and Specialty Pharmacy 2017;23:S76-S77.
36	Ou *et al.* (2019)	Ou H-T, Chung W-P, Su P-F, et al. Health-related quality of life associated with different cancer treatments in Chinese breast cancer survivors in Taiwan. European Journal of Cancer Care 2019;28:e13069.
37	Palumbo *et al.* (2019)	Palumbo R, Torrisi R, Quaquarini E, et al. Patterns of treatment and outcome of Palbociclib plus endocrine therapy in hormone receptor-positive (HR+)/HER2 receptor-negative (HER2-) metastatic breast cancer (MBC): a real life multicenter Italian study, In Cancer Research, Amer Assoc Cancer Research 2019.
38	Parikh *et al.* (2020)	Parikh RC, Niyazov A, Esteberg E, et al. PCN314 REAL-WORLD PATIENT DEMOGRAPHICS, TREATMENT PATTERNS AND HEALTHCARE RESOURCE UTILIZATION (HRU) AMONG HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR 2 NEGATIVE (HER2-) ADVANCED BREAST CANCER (ABC) PATIENTS WITH BRCA1/2 MUTATIONS (BRCA1/2MUT). Value in Health 2020.
39	Park *et al.* (2019)	Park JA, Koh H, Jung J, et al. PCN492 TREATMENT PATTERN OF HORMONE RECEPTOR-POSITIVE, HUMAN EPIDERMAL GROWTH FACTOR-2 NEGATIVE ADVANCED BREAST CANCER PATIENTS: ANALYSIS OF REAL-WORLD NATIONAL CLAIMS DATA. Value in Health 2019.

	Author, year	Citation
40	Perez-Zincer *et al.* (2020)	Perez-Zincer, Serrano JA, Martinez-Herrera JF, et al. e13053 Real-world clinical outcomes in patients receiving cyclin-dependent kinase 4/6 inhibitors (iCDK 4/6) for hormone receptor-positive, human epidermal growth factor receptor 2-negative (HR+/HER2-) metastatic breast cancer in Mexico. K Clin Oncol 2020.
41	Piccinni *et al.* (2019)	Piccinni C, Dondi L, Ronconi G, et al. HR+/HER2- Metastatic Breast Cancer: Epidemiology, Prescription Patterns, Healthcare Resource Utilisation and Costs from a Large Italian Real-World Database. Clin Drug Investig 2019;39:945-951.
42	Princic *et al.* (2017)	Princic N, Brouillette M, Tang D, et al. Real-world dosing patterns of everolimus-based lines of therapy among post-menopausal women with hormone receptor-positive and human epidermal growth factor receptor-negative (HR+/HER2-) metastatic breast cancer (mBC): American Society of Clinical Oncology, 2017.
43	Quek *et al.* (2018)	Quek R MJ. Real-world outcomes in hormone receptor-positive/ human epidermal growth factor receptor 2-negative metastatic breast cancer: A comparison between younger and older patients with germline BRCA mutation. Journal of Managed Care and Specialty Pharmacy 2018;24:S25.
44	Rajan *et al.* (2020)	Rajan N, Wei A, Cheng R, et al. PCN104 Treatment Patterns and Health Resource Utilization in Patients with HR+/HER2- Locally Advanced or Metastatic Breast Cancer in Real World Setting in Taiwan. Value in Health Regional Issues 2020.
45	Rauthan *et al.* (2020)	Rauthan A, Patil P, Somashekhar SP, et al. e13057 Palbociclib in hormone positive metastatic breast cancer: A real world multicenter Indian experience. J Clin Oncol 2020.
46	Rider *et al.* (2020)	Rider A, Bailey A, Lewis K, et al. PCN361 POOR PROGNOSTIC FACTORS AND THEIR IMPACT ON TREATMENT PATTERNS AND OUTCOMES FOR WOMEN WITH HORMONE RECEPTOR-POSITIVE, HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR-NEGATIVE (HR+/HER2-) ADVANCED BREAST CANCER (ABC) IN CANADA. ISPOR International 2019.
47	Rihova *et al.* (2018)	Rihova B, Demlova R, Cerna R. PCN27-THE REAL-WORLD COST AND EFFECTIVENESS OF EVEROLIMUS IN METASTATIC BREAST CANCER IN THE CZECH REPUBLIC. Value in Health 2018;21:S19.
48	Rugo *et al.* (2019)	Rugo HS, Andre F, Yamashita T, et al. Alpelisib (ALP)+ fulvestrant (FUL) for patients with hormone receptor–positive (HR+), HER2− advanced breast cancer (ABC): Management and time course of key adverse events of special interest (AESIs) in SOLAR-1. Annals of Oncology 2019.
49	Stickeler *et al.* (2019)	Stickeler E, Harbeck N, Thill M, et al. P2-17-01 Therapy of advanced breast cancer for patients with hormone receptor-positive/HER2-negative and HER2-positive tumors is changing in real life: First results from the prospective, national research platform OPAL for patients with advanced breast cancer in Germany. SABCS 2019.
50	Rugo *et al.* (2019)	Rugo HS, Andre F, Yamashita T, et al. Alpelisib (ALP)+ fulvestrant (FUL) for patients with hormone receptor–positive (HR+), HER2− advanced breast cancer (ABC): Management and time course of key adverse events of special interest (AESIs) in SOLAR-1. Annals of Oncology 2019.
51	Tang *et al.* (2017)	Tang DH, Li N, Du EX, et al. First-line treatment disruption among post-menopausal women with HR+/HER2–metastatic breast cancer: a retrospective US claims study. Current medical research and opinion 2017;33:2137-2143.

	Author, year	Citation
52	Taylor-Stokes *et al.* (2020)	Taylor-Stokes G, Zhan L, Mycock KL, et al. Real world treatment patterns and clinical outcomes associated with palbociclib combination therapy in the European countries: Results from the IRIS study. Annals of Oncology 2020.
53	Verhoeven *et al.* (2019)	Verhoeven DMEC, Duhoux FP, de Azambuja E, et al. 224P A critical appraisal of quality indicators of breast cancer treatment in Belgium. Annals of Oncology 2019.
54	Villanueva *et al.* (2018)	Villanueva C, Yazbek G, Beuzeboc P, et al. 335P Breast cancer (BC) treatment (tx) with everolimus (EVE) and exemestane (EXE) in hormone receptor positive (HR+)/HER2- negative (HER2−) postmenopausal women: Final analysis of the French observational TANGO study. Annals of Oncology 2018;29:mdy272. 325.
55	Wan *et al.* (2019)	Wan X, Zhang Y, Ma J, et al. Ribociclib in hormone-receptor-positive advanced breast cancer: Establishing a value-based cost in China. The Breast 2019;43:1-6.
56	Welt *et al.* (2020)	Welt A, Thill M, Stickeler E, et al. What affects the choice of first-line treatment for hormone-receptor-positive, HER2-negative advanced breast cancer? Data from the German research platform OPAL. Annals of Oncology 2020.
57	Zanotti *et al.* (2016)	Zanotti G, Hunger M, Perkins J, et al. Clinical Characteristics, Treatment Patterns And Health Care Utilization In Er+/Her2-Metastatic Postmenopausal Breast Cancer Patients: Results From A Retrospective Medical Record Review In The United States. Value in Health 2016;19:A137-A138.

Abbreviations: SLR: systematic literature review.

B.3.5.1 Intervention and comparators' costs and resource use

Model inputs for costs included within the economic model comprise *PIK3CA* mutation testing, treatment acquisition costs, the costs of treating AEs, costs of post-progression therapy, costs of healthcare resources associated with follow-up and monitoring, and end-of-life costs. Scenario analyses were conducted whereby these categories of costs were excluded in turn, to estimate the impact of these costs on the base case ICER (see Section B.3.8.3).

B.3.5.1.1 PIK3CA mutation testing

PIK3CA mutation testing costs were applied to patients receiving alpelisib plus fulvestrant. The unit cost per *PIK3CA* mutation test (£261.42) was based on the published findings of a study by Hamblin *et al.* (2017),[180] which assessed the technical validation of panel testing and comparative costing of various mutations utilising the existing technologies used in UK clinical practice. The value of *PIK3CA* testing in 2017 from Hamblin *et al.* of £239 was adjusted to a 2020 value of £261.42 using the medical services CPI.[181]

It should be noted that the inclusion of this test on the national directory would likely have an impact on the cost of *PIK3CA* testing, and the cost would likely be reduced with more frequent use. As such, the estimated cost of *PIK3CA* testing is considered to be conservative. Furthermore, *PIK3CA* mutation testing is anticipated to be included in a future iteration of the test directory as part of the adoption of the NHS Genomic Medicine Service and therefore from that point onwards would be a common cost for all patients (i.e. not an additional cost for alpelisib plus fulvestrant). As such, the impact of removing the cost of *PIK3CA* mutation testing was explored in a scenario analysis (see Section B.3.8.3).

The prevalence of *PIK3CA* mutations among breast cancer patients was estimated to be 36.4% based on an SLR of *PIK3CA* mutations in HR+, HER2– metastatic breast cancer by Mollon *et al.* (2018).[182] Lacking data on the rate of invalid *PIK3CA* mutation tests, it was assumed that 0% of tests would yield invalid results. Therefore, 1/36.4% = 2.75 patients were considered to require testing to identify one patient with a *PIK3CA* mutation. The cost of *PIK3CA* mutation testing for each patient receiving alpelisib was therefore estimated to be 2.75 x £261.42 = £718.19 per patient.

B.3.5.1.2 Treatment costs

Medication costs were calculated by combining estimates of the probability of being on therapy by time since therapy initiation with estimates of costs for those patients remaining on therapy. The cost of medication per cycle was calculated by multiplying expected days of medication received per cycle by the expected cost of medication per day of use. For any given model cycle, the expected days of use of medication for each treatment were calculated as the product of TTD at the beginning of that cycle multiplied by a variable representing the average proportion of that cycle receiving treatment. Medication costs per day of use were calculated by multiplying the costs per unit (e.g. mg) by the number of units used per day. Costs per unit were obtained by dividing the list price per pack/vial by the number of mg/ug per pack.

The drug acquisition costs for alpelisib plus fulvestrant and everolimus plus exemestane are summarised in Table 65. Note in the base case economic analyses, given the PAS for everolimus is known to Novartis, the PAS price for everolimus was utilised throughout, as well as the assumed generic price for fulvestrant. [redacted]. For alpelisib, results are presented both at list price and at PAS price.

Table 65: Unit costs of study medications

Drug	Form	Strength per tablet/mL (mg)	Package or vial size	Strength per package or vial, mg	Cost per vial/pack (NHS list price) (£)	Cost per unit (£)	Source
Alpelisib	Tablet	300	28 tablets	8,400	List price: [redacted] PAS price: [redacted]	0.49	Novartis Data on File
Fulvestrant	Injection	250	2 pre-filled disposable injections	500	[redacted]*	0.15	Assumption; BNF[43]
Everolimus	Tablet	10	30 tablets	300	List price: 2,673.00 [redacted]	8.91	eMIT[161]
Exemestane	Tablet	25	30 tablets	750	5.58	0.01	eMIT[161]

*The price of fulvestrant is assumed, based on an [redacted] discount on the originator list price of Faslodex (£522.41).
Abbreviations: BNF: British National Formulary; eMIT: Drugs and Pharmaceutical Electronic Market Information Tool.

Dosing schedules

The dosing schedule for alpelisib plus fulvestrant and everolimus plus exemestane were based on the relevant clinical trials and/or prescribed information and are presented below in Table 66.

Table 66: Dosage schedule by study medication

Drug	Method of administration	Daily dose (mg/µg)	Basis of dose	Days doses per cycle	Cycle length (days)	Max cycles	Source
Alpelisib	Oral	300	Per patient	28	28	-	SOLAR-1 CSR[121]
Fulvestrant (loading)	IM	500	Per patient	2	28	1	SOLAR-1 CSR[121]
Fulvestrant	IM	500	Per patient	1	28	-	SOLAR-1 CSR[121]
Everolimus	Oral	10	Per patient	28	28	-	Yardley *et al.* (2013)[62]
Exemestane	Oral	25	Per patient	30	30	-	Yardley *et al.* (2013)[62]

Abbreviations: CSR: clinical study report; IM: intramuscular.

Relative dose intensity

Mean RDIs for alpelisib plus fulvestrant were based on data from BYLieve, where dose intensity was defined as the actual cumulative dose divided by the planned cumulative dose. For everolimus plus exemestane, mean RDIs were based on reported values from key clinical trials, as shown in Table 67.

Table 67: Mean RDI by drug

Treatment	Drug	Mean RDI	Source
Alpelisib plus fulvestrant	Alpelisib	[redacted]	BYLieve FIR[108]
	Fulvestrant (loading dose)	[redacted]	BYLieve FIR[108]
	Fulvestrant	[redacted]	BYLieve FIR[108]
Everolimus plus exemestane	Everolimus	0.79	BOLERO-2 (Yardley *et al.* [2013])[62]
	Exemestane	0.98	BOLERO-2 (Yardley *et al.* [2013])[62]

Abbreviations: FIR: first interpretable results; RDI: relative dose intensity.

Cost of administration/dispensing

The cost of dispensing alpelisib was assumed to be £10.40 based on the cost of 12 minutes of time for a hospital pharmacist (hourly rate of a hospital pharmacist including qualification, overhead, and salary on-costs £52÷5=£10.40, based on PSSRU estimates from 2020 (Table 68).[183] Facility costs for the administration of fulvestrant were assumed to be £136.03 in the first cycle based on the 2019–2020 NHS reference cost of initial consultation with an oncologist (WF01B – non-consultant led non-admitted face-to-face: service code 370 – Medical Oncology) – assuming that patients initiating fulvestrant would be administered after this visit – and £83.46 thereafter.[184] Facility costs for the administration of the fulvestrant loading dose was based on a weighted average of the outpatient and day case 2019–2020 NHS reference costs for delivery of simple parenteral chemotherapy at first attendance.[184]

Whilst everolimus is an oral medication, and therefore not associated with administration costs, discussion with a clinical expert has indicated that patients treated for ABC would often receive bisphosphonate intravenous for the treatment of any bone metastases. As patients receiving alpelisib plus fulvestrant would attend hospital to receive treatment with fulvestrant, it is assumed that these patients would receive bisphosphonates within the same appointment. However, hospital visits for patients receiving everolimus plus exemestane to receive bisphosphonates would require an additional visit (as they would not be attending hospital already for drug administration). Therefore, within the cost-effectiveness model, it is assumed that 25% of patients receiving everolimus plus exemestane incur a monthly cost of a non-consultant led appointment to account for the administration of bisphosphonates (WF01A – non-consultant led non-admitted face-to-face: service code 370 – Medical Oncology).[184]

Table 68: Administration and dispensing costs for alpelisib and fulvestrant

Drug	Administration cost (£)	Dispensing cost (£)	Source
Alpelisib	-	10.40	Curtis & Burns (2020)[183]
Fulvestrant (loading)	136.03	-	NHS reference costs 2019–2020[184] Curtis & Burns (2020)[183]

Fulvestrant	83.46	-	NHS reference costs 2019–2020[184] Curtis & Burns (2020)[183]
Everolimus	43.10	10.40	NHS reference costs 2019–2020[184]; Curtis & Burns (2020)[183]; clinical expert opinion[1]
Exemestane	-	10.40	Curtis & Burns (2020)[183]

Abbreviations: NICE: National Institute for Health and Care Excellence.

B.3.5.2 Health state unit costs and resource use

B.3.5.2.1 Post-progression treatments

The model does not include explicit health states for subsequent lines of treatment. However, the model does consider medication and administration costs for post-progression treatment. Specific treatments were not considered; rather 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). This is aligned with the approach taken in previous NICE TAs for ABC (TA495, TA496, TA503 and TA687/TA593),[4, 85, 100, 101] and is considered justified as the treatment pathway that patients follow in ABC is varied and will depend on a number of different factors. Given the level of complexity required in deriving a specific treatment flow for the progression health state, it was considered that a simple fixed cost, elicited through clinical validation, would be a reasonable approach.

Based on review of previous NICE TAs of treatments for ABC (TA495, TA496, TA503 and TA687/TA593),[4, 85, 100, 101] there are several treatment options available following disease progression on second-line treatment in the UK. In these appraisals, the monthly post-progression treatment-related costs ranged from £800 to £2,000. In a recent TA of treatment for ABC, however, the ERG concluded that post-progression treatment-related costs of £1,500 per month would be appropriate.[4] In the base case a value of £1,500 per month for post-progression treatment-related costs was used.

B.3.5.2.2 Follow-up and monitoring

Resource use for follow-up and monitoring of patients within the PFS and PPS states were based on recommendations in NICE CG81 and previous NICE technology appraisals in HR+, HER2– ABC.[7]

Table 69: Monthly resource use for follow-up and monitoring services based on NICE CG81, by health state

Service	PFS		PPS	
	Frequency per month	% of patients receiving	Frequency per month	% of patients receiving
GP visit	0.3	100%	0.3	100%
Oncology consultant office	0.2	100%	0.2	100%
Community nurse	0.3	100%	0.3	100%
Clinical nurse specialist	1.0	100%	1.0	100%
CT scan	1.0	100%	1.0	100%

Social worker	-	-	0.5	100%

Abbreviations: CT: computerised tomography; GP: general practitioner; NICE: National Institute for Health and Care Excellence.
Source: NICE CG81.[7]

Estimates of monthly additional treatment-specific follow-up and monitoring services required for patients upon therapy initiation are shown in Table 70. For alpelisib, resource use estimates associated with fasting plasma glucose testing and HbA1c monitoring have been estimated based on the SmPC.

Table 70: Monthly treatment-specific follow-up and monitoring for patients in first month of therapy

Service	Alpelisib plus fulvestrant	Everolimus plus exemestane
Complete blood count	0	1
Fasting plasma glucose	3	0
HbA1c monitoring	1	0

Abbreviations: LFT: liver function test.
Source: Alpelisib SmPC;[38] Afinitor SmPC.[162]

Estimates of additional repeat follow-up and monitoring services for patients while on therapy are shown in Table 71.

Table 71: Monthly treatment-specific follow-up and monitoring for patients while on therapy

Service	Alpelisib plus fulvestrant	Everolimus plus exemestane
Complete blood count	0	0.2
Fasting plasma glucose	1.0	0
HbA1c monitoring	0.3	0

Source: Afinitor SmPC.[162]

Unit costs of all serves for follow-up and monitoring were based on 2019–2020 NHS Reference costs and the PSSRU 2020, and are presented in Table 72.

Table 72: Unit costs for follow-up and monitoring services

Service	Unit cost (£)	Cost source
Complete blood count	2.58	NHS Reference Costs 2019–2020 NHS Trusts and Foundation Trusts. DAPS DAPS05[184]
Fasting plasma glucose	18.03	Unit cost of £6.10 (2006) from Economic Modelling for Vascular checks inflated to £10.23 (2020) based on ONS CPI for Medical Services plus 12 minutes of nurse time from PSSRU 2020 (Table 10.1 Band 5 cost per working hour £39.00/5 = £7.80)[185]
HbA1c monitoring	17.20	Unit cost of £14.40 (2014) from Gillet *et al.* (2015) inflated to £17.20 (20) based on ONS CPI for Medical Services[186]
GP visit	39.23	PSSRU 2020 (cost per surgery consultation lasting 9.22 minutes, including direct care staff cost and with qualification costs)[183]

Oncology consultant office	153.55	NHS Reference Costs 2019–2020 NHS Trusts and Foundation Trusts. Weighted average of first and five follow-up visits for clinical oncology (service code = 800):[184] • CL WF01B Non-Admitted Face-to-Face Attendance, First (£166.19) • CL WF01A Non-Admitted Face-to-Face Attendance, Follow-up (£151.03)
Community nurse	39.00	PSSRU 2020 (cost per working hour, band 5)[183]
Clinical nurse specialist	50.00	PSSRU 2020 (cost per working hour, band 5)[183]
CT Scan	145.35	NHS Reference Costs 2019–2020 NHS Trusts and Foundation Trusts. Total HRG RD24Z Computerised Tomography Scan of Two Areas, with Contrast[184]
Social worker	51.00	PSSRU 2020 (cost per house of client-related work with qualifications)[183]

Abbreviations: CL: Consultant led; CPI: Consumer Prices Index; CT: computerised tomography; DADS: Directly accessed diagnostic services; DAPS: Directly accessed pathology services; GP: general practitioner. LFT: Liver function test; NHA: National Health Service; ONS: Office for National Statistics.

B.3.5.3 Adverse reaction unit costs and resource use

Costs of treatment for AEs were calculated by multiplying the incidence of AEs by the expected cost of these events. The total cost of all AEs per patient was calculated by summing these costs across events. The costs of treatment of AEs (per event) were assumed to be independent of treatment strategy and were estimated using 2019–2020 NHS Reference Costs for HRG codes corresponding to each AE. Estimated costs of AE are shown in Table 73.

Table 73: Estimates of direct medical costs for treatment of Grade 3/4 AEs

AE	Cost per AE (£)	Cost source
Anaemia	601.37	NHS Reference Costs 2019–20 Trusts and Foundation Trusts. Weighted average (based on frequency) of Non-Elective Short Stay: • NES SA44A Single Plasma Exchange or Other Intravenous Blood Transfusion, 19 years and over (£694.28, Frequency: 9,209) • NES SA45A Injection of Rh Immune Globulin or Other Blood Transfusion, 19 years and over (£394.60, Frequency: 4,138)
Diarrhoea	151.03	• NHS Reference Costs 2019–20 Trusts and Foundation Trusts. CL WF01A Non-Admitted Face-to-Face Attendance, Follow-up (Service Code = 800, Clinical Oncology)
Dyspnoea	2,203.86	NHS Reference Costs 2019–20 Trusts and Foundation Trusts. Weighted average (based on frequency) of Other Respiratory Disorders: • NES DZ19H Other Respiratory Disorders with Multiple Interventions (£6,007.06, Frequency: 18) • NES DZ19J Other Respiratory Disorders with Single Intervention, with CC Score 5+ (£1,955.08, Frequency: 119) • NES DZ19K Other Respiratory Disorders with Single Intervention, with CC Score 0-4 (£1,632.52;

		Frequency: 68)
Fatigue	151.03	NHS Reference Costs 2019–20 Trusts and Foundation Trusts. CL WF01A Non-Admitted Face-to-Face Attendance, Follow-up (Service Code = 800, Clinical Oncology)
Hyperglycaemia	552.78	NHS Reference Costs 2019–20 Trusts and Foundation Trusts. Weighted average (based on frequency) of Diabetes with Hyperglycaemia Disorders: • NES KB02G Diabetes with Hyperglycaemic Disorders, with CC Score 8+ (£821.50, Frequency: 5,571) • NES KB02H Diabetes with Hyperglycaemic Disorders, with CC Score 5–7 (£599.45, Frequency: 6,616) • NES KB02J Diabetes with Hyperglycaemic Disorders, with CC Score 2–4 (£493.18, Frequency: 12,059) • NES KB02K Diabetes with Hyperglycaemic Disorders, with CC Score 0–1 (£433.74, Frequency: 9,133)
Increased GGT	151.03	NHS Reference Costs 2019–20 Trusts and Foundation Trusts. WF01A (service code 800 [Clinical Oncology (Previously Radiotherapy)]) Non-admitted face to face attendance, follow-up
Rash	151.03	NHS Reference Costs 2019–20 Trusts and Foundation Trusts. WF01A (service code 800 [Clinical Oncology (Previously Radiotherapy)]) Non-admitted face to face attendance, follow-up
Rash maculopapular	151.03	NHS Reference Costs 2019–20 Trusts and Foundation Trusts. WF01A (service code 800 [Clinical Oncology (Previously Radiotherapy)]) Non-admitted face to face attendance, follow-up
Stomatitis	484.89	NHS Reference Costs 2019–20 Trusts and Foundation Trusts. Weighted average (based on frequency) of Non-Elective Short Stay: • NES CB02A Non-Malignant, Ear, Nose, Mouth, Throat or Neck Disorders, with Interventions, with CC Score 5+ (£2,189.73, Frequency: 1,081) • NES CB02B Non-Malignant, Ear, Nose, Mouth, Throat or Neck Disorders, with Interventions, with CC Score 1–4 (£1,376.08, Frequency: 1,571) • NES CB02C Non-Malignant, Ear, Nose, Mouth, Throat or Neck Disorders, with Interventions, with CC Score 0 (£1,239.70, Frequency: 944) • NES CB02D Non-Malignant, Ear, Nose, Mouth, Throat or Neck Disorders, without Interventions, with CC Score 5+ (£555.94, Frequency: 50,124) • NES CB02E Non-Malignant, Ear, Nose, Mouth, Throat or Neck Disorders, without Interventions, with CC Score 1–4 (£423.20, Frequency: 61,995) • NES CB02F Non-Malignant, Ear, Nose, Mouth, Throat or Neck Disorders, without Interventions, with CC Score 0 (£378.61; Frequency: 34,745)

Abbreviations: AE: adverse event; CL: Consultant led; GGT: gamma-glutamyl transpeptidase.

B.3.5.4 Miscellaneous unit costs and resource use

End-of-life costs were estimated based on the resource use and unit costs reported in NICE CG81.[7] The hospital health services (ONS) index was employed to inflate costs from 2006 to 2020 prices (the most recent year for which the ONS index is available). The total costs associated with end-of-life were estimated to be £6,143.77.

These costs are applied upon entry into the death state by multiplying the estimated cost of terminal care by the marginal death rate in each cycle. In the model, the marginal death rate in cycle t is calculated as 1 minus OS[t] minus the cumulative death rate for since model start. The cumulative death rate is the sum of marginal death rates in all prior cycles.

Table 74: Terminal care resource use and unit costs

Clinical setting	% of deaths	Unit cost (£) (2006/2007)	Unit cost total (£) (2020)
Hospital	40%	4,706	6,143.77
Marie Curie hospice	10%	5,867	
At home (with community support)	50%	2,428	

Source: NICE CG81.[7]

B.3.6 Summary of base case analysis inputs and assumptions

B.3.6.1 Summary of base case analysis inputs

A summary of the base case model inputs is provided in Table 75.

Table 75: Summary of variables applied in the economic model

Variable	Value	Measurement of uncertainty: SE (distribution)	Reference to section in submission
Model settings			
Discount rate (costs)	3.5%	N/A (Normal)	B.3.2
Discount rate (benefits)	3.5%	N/A (Normal)	
Time horizon	Lifetime (40 years)	N/A	
Patient characteristics			
Starting age (years)	57	N/A (Normal)	B.3.2.2
Percent female	100%	N/A	B.3.3.5
RDI			
Alpelisib as a component of alpelisib plus fulvestrant	[redacted]	[redacted] (Beta)	B.3.5.1
Fulvestrant, loading as a component of alpelisib plus fulvestrant	[redacted]	N/A	
Fulvestrant as a component of alpelisib plus fulvestrant	[redacted]	N/A	

Everolimus as a component of everolimus plus exemestane	0.79	0.08 (Beta)	
Exemestane as a component of everolimus plus exemestane	0.98	0.10 (Beta)	
Probabilities of AEs: alpelisib plus fulvestrant			
Diarrhoea	0.06	0.02 (Beta)	B.3.3.4
Dyspnoea	0.02	0.01 (Beta)	
Fatigue	0.01	0.01 (Beta)	
Hyperglycaemia	0.28	0.02 (Beta)	
Rash	0.09	0.03 (Beta)	
Rash maculopapular	0.09	0.03 (Beta)	
Stomatitis	0.02	0.01 (Beta)	
Probabilities of AEs: everolimus plus exemestane			
Anaemia	0.08	0.01 (Beta)	B.3.3.4
Diarrhoea	0.03	0.01 (Beta)	
Dyspnoea	0.06	0.01 (Beta)	
Fatigue	0.05	0.01 (Beta)	
Hyperglycaemia	0.06	0.01 (Beta)	
Increased GGT	0.07	0.01 (Beta)	
Rash	0.01	0.00 (Beta)	
Stomatitis	0.08	0.01 (Beta)	
AE costs			
Anaemia	601.37	60.14 (Gamma)	B.3.5.3
Diarrhoea	151.03	15.10 (Gamma)	
Dyspnoea	2,203.86	220.39 (Gamma)	
Fatigue	151.03	15.10 (Gamma)	
Hyperglycaemia	552.78	55.28 (Gamma)	
Increased GGT	151.03	15.10 (Gamma)	
Rash	151.03	15.10 (Gamma)	
Rash maculopapular	151.03	15.10 (Gamma)	
Stomatitis	484.89	48.49 (Gamma)	
Drug acquisition costs (list price)			
Alpelisib	[redacted]	N/A	B.3.5.1.2
Fulvestrant	[redacted]	N/A	
Everolimus	2,673.00	N/A	
Exemestane	5.58	N/A	
Drug administration and dispensing costs			
Administration cost of fulvestrant (loading)	136.03	13.60 (Gamma)	B.3.5.1.2
Administration cost of fulvestrant	83.46	8.35 (Gamma)	
Dispensing cost of alpelisib	10.40	1.04 (Gamma)	
Dispensing cost of everolimus	10.40	1.04 (Gamma)	
Dispensing cost of exemestane	10.40	1.04 (Gamma)	

Administration cost for bisphosphonates (additional costs for patients receiving everolimus plus exemestane compared with patients receiving alpelisib plus fulvestrant)	43.10	4.31 (Gamma)	
Terminal care			
Cost of terminal care	6,143.77	614.38 (Gamma)	B.3.5.4
Costs of follow-up and monitoring			
Initial and repeat follow-up, cost of complete blood count	2.58	0.26 (Gamma)	B.3.5.2.2
Initial and repeat follow-up, cost of fasting plasma glucose	18.03	1.80 (Gamma)	
Initial and repeat follow-up, cost of HbA1C monitoring	17.20	1.72 (Gamma)	
Repeat services, cost of GP visits	39.23	3.92 (Gamma)	
Repeat services, cost of oncology consultant office	153.55	15.36 (Gamma)	
Repeat services, cost of community nurse	39.00	3.90 (Gamma)	
Repeat services, cost of clinical nurse specialist	50.00	5.00 (Gamma)	
Repeat services, cost of CT scan	145.35	14.54 (Gamma)	
Repeat services, cost of social worker	51.00	5.10 (Gamma)	
Health state utility values			
Mean utility value at baseline	[redacted]	[redacted]	B.3.4.5
PFS on treatment utility, alpelisib plus fulvestrant	[redacted]	[redacted]	
PFS on treatment utility, everolimus plus exemestane	[redacted]	[redacted]	
PFS off treatment utility, alpelisib plus fulvestrant	[redacted]	[redacted]	
PFS off treatment utility, everolimus plus exemestane	[redacted]	[redacted]	
PPS base utility, alpelisib plus fulvestrant	[redacted]	[redacted]	
PPS base utility, everolimus plus exemestane	[redacted]	[redacted]	
Disutility applied within 28 days of death	[redacted]	[redacted]	
General population utility values			
Entered female general population utility, age category 1	0.9010	N/A	B.3.4.5
Entered female general population utility, age category 2	0.8710	N/A	

Entered female general population utility, age category 3	0.8420	N/A	
Entered female general population utility, age category 4	0.8230	N/A	
Entered female general population utility, age category 5	0.7900	N/A	
Entered female general population utility, age category 6	0.7360	N/A	
Entered male general population utility, age category 1	0.9010	N/A	
Entered male general population utility, age category 2	0.8710	N/A	
Entered male general population utility, age category 3	0.8420	N/A	
Entered male general population utility, age category 4	0.8230	N/A	
Entered male general population utility, age category 5	0.7900	N/A	
Entered male general population utility, age category 6	0.7360	N/A	
Efficacy			
HR applied to PFS segment 1: everolimus plus exemestane	[redacted]	[redacted]	
HR applied to PPS segment 1: everolimus plus exemestane	[redacted]	[redacted]	
HR applied to TTD segment 1: everolimus	1.27	0.12 (Lognormal [HR])	
HR applied to TTD segment 1: exemestane	1.27	0.12 (Lognormal [HR])	
Parametric distributions			
PFS for alpelisib plus fulvestrant	Lognormal	N/A	B.3.3.1
OS for alpelisib plus fulvestrant	Log-logistic	N/A	B.3.3.2
TTD for alpelisib	Exponential	N/A	B.3.3.3
TTD for fulvestrant	Exponential	N/A	

Abbreviations: AE: adverse event; CT: computerised tomography; GGT: gamma-glutamyl transpeptidase; GP: general practitioner; HR: hazard ratio; OS: overall survival; PFS: progression-free survival; PPS: post-progression survival; N/A: not applicable; RDI: relative dose intensity; SE: standard error; TTD: time to discontinuation.

B.3.6.2 Assumptions

The key assumptions used in the base case analysis are described in Table 76, with a description of the scenarios conducted to explore the potential impact of these assumptions, where appropriate.

Table 76: Key model assumptions and inputs

Model input	Source/assumption	Justification
Estimation of PFS and OS for alpelisib plus fulvestrant and everolimus plus exemestane	• Alpelisib plus fulvestrant: Derived from second-line data of the BYLieve trial • Everolimus plus exemestane: Derived from a Bucher ITC of second-line data for alpelisib plus fulvestrant and everolimus plus exemestane from a network including SOLAR-1 and BOLERO-2	• Data were used directly from the BYLieve trial to estimate PFS and OS for alpelisib plus fulvestrant in the BYLieve trial. A range of alternative parametric distributions fit to the PFS/OS curves for alpelisib plus fulvestrant from the second-line population of BYLieve (based on the top six best-fitting curves) were tested to explore the impact of alternative distributions (see Section B.3.8.3) • In the absence of published data for everolimus plus exemestane in the post-CDK4/6i population, estimates of relative efficacy in terms of PFS and OS between alpelisib plus fulvestrant and everolimus plus exemestane were derived from an ITC of second-line data from the SOLAR-1 and BOLERO-2 trials. • The proportional hazards assumption held within the second-line populations of SOLAR-1 and BOLERO-2 (as described in Section B.2.7). Therefore, a frequentist approach (Bucher approach) was considered appropriate. SOLAR-1 data were included (rather than BYLieve) as BYLieve could not be included in the network for the ITC given its single-arm design
Estimation of TTD	• TTD for alpelisib plus fulvestrant was estimated separately for alpelisib and fulvestrant, based on data from the second-line population of the BYLieve trial • TTD for everolimus plus exemestane was estimated using a HR between PFS and TTD derived from the BOLERO-2 trial	• For alpelisib plus fulvestrant, scenario analyses were conducted whereby a range of alternative parametric distributions fit to the TTD curve for alpelisib and fulvestrant (based on the top six best-fitting curves) were explored (see Section B.3.8.3) • For everolimus plus exemestane, scenario analyses were conducted for both populations to explore the impact of using the upper and lower limits of the 95% CI for the HR between PFS and TTD for everolimus plus exemestane (see Section B.3.8.3)
AEs	• AEs considered in the model were all-cause ≥Grade 3 AEs with an incidence ≥5% for either alpelisib plus fulvestrant (from BYLieve) or everolimus plus exemestane (from BOLERO-2) • The impact of AEs on HRQoL associated with alpelisib plus fulvestrant and everolimus plus exemestane was assumed to be captured in the health state utility values • The costs of treatment of AEs (per event) were	• The costs of grade 1 or 2 AEs were not considered because they are generally self-limiting and are therefore not likely to be associated with substantial treatment costs or reductions in HRQoL • The application of a disutility for AEs for alpelisib plus fulvestrant and everolimus plus exemestane would have led to double counting • The effect of removing AE costs is explored in a scenario analysis (see Section B.3.8.3)

	assumed to be independent of treatment strategy and were estimated using 2019–2020 NHS Reference Costs	
Health state utility values	• Health state utility values were derived from EQ-5D data from the second-line population from SOLAR-1 for alpelisib plus fulvestrant and BOLERO-2 for everolimus plus exemestane • For alpelisib plus fulvestrant, EQ-5D-3L utility values were estimated using patient item responses to the EQ-5D-5L and the response mapping algorithm developed by van Hout et al. (2012)[165] • For everolimus plus exemestane, utility values were obtained by mapping from the EORTC QLC-C30 to the EQ-5D	• EQ-5D data were not collected from BYLieve; therefore, utility values from the second-line population of SOLAR-1 were considered to be an appropriate proxy, given that all patients in BYLieve Cohort A were second-line or beyond in the treatment pathway for ABC, and SOLAR-1 included both first- and second-line ABC patients • Utility values for both alpelisib plus fulvestrant and everolimus plus exemestane were mapped to the EQ-5D in line with the NICE reference case • The impact of varying the utility values utilised in the model are explored in scenario analyses (see Section B.3.8.3)
PIK3CA mutation testing	• *PIK3CA* mutation testing costs were applied to patients receiving alpelisib plus fulvestrant • The unit cost per *PIK3CA* mutation test was £261.42 • The prevalence of *PIK3CA* mutations among breast cancer patients was estimated to be 36.4% (Mollon *et al.* [2018])[182] • It was assumed that 0% of tests would yield invalid results	• The unit cost per *PIK3CA* mutation test (£261.42) was based on the published findings of a study by Hamblin and colleagues,[180] which assessed the technical validation of panel testing and comparative costing of various mutations utilising the existing technologies used in UK clinical practice • Lacking data on the rate of invalid *PIK3CA* mutation tests, it was assumed that 0% of tests would yield invalid results • *PIK3CA* mutation testing will be included in a future iteration of the test directory as part of the adoption of the NHS Genomic Medicine Service and would therefore from that point onwards be a common cost for all patients (i.e. not an additional cost for alpelisib plus fulvestrant). Thus, the effect of removing this cost is explored in scenario analyses (see Section B.3.8.3)
Treatment costs	• Given the PAS for everolimus is known to Novartis, the PAS price for everolimus ([redacted] per pack) was utilised throughout the base case cost-effectiveness analyses. For alpelisib, results are presented both at list price and at PAS price (list price: [redacted] per pack; PAS price: [redacted] per pack) • Cost of fulvestrant (assumed generic price per vial, representing a [redacted] discount on the originator list price of	• The assumptions made with regards to treatment costs most accurately reflect the costs of treatment that would be incurred by the NHS; costs were sourced from the BNF 2020 online where possible[43] • Administration and dispensing costs were derived from the PSSRU 2020 and 2019–2020 NHS reference costs[158]

	Faslodex [£522.41]): £[redacted] • Cost of exemestane (list price per pack): £5.58 • The cost of dispensing alpelisib was assumed to be £10.40 • Facility costs for the administration of fulvestrant were assumed to be £136.03 in the first cycle and £83.46 thereafter	
Post-progression treatments	• A value of £1,500 per month for post-progression treatment-related costs was used for both base cases	• Based on review of previous NICE technology appraisals of treatments for ABC (TA495, TA496 and TA503),[85, 100, 101] there are several treatment options available following disease progression on second-line in the UK. In these appraisals, the monthly post-progression treatment-related costs ranged from £800 to £2,000. In a recent TA of treatment for ABC,[4] however, the ERG concluded that post-progression treatment-related costs of £1,500 per month would be most appropriate • The effect of removing this cost is explored in scenario analyses (see Section B.3.8.3)
Follow-up and monitoring	• Resource use for follow-up and monitoring of patients within the PFS and PPS states were based on recommendations in NICE CG81 and previous NICE technology appraisals in HR+, HER2− ABC • Unit costs of all services for follow-up and monitoring were based on 2019–2020 NHS Reference costs and the PSSRU 2020	• Resource use estimates for follow-up and monitoring were based on published clinical guidelines and recent NICE appraisals in the same indication • The effect of removing these costs is explored in scenario analyses (see Section B.3.8.3)
End-of-life costs	• End-of-life costs were estimated based on the resource use and unit costs reported in NICE CG81[7] • The terminal care cost was £6,143.77	• The effect of removing this cost is explored in scenario analyses (see Section B.3.8.3)

Abbreviations: ABC: advanced breast cancer; AE: adverse event; BNF: British National Formulary; EORTC QLQ-C30: European Organisation for Research and Treatment Quality of Life Questionnaire; EQ-5D: EuroQoL-5 Dimensions; HER2: human epidermal growth factor receptor 2; HR: hazard ratio; HR: hormone receptor; HRQoL: health-related quality of life; ITC: indirect treatment comparison; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; NMA: network meta-analysis; PAS: patient access scheme; *PIK3CA*: phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PFS: progression-free survival; PPS: post-progression survival; Personal Social Services Research Unit; RCT: randomised controlled trial; RDI: relative dose intensity; TA: technology appraisal; TTD: time to discontinuation.

B.3.7 Base case cost-effectiveness analysis results

The base case results are presented in Table 77 (with alpelisib at PAS price) and Table 78 (with alpelisib at list price).

In the base case analysis (when alpelisib is provided with the confidential PAS discount, applying the known PAS discount of everolimus and with an assumed discount of [redacted] for fulvestrant), alpelisib plus fulvestrant was associated with increased QALYs ([redacted]) and increased costs ([redacted]) versus everolimus plus exemestane, resulting in an ICER of £49,907. As these patients meet NICE's end-of-life criteria (and therefore considering a willingness-to-pay threshold of £50,000 per QALY gained), alpelisib plus fulvestrant represents a cost-effective use of NHS resources in this population.

Table 77: Base case results – WITH PAS

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Alpelisib plus fulvestrant	[redacted]	2.36	[redacted]	[redacted]	0.62	[redacted]	49,907
Everolimus plus exemestane	[redacted]	1.73	1.21	-	-	-	-

Abbreviations: AI: aromatase inhibitor; CDK: cyclin-dependent kinase; ICER: incremental cost-effectiveness ratio; LYG: life years gained; PAS: patient access scheme; QALYs: quality-adjusted life years.

Table 78: Base case results – LIST PRICE

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Alpelisib plus fulvestrant	[redacted]	2.36	[redacted]	[redacted]	0.62	[redacted]	[redacted]
Everolimus plus exemestane	[redacted]	1.73	1.21	-	-	-	-

Abbreviations: AI: aromatase inhibitor; CDK: cyclin-dependent kinase; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years.

B.3.8 Sensitivity analyses

B.3.8.1 Probabilistic sensitivity analysis

Probabilistic sensitivity analyses (PSA) were conducted in order assess the simultaneous effect of uncertainty in the different model parameters. A Monte-Carlo simulation with 1,000 iterations was performed and, in each iteration, model inputs were randomly sampled from the specified probability distributions in Table 79.

For selected parameters derived from BYLieve (i.e., parametric survival distributions), the model samples from the joint bootstrap distributions for these parameter estimates that were derived from bootstrap samples of data from the BYLieve trial. The use of the bootstrap distributions for the parameter estimates ensures that the parameters of the survival distributions PFS, OS, and TTD, as well as the other parameters derived from the BYLieve trial, are appropriately correlated.

The majority of input parameters were varied, and an arbitrary SE of 10% around the mean was assumed when the SE or 95% CI was not available. For each simulation, expected costs and QALYs were calculated for each comparator, along with the differences between comparators in expected costs and QALYs.

Table 79: PSA parameters and distributions

Parameter	Distribution	Mean	Alpha	Beta	SE
RDI					
Alpelisib as a component of alpelisib plus fulvestrant	Beta	[redacted]	[redacted]	[redacted]	[redacted]
Everolimus as a component of everolimus plus exemestane	Beta	0.79	20.21	5.37	0.08
Exemestane as a component of everolimus plus exemestane	Beta	0.98	1.02	0.02	0.10
Probabilities of AEs: alpelisib plus fulvestrant					
Diarrhoea	Beta	0.06	6.94	119.06	0.02
Dyspnoea	Beta	0.02	2.98	123.02	0.01
Fatigue	Beta	0.01	0.99	125.01	0.01
Hyperglycaemia	Beta	0.28	35.72	90.28	0.04
Rash	Beta	0.09	11.91	114.09	0.03
Rash maculopapular	Beta	0.09	11.91	114.09	0.03
Stomatitis	Beta	0.02	1.98	124.02	0.01
Probabilities of AEs: everolimus plus exemestane					
Anaemia	Beta	0.08	38.48	442.52	0.01
Diarrhoea	Beta	0.03	14.43	466.57	0.01
Dyspnoea	Beta	0.06	28.86	452.14	0.01
Fatigue	Beta	0.05	24.05	456.95	0.01
Hyperglycaemia	Beta	0.06	28.86	452.14	0.01
Increased GGT	Beta	0.07	33.67	447.33	0.01
Rash	Beta	0.01	4.81	476.19	0.00
Stomatitis	Beta	0.08	38.48	442.52	0.01
AE costs					
Anaemia	Gamma	601.37			60.14
Diarrhoea	Gamma	151.03	-15153.65	15053.31	15.10
Dyspnoea	Gamma	2203.86	-222490.34	222389.39	220.39
Fatigue	Gamma	151.03	-15153.65	15053.31	15.10
Hyperglycaemia	Gamma	552.78	-55730.40	55629.58	55.28
Increased GGT	Gamma	151.03	-15153.65	15053.31	15.10
Rash	Gamma	151.03	-15153.65	15053.31	15.10

Rash maculopapular	Gamma	151.03	-15153.65	15053.31	15.10
Stomatitis	Gamma	484.89	-48873.84	48773.05	48.49
Drug administration and dispensing costs					
Administration cost of fulvestrant, loading	Gamma	136.03	-100.2648522	-13638.73	13.60
Administration cost of fulvestrant	Gamma	83.46	-99.80185297	-8329.68	8.35
Dispensing cost of alpelisib	Gamma	10.4	-950.40	859.02	1.04
Dispensing cost of everolimus	Gamma	10.4	-950.40	859.02	1.04
Dispensing cost of exemestane	Gamma	10.4	-950.40	859.02	1.04
Administration cost for bisphosphonates (additional costs for patients receiving everolimus plus exemestane compared with patients receiving alpelisib plus fulvestrant)	Gamma	43.10	-4252.76	4154.08	4.31
Terminal care costs					
Cost of terminal care	Gamma	6143.77	-620420.77	620319.79	614.38
Costs of follow-up and monitoring					
Initial and repeat follow-up, cost of complete blood count	Gamma	2.58	-160.29	98.09	0.26
Initial and repeat follow-up, cost of fasting plasma glucose	Gamma	18.03	-1721.43	1625.97	1.80
Initial and repeat follow-up, cost of HbA1C monitoring	Gamma	17.20	-1637.53	1542.34	1.72
Repeat services, cost of GP visits	Gamma	39.23	-3862.23	3763.78	3.92
Repeat services, cost of oncology consultant office	Gamma	153.55	-15409.02	15308.67	15.36
Repeat services, cost of community nurse	Gamma	39.00	-3839.00	3740.56	3.90

Repeat services, cost of clinical nurse specialist	Gamma	50.00	-4950.00	4851.00	5.00
Repeat services, cost of CT scan	Gamma	145.35	-14580.40	14480.09	14.54
Repeat services, cost of social worker	Gamma	51.00	-5051.00	4951.96	5.10
Health state utility values					
Mean utility value at baseline	Beta	[redacted]	[redacted]	[redacted]	[redacted]
PFS on treatment utility, alpelisib plus fulvestrant	Multivariate Normal	[redacted]	[redacted]	[redacted]	[redacted]
PFS on treatment utility, everolimus plus exemestane	Multivariate Normal	[redacted]	[redacted]	[redacted]	[redacted]
PFS off treatment utility	Multivariate Normal	[redacted]	[redacted]	[redacted]	[redacted]
PPS base utility	Multivariate Normal	[redacted]	[redacted]	[redacted]	[redacted]
Disutility applied within 28 days of death	Multivariate Normal	[redacted]	[redacted]	[redacted]	[redacted]
Efficacy					
HR applied to PFS segment 1: everolimus plus exemestane	Lognormal (HR)	[redacted]	[redacted]	[redacted]	[redacted]
HR applied to PPS segment 1: everolimus plus exemestane	Lognormal (HR)	[redacted]	[redacted]	[redacted]	[redacted]
HR applied to TTD segment 1: everolimus	Lognormal (HR)	1.27	-30.57	6.50	0.12
HR applied to TTD segment 1: exemestane	Lognormal (HR)	1.27	-30.57	6.50	0.12

Abbreviations: AE: adverse event; CT: computerised tomography; GGT: gamma-glutamyl transpeptidase; GP: general practitioner; HR: hazard ratio; PFS: progression-free survival; PPS: post-progression survival; PSA: probabilistic sensitivity analysis; RDI: relative dose intensity; SE: standard error; TTD: time to discontinuation.

Results of the PSA

The results of the PSA (1,000 iterations) are presented in Table 80 (with alpelisib at PAS price) and Table 81 (with alpelisib at list price).

Table 80: PSA results – WITH PAS

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)

Alpelisib plus fulvestrant	[redacted]	[redacted]	[redacted]	[redacted]	55,492
Everolimus plus exemestane	[redacted]	1.35	-	-	-

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; PAS: patient access scheme; QALYs: quality-adjusted life years.

Table 81: PSA results – LIST PRICE

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Alpelisib plus fulvestrant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Everolimus plus exemestane	[redacted]	1.35	-	-	-

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; PAS: patient access scheme; QALYs: quality-adjusted life years.

Scatter plots showing the incremental costs and QALYs from the 1,000 iterations of the PSA for alpelisib plus fulvestrant versus everolimus plus exemestane are presented in Figure 30 (with alpelisib at PAS price) and Figure 31 (with alpelisib at list price), respectively.

Figure 30: Cost-effectiveness plane – WITH PAS

Abbreviations: PAS: patient access scheme; PSA: probabilistic sensitivity analysis; QALYs: quality-adjusted life years.

Figure 31: Cost-effectiveness plane – LIST PRICE

Abbreviations: PSA: probabilistic sensitivity analysis; QALYs: quality-adjusted life years.

Cost-effectiveness acceptability curves for alpelisib plus fulvestrant versus everolimus plus exemestane are presented in Figure 30 (with alpelisib at PAS price) and Figure 31 (with alpelisib at list price), respectively.

Figure 32: Cost-effectiveness acceptability curve – WITH PAS

Abbreviations: PAS: patient access scheme; WTP: willingness to pay.

Figure 33: Cost-effectiveness acceptability curve – LIST PRICE

Abbreviations: WTP: willingness-to-pay.

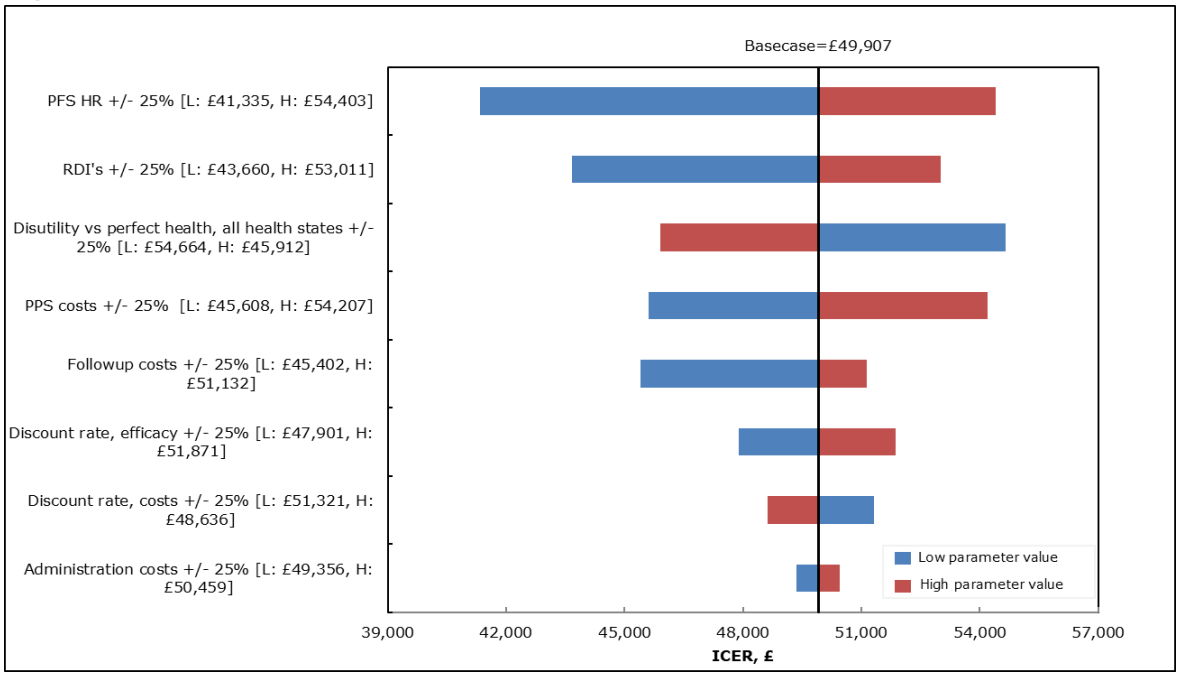
B.3.8.2 Deterministic sensitivity analysis

Deterministic sensitivity analyses (DSA) were undertaken to explore the impact of changing assumptions concerning key model parameter values on the base case ICERs. Parameters were varied by +/- 25% in order to assess the relative impact of these parameters on the cost-effectiveness estimates.

The tornado diagrams showing the key drivers of the DSA are presented in Figure 34 (with alpelisib at PAS price) and Figure 35 (with alpelisib at list price), respectively.

In both sensitivity analyses, the key drivers were the RDIs and the HR for PFS between alpelisib plus fulvestrant and everolimus plus exemestane. However, in general, the ICER was robust, varying between £41,335 and £54,664 for alpelisib plus fulvestrant (with alpelisib at PAS price) and [redacted] to [redacted] (with alpelisib at list price).

Figure 34: DSA – WITH PAS



Abbreviations: DSA: deterministic sensitivity analysis; HR: hazard ratio; ICER: incremental cost-effectiveness ratio; OS: overall survival; PAS: patient access scheme; PFS: progression-free survival; PPS: post-progression survival; RDI: relative dose intensity.

Figure 35: DSA – LIST PRICE

Abbreviations: AI: aromatase inhibitor; CDK: cyclin-dependent kinase; DSA: deterministic sensitivity analysis; HR: hazard ratio; ICER: incremental cost-effectiveness ratio; OS: overall survival; PFS: progression-free survival; PPS: post-progression survival; RDI: relative dose intensity.

B.3.8.3 Scenario analyses

Alpelisib plus fulvestrant: PFS

In the base case analysis, the efficacy of alpelisib plus fulvestrant in terms of PFS and OS was estimated based on data from the second-line population of the BYLieve trial, extrapolated based on a lognormal distribution (see Section B.3.3). Scenario analyses were conducted whereby a range of alternative parametric distributions fit to the PFS curve for alpelisib plus fulvestrant from BYLieve (based on the top five best-fitting curves) were explored. The results of these scenarios are presented below and demonstrate that for every alternative distribution explored, the ICER decreases, thus the base case distribution choice can be considered to be conservative.

Table 82: Alpelisib plus fulvestrant PFS scenario analyses

Description	LIST PRICE			WITH PAS		
	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Base case: lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	49,907
Loglogistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	47,885
RCS 3 Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	43,660
RCS 3 Loglogistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	39,388
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	45,843
RCS 3 Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	45,765

Abbreviations: ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; PFS: progression-free survival; QALY: quality-adjusted life year; RCS: restricted cubic spline.

Alpelisib plus fulvestrant: OS

In the base case analysis, the efficacy of alpelisib plus fulvestrant in terms of PFS and OS was estimated based on data from the second-line population of the BYLieve trial (see Section B.3.3). Scenario analyses were conducted whereby a range of alternative parametric distributions fit to the OS curve for alpelisib plus fulvestrant from BYLieve (based on the top six best-fitting curves) were explored. The results of these scenarios are presented below. It should be noted that the projected hazards for the Gompertz, Weibull, and RCS 1 Weibull are constantly increasing, which is inconsistent with the observed hazard rates. In addition, both the Gompertz and Weibull yield projected OS that is less than projected PFS by five years. As such, the scenario analyses using the Gompertz and Weibull distributions are presented for transparency only, given that these distributions are not clinically plausible. The results of these scenarios demonstrate that the chosen curve for the base case analysis can be considered appropriate based on clinical plausibility and appears to be intermediate among the other best fitting models.

Table 83: Alpelisib plus fulvestrant OS scenario analyses

Description	LIST PRICE			WITH PAS		
	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Base case: Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	49,907

Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	94,598
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	71,376
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	45,826
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	45,124
RCS 1 Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	79,575

Abbreviations: ICER: incremental cost-effectiveness ratio; OS: overall survival; PAS: patient access scheme; QALY: quality-adjusted life year; RCS: restricted cubic spline.

Alpelisib: TTD

In the base case analysis, TTD for alpelisib plus fulvestrant was estimated separately for alpelisib and fulvestrant, based on data from the second-line population of the BYLieve trial (see Section B.3.3). Scenario analyses were conducted whereby a range of alternative parametric distributions fit to the TTD curve for alpelisib from BYLieve (based on the top five best-fitting curves) were explored. The results of these scenarios are presented below.

Table 84: Alpelisib TTD scenario analyses

Description	LIST PRICE			WITH PAS		
	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Base case: Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	49,907
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	55,801
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	55,577
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	55,940
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	55,932
RCS 1 Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	55,897

Abbreviations: ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; QALY: quality-adjusted life year; RCS: restricted cubic spline; TTD: time to discontinuation.

Fulvestrant: TTD

Scenario analysis were conducted whereby a range of alternative parametric distributions fit to the TTD curve for fulvestrant from BYLieve (based on the top 6 best-fitting curves) were explored. The results of these scenarios are presented below, and demonstrate that the choice of parametric distribution to model TTD for fulvestrant has minimal impact on the base case ICER.

Table 85: Fulvestrant TTD scenario analyses

Description	LIST PRICE			WITH PAS		
	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Base case: Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	49,907
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	49,953
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	49,954

Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	49,949
RCS 1 Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	49,951
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	49,941

Abbreviations: ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; QALY: quality-adjusted life year; RCS: restricted cubic spline; TTD: time to discontinuation.

Everolimus plus exemestane: HRs for PFS, OS and TTD

In the base case analysis, efficacy for everolimus plus exemestane in terms of PFS and OS was estimated using a HR derived from a Bucher ITC using second-line SOLAR-1 and BOLERO-2 data (see Section B.3.3). To explore the impact of any uncertainty in these HRs, scenario analyses were conducted whereby the upper limits of the 95% CIs for each HR were used.

An additional scenario was conducted using the HRs for PFS and OS derived from the PAIC. This scenario had a minimal impact on the base case ICER. As described above, Novartis acknowledge the limitations associated with this PAIC approach (as described in B.2.7.4), hence why the Bucher ITC was utilised in the base case. However, the PAIC provides supportive evidence for a potentially beneficial effect of alpelisib plus fulvestrant versus everolimus plus exemestane using an alternative methodology, and investigation of this approach is in line with ERG feedback from the terminated NICE appraisal for alpelisib plus fulvestrant in 2020.

In the base case analysis, TTD for everolimus plus exemestane was estimated using a HR between PFS and TTD derived from the BOLERO-2 trial. Scenario analyses were conducted to explore the impact of using the upper and lower limits of the 95% CI for the HR between PFS and TTD. These scenarios had a minimal impact on the base case ICER.

Table 86: Everolimus plus exemestane efficacy and TTD scenario analyses

Description	LIST PRICE			WITH PAS		
	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Base case: PFS HR: [redacted] OS HR: [redacted] TTD HR (vs PFS): [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	49,907
PFS HR (upper 95% CI bound: [redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	44,012
OS HR (upper 95% CI bound: [redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	39,316
PAIC: PFS HR: [redacted] OS HR: [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	49,757
TTD HR (vs PFS) (upper 95% CI bound: [redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	52,465

TTD HR (vs PFS) (lower 95% CI bound: [redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	46,539

Abbreviations: CI: confidence interval; HR: hazard ratio; ICER: incremental cost-effectiveness ratio; OS: overall survival; PAS: patient access scheme; PFS: progression-free survival; QALY: quality-adjusted life year; TTD: time to discontinuation.

Cost scenarios

The base case analysis includes the costs associated with *PIK3CA* testing, all-cause ≥Grade 3 AEs with an incidence ≥5% for either alpelisib plus fulvestrant or everolimus plus exemestane, follow-up and monitoring costs, a monthly post-progression therapy cost (£1,500.00 per month) and terminal care costs (£6,143.77) (see Section B.3.5).

Scenario analyses were conducted whereby these categories of costs were excluded, to estimate the impact of these costs on the base case ICER. The results of these scenarios are presented below and demonstrate that the inclusion or exclusion of *PIK3CA* testing costs, AE costs, or terminal care costs has a minimal impact on the base case ICER. In particular, exclusion of *PIK3CA* testing costs results in a decrease to the base case ICERs (at both list and PAS price), from [redacted] and £49,907 to [redacted] and £48,369, respectively indicating its inclusion in the base case is a conservative approach given *PIK3CA* testing is anticipated to be included in the NHS Genomic Test Directory in the near future. The categories of costs with the largest impact on the base case ICER are follow-up and monitoring costs and post-progression therapy costs. The impact of increasing or decreasing these categories of costs by +/- 25% is explored in the DSA in Section B.3.8.2.

Table 87: Cost scenarios

Description	LIST PRICE			WITH PAS		
	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Base case: inclusion of all costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	49,907
Exclusion of *PIK3CA* testing costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	48,369
Exclusion of AE costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	49,956
Exclusion of follow-up and monitoring costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	44,863
Exclusion of post-progression costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	32,709
Exclusion of terminal care costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	50,201

Abbreviations: AE: adverse event; ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; *PIK3CA*: phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; QALY: quality-adjusted life year.

Utility values

The base case analysis includes health state utility values for BYLieve based on data for second-line patients from SOLAR-1 (see Section B.3.4). Scenario analyses were conducted to explore the impact of using the upper and lower limits of the 95% CI for these utility values. These scenarios had a minimal impact on the base case ICER. An additional scenario was conducted using the literature value of 0.505 as the estimate for PPS utility.[94] This has a reasonably large effect on the ICER; however as described in Section B.3.4 and based on clinical expert opinion, this estimate is considered to be less clinically valid than the estimate used in the base case.

Table 88: Utility values scenario

Description	LIST PRICE			WITH PAS		
	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Base case: PFS on treatment (alpelisib plus fulvestrant): [redacted] PFS off treatment: [redacted] PPS: [redacted] Terminal phase (disutility): [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	49,907
PFS on treatment (alpelisib plus fulvestrant) (upper 95% CI: [redacted])[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	49,572
PFS on treatment (alpelisib plus fulvestrant) (lower 95% CI: [redacted])[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	50,253
PFS off treatment (upper 95% CI: [redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	50,462
PFS off treatment (lower 95% CI: [redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	49,364
PPS (upper 95% CI: [redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	48,311
PPS (lower 95% CI: [redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	51,614
PPS (literature, Lloyd et al: 0.505)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	61,538
Terminal phase (disutility) (upper 95% CI: [redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	49,982
Terminal phase (disutility) (lower 95% CI: [redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	49,833

[a] In these scenarios, the utility value of everolimus plus exemestane is also amended via utilisation of the 95% CIs for the on-treatment utility value for placebo plus fulvestrant (95% CI: [redacted]), upon which the utility value for everolimus plus exemestane is based. This ensures that the utility value for everolimus plus exemestane is always associated with a 0.03 decrement versus placebo plus fulvestrant.
Abbreviations: CI: confidence interval; ICER: incremental cost-effectiveness ratio; PAS: patient access scheme;

PFS: progression-free survival; PPS: post-progression survival; QALY: quality-adjusted life year.

Time horizon

Scenario analyses were conducted whereby the time horizon of the model was varied from the lifetime horizon utilised in the base case (see Section B.3.2). The impact on the base case ICER (with PAS) was minimal.

Table 89: Time horizon scenario analyses

Description	LIST PRICE			WITH PAS		
	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	49,907
Time horizon 10 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	52,174
Time horizon 20 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	50,279

Abbreviations: ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; QALY: quality-adjusted life year.

Annual discount rate

Scenario analyses were conducted whereby the discount rate for costs and benefits was varied from the 3.5% discount utilised in the base case (see Section B.3.2). The impact on the base case ICER (with PAS) was minimal.

Table 90: Annual discount costs/benefits

Description	LIST PRICE			WITH PAS		
	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	49,907
Annual discount 1.5%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	48,416
Annual discount 6%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	51,725

Abbreviations: ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; QALY: quality-adjusted life year.

B.3.8.4 Summary of sensitivity analyses results

In the base case analysis, alpelisib plus fulvestrant is associated with higher QALYs and higher costs that everolimus plus exemestane, with an ICER of £49,907 per QALY gained (with PAS for alpelisib). Importantly, as patients with HR+, HER2– ABC with a *PIK3CA* mutation who have received prior CDK4/6i therapy meet NICE's end-of-life criteria, the ICER for this population can be considered a cost-effective use of NHS resources considering a willingness to pay threshold of £50,000.

Results of the PSA, DSA and scenario analyses show the base case results to be robust to exploration of model parameter and structural uncertainty, and the adoption of alternative assumptions. Key drivers of cost-effectiveness results were identified as RDIs and the HR for PFS for everolimus plus exemestane versus alpelisib plus fulvestrant.

B.3.9 Subgroup analysis

No economic subgroup analyses were conducted as part of this appraisal.

B.3.10 Validation

B.3.10.1 Validation of cost-effectiveness analysis

Clinical validation

Expert clinical input was sought during the development of the UK cost-effectiveness model to ensure that the inputs and assumptions used in the analysis were relevant to UK clinical practice and to validate the clinical plausibility of the outcomes predicted by the model.[93]

As detailed throughout the submission, the clinical experts were in agreement with the approaches and assumptions taken in the development of the cost-effectiveness model and full details of the clinical validation are provided in the reference pack accompanying this submission. In addition to the validation of survival outcomes, expert clinical opinion was sought to validate the following model inputs:

- Treatment pathway and relevant comparators
- Estimates of PFS and OS
- Patient baseline characteristics
- AE rates
- Monitoring and follow-up resource use assumptions

Technical validation

The model was validated by an independent group of analysts ("validation team"). The following validation checks were performed:

- Pressure testing on extreme value/edge cases;
- Checking results of sensitivity analyses against priors;
- Check internal consistency of results;
- Checking results of PSA against point estimates
- Identification of #REF, #NUM, and #NA errors;
- Identify unused calculations;
- Identify unused named ranges;
- Identify hard-coded values within formulas;
- Identify overly complex/difficult to parse formulas;
- Check that there are no links to other workbooks or external files;
- Check index/lookup functions for offset errors;
- Check that discounting is applied appropriately;

- Check that half-cycle correction is applied appropriately (if applicable);
- Check that model restores appropriately if simulation is terminated prematurely;
- Test Model control objects (buttons etc.) for functionality;
- Check that “restore defaults” or similar functionality works correctly;
- Check the Model inputs against the study report (if available);
- Check that all input vales are appropriately referenced;
- Check Model formatting (e.g., inputs one color fill, results a different color fill);
- Check that x- and y-axis ranges on Model charts change as results change;
- Check that Model is free of spelling and grammar errors;
- Test the Model on a (limited) set of different computers; and
- Test the Model on a (limited) set of Excel installs.

To test whether the model generates results consistent with expectations, deterministic sensitivity analyses were generated for the difference in LYs, QALYs, and costs versus the base case were calculated for each treatment for each scenario. For each treatment and scenario, we then specified our expectations for changes (increase, decrease, or no change) in the life years, QALYs, and costs that would be expected for the given change in the parameter value. We then compared the expected change with the actual change. If differences between actual and expected results were identified, then the model calculations were checked and modified as appropriate.

The following steps were undertaken to check the internal consistency of the results:

- Divide QALYs for each health state by LYs for each health state and check that result is approximately equal to state specific utility value;
- Divide expected cost for each health state by LYs for each health state and check that result is approximately equal to state specific annual cost;
- Set probability of PFS events equal to zero and check that LYs are approximately equal to age- and sex-matched general population life expectancy

B.3.10.2 Interpretation and conclusions of economic evidence

Evidence for the efficacy of alpelisib plus fulvestrant as a treatment for patients with HR+, HER2– ABC with a *PIK3CA* mutation who have received prior CDK4/6i therapy derives from the Phase II BYLieve trial (Cohort A) and the Phase III RCT, SOLAR-1.[29, 41, 108, 121]

For the post-CDK4/6i population, prognosis is extremely poor, and these patients meet NICE’s end-of-life criterion of a short life expectancy of <24 months. Based on the evidence presented in B.2.11.3, alpelisib plus fulvestrant should be assessed according to the higher willingness-to-pay threshold of £50,000/QALY gained in this population. In the base case economic analysis (when alpelisib is provided with the confidential PAS discount, applying the known PAS discount of everolimus and with an assumed discount of [redacted] for fulvestrant), alpelisib plus fulvestrant was associated with increased QALYs ([redacted]) and increased costs ([redacted]) versus everolimus plus exemestane, resulting in an ICER of £49,907. Therefore, in this population, alpelisib plus

fulvestrant can be considered to represent a cost-effective use of NHS resources.

Results of the PSA, DSA and scenario analysis show the base case results to be robust to exploration of model parameter and structural uncertainty, and the adoption of alternative assumptions.

Finally, the results of the budget impact analysis suggests that the introduction of alpelisib plus fulvestrant is not expected to exceed £20 million in any of the first three years of use in the NHS.

In summary, alpelisib is the first alpha-selective PI3K inhibitor to be licensed by the FDA and EMA, and represents a substantial change in the management of patients with HR+, HER2– ABC with a *PIK3CA* mutation as the first licensed therapy to directly target this mutation.[70] For patients with HR+, HER2– ABC with a *PIK3CA* mutation, current treatment options are limited and, particularly for the post-CDK4/6i population, prognosis is extremely poor and these patients meet NICE's end-of-life criterion of a short life expectancy of <24 months. Alpelisib plus fulvestrant represents a cost-effective use of NHS resources and provides patients with an effective, tolerable therapy that is personalised to specifically target tumours harbouring the *PIK3CA* mutation that are associated with a worse prognosis compared with wild-type disease.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Alpelisib in combination with fulvestrant for treating advanced hormone-receptor positive, HER2-negative, *PIK3CA*-mutated breast cancer [ID3929]

Clarification questions

August 2021

File name	Version	Contains confidential information	Date
ID3929_Novartis_Alpelisib_ERG Clarification Questions_260821_FINAL_Fully Redacted	FINAL	No	26th August 2021

Notes for company

Highlighting in the template

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Please note that similar questions which were asked in the previous appraisal of alpelisib have been marked with an asterisk (*).

Section A: Clarification on effectiveness data

Literature searching

A1.* CS Appendix D1.2, page 12. The company's submission (CS) states that reference lists of included systematic reviews were checked for missed studies. Were the bibliographies of included primary studies also checked for the same purpose?

Only reference lists of included systematic reviews were hand-searched. Based on experience, this approach does not result in the loss of any relevant evidence.

A2.* CS Appendix D1.2, page 13. A 2014 study by Glanville *et al*. (https://doi.org/10.3163/1536-5050.102.3.007) recommends searching both ClinicalTrials.gov and the International Clinical Trials Registry Platform (ICTRP); however, the CS only reports searches of the former. Please confirm that the ICTRP has not been searched.

The International Clinical Trials Registry Platform (ICTRP) was not searched. Given that the Cochrane CENTRAL Repository of Trials was searched, which contains the ICTRP records, it is not anticipated this would have had an impact on the sensitivity of the systematic literature reviews (SLRs).

A3.* CS Appendix D and Appendix G. Please confirm the sources of the search filters used to identify RCT and non-RCT evidence and economic/utility evidence respectively, including citations to published validation studies where available.

The randomised controlled trial (RCT) and non-RCT filters have been adapted from Scottish Intercollegiate Guidelines Network (SIGN) filters. The filters used to identify economic and utility evidence were adapted from SIGN, Canadian Agency for Drugs and Technologies in Health (CADTH) and National Health Service Economic Evaluation Database (NHS-EED) filters.[1-3] The filters used in the SLRs have not been validated in published literature. However, while validation has not been performed on the original SIGN and CADTH filters, they have been demonstrated to be both sensitive and accurate.[4-6] The NHS-EED filters have been validated against gold standard search filters and shown to be highly sensitive and specific.[7]

Clinical evidence

A4. Please clarify if are there any plans to undertake an RCT of alpelisib plus fulvestrant in the post-CDK4/6i population?

Novartis is planning to conduct a phase III, randomised, double-blind, placebo-controlled trial of alpelisib in combination with fulvestrant for men and postmenopausal women with hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2–), advanced

breast cancer (ABC) with a phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (*PIK3CA*) mutation, who have progressed on or after a cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) and an aromatase inhibitor (AI). This trial is referred to as EPIK-B5. The population of EPIK-B5 is expected to be comparable to Cohort A of BYLieve and therefore will be consistent with the population addressed within the decision problem of this submission.

Novartis anticipates that the EPIK-B5 trial will be initiated in [redacted], with first results expected in [redacted]. Outcomes anticipated to be reported include progression-free survival (PFS), overall survival (OS) and patient-reported outcomes using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30).

A5. CS, Section B1.3.2, page 26. The CS states that "In UK clinical practice, alpelisib plus fulvestrant is anticipated to be used mainly in the post-CDK4/6i population, which has limited treatment options and poorer prognosis". Please clarify where else alpelisib in combination with fulvestrant is anticipated to be used?

The anticipated licence for alpelisib plus fulvestrant following a Type II variation by the Medicines and Healthcare products Regulatory Agency (MHRA) to the current European Medicines Agency (EMA) licence is [redacted].[8] Following the National Institute of Health and Care Excellence (NICE) approval of ribociclib, abemaciclib and palbociclib in combination with an aromatase inhibitor (AI),[9-11] these cyclin-dependent kinase 4/6 inhibitors (CDK4/6is) in combination with AIs are now considered the standard endocrine-based therapy for first line treatment in the metastatic setting for those who are sensitive to endocrine therapy. This means that within the anticipated licence, the primary use of alpelisib plus fulvestrant will be in patients who have previously received CDK4/6i plus AI, rather than following other endocrine-based therapy such as endocrine monotherapy.

A6.* CS, Section B.1.2, page 18. If the Type II variation to the EMA licence is granted, is it anticipated that the Summary of Product Characteristics will include any form of stopping rule for alpelisib plus fulvestrant?

The current Summary of Product Characteristics (SmPC) from the EMA does not include any stopping rule. It is stated in the SmPC that treatment with alpelisib plus fulvestrant should continue as long as clinical benefit is observed or until unacceptable toxicity occurs; dose modifications may be necessary to improve tolerability.[8] It is not anticipated that this wording will change following an MHRA Type II variation to the EMA licence.

A7. CS, Section B.2.2.1, pages 37 and 38. During the earlier appraisal of alpelisib, the company's previous clarification response (Table 3) reported that there were [redacted] patients in SOLAR-1 with endocrine-resistant PIK3CA mutation after prior CDK4/6i, whilst the CS refers to 20 patients post-CDK4/6i (Section B.2.2.1, pages 37 and 38).

Are [redacted] of these 20 patients endocrine-sensitive (hence, not relevant to the company's proposed positioning of alpelisib)?

In the clarification response for the earlier appraisal, the reported [redacted] patients ([redacted] patients in the alpelisib plus fulvestrant arm and [redacted] in the placebo plus fulvestrant arm) had received a prior CDK4/6i, and were at second-line for ABC treatment i.e. analogous to the Bii and Biii patient population terminology.* However, the 20 patients specified in the current submission (9 in the alpelisib plus fulvestrant arm, and 11 in the placebo plus fulvestrant arm) comprises any patients in SOLAR-1 that had previously received a CDK4/6i and were at any point of the treatment pathway for ABC i.e. first- or second-line.

Novartis can confirm that all 20 patients are endocrine-resistant and are thus aligned with the proposed positioning of alpelisib plus fulvestrant addressed within the Company Submission.

A8. CS, Section B.2.3, Table 8 (page 45). BYLieve Cohort A included 22% premenopausal women and 78% postmenopausal women, whereas the licence for alpelisib is restricted to postmenopausal women and men. How might this difference affect the study results?

Subgroup data, split by menopausal status, for the primary endpoint (proportion of patients alive without disease progression at 6 months) and secondary endpoint (PFS) of BYLieve are presented in Table 1 and Table 2 below (17th December 2019 data cut-off). Results for the overall population, as presented in the Company Submission, are also presented for comparison.

Novartis does not anticipate there to be substantial differences in response between premenopausal and postmenopausal women. This is supported by the PFS analyses below, which shows that the results for the primary endpoint are similar between premenopausal and postmenopausal women. Results for the postmenopausal subgroup are numerically more favourable than the premenopausal subgroup, in line with the intended licence of alpelisib plus fulvestrant.

When considering the results of the primary and secondary endpoint collectively, results between the postmenopausal subgroup and overall population are very similar. Therefore, Novartis considers it appropriate to use the intention-to-treat (ITT) results so as to maintain the largest possible sample size from BYLieve. In addition, the inclusion of premenopausal patients may even be conservative given the numerically more favourable results for the postmenopausal population (albeit there are only small numbers in the premenopausal subgroup, so conclusions should be made with caution).

Table 1: Proportion of patients alive without disease progression at 6 months as per local Investigator assessment in Cohort A of BYLieve (mFAS), overall and by menopausal status

Menopausal status	Alive without PD, n	Proportion, n (95% CI)

* **Bii:** patients who relapsed with documented evidence of progression >12 months from completion of (neo)adjuvant ET and then subsequently progressed while on or after only one line of ET for metastatic disease. **Biii:** patients with advanced disease at the time of diagnosis that progressed on or after ET for advanced disease with no previous (neo)adjuvant treatment for early disease.

Overall	61/121	50.4 (41.2, 59.6)
Postmenopausal	[redacted]	[redacted]
Premenopausal	[redacted]	[redacted]

Abbreviations: mFAS: modified full analysis set; PD: progressed disease.
Source: Novartis Data on File.[12]

Table 2: PFS as per local Investigator assessment in Cohort A of BYLieve (mFAS), overall and by menopausal status

Cohort	Overall	Postmenopausal	Premenopausal
n/N (%)	61/121 (50.4)	57/95 (60.0)	15/26 (57.7)
Percentiles (95% CI):[a]			
25th	[redacted]	[redacted]	[redacted]
50th	7.3 (5.6, 8.3)	[redacted]	[redacted]
75th	[redacted]	[redacted]	[redacted]
% Event-free probability estimates (95% CI)[b]			
6 months	53.9 (44.4, 62.5)	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]

[a] Percentiles with 95% CIs are calculated using the Brookmeyer and Crowley (1982) method.
[b] Percentage event-free probability estimate is the estimated probability that a patient will remain event-free up to the specified time point. Percentage event-free probability estimates were obtained from the Kaplan-Meier survival estimates for all treatment groups; Greenwood formula is used for CIs of Kaplan-Meier estimates.
n: Total number of events included in the analysis; N: Total number of patients included in the analysis.
Abbreviations: CI: confidence interval; mFAS: modified full analysis set; NE: not estimable; NR: not reported; PFS: progression-free survival.
Source: Novartis Data on File.[12]

A9.* CS, Sections B.2.3.1 (pages 38 and 39), B.2.3.3. (pages 44 to 47) and B.2.4.1 (pages 54 to 56) and Appendix F.2.3 (pages 174 to 177). Were the characteristics of second-line patients in BYLieve Cohort A substantially different to the characteristics of second-line patients in SOLAR-1 (other than that patients in BYLieve Cohort A had received prior CDK4/6 inhibitors + aromatase inhibitors while the majority of patients in SOLAR-1 had received aromatase inhibitors alone)?

The overall patient populations in BYLieve Cohort A and the second-line population of SOLAR-1 are broadly similar. However, there are some differences in trial eligibility criteria:

- As noted in this question, the principal difference between second-line patients in BYLieve Cohort A and SOLAR-1 is that all patients in BYLieve (n=127 in Cohort A) had received prior treatment with a CDK4/6i plus AI compared with only nine patients (5.3%) treated with alpelisib plus fulvestrant in SOLAR-1. This represents a key difference between the trials due to the poorer prognosis for the post-CDK4/6i population and the limited treatment options available to them (as outlined in Section B.1.3.2.3 of Document B of the Company Submission).
- Additionally, BYLieve included premenopausal and postmenopausal women, whilst SOLAR-1 was restricted to postmenopausal women, and men (see response to A8 above).[13, 14]

A10.* CS, Section B.2.3.6. Please provide results for progression-free survival (PFS), overall survival (OS) and time to treatment discontinuation (TTD) for the second-line population of BYLieve Cohort A, as used in the economic model.

Results for PFS, OS, and TTD for the second-line population (n=[redacted]) from Cohort A of BYLieve are presented in Table 3 below.

Table 3: PFS, OS, and TTD results for the second-line population in Cohort A of BYLieve

	Alpelisib plus fulvestrant (n=[redacted])
PFS	
Number of events	[redacted]
Number of censored events	[redacted]
Median PFS (95% CI), months	[redacted]
OS	
Number of events	[redacted]
Number of censored events	[redacted]
Median OS (95% CI), months	[redacted]
TTD	
Number of events	[redacted]
Number of censored events	[redacted]
Median TTD (95% CI), months	[redacted]

Abbreviations: CI: confidence interval; NR: not reported; OS: overall survival; PFS: progression-free survival; TTD: time to discontinuation.

A11. CS, Section B.2.4.2.1, Table 18 (page 57). Please confirm that the median PFS values for alpelisib+fulvestrant and placebo+fulvestrant are incorrectly reported for the full analysis set (FAS) population (the reported results suggest that alpelisib+fulvestrant is less effective than placebo+fulvestrant and may be the wrong way around). Please provide a corrected version of this table.

Thank you for highlighting this, and apologies for this error. The corrected table has been provided below (Table 4).

Table 4: Descriptive PFS update in the *PIK3CA*-mutated cohort with prior CDK4/6i use in SOLAR-1, compared with FAS (data cut-off 23rd April 2020)

Post-CDK4/6i population	Alpelisib plus fulvestrant (n=9)	Placebo plus fulvestrant (n=11)
Number of PFS events, n (%)	[redacted]	[redacted]
Median PFS (95% CI)	[redacted]	[redacted]
HR (95% CI)	[redacted]	
FAS (descriptive update; for comparison)	**Alpelisib plus fulvestrant (n=169)**	**Placebo plus fulvestrant (n=172)**
Median PFS (95% CI)	[redacted]	[redacted]
HR (95% CI)	[redacted]	

Abbreviations: CDK4/6i: cyclin dependent kinase 4/6 inhibitor; CI: confidence interval; HR: hazard ratio; FAS:

full analysis set; PFS: progression-free survival; *PIK3CA*: phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.
Source: Novartis Data on File.[15]

A12.* CS, Section B.2.3.3, page 44. The CS states "BYLieve recruited patients from 21 European (n=55) and two UK (n=3) study centres in Cohort A." Please provide the equivalent figures for the second-line population in Cohort A of BYLieve only.

In the second-line population of Cohort A of BYLieve, [redacted] patients were recruited from Europe, including [redacted] patient from the UK.

A13.* CS, Section B.2.3.4, page 48. The hypothesis test around the primary endpoint in BYLieve required that the lower bound of the 95% CI for the observed PFS proportion at 6 months was greater than 30% in order to reject the null hypothesis. Please clarify where this 30% threshold comes from and how the results of this analysis should be interpreted from a clinical perspective.

A median PFS of at least 6 months (or 50% of patients who are alive without progression after 6 months) has been observed for alpelisib 300 mg plus fulvestrant 500 mg and also for palbociclib 125 mg plus fulvestrant 500 mg in *PIK3CA*-mutated patients previously treated with AI therapy (without a CDK4/6i) in the CBYL719X2101 and PALOMA-3 studies, respectively.[16, 17] At the time of commencing the BYLieve trial, there were no data in the post-CDK4/6i setting in patients with *PIK3CA*-mutated ABC, and even now data are limited. A proportion of 30% of patients alive without progression after 6 months was considered a clinically meaningful threshold in both cohorts for this study based on steering committee discussions on 9th October 2017, whereby clinicians (Hope Rugo, MD; Eva Ciruelos-Gil, MD; Stephen Chia, MD; Dejan Juric, MD) agreed to the primary analysis of treatment effect being tested using the following hypothesis: H0: p ≤0.30 versus H1: p >0.30 where p is the proportion of patients alive without progression at 6 months.

A14.* CS, Table 31, page 76. indicates that there was 1 fatal serious adverse event (SAE) in BYLieve. Please provide details of this fatal SAE.

One fatal serious adverse event (SAE) occurred in BYLieve on [redacted]

[redacted]

It should be noted that there are no restrictions or special warnings included in the current SmPC from the EMA relating to [redacted]. It is not anticipated that

the SmPC from the MHRA Type II variation to the EMA licence will include additional restrictions or special warnings.

Indirect treatment comparisons

A15. CS, Section B.2.7.2.1, page 44. The CS states that indirect treatment comparisons (ITCs) for PFS and OS were conducted using data for patients in second-line advanced breast cancer as a proxy for the post-CDK4/6i setting. However, the median PFS and OS for both arms in SOLAR-1 for the second-line setting (CS Appendix D, Tables 27 and 28, pages 150 and 151) are more favourable than PFS and OS for post-CDK4/6i patients from both SOLAR-1 and BYLieve (CS Tables 13, 18 and 19), which are summarised in Table 5 and Table 6. Please explain whether this proxy is appropriate.

Table 5: PFS in different subgroups

Population	Reference in CS	N: Alp/Fulv	N: Pbo/Fulv	Median PFS: Alp/Fulv	Median PFS: Pbo/Fulv	HR (95% CI)
SOLAR-1 full analysis set	CS Table 18	169	172	[redacted]	[redacted]	[redacted]
SOLAR-1 second-line population	CS Appendix Table 27	79	82	10.9	3.7	0.61 (0.43, 0.86)
SOLAR-1 post-CDK4/6i population	CS Table 18	9	11	[redacted]	[redacted]	[redacted]
BYLieve Cohort A: post-CDK4/6i, all lines	CS Table 13	121	-	7.3	-	-

† As noted in question A11, the ERG believes that the median PFS for the FAS are reported the wrong way around in CS Table 18. This has been corrected in this table

Table 6: OS in different subgroups

Population	Reference in CS	N: Alp/Fulv	N: Pbo/Fulv	Median OS: Alp/Fulv	Median OS: Pbo/Fulv	HR (95% CI)
SOLAR-1 full analysis set	CS Table 19	169	172	39.3	31.4	0.86 (0.64, 1.15)
SOLAR-1 second-line population	CS Appendix Table 28	79	82	37.2	31.2	0.92 (0.61, 1.40)
SOLAR-1 post-CDK4/6i population	CS Table 19	9	11	[redacted]	[redacted]	[redacted]
BYLieve Cohort A: post-CDK4/6i, all lines	CS Table 14	121	-	17.3	-	-

Overall, it is expected that the median PFS and OS of the second-line ABC population in SOLAR-1 are more favourable than that of the post-CDK4/6i population (in both BYLieve and SOLAR-1) due to the known poorer prognosis of the post-CDK4/6i population. However, the assumption of a similar treatment effect in both second-line ABC and the post-CDK4/6i population is considered reasonable, and does not assume similarities in median survival, but rather that the difference in efficacy between alpelisib plus fulvestrant and everolimus plus exemestane would be similar in the second-line ABC versus post-CDK4/6i population.

Considering the small sample size in the post-CDK4/6i population in SOLAR-1 (n=9 in the alpelisib plus fulvestrant arm, and n=11 in the placebo plus fulvestrant arm), the median PFS in the post-CDK4/6i population is broadly similar to that in BYLieve (5.5 and 7.3 months, respectively). The difference in median OS between the post-CDK4/6i populations in SOLAR-1 and BYLieve can also be explained by the small sample size in SOLAR-1. This is clearly demonstrated by examining the shape of the Kaplan-Meier (KM) curve for OS for the post-CDK4/6i population of SOLAR-1 (Figure 1), which shows the small sample size conferring median OS difficult to robustly determine. Therefore, conclusions regarding the duration of survival in post-CDK4/6i patients using SOLAR-1 only should be made with caution.

Figure 1: KM curve for OS for the post-CDK4/6i population of SOLAR-1 (23rd April 2020 data cut-off)

Abbreviations: ALP: alpelisib; CDK4/6i: cyclin-dependent kinase 4/6 inhibitor; FUL: fulvestrant; KM: Kaplan-Meier; OS: overall survival.

The fact that there was only a very small number of post-CDK4/6i patients in SOLAR-1 meant that utilising data from BYLieve as the baseline curve for the cost-effectiveness model was the preferred approach. As BYLieve was a single-arm trial, a treatment effect was required to generate data for everolimus plus exemestane. However, the small number of post-CDK4/6i patients in SOLAR-1 also necessitated deriving a treatment effect from second-line patients from SOLAR-1 and BOLERO-2 as a proxy for the treatment effect in post-CDK4/6i patients.

Therefore, for the purposes of the cost-effectiveness model, it is assumed that the relative treatment effect between alpelisib plus fulvestrant and everolimus plus exemestane is consistent

between second-line ABC and post-CDK4/6i population through the application of a hazard ratio (HR) derived from second-line ABC data to extrapolated data from BYLieve (the latter of which is derived from a post-CDK4/6i population specifically). That the treatment effect would be consistent in the post-CDK4/6i population was validated by clinical expert opinion.[18]

The notion of a consistent relative treatment effect between the second-line ABC population and post-CDK4/6i population is further supported by the similar HRs observed between the full analysis set (FAS) and post-CDK4/6i population of SOLAR-1 (PFS: 0.64 and 0.48 respectively; OS: 0.86 and 0.67, respectively).[15]

A16.* Priority: CS Appendix D, Section 5.1, page 131. The indirect treatment comparison requires two additional trials (CONFIRM and SoFEA) to link the two trials of interest (SOLAR-1 and BOLERO-2). Differences in patient populations and imbalances in treatment effect modifiers mean that the results of this indirect comparison may be biased.

- CS Appendix D, Section 5.1, page 131. CONFIRM did not meet the eligibility criteria for the SLR as results were not reported separately according to HER2 status. Evidence is presented to suggest that this may be an important treatment effect modifier; hence, results of the NMAs are likely to be biased. Please comment on the likely effect of this bias (e.g. on the direction of the treatment effects).

HRs for PFS and OS from CONFIRM were not reported for patients split by HER2 status. As such, we cannot use information from this trial to inform the likely direction of the treatment effects for fulvestrant 500 mg versus fulvestrant 250 mg from HER2 status.

The only other RCT that did report HRs for both PFS and OS was SoFEA, which compared fulvestrant 250 mg versus exemestane. As stated in Appendix D of the Company Submission, the estimated treatment effect modification of HER2 status on both PFS and OS suggests that the effect of fulvestrant 250 mg versus exemestane is favourable in patients with HER2+ tumours and unfavourable in those with HER2− tumours. One might assume that the direction of the effect of fulvestrant 250 mg versus exemestane would be the same for fulvestrant 250 mg versus fulvestrant 500 mg. Consequently, the effect of fulvestrant 500 mg versus fulvestrant 250 mg would be unfavourable in those with HER2+ tumours and favourable in those with HER2− tumours – that is, the direction of the effect would be the reverse of fulvestrant 250 mg versus exemestane. However, this consideration must be interpreted with caution as approximately one third of patients in SoFEA had unknown HER2 status and therefore the HR for patients with known HER2 status may be biased. Additionally, the numbers of patients with HER2+ tumours in SoFEA were small (n=31).

- Appendix D, Section 5.3, Table 27. For SoFEA, the HR for PFS presented in Table 27 relates to all patients irrespective of HER2 status, rather than the subgroup data for HER2- patients presented in Johnston *et al*. (2013). Please explain this decision.

The HR based on all patients (n=480) was used for two reasons; firstly, approximately 35% of patients had unknown HER2 status (n=166). It is possible, therefore, that the estimated HRs for people with known HER2 status would be affected by information bias. Secondly, the numbers of patients with known HER2+ status were small (6% or n=31) and so the estimates for these patients may have been unreliable.

- Appendix D, Section 5.3, Tables 27 and 28, pages 150 and 151. For SoFEA and CONFIRM, separate results for second-line patients were not available. Please comment on the likely bias and validity of these results for the second-line population.

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 treatment effects for first versus second line therapy in SoFEA and CONFIRM cannot be assessed because it is not clear how many patients were in each line of therapy in each trial, and results were not reported by line of therapy. Additionally, the direction of the effect modification from line of therapy was inconsistent in SOLAR-1 and BOLERO-2, as shown in Appendix D in the Company Submission.

A17.* Priority: A Bucher ITC was conducted for the second-line population.

- This assumes fixed effects (zero heterogeneity) in treatment effects between trials. Please comment on the validity of this assumption. Why was a random effects NMA not conducted?

Random effects analyses account for between-trial heterogeneity and are therefore useful when efficacy data for individual treatments derive from multiple trials. As this was not the case for the Bucher indirect treatment comparison (ITC), the use of a fixed or random effects approach would have yielded identical HRs and confidence intervals and therefore only a fixed effects approach was conducted.

- The assumption of proportional hazards was considered for the observed trial period. Please provide the graphs of the log(-log(survival)) versus the log of survival time for checking the proportional hazards assumption. Please also comment on the plausibility of this assumption for the extrapolation. Why was an approach allowing time-varying hazards not used?

A time-varying hazards approach was not used in this population because the assessment of proportional hazards held for both PFS and OS in the second line population (Table 24 of Document B of the Company Submission). Whilst the assumption has to be made that proportional hazards also holds for the extrapolation period, this assumption was considered reasonable compared with potential limitations that may be introduced by conducting the more complex time-varying hazard network meta-analysis (NMA). Plots of the log-cumulative hazards from the second-line population of SOLAR-1 are shown in Figure 2 below.

Figure 2: Transformation diagnostics for the second-line subgroup of SOLAR-1

A. PFS

B. OS

Abbreviations: ALP: alpelisib; FUL: fulvestrant; PBO: placebo; PFS: progression-free survival; OS: overall survival.

A18.* Priority: For SOLAR-1, there are differences between the HRs presented in Section B.2.4.2, page 56-58 and those used in the indirect treatment comparison (Appendix D, Table 27-28, page 150-151). Please explain these differences.

The HRs presented in Section B.2.4.2 are for the post-CDK4/6i population and FAS (all patients who received alpelisib plus fulvestrant in the *PIK3CA*-mutated cohort, irrespective of line of therapy or prior treatment), while the HRs used for the ITC reflect the second-line population of SOLAR-1, irrespective of receipt of prior CDK4/6i. The use of the second-line populations of SOLAR-1 and BOLERO-2 as a proxy for the post-CDK4/6i population in the Bucher ITC was

necessary due to the absence of data for everolimus plus exemestane in a post-CDK4/6i population, and due to the fact that BYLieve was a single-arm trial (Section B.2.7.2 of Document B of the Company Submission).

A19.* Priority: For BOLERO-2 and CONFIRM, there are a number of differences between the HRs for PFS and OS used in the indirect treatment comparison (Appendix D, Tables 27 and 28, pages 150 and 151) and those presented in the trial publications. These differences include:

- For BOLERO-2, the HRs for PFS presented in Appendix D (Table 27) are less favourable to everolimus + exemestane than those reported in Moynahan *et al*. (2017) and Yardley *et al*. (2013).
- For CONFIRM, the HR for OS presented in Appendix D (Table 28) is different to that reported in Di Leo *et al*. (2010).

Please explain these differences and indicate which are the correct data.

The reasons for these differences are described below:

- Moynahan *et al.* (2017) is based on *PIK3CA* mutation identified by cell free DNA in serum, while the estimates used in the NMA were based on *PIK3CA* identified by archival tumour tissue samples[19]
- Neither Moynahan *et al.* (2017), or Yardley *et al.* (2013) analysed data from BOLERO-2 stratified by line of therapy.[19, 20] The analyses of data from BOLERO-2 used in the ITC were based on patients with one prior line of therapy for metastatic disease (second-line population)
- The HR reported in Di Leo *et al*. (2010) is based on the initial analysis of survival for the CONFIRM trial. The HR used in the ITC was taken from Di Leo *et al.* (2014), which reports the HR for the final OS analysis (HR=0.81 [0.69, 0.96])[21, 22]

Overall, it is important to also note that for BOLERO-2 (and SOLAR-1), individual patient data (IPD) for patients with *PIK3CA* mutations and at second-line for ABC were used to derive HRs in the Bucher ITC. Therefore, these HRs are not available in published sources.

A20. Priority: Appendix D, pages 138 and 139. HER2 status was found to be a statistically significant effect modifier on PFS and OS (Appendix D pages 138 and 139). Please provide an updated Bucher ITC analysis using HER2- subgroup results from SoFEA for both PFS and OS.

In the Company Submission, the HR derived from the Bucher ITC based on all patients from SoFEA was used for the following reasons: firstly, approximately one-third of patients in SoFEA had unknown HER2 status. It is possible, therefore, that the estimated HRs for people with known HER2 status would be affected by information bias. Secondly, the numbers of patients with known HER2+ status were small and so the estimates for these patients may have been unreliable. In addition, as per question A16 above, given data for CONFIRM were not available by HER2 status, the use of the whole population of SoFEA may have allowed for a balance of the potential effects of including HER2+ patients in the network, as for CONFIRM, the effect of

fulvestrant 500 mg versus fulvestrant 250 mg would be unfavourable in those with HER2+ tumours and favourable in those with HER2− tumours, and for SoFEA, the effect of fulvestrant 250 mg versus exemestane is favourable in patients with HER2+ tumours and unfavourable in those with HER2− tumours.

For transparency, Novartis has conducted a Bucher ITC using the HRs for PFS and OS based on the HER2– subgroup of the SoFEA trial as requested (Johnston *et al.* [2013]; Johnston *et al.* [2013] Supplementary Appendix). All other characteristics of the ITC are identical to the original ITC presented in the Company Submission (e.g., HRs for other comparators, trials included in the evidence network). The HRs (95% CI) for PFS and OS used for fulvestrant 250 mg versus exemestane were 1.06 (0.83, 1.34) and 1.26 (0.95, 1.66), respectively.[23] Resulting HRs from the revised ITC are summarised in Table 7 below, alongside the HRs from the base case ITC as presented in the Company Submission.

Table 7. Results of revised Bucher ITCs of PFS and OS

Comparator	HR (95% CI) of comparator versus:	
	Fulvestrant	Alpelisib plus fulvestrant
Previously presented base case HRs based on all patients in SoFEA regardless of HER2 status		
PFS		
Alpelisib plus fulvestrant	[redacted]	[redacted]
Everolimus plus exemestane	[redacted]	[redacted]
Fulvestrant	[redacted]	[redacted]
OS		
Alpelisib plus fulvestrant	[redacted]	[redacted]
Everolimus plus exemestane	[redacted]	[redacted]
Fulvestrant	[redacted]	[redacted]
Revised HRs based on the HER2– subgroup of SoFEA		
PFS		
Alpelisib plus fulvestrant	[redacted]	[redacted]
Everolimus plus exemestane	[redacted]	[redacted]
Fulvestrant	[redacted]	[redacted]
OS		
Alpelisib plus fulvestrant	[redacted]	[redacted]
Everolimus plus exemestane	[redacted]	[redacted]
Fulvestrant	[redacted]	[redacted]

Abbreviations: CI: confidence interval; 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.

A21. Please provide the correct documents for the folder called “Novartis Data on File WinBugsCodeDataInput” as this file currently contains the code, data and initial values for conducting fractional polynomial NMAs, not the Bucher ITC.

The Bucher ITCs were conducted using Microsoft Excel workbooks, which have been provided as accompanying files to this document (‘ID3929 Alpelisib_Bucher ITC Workbook_PFS.xlsx’ and ‘ID3929 Alpelisib_Bucher ITC Workbook_OS.xlsx’).

A22.* Priority: CS, Appendix D, Section 5.3, Tables 27 and 28, pages 150 to 151. For the PFS and OS data used in the indirect treatment comparison, please add the number of patients to column “population” and describe exactly which patients are included in each analysis, and the number of excluded patients and reasons for exclusion, as indicated in Table 8 and Table 9 below.

The information requested by the ERG is presented in the tables below. The patient numbers and reasons for exclusion are identical between PFS and OS analyses.

Table 8: HRs for PFS for trials used in the ITC

Trial	Treatment	Control	*PIK3CA* (%)	N, treatment / control	Median PFS (months)		HR (95% CI)	Source/notes	N original trial	Exclusion
					Treatment	Control				
BOLERO-2	Everolimus plus exemestane	Exemestane	100%[a]	36 / 21	7.8	3.3	0.61 (0.33, 1.14)	Cox PH regression of BOLERO-2 IPD. Patients were those with *PIK3CA*-mutated disease and one prior line of therapy in the metastatic setting (data on file).	724	Patients with wildtype *PIK3CA* (n=362) or received fewer than one prior line of therapy (n=23) or more than one prior line of therapy for metastatic disease (n=282)
CONFIRM	Fulvestrant 500 mg	Fulvestrant 250 mg	NR	362 / 374	6.5	5.5	0.80 (0.68, 0.94)	Approximately 50% of patients enrolled in the trial were first-line and 50% second-line; HER2 status was not evaluated.[21]	736	N/A
SoFEA	Fulvestrant 250 mg	Exemestane	NR	231 / 249	4.8	3.4	0.95 (0.79, 1.14)	Trial included patients receiving both first/second-line treatment for ABC, however, approximately 80% were second-line. Approximately 7% of patients were HER2+, while ~33% had unknown status.[23]	480	N/A
SOLAR-1	Alpelisib plus fulvestrant	Fulvestrant	100%[a]	[redacted]	10.9	3.7	0.61 (0.43, 0.86)	Cox PH regression of SOLAR-1 IPD. Patients were those with *PIK3CA*-mutated disease and one prior line of therapy in the advanced setting (data on file).	[redacted]	Patients with wildtype *PIK3CA* ([redacted]) or received fewer than one prior line of therapy ([redacted]) or more than one prior line of therapy for metastatic disease ([redacted]), or were endocrine sensitive ([redacted])

[a] Analysis was for a subgroup of patients with *PIK3CA* mutation.
Abbreviations: ABC: advanced breast cancer; CI: confidence interval; ET: endocrine therapy; HER2–: human epidermal growth factor receptor 2 negative; HR: hazard ratio; HR+: hormone receptor positive; IPD: individual patient data; ITT: intention-to-treat; NR: not reported; PFS: progression-free survival; *PIK3CA*: phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

Table 9: HRs for OS for trials used in the ITC

Trial	Treatment	Control	*PIK3CA* (%)	N, treatment / control	Median OS (months)		HR (95% CI)	Source/notes	N original trial	Exclusion
					Treatment	Control				
BOLERO-2	Everolimus plus exemestane	Exemestane	100%[a]	36 / 21	31.0	26.6	1.09 (0.58, 2.03)	Cox PH regression of BOLERO-2 IPD. Patients were those with *PIK3CA*-mutated disease and one prior line of therapy in the metastatic setting (data on file).	724	Patients with wildtype *PIK3CA* (n=362) or received fewer than one prior line of therapy (n=23) or more than one prior line of therapy for metastatic disease (n=282)
CONFIRM	Fulvestrant 500 mg	Fulvestrant 250 mg	NR	362 / 374	26.4	22.3	0.81 (0.69, 0.96)	Approximately 50% of patients enrolled in the trial were first-line and 50% second-line; HER2 status was not evaluated.[21]	736	N/A
SoFEA	Fulvestrant 250 mg	Exemestane	NR	231 / 249	19.4	21.6	1.05 (0.84, 1.29)	Trial included patients receiving both first/second-line treatment for ABC, however, approximately 80% were second-line. Approximately 7% of patients were HER2+, while ~33% had unknown status.[23]	480	N/A
SOLAR-1	Alpelisib plus fulvestrant	Fulvestrant	100%[a]	[redacted]	37.2	31.2	0.92 (0.61, 1.40)	Cox PH regression of SOLAR-1 IPD. Patients were those with *PIK3CA*-mutated disease and one prior line of therapy in the advanced setting (data on file).	[redacted]	Patients with wildtype *PIK3CA* ([redacted]) or received fewer than one prior line of therapy ([redacted]) or more than one prior line of therapy for metastatic disease ([redacted]), or were endocrine sensitive ([redacted])

[a] Analysis was for a subgroup of patients with *PIK3CA* mutation.
Abbreviations: ABC: advanced breast cancer; CI: confidence interval; ET: endocrine therapy; HER2–: human epidermal growth factor receptor 2 negative; HR: hazard ratio; HR+: hormone receptor positive; IPD: individual patient data; ITT: intention-to-treat; NR: not reported; OS: overall survival; *PIK3CA*: phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

A23. CS, Section B.2.7.3, pages 67 to 69. The company has undertaken a patient-adjusted indirect comparison (PAIC) as supportive analysis:

(a) The inverse probability of treatment weighting (IPTW) method was used to balance the measured covariates between SOLAR-1 and BOLERO-2. As unanchored indirect treatment comparisons (ITCs) were performed for PFS and OS, please clarify why IPTW was not performed for the relevant arms between SOLAR-1 and BOLERO-2 (the alpelisib plus fulvestrant arm from SOLAR-1 and the everolimus plus exemestane arm from BOLERO-2). Please also comment on how this alternative approach could impact on the results of the analysis.

For the patient-adjusted indirect comparison (PAIC) of alpelisib plus fulvestrant versus everolimus plus exemestane using inverse probability of treatment weighting (IPTW), patients in the alpelisib plus fulvestrant arm of SOLAR-1 were matched to the patients in the everolimus plus exemestane arm of BOLERO-2, while those in the placebo plus fulvestrant arm were matched to patients in the placebo plus exemestane arm. This approach is consistent with the 'alternative approach' suggested above.

(b) Since the balance was not achieved very well, please clarify if alternative propensity score models were considered to improve the performance of the IPTW.

In secondary analyses, the logistic equation for estimating propensity scores was estimated with several alternative sets of selected covariates as follows:

- **All covariates with trimmed weights**: In these analyses, weights were set to the minimum of the estimated weight or the 90th percentile of all weights
- **Stepwise selection**: With this approach, covariates were selected based on stepwise selection using entry and exit p-value criteria of 0.20 (the p-value is arbitrary but chosen to ensure that the criteria for inclusion are not overly stringent)
- **Selection based on Akaike information criterion (AIC)**: With this approach, covariates were selected using stepwise selection based on AIC criteria (covariates were included if AIC improved, and dropped if AIC worsened)
- **Selection based on sum of standardised mean differences (SMDs)**: With this approach, covariates were selected with the lowest sum of the absolute SMDs for all covariates. In order to limit the number of sets of covariates considered, for each set of models with the same number of covariates, only the 30 best fitting models based on AIC were considered.

These analyses were conducted 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. Results from the analyses of the 2019 data are provided below. In no cases were results of the secondary analyses qualitatively different from the primary analyses. For PFS, the HRs for alpelisib plus fulvestrant were somewhat less favourable in secondary analyses than in the primary analyses while for OS the HRs were somewhat more favourable.

Table 10: 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

Method	N (Weighted)		HR (95% CI)	P-value
	Alpelisib plus fulvestrant	Everolimus plus exemestane		
PFS				
All covariates	[redacted]	[redacted]	[redacted]	[redacted]
All covariates – trim 90th percentiles	[redacted]	[redacted]	[redacted]	[redacted]
Stepwise selection – p-values	[redacted]	[redacted]	[redacted]	[redacted]
Stepwise selection – AIC	[redacted]	[redacted]	[redacted]	[redacted]
Minimise sum of SMDs	[redacted]	[redacted]	[redacted]	[redacted]
OS				
All covariates	[redacted]	[redacted]	[redacted]	[redacted]
All covariates – trim 90th percentiles	[redacted]	[redacted]	[redacted]	[redacted]
Stepwise selection – p-values	[redacted]	[redacted]	[redacted]	[redacted]
Stepwise selection – AIC	[redacted]	[redacted]	[redacted]	[redacted]
Minimise sum of SMDs	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AIC: Akaike information criterion; CI: confidence interval; HR: hazards ratio; OS: overall survival; PFS: progression-free survival; SMD: standardised mean differences.

The stepwise approach based on p-value criteria appears to be marginally better at reducing SMDs between the trials compared with the primary analysis (Figure 3). As shown in Table 10 above, the HR for OS is numerically more favourable based on the stepwise approach compared with the primary analysis (HR [redacted] and [redacted] respectively), while the HR for PFS is somewhat less favourable based on the stepwise approach compared with the primary analysis (HR [redacted] and [redacted] respectively).

Figure 3: SMD plots for baseline patient characteristics for second-line patients in SOLAR-1 versus BOLERO-2

A. Primary analysis

B. Trimmed analysis

C. Stepwise selection based on p-values

D. Stepwise selection based on AIC

E. Minimise sum of SMDs

Abbreviations: ECOG: Eastern Cooperative Oncology Group; met: metastatic; q: quartile; SMD: standardised mean differences; vs.: versus

(c) Please clarify why population-adjusted indirect comparisons were not performed using the alpelisib plus fulvestrant data from BYLieve and the everolimus plus exemestane arm of BOLERO-2.

Novartis does not consider a PAIC between BYLieve Cohort A and BOLERO-2 to be appropriate, as BYLieve Cohort A enrolled patients who had received prior CDK4/6i therapy, while patients in BOLERO-2 had not received prior CDK4/6i treatment. This is a fundamental difference between the patient populations given the poorer prognosis of the post-CDK4/6i population. As these two trial populations are not comparable, a PAIC would not produce meaningful results.

This also links to the above response for question A15, where the company clarified that median survival for patients who have received prior CDK4/6i treatment would be expected to be less favourable as compared with patients who have not received a CDK4/6i previously, as is demonstrated via a comparison of SOLAR-1 and BYLieve survival data.

A24. CS, Section B.2.5.1, pages 58 to 63. The company has undertaken a matching/weighted analysis as supportive analysis:

(a) Please clarify the purpose of the comparison between BYLieve and Flatiron Clinicogenomics Database (CGDB). Why was the output of this comparison not included in the economic model? Why was the analysis undertaken for PFS, but not for OS?

The purpose of this analysis was to support the comparative effectiveness of alpelisib plus fulvestrant in the post CDK4/6i population specifically, as other indirect analyses conducted have only been in second-line ABC populations and were then used as a proxy for relative efficacy in post-CDK4/6i patients.

The matching/weighted analysis was initially conducted for PFS only as the primary endpoint for BYLieve was proportion of patients that were progression-free at 6 months. Since that time, the dataset subsequently became no longer available and, as such, an analysis of OS could not be performed. Hence, only PFS results were available to be reported in the Company Submission.

Due to the absence of OS results, Novartis preferred to incorporate PFS and OS results from the ITC as a single source into the economic model, instead of providing data from a mix of sources (i.e. PFS from the matching/weighted analysis and OS from the ITC).

(b) Three matching/weighted methods were used (weighting by odds, propensity score greedy matching and exact matching). Please provide comments on the baseline characteristics of patients in the Flatiron and BYLieve datasets after matching/weighted analysis with respect to each of the methods used.

Pre-weighted and post-weighting baseline characteristics have been presented by Turner *et al.*, and are replicated in Table 11 below. The SMDs between the populations were all <25%, indicating that the patient baseline characteristics between the populations were balanced, as defined by the study protocol.[24]

The primary analysis of the comparison was based on the weighting by odds, which reflects the use of the average treatment effect in the treated (ATT) IPTW approach. With this approach, patients in Flatiron were weighted so that their baseline characteristics matched those for BYLieve. This was taken forward as the primary analysis as this preserved the sample size of the BYLieve trial population without having a large difference in ability to balance on key covariates. Overall, this approach yielded a good match on the baseline characteristics used in the calculation of propensity scores/weights. The other approaches (greedy or exact matching) were used in sensitivity analyses and did not materially improve the matching but yielded smaller matched samples with qualitatively similar results.

Table 11: Patient characteristics and baseline disposition: BYLieve versus real-world cohort with standard treatment post-CDK4/6i

	Pre-weighted			Post-weighting by odds			Post-1:1 Greedy nearest neighbour matching			Post-1:1 Exact matching		
	CGDB (N=95)	BYLieve (N=120)	SMD (%)	CGDB (N=116)	BYLieve (N=120)	SMD (%)	CGDB (N=76)	BYLieve (N=76)	SMD (%)	CGDB (N=61)	BYLieve (N=61)	SMD (%)
	n (%)	n (%)		n (%)	n (%)		n (%)	n (%)		n (%)	n (%)	
Age at indexing, years												
<50	13 (13.7)	35 (29.2)	38.2	30 (26.0)	35 (29.2)	7.9	13 (17.1)	13 (17.1)	0.0	7 (11.5)	7 (11.5)	0.0
50–<65	49 (51.6)	54 (45.0)	–13.1	56 (48.1)	54 (45.0)	–6.1	42 (55.3)	44 (57.9)	5.3	37 (60.7)	37 (60.7)	0.0
≥65	33 (34.7)	31 (25.8)	–19.4	30 (26.0)	31 (25.8)	–0.3%	21 (27.6)	19 (25.0)	–5.7	17 (27.9)	17 (27.9)	0.0
Pooled number of metastatic sites												
<3	57 (60.0)	84 (70.0)	21.0	79 (68.2)	84 (70.0)	3.8	48 (63.2)	50 (65.8)	5.5	41 (67.2)	41 (67.2)	0.0
≥3	38 (40.0)	36 (30.0)	–21.0	37 (31.8)	36 (30.0)	–3.8	28 (36.8)	26 (34.2)	–5.5	20 (32.8)	20 (32.8)	0.0
Site of metastases												
Bone only	20 (21.1)	22 (18.3)	–6.8	24 (20.5)	22 (18.3)	–5.4	14 (18.4)	17 (22.4)	9.9	13 (21.3)	13 (21.3)	0.0
Lung/liver	56 (59.0)	80 (66.7)	15.9	73 (63.0)	80 (66.7)	7.6	47 (61.8)	45 (59.2)	–5.4	36 (59.0)	36 (59.0)	0.0
Time from initial diagnosis to index date, months												
<27	22 (23.2)	31 (25.8)	6.2	31 (26.3)	31 (25.8)	–1.1	18 (23.7)	18 (23.7)	0.0	15 (24.6)	15 (24.6)	0.0
27 –<60	24 (25.3)	30 (25.0)	–0.6	29 (25.0)	30 (25.0)	0.0	17 (22.4)	16 (21.1)	– (3.0)	12 (19.7)	12 (19.7)	0.0
60–<128	24 (25.3)	31 (25.8)	1.3	31 (26.9)	31 (25.8)	–2.5	20 (26.3)	20 (26.3)	0.0	17 (27.9)	17 (27.9)	0.0
≥128	25 (26.3)	28 (23.3)	–6.9	25 (21.8)	28 (23.3)	3.6	21 (27.6)	22 (29.0)	3.0	17 (27.9)	17 (27.9)	0.0

Abbreviations: CDK4/6i: cyclin-dependent kinase 4/6 inhibitor; CGDB: Clinicogenomics Database; SMD: standardised mean difference.

Section B: Clarification on cost-effectiveness data

Economic model population and interventions

B1. CS, Section B.3.2.1, page 106. The text states that *"Within the de novo cost-effectiveness model, only a subset of the above patients receiving alpelisib plus fulvestrant as second-line therapy second-line (n=[redacted]) are considered as these patients are those most relevant to the decision problem."*

- Is the company seeking a positive NICE recommendation for alpelisib plus fulvestrant in second-line, or in any line post-CDK4/6i?

Novartis is seeking a positive recommendation for alpelisib plus fulvestrant in second and subsequent lines of therapy post-CDK4/6i. The anticipated licence for alpelisib in combination with fulvestrant is [redacted]. In the UK, CDK4/6is are the mainstay of therapy at first-line in the advanced setting following progression on endocrine therapy. Therefore, based on current UK clinical practice, it is anticipated that the majority of patients who would be eligible to receive alpelisib plus fulvestrant would receive it in the second-line setting.

It is acknowledged that very few patients have been evaluated following receipt of alpelisib plus fulvestrant beyond second-line. However, there were some patients in BYLieve Cohort A beyond second line ([redacted] patients in third line and [redacted] patient in fourth line), and therefore a recommendation should not preclude such patients from receiving alpelisib plus fulvestrant in the future.

- Is the company also seeking a positive recommendation in the first-line setting where patients received a CDK4/6i as adjuvant/neo-adjuvant treatment?

Based on current clinical practice, patients receive CDK4/6i therapy mainly in the first-line advanced setting – this is taken into consideration in our proposed positioning of alpelisib plus fulvestrant following receipt of CDK4/6i therapy, i.e. at second-line and beyond for ABC. Whilst (neo)adjuvant use of CDK4/6i therapies is not currently standard practice, should this be implemented in future practice, then it is anticipated that alpelisib plus fulvestrant would be an option for patients who progress on this earlier CDK4/6i therapy. [redacted] patients in BYLieve Cohort A received alpelisib plus fulvestrant at first-line in the advanced setting, therefore, there are some data to support the use of alpelisib plus fulvestrant at this point in the treatment pathway.

- If the intended target population is broadly defined as patients who have previously received a CDK4/6i, why was it necessary to restrict the BYLieve analysis to the second-line population (N=[redacted])?

In the economic model, the relative treatment effect between alpelisib plus fulvestrant and everolimus plus exemestane was derived from an ITC of second-line data from SOLAR-1 and BOLERO-2, as no patients beyond second-line were included in SOLAR-1. This treatment effect was then applied to survival curves generated from BYLieve data. In order to ensure consistency

and avoid introducing further uncertainty in the treatment effect, Novartis thus preferred to use BYLieve data from second-line patients only.

In addition, given the majority of patients receiving alpelisib plus fulvestrant in UK clinical practice (in the post-CDK4/6i setting) would be anticipated to receive treatment at second-line, and given the small patient numbers in BYLieve beyond second line, it was not considered appropriate to conduct any analyses using BYLieve data from these subsequent treatment lines. Thus, patients in BYLieve Cohort A receiving alpelisib plus fulvestrant at other lines of therapy ([redacted] patients in first line, [redacted] patients in third line and [redacted] patient in fourth line) were excluded from the economic analysis.

Survival modelling and treatment effects models

B2.* CS, Section B.3.3.1, page 110. The text states "*For RCS distributions, Weibull, log-logistic and lognormal distributions were estimated...*" Do you mean that the scale used to estimate the splines was varied to be the log cumulative hazard, odds, and "normal"?

Yes, this is correct.

B3.* Priority: CS, Section B.3.3, pages 115, 116, 121, 122, 130 and 131. Please justify the application of hazard ratios from the Bucher ITCs to accelerated failure time models for PFS, OS and TTD within the economic model.

The accelerated failure time models were chosen as the most appropriate models for PFS, OS and TTD; thus, it followed that HRs had to be applied to non-proportional hazards distributions. It is acknowledged that if the underlying distributions to which the HRs are applied are not proportional hazards distributions (e.g. exponential and Weibull are proportional hazards distributions whereas lognormal is an accelerated failure time distribution and log-logistic is a proportional odds distribution), the application of these HRs to these non-proportional hazards distributions results in a distribution that is of a different form than the original (i.e. applying a HR to a lognormal distribution results in a distribution that is not lognormal). However, there is no obvious reason why this should be biased. Furthermore, this approach has been adopted in several previous appraisals; it was considered more appropriate to select models that more accurately reflected the available data.

Health-related quality of life

B4.* CS, Section B.3.4.5, page 140. Please clarify why the age-adjustment of utilities is based on absolute decrements rather than a utility multiplier relative to the model start age.

Both approaches specified in the question are valid approaches; however, in the model, it is assumed that the absolute age-related declines in utility values would be the same as that in the general population. It is unlikely that this would materially impact the results because virtually all patients are projected to be dead within approximately 15 years. In fact, it is considered that using the absolute reduction is conservative since higher utility values yield more favourable ICERs. Use of the absolute reduction approach results in a greater reduction than the use of the

relative reduction approach, as the relative reduction approach would be based on a smaller starting value (0.83 for general population aged 57 years versus 0.77 for PFS on-treatment with alpelisib plus fulvestrant).

B5.* CS, Section B.3.4.1, page 133. The text states *"Nevertheless, EQ-5D-5L data were largely missing after progression."* Please comment on the potential for the post-progression utility estimates to be subject to informative censoring due to data collection stopping shortly after patients progressed in SOLAR-1.

It is common for EQ-5D data to be missing for patients post-progression. 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.

In addition, a scenario analysis was provided within the company submission whereby an alternative post-progression utility value was utilised from Lloyd *et al.* (2006).[25] This has a reasonably large effect on the ICER; however as described in Section B.3.4 and based on clinical expert opinion, this estimate is considered to be less clinically valid than the estimate used in the base case.[26]

B6.* CS, Section B.3.4.5.1, page 135. Please clarify the basis for assuming that HRQoL is lower in the last 84 days of life, and for using 84 days as the *"terminal period"* period preceding death.

Generalised Estimating Equation (GEE) regression models were explored that included a covariate for a terminal phase (defined as assessments within 84 days of the recorded date of death) as well as models that did not include this covariate. An alternative time period of 28 days was also explored, but there were very few assessments during this time period. Exploration of the time period of 84 days found that for the second-line population of SOLAR-1, the p-value for the terminal phase covariate was statistically significant in each of the models where the covariate was included. This suggested that patients' health-related quality of life (HRQoL) was adversely affected in the 84 days preceding the date of death, and as such, HRQoL was assumed to diminish during this period within the economic analysis.

B7.* CS, Section B.3.4.5.2, page 139. The text states *"The utility values from BOLERO-2 (presented in Appendix L) were used to estimate a utility decrement for everolimus plus exemestane versus exemestane alone. It was then assumed that the utility value for exemestane would be equal to that for fulvestrant."*

- Please clarify the basis for using this approach;
- Given that the analysis assumes that the utility value for exemestane is the same as fulvestrant, please clarify why the utilities for the on/off treatment PFS states were not instead simply based on the fulvestrant arm of SOLAR-1;

- What evidence is there to demonstrate that HRQoL differs between the treatments for patients who are progression-free?

This approach is based on the NICE submission for ribociclib plus fulvestrant for treating HR+, HER2– ABC (TA687/TA593).[27]

It should be noted that the purpose of this exercise was not to estimate health state utility for exemestane but rather to estimate the health state utility for everolimus plus exemestane using what is effectively an ITC approach under the assumption that the utility value for fulvestrant is equal to that for exemestane alone. Under this assumption, the utility value for everolimus plus exemestane was calculated by adding the estimated difference in utility between everolimus plus exemestane versus exemestane alone (fulvestrant) to the utility value for fulvestrant from SOLAR-1.

Novartis is not aware of any other evidence besides the data from BOLERO-2, which suggest there is a difference in utility for everolimus plus exemestane versus exemestane.

B8.* Model, worksheet "Utilities_AE". The executable model includes disutilities associated with AEs, but these are not included in the base case model. Please clarify what evidence there is to support the following assumption: *"Since the health state utility values in the model are estimated from the SOLAR-1 and BOLERO-2 trials, respectively, the impact of AEs on HRQoL associated with alpelisib plus fulvestrant and everolimus plus exemestane has already been accounted for"* (CS, Section B.3.4.4, page 134).

It is a common approach to consider that AE disutility is captured in health state utility values derived from EQ-5D data collected directly from patients within a trial, and therefore the application of AE disutilities could be considered double counting. This approach is aligned with the NICE appraisal for ribociclib plus fulvestrant for treating HR+, HER2– ABC (TA687/TA593),[27] where Novartis also assumed that any disutility resulting from AEs would have been captured in the utilities elicited from patients in the MONALEESA-3 trial, and therefore, did not incorporate additional disutilities. This was not considered a key concern for the ERG in TA687/593 and it is not anticipated that the inclusion of additional disutilities would have a large impact on the base case results of the economic analysis.[27]

Employing this approach is also supported by evidence that in oncology, the inclusion of AE costs and disutilities could be considered negligible compared to the costs of treatment and severity of the disease.[28]

B9. CS, Section 3.4.5, Table 63, page 139. The health utility estimates obtained from the GEE model are different to the estimates presented in the earlier version of the CS. Please clarify the basis for this difference, if due to a later data-cut of SOLAR-1?

Novartis can confirm that the health state utility estimates were updated for the current submission based on the 23rd April 2020 data cut-off of SOLAR-1.

Cost inputs

B10.* Priority: CS, Section B.3.5.2.1, page 149. Which specific treatments are assumed to be used in the model for subsequent lines (after progression on alpelisib plus fulvestrant or after everolimus plus exemestane)?

As described in Section B.3.5.2.1 of Document B of the Company Submission, the model considered medication and administration costs for post-progression treatment. However, specific treatments were not considered; rather 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).

This is aligned with the approach taken in previous NICE TAs for ABC (TA687/593, TA495, TA496 and TA503), and is considered justified as the treatment pathway that patients follow in ABC is varied and will depend on a number of different factors.[9, 10, 27, 29] 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 most recent appraisal, TA687/TA593, post-progression treatment-related costs of £1,500 per month were applied;[27] this same value was used in the base case for this submission.

B11.* Priority: Model. Please clarify if wastage is included in the model for all therapies? If it is not included, please clarify why this is the case.

Wastage was not included in the model. It was not considered necessary to account for wastage in the model because no treatments were included for which dosage was dependent on weight or body surface area (BSA).

B12. CS, Section B.3.5.1.1, pages 145 and 146, and model worksheet 'Costs_Other' cell H13. Please clarify if there is an error in the value used in the model for the cost of the PIK3CA test. The value used in the model is £254.54, whilst the CS reports the unit cost per PIK3CA mutation test as £261.42.

Thank you for highlighting this, we can confirm that the correct value should be £261.42, as reported in the Company Submission and utilised in the Budget Impact Model. Updated cost-effectiveness results are presented in Table 12 and Table 13 below. Please note that these results also include a minor correction based on question B13 below. These corrections result in only a very minor change to the base case ICER as compared with that presented within the Company Submission.

Table 12: Updated base case results – with PAS

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Previously presented base case results, with a *PIK3CA* mutation test unit cost of £254.54 and a 28-day supply of everolimus applied (please see question B13)							
Alpelisib plus fulvestrant	[redacted]	2.36	[redacted]	[redacted]	0.62	[redacted]	49,907

Everolimus plus exemestane	[redacted]	1.73	1.21	-	-	-	-
Updated base case results, with a *PIK3CA* mutation test unit cost of £261.42 and a 30-day supply of everolimus applied (please see Question B13)							
Alpelisib plus fulvestrant	[redacted]	2.36	[redacted]	[redacted]	0.62	[redacted]	49,999
Everolimus plus exemestane	[redacted]	1.73	1.21	-	-	-	-

Results were calculated by applying the known PAS discount of everolimus and the assumed discount of [redacted] for fulvestrant.
Abbreviations: AI: aromatase inhibitor; CDK: cyclin-dependent kinase; ICER: incremental cost-effectiveness ratio; LYG: life years gained; PAS: patient access scheme; QALYs: quality-adjusted life years.

Table 13: Updated base case results – with list price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Previously presented base case results, with a *PIK3CA* mutation test unit cost of £254.54 and a 28-day supply of everolimus applied (please see question B13)							
Alpelisib plus fulvestrant	[redacted]	2.36	[redacted]	[redacted]	0.62	[redacted]	[redacted]
Everolimus plus exemestane	[redacted]	1.73	1.21	-	-	-	-
Updated base case results, with a *PIK3CA* mutation test unit cost of £261.42 and a 30-day supply of everolimus applied (please see Question B13)							
Alpelisib plus fulvestrant	[redacted]	2.36	[redacted]	[redacted]	0.62	[redacted]	[redacted]
Everolimus plus exemestane	[redacted]	1.73	1.21	-	-	-	-

Results were calculated by applying the known PAS discount of everolimus and the assumed discount of [redacted] for fulvestrant.
Abbreviations: AI: aromatase inhibitor; CDK: cyclin-dependent kinase; ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years.

B13. CS, Section B.3.5.1.2., Tables 65 and 66, page 147 and model worksheet 'MedCalc'. Please clarify if there is an error in the formula used to calculate administration costs for everolimus. Given that everolimus is available in packs of 30 tablets, should the value in cell Y26 be adjusted to reflect the 28-day cycle length (as is done for exemestane in cell Y27)? Please also confirm if there is an error in the "Days doses per cycle" for everolimus in Table 66 (should this be "30" rather than "28")?

There is not an error on the 'MedCalc' sheet in cell Y26. This array of cells calculates the number of 'drug cycles' (i.e., the number of days per cycles defined by the schedule on the 'Regimens_Dose' sheet) per model cycles (i.e., 28-day periodicity). Since a 28-day cycle was specified for everolimus, it is working as intended (note that this cell also is used to calculate

drug costs per cycle, in addition to administration costs). However, there is an error on the 'Regimens_Dose' sheet in cells H28 and I28. The value 28 is entered in both of these cells, which are the days dosed per cycle (i.e., days of receipt of medication) and days per cycle for everolimus. These should reflect that everolimus is available in packs of 30 tablets (i.e., a 30-day supply) rather than 28 tablets (i.e., a 28-day supply). The implication of this change is that the administration and dispensing costs related to everolimus are applied once every 30 days (i.e., based on the number of tablets in a pack) rather than once every 28 days (i.e., a difference of 2 days). The drug costs are not impacted because everolimus is taken every day (i.e., the cost is the same whether it is taken 28 times in a 28-day period or 30 times in a 30-day period), whereas the administration costs are applied once per drug cycle. This would cause the total costs with everolimus plus exemestane to reduce from [redacted] in the base case to [redacted]; the with-PAS ICER then changes from £49,907 to £49,999 (with a corrected *PIK3CA* mutation test unit cost, as per question B12).

B14. CS, Section B.3.3.4., Table 57, page 132 and model worksheet 'AE_Incidence'. The incidence of Grade ≥3 AEs included in the model is different to the estimates presented in the earlier version of the CS, and some AEs with an incidence ≥5% (such as hypertension and pneumonia) have been excluded. Please explain the reasons for these differences.

It had come to our attention that there were inconsistencies in the previous Company Submission with regards to the AEs considered in the model. As such, these were updated for this submission to ensure that the included AEs and their incidences were consistent with the relevant sources, which have been replicated in Table 14 below. Overall, AEs considered in the cost-effectiveness model were all-cause ≥Grade 3 AEs with an incidence ≥5% for either alpelisib plus fulvestrant (based on BYLieve data from Rugo *et al.* [2021]) or everolimus plus exemestane (based on BOLERO-2 data from Yardley *et al.* [2013]).[14, 20] Therefore, all AEs reported in patients at ≥Grade 3 in either Rugo *et al.* (2021) or Yardley *et al.* (2013) have been presented below, with those selected for inclusion within the cost effectiveness model highlighted in yellow.[14, 20]

Table 14: Grade 3 or 4 AEs associated with alpelisib plus fulvestrant and everolimus plus exemestane

AE	Alpelisib plus fulvestrant (n=127)		Everolimus plus exemestane (n=485)	
	Grade 3 (%)	Grade 4 (%)	Grade 3 (%)	Grade 4 (%)
Diarrhoea	6	0	2	<1
Hyperglycaemia	28	1	5	<1
Nausea	0	0	<1	<1
Fatigue	1	0	4	<1
Decreased appetite	1	0	1	0
Rash	9	1	1	0
Stomatitis	2	0	8	0
Vomiting	2	0	<1	<1
Asthenia	1	0	2	<1
Headache	1	0	<1	0

AE	Alpelisib plus fulvestrant (n=127)		Everolimus plus exemestane (n=485)	
	Grade 3 (%)	Grade 4 (%)	Grade 3 (%)	Grade 4 (%)
Dry skin	1	0	NR	NR
Pruritus	2	0	<1	0
Dyspnoea	2	1	5	<1
Rash maculopapular	9	0	NR	NR
Abdominal pain	2	0	NR	NR
Pyrexia	0	0	<1	0
Weight decreased	2	0	1	0
Aspartate aminotransferase increased	3	0	3	<1
Urinary tract infection	2	0	<1	0
Cough	1	0	<1	0
Alanine aminotransferase increased	3	0	3	<1
Blood creatinine increased	1	0	NR	NR
Arthralgia	NR	NR	<1	0
Peripheral oedema	NR	NR	1	0
Anaemia	NR	NR	7	<1
Constipation	NR	NR	<1	0
Back pain	NR	NR	<1	0
Insomnia	NR	NR	<1	0
Pain in extremity	NR	NR	<1	0
Gamma-glutamyl transpeptidase increase	NR	NR	5	2

Grade 4 AEs reported in Yardley *et al.* (2013) were sometimes reported as occurring in '<1%'patients. In this instance, within the cost-effectiveness model, the AE has been assumed to have an incidence of 1% at Grade 4.[20] Values were reported to 0 decimal places in this table and may therefore differ slightly from the values in the model due to rounding. AEs that were not reported ('NR') were assumed to be 0%.
Source: Rugo *et al.* (2021);[14] Yardley *et al.* (2013).[20]
Abbreviations: AE: adverse event; NR: not reported.

Economic model implementation and results

B15.* Model, worksheets "comp1.calc" and "comp6.calc", range AD593:AG594. Please clarify why drug acquisition costs are calculated using the half-cycle corrected TTD survivor functions.

Drug acquisition costs were calculated based on half-cycle corrected TTD to be consistent with the calculation of LYs and QALYs, which also employed the same approach. It should be noted

that the model does include a toggle that allows users to turn the half-cycle correction for TTD on/off as necessary. The impact of this change on the base case ICERs is extremely minimal.

B16.* CS, Section B.3.7,Tables 77 and 78 (page 160) and Section B.3.8, Tables 80 and 81 (page 164). There is a noticeable difference between the results of the deterministic and probabilistic analyses. Please explain this difference.

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. It is considered that not all iterations of the PSA represent plausible scenarios. Clinical expert opinion has indicated that it would be reasonable to assume that alpelisib plus fulvestrant is always a more efficacious treatment than everolimus plus exemestane for HR+, HER2– ABC with a *PIK3CA* mutation following treatment with a CDK4/6i.[26] Whilst a constraint (ensuring that all sampled HRs favoured alpelisib plus fulvestrant) was not added to the efficacy estimates for transparency, it is necessary to acknowledge that the probabilistic analyses are conservative, and the ICER is anticipated to be aligned more closely with the deterministic base case.

To test this, Novartis have rerun a probabilistic analysis in which the treatment effect between alpelisib plus fulvestrant and everolimus plus exemestane is fixed (i.e. it is not varied at all in the PSA). The resulting probabilistic ICER (with PAS) is presented in Table 15 below, and was both closer to the base case and <£50,000/QALY.

Table 15: PSA results – WITH PAS

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Base case results without a fixed treatment effect between alpelisib plus fulvestrant					
Alpelisib plus fulvestrant	[redacted]	[redacted]	[redacted]	[redacted]	49,999
Everolimus plus exemestane	[redacted]	1.21	-	-	-
Updated PSA results with a fixed treatment effect					
Alpelisib plus fulvestrant	[redacted]	1.70	[redacted]	[redacted]	49,011
Everolimus plus exemestane	[redacted]	1.23	-	-	-

Please note that both the base case and updated PSA results in this table have incorporated the updated *PIK3CA* mutation test unit cost and 30-day supply of everolimus as per questions B12 and B13. The known PAS discount of everolimus and the assumed discount of [redacted] for fulvestrant have also been applied.
Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; PAS: patient access scheme; QALYs: quality-adjusted life years.

In addition, the sampling of the HRs specifically may also lead to this difference. Within the model, the log of the HR is assumed to be distributed normally with the SE on the log scale derived from the 95% CI. The mean of the sampled HR (mean of the exponentiate normal random variable) was not equal to the point estimate, as the two differ by the Smearing factor, which is equal to the exponent of ½ of the variance. If the comparison is using HRs, and the SE on the log(HR) is large, the difference between the results for the deterministic and probabilistic results may be material.

B17. CS, Section B.3, page 104. The CS states that *"considering a willingness-to-pay threshold of £50,000 per QALY gained, alpelisib plus fulvestrant represents a cost-effective use of NHS resources in this BYLieve population with a critical unmet need."* However, CS Table 80 (page 164) reports a probabilistic ICER of £55,492 per QALY gained. Does the company intend to provide a cost-effective mean probabilistic ICER? If not, please explain why.

The statement outlining the cost-effectiveness of alpelisib plus fulvestrant was made in the context of the deterministic cost-effectiveness results, rather than the probabilistic results. The deterministic ICER from the Company Submission was £49,907 and is therefore considered cost-effective. Even following minor corrections as suggested by the ERG, the ICER remains <£50,000 at £49,999. As specified in our previous response to question B16, the ICER from the probabilistic analysis likely represents a conservative estimate and may reflect a series of iterations utilising potentially implausible scenarios where alpelisib plus fulvestrant is assumed to be less efficacious than everolimus and exemestane.

Model validation

B18. CS, Section B.3.3.1, page 115. The CS states that "the choice of lognormal distribution was also validated by a clinical expert during a one-to-one teleconference call between the clinician and Novartis" regarding the clinical plausibility of the PFS estimates. Please clarify:

- How this validation exercise was undertaken;
- If clinicians were also asked about plausibility of OS models;
- If clinicians were also asked about plausibility of PFS and OS estimates for everolimus and exemestane;
- If any information was elicited from the experts regarding their expectations about the nature of the hazard functions for PFS and OS.

A validation meeting was conducted on 28th June 2021 to elicit clinical expert opinion on the treatment pathway for HR+, HER2– ABC in the UK, and to validate assumptions in the cost-effectiveness model. Novartis prepared a clinical validation presentation and shared this with a consultant medical oncologist in a virtual meeting.

The clinician was presented with extrapolated PFS and OS curves based on the second-line population of BYLieve and confirmed that the log-normal and log-logistic curves (employed in the base case of the Company Submission) were the most reasonable in their estimates for PFS and OS, respectively, based on the clinical plausibility of predicted survival rates.

The clinical expert was not consulted explicitly about plausible PFS and OS estimates for everolimus plus exemestane, as the alpelisib plus fulvestrant curves were considered a priority for validation, as the ITC approach employed in the model means that a HR is applied to the BYLieve extrapolations to generate the comparator curve. However, in a previous validation

meeting conducted to inform the previous NICE submission, the clinical expert indicated that approximately a third of post-CDK4/6i patients would be alive at two years, and approximately 5% would be alive at five years, which is well aligned with the predicted survival for everolimus plus exemestane as per the cost-effectiveness model, highlighting the validity of the results.[30]

Information was not elicited from clinical experts with regards to the nature of the hazard functions for PFS and OS.

B19. CS Section B.3.10.2, page 175 and 176. Please clarify the evidence to support the assertion that alpelisib meets the first condition of the end-of-life criteria (<24 months survival on standard care).

As described in Section B.2.11.3 of the Company Submission, based on data from Cohort A of BYLieve, the median OS was 17.3 months (95% CI: 17.2, 20.7) following treatment with alpelisib plus fulvestrant;[14] thus, as treatment with alpelisib plus fulvestrant has been shown to extend OS versus everolimus plus exemestane (as per the Bucher ITC presented within the Company Submission), it is estimated that median OS with everolimus plus exemestane in this patient population would be <17.3 months and therefore <24 months.

In addition, in the base case analysis for the cost-effectiveness model, the estimated life years gained (LYG) (undiscounted) for everolimus plus exemestane was 1.81 (21.7 months, i.e., <24 months). This estimate is based on HRs for PFS and OS (derived from a Bucher ITC for second-line data of SOLAR-1 and BOLERO-2) between everolimus plus exemestane and alpelisib plus fulvestrant, applied to the PFS and OS curves of the second-line population in the BYLieve trial. With total LYG of 2.58, alpelisib plus fulvestrant was associated with 0.76 additional LYG (9.1 months) as compared with everolimus plus exemestane.

In the final OS analysis of the post-CDK4/6i population in SOLAR-1, median OS was [redacted] in the placebo plus fulvestrant arm and therefore <24 months. Median OS was extended by [redacted] in the alpelisib plus fulvestrant arm to [redacted].[15] As described in question A15, conclusions regarding the duration of survival in the post-CDK4/6i population of SOLAR-1 should be made with caution, considering the small sample size. Nonetheless, this further supports results from BYLieve, which provide evidence for the value of alpelisib plus fulvestrant in extending OS in post-CDK4/6i patients who would otherwise have a survival duration <24 months on standard care.

Section C: Textual clarification and additional points

C1.* Priority. Please undertake a matched indirect comparison of alpelisib plus fulvestrant versus everolimus plus exemestane using data from BYLieve and BOLERO-2.

In line with the response to question A23 above, Novartis does not consider a matched indirect comparison (MAIC) between BYLieve Cohort A and BOLERO-2 to be appropriate, as BYLieve Cohort A enrolled patients who had received prior CDK4/6i therapy, while patients in BOLERO-2 had not received prior CDK4/6i treatment. This is a fundamental difference between the patient populations given the poorer prognosis of the post-CDK4/6i population. As these two trial populations are not comparable, a MAIC would not produce meaningful results. Conducting such

an analysis would also extend beyond the population of interest in the Company Submission, i.e., the post-CDK4/6i population.

This also links to the above response for question A15, where the company clarified that median survival for patients who have received prior CDK4/6i treatment would be expected to be less favourable as compared with patients who have not received a CDK4/6i previously, as is demonstrated via a comparison of SOLAR-1 and BYLieve survival data.

C2. Priority: Please explore whether it is possible to undertake indirect comparisons of alpelisib plus fulvestrant against tamoxifen monotherapy and exemestane monotherapy, as these other two comparators are listed in the final NICE scope. This may require the use of aggregate published data for the comparator arms.

- Please ensure that the reporting of these analyses adheres to the analysis and reporting recommendations as described in the NICE Technical Support Documents.
- Please update the economic model for these comparisons, if possible.

As stated in the Decision Problem table (Table 1) of Document B of the Company Submission, based on clinical expert feedback, exemestane monotherapy and tamoxifen are not relevant comparators to alpelisib plus fulvestrant as they are not widely used in UK clinical practice in this setting, and therefore, are not considered standard of care. This approach with regards to comparators is consistent with that taken in other recent appraisals in HR+, HER2– ABC (TA579, TA619 or TA687/TA593).[27, 31, 32]

Monotherapies such as exemestane monotherapy or tamoxifen monotherapy would be reserved for frail patients who cannot tolerate other therapeutic options such as everolimus (as part of everolimus plus exemestane) and would therefore not be the same patient population expected to receive alpelisib plus fulvestrant. Overall, therefore, the only relevant comparator to alpelisib plus fulvestrant is everolimus plus exemestane.

C3. CS, Section B.3.3.4, page 132. The text states that *"Data from Cohort A of BYLieve and SOLAR-1 were used to estimate the incidence of all-cause ≥Grade 3 AEs for alpelisib plus fulvestrant for the BYLieve and SOLAR-1 populations, respectively."* Please clarify if this is a typographical error.

Apologies for this oversight – this is indeed a typographical error. The statement should instead read 'Data from Cohort A of BYLieve were used to estimate the incidence of all-cause ≥Grade 3 AEs for alpelisib plus fulvestrant'.

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Alpelisib in combination with fulvestrant for treating advanced hormone-receptor positive, HER2-negative, PIK3CA-mutated breast cancer [ID3929]

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

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

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

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

Information on completing this submission

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

About you

1.Your name	[redacted]
2. Name of organisation	Breast Cancer Now
3. Job title or position	Policy Manager
4a. Brief description of the organisation (including who funds it). How many members does it have?	Breast Cancer Care and Breast Cancer Now merged on 1 April 2019 to create one charity – Breast Cancer Now. From research to care, our charity has people affected by breast cancer at its heart – providing support for today and hope for the future. United, we have the ability to carry out even more world-class research, provide even more life-changing support and campaign even more effectively for better services and care. All of our funding comes from the public and our partners.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	In the last 12 months, Breast Cancer Now has received the following funding from manufacturers listed in the appraisal matrix. Please note, Breast Cancer Now does not receive any pharmaceutical funding for our Policy, Evidence and Influencing work. Our work on access to drugs is independent of any funding we may receive from the pharmaceutical industry and is based on the evidence of the clinical effectiveness of drugs. **Novartis** June 2020 - £17,835 towards our Helpline. May 2021 - £20,000 towards our Helpline **Lilly UK** December 2020 - £21,060 towards our Living with Secondary Breast Cancer Service **Pfizer**

If so, please state the name of manufacturer, amount, and purpose of funding.	November 2020 - £40,900 towards our Personalised Support package
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	N/A
5. How did you gather information about the experiences of patients and carers to include in your submission?	At Breast Cancer Now we utilise our various networks of those affected by breast cancer to gather information about patient experience.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Secondary (also known as advanced, metastatic or stage 4) breast cancer is when cancer originating in the breast has spread to other parts of the body; most commonly the lungs, brain, bones or liver. There is no cure for secondary breast cancer. Treatment aims to control and slow the spread of the cancer, relieve any symptoms, and maintain health, wellbeing and a good quality of life for as long as possible. A patient can be diagnosed with secondary breast cancer initially, or they can develop the condition years after treatment for their primary breast cancer has ended. Being diagnosed with secondary breast cancer is extremely difficult to come to terms with both for patients and their family and friends. Everyone's experience of being diagnosed and living with secondary breast cancer is different. Many people will feel upset and shocked or anxious, as well as angry and

	alone. The uncertainty of living with secondary breast cancer can be the hardest part for many people, with people telling us it has fundamentally changed their perspective on life and they feel they are living on borrowed time. These common feelings can have a huge impact on people's mental health. A diagnosis of secondary breast cancer can also affect people's relationship with those closest to them which can be particularly difficult to cope with. People living with secondary breast cancer have told us: "How confused and scared I am all the time; even when I'm happy it's always there in the back of your mind". "It is scary. I am permanently scared about my future and what my family will have to deal with without me". As well as the huge emotional toll of living with metastatic breast cancer, patients often have to cope with numerous practical concerns, such as managing their day to day activities, which may include working, household responsibilities and travelling to and from hospital appointments. Someone with secondary breast cancer explains that "it totally and completely affects your life after diagnosis. Endless doctors' appointments can begin to wear you down in no time at all". The symptoms of secondary breast cancer can vary depending on where the cancer has spread to. For example, if it has spread to the bones the main symptoms can include pain in the bones or bone fractures. If breast cancer has spread to the lungs, someone may experience symptoms such as breathlessness or continuous pain and tightness in the chest. Also all breast cancer treatments can cause some side effects and although everyone reacts differently to drugs, for those people who experience more side effects than others, it can cause a significant impact on their day to day lives and health and wellbeing. Patients are keen to find treatments that will halt progression and extend life for as long as possible. As patients' time is limited, people tell us that quality of life is just as important to take into account as length

	of life, as this enables them to spend quality time with their loved ones. Therefore, the type and severity of treatment side effects are also important for patients when considering their treatment decisions. PIK3CA mutations are not currently tested for on the NHS, therefore we have been unable to identify patients with this precise mutation to be able to hear their experiences.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Hormone therapy (also known as endocrine therapy) is commonly given to patients with hormone receptor positive, HER2 negative secondary breast cancer and patients may receive this alongside a targeted treatment. People with hormone receptor positive, HER2 negative secondary breast cancer that has progressed after prior hormone based therapy may receive a number of treatment options depending on their particular circumstances. Since 2019 three CDK 4/6 inhibitors (abemaciclib, palbociclib and ribociclib) in combination with fulvestrant have been available for use on the NHS through the Cancer Drugs Fund (CDF), with ribociclib with fulvestrant now routinely available. CDK 4/6 inhibitors tend to be generally well tolerated by patients. The introduction of CDK 4/6 inhibitors with fulvestrant can also help delay the need for chemotherapy and the difficult side effects that come with it which is hugely welcome by patients and loved ones. CDK 4/6 inhibitors are also routinely available on the NHS when used with an aromatase inhibitor. If a patient progresses on this treatment they would be unable to receive a further CDK 4/6 inhibitor (in combination with fulvestrant) so other treatment options would be considered including everolimus in combination with exemestane. Everolimus in combination with exemestane is another treatment option available for patients with secondary breast cancer after hormone therapy. During the NICE appraisals of CDK 4/6 inhibitors, it was recognised that everolimus with exemestane can be associated with higher toxicity than the CDK 4/6 inhibitors which restricts its use for certain people and that the CDK 4/6 inhibitors would be a preferred treatment choice for many.

8. Is there an unmet need for patients with this condition?	Although the PIK3CA mutation is common and estimated to occur in the tumours of about 30- 40% of people with hormone receptor positive secondary breast cancer there are currently no targeted treatments available on the NHS specifically targeting the PIK3CA mutation. There is significant work being undertaken to tailor treatment to individual cancers and target mutations and PIK3CA is one which could be tested for and a treatment identified for. If this treatment was made available with routine PIK3CA genomic testing on the NHS, it would open the door to a more tailored and personalised treatment approach and provide another treatment option for patients and clinicians to consider. In recent years, we have seen a number of advancements in the treatment of hormone receptor positive, HER2 negative secondary breast cancer with the introduction of CDK 4/6 inhibitors on the NHS. However, patients still experience progression on CDK 4/6 inhibitors and it is reported that resistance to endocrine based therapies is common and can result from increased PI3K pathway signalling as a result of mutations in PIK3CA.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Despite the efficacy of CDK 4/6 inhibitors, progression will eventually occur and we need to continue to find new treatment strategies for patients. The introduction of new treatments which can improve progression free survival is crucial for this group. Progression free survival is highly valued by patients with incurable breast cancer. We know patients value this extra time, as delaying disease progression means more quality time to spend with their relatives and friends. Maintaining a good quality of life for as long as possible is a crucial outcome for this patient group. Delaying progression can also have a positive impact on patients' emotional wellbeing and mental health, as it may mean that the individual can continue doing the activities they enjoy.

	Increasing the time until a patient's disease progresses is also likely to bring some comfort to their relatives and friends which in turn could help to reduce any stress the patient is experiencing worrying about the impact on those closest to them. BYLieve (Cohort A) highlights a median progression free survival of 7.3 months and suggests a median overall survival of 17.3 months. Due to a lack of comparator group we understand the analysis throughout the NICE appraisal to the comparators in scope, will be crucial. In SOLAR1 where only a small group had received prior CDK 4.6 inhibitor, median progression free survival was 5.5 months compared to 1.8 in the placebo arm. Importantly, the introduction of this treatment would provide another treatment option which could be considered and tailored to people if they have the PIK3CA mutation and delay the use of chemotherapy which is traditionally associated with more severe side effects and potentially a poorer quality of life for patients. People can also often be particularly anxious and worried about starting chemotherapy treatment.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	As with all breast cancer treatments, patients may experience side effects which could potentially impact on their quality of life. The most common side effect of this treatment as demonstrated in the SOLAR-1 clinical trial is hyperglycemia. This can result in symptoms such as fatigue, nausea and blurred vision which could impact on a patient's quality of life. If this treatment was made available it would be important that the patients glucose levels were monitored and managed appropriately. This would include blood tests which will require fasting beforehand which could cause some inconvenience to patients, as well as the need to attend regular appointments. Given this treatment could result in hyperglycemia, there are certain people it may not be appropriate for, such as people with diabetes. Other side effects of alpelisib in combination with fulvestrant include rash and diarrhoea which can impact on people's lives if they are not appropriately managed.

	In the ongoing Phase 2 BYLieve trial results from cohort one confirms the most frequent grade 3 or worse side effect was hyperglycaemia. In BYLieve fewer treatment discontinuations due to side effects were observed compared to SOLAR1. It has been suggested that monitoring and management played a considerable role in this. Every treatment for breast cancer has some side effects and each patient's situation will be different with side effects affecting some patients more than others. Patients' willingness to receive treatments will vary, however, as long as all the side effects are clearly discussed with the patient, they will be able to make their own choice as to the level of risk they will be willing to take balanced against the potential benefit of that treatment option. The administration method of a treatment can also be important for many patients. Alpelisib is taken daily in tablet form which many patients may find particularly convenient. Patients would also need to attend an appointment for fulvestrant to be administered, as this is given as an intramuscular injection which could be inconvenient for some. However, for many patients, any inconvenience caused by needing to attend a hospital appointment the administration of fulvestrant, or any discomfort from the injection will be outweighed for many by the advantages of this treatment – primarily the increase in progression free survival and delaying the use of chemotherapy. One patient with experience of fulvestrant injections has told us that although the injection is not the most pleasant experience it is not excruciating pain and the discomfort is minor and is acceptable given the benefits of treatment.

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	As per scope, those with PIK3CA mutation.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	None that we are aware of.

Other issues	
13. Are there any other issues that you would like the committee to consider?	Although research suggests PIK3CA mutations are found in around 40% of hormone receptor positive, HER2 negative tumours, breast cancer patients are not routinely tested for this mutation on the NHS. In order for this treatment to be introduced on the NHS, PIK3CA testing would need to be routinely available to ensure all patients who could potentially benefit from this treatment are tested in a timely manner. In the clinical trial SOLAR-1 only a small number of patients had previously received a CDK 4/6 inhibitor. Given CDK 4/6 inhibitors are available on the NHS and widely used, the BYLIEVE trial will be important to consider during this appraisal to better understand the use of alpelisib with fulvestrant after a patient has progressed on a CDK 4/6 inhibitor and its exact positioning in the treatment pathway.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission:

- A diagnosis of incurable secondary breast cancer can cause considerable anxiety and fear for people and their loved ones, impacting on all aspects of their lives. The uncertainty can be the hardest part for many people.
- A delay in disease progression is important as it enables patients to spend quality time with their friends and families, as well as increasing the likelihood of people being able to continue with their daily activities, which can improve the emotional wellbeing of both patients and their families.
- There are some increased side effects from this treatment option, in particular hyperglycemia and regular monitoring through blood tests is required. The benefits and risks of this treatment need to be clearly discussed with the patient so they can make a decision that is right for them.

- This treatment adds to the drug options available for patients with this type of breast cancer which is incurable and would introduce a more personalised approach to treatment decisions targeted around the PIK3CA mutation. Any new treatments that can delay the need to start on chemotherapy which is generally associated with more severe side effects and a poorer quality of life is welcomed by patients.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Alpelisib in combination with fulvestrant for treating advanced hormone-receptor positive, HER2-negative, PIK3CA-mutated breast cancer [ID3929]]

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

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**NCRI-ACP-RCP-RCR**

3. Job title or position	**RCP registrar**
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**NCRI-ACP-RCP-RCR**
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	**None**

If so, please state the name of manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The main aim of this treatment would be to stop the progression of the disease (PFS - progression free survival) and improve functioning and quality of life of patients. Other aims would be using an oral targeted therapy which allows for time away from the hospital, manageable side-effects, and ability to continue caring and employment roles. As with all treatments it is also hoped that there would be an improvement in overall survival.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by	Clinically significant reduction in tumour size can vary for individuals depending on the site of the tumour and the symptoms it produces such that a 10% reduction in a lymph node causing compressive symptoms in the airway may lead to significant clinical improvement. However, in general this is rarely achieved with a response reduction of less than 20% in assessable disease. Symptomatic improvement of eg fatigue can be rapidly achieved without clear radiological response and is seen with these agents.

x cm, or a reduction in disease activity by a certain amount.)	
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	ER+ve breast cancer accounts for approximately 70% of breast cancer patients. Despite major advances in the treatment in advanced disease in this group, a significant number progress on their current standard of care treatments of which 40% will be amenable to APELISIB. This, in terms of numbers within England and UK, represents a large number of breast cancer patients for whom a targeted approach such as this is an unmet need.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	The current standard of care for this group is to receive CDK4/6 inhibitors as per NICE guidance (TA 495, 496,563) in first line. Patients have to be post-menopausal and many clinicians will render pre – menopausal patients post-menopausal with a GnRH agonist so that they can have access to these effective non-toxic agents. This approach would only not be recommended where the patient needs a very rapid response that the clinician feels is afforded only by chemotherapy (often referred to as visceral crisis) or they are too frail to tolerate even the modest toxicity of CDK4/6 inhibitors and would thus receive endocrine monotherapy. On relapse from endocrine monotherapy, if not already exposed to CDK4/6 patients would receive these agents with fulvestrant (NICE TA 619,579,593) again if clinician feels chemotherapy is not preferential and they can tolerate them. Patients relapsing on CDK4/6 may be offered everolimus exemestane as per NICE guidance (TA 421) or chemotherapy. On third line relapse and beyond they would be considered for various untargeted chemotherapy options eg capecitabine, vinorelbine, paclitaxel and eribulin (TA 423) and at any point supportive treatment alone.
• Are any clinical guidelines used in the treatment of the	NICE guidelines for Advanced Breast Cancer with updated flowchart (2020) together with other international guidelines eg ESMO (European Society of Medical Oncology: Advanced Breast Cancer

condition, and if so, which?	Consensus Recommendations ABC5 (Ann Oncol 2020; 31:12 1623-1649) and National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology v5 June 28,2021.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	There is no agreed prescriptive algorithm for the treatment of advanced breast cancer as individual patient variations make this clinically inappropriate. This is the view internationally hence the above guidelines being as such and not treatment algorithms. The variation in practice across England and UK is in the delivery of chemotherapy over CDK4/6 inhibitor as first line treatment for ER+ve disease. Data from pharma and other ESMO sources suggest this is around 50% and efforts continue to educate clinicians into using these agents first line due to their lack of toxicity and superior effectiveness even with extensive visceral disease (but not visceral crisis); an area traditionally thought to need chemotherapy. When chemotherapy is employed after CDK4/6 there is variation based on patient fitness/ social situation, choice of delivery ie oral or IV as there is little data to suggest specific order of chemotherapy drugs. Activity after CDK4/6 is still seen with most agents (Turner et al N Engl J Med 2018;379:1926-36).
• What impact would the technology have on the current pathway of care?	At present there is still a cohort of patients, between 10-30%, who receive endocrine monotherapy as first line treatment for advanced ER+ve breast cancer. As mentioned above these are mostly the frail patients considered unable to cope with the moderate toxicity of CDK4/6 inhibitors. It is for this group of patients that the technology could potentially apply if they were PIK3CA +ve. This is the SPC indication. There is no data, however, to support patients with PIK3CA mutations benefitting from having Apelisib ahead of CDK4/6 inhibitors or not, with data suggesting that PIK3CA is NOT a predictive biomarker for response to CDK4/6 inhibitors (O'Leary et al Nat Communs 2018;9:896, Turner et al N Engl J Med 2018;379:1926-36). This data suggests that the benefit of CDK4/6 exists irrespective of PIK3CA status and this status should not be used to defer the use of CDK4/6 inhibitors. Due to the effectiveness and excellent tolerance of CDK4/6 inhibitors, it is therefore difficult to assess if clinicians would select Apelisib/Fulvestrant over CDK4/6 /Fulvestrant after relapse on monotherapy as this randomised comparison has not been tested. On relapse following CDK4/6 with aromatase inhibitors, a non-randomised, non-comparative phase II trial data supports the use of Apelisib and Fulvestrant in PIK3CA mutant (positive) patients. (BYlieve Rugo et al Lancet Oncology 2021 22;4, 489-498). A small cohort (approx. 20 patients) in the registration trial, SOLAR-1, also supports this use (Andre et al NEJM 2019 380;20,1929). However, there is a growing cohort of patients relapsing on adjuvant aromatase inhibitors due to the extended use of these agents. They thus only become amenable to CDK4/6 in the second line or aromatase inhibitor resistant setting ie TA619

	where they are used with Fulvestrant. The SOLAR-1 trial did not allow entry of patients who had received fulvestrant and BYlieve used fulvestrant only in those patients who had received aromatase inhibitors. Thus, there is little data to support or refute the use of Apelisib/ Fulvestrant after CDK4/6/ Fulvestrant.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	If the comparator is considered as per the trials ie fulvestrant, then there would be change with regards to need for blood tests and increased attendance that is required for APELISIB. There may also be the use of prophylactic medications to ameliorate the toxicities of APELISIB.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care within specialist breast clinics for prescribing but delivery by general chemotherapy trained nurses and pharmacists.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	This is an oral medication for use with fulvestrant. Due to use of fulvestrant with CDK4/6 most units have the capacity to deliver this, and delivery training has been afforded. There may be some units however that need to develop this. The management of the toxicity of Apelisib is experienced with other medications where training has already been undertaken. The management of hyperglycaemia and rash may require other generic medications as mentioned above.
11. Do you expect the technology to provide clinically	

meaningful benefits compared with current care?	
• Do you expect the technology to increase length of life more than current care?	As the current care is not predominantly the trial comparator ie single agent Fulvestrant but CDK4/6/fulvestrant or chemotherapy, there is currently no data to show increased overall survival compared to current care but this might be anticipated for those who achieve a good progression free survival as per the updated data from SOLAR-1(see below).
• Do you expect the technology to increase health-related quality of life more than current care?	In PALOMA -3 trial where CDK4/6 inhibitor palbociclib with fulvestrant was compared to fulvestrant alone there was significantly better overall global quality of life scores compared to fulvestrant despite the mild but increased toxicity associated with the CDK4/6. This is thought to be due to the correlation of improved progression free status with improved QOL seen in many studies. QOL was maintained in both the SOLAR-1 and ByLieve Trials.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	PIK3CA mutant (positive) patients only as assessed by polymerase chain reaction on tumour tissue.
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare	As in response to 10 pt 3 there should be no increased difficulty for chemotherapy teams as many of the toxicities are seen when using other medications. Physicians would need to familiarise themselves with monitoring procedures and prophylactic measures particularly related to the key toxicities of apelisib of

professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	hyperglycaemia, diarrhoea and rash. In their recent updated paper on toxicity from the SOLAR-1 trial, authors gave further evidence that with prophylactic supportive treatments these toxicities can be managed to reduce dicontinuations and maintain dose intensity (Rugo et al, Annals of Oncology. 2020;31:8: 1001-1010). With the routine use of immunotherapy and the extensive toxicity profile which is attributed to these agents, chemotherapy staff have become trained in recognising and managing metabolic effects, such that hyperglycaemia would be within the scope of units.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Fasting plasma glucose together with other markers of glucose metabolism would need to be an additionally monitored and the protocol used is likely to be that as from the recent paper above. This is to be confirmed and updated by the Company. ESMO/ABC5 guidelines may also be adopted regards other side-effects such as rash.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the	As with previous technology assessments the value for patients being disease stable or non-progressive is not given enough weight in the QALY. Having non-progressive disease and the health related benefit impacts on economic and social functioning of patients in terms of employment, elderly and childcare. These overall impacts are not adequately addressed in the QALY.

quality-adjusted life year (QALY) calculation?	
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Apelisib with fulvestrant is a 'step change' as it is the only treatment to be evaluated for the PIK3CA +ve patients both after endocrine monotherapy (randomised SOLAR-1 registration trial see above) and prospectively evaluated following CDK4/6 inhibitors (ByLieve study see above). This, targeted agent allows for individualised care, with a greater potential for response rather than the 'one size fits all' approach of chemotherapy. Other options such as Evorolimus have not been evaluated in this setting and have significant pulmonary toxicity which has become a concern more recently with the Coronavirus pandemic and both the risk of contracting COVID-19 and diagnostic uncertainty.

	The problem as stated above is the application is as per licence ie after first line monotherapy rather than after CDK4/6.
• Does the use of the technology address any particular unmet need of the patient population?	PIK3CA has been identified as potentially targetable for several years and this is the first possibility of treating a significant number of patients with the correct agent.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	As addressed in 13 and 14, knowledge of these toxicities and improved prophylactic measures have significantly improved the toxicity profile of APELISIB. QOL was maintained in both trials as stated above and as with other agents it is hoped that the impact of improved progression free survival together with manageable toxicity will result in improved quality of life
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	
• If not, how could the results be extrapolated to the UK setting?	The registration SOLAR-1 trial studied apelisib and fulvestrant predominantly in the endocrine resistant group who relapsed on adjuvant or advanced use aromatase inhibitors monotherapy (>80%) and would currently receive CDK4/6 inhibitors as per TA 579,593 and 619. There is no direct comparison of the use of apelisib/ fulvestrant versus CDK4/6/ fulvestrant or aromatase inhibitors in PIK3CA mutant patients so these groups should not be used as a comparator. As mentioned above, PIK3CA mutations are not a predictive

	marker for CDK4/6 response and have shown to be effective across all groups (Turner et al N Engl J Med 2018;379:1926-36). The SOLAR-1 trial did show improvement in PFS for the small number of patients who had received CDK4/6 in the first line setting and ByLieve Trial also showed benefit after CDK4/6. This reflects current UK practice. For patients who relapse early on their adjuvant hormonal therapy it could be argued from the SOLAR-1 trial that they may benefit most from use of targeted PIK3CA therapy. The application is not intended to cover this group ie 'after monotherapy' is presumed to mean after advanced disease endocrine monotherapy. However, if the licence covers 'monotherapy' in the adjuvant setting then this could be a cohort that would be preferentially selected to use this technology before CDK 4/6. There is however no level 1 evidence to support use ahead or not of CDK4/6 inhibitors. The use of CDK4/6 would have to be with fulvestrant again and there is level 1 evidence for this. CDK4/6/fulvestrant as treatment after relapse on aromatase inhibitor monotherapy for PIK3CA positive patients is effective and there is evidence of improvement in overall survival in those who relapse after 2 yrs on adjuvant aromatase inhibitor treatment and sustained 24 months clinical benefit on previous endocrine treatment for advanced disease (Turner et al N Engl J Med 2018;379:1926-36.)
• What, in your view, are the most important outcomes, and were they measured in the trials?	The most important outcome is always overall survival and although a secondary endpoint this has been reported in SOLAR-1, with statistically non-significant but clinically significant approximate 8-month

	improvement in overall survival with Apelsib/Fulvestrant over Fulvestrant alone (Andre et al Ann Oncol 2021 Feb;32(2):208-217.) Progression free survival, however, can be a surrogate for OS improvements as seen with recent CDK4/6 trials (Turner et al N Engl J Med 2018;379:1926-36.) Progression free survival was improved significantly in SOLAR-1 by 5.3 months in the Apelisib/Fulvestrant group. Quality of life was maintained in the SOLAR-1 and ByLieve trials.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	See re PFS
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not aware of any
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	

20. Are you aware of any new evidence for the comparator treatment(s) since the publication of similar NICE technology appraisal guidance?	The only true comparator can be that within the registration trial ie Fulvestrant. Others are current 'best clinical practice' that may be used in similar clinical scenarios as Apelisib and fulvestrant but have not been evaluated using PIK3CA status to target the therapy or compared in a randomised control trial with the technology. Since the other technologies were published involving CDK4/6 inhibitors, a meta-analysis has indicated overall survival advantage of these agents over endocrine monotherapy. The trials involved had patients who were PIK3CA +ve and -ve (mutant and wild type) (Schettini et al J Natl Cancer Inst 2020;112(11): 1089-1097). As mentioned CDK4/6 therapy with hormonal options shows no treatment difference for PIK3CA positive or negative.
21. How do data on real-world experience compare with the trial data?	There is limited real-world data on Apelisib but as colleagues use this drug with more skill with regards to the key toxicities, they find that it is well tolerated with anecdotally lower levels of fatigue, nausea and mucositis than many other chemotherapeutic agents.
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	Unaware of any equality issues.

22b. Consider whether these issues are different from issues with current care and why.	

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.

- This technology is an effective targeted therapy for PIK3CA positive patients after endocrine monotherapy who cannot receive CDK4/6 for significant medical reasons.
- This technology is a potentially effective targeted therapy for PIK3CA positive patients after CDK4/6 and hormonal therapy which should be further evaluated in formal patient access programmes and clinical trials.
- The effectiveness of CDK4/6 inhibitors in this group of patients currently does not justify removing this therapy from PIK3CA positive patient's clinical pathway.
- Further review with updated BYlieve study would be appropriate for the Company to review the position of the license.
- Further quality of life data would be of benefit for this technology

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

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Declared competing interests of the authors

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

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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.

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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.

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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

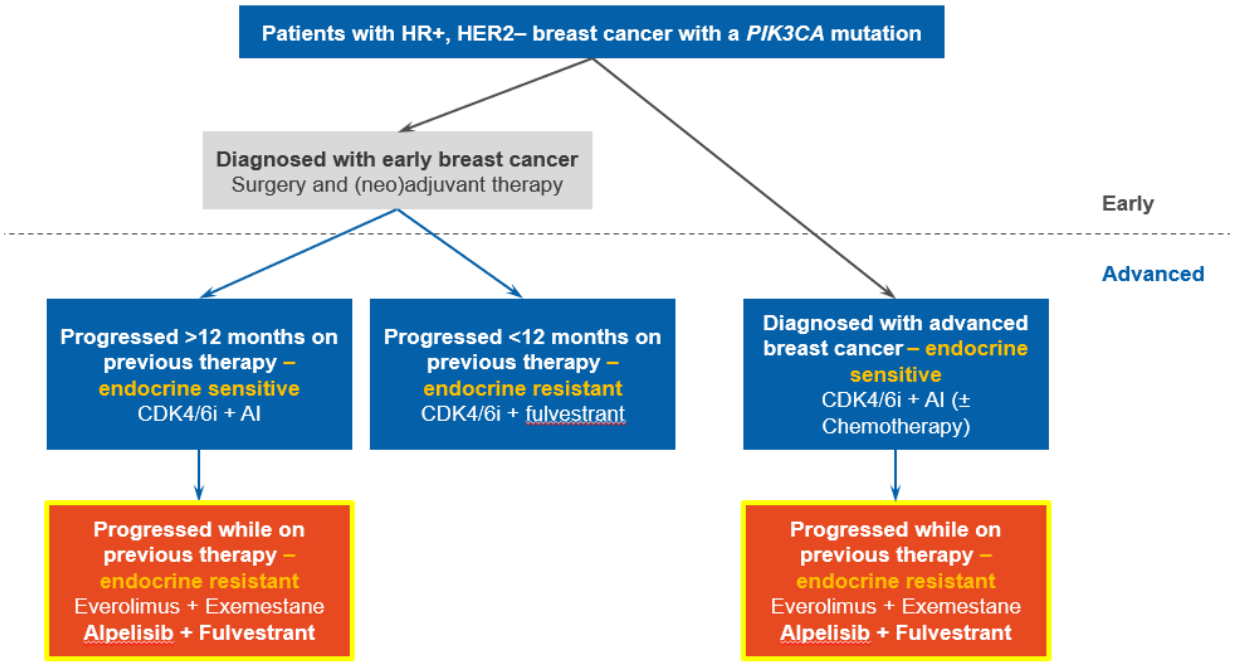
Advanced breast cancer (ABC) includes both unresectable locally advanced disease and metastatic disease. Although the disease is much more common in women, it can also affect men. The company's submission (CS)[1] (Section B.1.3.1) states that approximately 5-6% of women with breast cancer in the UK have 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

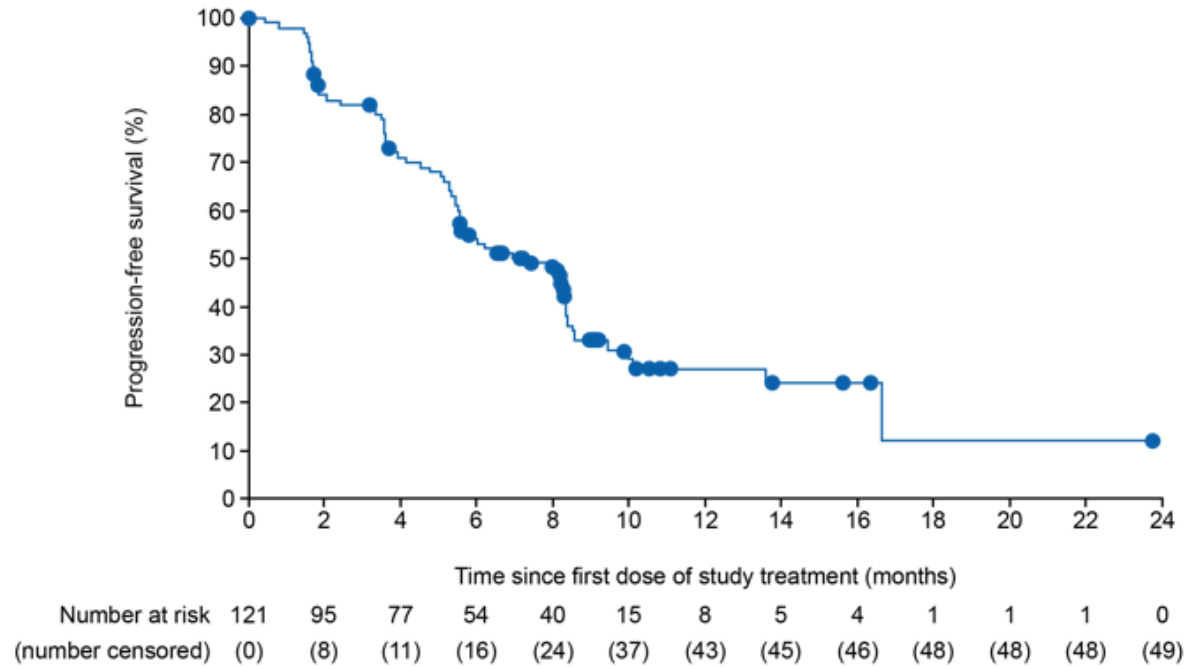
Alp - alpelisib; CDK4/6i - cyclin-dependent kinase 4/6 inhibitor; CI - confidence interval; CS - company's submission; Fulv - fulvestrant; mFAS - modified full analysis set; N - number; PFS - progression-free survival

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

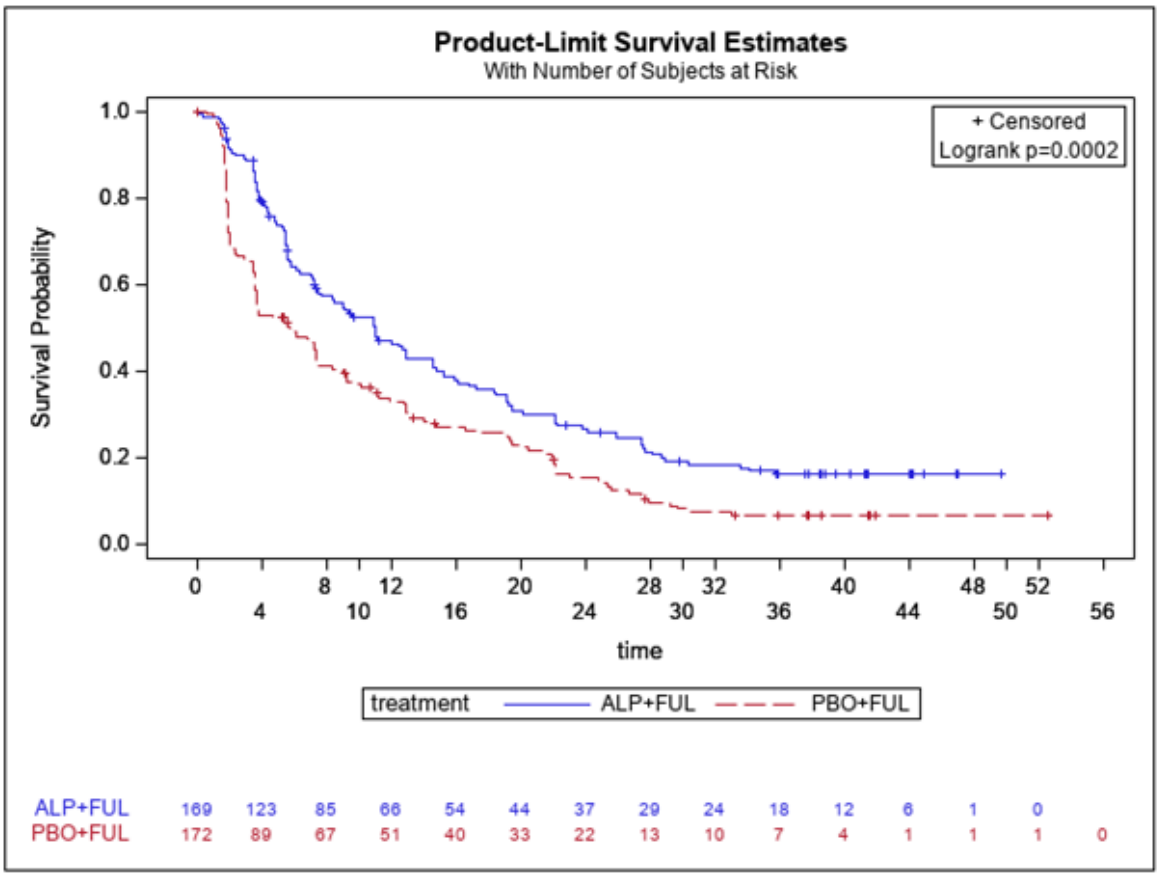
Alp - alpelisib; CDK4/6i - cyclin-dependent kinase 4/6 inhibitor; CI - confidence interval; CS - company submission; FAS - full analysis set; Fulv - fulvestrant; HR - hazard ratio; ITC - indirect treatment comparison; N - number; NR - not reported; Pbo - placebo; PFS - progression-free survival

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).

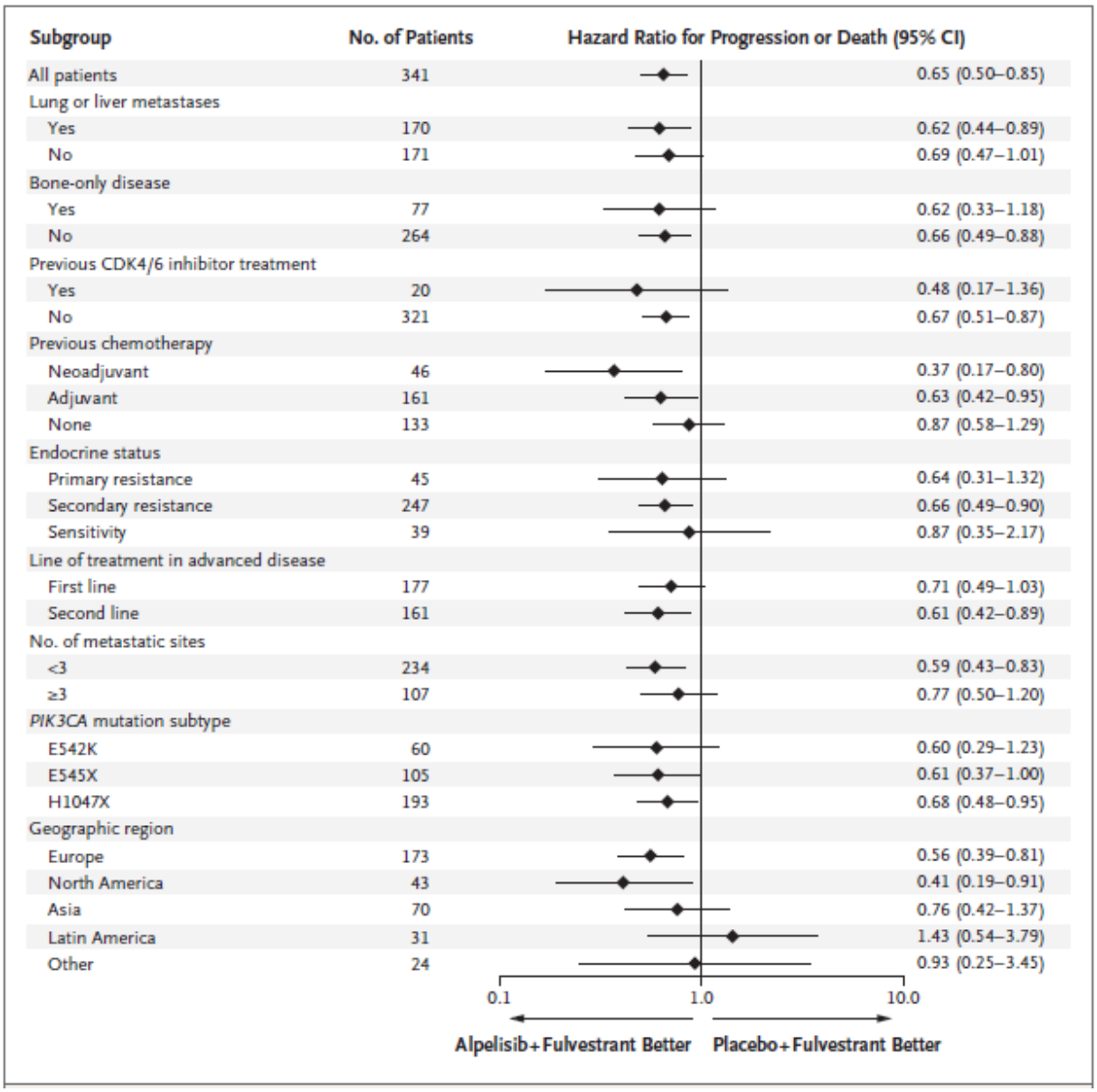
BYLieve Cohort A: PFS subgrouped by menopausal status

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

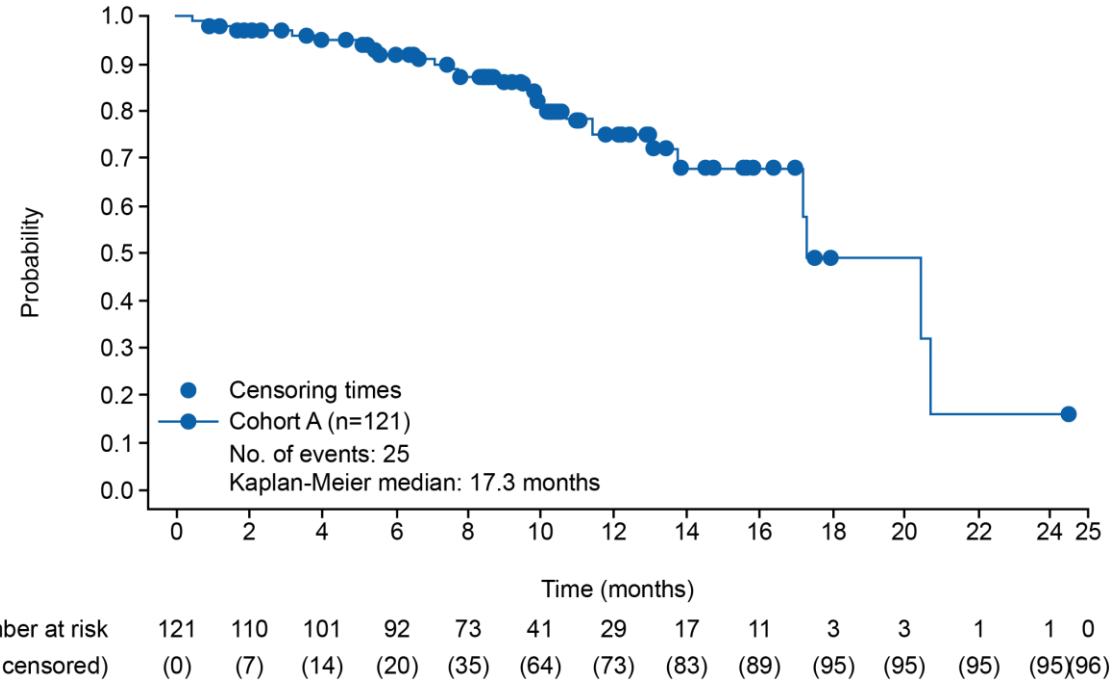
Alp - alpelisib; CDK-4/6i - cyclin-dependent kinase 4/6 inhibitor; CI - confidence interval; CS - company's submission; Fulv - fulvestrant; mFAS - modified full analysis set; N - number; OS - overall survival

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

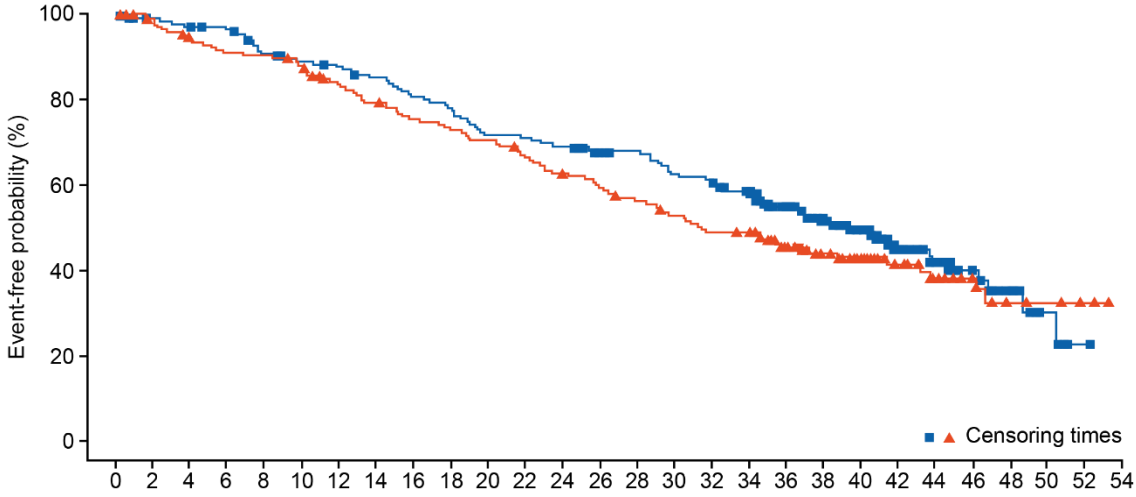
Figure 5: Kaplan-Meier plot of OS in BYLieve Cohort A, mFAS population (reproduced from CS, Figure 5)



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 (vs.). There (%) 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				
SAEs				
Treatment-related				
Fatal SAEs				
Treatment-related[a]				
AEs leading to discontinuation				
Treatment-related				
AEs leading to dose adjustment/ interruption				
AEs requiring additional therapy				

[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)

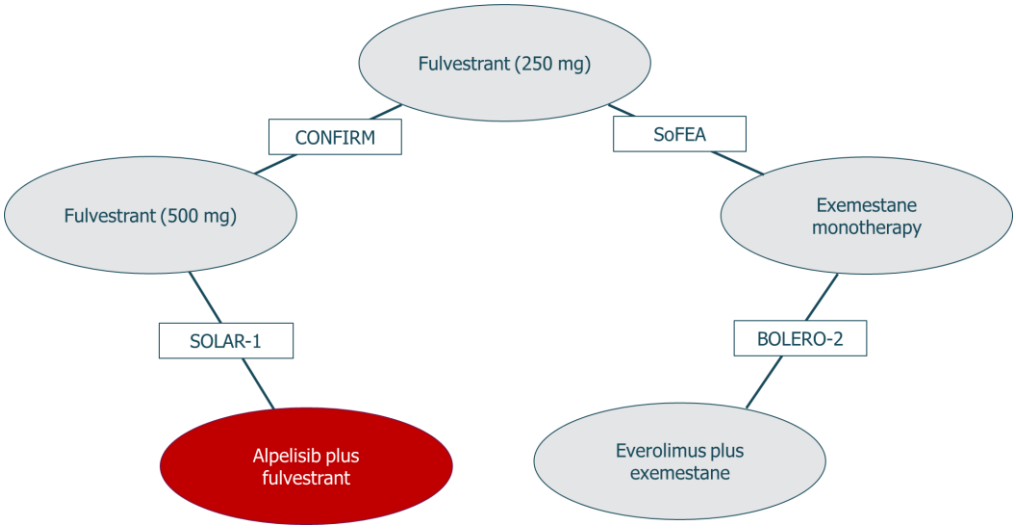


Table 23: Studies and cohorts included in ITC (adapted from CS, Table 23, CS Appendix D, Tables 27 and 28, and clarification response, question A22)

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 ( )	Eve/Exe ( )			
OS	Yes	Alp/Fulv ( )	Eve/Exe ( )			

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 to and the estimated HR of OS ranged from to . 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).

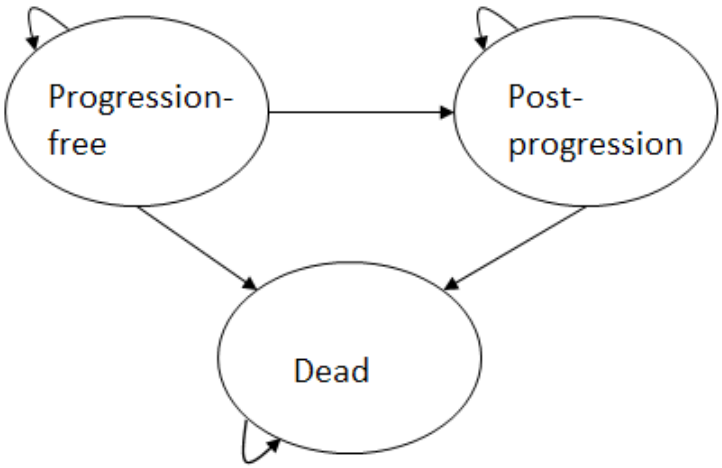
Comparators

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.

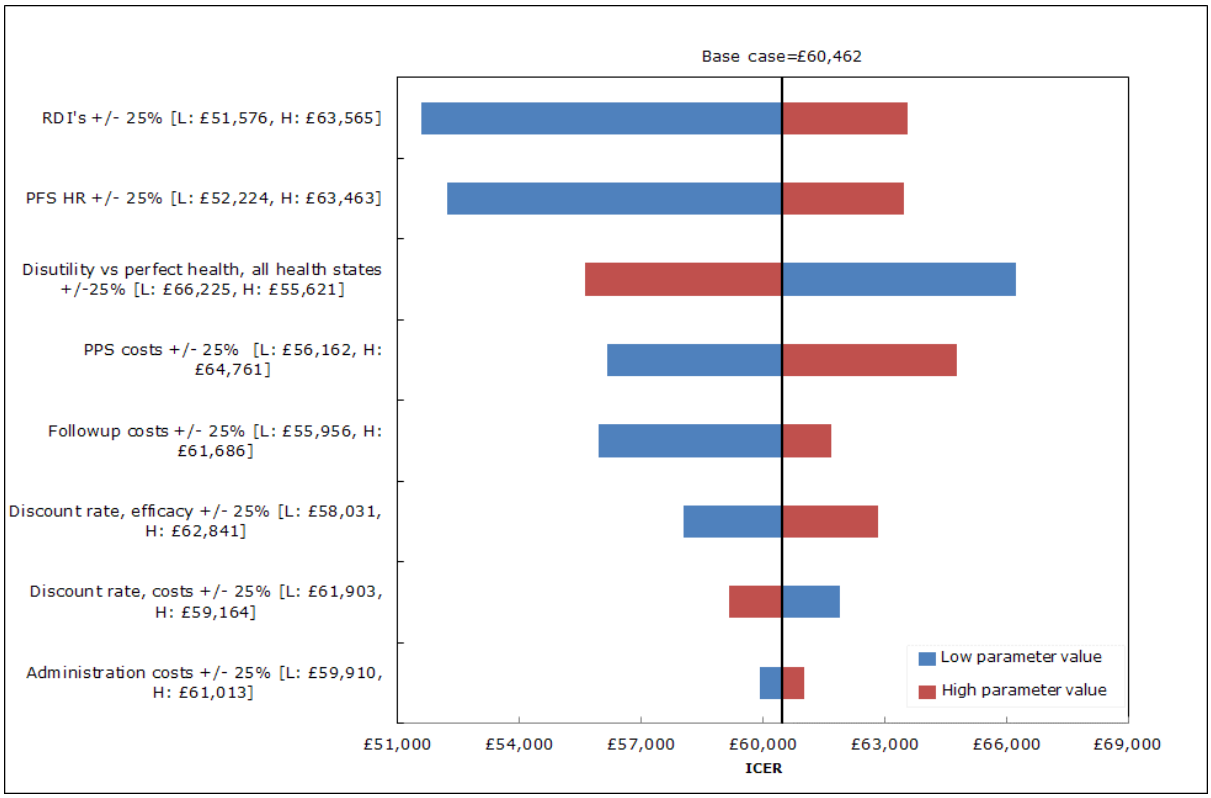
Figure 20: Company's PSA results – CEACs, alpelisib plus fulvestrant versus everolimus plus exemestane, including PAS discounts for alpelisib and everolimus (generated by the ERG)

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

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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"

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

Alpelisib in combination with fulvestrant for treating advanced hormone-receptor positive, HER2-negative, PIK3CA-mutated breast cancer [ID3929]

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on 5 October 2021** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Section 1: Typographical clarifications

Population

Issue 1 Positioning of alpelisib plus fulvestrant

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 6: The company's economic analysis is mostly based on data from a subset of the Cohort A of BYLieve study population (patients who received prior CDK4/6i+AI treatment as first-line therapy in the advanced setting).	Please amend as follows: 'The company's economic analysis is mostly based on data from a subset of the Cohort A of BYLieve study population (patients who received prior CDK4/6i+AI treatment as immediate prior therapy ~~as first-line therapy in the advanced setting~~).'	Patients in Cohort A of BYLieve received alpelisib plus fulvestrant following CDK4/6i+AI as immediate prior therapy, as reported on page 38–39 of Document B of the Company Submission. Some patients in Cohort A of BYLieve received CDK4/6i+AI in the (neo)adjuvant setting, as per our response to Clarification Question B1.	The ERG believes that the company has misunderstood that the text in brackets relates specifically to the [redacted] second-line patients who contribute data to the model, rather than the broader group in Cohort A of BYLieve. For clarity, the text has been amended to read: *"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."*

Comparators

Issue 2 Relevance of tamoxifen, exemestane, fulvestrant and chemotherapy as comparators

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 6: The ERG's clinical	Please amend as follows:	The ERG noted that tamoxifen	These points are already

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.	'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. In addition, the company considered that monotherapies such as tamoxifen would be reserved for frail patients who cannot tolerate other therapeutic options such as everolimus (as part of everolimus plus exemestane) and would therefore not be the same patient population expected to receive alpelisib plus fulvestrant.'	monotherapy, fulvestrant monotherapy and chemotherapy may be used in patients who are older/unfit or are at high risk of visceral crisis. However, these treatments are not widely used in practice, and monotherapies such as exemestane monotherapy or tamoxifen monotherapy would be reserved for frail patients who cannot tolerate other therapeutic options such as everolimus (as part of everolimus plus exemestane) and would therefore not be the same patient population expected to receive alpelisib plus fulvestrant. This approach to comparators aligns with previous appraisals in HR+, HER2– ABC (TA579, TA619 or TA687/TA593).[1-3] In addition, fulvestrant monotherapy has received a negative recommendation from NICE for the treatment of oestrogen-receptor-positive, locally advanced or metastatic breast cancer in postmenopausal women whose cancer has relapsed on or after adjuvant anti-oestrogen therapy, or who have disease progression on anti-oestrogen therapy (TA239).[4]	made in the ERG report. To avoid unnecessary repetition, the ERG report has been amended more briefly to state that "*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.*"
Page 15–16: However, the ERG notes that the NICE scope[12] also lists Exe and Tam monotherapy	Please amend as follows: 'However, the ERG notes that the NICE	As above, exemestane monotherapy and tamoxifen are not relevant comparators to alpelisib	This amendment is not necessary as the quote directly below the suggested

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.	scope[12] also lists Exe and Tam monotherapy as comparators, but these options are not included in the CS as they are not used widely in clinical practice.[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.	plus fulvestrant as they are not widely used in UK clinical practice in this setting.	amendment already states that the use of Exe and Tam is not widespread.

Network meta-analysis (NMA)

Issue 3 Applicability of the Bucher Indirect Treatment Comparison (ITC) and the Patient-Adjusted Indirect Comparison (PAIC) to the post-CDK4/6i setting

Description of problem	Description of proposed amendment	Justification for amendment	ERG response

Page 57: 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).	Please amend as follows: '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); however, these HRs are applied to data from BYLieve, which are specific to the post-CDK4/6i population.'	While the ERG has correctly pointed out that the Bucher ITC and the PAIC are informed by data from SOLAR-1, the HRs generated from these analyses were applied to survival curves generated from BYLieve data. In the absence of head-to-head data comparing alpelisib plus fulvestrant against everolimus plus exemestane in the post-CDK4/6i setting, the Company maintains that these indirect comparisons are the most appropriate methodologies with the available data.	This is not a factual inaccuracy. The text is describing the methods used to estimate relative treatment effects and their relevance to the target population, not how those treatment effect estimates are used in the economic model. However, for clarity the text has been amended to read: *"…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."*
Page 78: 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 (see Section 4.4).	Please amend as follows: '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 nature of this trial (see Section 4.4).'	It is important to note the reasoning for the exclusion of BYLieve.	This is not factually inaccurate, but the text has been amended in line with the company's suggestion. The ERG notes that the Section number provided in the ERG report was incorrect; this has been amended to instead refer to Sections 4.8 and 4.9.

Issue 4 Subgroups of studies used in the Bucher ITC

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 66: • CONFIRM[21] and SoFEA[22] did not restrict the population to PIK3CA mutant patients • CONFIRM[21] and SoFEA[22] did not restrict the population to HER2- patients; clinical advisors to the ERG and subgroup analyses presented by 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]	Please amend as follows: • As CONFIRM[21] and SoFEA[22] did not measure *PIK3CA* status, ~~did not~~ restriction of the population to *PIK3CA* mutant patients could not be performed • As HER2- status was not measured in CONFIRM,[21] ~~and SoFEA[22] did not~~ restriction of the population to HER2- patients could not performed.~~; c~~Clinical advisors to the ERG and subgroup analyses presented by 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]	It is important to clarify that population restrictions could not be performed in the absence of relevant subgroup data from the source trials. As the ERG noted, the Company has provided ITC results using the HER2- subgroup from SoFEA.	For clarity, the first bullet point has been amended as suggested by the company. The second bullet-point has been amended to read: • *As CONFIRM21 and SoFEA22 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]"
Page 66: The data from CONFIRM[21] and SoFEA[22] were not restricted to the second-line population	Please amend as follows: 'The data from CONFIRM[21] and SoFEA[22] were not able to be restricted to the second-line population due to a lack of subgroup data by line of therapy for these trials'	It is important to clarify that population restrictions could not be performed in the absence of subgroup data from the source trials.	The ERG agrees. The text has been amended to read *"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"*

Issue 5 Selection of propensity score model used in the PAIC

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 70: 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.	Please amend as follows: '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; however, 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 in response to clarification	The logistic equation for estimating propensity scores was estimated with several alternative sets of selected covariates as per the company response to question A23.	This is not factually inaccurate, but the text has been amended for clarity to read: *"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,*

	from the ERG.'		*using different model/variable selection methods, but provided no additional information on how the best method was selected."*

Clinical data from BYLieve (Cohort A)

Issue 6 Endocrine status of participants in BYLieve

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 35: In SOLAR-1, 11% were endocrine-sensitive and 89% were endocrine-resistant (this was not reported for BYLieve).	Please amend as follows: '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 80.3% of patients were endocrine-resistant (percentages do not sum to 100% due to incomplete data) ~~(this was not reported for BYLieve)~~.'	The endocrine status at study entry of participants in Cohort A of BYLieve is listed in the Baseline characteristics table (Table 8) of Document B of the Company Submission. Additionally, the data for SOLAR-1 are incorrect and should be updated in line with the data reported in Table 33 of the Appendices of the Company Submission.	The text has been amended as suggested by the company.

Issue 7 Subgroup analysis of BYLieve

Description of problem	Description of proposed amendment	Justification for amendment	ERG response

Page 41: A *post hoc* analysis of BYLieve (Cohort A and B) 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. It is not clear to the ERG why this analysis was not restricted to Cohort A.	Please amend as follows: 'A *post hoc* analysis of BYLieve (Cohort A ~~and B~~) 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. ~~It is not clear to the ERG why this analysis was not restricted to Cohort A.~~'	The *post hoc* analysis was done on both Cohort A and B of BYLieve separately. For the purpose of the Company Submission, we have reported results relevant to Cohort A only. Removing 'Cohort B' may clarify that the results reported in Table 16 are specific to Cohort A only.	The text has been amended as suggested by the company.

Issue 8 Outcomes in BYLieve

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 48: No patient-reported outcomes (PROs) were reported for BYLieve.[31]	Please amend as follows: 'No patient-reported outcomes (PROs) were measured in ~~reported for~~ BYLieve.[31]'	PROs were not measured in BYLieve; rather than PROs being measured but not reported.	The ERG agrees. The text has been amended as suggested by the company.
Page 49: Discontinuations due to AEs occurred in 18/127 patients (14%). Dose adjustments are not reported in the CS.[1]	Please amend as follows: 'Discontinuations due to AEs occurred in 18/127 patients (14%). AEs leading to dose adjustments/interruptions are ~~not~~ reported in Table 31 of Document B of the CS.[1]'	AEs leading to dose adjustments/interruptions are reported in Table 31 of Document B of the Company Submission.	The text has been amended as follows: *"Discontinuations due to AEs occurred in 18/127 patients (14%). AEs leading to dose adjustments/ interruptions occurred in*

			82/127 patients (65%).”

Economic analysis

Issue 9 Justification of survival curve extrapolation

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 107: **Table 38: Summary of company’s justification of PFS and OS model selection** PFS – Alp/Fulv: None documented in minutes OS – Alp/Ful: None documented in minutes	Please amend as follows: **Table 38: Summary of company’s justification of PFS and OS model selection** PFS – Alp/Fulv: ~~None documented in minutes~~ Clinician agreed that the log-normal curve was the most reasonable in estimating PFS, based on clinical plausibility of predicted survival rates OS – Alp/Ful: ~~None documented in minutes~~ Clinician agreed that the log-logistic curve was the most reasonable in estimating PFS, based on clinical plausibility of predicted survival rates	Clinician validation of the curve extrapolations for PFS and OS was recorded in the Company’s ‘Novartis DoF. UK Clinician Interview (June 2021)’ reference provided in the reference pack at the Clarification Questions stage.	The ERG agrees. The text has been amended as suggested by the company. For consistency, the paragraph before the table has been amended to read as follows: *“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, which were shared by the company as part of the CS and clarification response reference packs, respectively.”*

Page 107–108: • 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 and relative statistical goodness-of-fit to the observed data. Clinical plausibility of the selected PFS function is not discussed in either the CS[1] or in the minutes of the advisory board.[58] However, sensitivity analyses assessing alternative PFS models are presented in the CS for this endpoint (see **Error! Reference source not found.**). • 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, according to the CS,[1] the projections were *"validated by clinical expert opinion."* The advisory board minutes[58] do not mention that this model was discussed during the meeting. However, sensitivity analyses assessing alternative OS models are presented in the CS for this endpoint (see **Error! Reference source not**	Please amend as follows: • 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, ~~and~~ relative statistical goodness-of-fit to the observed data and clinical plausibility. The choice of survival curve extrapolation was validated by clinical expert opinion, where survival estimates were considered to be clinically plausible. ~~Clinical plausibility of the selected PFS function is not discussed in either the CS[1] or in the minutes of the advisory board.[58] However,~~ ~~s~~Sensitivity analyses assessing alternative PFS models are presented in the CS for this endpoint (see **Error! Reference source not found.**). • 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. ~~according to the CS,[1] the projections were *"validated by clinical expert opinion."*~~ The choice of survival curve extrapolation was validated by clinical expert opinion, where survival estimates were considered to be clinically plausible. ~~The advisory board minutes[58] do not mention that this model was discussed during the meeting. However,~~ ~~s~~Sensitivity analyses assessing alternative OS models are presented in the CS for this endpoint (see **Error! Reference source not found.**).	As above.	The ERG agrees – The text has been amended in line with the company's suggestions. For consistency of the ERG report, additional amendments have been made. The text of the first three bullet points in the page after Table 38 read as follows: " • *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*

found.).			*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 meeting59 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).”*

Comparators

Issue 10 Removal of brand name for generic fulvestrant

Description of problem	Description of proposed amendment	Justification for amendment	ERG response

Page 24: The intervention under consideration is alpelisib (Piqray®) plus fulvestrant (Faslodex®).	Please amend as follows: 'The intervention under consideration is alpelisib (Piqray®) plus fulvestrant ~~(Faslodex®)~~.'	Fulvestrant is available as a generic.	The ERG has amended the text in line with the company's suggestion.

Economic analysis results

Issue 11 Frequency of tests and clinical visits

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 99: In addition, the ERG was unable to check the frequencies of tests and clinical visits used to calculate disease management costs as the CS[1] does not specify the TAs from which these estimates were drawn.	Please remove this text.	The frequencies of tests and clinical visits were reported in Table 69–71 in Document B of the Company Submission. These frequencies were sourced from NICE CG81, and the respective Summary of Product Characteristics (SmPC) documents, as reported in the table footnotes.	The ERG agrees in part with the company's suggestion. The ERG was still unable to verify some of the values reported in the submission (Tables 69 to 71) and used in the model, with their original sources (CG81 and the SmPC for Afinitor). The text in the report has been amended to read: *"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."*

Section 2: Misreporting from the Company Submission

Issue 12 Misreporting from the Company Submission

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 25: 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 after four weeks of treatment and every three months thereafter.	Please amend as follows: '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, ~~after~~ four weeks of treatment and every three months thereafter.'	The current wording is incomplete and should be updated to align with the monitoring schedule of HbA1c, as reported in the Technology being appraised table (Table 2) of Document B of the Company Submission.	The ERG agrees. The text has been amended in line with the company's suggestion.
Page 36, Table 5: Endocrine status Endocrine-resistant: NR; 149 (88.2%); 153 (89.0)	Please amend as follows: Endocrine status Endocrine-resistant: NR; 143 (84.6); 149 (86.6)	These data are incorrect and should be updated in line with the data reported in Table 33 of the Appendices of the Company Submission.	The data in Table 5 have been amended as suggested by the company. An additional row has been added to show the number of patients for whom endocrine status was not available.

Section 3: Confidentiality highlighting

Issue 13 Confidentiality highlighting amendments

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 7: AIC highlighting is required for the results from the	Please amend as follows to add AIC highlighting:	Results from the Bucher ITC are not anticipated to be published.	All requested amendments to highlighting have been made

Bucher ITC	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 the ERG report. Please note that we have removed all marking of LYGs generated by the model in the ERG report, except for Figure 22.
Page 7: AIC highlighting is required for the results from the second-line endocrine-resistant patients from SOLAR-1	Please amend as follows: 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]).	Novartis apologise that these were incorrectly marked in the submission, however results from the second-line endocrine-resistant population in SOLAR-1 are not anticipated to be published.	
Page 38: AIC highlighting is required for the results from the second-line endocrine-resistant patients from SOLAR-1	Please amend as follows: '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]'	Results from the second-line endocrine-resistant population in SOLAR-1 are not anticipated to be published.	
Page 39, Table 7: AIC highlighting is required for the results from the second-line endocrine-resistant patients from SOLAR-1	Please amend as follows: Median PFS: Alp/Fulv [redacted]; Pbo/Fulv [redacted] HR (95% CI): [redacted]	Results from the second-line endocrine-resistant population in SOLAR-1 are not anticipated to be published.	
Page 43: AIC highlighting is required for the results from the	Please amend as follows: 'In second-line endocrine-resistant patients (n=	Results from the second-line endocrine-resistant population in	

second-line endocrine-resistant patients from SOLAR-1	[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]).'	SOLAR-1 are not anticipated to be published.	
Page 44, Table 9: AIC highlighting is required for the results from the second-line endocrine-resistant patients from SOLAR-1	Please amend as follows: Median OS: Alp/Fulv [redacted]; Pbo/Fulv [redacted] HR (95% CI): [redacted]	Results from the second-line endocrine-resistant population in SOLAR-1 are not anticipated to be published.	
Page 59: AIC highlighting is required for the SOLAR-1 OS data from the 2020 data-cut.	Please amend as follows: '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 **Error! Reference source not found.** and **Error! Reference source not found.** in this report)'	These results are not anticipated to be published.	
Page 75: AIC highlighting is not required for the proportion of female patients in the model	Please amend as follows: 'Patients are assumed to have a mean age of 57 years at model entry and all patients are assumed to be female.'	Confidentiality highlighting is not required here.	
Page 80: AIC highlighting is not required for the proportional of female patients in the model	Please amend as follows: '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.'	Confidentiality highlighting is not required here.	
Page 87, Figure 17: AIC highlighting is required for the	Please add AIC highlighting to Figure 17: Observed Kaplan-Meier plot and modelled	The TTD curves are not anticipated to be published.	

TTD curves for alpelisib	TTD, alpelisib* (re-drawn by the ERG)		
Page 96, Figure 20: CIC highlighting is required for the results of the PSA	Please add CIC highlighting to 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)	Results of the PSA are based on the confidential list price and proposed PAS price for alpelisib and confidential PAS price for everolimus.	
Page 114, Figure 22: AIC highlighting is required for data relating to the OS results from the ITC	Please add AIC highlighting to Figure 22: Distribution of incremental OS from company's PSA, alpelisib plus fulvestrant versus everolimus plus exemestane	Results from the ITC are not anticipated to be published.	
Page 122: CIC highlighting is not required for the estimates of LYG from the model	Please amend as follows: 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	Confidentiality highlighting is not required here.	
Page 122, Table 45: CIC highlighting in not required for the estimates of LYG from the model	Please amend to remove all CIC highlighting from Table 45	Confidentiality highlighting is not required here.	

References

1. National Institute for Health and Care Excellence (NICE): TA579. Abemaciclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy. Available at: https://www.nice.org.uk/guidance/ta579 [Last accessed: 14 July 2021].
2. National Institute for Health and Care Excellence (NICE): TA619. Palbociclib with fulvestrant for treating hormone receptor-positive, HER2-negative, advanced breast cancer. Available at: https://www.nice.org.uk/guidance/TA619 [Last accessed: 14 July 2021].
3. National Institute for Health and Care Excellence (NICE): TA687. Ribociclib with fulvestrant for treating hormone receptor-positive, HER2-negative, advanced breast cancer. Available at: https://www.nice.org.uk/guidance/TA687 [Last accessed: 9 May 2021].
4. National Institute for Health and Care Excellence (NICE): TA239. Fulvestrant for the treatment of locally advanced or metastatic breast cancer. Available at: https://www.nice.org.uk/guidance/ta239 [Last accessed: 01 October 2021].

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Technical engagement response form

Alpelisib in combination with fulvestrant for treating advanced hormone-receptor positive, HER2-negative, PIK3CA-mutated breast cancer [ID3929]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments**: 5pm, 11 November 2021**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.

- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under [redacted], all information submitted under [redacted], and all information submitted under [redacted] in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	Novartis Pharmaceuticals UK Ltd
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Since April 2005 Novartis has exclusively licensed glycopyrronium bromide and certain intellectual property relating to its use and formulation from Vectura and its co-development partner, Sosei Heptares.

	The following inhaled medications are comprised of, or contain glycopyrronium bromide: • Seebri® Beezhaler® (glycopyrronium bromide) (used as a maintenance treatment for Chronic Obstructive Pulmonary Disease [COPD]) • Ultibro® Breezhaler® (indacaterol/glycopyrronium bromide) is used as a maintenance treatment for COPD • Enerzair® Breezhaler® (indacaterol/glycopyrronium bromide/mometasone furoate) is used as a maintenance treatment for asthma uncontrolled with LABA/ICS. Phillip Morris International (a tobacco company) is currently in the process of acquiring Vectura Group plc.

NICE National Institute for Health and Care Excellence

Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Key issue
Key issue 1: Uncertainty surrounding the relevance of the evidence to the target population	**No**	Novartis is awaiting a decision by the Medicines and Healthcare products Regulatory Agency (MHRA) regarding the Type II variation to the existing licence from the European Medicines Agency (EMA). Initial questions from the MHRA regarding the application have been received, and a decision is therefore anticipated later in [redacted]. Based on engagement with the MHRA thus far, a negative result is not anticipated. Novartis will inform NICE as soon as an update is received.
Key issue 2: Restrictions of the evidence used to inform the model - comparison against a single comparator (Everolimus/Exemestane) in the second-line population	**No**	**Modelled population versus target population** As described in the company submission, the anticipated licence wording for alpelisib plus fulvestrant is "[redacted]" In UK clinical practice, a cyclin-dependent kinase inhibitors (CDK4/6i) plus endocrine therapy is the standard of care for patients with HR+, HER2– advanced breast cancer with a *PIK3CA* mutation as first-line therapy. Therefore, in line with the anticipated licence in the UK, the most relevant evidence from BYLieve is that of patients who received alpelisib plus fulvestrant in the second-line setting, following use of a CDK4/6i

		and aromatase inhibitor (AI) at first-line. The patient population in BYLieve who receive a CDK4/6i + AI in other lines of treatment is not reflective of the use of CDK4/6i + AI in UK clinical practice and therefore were not considered within the submission. Novartis consider that any recommendation from NICE should reflect the anticipated licence wording as presented in the company submission. **Relevant comparators** The ERG has identified tamoxifen monotherapy, fulvestrant monotherapy and chemotherapy as possible comparators that may be used in older/unfit patients or patients at high risk of visceral crisis. However, as discussed in the Decision Problem table of Document B of the Company Submission and question C2 of the Clarification Questions, tamoxifen and fulvestrant monotherapies are not widely used in UK clinical practice in this setting and are not considered standard of care. Instead, they are typically reserved for frail patients who cannot tolerate therapeutic options such as everolimus and would therefore not be the same patient population expected to receive alpelisib plus fulvestrant. Similarly, patients at high risk of visceral crisis would typically be offered chemotherapy (irrespective of the availability of alpelisib plus fulvestrant or everolimus plus exemestane). Therefore, and overall, Novartis maintains that everolimus plus exemestane is considered the main comparator for alpelisib plus fulvestrant.
Key issue 3: Uncertainty surrounding relative treatment effects for Alpelisib/Fulvestrant versus Everolimus/Exemestane	**No**	In the absence of head-to-head data comparing alpelisib plus fulvestrant and everolimus plus exemestane, Novartis has provided the following analyses to the ERG and NICE to this point, representing a range of methodological approaches based on what was feasible given the relevant, available data: • A Bucher ITC comparing alpelisib plus fulvestrant and everolimus plus exemestane (Section B.2.7.2 of the Company Submission) – In the absence of head-to-head data, a network comprising the CONFIRM and SoFEA trials was

		required to connect the SOLAR-1 and BOLERO-2 trials. SOLAR-1 was used as BYLieve could not be included in the network due to its single-arm nature. As the ERG noted, none of these trials were exclusively conducted in the post-CDK4/6i population. Hence, the second-line populations of SOLAR-1 and BOLERO-2 were used as a proxy for the post-CDK4/6i population. The hazard ratios (HRs) for progression-free survival (PFS) and overall survival (OS) were in favour of alpelisib plus fulvestrant. The resulting HRs (95% confidence interval [CI]) from this Bucher ITC for everolimus plus exemestane vs. alpelisib plus fulvestrant were [redacted] for PFS and [redacted] for OS. ○ In the economic model, the HRs derived from the Bucher ITC described above were applied to extrapolated data from BYLieve (question A15 of the Clarification Questions). This approach assumes that the treatment effect between alpelisib plus fulvestrant and everolimus plus exemestane is consistent between second-line ABC and post-CDK4/6i populations. This assumption was validated by clinical expert opinion who considered that, despite the limited direct evidence comparing alpelisib plus fulvestrant and everolimus plus exemestane in the post-CDK4/6i setting, there is no reason to believe that the treatment effect would be different in this population.[1] ○ Upon the ERG's request, Novartis has also performed a revised Bucher ITC using data from the HER2– subgroup from SoFEA (question A20 of the Clarification Questions). The HRs for PFS and OS for alpelisib plus fulvestrant and everolimus plus exemestane are directionally similar to that in the Bucher ITC using SoFEA data regardless of HER2– status. • Matching/weighted analysis of BYLieve versus real-world standard of care (Section B.2.5.1 of the Company Submission) – Compared with therapies received after CDK4/6is in the real-world setting, there was a consistent trend in the PFS HRs in favour of alpelisib plus fulvestrant

		• Patient-adjusted indirect comparison (PAIC) (Section B.2.7.3 of the Company Submission) – A PAIC was conducted using second-line data from SOLAR-1 and BOLERO-2. The HRs for PFS and OS favour alpelisib plus fulvestrant as compared with everolimus plus exemestane Overall, each of these approaches support a benefit with alpelisib plus fulvestrant versus current treatment options, with the matching/weighted analysis providing evidence in a post-CDK4/6i population specifically. However, Novartis acknowledge the limitations associated with each approach. Therefore, in the absence of a more robust indirect analysis in the post-CDK4/6i population, the Bucher ITC is considered a reasonable proxy for the relative efficacy of alpelisib plus fulvestrant in the post-CDK4/6i population. In addition, despite the uncertainty associated with the ITC methodologies employed, clinical advisors consulted by the ERG did consider the company's OS models to be plausible, supporting that the cost-effectiveness model clinical outputs were reasonable and in line with anticipated UK practice. Finally, Novartis is planning to conduct a phase III, randomised, double-blind, placebo-controlled trial of alpelisib plus fulvestrant in the post-CDK4/6i setting (EPIK-B5). As per question A4 of the Clarification Questions, this trial is anticipated to be initiated in [redacted], with initial results anticipated in [redacted]. The population is expected to be comparable with Cohort A of BYLieve, as well as the population addressed in the Company Submission. The comparator for this trial is placebo plus fulvestrant.[2] Therefore, the results from EPIK-B5 may reduce uncertainty in terms of the consistency of the benefit of alpelisib plus fulvestrant versus placebo plus fulvestrant in a CDK4/6i naïve and experienced population through comparison to the results of SOLAR-1, and therefore support that the results from the Bucher ITC in a largely CDK-4/6i naïve network are likely applicable to the post-CDK4/6i population. However, EPIK-B5 would still require the CONFIRM and SoFEA trials to connect to everolimus plus exemestane in a future Bucher ITC, and therefore the same degree of uncertainty in this regard would remain.

Key issue 4: Concerns regarding company's HRQoL assumptions	**Yes**	In the original company submission, a utility value of [redacted] following progression was applied in the base case based on EQ-5D-5L data (cross-walked to 3L) derived from SOLAR-1; this utility value was validated by clinical expert opinion that stated that beyond the second-line setting for ABC (i.e. equivalent to patients in the post-progression state in the cost-effectiveness model) patients would still have various treatment options open to them (as reflected with the inclusion of costs for post-progression therapies in the model), and their utility would therefore not be substantially decreased as compared to earlier treatment lines.[1] The ERG noted some concerns around potential bias in the use of the SOLAR-1 utility values resulting from potential informative censoring due to EQ-5D-5L data being largely missing after progression; the ERG consequently favoured deviating from the NICE reference case and using the published post-progression utility value from Lloyd *et al.* (0.505) which has been used in previous NICE appraisals in ABC.[3] Novartis maintains that applying the utility value from Lloyd *et al.* (2006) in the base case and/or scenario analysis is not appropriate. Lloyd *et al.* (2006) is now a relatively old publication and the treatment landscape for ABC has changed substantially in the time since the Lloyd utility values were published.[3] The post-progression health state from Lloyd *et al.* (2006) is described as follows: • *"You have a life-threatening illness and your condition is getting worse. You are on stronger medication to relieve any increasing pain. You experience severe fatigue. You have lost your appetite and have experienced significant weight loss.* • *You feel too tired to go out or to see family and friends. Some of your relationships with them are strained.* • *You are able to wash and dress yourself with some assistance. You are often unable to do jobs around the house or other daily activities. You are reliant on others.*

		• *You feel your physical appearance is deteriorating and you have little or no sexual drive.* • *You feel depressed and feel dependent on your family and friends. You have little hope for the future."* Considering the changes to the treatment landscape in ABC over the last 15 years, the vignette description from Lloyd *et al.* (2006) no longer reflects the experiences of patients in the modelled post-progression health state.[3] In addition, the most recently appraised technology in ABC (TA725; abemaciclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy) proposed an alternative utility value for the post-progression survival (PPS) state from Mitra *et al.* (2016), with a value for the PPS health state of 0.69 (note that in TA725, this is reported as 0.670; however, the source publication states that the utility value for third-line or later patients with ABC is 0.69).[4, 5] In TA725, this value was considered to be methodologically preferable as compared to that derived from Lloyd *et al.* (2006) due to the use of EQ-5D to measure health-related quality of life in people with breast cancer.[3-5] This value was used as part of the base case on which the NICE Appraisal Committee based their decision to recommend the technology. Further to the uncertainty around the utility source for the PPS state, the original company base case also included an assumed disutility of 0.03 that was applied to everolimus plus exemestane in the on-treatment, PFS health state; alpelisib plus fulvestrant was modelled with an on-treatment PFS utility of [redacted] and therefore, everolimus and exemestane had an on-treatment PFS utility of [redacted]. The derived difference in utility between the two treatment groups may reflect differences in the impact of adverse events, however, may also be the consequence of patient heterogeneity or use of different utility instruments and mapping algorithms. The ERG's clinical advisors considered this assumption may not be appropriate and

instead considered it reasonable to expect that utility would be similar for both alpelisib plus fulvestrant and everolimus plus exemestane.

Given the availability of various sources for the utility value for the PPS state and the uncertainty in the assumption for the on-treatment PFS state, Novartis have conducted a series of interviews with four additional clinical experts to inform this technical engagement response with the aim of resolving uncertainty around the most appropriate utility values to apply in the cost-effectiveness model. The experts were presented with the base case assumptions that were used in the company submission, along with the feedback received from the ERG regarding the uncertainty of those values, and the alternative approaches and values from Lloyd *et al.* (2006) and Mitra *et al.* (2016).[3, 4] The responses from the experts are summarised in Table 1.[6]

Table 1: Summary of clinical expert preferences relating to utility values of PPS and on-treatment, PFS health states

	Date of Interview	Preferred PPS health state utility	Preferred on-treatment, PFS health state
Expert 1: Consultant in Medical Oncology	1st Nov 2021	SOLAR-1 ([redacted]) or Mitra *et al.* (0.69)	No data to support difference in utilities
Expert 2: Medical Oncologist	2nd Nov 2021	SOLAR-1 ([redacted])	No data to support difference in utilities
Expert 3: Consultant Oncologist	5th Nov 2021	Mitra *et al.* (0.69)	No data to support difference in utilities
Expert 4: Consultant Oncologist	5th Nov 2021	Mitra *et al.* (0.69)	Alpelisib plus fulvestrant may have higher utility than everolimus plus exemestane

Abbreviations: PFS: progression-free survival; PPS: post-progression survival.
Source: Novartis Data on File.[6]

		All four of the clinical experts interviewed by Novartis considered that the patients seen in their practice at third-line (i.e. equivalent to the post-progression state in the cost-effectiveness model) would have a utility that is reflective of the Mitra *et al.* (2016) publication, noting that this value is very similar to the PPS value of [redacted] measured in the SOLAR-1 trial. They did not believe that the utility for progressive, metastatic breast cancer given by Lloyd *et al.* (2006) is reflective of their patients at this point in their disease and stated that the treatment pathway for advanced breast cancer has evolved significantly in the 15 years since its publication.[6] Additionally, the clinical experts agreed that, in the absence of direct evidence to support a difference, an assumption of equal utility for the on-treatment, progression-free state was fair.[6] As such, given the reasons outlined above, Novartis have included the PPS utility value from Mitra *et al.* (2016) in the updated base case along with utilising the same on-treatment PFS utility of [redacted] (derived from SOLAR-1 data) for both alpelisib plus fulvestrant and everolimus plus exemestane (see Table 3).
Key issue 5: Discrepancy between deterministic and probabilistic model results	**No**	Novartis acknowledges the difference observed between the deterministic and probabilistic results (Table 40 of the ERG Report). As noted by the ERG, the probabilistic sampling of OS suggested that alpelisib plus fulvestrant is associated with reduced survival as compared to everolimus plus exemestane in ~18% of samples, which, as discussed with a clinical expert, is not considered clinically plausible (Figure 22 of the ERG Report).[7] Some individual iterations of the PSA in particular are highly implausible, with estimates of a difference in life years gained of up to 8 years in favour of everolimus and exemestane. Given the limitations described above, the ERG was unable to recommend the use of the results from the probabilistic analyses to the Appraisal Committee for decision-making. Hence, whilst the probabilistic results may be useful to inform decision making in other appraisals, the use of the probabilistic results in this instance could introduce biases in interpretation of the results informing decision making given the proportion of

		unfeasible samples predicting poorer survival outcomes with alpelisib plus fulvestrant versus everolimus plus exemestane that would not be realised in practice. Therefore, Novartis consider the deterministic results to be more appropriate to inform the cost-effectiveness of alpelisib plus fulvestrant against everolimus plus exemestane.

Additional issues

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
ASA1: Alternative treatment duration	Section 5.4.2, Table 42, page 118	Yes	While Novartis does not consider the scenarios presented by the ERG assuming waning treatment effect to be relevant, Novartis has concerns about the methodological approach employed by the ERG when implementing these scenarios. The ERG extrapolates PFS and OS from BYLieve and applies a HR to the alpelisib plus fulvestrant curve from BYLieve to obtain the survival curves for everolimus plus exemestane. The ERG then uses the calculated hazard for everolimus plus exemestane (derived from the BYLieve parametric extrapolations adjusted by a HR) in the alpelisib plus fulvestrant arm after 3 or 5 years in the scenarios assuming treatment effect waning. Novartis believes that the approach used by the ERG is methodologically inconsistent with the modelling approach, in which the treatment effect is based on the relative efficacy of everolimus plus exemestane versus alpelisib plus fulvestrant and not vice versa. Novartis therefore believes that a more consistent approach would be to keep the survival distribution for alpelisib plus fulvestrant from BYLieve unchanged and to set the HR for everolimus versus exemestane versus alpelisib plus fulvestrant to 1.0 after the time when no treatment effect is assumed (i.e., the same hazard between treatment arms).

In addition to being methodologically inconsistent, Novartis are also concerned that the approach taken by the ERG overestimates the ICERs for these scenarios, as shown in Table 2 below (ICERs presented in Table 42 of the ERG report for the scenarios ASA1a and ASA1b are replicated using the ERG implementation and proposed alternative approach).

Table 2: Impact of waning treatment effect scenarios

Option	Inc. LYGs	Inc. QALYs	Inc. costs	ICER
ASA1a: Treatment effect duration = 3 years				
ERG implementation	[redacted]	[redacted]	[redacted]	£92,195
Alternative implementation	[redacted]	[redacted]	[redacted]	£85,021
ASA1b: Treatment effect duration = 5 years				
ERG implementation	[redacted]	[redacted]	[redacted]	£83,640
Alternative implementation	[redacted]	[redacted]	[redacted]	£80,435

Abbreviations: ERG: Evidence Review Group; ICER: incremental cost-effectiveness ratio; LYG: life-years gained; QALY: quality-adjusted life year.

Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER
N/A (Correction of errors)	The original submitted model included the following minor errors: (a) incorrect calculation of administration of Eve and (b) incorrect cost estimate for *PIK3CA* testing.	These errors identified by the ERG have been corrected in the updated company base case in line with EA1 of the ERG report.	See Table 3 below.
N/A (drug wastage)	Drug wastage was not considered in the model.	In line with EA4 of the ERG report, the updated base case incorporates seven days' wastage for all oral drugs (alpelisib, everolimus and exemestane). Wastage costs were assumed not to apply to fulvestrant, as this is not an orally administered therapy.	See Table 3 below.
Key issue 4: Concerns regarding company's HRQoL assumptions	On-treatment utility values for PFS were derived from SOLAR-1 data for alpelisib plus fulvestrant and BOLERO-2 for everolimus plus exemestane, respectively.	On-treatment utility values for PFS are now the same for both alpelisib plus fulvestrant and everolimus plus exemestane based on data from SOLAR-1.	See Table 3 below.
Key issue 4: Concerns regarding company's HRQoL assumptions	The post-progression utility value was derived from SOLAR-1.	Based on a previous NICE appraisal and clinical validation sought as part of this technical engagement response, the post-progression utility value is now derived from Mitra *et al.* (2016; 0.69).[4, 5]	See Table 3 below.

N/A (generic price for fulvestrant)	In the original company submission, an anticipated generic price for fulvestrant was utilised. In the ERG report, the list price of fulvestrant was used.	Since the original company submission, an eMIT price for fulvestrant has become available (£124.51; representing a 76% discount on the list price). This price is utilised in the updated base case.	See Table 3 below.
N/A (incorporation of updated PAS for alpelisib)	In the original company submission, a PAS of [redacted]% was used.	This PAS has now been revised to [redacted]%.	See Table 3 below.

Table 3: Updated base case results – PAS price for alpelisib

	Incremental QALYs	Incremental cost	ICER (change from line above) – with previous PAS for alpelisib ([redacted]%)*
Company's base case (assuming list price for fulvestrant)	[redacted]	[redacted]	**£60,462**
Updates to previous base case (cumulative)			
+ EA1: Correction of errors	[redacted]	[redacted]	£60,554 (+92)
+ EA4: Drug wastage	[redacted]	[redacted]	£61,342 (+788)
+ Key issue 4: Concerns regarding company's HRQoL assumptions (Equal utility for the progression-free on-treatment state in both groups)	[redacted]	[redacted]	£63,236 (+1,894)
+ Key issue 4: Concerns regarding company's HRQoL assumptions (Post-progression utility value from Mitra *et al.*)	[redacted]	[redacted]	£64,044 (+808)
+ Additional issue (Generic price for fulvestrant)	[redacted]	[redacted]	£54,192 (-9,852)
+ Updated company base case (Incorporation of updated PAS for alpelisib)	[redacted]	[redacted]	**£49,881**

* [redacted] PAS applied for alpelisib in all rows with exception of final row where updated PAS is included ([redacted]).
Abbreviations: HRQoL: health-related quality of life; ICER: incremental cost-effectiveness ratio; PAS: Patient Access Scheme; QALY: quality-adjusted life year.

References:

1. Novartis. Alpelisib plus fulvestrant for the treatment of HR+, HER2– advanced breast cancer with a PIK3CA mutation. Clinical Validation (May 2020). Data on File. 2020.
2. ClinicalTrials.gov. Study to Assess the Efficacy and Safety of Alpelisib Plus Fulvestrant in Participants With HR-postitive (HR+), HER2-negative, Advanced Breast Cancer After Treatment With a CDK4/6 Inhibitor and an Aromatase Inhibitor. (EPIK-B5). Available from: https://clinicaltrials.gov/ct2/show/NCT05038735. Last accessed: 28 October 2021.
3. Lloyd A, Nafees B, Narewska J, et al. Health state utilities for metastatic breast cancer. British journal of cancer 2006;95:683-690.
4. Mitra D, Wood R, De Courcy J, et al. Patient reported health utility in HR+/HER2-advanced/metastatic breast cancer. Value in Health 2016;19 (7):A749.
5. National Institute for Health and Care Excellence (NICE): TA725. Abemaciclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy. Available at: https://www.nice.org.uk/guidance/ta725 [Last accessed: 29 October 2021].
6. Novartis. Interviews with UK Clinicians (November 2021). Data on File. 2021.
7. Novartis. Interview with UK Clinician (June 2021). Data on File. 2021.

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Technical engagement response form

Alpelisib in combination with fulvestrant for treating advanced hormone-receptor positive, HER2-negative, PIK3CA-mutated breast cancer [ID3929]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments**: 5pm, 11 November 2021**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**NIHR/ACP/UKBI/RCP**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**Nil**

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Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Uncertainty surrounding the relevance of the evidence to the target population	No	**In agreement with the ERG. The current EMA licence does not relate to the target population but the expectation is of achieving the MHRA Type II variation. The exact wording of this is not available but is thought to include the target population. As such the submission has merit and reflects the clinical need post CDK4/6 inhibitors. Across Europe, Apelisib is being utilised outside of its licence reflecting pragmatic clinical practice after CDK4/6 with aromatase inhibitors (as per** NICE TA 495.496 and 563)**. This is evidenced by the ESMO ABC5 Guidelines quoted and other international guidelines.**
Key issue 2: Restrictions of the evidence used to inform the model - comparison against a single comparator (Everolimus/Exemestane) in the second-line population	**No**	**For this submission will use the term Endocrine+ to relate to treatments that contain endocrine agent and another targeted agent. Examples are Everolimus/ Exemestane and Apelisib and Fulvestrant. Clinically, as expressed by the ERG, the Everolimus/Exemestane comparator is too limiting and although there is no scientific reason why patients, post progression on CDK4/6, should not respond to Endocrine+ option, BOLERO-2 did not investigate this population. When looking at the guidance above, these quote the use of Everolimus and Exemestane as options at the same point in the pathway as the Company Submission (CS). These guidelines seek to extend the period before the use of chemotherapy as long as possible with these Endocrine + options. In the UK /England the use of Everolimus (at the**

		licensed approved dose for TA 421) with Exemestane, has not been popular (data should be available from Bluteq applications for 421) due to its toxicity eg mucositis and pneumonitis. Many clinicians select a single agent oral chemotherapy over this Endocrine + option, as they consider the efficacy/toxicity profile of this Endocrine +option less favourable than single agent oral Capecitabine chemotherapy. The comparator of chemotherapy and particularly single agent Capecitabine, should therefore be utilised. Fulvestrant is an evidence based comparator based on the SOLAR-1 study but its use in England is not fully funded with approximately 50% of England having locally funding arrangements. This practically does not make it a suitable comparator in England. The other options, are very small numbers and the single agent endocrine options eg Tamoxifen and Exemestane would and only apply where patient choice dictated a low toxicity/low hospital attendance options. This is because the response of these single agent endocrine options is historically very low ie under 15% in second line settings.
Key issue 3: Uncertainty surrounding relative treatment effects for Alpelisib/Fulvestrant versus Everolimus/Exemestane	**NO**	**Agree that the indirect modelling methods to compare with Everolimus/Exemestane with Alpelisib /Fulvestrant are not appropriate because as mentioned above, BOLERO-2 did not contain the target population of post CDK4/6. They are unlikely, however, to ever be directly compared in a randomised controlled trial.**
Key issue 4: Concerns regarding company's HRQoL assumptions	**NO**	**Do not agree that the HRQoL would be different between these two Endocrine + options ie particularly that the Apelisbib/Fulvestrant option would be superior. Both these Endocrine +options carry with them toxicity that can result in more attendances and feed into QOL outcomes. Clinicians would consider these impacts at best similar and at worst more significant for Apelisib, in part due to the increase attendances as a result of hyperglycaemia monitoring.**

Key issue 5: Discrepancy between deterministic and probabilistic model results	YES	**Do not accept there is enough evidence to suggest this application fits the NICE End of Life Criteria. The use of CDK4/6 inhibitors with AI as per NICE TA 495.496 and 563, has led to improvements of progression free survival (PFS) with median PFS from the registration studies of approximately 2 years. After these treatments subsequent therapies would include the Endocrine + options as above and then several lines of chemotherapy. The most recent survival analysis from MONALESSA-2 (basis for TA496) presented at ESMO 2021 shows that at 6 yrs, survival was 44 % for the CDK4/6 group with the median overall survival 63.9 months with the CDK4/6 (Hortobagyi et al LBA17 esmo 2021). There is perhaps a small group of patients that relapse very early after CDK4/6 that may be considered as reaching the NICE criteria but data is not presented on this potential cohort within the CS or ERG.**

Additional issues

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response

Additional issue 1: ERG Issue 8 Concerns regarding company cost assumptions.	**5.3.4 pg 114** 5.4 pg 117	**YES**	**CS explains that need PIK3CA on liquid biopsy and if negative tumour tissue . Need clarification that this whole cost is covered.**
Additional issue 2: International Guidelines and applicability to UK practice.	**Whole submission- summary comments**	**YES**	**The BYLieve study unfortunately had no comparator and, the randomised clinical trials will likely never be done to provide a better UK post CDK4/6 comparator. The updated BYlieve data (provided by the company) should therefore be utilised as likely to be the only large dataset of post CDK4/6 that reflects modern practice. The post CDK4/6, PIK3 CA mutant cohort have only been investigated in the SOLAR-1 and BYlieve trials and data from any future randomised trial (mentioned EPIK-B5 as due to start in the ERG submission) would take several years to report. If this trial utilised Fulvestrant as the comparator, again one could argue that this is not a useful UK comparator due to the usage/funding issues of Fulvestrant mentioned above. A chemotherapy comparator would reflect the most real world UK comparator but it is unknown if this trial is planned and again would take several years to report. Therefore as direct randomised evidence applicable to UK practice is unlikely to occur, not accepting this submission would remove the additional treatment option for this group in line with international guidelines. Due to the toxicity of this agent clinicians would make a judgement (as**

			they do with Everolimus) as to if they offer this drug with its toxicity profile or accept chemotherapy toxicity instead. It is unlikely therefore, that it would be similar to the more prescribed pathway of care that follows in HER-2 disease, where until the most recent addition (TA 704) the agents have a low toxicity /high efficacy profile and clinicians fully utilise the NICE approved accepted agents. This should mean that the numbers using this drug will be relatively small and the absolute cost lower than expected. Having it is an internationally accepted option would be appropriate.
Additional issue N: Insert additional issue			**[INSERT / DELETE ROWS AS REQUIRED]**

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Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER
Insert key issue number and title as described in the ERG report	**Briefly describe the company's original preferred assumption or analysis**	**Briefly describe the change(s) made in response to the ERG report**	**Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER**
..	..	..	**[INSERT / DELETE ROWS AS REQUIRED]**
Company's preferred base case following technical engagement	**Incremental QALYs: [QQQ]**	**Incremental costs: [£££]**	**Please provide the revised company base-case ICER resulting from combining the changes described, and the change from the company's original base-case ICER**

NICE National Institute for Health and Care Excellence

Clinical expert statement & technical engagement response form

Alpelisib in combination with fulvestrant for treating advanced hormone-receptor positive, HER2-negative, PIK3CA-mutated breast cancer [ID3929]

Thank you for agreeing to comment on the ERG report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form:

- In **part 1** we are asking you to complete questions where we ask for your views on this technology. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.
- In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.
- The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a clinical perspective could help either:
- resolve any uncertainty that has been identified
  OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

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Please return this form by **5pm** on **11 November 2021**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow.If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

PART 1 – Treating a patient with advanced hormone-receptor positive, HER2-negative, PIK3CA-mutated breast cancer and current treatment options	
About you	
1. Your name	[redacted]
2. Name of organisation	[redacted]
3. Job title or position	**Consultant in Medical Oncology**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? **x** a specialist in the treatment of people with advanced hormone-receptor positive, HER2-negative, PIK3CA-mutated breast cancer? **x** a specialist in the clinical evidence base for advanced hormone-receptor positive, HER2-negative, PIK3CA-mutated breast cancer or the technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it **X** other (they didn't submit one, I don't know if they submitted one etc.) Not sure who nominated me

nominating organisation's submission)	
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**
The aim of treatment for advanced hormone-receptor positive, HER2-negative, PIK3CA-mutated breast cancer	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The aim of palliative treatment of advanced breast cancer is to prolong survival with best possible quality of life. This includes slowing time to progression, as progression may mean increase in symptom burden and/or escalation to more toxic treatments (including chemotherapy).
9. What do you consider a clinically significant treatment	A delay to median time to progression of 3 months or more. Naturally any apparent benefit has to be weighed against toxicity/convenience of treatment.

response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	
10. In your view, is there an unmet need for patients and healthcare professionals in advanced hormone-receptor positive, HER2-negative, PIK3CA-mutated breast cancer?	Advanced breast cancer remains an incurable malignancy. On that basis there remains a need to prolong survival as much as possible and with best possible quality.
What is the expected place of the technology in current practice?	
11. How is the condition currently treated in the NHS?	
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE Guidance Advanced breast cancer, however these struggle to keep up to date with the rapid pace of change in the management of breast cancer. Therefore more reliance on international: ESMO, ABC4, ASCO and NCCN guidelines.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please	The majority of patients with advanced HR positive HER2 negative breast cancer will receive 1st line endocrine therapy plus a CDK4/6 inhibitor. A small proportion of patients will receive 1st line chemotherapy followed by maintenance endocrine therapy/CDK4/6 inhibitor. A further very small proportion of (usually frail) patients will receive endocrine therapy alone. There will be general agreement about this, although relative proportions between centres might vary. In the second line setting, options include: 1) Exemestane and everolimus

state if your experience is from outside England.)	2) Endocrine therapy monotherapy: exemestane, fulvestrant, tamoxifen 3) Oral chemotherapy (Capecitabine) 4) IV chemotherapy: if significant progression/burden of metastatic disease.
• What impact would the technology have on the current pathway of care?	Introduction of a new option into 2nd line therapy.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	If we assume exemestane/everolimus is current standard then patients will need to come in to clinic for Fulvestrant injections, as well as more frequent visits for monitoring toxicity/bloods. There will be some resource implications for management of blood sugars.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	None.

13. Do you expect the technology to provide clinically meaningful benefits compared with current care?	
• Do you expect the technology to increase length of life more than current care?	Yes: as introduces an additional option.
• Do you expect the technology to increase health-related quality of life more than current care?	This depends on the real-life toxicity profile of Alpelisib and how this compares with E and E. At present it is difficult to answer this question.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	There are concerns about using Alpelisib in those with greater risks from hyperglycaemia, including those aged more than 75, BMI>30 and diabetic or pre-diabetic patients.
The use of the technology	
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any	More difficult, as will require glucose monitoring (which is not currently required to such a degree) and management of hyperglycaemia which will require upskilling of HCP workforce. Ideally patients would be provided with BM monitors.

practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Close monitoring of blood sugars and management of this side-effect will need to follow the SPC and the company-provided resources.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No
18. Do you consider the technology to be innovative in its potential to make a significant and	Yes

substantial impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes: because it is a targeted therapy (to PIK3CA) going beyond simply treating all patients with HR positive HER2 negative breast cancer in the same/similar manner.
• Does the use of the technology address any particular unmet need of the patient population?	
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Yes hyperglycaemia, rash and diarrhoea.
Sources of evidence	
20. Do the clinical trials on the technology reflect current UK clinical practice?	No

• If not, how could the results be extrapolated to the UK setting?	The pivotal trial: SOLAR-1 did not include any significant number of patients who had received a CDK4/6 inhibitor. Hence the reliance on BYLIEVE Cohort A: this is well elaborated in the submission and ERG appraisal.
• What, in your view, are the most important outcomes, and were they measured in the trials?	PFS and OS and toxicity: yes these were reported.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No. Well elaborated and described in published evidence and presentations.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator treatment(s) since the publication	No

of NICE technology appraisal guidance [TA421]	
23. How do data on real-world experience compare with the trial data?	There is very little data on RWE as access in UK has been very limited.
Equality	
24a. Are there any potential equality issues that should be taken into account when considering this treatment?	Not that I am aware of.
24b. Consider whether these issues are different from issues with current care and why.	
Topic-specific questions	
25. Is the eligible population in England expected to differ to the population in BYLieve trial? Are	Not significantly.

the inclusion/exclusion criteria appropriate?	
26. Would you expect to give alpelisib plus fulvestrant until progression or for a limited cycle or duration?	Until progression or unmanageable toxicity
27. From the NICE scope, everolimus plus exemestane was identified as the only relevant comparator by the company. Is the exclusion of the other comparators appropriate and representative of established practice in the NHS in England?	I would regard oral capecitabine chemotherapy as well as exemestane and everolimus as appropriate comparators.
28. Do you expect a difference in the HRQoL between alpelisib plus fulvestrant and everolimus plus exemestane?	Unknown at present. No direct evidence.

PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the professional organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
Issue 1: Uncertainty surrounding the relevance of the evidence to the target population	There is not a good biological reason that Fulvestrant/Alpelisib should be any the less effective after endocrine therapy/CDK46 compared with after endocrine therapy alone. For that reason it would seem reasonable to assume maintained activity: as has been assumed by regulators in a number of countries. Some evidence is provided post CDK4/6 and it would seem reasonable to accept the extrapolation of the data into this population. It is unlikely further data will be forthcoming.
Issue 2: Restrictions of the evidence used to inform the model - comparison against a single comparator (Everolimus/Exemestane) in the second-line population	As above: in my view oral capecitabine chemotherapy should also be a comparator. This will often be used post-CDK4/6. Note the BOLERO 6 study comparing capecitabine and exemestane/everolimus.

Issue 3: Uncertainty surrounding relative treatment effects for Alpelisib/Fulvestrant versus Everolimus/Exemestane	There is no direct comparative data: so cannot comment.
Issue 4: Concerns regarding company's HRQoL assumptions	Fulvestrant/Alpelisib is a combination not without toxicity.
Issue 5: Discrepancy between deterministic and probabilistic model results	No comment
Are there any important issues that have been missed in ERG report?	I could not see (not sure if I missed it), where the funding and proposed pathway for PIK3CA testing is stated. This is not routinely performed in NHS practice and it vital to identifying target population.
PART 3 -Key messages	
16. In up to 5 sentences, please summarise the key messages of your statement:	

- Capecitabine should be a comparator
- Reasonable to assume activity of combination post CDK4/6 inhibitor similar to that seen post endocrine therapy monotherapy.
- Increased burden of hospital visits and toxicity management (in particular hyperglycaemia),
-
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

.....

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

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Technical engagement response form

Alpelisib in combination with fulvestrant for treating advanced hormone-receptor positive, HER2-negative, PIK3CA-mutated breast cancer [ID3929]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments**: 5pm, 11 November 2021**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**NCRI-ACP-RCP-RCR**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

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Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Uncertainty surrounding the relevance of the evidence to the target population	No	Our experts are in agreement with the ERG. The current EMA licence does not relate to the target population but the expectation is of achieving the MHRA Type II variation. The exact wording of this is not available but is thought to include the target population. As such the submission has merit and reflects the clinical need post CDK4/6 inhibitors. Across Europe, Apelisib is being utilised outside of its licence reflecting pragmatic clinical practice after CDK4/6 with aromatase inhibitors (as per NICE TA 495.496 and 563). This is evidenced by the ESMO ABC5 Guidelines quoted and other international guidelines.
Key issue 2: Restrictions of the evidence used to inform the model - comparison against a single comparator (Everolimus/Exemestane) in the second-line population	No	For this submission will use the term Endocrine+ to relate to treatments that contain endocrine agent and another targeted agent. Examples are Everolimus/ Exemestane and Apelisib and Fulvestrant. Clinically, as expressed by the ERG, the Everolimus/Exemestane comparator is too limiting and although there is no scientific reason why patients, post progression on CDK4/6, should not respond to Endocrine+ option, BOLERO-2 did not investigate this population. When looking at the guidance above, these quote the use of Everolimus and Exemestane as options at the same point in the pathway as the Company Submission (CS). These guidelines seek to extend the period before the use of chemotherapy as long as possible with these Endocrine + options. In the UK /England the use of Everolimus (at the licensed approved dose for TA 421) with Exemestane, has not been popular (data should be available from Bluteq applications for 421) due to its toxicity eg mucositis and pneumonitis. Many clinicians select a single agent oral chemotherapy over this Endocrine + option, as they consider the efficacy/toxicity

		profile of this Endocrine +option less favourable than single agent oral Capecitabine chemotherapy. The comparator of chemotherapy and particularly single agent Capecitabine should therefore be utilised. Fulvestrant is an evidence-based comparator based on the SOLAR-1 study but its use in England is not fully funded with approximately 50% of England having locally funding arrangements. This practically does not make it a suitable comparator in England. The other options, are very small numbers and the single agent endocrine options eg Tamoxifen and Exemestane would and only apply where patient choice dictated a low toxicity/low hospital attendance options. This is because the response of these single agent endocrine options is historically very low ie under 15% in second line settings.
Key issue 3: Uncertainty surrounding relative treatment effects for Alpelisib/Fulvestrant versus Everolimus/Exemestane	No	Our experts agree that the indirect modelling methods to compare with Everolimus/Exemestane with Alpelisib /Fulvestrant are not appropriate because as mentioned above, BOLERO-2 did not contain the target population of post CDK4/6. They are unlikely, however, to ever be directly compared in a randomised controlled trial.
Key issue 4: Concerns regarding company's HRQoL assumptions	No	Our experts do not agree that the HRQoL would be different between these two Endocrine + options ie particularly that the Apelisbib/Fulvestrant option would be superior. Both these Endocrine +options carry with them toxicity that can result in more attendances and feed into QOL outcomes. Clinicians would consider these impacts at best similar and at worst more significant for Apelisib, in part due to the increase attendances as a result of hyperglycaemia monitoring.

Key issue 5: Discrepancy between deterministic and probabilistic model results	Yes	Our experts do not accept there is enough evidence to suggest this application fits the NICE End of Life Criteria. The use of CDK4/6 inhibitors with AI as per NICE TA 495.496 and 563, has led to improvements of progression free survival (PFS) with median PFS from the registration studies of approximately 2 years. After these treatments subsequent therapies would include the Endocrine + options as above and then several lines of chemotherapy. The most recent survival analysis from MONALESSA-2 (basis for TA496) presented at ESMO 2021 shows that at 6 yrs, survival was 44 % for the CDK4/6 group with the median overall survival 63.9 months with the CDK4/6 (Hortobagyi et al LBA17 esmo 2021). There is perhaps a small group of patients that relapse very early after CDK4/6 that may be considered as reaching the NICE criteria, but data is not presented on this potential cohort within the CS or ERG.

Additional issues

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response

Additional issue 1: ERG Issue 8 Concerns regarding company cost assumptions.	**5.3.4 pg 114** 5.4 pg 117	Yes	CS explains that need PIK3CA on liquid biopsy and if negative tumour tissue. Need clarification that this whole cost is covered.

Additional issue 2: International Guidelines and applicability to UK practice.	**Whole submission-summary comments**	**YES**	The BYLieve study unfortunately had no comparator and, the randomised clinical trials will likely never be done to provide a better UK post CDK4/6 comparator. The updated BYlieve data (provided by the company) should therefore be utilised as likely to be the only large dataset of post CDK4/6 that reflects modern practice. The post CDK4/6, PIK3 CA mutant cohort have only been investigated in the SOLAR-1 and BYlieve trials and data from any future randomised trial (mentioned EPIK-B5 as due to start in the ERG submission) would take several years to report. If this trial utilised Fulvestrant as the comparator, again one could argue that this is not a useful UK comparator due to the usage/funding issues of Fulvestrant mentioned above. A chemotherapy comparator would reflect the most real-world UK comparator, but it is unknown if this trial is planned and again would take several years to report. Therefore, as direct randomised evidence applicable to UK practice is unlikely to occur, not accepting this submission would remove the additional treatment option for this group in line with international guidelines. Due to the toxicity of this agent clinicians would make a judgement (as they do with Everolimus) as to if they offer this drug with its toxicity profile or accept chemotherapy toxicity instead. It is unlikely therefore, that it would be like the more prescribed pathway of care that follows in HER-2 disease, where until the most recent addition

			(TA 704) the agents have a low toxicity /high efficacy profile and clinicians fully utilise the NICE approved accepted agents. This should mean that the numbers using this drug will be relatively small and the absolute cost lower than expected. Having it is an internationally accepted option would be appropriate.
Additional issue N: Insert additional issue			**[INSERT / DELETE ROWS AS REQUIRED]**

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Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER
Insert key issue number and title as described in the ERG report	**Briefly describe the company's original preferred assumption or analysis**	**Briefly describe the change(s) made in response to the ERG report**	**Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER**
..	..	..	**[INSERT / DELETE ROWS AS REQUIRED]**
Company's preferred base case following technical engagement	**Incremental QALYs: [QQQ]**	**Incremental costs: [£££]**	**Please provide the revised company base-case ICER resulting from combining the changes described, and the change from the company's original base-case ICER**

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

Addendum: ERG commentary of company's technical engagement response

Produced by	The School of Health and Related Research (ScHARR), The University of Sheffield
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Date completed	13th December 2021

1. Introduction

In November 2021, the company submitted their technical engagement (TE) response for the appraisal of alpelisib in combination with fulvestrant (Alp/Fulv) for treating advanced hormone receptor positive, HER2-negative, *PIK3C*A-mutated breast cancer.[1] Three additional responses from clinical commentators were also received.[2-4] This ERG addendum provides a brief commentary on the company's TE response. Additional information provided by the external clinical commentators has also been considered in the ERG's commentary.

2. ERG comments on company's TE response

Key Issue 1: Uncertainty surrounding the relevance of the evidence to the target population

The company's response[1] states that Novartis are awaiting a decision from the Medicines and Healthcare products Regulatory Agency (MHRA) regarding the Type II variation to the existing licence from the European Medicines Agency (EMA). A decision outcome is anticipated in [redacted]. No new evidence has been presented within the company's TE response. The ERG has no further comments on this issue.

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

The company's TE response[1] argues that the most relevant evidence from BYLIEVE[5] relates to those patients who received Alp/Fulv in the second-line setting following the use of a cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) plus an aromatase inhibitor (AI) in the first-line setting. The company's TE response also states that *"Novartis consider that any recommendation from NICE should reflect the anticipated licence wording as presented in the company submission."* The ERG considers that these two statements are not consistent. The anticipated wording of the MHRA variation to the EMA license is not restricted to a particular treatment line, yet the economic analysis presented in the company's submission (CS)[6] is restricted to the subgroup of BYLIEVE patients on second-line treatment. As discussed in the ERG report,[7] the company has not presented any evidence to support the cost-effectiveness of Alp/Fulv in other positions permitted under the marketing authorisation (i.e. as third- or later line therapy, or as first-line therapy where patients received a CDK4/6i+AI in the adjuvant/neo-adjuvant setting). The ERG's view therefore remains unchanged – it may be appropriate to consider the restricted population of the model in any future recommendation for Alp/Fulv.

With respect to the comparator, the company's TE response[1] maintains that everolimus plus exemestane (Eve/Exe) is the main comparator for Alp/Fulv. The clinical commentators mention capecitabine as a comparator. The ERG's clinical advisors mentioned the use of chemotherapy as a potential comparator, but only for those patients who are at risk of visceral crisis (see ERG report,[7] Sections 2.2 and 3.3). The company has not presented an economic comparison of Alp/Fulv against chemotherapy. Again, the

ERG believes that it may be appropriate to consider this in any future recommendation for Alp/Fulv, for example, by restricting the recommendation to people for whom Eve/Exe is the most appropriate alternative treatment. A similar approach was taken in the final NICE guidance for the use of the CDK4/6 inhibitors for ABC (TA619, TA689 and TA725).

Key Issue 3: Uncertainty surrounding relative treatment effects for Alp/Fulv versus Eve/Exe

The ERG considers the company's estimates of relative treatment effects for Alp/Fulv versus Eve/Exe, and the resulting quality-adjusted life year (QALY) estimates generated by the economic model, to be highly uncertain. A summary of these issues is presented in Section 4.12 of the ERG report.[7] No new evidence has been presented within the company's TE response; hence, the ERG's concerns regarding this uncertainty remain unchanged.

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

The company's base case model applies a utility value in the post-progression state of [redacted], based on EQ-5D data collected in SOLAR-1.[8] The ERG's preferred analysis uses a utility value of 0.51, based on a time-trade off (TTO) study reported by Lloyd *et al*.[9] The company's TE response[1] argues that the use of the value from Lloyd *et al.* is inappropriate, noting that:

- The study by Lloyd *et al.* is 15 years old and the treatment landscape for advanced breast cancer (ABC) has changed since this study was published
- The vignette description used in Lloyd *et al.* no longer reflects the experience of patients with disease progression (i.e. by third-line treatment)
- The recent Cancer Drugs Fund (CDF) review of abemaciclib plus fulvestrant for hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) ABC (NICE TA725[10]) used an alternative utility value of 0.69 for the progressed disease state, based on EQ-5D estimates reported by Mitra *et al*.[11]

The company's original base case model also applied a higher utility value in the progression-free state for the Alp/Fulv group compared with the Eve/Exe group (utility = [redacted] vs. [redacted]).

The company's TE response[1] states that the company undertook additional interviews with four clinical experts to obtain further information about their views on these issues:

- All four clinical experts considered that the patients seen in their clinical practice at third-line would have a utility value that is reflective of the estimate in Mitra *et al.*,[11] and that the value from Lloyd *et al.*[9] is not reflective of patients at this point in the disease pathway.
- Three of the four experts did not believe there are any data to support different utility values between Alp/Fulv and Eve/Exe in the progression-free state. The fourth expert suggested that patients receiving Alp/Fulv may have higher utility than those receiving Eve/Exe.

The company's TE response[1] includes an updated base case analysis which uses the post-progression utility value from Mitra *et al.*[11] and which applies the same utility value for the progression-free health state in both treatment groups. The utility values applied in the company's original and updated base case analyses are summarised in Table 1.

Table 1: Summary of utility values applied in company's original base case and updated TE base case

Model	Progression-free (on-treatment)	Post-progression	Sources
Copmany's original base case model[6]	Alp/Fulv = [redacted] Eve/Exe = [redacted]	Both groups = [redacted]	Both health states – SOLAR-1.[8] Decrement for Eve/Exe informed by BOLERO-2.[12]
Company's updated base case model in TE response[1]	Both groups = [redacted]	Both groups = [redacted]	PF – SOLAR-1[8] PD – Mitra *et al.*[11]

Alp/Fulv – alpelisib plus fulvestrant ; TE – technical engagement ; PF progression-free ; PD – progressed disease

The ERG believes that all three potential sources of post-progression utility values are subject to methodological issues which may impact on the robustness of the available utility estimates:

- SOLAR-1[8] included the use of the EQ-5D-5L, which was mapped to the 3L version by the company. The CS[6] states that EQ-5D-5L data in SOLAR-1 *"were largely missing after progression."* The ERG has concerns that the estimates obtained from SOLAR-1 may be subject to informative censoring and thus may not be representative of the broader group of patients with disease progression.
- As identified by the company, the study by Lloyd *et al.*[9] used a TTO vignette approach rather than the EQ-5D and is relatively old. This source has however been used in the majority of NICE appraisals in ABC (see ERG report,[7] Table 39).
- Mitra *et al.*[11] reports EQ-5D-3L estimates for patients with HR+/HER2- advanced/metastatic breast cancer in five major EU countries and the US, and reports a utility value specifically for patients at third-line or later. However, this study is only published as an abstract and it is unclear which EQ-5D tariffs have been used to generate the utility estimates. It is unlikely that these reflect the UK tariff.

One of the ERG's clinical advisors commented that there are women who progress on earlier lines of treatment (1-3) without a significant change in HRQoL *"because they have lower tumour burden, or their disease is not affecting critical organs or impinging upon nerve roots and we detect the progression on radiological imaging before the metastases can cause symptoms."* The advisor commented that a utility value of [redacted] would be consistent with this group, but noted that trial recruitment involves selecting for fitter patients. The advisor further stated that in their real-world experience, some women will have lower HRQoL, in particular those who develop spinal cord

compression, brain metastases or lung involvement resulting in oxygen requirement. The advisor commented that a mid-point of the estimates from Lloyd *et al.*[9] and Mitra *et al.*[11] might be more appropriate for patients with progressed disease state (i.e. utility = [redacted]). A second clinical advisor to the ERG commented that a value of [redacted] may be reasonable in the third-line setting. The use of an assumed utility value of [redacted] in the progressed disease state, together with the company's updated assumption for the same progression-free utility value in both groups, has been presented as a scenario analysis in this addendum (see Table 2). The ERG believes that further input from clinical experts on this issue may be helpful.

Key issue 5: Discrepancy between deterministic and probabilistic model results

As discussed in the ERG report[7] (Section 5.3.4), there is a marked difference between the results of the company's probabilistic and deterministic models. The deterministic model uses median rather than mean estimates of hazard ratios (HRs), whilst the probabilistic model samples from the distribution of the HRs, but produces a proportion of implausible samples. The discrepancy appears to be partly caused by the non-linear response of the model to extreme values of the HRs. This issue is further discussed in Section 5.3.4 of the ERG report. The company's TE response[1] argues that using the probabilistic results could introduce bias and that the deterministic results are more appropriate.

The company's TE response[1] does not contain any new analyses which address this issue. As such, the ERG's position remains unchanged – both analyses are subject to problems and it is unclear which results should be used to inform decision-making. A judgement is required by the Appraisal Committee regarding which analyses should be preferred.

Additional issue raised by company - Alternative treatment duration

The company's TE response raises a concern regarding the ERG's additional sensitivity analysis in which the HR is applied only for a finite period (see ERG report,[7] Table 42, ASA1). The company's model estimates outcomes for the Eve/Exe group by applying the HRs from the indirect comparison indefinitely to a parametric survival model fitted to the time-to-event data for the second-line subgroup in BYLIEVE[5] as baseline. In ASA1, outcomes for the Eve/Exe group are modelled using the HR-adjusted model, whereas outcomes for the Alp/Fulv group are modelled by using the hazards for the Alp/Fulv group until some waning timepoint (3 or 5 years) and then switching to the hazards for the Eve/Exe group. The company believes that it would be more appropriate to apply the waning assumption to the Eve/Exe group instead of the Alp/Fulv group, which would result in lower ICERs. The ERG disagrees as this would imply a turning point in the hazard for patients receiving Eve/Exe after which the hazard decreases, which is not consistent with the assumption that the effect of the intervention is lost after some period of time. The ERG has not undertaken further analyses around this issue.

3. Additional analyses undertaken by the company and the ERG

Table 2 presents a summary of results using the deterministic version of the model which contains: (i) the original company base-case and ERG preferred analyses, as presented in the ERG report[7] using the updated Patient Access Scheme (PAS) for alpelisib and the list prices for other drugs including fulvestrant; (ii) the company's updated base case, as presented in the company's TE response using the list price for fulvestrant; and (iii) an additional ERG scenario analysis, whereby the post-progression utility value for both treatment groups is assumed to be 0.60 (see key issue 4). The ERG does not present the results for the company's additional issue regarding the implementation of the Alp/Fulv treatment effect duration, as the ERG does not agree with the company's proposed approach. Table 3 presents the results from the probabilistic models for analyses (ii) and (iii). Results including the comparator PAS discounts are presented in a separate confidential appendix.

The results presented in Table 2 show that the alternative utility assumptions employed in the company's TE model (i.e. applying a treatment-independent utility value in the progression-free on treatment state and the post-progression utility value from Mitra *et al*.[11]) increases the company's base case ICER for Alp/Fulv versus Eve/Exe from £56,491 per QALY gained to £59,734 per QALY gained. The ERG's preferred analysis, which includes applying the post-progression utility value from Lloyd *et al*.[9] instead in both groups has a greater impact, increasing the ICER to £73,252 per QALY gained. Applying an alternative utility value of 0.60 to the post-progression state reduces the ICER to £65,626 per QALY gained. The probabilistic ICERs for the company's updated base case and the ERG's additional analysis are £68,591 per QALY gained and £75,093 per QALY gained, respectively.

Table 2: Summary of results - Alp/Fulv versus Eve/Exe, using new PAS for alpelisib ([redacted]) and fulvestrant list price, deterministic

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER
Company's original base case, ERG report (different progression-free on-treatment utility values for each group, post-progression utility value from SOLAR-1,[8])							
Alp/Fulv	2.58	[redacted]	[redacted]	0.76	[redacted]	[redacted]	**£56,491**
Eve/Exe	1.81	[redacted]	[redacted]				
Company's updated base case, TE response (same progression-free on-treatment utility value for both groups, post-progression utility value from Mitra *et al*.[11])							
Alp/Fulv	2.58	[redacted]	[redacted]	0.76	[redacted]	[redacted]	**£59,734**
Eve/Exe	1.81	[redacted]	[redacted]				
ERG preferred analysis, ERG report, deterministic (same progression-free on-treatment utility value for both groups, post-progression utility value from Lloyd *et al*.[9])							
Alp/Fulv	2.58	[redacted]	[redacted]	0.76	[redacted]	[redacted]	**£73,252**
Eve/Exe	1.81	[redacted]	[redacted]				
ERG additional analysis, TE response (same progression-free on-treatment utility value for both groups, post-progression utility value equals 0.60)							
Alp/Fulv	2.58	[redacted]	[redacted]	0.76	[redacted]	[redacted]	**£65,626**
Eve/Exe	1.81	[redacted]	[redacted]				

**undiscounted*

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

Table 3: Summary of results - Alp/Fulv versus Eve/Exe, using new PAS for alpelisib ([redacted]) and fulvestrant list price, probabilistic

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER
Company's updated base case, TE response (same progression-free on-treatment utility value for both groups, post-progression utility value from Mitra *et al.*[11])							
Alp/Fulv	2.71	[redacted]	[redacted]	0.54	[redacted]	[redacted]	**£68,591**
Eve/Exe	2.17	[redacted]	[redacted]				
ERG additional analysis, TE response (same progression-free on-treatment utility value for both groups, post-progression utility value equals 0.60)							
Alp/Fulv	2.71	[redacted]	[redacted]	0.54	[redacted]	[redacted]	**£75,093**
Eve/Exe	2.17	[redacted]	[redacted]				

**undiscounted*

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

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NICE National Institute for Health and Care Excellence

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

Lead team presentation

Brian Shine (Chair), Peter Baker, Michael V Holmes

ERG: Sheffield

Technical team: Jane Adam, Catherine Spanswick, Carl Prescott and Henry Edwards

Company: Novartis

15 March 2022

Key issues

Clinical: *what is committee's view on:*

- **Alpelisib + fulvestrant (A+F) positioning:** company positions post-CDK4/6 inhibitor, primarily 2nd line, but not excluding other lines – *where would A+F be used in NHS practice?*
- **A+F vs everolimus + exemestane (Ev/Ex) as sole comparator:**
  - ERG: Ev/Ex is most appropriate comparator, but others treatments might be used in some circumstances – *what is/are the most appropriate comparator/s?*
  - No direct comparative evidence – *are indirect analyses robust enough for decision?*

Cost: *what is committee's view on*:

- **Bucher indirect treatment comparison:** suitability of connecting trials – *is HER2 status an important modifier of treatment effect that should be taken into account?*
- **Modelling of OS:** Gompertz & Weibull provide slightly better fit than log-logistic – *which OS model should be used?*
- **Duration of treatment effect for A+F versus Ev/Ex:** company assumes no waning – *should time-limited treatment effect be assumed (i.e. 3- or 5- years)?*
- **Most appropriate model:** probabilistic ICER ≈£10K higher than deterministic – *is Bucher indirect treatment comparison suitable for informing probabilistic sensitivity analysis?*

End of life: *Does alpelisib meet end-of-life criteria?*

Alpelisib (Piqray)

Company's variation to licensed indication **approved** in UK, December 2021

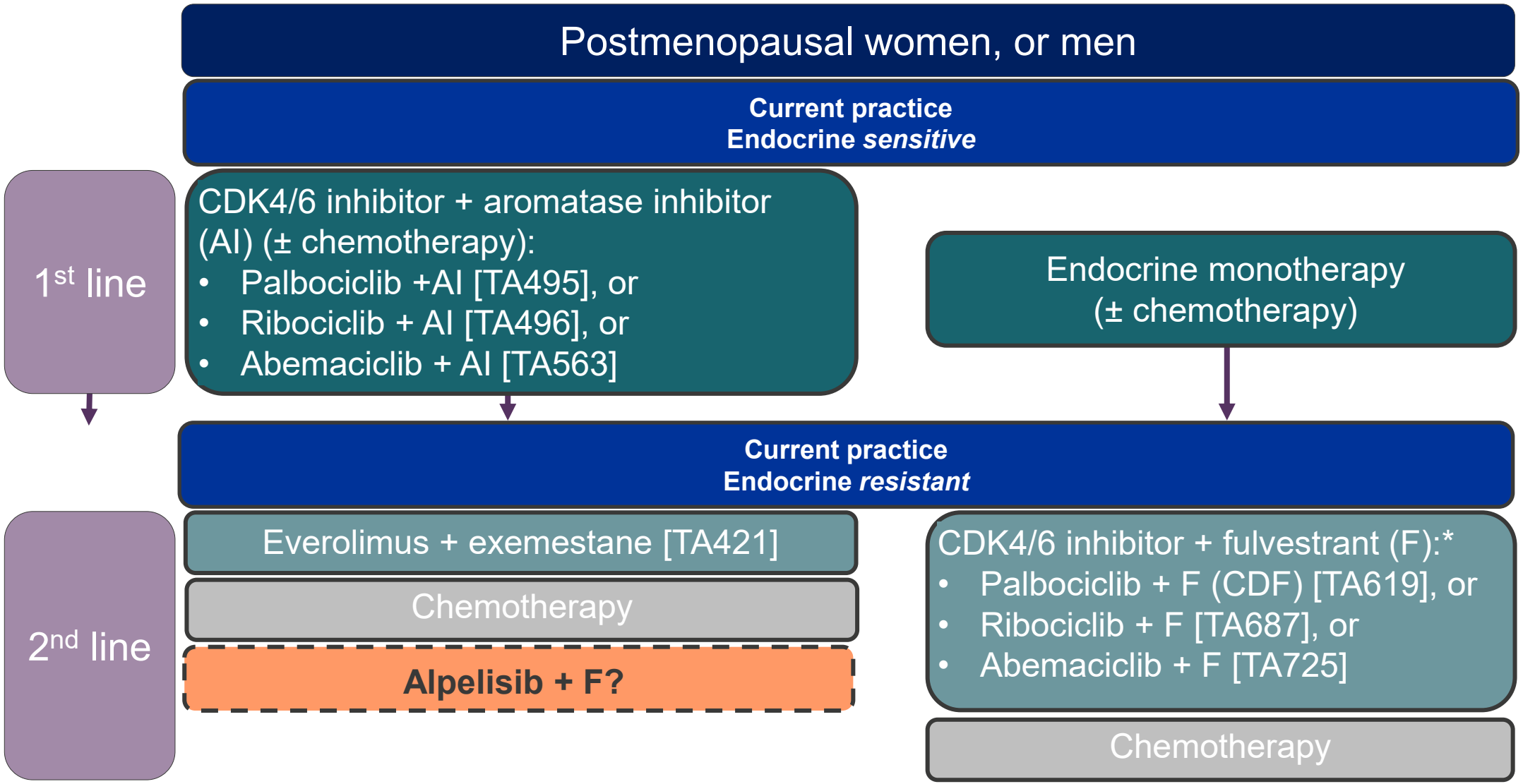
Marketing authorisation	Indicated in combination with fulvestrant for the treatment of postmenopausal women, and men, with hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer with a PIK3CA mutation after disease progression following endocrine-based therapy **Note**: company submission is narrower than licence, focusing on: People with HR+, HER2-negative advanced breast cancer with a PIK3CA mutation after disease progression following *a CDK4/6 inhibitor*
Dosage and administration	• Alpelisib 300 mg orally once daily until progression or unacceptable toxicity • Fulvestrant 500 mg intramuscularly on days 1, 15 and 29, and once monthly thereafter
Mechanism of action	Alpelisib is an oral tyrosine kinase inhibitor highly selective for the catalytic subunit alpha of PI3K
Average list price per course of treatment	Alpelisib: 150 mg film-coated tablets; pack 56 tablets £4,082.14 Fulvestrant (generic): £XX.XX for 250 mg per 5 mL solution for injection pre-filled syringes (×2) Patient Access Scheme (PAS) for alpelisib approved by NHS England

Abbreviations: HER2, human epidermal growth factor receptor 2; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha

Disease background

- Around 46,000 people diagnosed with breast cancer in England in 2017
- Approximately 13% have advanced disease (stage III or IV)
- Around 35% with early or locally advanced disease will progress to metastatic breast cancer in 10 years following diagnosis
- Approximately 64% metastatic breast cancer in UK hormone-receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative
- Mutations of phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) have been found in 30% to 40% of oestrogen receptor positive, HER2-negative tumours
- There is a high unmet need in HR+, HER2- breast cancer that has progressed after endocrine-based treatment, due to few treatment options including a lack of targeted treatments

Treatment pathway HR+, HER2- advanced breast cancer with a PIK3CA mutation



Note: Chemotherapy is 1st line treatment for ER-positive advanced breast cancer that is imminently life-threatening or involves visceral crisis. Tamoxifen and ovarian suppression is 1st line treatment for pre- and peri-menopausal women with ER-positive advanced breast cancer not previously treated with tamoxifen. *Only if exemestane plus everolimus is the most appropriate alternative to a CDK4/6 inhibitor. *CDF, cancer drugs fund; CDK4/6, cyclin-dependent kinase 4 and 6; ER, oestrogen receptor.*

Patient and carer perspectives (Breast Cancer Now)

- Being diagnosed with secondary breast cancer is extremely difficult to come to terms with both for patients and their family and friends. It affects patients mental health and day-to-day activities
- Patients want treatment that will halt progression, extend life for as long as possible, have good safety profile and give them good quality of life
- Patients experience progression on CDK4/6 inhibitors and resistance to endocrine-based therapies
- PIK3CA mutation is common and there is unmet need for targeted treatments to enable more tailored and personalised treatment

PIK3CA mutations are not currently tested for on the NHS, so we have been unable to identify patients with this precise mutation to be able to hear their experiences. People with secondary breast cancer have told us:

"It is scary. I am permanently scared about my future and what my family will have to deal with without me"

"It totally and completely affects your life after diagnosis. Endless doctors' appointments can begin to wear you down in no time at all"

"How confused and scared I am all the time; even when I'm happy it's always there in the back of your mind"

Decision problem

	Final scope issued by NICE	Evidence used in the model
Population	People with advanced HR+, HER2-negative, PIK3CA-mutated breast cancer that has progressed **after prior endocrine therapy** (in the neo/adjuvant or advanced setting)	People with advanced, HR+, HER2-negative PIK3CA-mutated breast cancer that has progressed **after prior CDK4/6 inhibitor** • Rationale: anticipated place in NHS practice
Intervention	Alpelisib plus fulvestrant (A+F)	As per final scope
Comparators	• CDK4/6 inhibitors plus fulvestrant - ribociclib - abemaciclib - palbociclib [*currently in CDF so not eligible as a comparator*] • Everolimus + exemestane (Ev/Ex) • Exemestane • Tamoxifen	Ev/Ex • Rationale: most relevant comparator in post-CDK4/6 inhibitor population in 2nd-line setting; • Second CDK4/6 inhibitor not usually given in 2nd-line setting • Exemestane monotherapy and tamoxifen not standard care
Outcomes	• Overall survival • Progression-free survival • Response rate • Adverse effects of treatment • Health-related quality of life	As per final scope Note: response rate includes overall response rate and clinical benefit rate

◉ *Is company's proposed target population appropriate?*
◉ *What are the relevant comparators?*

Relevance of the economic analysis to the target population

Key issue

Company positioning of alpelisib

Company positioning narrower than licence; endocrine-based therapy may include endocrine monotherapy

Background:

- *Licence:* progressed after **prior endocrine-based therapy***
  - Line of therapy and type of endocrine-based therapy not specified
- *Company submission:* progressed after **CDK4/6i**
  - "Population of interest" is "patients who have previously received a CDK4/6i and progress **following first-line treatment for advanced breast cancer**"
  - Trial and model population limited to 2nd line only, post 1st line CDK4/6i

Company:

- NICE guidance puts 1st line CDK4/6i now as standard care
- Unmet need if disease progresses after 1st line CDK4/6i, with Ev/Ex only treatment option

Clinical experts:

- 10-30% receive endocrine monotherapy as 1st line for advanced HR+ breast cancer
- Mostly frailer patients; A+F could be used in these patients if they had PIK3CA mutation

◉ *Where would alpelisib be used in NHS practice?*
◉ *Is the trial population (and economic model population) relevant to the target population?*
◉ *If recommended, should alpelisib be restricted to post 1st line CDK4/6i?*

NICE

Appropriateness of single comparator (everolimus plus exemestane) in 2nd line population

Key issue

Company considers Ev/Ex as main comparator for A+F

Uses single comparator Ev/Ex to inform model

Background:

- NICE scope has 4 comparators: CDK4/6 inhibitors plus fulvestrant, Ev/Ex, Ex and tamoxifen
- Company restricts comparator in model to Ev/Ex

ERG / clinical experts:

- **Agree Ev/Ex is main comparator in post-CDK4/6i + AI population,** and appropriate to exclude CDK4/6i + fulvestrant and Ex monotherapy. However:
  - Some given tamoxifen or fulvestrant as monotherapy; could have been considered by company. Ex mono used, but less often
  - Patients at risk of visceral crisis may be offered single-agent chemotherapy

Company – response to clarification question:

- Tamoxifen or fulvestrant monotherapy not widely used in NHS in this setting and not considered standard care
  - Reserved for frailer patients who cannot tolerate options such as Ev, therefore not the same patient population as expected to receive A+F
- Agree patients at high risk of visceral crisis would typically be offered chemotherapy irrespective of the availability of A+F or Ev/Ex

◉ *What is/are the most appropriate comparator/s?*
◉ *Is any potential recommendation going to be limited to post CDK4/6i only? If not, should CDK4/6is be considered a comparator for some patients?*

Clinical effectiveness

Clinical evidence

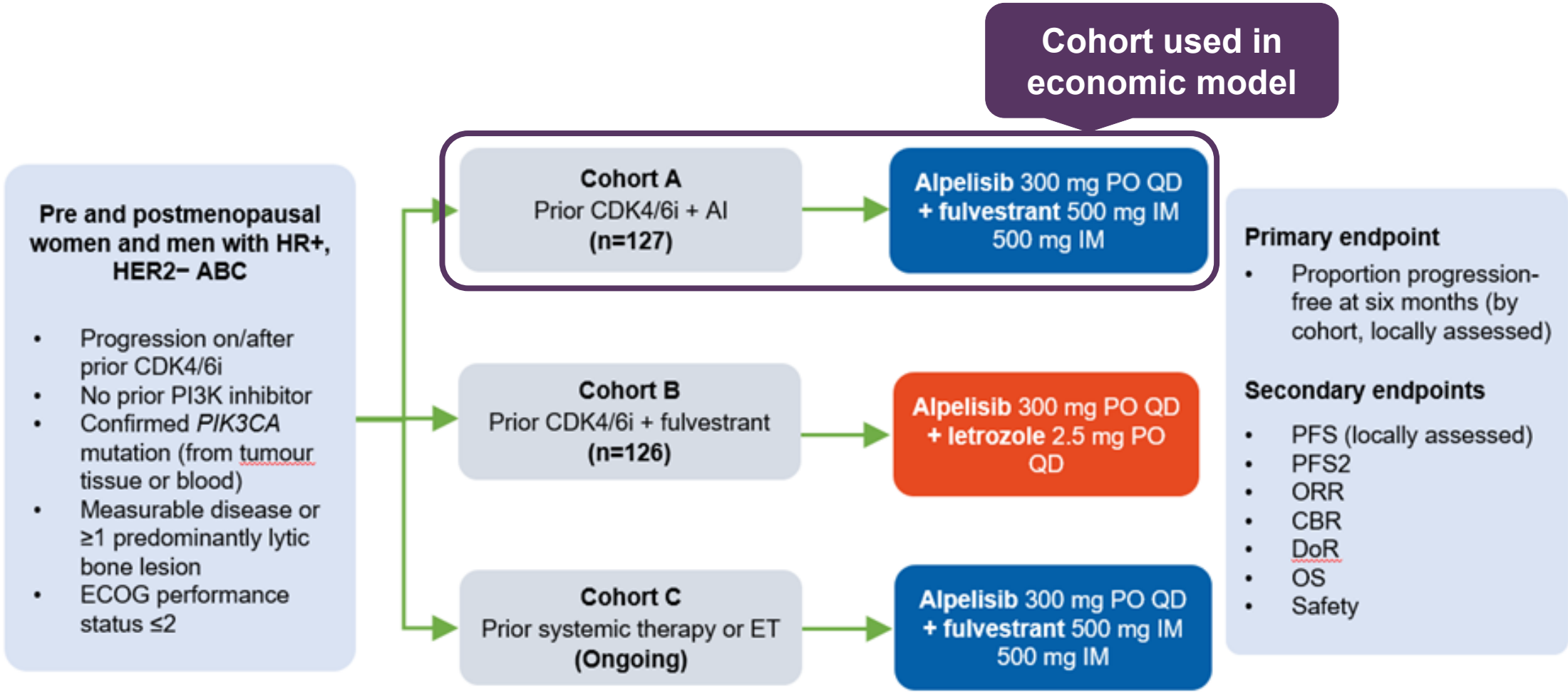
*Populations differ in 2 studies, but all in submission had confirmed PIK3CA mutation**

	BYLieve cohort A (N=127)	SOLAR-1 PIK3CA-mutated cohort (N=341; n=20 CDK4/6i pre-treated)
Study design	Non-randomised, open-label, three-cohort, non-comparative phase 2 trial	Randomised, double-blind, placebo-controlled, phase 3 trial
Population	• Pre-, peri- and post-menopausal women, or men • HR+, HER2− advanced breast cancer • Prior CDK4/6i + aromatase inhibitor (AI)	• Post-menopausal women, or men • HR+, HER2− advanced breast cancer • Prior AI treatment Note: most had no prior CDK4/6i
Intervention	Alpelisib + fulvestrant	
Comparator	None	Placebo + fulvestrant
1º endpoint	% patients alive without disease progression at 6 months (locally assessed)	PFS (locally assessed)
2º and other endpoints	• OS • PFS (locally assessed), PFS2 • Objective response rate, clinical benefit rate, duration of response • Safety • Clinical response in patients with PIK3CA mutation status (ctDNA)	• OS • Objective response rate, clinical benefit rate, time to response, duration of response • Safety
Quality of life	-	EQ-5D-5L

**Company excluded non-PIK3CA-mutated participants of SOLAR-1 from its submission*

BYLieve

Alpelisib + fulvestrant, after CDK4/6i + AI

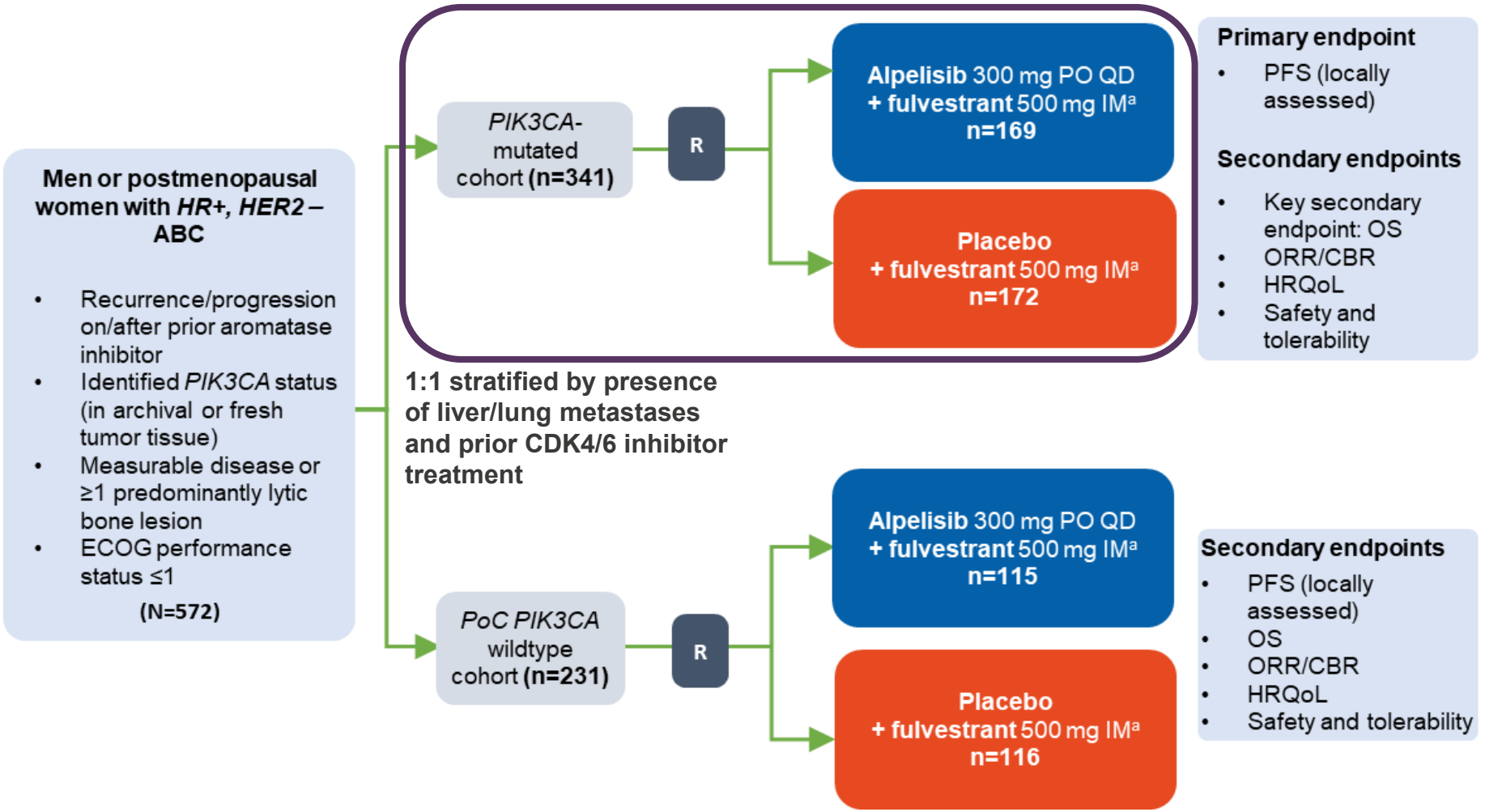


ABC, advanced breast cancer; AI, aromatase inhibitor; CBR, clinical benefit rate; CDK, cyclin dependent kinase; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IM, intramuscular; PFS, progression-free survival; PFS2, progression on next line therapy; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; ORR, overall response rate; OS, overall survival; PO, by mouth; QD, once daily; SC, subcutaneously

SOLAR-1

Alpelisib + fulvestrant, after AI

Subset of cohort used in indirect comparisons: 2nd line population (n=XXX)



ABC, advanced breast cancer; CBR, clinical benefit rate; CDK, cyclin dependent kinase; ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IM, intramuscular; PFS, progression-free survival; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; ORR, overall response rate; OS, overall survival; PO, by mouth; PoC, point of care; QD, once daily; R randomised

Results – BYLieve and SOLAR-1

Previous treatments differ in 2 trials

Baseline characteristics	BYLieve cohort A*	SOLAR-1 PIK3CA-mutated cohort	
	A+F	A+F	Placebo + F
Number of participants	127	169	172
Median age, years	58.0	63.0	64.0
Sex and menopausal status, n (%)			
Female	127 (100)	168 (99.4)	172 (100)
Postmenopausal	[redacted]	168 (99.4)	172 (100)
ECOG PS, n (%)			
0	79 (62.2)	112 (66.3)	113 (65.7)
1	41 (32.3)	56 (33.1)	58 (33.7)
Stage IV at study entry,[a] n (%)	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)
Line of treatment in advanced disease			
1st line	15 (12)	88 (52.1)	89 (51.7)
2nd line	89 (70)	79 (46.7)	82 (47.7)
3rd line+ or not specified	23 (18)	2 (1)	1 (0.6)
Endocrine sensitive,[b] (%)	NR	20 (11.8)	19 (11.0)
Endocrine resistant,[b] (%)	NR	143 (84.6)	149 (86.6)

** Full analysis set (FAS); modified FAS N=121 with confirmed PIK3CA mutation including n=[redacted] 2nd line*

[a] Others were stage III at study entry; [b] endocrine status not known in 10 patients in SOLAR-1

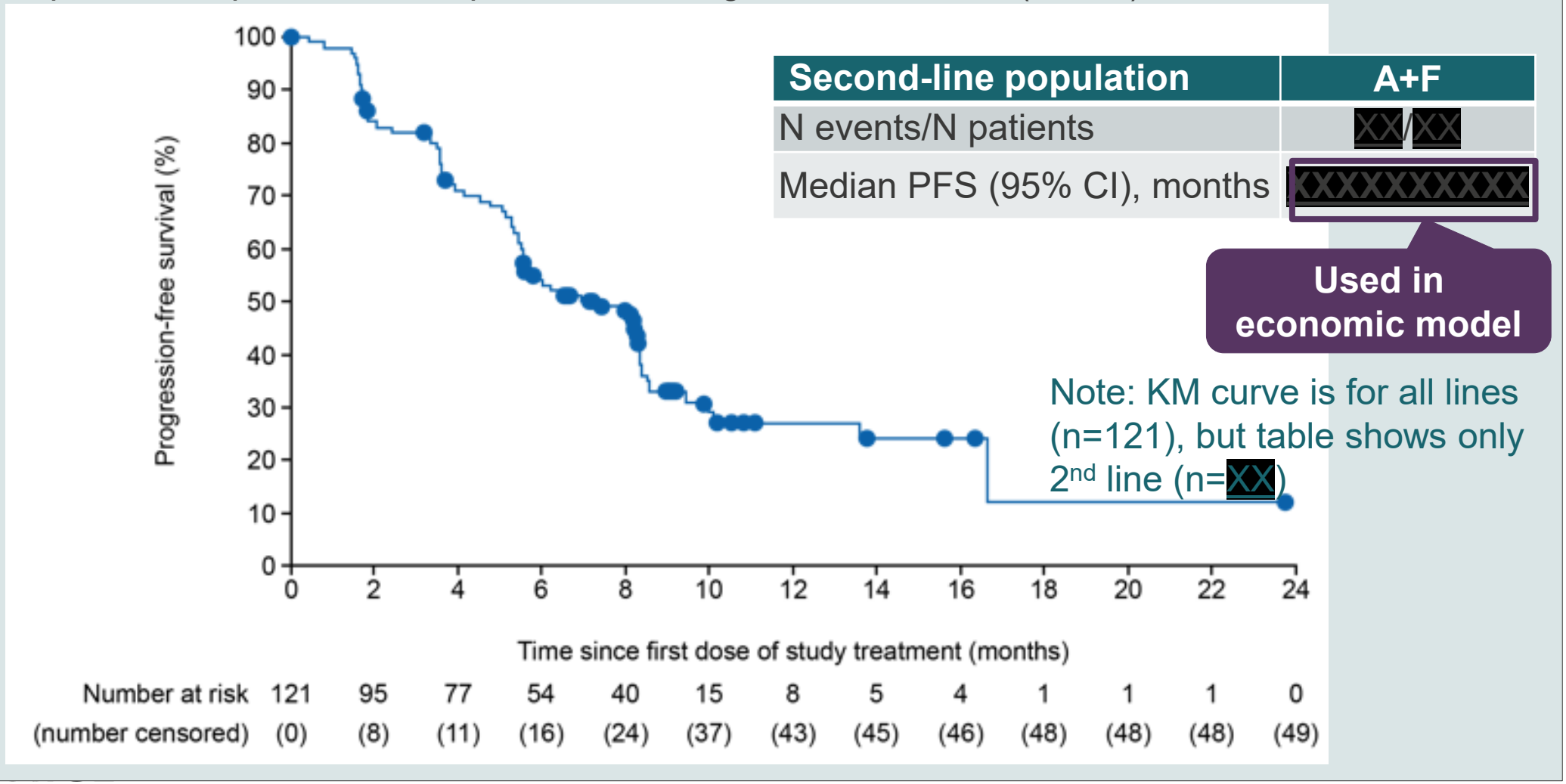
CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ECOG, Eastern Cooperative Oncology Group; F, fulvestrant; NR, not reported; PS, Performance status

◉ *Generalisable to NHS?*

PFS – BYLieve cohort A

- ***Primary endpoint met (mFAS, all lines):*** 50.4% of people alive without disease progression at 6 months (95% CI: 41.2, 59.6; lower bound of the 95% CI exceeding 30% – protocol-defined clinically meaningful threshold)

Kaplan-Meier plot of PFS as per local Investigator assessment (mFAS)



Second-line population	A+F
N events/N patients	XX/XX
Median PFS (95% CI), months	XXXXXXXXX

Used in economic model

Note: KM curve is for all lines (n=121), but table shows only 2nd line (n=XX)

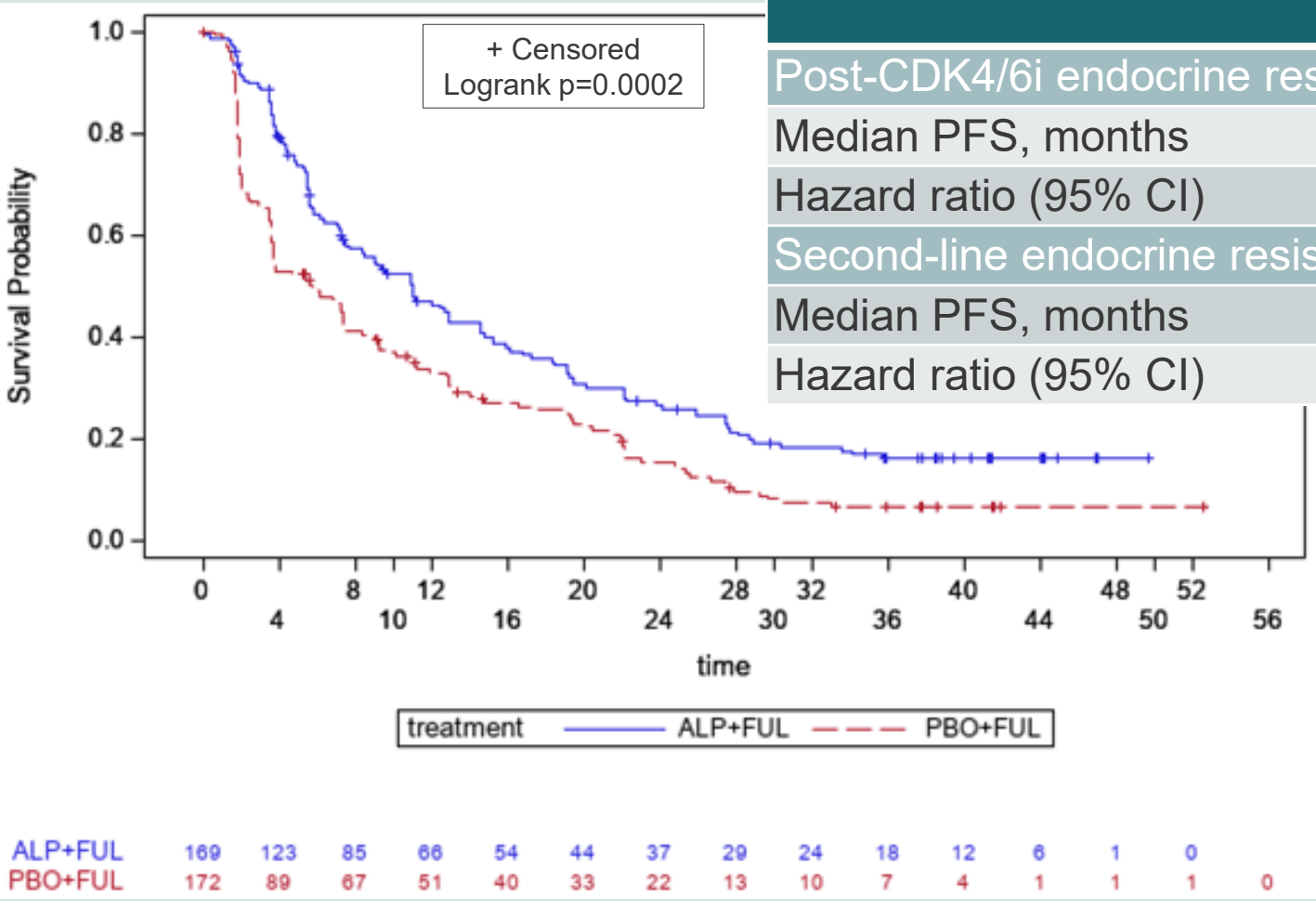
CI, confidence interval; mFAS, modified full analysis set

Median duration of follow-up was 11.7 months

PFS – SOLAR-1PIK3CA-mutated cohort

- ***Primary endpoint met (FAS, all lines):*** A+F statistically significantly prolonged PFS by 5.3 months more than placebo + F[a]

Kaplan-Meier plot of PFS (FAS[b])



	A+F	Placebo + F
Post-CDK4/6i endocrine resistant, n[b]	9	11
Median PFS, months	XXX	XXX
Hazard ratio (95% CI)	XXXXXXXXXX	
Second-line endocrine resistant, n[b]	XX	XX
Median PFS, months	XXX	XX
Hazard ratio (95% CI)	XXX XXXX XXX	

Used in indirect comparisons – more conservative than post-CDK4/6i

Note: KM curve is for all lines (n=341), but table shows only 2nd line (n=XXX) and post-CDK4/6i (n=20)

Median duration of follow-up was 20.0 months (primary) and 42.4 months (final)

[a] *Primary analysis (June 2018);* [b] *final OS analysis (April 2020)*
OS, overall survival; PFS, progression-free survival

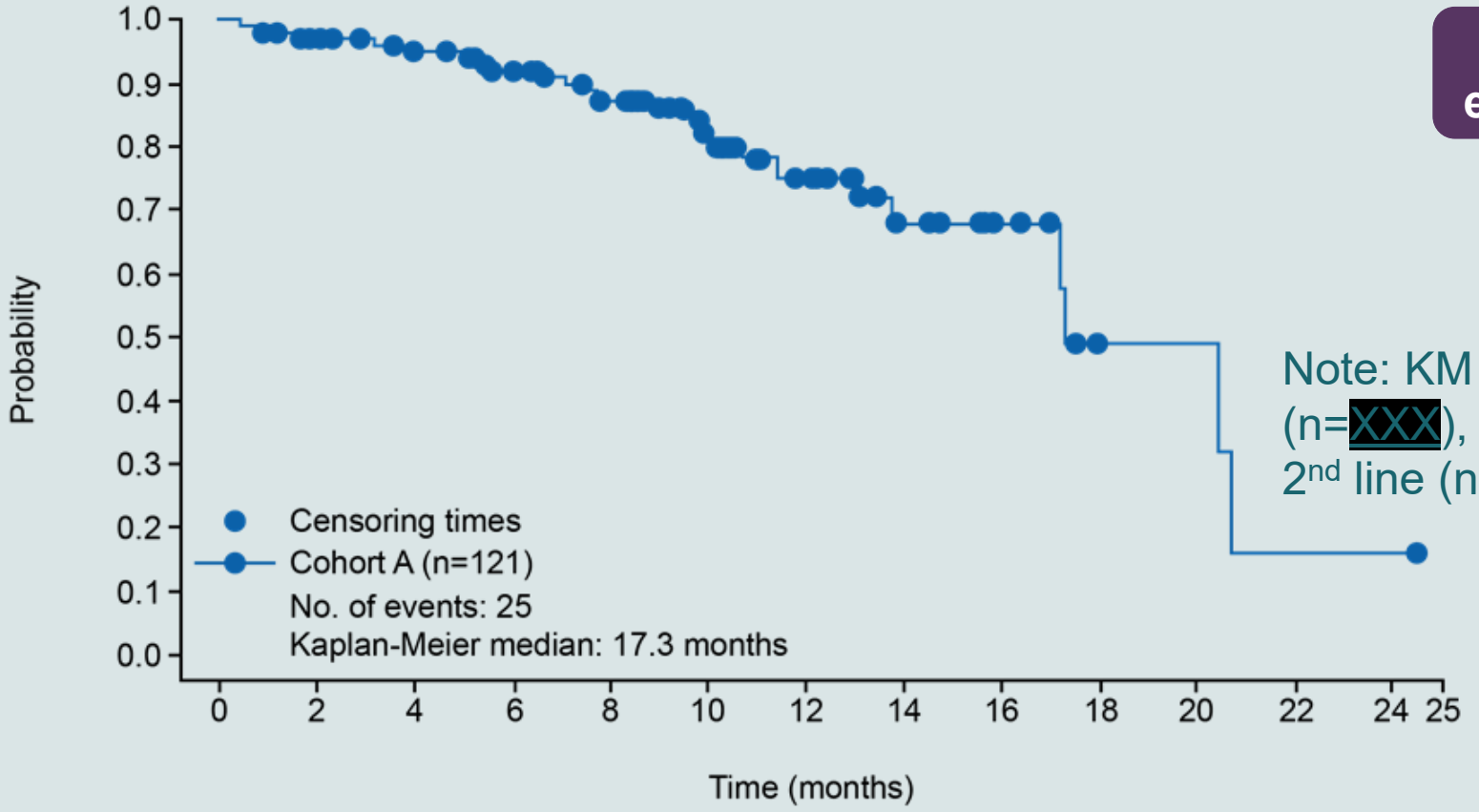
OS in BYLieve

Prior CDK4/6i plus AI therapy

Second-line population	A+F
N events/N patients	XX/XX
Median OS (95% CI), months	XXXXXXXXX

Used in economic model

BYLieve cohort A (mFAS)



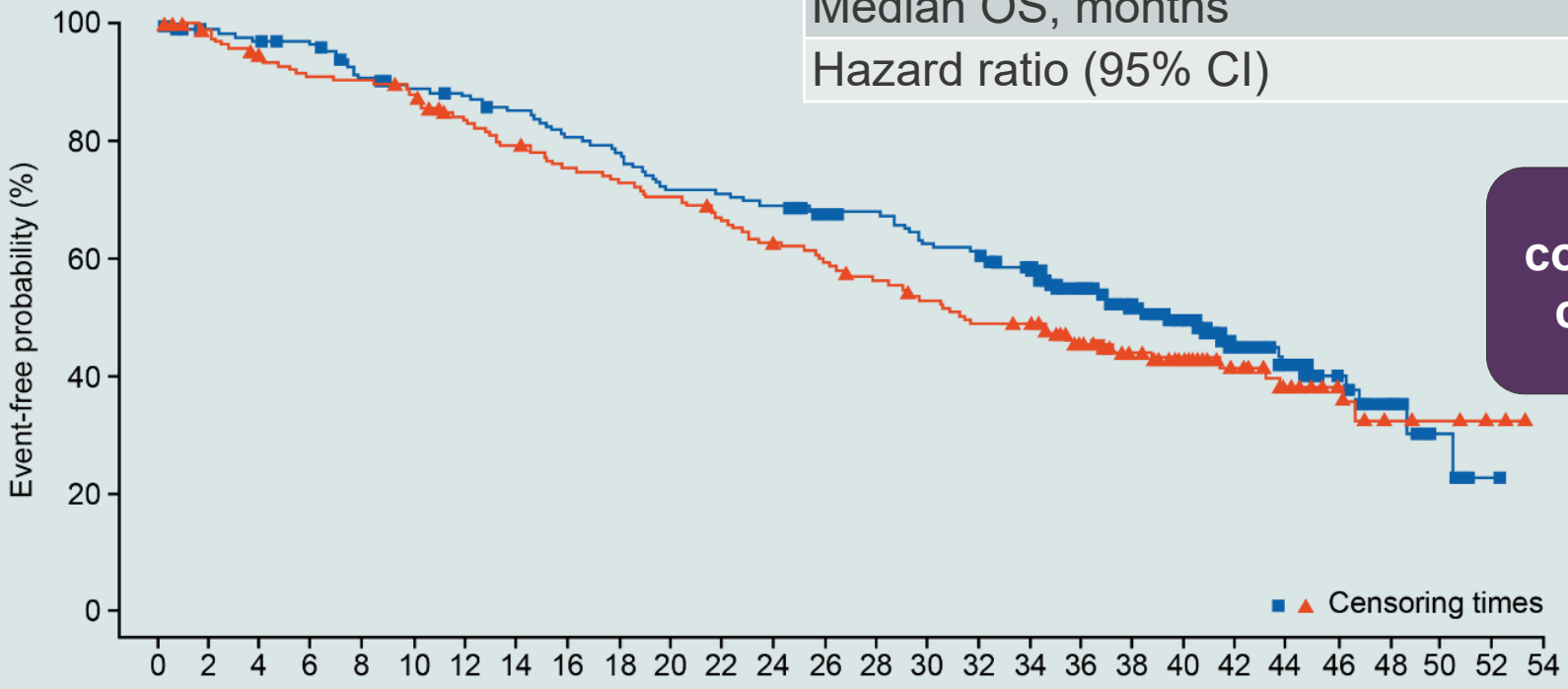
Number at risk	121	110	101	92	73	41	29	17	11	3	3	1	1	0
(number censored)	(0)	(7)	(14)	(20)	(35)	(64)	(73)	(83)	(89)	(95)	(95)	(95)	(95)	(96)

Note: KM curve is for all lines (n=XXX), but table shows only 2nd line (n=XX)

OS in SOLAR-1

	A+F	Placebo + F
Post-CDK4/6i endocrine resistant, n	9	11
Median OS, months	XXXX	XXXX
Hazard ratio (95% CI)	XXXXXXXXXX	
Second-line endocrine resistant, n	XX	XX
Median OS, months	XXX	XXX
Hazard ratio (95% CI)	XXX XXXXX	

SOLAR-1 PIK3CA-mutated cohort (FAS)



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

Used in indirect comparisons – more conservative than post-CDK4/6i

Note: KM curve is for all lines (n=341), but table shows only 2nd line (n=XXX) and post-CDK4/6i (n=20)

Clinical evidence – adverse events

A+F has AEs that are associated with PI3K pathway inhibition

Type of treatment-emergent adverse event (TEAE), n (%)	BYLieve cohort A	SOLAR-1 PIK3CA-mutated cohort	
	A+F (n=127)	A+F (n=284)	Placebo (n=287)
Any TEAE	126 (99.2)	[redacted]	[redacted]
TEAEs Grade ≥3	79 (62.2)	[redacted]	[redacted]
Most common TEAEs (≥5% in any group)	Grade ≥3	Grade 3 / 4	Grade 3 / 4
Hyperglycaemia	36 (28.3)	94 (33.1) / 11 (3.9)	2 (0.7) / 1 (0.3)
Rash	12 (9.4)	28 (9.9) / 0	1 (0.3) / 0
Rash maculo-papular	12 (9.4)	NR	NR
Diarrhoea	7 (5.5)	20 (7.0) / 0	2 (0.7) / 0
Weight decreased	2 (1.6)	15 (5.3) / 0	0 / 0

Company used 2 indirect analyses in modelling

No direct clinical evidence for A+F vs Ev+Ex

Approach	Treatment setting	Indirect comparison	Trial data used*	Used in company model?
Bucher indirect treatment comparison	Proxy – 2nd line treatment	A+F vs Ev/Ex	SOLAR-1 & BOLERO-2, connected via CONFIRM and SoFEA	**Yes** – base case
Patient-adjusted indirect comparisons	Proxy – 2nd line treatment	A+F vs Ev/Ex	SOLAR-1 & BOLERO-2	**Yes** – sensitivity analysis

*Please see next slide for full description of trials

ERG: large degree of uncertainty with these approaches

Additional trials used in indirect analyses

No direct clinical evidence for A+F vs Ev+Ex

- BOLERO-2 also used for health-related quality of life data

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

*Also vs fulvestrant + anastrazole.

EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire-C30 ; FACT-B, Functional Assessment of Cancer Therapy–Breast

Bucher indirect treatment comparison (1/2)

Background:

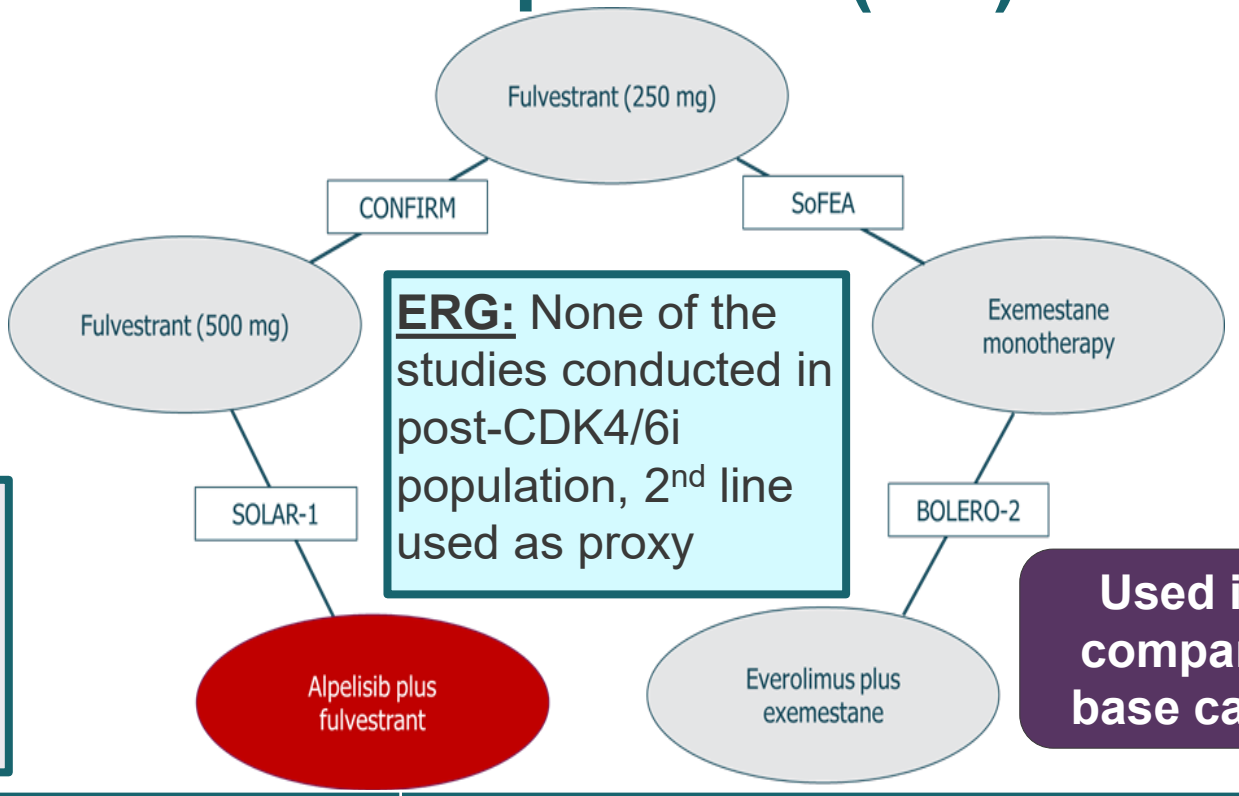
- Reverse Bucher method: known HRs for A+F used to calculate HRs for comparator Ev/Ex
- Equivalent to fixed effect network meta-analysis

Company:

- Lack of data Ev/Ex post-CDK4/6i
- No evidence of non-proportional hazards for any study in network

ERG:

- ERG did not identify other trials which could have been used
- HRs [redacted] (Table)
- **Wide interval around the HR for OS → confidence**



ERG: None of the studies conducted in post-CDK4/6i population, 2nd line used as proxy

Used in company base case

	HR (95%CI) of comparator versus:	
	Fulvestrant	Alpelisib + fulvestrant
Progression–free survival		
Alpelisib + fulvestrant	[redacted]	[redacted]
Ev/Ex	[redacted]	[redacted]
Fulvestrant	[redacted]	[redacted]
Overall survival		
Alpelisib + fulvestrant	[redacted]	[redacted]
Ev/Ex	[redacted]	[redacted]
Fulvestrant	[redacted]	[redacted]

Bucher indirect treatment comparison (2/2)

Broader proxy 2nd line population; uncertainty

ERG:

- CONFIRM and SoFEA do not restrict to 2nd line, HER2- or PIK3CA mutated patients

ERG / clinical experts:

- HER2 status may be an important effect modifier; SoFEA has HER2 subgroup data

Company – response to clarification questions:

- Provided additional analysis using the HER2- subgroup from SoFEA:

	HR (95%CI) of comparator versus:	
	Fulvestrant	Alpelisib + fulvestrant
Progression –free survival		
Ev/Ex	XXXXXXXXXX	XXXXXXXXXX
Overall survival		
Ev/Ex	XXXXXXXXXX	XXXXXXXXXX

ERG:

- Hazard ratios XXXXXXXXXX XXXXXXXXXXXXXXXXXXX using SoFEA HER2- subgroup
- Point estimates obtained for HRs equivalent to median values and ignore skewness of distribution
- **Results should be interpreted with caution**

Unanchored patient-adjusted indirect comparison (1/2)

Patient-level proxy data in people with ≤1 prior treatment with AI in (neo)adjuvant setting; used in company sensitivity analysis

Company:

- Alpelisib + fulvestrant (N=XXX FAS) in SOLAR-1 – 2nd line treatment in the PIK3CA-mutant cohort, excluding those who were endocrine therapy-sensitive
  - Ev/Ex (N=XXX FAS) in BOLERO-2 – intent-to-treat population with PIK3CA mutation, excluding those who had received >1 line of endocrine therapy for advanced disease
- Given small number in BOLERO-2 who met inclusion criteria and small effective sample sizes, results of this analysis should be interpreted with caution

Endpoint	Weighted	Arms		Cox proportional hazards regression
		Active (N)	Comparator (N)	HR (95% CI)
Progression-free survival	Yes	Alpelisib + fulvestrant (XX)	Ev/Ex (XX)	XXXXXXXXXX
Overall survival	Yes	Alpelisib + fulvestrant (XX)	Ev/Ex (XX)	XXXXXXXXXX

ERG:

- HRs for 2nd line patients suggest XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX (Table)

FAS, full analysis set

Unanchored patient-adjusted indirect comparison (2/2)

Small sample sizes; uncertainty

Company – responses to clarification questions:

- Provided results of Cox proportional hazards regressions for PFS and OS for 2nd line patients in SOLAR-1 vs BOLERO-2, using different model/variable selection methods

ERG:

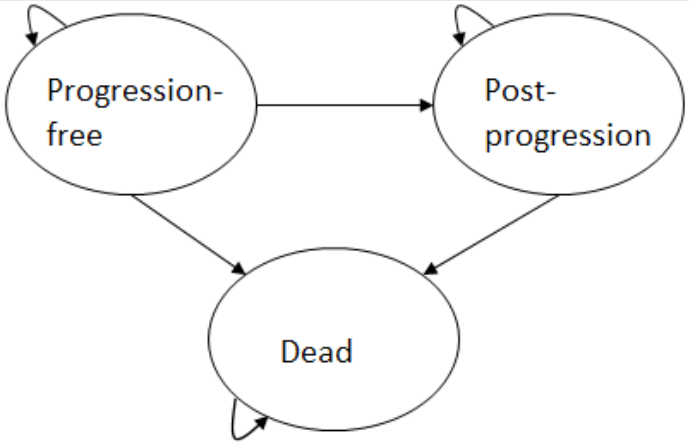
- Based on 2019 data cut-off results, estimated hazard ratios of PFS ranged from XXXX to XXXX and for OS ranged from XXXX to XXXX – no information from company about how method for estimating propensity scores was selected
- Noted company provided different model/variable selection methods for Cox proportional hazards regressions but provided no additional information; use of 2019 instead of 2020 data cut-off not explained
- Uncertainty – impact of including placebo arms from SOLAR-1 and BOLERO-2 in estimation of propensity scores, and any difference in results if only active arms included
- Unable to check programming code used (proprietary) company could not share
- Agrees with company that results should be interpreted with caution because of small sample sizes

◉ *What conclusions can be drawn about the comparative effectiveness of A+F and Ev/Ex?*
◉ *Which indirect analyses are suitable for informing the company's modelling?*
◉ *Is HER2 status an effect modifier of the Bucher indirect treatment comparison?*

Cost-effectiveness

Company's model

Model type	Partitioned survival model (progression-free, post-progression, dead)
Population	Adult women with endocrine resistant HR+, HER2- advanced breast cancer with a PIK3CA mutation, who have received prior CDK4/6 inhibitor therapy
Intervention	A+F
Comparator	Ev/Ex
Time horizon	40 years (lifetime)
Model cycle	28 days (half-cycle correction applied)
Discount rates	3.5% for both health and cost outcomes
Utility values	SOLAR-1 trial EQ-5D-5L, mapped to EQ-5D-3L, and published literature; adjusted for older-age decrease in health related quality of life
Costs	Price year 2019/2020 - BNF costs 2020 - NHS Reference Costs 2019/2020 - Confidential discounts available for modelled drugs. Discussed in private part 2 only
Perspective	NHS and Personal Social Services



BNF, British National Formulary; CMU, commercial medicines unit; eMIT, Drugs and pharmaceutical electronic market information tool; PAS, patient access scheme

Company modelling of OS, PFS and TTD

Company

- Model needed to link PFS distributions to OS data via an indirect treatment comparison
- Data from BYLieve are relatively mature, therefore fitting a curve directly to OS data considered appropriate
- Partitioned survival model has been adopted in multiple advanced oncology appraisals to date

Parameter	Source in company base case
Overall survival: A+F	Log-logistic, 2nd-line patients, BYLieve
Overall survival: Ev/Ex	HR derived from Bucher ITC applied to A+F OS model
Progression-free survival: A+F	Log-normal, 2nd-line patients, BYLieve
Progression-free survival: Ev/Ex	HR derived from Bucher ITC applied to A+F PFS model
Time to treatment discontinuation: A+F	Exponential model, second-line patients, BYLieve
Time to treatment discontinuation: Ev/Ex	HR for TTD vs PFS for first- and 2nd-line patients in BOLERO-2 applied to Ev/Ex PFS model

ERG

- **Clinical experts were satisfied with the comparator OS and PFS extrapolations**
- Did not change these assumptions in ERG base case
- Explored alternative extrapolations for OS and PFS (ICERs ranged from ≈£20K lower to ≈£65K higher than ERG base case)

HR, hazard ratio; ITC, indirect treatment comparison; PFS, progression-free survival; OS, overall survival; TTD, time to treatment discontinuation.

Company modelling of OS (1/2)

ERG: Gompertz & Weibull provide slightly better fit than log-logistic

Kaplan-Meier plot and modelled OS,
A+F (re-drawn by ERG)*

* Includes general population mortality constraint using life tables

◉ *Is log-logistic model appropriate?*

Company

- Log-logistic selected by goodness-of-fit statistics; visual inspection of fitted distributions; assumption that projected OS equal to or higher than projected PFS; examination of hazard plots and validation by clinical expert opinion

ERG

- Log-logistic function ranked 3rd best in terms of Akaike, corrected Akaike and Bayesian information criteria
- Gompertz and Weibull functions provided slightly better model fit than log-logistic

Company modelling of OS (2/2)

ERG: model may overestimate OS; alternative extrapolations explored

Kaplan-Meier plot and modelled OS, A+F versus Ev/Ex (re-drawn by ERG)*†

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

◉ *Do extrapolations of OS look realistic?*

Sources

Alpelisib + fulvestrant:

Individual patient data for 2nd line from Cohort A of BYLieve (n=XX)

Ev/Ex:

Constant HR derived from Bucher indirect treatment comparison (HR=XXX, 95% CrI XXX XXXXXX), estimated using data on OS for 2nd-line patients in SOLAR-1 and BOLERO-2, to log-logistic OS model for A+F group

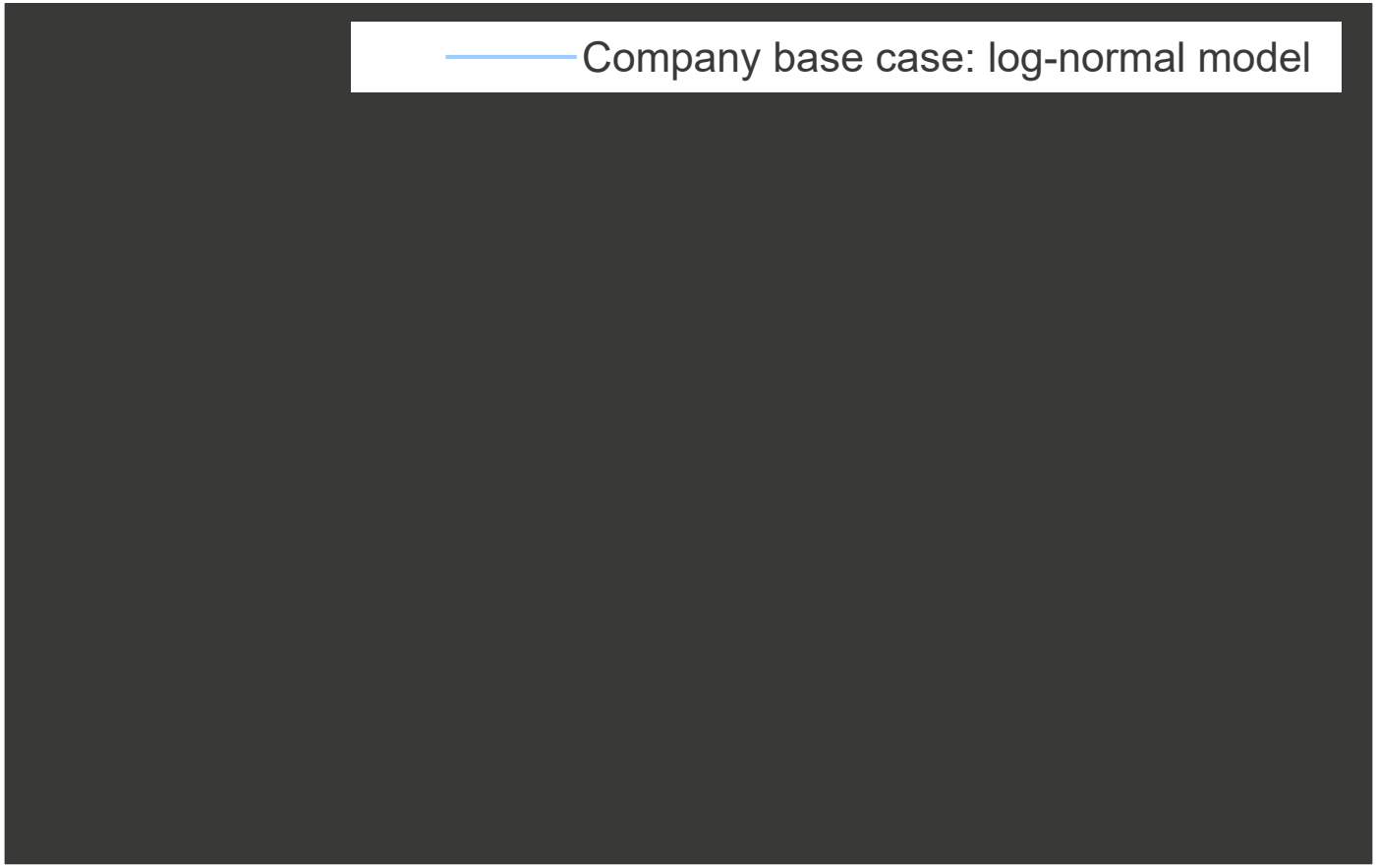
ERG

- **Satisfied with OS function used**
- Log-logistic model appears to over-estimate OS for A+F group after around 1.5 years, although very few events occur beyond this
- Log-logistic incremental LYGs = 0.76
- Explored alternative extrapolations – incremental LYGs ranged from 0.17 (Gompertz) to 1.12 (log-normal)

Company modelling of PFS (1/2)

ERG: log-normal amongst best fitting models

Kaplan-Meier plot and modelled PFS,
A+F (re-drawn by ERG)*



Company

- Log-normal selected by goodness-of-fit statistics; visual inspection of fitted distributions; hazard functions, time dependent HRs, diagnostic plots for treatment effects, and clinical plausibility.

ERG

- Log-normal function ranked 1st best on Bayesian information criteria and 4th best on Akaike and corrected Akaike

* Includes general population mortality constraint using life tables

◉ *Is log-normal model appropriate?*

Company's cumulative probabilities of PFS (2/2)

Same range of parametric survival models as for OS fitted

Kaplan-Meier plot and modelled PFS, A+F versus Ev/Ex (re-drawn by ERG)*

* Includes general population mortality constraint using life tables

◉ *Do extrapolations of PFS look realistic?*

Sources
Alpelisib + fulvestrant:
Individual patient data for 2nd-line patients from Cohort A of BYLieve (n=XX)
Ev/Ex:
Constant HR derived from Bucher indirect treatment comparison (HR=XXX, 95% CrI XXXXXXX), estimated using data on PFS for 2nd-line patients in SOLAR-1 and BOLERO-2, to log-normal PFS model for A+F group

ERG

- **Satisfied with PFS function used**
- Company fitted the same range of parametric survival models to the PFS data as for OS
- Incremental LYGs = 0.76 for all

Uncertainty surrounding relative treatment effects versus everolimus + exemestane

Key issue

Company's model uses data from Bucher indirect treatment comparison

Treatment effect and QALY estimates highly uncertain

ERG / clinical experts:

- **Considered relative treatment effects of A+F and EV/Ex plausible**

ERG

- Company assumes [redacted] for A+F compared with Ev/Ex
  - Analysis using HER2- subgroup from SoFEA shows treatment effect is [redacted]
- Treatment effect and QALY estimates generated by economic model **highly uncertain**:
  - Potentially biased due to imbalance in treatment effect modifiers such as HER2 mutation status
  - Assumption of proportional hazards for the 2nd-line population is questionable – company based this on lack of evidence for non-proportional hazards
  - Fixed effects models used – assumption of zero between-study variation is not appropriate, hence uncertainty is underestimated
  - Network involves a single chain of evidence (with no closed loops) and each comparison is informed by only 1 trial – not possible to assess consistency of evidence statistically
- **ERG additional analysis using HER2- subgroup from SoFEA greatly increases ICER**

◉ *What is the committee's view on the evidence of relative treatment effect of alpelisib + fulvestrant versus Ev/Ex? Are the Bucher or population-adjusted indirect analyses suitable for decision making?*

Assumptions surrounding duration of treatment effect

Additional issue

Company's assumes indefinite treatment effect

Assuming less optimistic duration of treatment effect increase the ICER

Background:

- Company assumes an indefinite duration of treatment effect for A+F compared with Ev/Ex – constant across 40 year time horizon – assumes **no waning of treatment effect**
- In related TA563 (abemaciclib + AI), it was noted that Bayesian network meta-analysis methods such as fractional polynomials can be used to compare treatments when proportional hazards are not supported or uncertain, to enable time-varying hazards to be incorporated

ERG / clinical experts:

- **Considered indefinite duration of treatment effect to be optimistic**

ERG

- Company did not present evidence to support assumption of no waning
- ERG performed additional sensitivity analysis to explore possibility that treatment effect for A+F on PFS and OS wanes and switches to that of Ev/Ex (derived from A+F) at 3 or 5 years:
  - Both lead to **large increase in ICER** vs ERG preferred analysis; greater increase with shorter duration of treatment effect (3 years)

Company:

- Concerned with ERG's approach – more consistent with model to apply waning to Ev/Ex, switching treatment effect to that of A+F at 3 and 5 years – **impact on ICERs reduced**

◉ *What does the committee think is the most appropriate duration of treatment effect to be modelled? Is an indefinite treatment effect duration reasonable?*

Utilities

Equal utilities assumed for both treatments

Broader proxy 2nd line population

Background:

- Age-adjusted utilities using absolute decrements (Ara & Brazier), mean age 57 years model entry
- Company does not include utility decrement for Grade 3/4 adverse events

Health state	Mean utility (95% CI)
	A+F and Ev/Ex
Progression-free, on treatment[a]	XXX
Progression-free, off treatment	XXX
Post-progression[b]	XXX
Terminal phase disutility	XXX

[a] Based on SOLAR-1 GEE regressions using data from 2nd-line patients;
[b] based on Mitra et al (as in TA725)

- No health-related quality of life data from BYLieve – findings after progression on a CDK4/6i not used to inform post-progression assumptions

ERG / clinical expert:

- Reasonable that health-related quality of life similar for A+F and Ev/Ex

Concerns about health state utility values used

Key issue

Company and ERG disagree on post-progression utility

Post-progression utility uncertain; may be over-estimated by company

ERG:

- SOLAR-1: EQ-5D-5L data largely missing after progression – utility uncertain, no reliable estimate
- Company over-estimates utility in post-progression state ([redacted] from Mitra et al)
  - EQ-5D-3L estimates in HR+/HER2- advanced/metastatic breast cancer in 5 EU countries and US, with utility value specifically for patients ≥3rd line; EQ-5D tariffs unlikely to reflect UK tariff
- ERG prefers value of 0.51 (Lloyd et al) – uses time trade-off vignette approach rather than EQ-5D
  - relatively old, but has been used in majority of NICE appraisals in advanced breast cancer

Company:

- Lloyd et al outdated, not reflecting today's patients and the treatment landscape
- [redacted] value (Mitra et al) used and preferred to Lloyd in TA725 of CDK4/6i (abemaciclib + AI)

ERG / clinical experts:

- SOLAR-1: [redacted] post-progression utility value consistent with patients who have radiological progression on 1–3 lines of treatment without a significant change in health-related quality of life
  - trial recruitment involves selecting for fitter patients; low tumour burden or disease not affecting critical organs or nerve structures
  - patients who develop spinal cord compression, brain metastases or lung involvement requiring oxygen will have lower health-related quality of life
- Mid-point between Lloyd et al and Mitra et al (i.e. [redacted]) or [redacted] may be more appropriate
- ERG exploratory analysis: **company ICER increases** if mid-point ([redacted]) or Lloyd (0.51) used

◉ *What is the committee's view on the likely post-progression utility value?*

Resource use and costs

Uncertainty in post-progression treatment costs

Additional issue

Costs in company base case

Post-progression treatment costs unclear

Background:

- Company assumes fixed cost of £1,500 per month for 'all future treatment-related costs' for people in post-progression state (excluding terminal care)
  - based on related appraisals TA496/TA687 (ribociclib + fulvestrant and its CDF review)

ERG:

- ERG unclear whether company assumption is reasonable
  - requested additional information on treatments used to justify assumption – company did not provide additional information
- Noted: lower estimated post-progression treatment costs (£1,140 to £1,200) preferred by committee in TA496 (ribociclib + fulvestrant)
- Conducted sensitivity analysis adjusting cost by +/- £750 – minor increase/decrease in ICER
- May be more appropriate to apply subsequent-line treatment costs based on observed post-progression treatments received in the clinical study

◉ *How should post-progression costs be estimated?*

Cost-effectiveness results

Discrepancy between deterministic and probabilistic cost-effectiveness results

Key issue

Company's deterministic and probabilistic model results differ (1/3)

Probabilistic ICER higher than deterministic estimate

Background – NICE's Decision Support Unit:

- Probabilistic methods are generally considered most appropriate for decision making – allow for full expression of the uncertainty in model parameters (unlike a deterministic approach)

ERG:

- Company probabilistic ICER almost £10K higher than the deterministic estimate
  - similar ICER difference also seen for ERG's preferred analysis
  - also differences in life-years gained, QALYs and costs between deterministic and probabilistic estimates of OS
  - *Results shown in Part 2*
- Probabilistic sampling was implemented correctly – fully replicated by ERG
- Additional analyses broadly aligned the results of the deterministic and probabilistic models

Company – response to clarification question:

- Larger ICERs obtained from probabilistic analysis due to the variation associated with treatment effect, with the sampled treatment effect being less favourable towards A+F at times
- A constraint could have been added to ensure that all sampled HRs favoured A+F, but was not included for sake of transparency – ERG agrees
  - probabilistic analyses likely conservative; ICER is more likely to be aligned with the deterministic analysis (which produces a comparatively lower ICER)

Company's deterministic and probabilistic model results differ (2/3)

Some probabilistic sampling of OS results implausible

ERG ***continued:***

- Agrees main driver of discrepancy between model results is very wide interval around the HR for OS ([redacted]) derived from Bucher indirect treatment comparison
- Company's probabilistic sampling of OS suggests A+F is less effective than Ev/Ex in >18% of samples
  - Extent of survival loss for A+F implausible in several samples

Company **–** ***clinical expert option:***

- Reasonable to assume A+F always more effective than Ev/Ex for HR+, HER2– advanced breast cancer with a PIK3CA mutation following treatment with a CDK4/6 inhibitor

Distribution of incremental OS from company's probabilistic sensitivity analysis, A+F versus Ev/Ex

[redacted]

- *Is the Bucher indirect treatment comparison suitable for informing the PSA?*
- *Is it reasonable to assume A+F always more effective than Ev/Ex in this population?*

Company's deterministic and probabilistic model results differ (3/3)

ERG unsure which model results more appropriate to rely on

ERG *continued:*

- Generally, probabilistic methods are considered most appropriate for decision making but may not be in this case
- Overall, interpretation of the results of the company's deterministic model is also problematic because of the use of median HRs (point estimates) rather than mean HRs
- However, there is a discrepancy in the results produced when using:
  - mean of the HR in the deterministic model → ICER is decreased
  - probabilistic samples of the HRs → expected ICER is increased, due to the non-linear response to extreme HRs
- Given these problems, the ERG is unsure whether more appropriate to rely on results of deterministic or probabilistic model

◉ *What is the most appropriate model to use as the basis for an ICER estimate?*

Key assumptions and impacts on ICER

Model driver
Unknown impact
Small/Moderate impact

Company and ERG differ

Parameter	Base case analysis		Impact on ICER
	Company	ERG	
Comparator	Ev/Ex	Ev/Ex	
Treatment effect for PFS, A+F vs E+E	HR: [redacted]	HR: [redacted] *High uncertainty*	
Treatment effect for OS, A+F vs E+E	HR: [redacted]	HR: [redacted] *High uncertainty*	
Treatment effect duration	Indefinite – constant across 40 year time horizon	Indefinite (additional sensitivity analysis: 3- or 5- year duration)	
Progression-free, on treatment utility value (A+F / E+E)	2nd-line patients in SOLAR-1: [redacted]	2nd-line patients in SOLAR-1: [redacted]	
Post-progression utility value (A+F / E+E)	Mitra et al: [redacted]	Lloyd et al: 0.51 (additional analysis: mid-point between Lloyd et al and Mitra et al: [redacted])	
Subsequent treatment costs, post-progression	£1,500 per month	£1,500 per month *Uncertainty*	
Analysis of cost-effectiveness results	Deterministic	Deterministic *Uncertainty*	

Does alpelisib + fulvestrant meet end-of-life criteria?

- Both criteria must be met:
  1. Treatment is indicated for patients with a short life expectancy, normally less than 24 months
  2. Sufficient evidence to indicate that treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment
- In addition, committee should be satisfied that:
  - estimates are robust
  - assumptions used in the reference case economic modelling are plausible, objective and robust

Company consider end-of-life criteria met

In people who have progressed following 1st-line treatment for advanced breast cancer with a CDK4/6i + AI

Life expectancy is <24 months

- BYLieve cohort A: median overall survival XXX months following treatment with A+F
- Bucher indirect treatment comparison shows estimated median overall survival under standard care (Ev/Ex) is lower than seen with A+F
  - ➢ Therefore, **criteria for life expectancy <24 months with standard care met**
- Also, SOLAR-1: median overall survival XXX months following treatment with comparator (placebo + fulvestrant) in post-CDK4/6 inhibitor population (n=20)

Extension of life by ≥3 months

- Deterministic base case model: mean overall survival gain 2.58 years for A+F and 1.81 years for Ev/Ex
- Incremental survival gain for A+F of 0.76 years (=9.1 months)
  - ➢ Therefore, **criteria for extension of life by ≥3 months over standard care met**

Deterministic and probabilistic model estimates differ

ERG:

- Company's base case model (deterministic) and ERG's preferred analysis → criteria met

Met: company's base case and ERG's preferred analysis

Not met

Bucher ITC population	Deterministic model		Probabilistic model	
	LYs with Ev/Ex	Additional LYGs, A+F vs Ev/Ex	LYs with Ev/Ex	Additional LYGs, A+F vs Ev/Ex
Unrestricted 2nd line population	**1.81 (<24 mo)**	**0.76 (>3 mo)**	2.17 (>24 mo)	**0.54 (>3 mo)**
Only HER2- subgroup of SoFEA	2.19 (>24 mo)	**0.38 (>3 mo)**	2.68 (>24 mo)	0.03 (<3 mo)

Not met

- Criteria not met using probabilistic base case model or only HER2- patients in SoFEA in Bucher indirect treatment comparison (deterministic or probabilistic)
- ERG unsure whether more appropriate to rely on results of deterministic or probabilistic model

◉ *Which population should be used in indirect treatment comparison, and which version of company model should be used, to whether end-of-life criteria are met?*

Key issues

Clinical: *what is committee's view on:*

- **Alpelisib + fulvestrant (A+F) positioning:** company positions post-CDK4/6 inhibitor, primarily 2nd line, but not excluding other lines – *where would A+F be used in NHS practice?*
- **A+F vs everolimus + exemestane (Ev/Ex) as sole comparator:**
  - ERG: Ev/Ex is most appropriate comparator, but others treatments might be used in some circumstances – *what is/are the most appropriate comparator/s?*
  - No direct comparative evidence – *are indirect analyses robust enough for decision?*

Cost: *what is committee's view on*:

- **Bucher indirect treatment comparison:** suitability of connecting trials – *is HER2 status an important modifier of treatment effect that should be taken into account?*
- **Modelling of OS:** Gompertz & Weibull provide slightly better fit than log-logistic – *which OS model should be used?*
- **Duration of treatment effect for A+F versus Ev/Ex:** company assumes no waning – *should time-limited treatment effect be assumed (i.e. 3- or 5- years)?*
- **Most appropriate model:** probabilistic ICER ≈£10K higher than deterministic – *is Bucher indirect treatment comparison suitable for informing probabilistic sensitivity analysis?*

End of life: *Does alpelisib meet end-of-life criteria?*

Innovation and Equality

Innovation:

Company:

- Alpelisib is 1st licensed alpha-selective PI3K inhibitor (EMA, FDA)
- It is 1st targeted treatment for endocrine resistant HR+, HER2- advanced breast cancer with PIK3CA mutation – personalised treatment option
- Limited treatment options and poor prognosis for patients in post-CDK4/6 inhibitor population – high unmet need
- Currently available standard care (Ev/Ex) may have limited survival benefit

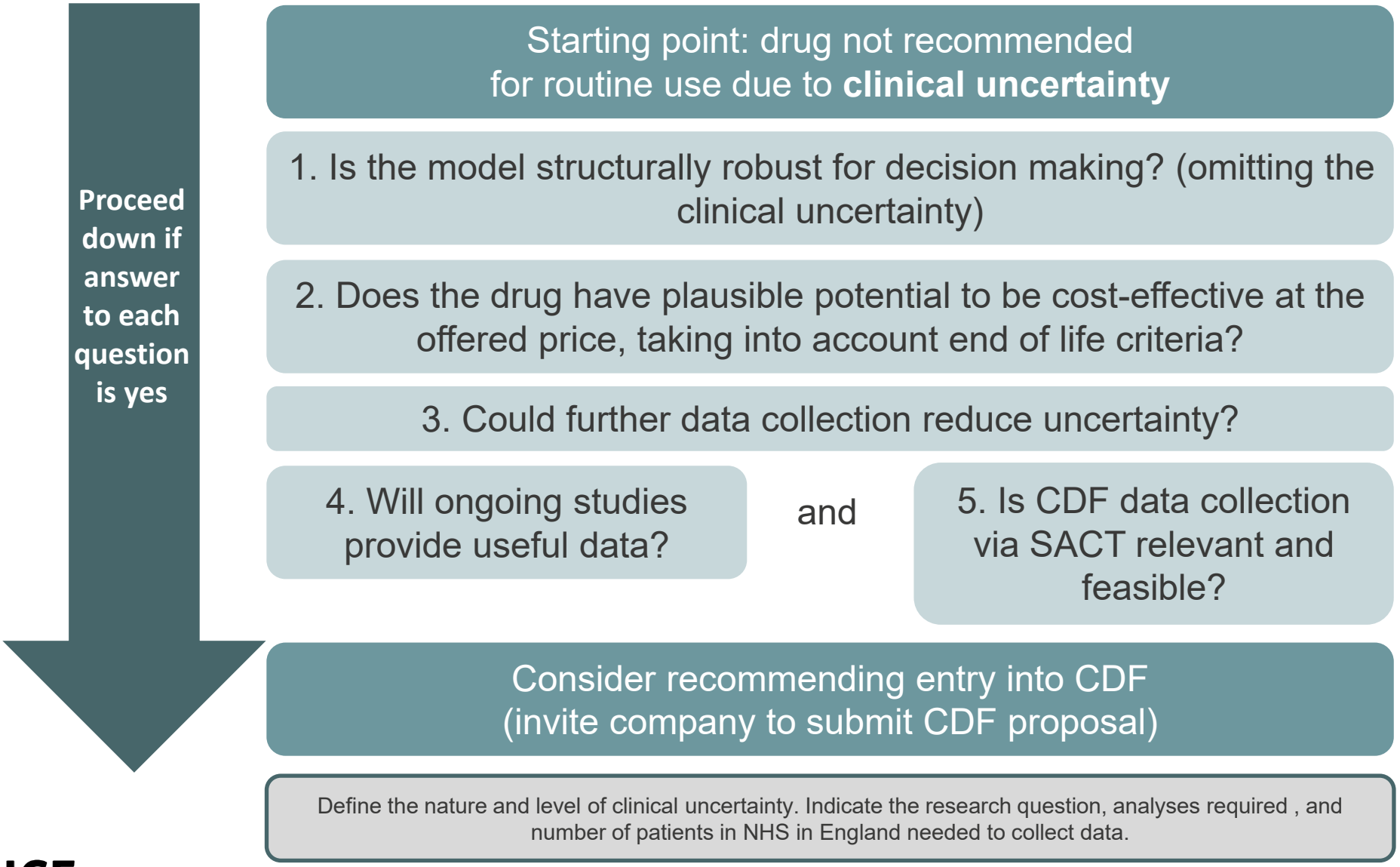
Equality issues:

Company:

- Use of alpelisib + fulvestrant not expected to raise any equality issues

No critique from ERG

Committee decision making: CDF recommendation criteria



Decision problem – EPIK-B5 trial

- Phase 3, randomised, double-blind, placebo-controlled, international, multicentre trial
- N ~234; stratified 1:1 by presence/absence of lung and/or liver metastases
- Estimated primary completion date: October 2026
- NCT05038735

	EPIK-B5	Aligned with company decision problem?	Addresses uncertainty?
Population	People with advanced, HR+, HER2-negative PIK3CA-mutated breast cancer that has progressed/relapsed on/after a CDK4/6i + AI • Note: CDK4/6i + AI does not need to be latest treatment regimen	Yes • Note: alpelisib + F was 2nd line after CDK4/6i + AI	Provides additional data in population of interest
Intervention	Alpelisib + F	Yes	Provides additional data in intervention of interest
Comparators	Placebo + F	No. Company compares against Ev/Ex in indirect analyses	Not compared with comparator of interest. But might provide additional data for indirect analyses (same comparator as used in SOLAR-1)
Outcomes	• Survival outcomes including OS, PFS	Yes	**Addresses key uncertainty –** OS extrapolation choice has big impact on ICER

Cost-effectiveness results

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