IQWiG Reports – Commission No. A20-81

Alpelisib (breast cancer) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.8 of the dossier assessment *Alpelisib (Mammakarzinom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 27 November 2020). Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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[2] Table numbers start with "2" as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BPI-SF	Brief Pain Inventory – Short Form
CDK	cyclin-dependent kinase
CTCAE	Common Terminology Criteria for Adverse Events
ECOG-PS	Eastern Cooperative Oncology Group Performance Status
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Cancer-30
EQ-5D-5L VAS	European-Quality-of-Life-Questionnaire-5-Dimensions-5-Level visual analogue scale
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HER2	human epidermal growth factor receptor 2
HR	hormone receptor
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PIK3CA	phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha
PFS	progression-free survival
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
VAS	visual analogue scale

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug alpelisib. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 1 September 2020.

Due to the working conditions during the coronavirus pandemic, the present assessment was conducted without the use of strictly confidential data presented in Module 5 of the company's dossier.

Research question

The aim of the present report is to assess the added benefit of alpelisib in combination with fulvestrant in comparison with the appropriate comparator therapy (ACT) in men and postmenopausal women with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative, locally advanced or metastatic breast cancer with phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) mutation and disease progression after endocrine monotherapy.

The G-BA distinguished a total of 4 different treatment scenarios based on line of treatment and sex. This resulted in 4 research questions for this benefit assessment; their respective indications and ACTs are presented in Table 2.

Table 2: Research questions of the benefit assessment of alpelisib in combination with fulvestrant

Research question	Therapeutic indication	ACT[a]
Men and postmenopausal women with HR-positive, HER2-negative, locally advanced or metastatic breast cancer[b] with PIK3CA mutation		
A1	Postmenopausal women after disease progression following endocrine monotherapy in the (neo)adjuvant treatment situation	▪ Ribociclib in combination with a nonsteroidal aromatase inhibitor or ▪ Ribociclib in combination with fulvestrant or ▪ Anastrozole or ▪ Letrozole or ▪ Fulvestrant or ▪ Possibly tamoxifen if aromatase inhibitors are not suitable
A2	Men after disease progression following endocrine monotherapy in the (neo)adjuvant treatment situation	Therapy upon the physician's discretion[c]
B1	Postmenopausal women after disease progression following endocrine monotherapy in the locally advanced or metastatic stage	Another endocrine therapy with ▪ abemaciclib in combination with fulvestrant or ▪ ribociclib in combination with fulvestrant or ▪ tamoxifen or ▪ anastrozole or ▪ fulvestrant monotherapy, only for patients with recurrence or progression following antioestrogen treatment[d] ▪ letrozole, only for patients with recurrence or progression following antioestrogen treatment or ▪ exemestane, only for patients with progression following antioestrogen treatment or ▪ everolimus in combination with exemestane, only for patients without symptomatic visceral metastasis after progression following nonsteroidal aromatase inhibitor therapy
B2	Men after progression following endocrine monotherapy in the locally advanced or metastatic stage	Therapy upon the physician's discretion[c]

a. Presented is the ACT specified by the G-BA.
b. For the given therapeutic indication, it is assumed that another endocrine therapy is indicated for the patient, while no indication exists for chemotherapy or (secondary) resection or radiotherapy with curative intent.
c. For men, the guidelines recommend the drugs tamoxifen and fulvestrant as well as aromatase inhibitors. Aromatase inhibitors and fulvestrant are not approved for the present indication. There is a discrepancy between the drugs approved for the indication versus those used in practice and recommended by guidelines. The following drugs are deemed adequate as comparators in clinical trials: tamoxifen, aromatase inhibitors in combination with a GnRH analogue, fulvestrant.
d. In this case, the approval states that fulvestrant is indicated only after antioestrogen treatment was administered. This represents a discrepancy between fulvestrant approval versus its routine use in practice as recommended by the guidelines, where it is administered not exclusively to patients with prior antioestrogen treatment but also to those with prior aromatase inhibitor therapy. In this special therapy and medical treatment situation, the G-BA sees a sufficient medical reason that, despite residual uncertainties, justifies assessing fulvestrant as a sufficiently suitable comparator in this case.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; GnRH: gonadotropin-releasing hormone; HER2: human epidermal growth receptor 2; HR: hormone receptor; PIK3CA: phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha

To improve readability, the treatment line for research questions A1 and A2 is referred to as first-line therapy in the advanced stage, while the treatment line for research questions B1 and B2 is referred to as second-line and subsequent-line therapy in the advanced stage.

The G-BA changed the ACT on 27 October 2020 as shown in Table 2. The company followed the G-BA's original specification of the ACT.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier in comparison with the ACT specified by the G-BA. Randomized controlled trials (RCTs) were used for the derivation of added benefit.

Results

Study pool

The relevant study for the benefit assessment of alpelisib in combination with fulvestrant is the SOLAR-1 study, which directly compares the combination of alpelisib + fulvestrant with placebo + fulvestrant. Due to its design and the included patients, the SOLAR-1 study is suitable for deriving conclusions on the added benefit of alpelisib in combination with fulvestrant for research questions A1 and B1.

Given that the SOLAR-1 study included only 1 man, no data are available for the benefit assessment regarding research questions A2 and B2.

Research questions A1 and B1

Study characteristics

SOLAR-1 is an RCT which included men and postmenopausal women with HR-positive, HER2-negative, locally advanced or metastatic breast cancer. With regard to prior therapy, patients had to exhibit recurrence or progression during or after endocrine therapy with an aromatase inhibitor, although said therapy did not have to be the most recently received therapy. Patients had to have received said endocrine therapy either in the advanced stage or exclusively as (neo)adjuvant therapy, or both. However, a maximum of 1 line of endocrine therapy in the advanced stage was allowed.

As part of screening, the tumour material was tested for a PIK3CA mutation, and patients were categorized into either the group with PIK3CA mutation or the group without PIK3CA mutation. Only the group with PIK3CA mutation was relevant for the present benefit assessment. This group included a total of 341 patients, who were randomized in a 1:1 ratio to treatment with alpelisib + fulvestrant or placebo + fulvestrant.

Treatment with the study drug was continued until either disease progression, unacceptable toxicity, withdrawal of consent, loss to follow-up, death, or treatment discontinuation for any other reason. Switching from placebo to alpelisib treatment was not allowed.

The primary outcome of the study was progression-free survival (PFS) in the group with PIK3CA mutation, while patient-relevant secondary outcomes included overall survival as well as outcomes on morbidity, health-related quality of life, and adverse events (AEs).

The data cut-off of 23 April 2020 was used for the benefit assessment, representing the predefined date of the final analysis regarding overall survival.

Relevant subpopulations

The relevant subpopulation for research question A1 was postmenopausal women who received the study drug as first-line therapy in the advanced stage. This included 88 patients in the intervention arm and 89 patients in the comparator arm (subpopulation A1).

The relevant subpopulation for research question B1 was postmenopausal women who received the study drug as second-line therapy in the advanced stage. This included 79 patients in the intervention arm and 82 patients in the comparator arm (subpopulation B1).

Risk of bias and reliability of results

The risk of bias across outcomes (study level) is low. The outcome-specific risk of bias is low only for the results on the outcome of overall survival. The results on all other outcomes for which usable analyses are available come with a high risk of bias.

For the outcome of overall survival, the available data can be used to derive no more than an indication, e.g. of added benefit, for either research question (A1 and B1). The results of the remaining outcomes for which usable analyses are available are each subject to a high risk of bias, and therefore, only hints, e.g. of added benefit, can be derived. The certainty of results on the specific outcome level, however, has not been downgraded in some cases (see description of results below).

Results on research question A1: postmenopausal women, first-line therapy in the advanced stage

Mortality – overall survival

For the outcome of overall survival, no statistically significant difference between treatment groups was found. Hence, there is no hint of added benefit of alpelisib + fulvestrant in comparison with fulvestrant; an added benefit is therefore not proven.

Morbidity – symptoms (symptom scales of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Cancer-30 [EORTC QLQ-C30]), pain (Brief Pain Inventory – Short Form [BPI-SF]), health status (European-Quality-of-Life-Questionnaire-5-Dimensions-5-Level visual analogue scale [EQ-5D-5L VAS])

No usable analyses are available for the outcomes regarding (1) symptoms as surveyed with the EORTC QLQ-C30 symptom scales, (2) pain as surveyed with the BPI-SF, and (3) health status as surveyed with the VAS of EQ-5D-5L. Hence, there is no hint of added benefit of alpelisib +

fulvestrant in comparison with fulvestrant for any of them; an added benefit is therefore not proven.

Health-related quality of life – global health status and functioning scales, surveyed using EORTC QLQ-C30

No usable analyses are available for outcomes regarding (1) health-related quality of life as surveyed with global health status and (2) the functioning scales of EORTC QLQ-C30. Hence, there is no hint of added benefit of alpelisib + fulvestrant in comparison with fulvestrant for any of them; an added benefit is therefore not proven.

AEs – serious AEs (SAEs) and discontinuation due to AEs

For each of the outcomes of SAEs and discontinuation due to AEs, there is a statistically significant difference to the disadvantage of alpelisib + fulvestrant in comparison with placebo + fulvestrant. This results in a hint of greater harm from alpelisib + fulvestrant in comparison with fulvestrant in each case.

AEs – severe AEs (operationalized as Common Terminology Criteria for Adverse Events [CTCAE] grade 3 or 4)

For the outcome of severe AEs, operationalized as CTCAE grade 3 or 4, a statistically significant difference to the disadvantage of alpelisib + fulvestrant was found in comparison with placebo + fulvestrant. Despite a high risk of bias of results, this outcome is associated with a high certainty of results due to the effect size already observed early in the study. Hence, there is an indication of greater harm from alpelisib + fulvestrant in comparison with fulvestrant.

AEs – specific AEs

For the relevant subpopulation, it was not possible to select specific AEs. Hence, there is no hint of greater or lesser harm from alpelisib + fulvestrant in comparison with fulvestrant; greater or lesser harm is therefore not proven.

Results on research question B1: postmenopausal women, second-line and subsequent-line therapy in the advanced stage

Mortality – overall survival

For the outcome of overall survival, no statistically significant difference between treatment groups was found. Hence, there is no hint of added benefit of alpelisib + fulvestrant in comparison with fulvestrant; an added benefit is therefore not proven.

Morbidity – symptoms (symptom scales of EORTC QLQ-C30), pain (BPI-SF), health status (EQ-5D-5L VAS)

No usable analyses are available for the outcomes regarding (1) symptoms as surveyed with the EORTC QLQ-C30 symptom scales, (2) pain as surveyed with the BPI-SF, and (3) health status as surveyed with the VAS of EQ-5D-5L. Hence, there is no hint of added benefit of alpelisib +

fulvestrant in comparison with fulvestrant for any of them; an added benefit is therefore not proven.

Health-related quality of life – global health status and functioning scales, surveyed using EORTC QLQ-C30

No usable analyses are available for outcomes on health-related quality of life, surveyed with global health status and the functioning scales of EORTC QLQ-C30. Hence, there is no hint of added benefit of alpelisib + fulvestrant in comparison with fulvestrant for any of them; an added benefit is therefore not proven.

AEs – SAEs and discontinuation due to AEs

For each of the outcomes of SAEs and discontinuation due to AEs, there is a statistically significant difference to the disadvantage of alpelisib + fulvestrant in comparison with placebo + fulvestrant. This results in a hint of greater harm from alpelisib + fulvestrant in comparison with fulvestrant in each case.

AEs – severe AEs (operationalized as CTCAE grade 3 or 4)

For the outcome of severe AEs, operationalized as CTCAE grade 3 or 4, a statistically significant difference to the disadvantage of alpelisib + fulvestrant was found in comparison with placebo + fulvestrant. Despite a high risk of bias of results, this outcome is associated with a high certainty of results due to the effect size already observed early in the study. Hence, there is an indication of greater harm from alpelisib + fulvestrant in comparison with fulvestrant.

AEs – specific AEs

For the relevant subpopulation, it was not possible to select specific AEs. Hence, there is no hint of greater or lesser harm from alpelisib + fulvestrant in comparison with fulvestrant; greater or lesser harm is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

On the basis of the results presented, the probability and extent of added benefit of the drug alpelisib plus fulvestrant in comparison with the ACT are assessed as follows:

Research question A1: postmenopausal women, first-line therapy in the advanced stage

All things considered, the available data show exclusively unfavourable effects for alpelisib plus fulvestrant in comparison with fulvestrant.

For each of the outcomes of SAEs and discontinuation due to AEs, a hint of greater harm of minor or considerable extent was found. For severe AEs, there is an indication of major greater harm. No data are available on other AE outcomes since it was not possible to select specific AEs. No usable analyses are available on outcomes of the categories of morbidity and health-related quality of life.

In summary, there is a hint of lesser benefit of alpelisib plus fulvestrant in comparison with fulvestrant for postmenopausal women with HR-positive, HER2-negative, locally advanced or metastatic breast cancer with PIK3CA mutation and progression of disease following endocrine monotherapy in the (neo)adjuvant treatment situation.

Research question A2: men, first-line therapy in the advanced stage

Given that no data are available for this research question, there is no proof of added benefit of alpelisib plus fulvestrant for these patients.

Research question B1: postmenopausal women, second-line and subsequent-line therapy in the advanced stage

All things considered, the available data show exclusively unfavourable effects for alpelisib plus fulvestrant in comparison with fulvestrant.

For each of the outcomes of SAEs and discontinuation due to AEs, a hint of greater harm of considerable extent was found. For severe AEs, there is an indication of major greater harm. No data are available on other AE outcomes since it was not possible to select specific AEs. No usable analyses are available on outcomes of the categories of morbidity and health-related quality of life.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

In summary, there is a hint of lesser benefit of alpelisib plus fulvestrant in comparison with fulvestrant for postmenopausal women with HR-positive, HER2-negative, locally advanced or metastatic breast cancer with PIK3CA mutation who experience progression of disease following endocrine monotherapy in the locally advanced or metastatic stage.

Research question B2: men, second-line and subsequent-line therapy in the advanced stage

Given that no data are available for this research question, there is no proof of added benefit of alpelisib plus fulvestrant for these patients.

Table 3 presents a summary of the probability and extent of the added benefit of alpelisib in combination with fulvestrant.

Table 3: Alpelisib in combination with fulvestrant – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
Men and postmenopausal women with HR-positive, HER2-negative, locally advanced or metastatic breast cancer[b] with PIK3CA mutation			
A1	Postmenopausal women after disease progression following endocrine monotherapy in the (neo)adjuvant treatment situation	▪ Ribociclib in combination with a nonsteroidal aromatase inhibitor or ▪ Ribociclib in combination with fulvestrant or ▪ Anastrozole or ▪ Letrozole or ▪ Fulvestrant or ▪ Possibly tamoxifen if aromatase inhibitors are not suitable	Hint of lesser benefit[c]
A2	Men after disease progression following endocrine monotherapy in the (neo)adjuvant treatment situation	Therapy upon the physician's discretion	Added benefit not proven
B1	Postmenopausal women after disease progression following endocrine monotherapy in the locally advanced or metastatic stage	Another endocrine therapy with ▪ abemaciclib in combination with fulvestrant or ▪ ribociclib in combination with fulvestrant or ▪ tamoxifen or ▪ anastrozole or ▪ fulvestrant monotherapy; only for patients with recurrence or progression following antioestrogen treatment or ▪ letrozole, only for patients with recurrence or progression following antioestrogen treatment or ▪ exemestane, only for patients with progression following antioestrogen treatment or ▪ everolimus in combination with exemestane, only for patients without symptomatic visceral metastasis after progression following nonsteroidal aromatase inhibitor therapy	Hint of lesser benefit[c]
B2	Men after progression following endocrine monotherapy in the locally advanced or metastatic stage	Therapy upon the physician's discretion	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. For the given therapeutic indication, it is assumed that another endocrine therapy is indicated for the patient, while no indication exists for chemotherapy or (secondary) resection or radiotherapy with curative intent.
c. The SOLAR-1 study provides data only on the comparison to fulvestrant (viewed by the G-BA as a sufficiently suitable comparator for research question B1, even following aromatase inhibitor therapy). Further, only patients with an ECOG-PS of 0 or 1 were included. It remains unclear whether the observed effects are transferable to patients with an ECOG-PS ≥ 2. Virtually all patients included in the study were in stage IV (breast cancer with distant metastases).

ACT: appropriate comparator therapy; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; HER2: human epidermal growth receptor 2; HR: hormone receptor; PIK3CA: phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha

The approach for deriving an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

2.2 Research question

The aim of the present report is to assess the added benefit of alpelisib in combination with fulvestrant in comparison with the ACT in men and postmenopausal women with HR-positive, HER2-negative, locally advanced or metastatic breast cancer with PIK3CA mutation and disease progression after endocrine monotherapy.

The G-BA distinguished a total of 4 different treatment scenarios based on treatment line and sex. This resulted in 4 research questions for this benefit assessment; their respective indications and ACTs are presented in Table 4.

Table 4: Research questions of the benefit assessment of alpelisib in combination with fulvestrant

Research question	Therapeutic indication	ACT[a]
Men and postmenopausal women with HR-positive, HER2-negative, locally advanced or metastatic breast cancer[b] with PIK3CA mutation		
A1	Postmenopausal women after disease progression following endocrine monotherapy in the (neo)adjuvant treatment situation	▪ Ribociclib in combination with a nonsteroidal aromatase inhibitor or ▪ Ribociclib in combination with fulvestrant or ▪ Anastrozole or ▪ Letrozole or ▪ Fulvestrant or ▪ Possibly tamoxifen if aromatase inhibitors are not suitable
A2	Men after disease progression following endocrine monotherapy in the (neo)adjuvant treatment situation	Therapy upon the physician's discretion[c]
B1	Postmenopausal women after disease progression following endocrine monotherapy in the locally advanced or metastatic stage	Another endocrine therapy with ▪ abemaciclib in combination with fulvestrant or ▪ ribociclib in combination with fulvestrant or ▪ tamoxifen or ▪ anastrozole or ▪ fulvestrant monotherapy, only for patients with recurrence or progression following antioestrogen treatment[d] ▪ letrozole, only for patients with recurrence or progression following antioestrogen treatment or ▪ exemestane, only for patients with progression following antioestrogen treatment or ▪ everolimus in combination with exemestane, only for patients without symptomatic visceral metastasis after progression following nonsteroidal aromatase inhibitor therapy
B2	Men after progression following endocrine monotherapy in the locally advanced or metastatic stage	Therapy upon the physician's discretion[c]

a. Presented is the ACT specified by the G-BA.
b. For the given therapeutic indication, it is assumed that another endocrine therapy is indicated for the patient, while no indication exists for chemotherapy or (secondary) resection or radiotherapy with curative intent.
c. For men, the guidelines recommend the drugs tamoxifen and fulvestrant as well as aromatase inhibitors. Aromatase inhibitors and fulvestrant are not approved for the present indication. There is a discrepancy between the drugs approved for the indication versus those used in practice and recommended by guidelines. The following drugs are deemed adequate as comparators in clinical trials: tamoxifen, aromatase inhibitors in combination with a GnRH analogue, fulvestrant.
d. In this case, the approval states that fulvestrant is indicated only after antioestrogen treatment was administered. This represents a discrepancy between fulvestrant approval versus its routine use in practice as recommended by the guidelines, where it is administered not exclusively to patients with prior antioestrogen treatment but also to those with prior aromatase inhibitor therapy. In this special therapy and medical treatment situation, the G-BA sees a sufficient medical reason that, despite residual uncertainties, justifies assessing fulvestrant as a sufficiently suitable comparator in this case.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; GnRH: gonadotropin-releasing hormone; HER2: human epidermal growth receptor 2; HR: hormone receptor; PIK3CA: phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha

To improve readability, the treatment line for research questions A1 and A2 is referred to as first-line therapy in the advanced stage, while the treatment line for research questions B1 and B2 is referred to as second-line and subsequent-line therapy in the advanced stage.

The G-BA changed the ACT on 27 October 2020 [3] as shown in Table 4. The company followed the ACT originally specified by the G-BA and named tamoxifen, anastrozole, fulvestrant (only for patients with recurrence following antioestrogen therapy), letrozole (only for patients with recurrence or progression following antioestrogen therapy), exemestane (only for patients with progression following antioestrogen therapy), everolimus in combination with exemestane (only for patients without symptomatic visceral metastasis following progression after nonsteroidal aromatase inhibitor therapy) as appropriate treatment options in the indication to be assessed. This assessment was conducted using the ACT specified by the G-BA on 27 October 2020 [3].

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs were used for the derivation of added benefit.

2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources cited by the company in the dossier:

- Study list on alpelisib (as of 19 June 2020)
- Bibliographic literature search on alpelisib (most recent search on 19 June 2020)
- Search in trial registries / study results databases on alpelisib (most recent search on 24 June 2020)
- Search on the G-BA website on alpelisib (most recent search on 24 June 2020)

To check the completeness of the study pool:

- Search in trial registries for studies on alpelisib (most recent search on 7 September 2020)

The check did not identify any additional relevant studies.

2.3.1 Included studies

The study listed in the table below was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant

Study	Study category			Available sources		
	Approval study for the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	Clinical study report (yes/no [reference])	Registry entries[b] (yes/no [reference])	Publication and other sources[c] (yes/no [reference])
CBYL719C2301 (SOLAR-1[d])	Yes	Yes	No	No[e]	Yes [4-6]	Yes [7-9]

a. Study sponsored by the company.
b. References of trial registry entries and any available reports on the study design and/or results listed in the trial registries.
c. Other sources: EPAR
d. In the tables below, the study will be referred to using this short name.
e. Due to the working conditions during the coronavirus pandemic, the present assessment was conducted without the use of strictly confidential data presented in Module 5 of the company's dossier.

EPAR: European Public Assessment Report; RCT: randomized controlled trial

The benefit assessment of alpelisib in combination with fulvestrant included the SOLAR-1 study, which directly compared the combination of alpelisib + fulvestrant with placebo + fulvestrant. This concurs with the company's study pool.

The study was to include men and postmenopausal women who both had previously received endocrine therapy only in the (neo)adjuvant setting as well as those who had already received a maximum of 1 endocrine therapy for treatment in the advanced stage. For the 1st group, treatment with the study drug was therefore first-line therapy in the advanced stage, while for the 2nd group, it was second-line therapy in the advanced stage.

On the basis of this study, the company assessed the added benefit for the entire population of men and postmenopausal women, without distinguishing by sex or treatment line. This approach departs from the G-BA's specification (see Table 4). In deviation from the company's approach, this assessment analyses the corresponding subpopulations.

Table 6 shows an overview of the data found in the SOLAR-1 study on the various research questions of the benefit assessment.

Table 6: Apelisib in combination with fulvestrant – overview of the data available for the benefit assessment, broken down by research question

Research question	Population	Available data
A1	Postmenopausal women, first-line therapy in the advanced stage	Subpopulation of the SOLAR-1 study
A2	Men, first-line therapy in the advanced stage	–[a]
B1	Postmenopausal women, second-line and subsequent-line therapy in the advanced stage	Subpopulation of the SOLAR-1 study
B2	Men, second-line and subsequent-line therapy in the advanced stage	–[a]
a. Only 1 man was included in the SOLAR-1 study.		

For the analysis broken down by treatment line, Module 4 A presents results in the form of subgroup analyses for first-line and second-line therapies. In this benefit assessment, the corresponding subgroups are used as relevant subpopulations for research questions A1 and B1 (see Sections 2.4 and 2.6). Given that the SOLAR-1 study included only 1 man, no data are available for the benefit assessment regarding research questions A2 and B2 (see Sections 2.5 and 2.7). It is unknown which of the 2 treatment line subgroups includes the 1 male patient, but this information is deemed negligible for research questions A1 and B1.

2.4 Research question A1: postmenopausal women, first-line therapy in the advanced stage

2.4.1 Study characteristics

Table 7 and Table 8 present the study used in the benefit assessment.

Table 7: Characterization of the included study – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant (multi-page table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and time period conducted	Primary outcome; secondary outcomes[a]
SOLAR-1	RCT, parallel-group, double-blind	Men and postmenopausal women[b] with HR-positive, HER2-negative, locally advanced[c] or metastatic breast cancer with known PIK3CA mutation status[d] and progression following endocrine therapy[e] as well as an ECOG-PS ≤ 1	▪ Without PIK3CA mutation[f]: alpelisib + fulvestrant (N = 115) placebo + fulvestrant (N = 116) ▪ With PIK3CA mutation: alpelisib + fulvestrant (N = 169) placebo + fulvestrant (N = 172) <u>Relevant subpopulations thereof:</u> ▫ Without prior endocrine treatment in the advanced stage (first line): alpelisib + fulvestrant (n = 88) placebo + fulvestrant (n = 89) ▫ With prior endocrine treatment in the advanced stage (second line): alpelisib + fulvestrant (n = 79) placebo + fulvestrant (n = 82)	Screening: up to 35 days Treatment: until disease progression[g], unacceptable toxicity, withdrawal of consent, loss to follow-up, death, or treatment discontinuation for any other reason Follow-up[h]: outcome-specific, at the longest until death, loss to follow-up, or withdrawal of consent for follow-up of overall survival	A total of 275 study centres in Argentina, Australia, Austria, Belgium, Brazil, Bulgaria, Canada, Chile, Czech Republic, Denmark, France, Germany, Greece, Hong Kong, Hungary, India, Israel, Italy, Japan, Lebanon, Mexico, Netherlands, Peru, Portugal, Romania, Russia, South Korea, Spain, Sweden, Taiwan, Thailand, United Arab Emirates, United Kingdom, United States 7/2015–4/2020 Data cut-off dates: ▪ 1st data cut-off: 12/06/2018 ▪ 2nd data cut-off: 30/09/2019 ▪ 3rd data cut-off: 23/04/2020	Primary: PFS (in patients with PIK3CA mutation) Secondary: overall survival, morbidity, health-related quality of life, AEs

Table 7: Characterization of the included study – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant (multi-page table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and time period conducted	Primary outcome; secondary outcomes[a]

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes include only information on relevant available outcomes for this benefit assessment.
b. Since alpelisib increases the risk of hyperglycaemia, patients with diabetes mellitus type 1 or uncontrolled type 2 were ineligible for study participation. Patients had to have a fasting plasma glucose ≤ 140 mg/dL (7.7 mmol/L) and HbA1c ≤ 6.4% (both criteria had to be met; the permitted HbA1c value was initially defined as < 8% and lowered to ≤ 6.4% over the course of the study).
c. Patients with locally advanced breast cancer had to be ineligible for curative therapy.
d. As part of screening, the PIK3CA mutation status was determined. If possible, the tumour sample was to be taken after the most recent progression or recurrence. The study included patients with positive as well as negative PIK3CA mutation status.
e. Prior endocrine therapy could be administered either as (neo)adjuvant therapy or in an advanced stage. Even patients who had received exclusively (neo)adjuvant prior therapy were eligible for study inclusion. All patients had to exhibit progression during or after aromatase inhibitor therapy, although said therapy did not have to be the most recently received therapy.
f. This subpopulation is irrelevant for the assessment and is not presented in the tables below.
g. Surveyed using imaging techniques based on the RECIST guidelines, version 1.1.
h. Outcome-specific information is provided in Table 9.

AE: adverse event; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; HbA1c: haemoglobin A1c; HER2: human epidermal growth factor receptor-2; HR: hormone receptor; n: relevant subpopulation; N: number of randomized (included) patients; PFS: progression-free survival; PIK3CA: phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; RCT: randomized controlled trial; RECIST: Response Evaluation Criteria In Solid Tumours

Table 8: Characterization of the intervention – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant (multi-page table)

Study	Intervention	Comparison
SOLAR-1	Alpelisib 300 mg orally, once daily, cycle duration: 28 days + fulvestrant 500 mg i.m. on Day 1 and Day 15 in the 1st cycle and Day 1 of the following cycles	Placebo orally, once daily, cycle duration: 28 days + fulvestrant 500 mg i.m. on Day 1 and Day 15 in the 1st cycle and Day 1 of the following cycles
	Dose modifications: ▪ Alpelisib/placebo: ▫ In case of toxicities, ≤ 2 dose reductions (first to 250 mg and then to 200 mg) as well as treatment interruptions (up to 28 days) or treatment discontinuation while continuing fulvestrant were allowed[a,b] ▫ In case of dose reductions, no subsequent dose increases were allowed. ▪ Fulvestrant: ▫ No dose adjustment options specified; delay of administration by up to 35 days or treatment discontinuation while continuing alpelisib/placebo allowed[b]	
	Prior treatment: ▪ **Required:** ▫ Endocrine therapy with an aromatase inhibitor[c,d] ([neo]adjuvant or first-line for advanced stage) ▪ **Allowed:** ▫ Endocrine therapies[d] other than fulvestrant ([neo]adjuvant or first-line for advanced stage) ▫ (Neo)adjuvant chemotherapy[d] ▪ **Disallowed:** ▫ Prior chemotherapy (except [neo]adjuvant) or treatment with fulvestrant or a PI3K/mTOR/AKT inhibitor ▫ Participation in an investigative study ≤ 30 days before treatment start or within 5 half-lives of the employed experimental intervention ▫ Radiotherapy ≤ 4 weeks or limited field radiation for palliation ≤ 2 weeks prior to randomization[d] and/or irradiation of ≥ 25% of the bone marrow ▫ Surgery ≤ 2 weeks prior to starting treatment or without recovery from major side effects of such a procedure ▫ Systemic corticosteroids ≤ 2 weeks prior to treatment start or with persistent side effects from such treatment ▫ Drugs prolonging the QT interval or inducing Torsade de Pointes tachycardia or herbal preparations < 7 days prior to treatment start or during treatment **Permitted concomitant therapy:** ▪ Corticosteroids in the form of single doses, topical application (e.g. for skin rash), inhaled sprays (e.g. for obstructive airway disorders), eye drops or local injections (e.g. intraarticular) ▪ Supportive measures and information for the treatment of hyperglycaemia[e] (preferably metformin, up to 1000 mg twice daily, or other antidiabetic drugs if metformin is not tolerated or unavailable), skin toxicities (including topical and low-dose oral corticosteroids, oral antihistamines, oral or topical antibiotics, GABA antagonists), diarrhoea (preferably loperamide, alternatively diphenoxylate hydrochloride / atropine sulfate, depending on the severity and duration of diarrhoea, possibly opium tincture, dihydrocodeine tartrate tablets/injections, octreotide), and stomatitis/oral mucositis (nonalcoholic mouth wash, local anaesthetics with or without topical corticosteroid[s]) ▪ Further supportive therapies (e.g. analgesics, antiemetics) ▪ Bisphosphonate/denosumab if stable dose from ≥ 2 weeks before randomization	

Table 8: Characterization of the intervention – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant (multi-page table)

Study	Intervention	Comparison
	▪ Haematopoietic growth factors (according to ASCO guidelines) **Prohibited concomitant therapy:** ▪ Other cancer treatment	

a. Decision was made based on severity and type of toxicity. This approach meets the specifications in the Summary of Product Characteristics (SPC) for alpelisib [10].
b. Among the total population with PIK3CA mutation in the intervention arm, 44 patients (26.0%) discontinued alpelisib treatment and 6 patients (3.6%) discontinued fulvestrant treatment due to AEs. In the comparator arm, 10 patients (5.8%) discontinued placebo and 3 patients (1.8%) discontinued fulvestrant treatment due to AEs.
c. For study inclusion, all patients had to have disease progression during or after aromatase inhibitor therapy, although said therapy did not have to be the most recently received endocrine therapy.
d. Patients had to have recovered from the AEs of prior cancer therapies to CTCAE grade ≤ 1 (with the exception of alopecia).
e. In case of hyperglycaemia, a diabetologist was to be consulted and measures recommended as per the guidelines of the American Diabetes Association.

AE: adverse event; AKT: protein kinase B; ASCO: American Society of Clinical Oncology; CTCAE: Common Terminology Criteria for Adverse Events; GABA: gamma aminobutyric acid; i.m.: intramuscular; mTOR: mammalian target of rapamycin; PIK3CA: phosphatidyl inositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PI3K: phosphatidylinositol 3-kinase; RCT: randomized controlled trial

The SOLAR-1 study is a multicentre, randomized, actively controlled study comparing alpelisib + fulvestrant with placebo + fulvestrant. The study included men and postmenopausal women with HR-positive, HER2-negative, locally advanced or metastatic breast cancer. At screening, patients had to have relapsed or exhibit progression. Patients with locally advanced breast cancer had to be ineligible for curative therapy. With regard to prior therapy, patients had to exhibit recurrence or progression during or after endocrine therapy with an aromatase inhibitor, although said therapy did not have to be the most recently received therapy. Patients had to have received said endocrine therapy either in the advanced stage or exclusively as (neo)adjuvant therapy, or both. Patients who had not received endocrine therapy in any setting were ineligible for participation. Any prior chemotherapy had to have been conducted in a (neo)adjuvant setting. Additional restrictions regarding the number of prior therapies received as well as on the time of recurrence or progression are described in the appropriate sections on the subpopulations relevant for research questions A1 and B1. All patients had to have an Eastern Cooperative Oncology Group Performance Status (ECOG-PS) of 0 or 1.

As part of screening, the tumour material was tested for PIK3CA mutation (test systems used: Novartis PIK3CA PCR mutation CTA or QIAGEN therascreen PIK3CA RGQ PCR kit). Patients with and without PIK3CA mutation in the tumour tissue were included.

The study included a total of 572 patients, of which 231 were in the group without PIK3CA mutation and 341 in the group with PIK3CA mutation. In both groups, patients were randomized in a 1:1 ratio to treatment with alpelisib + fulvestrant or placebo + fulvestrant. Randomization was stratified by the presence of metastases in the lung and/or liver (yes/no) as

well as prior treatment with a cyclin-dependent kinase (CDK)4/6 inhibitor (yes/no). The group without PIK3CA mutation is irrelevant for the present assessment since the approval of alpelisib in combination with fulvestrant applies only to patients with evidence of PIK3CA mutation in the tumour tissue. Since only 1 man was included in the group with PIK3CA mutation, only women are discussed below in terms of the patient population (also see Section 2.3.1).

Among the patients in the group with PIK3CA mutation, only a subpopulation is relevant for research question A1 (see the corresponding section below), which is referred to as subpopulation A1 below.

Treatment with alpelisib as well as fulvestrant was largely in accordance with the information provided in the respective SPC [10,11]. Deviations did exist in terms of some off-label prior treatment with alpelisib or fulvestrant, but this is of no consequence for the present benefit assessment (see discussion below).

Treatment with the study drug was continued until either disease progression, unacceptable toxicity, withdrawal of consent, loss to follow-up, death, or treatment discontinuation for any other reason.

The primary outcome of the study was PFS in the group with PIK3CA mutation, while patient-relevant secondary outcomes included overall survival as well as outcomes on morbidity, health-related quality of life, and AEs.

SOLAR-1 subpopulation relevant for the assessment of research question A1

For research question A1, the relevant subpopulation is postmenopausal women who received the study drug as first-line therapy in the advanced stage and therefore had received exclusively (neo)adjuvant prior therapy at study start. Subpopulation A1 included 88 patients in the intervention arm and 89 patients in the comparator arm. At study start, these patients were included regardless of the timing of recurrence. Both patients with recurrence during (neo)adjuvant endocrine therapy or within 12 months after completion of this therapy and patients with recurrence at a later point were eligible for study participation. As per Amendment 2 of the study protocol dated 30 August 2016, patients whose recurrence had occurred more than 12 months after completion of (neo)adjuvant endocrine therapy were no longer eligible for inclusion. Consequently, the relevant subpopulation represents these patients, who have indications as per the approval, only to a small degree. The subpopulation relevant for this research question is subpopulation A1; of the patients who had a recurrence more than 12 months after completion of (neo)adjuvant endocrine therapy, a total of 20 patients were included in the intervention arm (22.7%) and 19 in the comparator arm (21.3%).

Prior treatment with endocrine monotherapy

In the present therapeutic indication, the use of alpelisib in combination with fulvestrant is restricted to patients who received prior endocrine therapy in the form of monotherapy.

The inclusion criteria of the SOLAR-1 study did not restrict prior therapy in this way. Among the overall population with PIK3CA mutation, 9 patients in the intervention arm (5.3%) and 11 patients in the comparator arm (6.4%) received prior CDK4/6 inhibitor therapy (see Table 26 in Appendix A). No data are available on which percentage of the relevant subpopulation is not covered by the therapeutic indication. However, since these patients make up a low percentage of the total population with PIK3CA mutation, they are not expected to have a relevant influence on the available results.

Suitability of fulvestrant as comparator therapy

The G-BA defined fulvestrant as 1 of the options for the ACT in research question A1.

However, fulvestrant is approved only for postmenopausal women previously untreated with endocrine therapy or experiencing disease recurrence during or after adjuvant antioestrogen therapy or presenting with disease progression on antioestrogen therapy [11]. Consequently, the approved therapeutic indication does not provide for an additional endocrine therapy other than the directly preceding therapy – e.g. with an aromatase inhibitor. In the SOLAR-1 study, patients were eligible for inclusion only if they had disease recurrence or progression during or after endocrine therapy with an aromatase inhibitor, although said therapy did not have to be the most recently received therapy. This means that all included patients had received prior endocrine therapy. From the total population with PIK3CA mutation, 25 patients in the intervention arm (15%) and 29 patients in the comparator arm (17%) had received antioestrogen therapy as the last therapy before study start, the majority of them with tamoxifen (see Table 26 in Appendix A of the full dossier assessment). For these patients, fulvestrant treatment was in accordance with approval. No information is available on the distribution of these patients among the relevant subpopulations. However, in this treatment situation, the G-BA specified fulvestrant as an ACT without any restrictions. The entire subpopulation A1 is therefore relevant for deriving any added benefit.

Data cut-off dates

In Module 4A, the company provided results on 3 data cut-offs:

- 1st data cut-off: 12/06/2018
- 2nd data cut-off: 30/09/2019
- 3rd data cut-off: 23/04/2020

All 3 data cut-offs were predefined. The 1st data cut-off is the final analysis of PFS (to occur after about 243 PFS events), while the 2nd and 3rd data cut-offs represent an interim and final analysis of overall survival (to occur after about 151 and 178 deaths). For the benefit assessment, the final 3rd data cut-off was used.

Planned duration of follow-up observation

Table 9 shows the planned duration of patient follow-up observation for the individual outcomes.

Table 9: Planned follow-up observation – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant

Study Outcome category Outcome	Planned follow-up observation
SOLAR-1	
Mortality	
Overall survival	Until death, loss to follow-up, or withdrawal of consent to the follow-up of overall survival
Morbidity	Until disease progression, death, withdrawal of consent, loss to follow-up, patient decision
Symptoms (EORTC QLQ-C30)	
Pain (BPI-SF)	
Health status (EQ-5D-5L VAS)	
Health-related quality of life (EORTC QLQ-C30)	
AEs	
All outcomes of the AE category	Up to 30 days after treatment end

AE: adverse event; BPI-SF: Brief Pain Inventory – Short Form; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Cancer-30; EQ-5D-5L: European Quality of Life-5 Dimensions-5 Level; RCT: randomized controlled trial; VAS: visual analogue scale

The follow-up periods for the outcomes of morbidity, health-related quality of life, and AEs have been systematically shortened since they were surveyed at maximum until disease progression (morbidity, health-related quality of life) or for the period of treatment with the study drug plus 30 days (AEs). To allow drawing reliable conclusions over the entire study period or until patient death, however, these outcomes, like survival, would have to be measured and analysed over the entire study period.

Characterization of the study population

No separate data are available on patient characteristics for the relevant subpopulation A1.

Data are available only for the total population with PIK3CA mutation; these are presented in Table 26 of Appendix A. The characteristics of the patient population are comparable between the two study arms. At study start, the mean patient age was about 63 years, and the majority of patients were from Europe (51%). About two-thirds had an ECOG-PS of 0, and almost all patients were in the metastatic stage (stage IV).

Data on the course of the study

For the relevant subpopulation A1, data are available neither on treatment duration nor on the follow-up period for individual outcomes.

Data on the total population with PIK3CA mutation are shown in Table 27 of Appendix A of the full dossier assessment. Data on treatment duration with the individual drugs or placebo are available only by study arm. On the basis of the total population with PIK3CA mutation, the median treatment duration in the intervention arm was 5.5 months for alpelisib and 8.3 months for fulvestrant. In the comparator arm, the median treatment duration with placebo was 4.6 months, and with fulvestrant, 5.5 months. The follow-up period for each individual outcome was substantially longer in the intervention arm than in the comparator arm (in the majority of them, about twice as long). It is unclear why some of the follow-up periods for morbidity outcomes and health-related quality of life are much shorter than the follow-up periods for AEs. As per study protocol, these outcomes were to be followed up until disease progression, which was the main reason for treatment discontinuation in both study arms. In this case, a final survey of the outcomes on morbidity and health-related quality of life was to be taken within 14 days after treatment discontinuation.

Information on subsequent therapies

In the SOLAR-1 study, the treating physician was free to choose any subsequent therapy after discontinuation of the study drug. Switching from placebo to alpelisib treatment was not allowed. No data are available on the subsequent therapies received in the relevant subpopulation A1.

Risk of bias across outcomes (study level)

Table 10 shows the risk of bias across outcomes (risk of bias at study level).

Table 10: Risk of bias across outcomes (study level) – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of results	No additional aspects	Risk of bias at study level
			Patients	Treatment providers			
SOLAR-1	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes is rated as low for the SOLAR-1 study. This concurs with the company's assessment.

Transferability of the study results to the German healthcare context

In Module 4 A, the company asserts that the results of the SOLAR-1 study are fully transferable to the German healthcare context since both in the total population with PIK3CA mutation and in the ECOG-PS 1 subgroup analysed by the company, about two-thirds of patients at study start had white skin colour and lived in European or North American countries, whose healthcare standards it deemed comparable with those in Germany. The company added that no relevant effect modifications were found by the attribute of racial descent (white versus Asian versus black/African American versus others) and that the subgroup of patients treated in Europe did not differ from the total population in terms of study results.

The company did not present any further information on the transferability of study results to the German healthcare context.

2.4.2 Results on added benefit

2.4.2.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment:

- Mortality
  - Overall survival
- Morbidity
  - Symptoms, measured with the symptom scales of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Cancer-30 (EORTC QLQ-C30)
  - Pain, measured with the Brief Pain Inventory – Short Form (BPI-SF)
  - Health status, surveyed with the visual analogue scale (VAS) of the European Quality of Life Questionnaire 5 Dimensions 5 Level (EQ-5D-5L) questionnaire
- Health-related quality of life
  - As surveyed with global health status and the EORTC QLQ-C30 functioning scales
- AEs
  - SAEs
  - Severe AEs (operationalized as Common-Terminology-Criteria-for-Adverse-Events [CTCAE] grade 3 or 4)
  - Discontinuation due to AEs
  - Further specific AEs, if any

The choice of patient-relevant outcomes deviates from that of the company, which relied on further outcomes in the dossier (Module 4 A).

Table 11 shows the outcomes for which data are available in the study included on subpopulation A1.

Table 11: Matrix of outcomes – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant (research question A1: postmenopausal women, first-line therapy in the advanced stage)

Study	Outcomes								
	Overall survival	Symptoms (EORTC QLQ-C30)	Pain (BPI-SF)	Health status (EQ-5D-5L VAS)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs[a]	Discontinuation due to AEs	Specific AEs
SOLAR-1	Yes	No[b]	No[b]	No[b]	No[b]	Yes	Yes	Yes	No[c]

a. Operationalized as CTCAE grade 3 or 4.
b. No usable analyses available; reasoning provided in the text below the table.
c. It is not possible to select specific AEs since, for the relevant subpopulation, only incomplete data are available on common AEs, severe AEs (operationalized as CTCAE grade 3 or 4), and SAEs.

AE: adverse event; BPI-SF: Brief Pain Inventory – Short Form; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; EQ-5D-5L: European Quality of Life -5 Dimensions 5 Level; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

No usable analyses or data are available on the following patient-relevant outcomes:

- Symptoms, health-related quality of life (each surveyed with EORTC QLQ-C30), pain (surveyed with BPI-SF), and health status (surveyed with EQ-5D-5L VAS). For each of them, the company provided both responder analyses on the time until deterioration and supplementary continuous analyses on the basis of a linear mixed model.
  - Event-time analyses: The individual instruments were surveyed every 2 months for the first 18 months after randomization and every 3 months thereafter. For each of the listed outcomes, the company presented analyses on time to deterioration, with different response criteria depending on the outcome (EORTC QLQ-C30: ≥ 10 points; BPI-SF: ≥ 2 points; EQ-5D-5L VAS: ≥ 7 and ≥ 10 points).

    In all analyses, a deterioration of the respective response criterion was rated as an event only if it also applied to all subsequent values or if the value was the one most recently obtained. Therefore, on the basis of this operationalization, both an initial deterioration as well as a deterioration which persists across various time periods can

be rated as an event, depending on when the event occurs and how long the patient is followed up thereafter.

While no information is available on the follow-up duration for the relevant subpopulation A1, the median follow-up duration for these outcomes in the total population with PIK3CA mutation was about twice as long in the intervention arm as in the comparator arm, where it equalled less than 4 months in most cases (see Table 27 of Appendix A of the full dossier assessment). Given the survey frequency of once every 2 months, this means that half of the patients in the comparator arm had only 1 to 2 follow-up surveys after study start, while most patients in the intervention arm had at least 3 to 4 follow-up surveys, depending on the outcome. Since the study arms differed in the number of follow-up surveys, it can be assumed that, for the most part, single deteriorations in the comparator arm were compared with persistent deteriorations in the intervention arm. This comparison is inappropriate, and therefore, the available analyses of time to deterioration were disregarded. Instead, an analysis of initial deterioration would be meaningful in the described situation.

Regarding the response criteria chosen by the company, the following should be noted: As discussed in IQWiG General Methods [1,12], a response criterion should cover at least 15% of the range of an instrument's scale (for post hoc analyses, exactly 15% of the range of the scale) in order to reflect with sufficient certainty a change that is perceivable for patients.

- Continuous analyses: For the listed outcomes, the company presents as supplementary information the estimates of the mean change over baseline and its difference between the two treatment groups at the individual survey time points (baseline, Week 8, Week 16, etc.), calculated on the basis of a linear mixed model. It is unclear how many patients were included in each analysis. Additionally, for the relevant subpopulation, no baseline data or return rates for the individual survey time points are available.

  Further, for many of the scales, the estimates of mean change over baseline varied greatly over the course of the study. In view of the individual scales, these fluctuations led to some major differences in the effect estimates at the different survey times. Appendix B shows, as an example, the change-over-time curves for 2 outcomes (loss of appetite and social functioning) on the basis of the total population with PIK3CA mutation (due to a lack of corresponding figures for the relevant subpopulation). For these analyses, the survey time point does not seem to have been predefined.

  In the present data situation, the analysis of a single survey time point is not deemed meaningful. For a meaningful assessment of the data on morbidity and health-related quality of life, the present data situation requires an estimate of the mean change from baseline, as an average taken over the study's entire follow-up period. The statistical model defined by the company would have been suitable for this purpose, but no results are available for any of the outcomes.

It must also be noted that no results are available regarding the relevant subpopulation as per the 3rd data cut-off. This is because the company calculated subgroup data for the continuous analyses only as per the 2nd data cut-off.

- Both assessments presented by the company (event-time analysis and continuous analysis) fail to clarify whether the analyses of the individual outcomes included all predefined surveys (including those to be performed after discontinuation of treatment, see Section 2.4.1 on the course of the study).

- Specific AEs: It is not possible to select specific AEs since for the relevant subpopulation, only incomplete data are available on common AEs, severe AEs (operationalized as CTCAE grade 3 or 4), and SAEs. In Module 4 A, results on the relevant subpopulation are available only for common AEs / severe AEs / SAEs, for which a statistically significant difference between treatment groups was found in the total population with PIK3CA mutation. Additionally, due to the low number of patients, the absolute thresholds for the presentation of common AEs/severe AEs/SAEs is lower in the relevant subpopulation than in the total population with PIK3CA mutation. Furthermore, Module 4 A describes neither how the AEs of special interest, as viewed by the company, are operationalized nor whether they were defined a priori.

2.4.2.2 Risk of bias

Table 12 presents the risk of bias for the results of the relevant outcomes in subpopulation A1.

Table 12: Risk of bias at study and outcome levels – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant (research question A1: postmenopausal women, first-line therapy in the advanced stage)

Study		Outcomes								
	Study level	Overall survival	Symptoms (EORTC QLQ-C30)	Pain (BPI-SF)	Health status (EQ-5D-5L VAS)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs[a]	Discontinuation due to AEs	Specific AEs
SOLAR-1	L	L	–[b]	–[b]	–[b]	–[b]	H[c]	H[c]	H[d]	–[e]

a. Operationalized as CTCAE grade 3 or 4.
b. No usable analyses are available for the outcomes on the categories of morbidity and health-related quality of life; see Section 2.4.2.1 for the rationale.
c. Incomplete follow-up for potentially informative reasons in the presence of different lengths of follow-up observation periods between treatment arms (see available information on the total population with PIK3CA mutation, Table 27 in Appendix A of the full dossier assessment); no data are available on the follow-up period for subpopulation A1.
d. Due to the known AE profile of alpelisib, it was presumably impossible to maintain blinding over the course of the study.
e. It is not possible to select specific AEs since, for the relevant subpopulation, only incomplete data are available on common AEs, severe AEs (operationalized as CTCAE grade 3 or 4), and SAEs (see Section 2.4.2.1).

AE: adverse event; BPI-SF: Brief Pain Inventory – Short Form; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; EQ-5D-5L: European Quality of Life-5 Dimensions-5-Level; H: high; L: low; PIK3CA: phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

The risk of bias for the result on overall survival is rated as low.

No usable analyses are available for the outcomes on symptoms (EORTC QLQ-C30), pain (BPI-SF), health status (EQ-5D-5L VAS), and health-related quality of life (EORTC QLQ-C30), and no usable data are available on specific AEs (see Section 2.4.2.1); therefore, the risk of bias was not assessed.

Due to incomplete follow-up for potentially informative reasons in the presence of different follow-up periods between treatment arms (see available information on the total population with PIK3CA mutation in Table 27 of Appendix A of the full dossier assessment), there is a high risk of bias for the results of the outcomes of SAEs and severe AEs (operationalized as CTCAE grade 3 or 4).

Likewise, there is a high risk of bias regarding the results on the outcome of discontinuation due to AEs. This can be explained by the assumption that blinding was not maintainable over the course of the study in light of the known AEs of alpelisib, e.g. hyperglycaemia and skin disorders, which the majority of patients developed at an early point in the study [9].

This assessment concurs with that of the company for the results on the outcomes for which the risk of bias was assessed. However, the company assessed the risk of bias on the basis of the total population with PIK3CA mutation and derived the high risk of bias of the results on the outcome of discontinuation due to AEs from unequal follow-up periods in combination with potential informative censoring.

2.4.2.3 Results

Table 13 summarizes the results of the comparison of alpelisib + fulvestrant with placebo + fulvestrant in postmenopausal women with HR-positive, HER2-negative, locally advanced or metastatic breast cancer with PIK3CA mutation and disease progression after endocrine monotherapy administered in a (neo)adjuvant treatment situation. Where necessary, calculations conducted by IQWiG are provided in addition to the data from the company's dossier.

No Kaplan Meier curves on the event-time analyses are available for the relevant subpopulation, and no complete listing of common AEs, SAEs, severe AEs (operationalized as CTCAE grade 3 or 4) and discontinuation due to AEs exists; therefore, it was impossible to present them for the relevant subpopulation.

Table 13: Results (mortality, morbidity, health-related quality of life, AEs) – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant (research question A1: postmenopausal women, first-line therapy in the advanced stage)

Study Outcome category Outcome	Alpelisib + fulvestrant N	Alpelisib + fulvestrant Median time to event in months [95% CI] Patients with event n (%)	Placebo + fulvestrant N	Placebo + fulvestrant Median time to event in months [95% CI] Patients with event n (%)	Alpelisib + fulvestrant vs. placebo + fulvestrant HR [95% CI]; p-value[a]
SOLAR-1 (3rd data cut-off: 23/04/2020)					
Mortality					
Overall survival	88	41.9 [34.1; NC] 41 (46.6)	89	34.5 [24.3; 46.7] 49 (55.1)	0.78 [0.51; 1.19]; 0.253
Morbidity					
Symptoms (EORTC QLQ-C30, symptom scales) Pain (BPI-SF) Health status (EQ-5D-5L VAS)	No usable analyses[b]				
Health-related quality of life					
EORTC QLQ-C30 (global health status, functioning scales)	No usable analyses[b]				
AEs					
AEs (supplementary information)	88	0.3 [0.2; 0.3] 88 (100)	89	0.5 [0.4; 0.9] 82 (92.1)	–
SAEs	88	38.6 [17.0; NC] 32 (36.4)	89	NR [29.6; NC] 18 (20.2)	1.85 [1.04; 3.30]; 0.035
Severe AEs[c]	88	1.0 [0.6; 1.4] 71 (80.7)	89	NR [6.7; NC] 33 (37.1)	3.48 [2.30; 5.29]; < 0.001
Discontinuation due to AEs[d]	88	NA [22.7; NC] 25 (28.4)	89	NR [30.7; NC] 6 (6.7)	4.62 [1.89; 11.26]; < 0.001
Specific AEs	No usable data[e]				

a. HR and CI: Cox proportional hazards model; p-value: log-rank test; each stratified by prior therapy with a CDK 4/6 inhibitor (yes vs. no) and by the presence of liver and/or lung metastases (yes vs. no).
b. No usable analyses are available for the outcomes of the categories of morbidity and health-related quality of life; see Section 2.4.2.1 for a rationale.
c. Operationalized as CTCAE grade 3 or 4.
d. Discontinuation of alpelisib treatment or placebo and/or fulvestrant.
e. It is not possible to select specific AEs since for the relevant subpopulation, only incomplete data are available on common AEs, severe AEs (operationalized as CTCAE grade 3 or 4), and SAEs (see Section 2.4.2.1).

AE: adverse event; BPI-SF: Brief Pain Inventory – Short Form; CDK: cyclin-dependent kinase; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; EQ-5D-5L: European Quality of Life 5-Dimensions 5-Level; HR: hazard ratio; n: number of patients with (at least 1) event; N: number of analysed patients; NC: not calculable; NR: not reached; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

The available data allow deriving no more than indications, e.g. of an added benefit, for the outcome of overall survival. The results of the remaining outcomes on which usable analyses are available are each subject to a high risk of bias, and therefore, no more than hints, e.g. of added benefit, can be derived. However, the certainty of results on the specific outcome level has not been downgraded in some cases (see below description of results).

For deriving any added benefit, the company used both the results on the total population with PIK3CA mutation and the subgroup with ECOG-PS 1 at baseline. The subgroup characteristic of ECOG-PS at baseline (0 versus 1) is irrelevant for the present benefit assessment (see Section 2.4.2.4); therefore, the comments below apply only to the company's approach regarding the results on the total population with PIK3CA mutation.

Mortality

Overall survival

For the outcome of overall survival, no statistically significant difference between treatment groups was found. Hence, there is no hint of added benefit of alpelisib + fulvestrant in comparison with fulvestrant; an added benefit is therefore not proven.

This coincides with the company's assessment insofar as, based on the results of the total population with PIK3CA mutation, it arrives at the same conclusion.

Morbidity

Symptoms (symptom scales of EORTC QLQ-C30), pain (BPI-SF), health status (EQ-5D-5L VAS)

No usable analyses are available for symptom outcomes, surveyed with the EORTC QLQ-C30 symptom scales, for pain, surveyed with the BPI-SF, or for health status, surveyed with the EQ-5D-5L VAS (see Section 2.4.2.1). Hence, there is no hint of added benefit of alpelisib + fulvestrant in comparison with fulvestrant for any of them; an added benefit is therefore not proven.

This coincides with the company's assessment insofar as, based on the results of the total population with PIK3CA mutation at the 2nd data cut-off, it arrives at the same result.

Health-related quality of life

Global health status and functioning scales, surveyed with EORTC QLQ-C30

No usable analyses are available for health-related quality of life outcomes, surveyed with global health status and the functioning scales of EORTC QLQ-C30 (see Section 2.4.2.1). Hence, there is no hint of added benefit of alpelisib + fulvestrant in comparison with fulvestrant for any of them; an added benefit is therefore not proven.

This coincides with the company's assessment insofar as, based on the results of the total population with PIK3CA mutation at the 2nd data cut-off, it arrives at the same result.

AEs

SAEs

For the outcome of SAEs, there is a statistically significant difference to the disadvantage of alpelisib + fulvestrant in comparison with placebo + fulvestrant. Hence, there is a hint of greater harm from alpelisib + fulvestrant in comparison with fulvestrant.

This coincides with the company's assessment insofar as, based on the results of the total population with PIK3CA mutation at the 2nd data cut-off, it derives greater harm with reduced certainty of results.

Severe AEs (operationalized as CTCAE grade 3 or 4)

For the outcome of severe AEs, operationalized as CTCAE grade 3 or 4, a statistically significant difference to the disadvantage of alpelisib + fulvestrant was found in comparison with placebo + fulvestrant. Due to the effect size found already at an early point in the study (see Kaplan-Meier curves on the total population with PIK3CA mutation in Appendix C of the full dossier assessment; a corresponding presentation is not available for the relevant subpopulation), the certainty of results is high despite the high risk of bias of results. Hence, there is an indication of greater harm from alpelisib + fulvestrant in comparison with fulvestrant.

This coincides with the company's assessment insofar as, based on the results of the total population with PIK3CA mutation at the 2nd data cut-off, it derives greater harm, albeit with reduced certainty of results.

Discontinuation due to AEs

For the outcome of discontinuation due to AEs, there is a statistically significant difference to the disadvantage of alpelisib + fulvestrant in comparison with placebo + fulvestrant. Hence, there is a hint of greater harm from alpelisib + fulvestrant in comparison with fulvestrant.

This coincides with the company's assessment insofar as, based on the results of the total population with PIK3CA mutation at the 2nd data cut-off, it derives greater harm with reduced certainty of results.

Specific AEs

For the relevant subpopulation, it was impossible to select specific AEs (see Section 2.4.2.1). Hence, there is no hint of greater or lesser harm from alpelisib + fulvestrant in comparison with fulvestrant; greater or lesser harm is therefore not proven.

This departs from the company's assessment insofar as, based on the results of the total population with PIK3CA mutation at the 2nd data cut-off, the company derived greater harm, at reduced certainty of results, for some of the AEs of special interest it analysed.

2.4.2.4 Subgroups and other effect modifiers

Added benefit was assessed on the basis of a subpopulation of the SOLAR-1 study. For research question A1, no data are available on subgroups of the subpopulation viewed.

For the derivation of any added benefit, the company used not only the results of the total population with PIK3CA mutation, but also the results of the subgroup with an ECOG-PS of 1 at baseline. It justified this approach with the fact that, for the subgroup characteristic of ECOG-PS at baseline (0 versus 1), an effect modification was found in several outcomes. The company's approach is not appropriate. On the one hand, the company failed to take into account any outcome-related interactions. On the other hand, when deriving the added benefit, the company did not discuss the results for the subgroup with an ECOG-PS of 0 at baseline despite the fact that this subgroup includes the majority of the population with PIK3CA mutation. Irrespective of the above, a comparison between ECOG-PS 0 and ECOG-PS 1 is unsuitable for distinguishing between different degrees of severity of the disease.

2.4.3 Probability and extent of added benefit

The following describes how the probability and extent of added benefit for the relevant subpopulation A1 are derived at the outcome level. The various outcome categories and the effect sizes are taken into account. The methods used for this purpose are explained in the IQWiG General Methods [1].

The methodology of aggregating the conclusions reached at outcome level to infer an overall conclusion on any added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

2.4.3.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated on the basis of the results presented in Section 2.4.2 (see Table 14).

Determination of the outcome category for the outcome of discontinuation due to AEs

Not for all outcomes considered in this benefit assessment does the dossier permit inferences as to whether they were serious/severe or non-serious/non-severe. The classification of these outcomes is justified below.

For the outcome of discontinuation due to AEs, information on the percentages of SAEs or severe AEs (operationalized as CTCAE grade 3 or 4) is not available for either the relevant subpopulation or the total population with PIK3CA mutation. Therefore, the outcome of discontinuation due to AEs is allocated to the outcome category of non-serious/non-severe AEs.

The company did not allocate discontinuation due to AEs to any outcome category.

Table 14: Extent of added benefit at outcome level: RCT, direct comparison: alpelisib + fulvestrant vs. fulvestrant (research question A1: postmenopausal women, first-line therapy in the advanced stage) (multi-page table)

Outcome category **Outcome**	**Alpelisib + fulvestrant vs. fulvestrant** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival	41.9 vs. 34.5 months HR: 0.78 [0.51; 1.19]; p = 0.253	Lesser/added benefit not proven
Morbidity		
Symptoms (EORTC QLQ-C30, symptom scales)	No usable analyses[c]	Lesser/added benefit not proven
Pain (BPI-SF)	No usable analyses[c]	Lesser/added benefit not proven
Health status (EQ-5D-5L VAS)	No usable analyses[c]	Lesser/added benefit not proven
Health-related quality of life		
EORTC QLQ-C30 (global health status, functioning scales)	No usable analyses[c]	Lesser/added benefit not proven
AEs		
SAEs	38.6 months vs. NR HR: 1.85 [1.04; 3.30] HR: 0.54 [0.30; 0.96][d]; p = 0.035 Probability: hint	Outcome category: serious/severe AEs $0.90 \leq CI_u < 1.00$ Greater harm; extent: minor
Severe AEs[e]	1.0 month vs. NR HR: 3.48 [2.30; 5.29] HR: 0.29 [0.19; 0.43][d]; p < 0.001 Probability: indication[f]	Outcome category: serious/severe AEs $CI_u < 0.75$ and risk ≥ 5% Greater harm; extent: major
Discontinuation due to AEs[g]	NR vs. NR HR: 4.62 [1.89; 11.26] HR: 0.22 [0.09; 0.53][d]; p < 0.001 Probability: hint	Outcome category: non-serious/non-severe AEs $CI_u < 0.80$ greater harm; extent: considerable
Specific AEs	No usable data[c]	Greater/lesser harm not proven

a. Probability is stated if a statistically significant and relevant effect is present.
b. Estimations of effect size are made depending on the outcome category, with different limits based on the upper limit of the confidence interval (CI_u).
c. See Section 2.4.2.1 for a rationale.
d. IQWiG calculation, reversed direction of effect to enable use of limits to derive the extent of added benefit.
e. Operationalized as CTCAE grade 3 or 4.
f. Despite the high risk of bias, the certainty of results has not been downgraded (see Section 2.4.2.3).
g. Discontinuation of alpelisib treatment or placebo and/or fulvestrant.

Table 14: Extent of added benefit at outcome level: RCT, direct comparison: alpelisib + fulvestrant vs. fulvestrant (research question A1: postmenopausal women, first-line therapy in the advanced stage) (multi-page table)

Outcome category **Outcome**	**Alpelisib + fulvestrant vs. fulvestrant** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
AE: adverse event; BPI-SF: Brief Pain Inventory – Short Form; CI: confidence interval; CI_u:upper limit of the confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; EQ-5D-5L: European Quality of Life 5-Dimensions 5-Level; HR: hazard ratio; NR: not reached; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale		

2.4.3.2 Overall conclusion on added benefit

Table 15 summarizes the results considered in the overall conclusion on the extent of added benefit.

Table 15: Favourable and unfavourable effects from the assessment of alpelisib in combination with fulvestrant (research question A1: postmenopausal women, first-line therapy in the advanced stage)

Favourable effects	**Unfavourable effects**
–	Serious/severe AEs ▪ SAEs: hint of greater harm – extent: minor ▪ Severe AEs: indication of greater harm – extent: major
–	Non-serious/non-severe AEs ▪ Discontinuation due to AEs: hint of greater harm – extent: considerable
No relevant data are available on the selection of specific AEs.	
No usable analyses are available on outcomes of the categories of morbidity and health-related quality of life.	
AE: adverse event; SAE: serious adverse event	

All things considered, the available data show exclusively unfavourable effects for alpelisib plus fulvestrant in comparison with fulvestrant.

For each of the outcomes of SAEs and discontinuation due to AEs, a hint of greater harm of minor or considerable extent was found. For severe AEs, there is an indication of major greater harm. No data are available on other AE outcomes since it was not possible to select specific AEs. No usable analyses are available on outcomes of the categories of morbidity and health-related quality of life.

In summary, there is a hint of lesser benefit of alpelisib plus fulvestrant in comparison with fulvestrant for postmenopausal women with HR-positive, HER2-negative, locally advanced or

metastatic breast cancer with PIK3CA mutation and progression of disease following endocrine monotherapy in the (neo)adjuvant treatment situation.

The above assessment departs from that made by the company, which derived a considerable added benefit with high certainty of results on the basis of the results of the SOLAR1-study and taking into account further outcomes without differentiating by treatment line or sex. Furthermore, the company derived a major added benefit for the subgroup with an ECOG-PS of 1 at baseline with high certainty of results.

2.5 Research question A2: Men, first-line therapy in the advanced stage

2.5.1 Results on added benefit

No data are available for assessing any added benefit of alpelisib plus fulvestrant in comparison with the ACT in men with HR-positive, HER2-negative, locally advanced or metastatic breast cancer with PIK3CA mutation and disease progression after endocrine monotherapy, which occurred in the (neo)adjuvant treatment situation. Hence, there is no hint of added benefit of alpelisib in combination with fulvestrant; an added benefit is therefore not proven.

2.5.2 Probability and extent of added benefit

Since no data are available for assessing any added benefit of alpelisib plus fulvestrant in comparison with the ACT in men with HR-positive, HER2-negative, locally advanced or metastatic breast cancer with PIK3CA mutation and disease progression following endocrine monotherapy in the (neo)adjuvant treatment situation, there is no proof of added benefit of alpelisib in combination with fulvestrant for these patients.

The above assessment departs from that by the company, which derived a considerable added benefit with high certainty of results on the basis of the results of the SOLAR1-study and taking into account further outcomes without differentiating by treatment line or sex. Furthermore, the company derived a major added benefit for the subgroup with an ECOG-PS of 1 at baseline with high certainty of results.

2.6 Research question B1: postmenopausal women, second-line and subsequent-line therapy in the advanced stage

2.6.1 Study characteristics

The study characteristics, information on data cut-offs, and the planned duration of follow-up in the SOLAR-1 study as well as notes on patients' prior treatment are described in detail in Section 2.4.1.

SOLAR-1 subpopulation relevant for the assessment of research question B1

For research question B1, the relevant subpopulation is the group receiving the study drug as second-line therapy in the advanced stage. This included 79 patients in intervention arm and 82 patients in the comparator arm. Patients with a recurrence within 12 months after completion

of (neo)adjuvant endocrine therapy and subsequent progression of metastatic disease during or after only 1 endocrine therapy as well as patients with more than 1 endocrine therapy for treatment in the advanced stage were excluded from the study despite being indicated for the treatment. The subpopulation relevant for research question B1 includes 16 patients in the intervention arm (20.3%) and 15 patients in the comparator arm (18.3%) who, before progression in the advanced stage, had a recurrence within 12 months after completion of the (neo)adjuvant treatment or had already received more than 1 endocrine therapy for treatment in the advanced stage.

Suitability of fulvestrant as comparator therapy

The G-BA listed fulvestrant as a potential ACT, including for postmenopausal women receiving second-line and subsequent-line therapy, but, in accordance with fulvestrant's approval [11], only for patients with recurrence or progression after antioestrogen treatment. Data on the percentage of patients who received antioestrogen therapy as the most recent treatment before study start are available only for the total population with PIK3CA mutation, but not for the relevant subpopulations (see Section 2.4.1 on the suitability of fulvestrant as a comparator therapy for research question A1). For research question B1, however, the G-BA sees a sufficient medical reason that, in the present exceptional case, justifies taking into account fulvestrant as a sufficiently suitable comparator, even following prior aromatase inhibitor treatment (see Table 4). The entire subpopulation B1 is therefore relevant for deriving the added benefit.

Characterization of the study population and information on the course of the study

For the relevant subpopulation B1, no data are available on patient characteristics or the course of the study.

Data are available only on the total population with PIK3CA mutation; these data are presented in Table 26, Appendix A of the full benefit assessment and described in Section 2.4.1.

Information on subsequent therapies

The SOLAR-1 specifications on subsequent therapies are described in Section 2.4.1. No data are available on the subsequent therapies received in the relevant subpopulation B1.

Risk of bias across outcomes (study level)

The risk of bias across outcomes (study level) for the SOLAR-1 study is assessed as low (see Section 2.4.1, Table 10).

Transferability of the study results to the German healthcare context

The company's rationale regarding the transferability of study results to the German healthcare context is described in Section 2.4.1.

2.6.2 Results on added benefit

2.6.2.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment:

- Mortality
  - Overall survival
- Morbidity
  - Symptoms surveyed with the symptom scales of the EORTC QLQ-C30
  - Pain, surveyed using BPI-SF
  - Health status, surveyed with the VAS of the EQ-5D-5L questionnaire
- Health-related quality of life
  - As surveyed with global health status and the EORTC QLQ-C30 functioning scales
- AEs
  - SAEs
  - Severe AEs (operationalized as CTCAE grade 3 or 4)
  - Discontinuation due to AEs
  - further specific AEs, if any

The choice of patient-relevant outcomes deviates from that by the company, which used further outcomes in the dossier (Module 4 A).

Table 16 shows the outcomes for which the included study provided data on subpopulation B1.

Table 16: Matrix of outcomes – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant (research question B1: postmenopausal women, second-line and subsequent-line therapy in the advanced stage)

Study	Outcomes								
	Overall survival	Symptoms (EORTC QLQ-C30)	Pain (BPI-SF)	Health status (EQ-5D-5L VAS)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs[a]	Discontinuation due to AEs	Specific AEs
SOLAR-1	Yes	No[b]	No[b]	No[b]	No[b]	Yes	Yes	Yes	No[c]

a. Operationalized as CTCAE grade 3 or 4.
b. No usable analyses available; see Section 2.4.2.1 for the reasoning.
c. It is not possible to select specific AEs since, for the relevant subpopulation, only incomplete data are available on common AEs, severe AEs (operationalized as CTCAE grade 3 or 4), and SAEs (see Section 2.4.2.1).

AE: adverse event; BPI-SF: Brief Pain Inventory – Short Form; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; EQ-5D-5L: European Quality of Life -5 Dimensions 5 Level; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

No usable analyses are available for the outcomes of symptoms, health-related quality of life (each surveyed with EORTC QLQ-C30), pain (surveyed with BPI-SF), and health status (surveyed with EQ-5D-5L VAS); for the reasoning, see Section 2.4.2.1. This section also provides the rationale explaining why it was impossible to select specific AEs for the relevant subpopulation B1.

2.6.2.2 Risk of bias

Table 17 presents the risk of bias for the results of the relevant outcomes in subpopulation B1.

Table 17: Risk of bias at study and outcome levels – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant (research question B1: postmenopausal women, second-line and subsequent-line therapy in the advanced stage)

Study		Outcomes								
	Study level	Overall survival	Symptoms (EORTC QLQ-C30)	Pain (BPI-SF)	Health status (EQ-5D-5L VAS)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs[a]	Discontinuation due to AEs	Specific AEs
SOLAR-1	L	L	–[b]	–[b]	–[b]	–[b]	H[c]	H[c]	H[d]	–[e]

a. Operationalized as CTCAE grade 3 or 4.
b. No usable analyses are available for the outcomes on the categories of morbidity and health-related quality of life; see Section 2.4.2.1 for the rationale.
c. Incomplete follow-up for potentially informative reasons in the presence of different lengths of follow-up observation periods between treatment arms (see available information on the total population with PIK3CA mutation, Table 27 in Appendix A of the full dossier assessment); no data are available on the follow-up period for subpopulation B1.
d. Due to the known AE profile of alpelisib, it was presumably impossible to maintain blinding over the course of the study.
e. It is not possible to select specific AEs since, for the relevant subpopulation, only incomplete data are available on common AEs, severe AEs (operationalized as CTCAE grade 3 or 4), and SAEs (see Section 2.4.2.1).

AE: adverse event; BPI-SF: Brief Pain Inventory – Short Form; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; EQ-5D-5L: European Quality of Life-5 Dimensions-5-Level; H: high; L: low; PIK3CA: phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

The risk of bias for the result on overall survival is rated as low.

No usable analyses are available for the outcomes on symptoms (EORTC QLQ-C30), pain (BPI-SF), health status (EQ-5D-5L VAS), and health-related quality of life (EORTC QLQ-C30), and no usable data are available on specific AEs (see Section 2.4.2.1); therefore, the risk of bias was not assessed.

Due to incomplete follow-up for potentially informative reasons given different follow-up periods between treatment arms (see available information on the total population with PIK3CA mutation in Table 27 of Appendix A of the full dossier assessment), there is a high risk of bias for the results of the outcomes of SAEs and severe AEs (operationalized as CTCAE grade 3 or 4).

Likewise, there is a high risk of bias regarding the results on the outcome of discontinuation due to AEs. This can be explained by the assumption that blinding was not maintainable over the course of the study in light of the known AEs of alpelisib, e.g. hyperglycaemia and skin disorders, which the majority of patients developed at an early point in the study [9].

This assessment concurs with that of the company for the results on the outcomes for which the risk of bias was assessed. However, the company assessed the risk of bias on the basis of the total population with PIK3CA mutation and derived the high risk of bias of the results on the outcome of discontinuation due to AEs from unequal follow-up periods in combination with potential informative censoring.

2.6.2.3 Results

Table 18 summarizes the results on the comparison of alpelisib + fulvestrant versus placebo + fulvestrant in postmenopausal women with HR-positive, HER2-negative, locally advanced or metastatic breast cancer with PIK3CA mutation and disease progression after endocrine monotherapy administered in the locally advanced or metastatic stage. Where necessary, calculations conducted by IQWiG are provided in addition to the data from the company's dossier.

No Kaplan Meier curves on the event-time analyses are available for the relevant subpopulation, and no complete listing of common AEs, SAEs, severe AEs (operationalized as CTCAE grade 3 or 4) and discontinuation due to AEs exists; therefore, it was impossible to present them for the relevant subpopulation.

Table 18: Results (mortality, morbidity, health-related quality of life, AEs) – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant (research question B1: postmenopausal women, second-line and subsequent-line therapy in advanced stage)

Study Outcome category Outcome	Alpelisib + fulvestrant N	Alpelisib + fulvestrant Median time to event in months [95% CI] Patients with event n (%)	Placebo + fulvestrant N	Placebo + fulvestrant Median time to event in months [95% CI] Patients with event n (%)	Alpelisib + fulvestrant vs. placebo + fulvestrant HR [95% CI]; p-value[a]
SOLAR-1 (3rd data cut-off: 23/04/2020)					
Mortality					
Overall survival	79	37.2 [25.6; 43.8] 44 (55.7)	82	31.2 [25.9; 43.2] 44 (53.7)	0.93 [0.61; 1.43]; 0.752
Morbidity					
Symptoms (EORTC QLQ-C30, symptom scales) Pain (BPI-SF) Health status (EQ-5D VAS)	No usable analyses[b]				
Health-related quality of life					
EORTC QLQ-C30 (global health status, functioning scales)	No usable analyses[b]				
AEs					
AEs (supplementary information)	79	0.2 [0.1; 0.3] 78 (98.7)	81	0.4 [0.3; 0.5] 72 (88.9)	–
SAEs	79	25.5 [8.2; 40.0] 34 (43.0)	81	21.6 [20.1; NC] 15 (18.5)	2.22 [1.19; 4.11]; 0.010
Severe AEs[c]	79	0.7 [0.5; 1.4] 67 (84.8)	81	NR [11.7; NC] 25 (30.9)	5.23 [3.24; 8.43]; < 0.001
Discontinuation due to AEs[d]	79	40.7 [21.2; NC] 21 (26.6)	81	NR [25.0; NC] 4 (4.9)	5.37 [1.83; 15.74]; < 0.001
Specific AEs	No usable data[e]				

a. HR and CI: Cox proportional hazards model; p-value: log-rank test; each stratified by prior therapy with a CDK 4/6 inhibitor (yes vs. no) and by the presence of liver and/or lung metastases (yes vs. no).
b. No usable analyses are available for the outcomes of the categories of morbidity and health-related quality of life; see Section 2.4.2.1 for a rationale.
c. Operationalized as CTCAE grade 3 or 4.
d. Discontinuation of alpelisib treatment or placebo and/or fulvestrant.
e. It is not possible to select specific AEs since for the relevant subpopulation, only incomplete data are available on common AEs, severe AEs (operationalized as CTCAE grade 3 or 4), and SAEs (see Section 2.4.2.1).

AE: adverse event; BPI-SF: Brief Pain Inventory – Short Form; CDK: cyclin-dependent kinase; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; EQ-5D-5L: European Quality of Life 5-Dimensions 5-Level; HR: hazard ratio; n: number of patients with (at least 1) event; N: number of analysed patients; NC: not calculable; NR: not reached; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

The available data allow deriving no more than indications, e.g. of an added benefit, for the outcome of overall survival. The results of the remaining outcomes on which usable analyses are available are each subject to a high risk of bias, and therefore, no more than hints, e.g. of added benefit, can be derived. However, the certainty of results on the specific outcome level is not downgraded in some cases (see below description of results).

For deriving any added benefit, the company used both the results on the total population with PIK3CA mutation and the subgroup with ECOG-PS 1 at baseline. The subgroup characteristic of ECOG-PS at baseline (0 versus 1) is irrelevant for the present benefit assessment (see Section 2.6.2.4); therefore, the comments below apply only to to the company's approach regarding the results on the total population with PIK3CA mutation.

Mortality

Overall survival

For the outcome of overall survival, no statistically significant difference between treatment groups was found. Hence, there is no hint of added benefit of alpelisib + fulvestrant in comparison with fulvestrant; an added benefit is therefore not proven.

This coincides with the company's assessment insofar as, based on the results of the total population with PIK3CA mutation, it arrives at the same conclusion.

Morbidity

Symptoms (symptom scales of EORTC QLQ-C30), pain (BPI-SF), health status (EQ-5D-5L VAS)

No usable analyses are available for the outcomes regarding (1) symptoms as surveyed with the EORTC QLQ-C30 symptom scales, (2) pain as surveyed with the BPI-SF, and (3) health status as surveyed with the VAS of EQ-5D-5L (for a discussion, see Section 2.4.2.1). Hence, there is no hint of added benefit of alpelisib + fulvestrant in comparison with fulvestrant for any of them; an added benefit is therefore not proven.

This corresponds to the company's assessment insofar as, based on the results of the total population with PIK3CA mutation at the 2nd data cut-off, it arrives at the same result.

Health-related quality of life

Global health status and functioning scales, surveyed with EORTC QLQ-C30

No usable analyses are available for outcomes on health-related quality of life, surveyed with global health status and the functioning scales of EORTC QLQ-C30 (for a discussion, see Section 2.4.2.1). Hence, there is no hint of added benefit of alpelisib + fulvestrant in comparison with fulvestrant for any of them; an added benefit is therefore not proven.

This coincides with the company's assessment insofar as, based on the results of the total population with PIK3CA mutation at the 2nd data cut-off, it arrives at the same result.

AEs

SAEs

For the outcome of SAEs, there is a statistically significant difference to the disadvantage of alpelisib + fulvestrant in comparison with placebo + fulvestrant. Hence, there is a hint of greater harm from alpelisib + fulvestrant in comparison with fulvestrant.

This coincides with the company's assessment insofar as, based on the results of the total population with PIK3CA mutation at the 2nd data cut-off, it derives greater harm with reduced certainty of results.

Severe AEs (operationalized as CTCAE grade 3 or 4)

For the outcome of severe AEs, operationalized as CTCAE grade 3 or 4, a statistically significant difference to the disadvantage of alpelisib + fulvestrant was found in comparison with placebo + fulvestrant. Due to the effect size found already at an early point in the study (see Kaplan-Meier curves on the total population with PIK3CA mutation in Appendix C of the full dossier assessment; a corresponding presentation is not available for the relevant subpopulation), the certainty of results is high despite the high risk of bias of results. Hence, there is an indication of greater harm from alpelisib + fulvestrant in comparison with fulvestrant.

This coincides with the company's assessment insofar as, based on the results of the total population with PIK3CA mutation at the 2nd data cut-off, it derives greater harm, albeit with reduced certainty of results.

Discontinuation due to AEs

For the outcome of discontinuation due to AEs, there is a statistically significant difference to the disadvantage of alpelisib + fulvestrant in comparison with placebo + fulvestrant. Hence, there is a hint of greater harm from alpelisib + fulvestrant in comparison with fulvestrant.

This coincides with the company's assessment insofar as, based on the results of the total population with PIK3CA mutation at the 2nd data cut-off, it derives greater harm with reduced certainty of results.

Specific AEs

For the relevant subpopulation, it was not possible to select specific AEs (for a discussion, see Section 2.4.2.1). Hence, there is no hint of greater or lesser harm from alpelisib + fulvestrant in comparison with fulvestrant; greater or lesser harm is therefore not proven.

This departs from the company's assessment insofar as, based on the results of the total population with PIK3CA mutation at the 2nd data cut-off, the company derived greater harm, at reduced certainty of results, for some of the AEs of special interest it analysed.

2.6.2.4 Subgroups and other effect modifiers

Added benefit was assessed on the basis of a subpopulation of the SOLAR-1 study. For research question B1, no data are available on subgroups of the subpopulation viewed.

For the derivation of any added benefit, the company used the results of the total population with PIK3CA mutation and, in addition, the results of the subgroup with an ECOG-PS of 1 at baseline. It justified this approach with the fact that, for the subgroup characteristic of ECOG-PS at baseline (0 versus 1), an effect modification was found in several outcomes. The company's approach is not appropriate. On the one hand, the company failed to take into account any outcome-related interactions. On the other hand, in the derivation of added benefit, the company did not discuss the results for the subgroup with an ECOG-PS of 0 at baseline despite the fact that this subgroup includes the majority of the population with PIK3CA mutation. Irrespective of the above, a comparison between ECOG-PS 0 and ECOG-PS 1 is unsuitable for distinguishing between different degrees of severity of the disease.

2.6.3 Probability and extent of added benefit

The following describes how the probability and extent of added benefit for the relevant subpopulation B1 are derived at the outcome level. The various outcome categories and the effect sizes are taken into account. The methods used for this purpose are explained in the IQWiG General Methods [1].

The methodology of aggregating the conclusions reached at outcome level to infer an overall conclusion on any added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

2.6.3.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.6.2 (see Table 19).

Determination of the outcome category for the outcome of discontinuation due to AEs

Not for all outcomes considered in the present benefit assessment does the dossier permit inferences as to whether they were serious/severe or non-serious/non-severe. The classification of these outcomes is justified below.

For the outcome of discontinuation due to AEs, information on the percentages of SAEs or severe AEs (operationalized as CTCAE grade 3 or 4) is not available for either the relevant subpopulation or the total population with PIK3CA mutation. Therefore, the outcome of discontinuation due to AEs is allocated to the outcome category of non-serious/non-severe AEs.

The company did not allocate discontinuation due to AEs to any outcome category.

Table 19: Extent of added benefit at outcome level: RCT, direct comparison: alpelisib + fulvestrant vs. fulvestrant (research question B1: postmenopausal women, second-line and subsequent-line therapy in the advanced stage)

Outcome category **Outcome**	**Alpelisib + fulvestrant vs. fulvestrant** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival	37.2 vs. 31.2 months HR: 0.93 [0.61; 1.43]; p = 0.752	Lesser/added benefit not proven
Morbidity		
Symptoms (EORTC QLQ-C30, symptom scales)	No usable analyses[c]	Lesser/added benefit not proven
Pain (BPI-SF)	No usable analyses[c]	Lesser/added benefit not proven
Health status (EQ-5D-5L VAS)	No usable analyses[c]	Lesser/added benefit not proven
Health-related quality of life		
EORTC QLQ-C30 (global health status, functioning scales)	No usable analyses[c]	Lesser/added benefit not proven
AEs		
SAEs	25.5 vs. 21.6 months HR: 2.22 [1.19; 4.11] HR: 0.45 [0.24; 0.84][d]; p = 0.010 Probability: hint	Outcome category: serious/severe AEs $0.75 \leq CI_u < 0.90$ greater harm; extent: considerable
Severe AEs[e]	0.7 months vs. NR HR: 5.23 [3.24; 8.43] HR: 0.19 [0.12; 0.31][d]; p < 0.001 Probability: Indication[f]	Outcome category: serious/severe AEs $CI_u < 0.75$ and risk ≥ 5% Greater harm; extent: major
Discontinuation due to AEs[g]	40.7 months vs. NR HR: 5.37 [1.83; 15.74] HR: 0.19 [0.06; 0.55][d]; p < 0.001 Probability: hint	Outcome category: non-serious/non-severe AEs $CI_u < 0.80$ greater harm; extent: considerable
Specific AEs	No usable data[c]	Greater/lesser harm not proven

a. Probability is stated if a statistically significant and relevant effect is present.
b. Estimations of effect size are made depending on the outcome category, with different limits based on the upper limit of the confidence interval (CI_u).
c. See Section 2.4.2.1 for a rationale.
d. IQWiG calculation, reversed direction of effect to enable use of limits to derive the extent of added benefit.
e. Operationalized as CTCAE grade 3 or 4.
f. The certainty of results was not downgraded despite the high risk of bias (see Section 2.6.2.3).
g. Discontinuation of alpelisib treatment or placebo and/or fulvestrant.

AE: adverse event; BPI-SF: Brief Pain Inventory – Short Form; CI: confidence interval; CI_u:upper limit of the confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; EQ-5D-5L: European Quality of Life 5-Dimensions 5-Level; HR: hazard ratio; NR: not reached; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

2.6.3.2 Overall conclusion on added benefit

Table 20 summarizes the results considered in the overall conclusion on the extent of added benefit.

Table 20: Favourable and unfavourable effects from the assessment of alpelisib in combination with fulvestrant (research question B1: postmenopausal women, second-line and subsequent-line therapy in the advanced stage)

Favourable effects	Unfavourable effects
–	Serious/severe AEs ▪ SAEs: hint of greater harm – extent: considerable ▪ Severe AEs: indication of greater harm – extent: major
–	Non-serious/non-severe AEs ▪ Discontinuation due to AEs: hint of greater harm – extent: considerable
No relevant data are available on the selection of specific AEs.	
No usable analyses are available on outcomes of the categories of morbidity and health-related quality of life.	
AE: adverse event; SAE: serious adverse event	

All things considered, the available data show exclusively unfavourable effects for alpelisib plus fulvestrant in comparison with fulvestrant.

For each of the outcomes of SAEs and discontinuation due to AEs, a hint of greater harm of considerable extent was found. For severe AEs, there is an indication of major greater harm. No data are available on other AE outcomes since it was not possible to select specific AEs. No usable analyses are available on outcomes of the categories of morbidity and health-related quality of life.

In summary, for postmenopausal women with HR-positive, HER2-negative, locally advanced or metastatic breast cancer with PIK3CA mutation and progression of disease after endocrine monotherapy in the locally advanced or metastatic stage, there is a hint of lesser benefit of alpelisib plus fulvestrant in comparison with fulvestrant.

The above assessment departs from that by the company, which derived a considerable added benefit with high certainty of results on the basis of the results of the SOLAR1-study and taking into account further outcomes without differentiating by treatment line or sex. Furthermore, the company derived a major added benefit for the subgroup with an ECOG-PS of 1 at baseline with high certainty of results.

2.7 Research question B2: men, second-line and subsequent-line therapy in the advanced stage

2.7.1 Results on added benefit

No data are available for the assessment of the added benefit of alpelisib plus fulvestrant in comparison with the ACT in men with HR-positive, HER2-negative, locally advanced or metastatic breast cancer with PIK3CA mutation and disease progression after endocrine

monotherapy administered in the locally advanced or metastatic stage. Hence, there is no hint of added benefit of alpelisib in combination with fulvestrant; an added benefit is therefore not proven.

2.7.2 Probability and extent of added benefit

Since no data are available for the assessment of any added benefit of alpelisib plus fulvestrant in comparison with the ACT in men with HR-positive, HER2-negative, locally advanced or metastatic breast cancer with PIK3CA mutation and disease progression after endocrine monotherapy administered in the locally advanced or metastatic stage, there is no proof of added benefit of alpelisib in combination with fulvestrant for these patients.

The above assessment departs from that by the company, which derived a considerable added benefit with high certainty of results on the basis of the results of the SOLAR1-study and taking into account further outcomes without differentiating by treatment line or sex. Furthermore, the company derived a major added benefit for the subgroup with an ECOG-PS of 1 at baseline with high certainty of results.

2.8 Probability and extent of added benefit – summary

The result of the assessment of the added benefit of alpelisib plus fulvestrant in comparison with fulvestrant is summarized in Table 21.

Table 21: Alpelisib in combination with fulvestrant – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
Men and postmenopausal women with HR-positive, HER2-negative, locally advanced or metastatic breast cancer[b] with PIK3CA mutation			
A1	Postmenopausal women after disease progression following endocrine monotherapy in the (neo)adjuvant treatment situation	▪ Ribociclib in combination with a nonsteroidal aromatase inhibitor or ▪ Ribociclib in combination with fulvestrant or ▪ Anastrozole or ▪ Letrozole or ▪ Fulvestrant or ▪ Possibly tamoxifen if aromatase inhibitors are not suitable	Hint of lesser benefit[c]
A2	Men after disease progression following endocrine monotherapy in the (neo)adjuvant treatment situation	Therapy upon the physician's discretion	Added benefit not proven
B1	Postmenopausal women after disease progression following endocrine monotherapy in the locally advanced or metastatic stage	Another endocrine therapy with ▪ abemaciclib in combination with fulvestrant or ▪ ribociclib in combination with fulvestrant or ▪ tamoxifen or ▪ anastrozole or ▪ fulvestrant monotherapy; only for patients with recurrence or progression following antioestrogen treatment or ▪ letrozole, only for patients with recurrence or progression following antioestrogen treatment or ▪ exemestane, only for patients with progression following antioestrogen treatment or ▪ everolimus in combination with exemestane, only for patients without symptomatic visceral metastasis after progression following nonsteroidal aromatase inhibitor therapy	Hint of lesser benefit[c]
B2	Men after progression following endocrine monotherapy in the locally advanced or metastatic stage	Therapy upon the physician's discretion	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. For the given therapeutic indication, it is assumed that another endocrine therapy is indicated for the patient, while no indication exists for chemotherapy or (secondary) resection or radiotherapy with curative intent.
c. The SOLAR-1 study includes data only on the comparison with fulvestrant (for research question B1, viewed by the G-BA as a sufficiently suitable comparator even after prior aromatase inhibitor therapy, see Section 2.6.1). Further, only patients with an ECOG-PS of 0 or 1 were included. It remains unclear whether the observed effects are transferable to patients with an ECOG-PS ≥ 2. Virtually all patients included in the study were in stage IV (breast cancer with distant metastases).

ACT: appropriate comparator therapy; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; HER2: human epidermal growth receptor 2; HR: hormone receptor; PIK3CA: phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha

The approach for deriving an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

1. Institute for Quality and Efficiency in Health Care. General Methods 6.0 (German version) [online]. 2020 [Accessed: 05.11.2020]. URL: https://www.iqwig.de/methoden/allgemeine-methoden_version-6-0.pdf.

2. Skipka G, Wieseler B, Kaiser T et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2016; 58(1): 43-58. https://dx.doi.org/10.1002/bimj.201300274.

3. Gemeinsamer Bundesausschuss. Nutzenbewertungsverfahren zum Wirkstoff Alpelisib (Mammakarzinom mit PIK3CA-Mutation, vorbehandelte Patienten, Kombination mit Fulvestrant): zweckmäßige Vergleichstherapie. [Demnächst verfügbar unter: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/581/#zweckmaessige-vergleichstherapie].

4. Novartis Pharma Services. SOLAR-1: a phase III randomized double-blind, placebo controlled study of alpelisib in combination with fulvestrant for men and postmenopausal women with hormone receptor positive, HER2-negative advanced breast cancer which progressed on or after aromatase inhibitor treatment [online]. [Accessed: 17.09.2020]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2015-000340-42.

5. Novartis Pharmaceuticals. Study assessing the efficacy and safety of alpelisib plus fulvestrant in men and postmenopausal women with advanced breast cancer which progressed on or after aromatase inhibitor treatment (SOLAR-1): study details [online]. 03.08.2020 [Accessed: 17.09.2020]. URL: https://ClinicalTrials.gov/show/NCT02437318.

6. Novartis Pharmaceuticals. Study assessing the efficacy and safety of alpelisib plus fulvestrant in men and postmenopausal women with advanced breast cancer which progressed on or after aromatase inhibitor treatment (SOLAR-1): study results [online]. 03.08.2020 [Accessed: 17.09.2020]. URL: https://clinicaltrials.gov/ct2/show/results/NCT02437318.

7. Andre F, Ciruelos E, Rubovszky G et al. Alpelisib for PIK3CA-mutated, hormone receptor-positive advanced breast cancer. N Engl J Med 2019; 380(20): 1929-1940. https://dx.doi.org/10.1056/NEJMoa1813904.

8. Rugo HS, Andre F, Yamashita T et al. Time course and management of key adverse events during the randomized phase III SOLAR-1 study of PI3K inhibitor alpelisib plus fulvestrant in patients with HR-positive advanced breast cancer. Ann Oncol 2020; 31(8): 1001-1010. https://dx.doi.org/10.1016/j.annonc.2020.05.001.

9. European Medicines Agency. Piqray: European public assessment report [online]. 28.05.2020 [Accessed: 21.09.2020]. URL: https://www.ema.europa.eu/documents/assessment-report/piqray-epar-public-assessment-report_en.pdf.

10. Novartis Pharma. Piqray: Fachinformation [online]. 07.2020 [Accessed: 07.09.2020]. URL: https://www.fachinfo.de/.

11. AstraZeneca. Fachinformation Faslodex 250 mg Injektionslösung [online]. 2020. URL: https://www.fachinfo.de.

12. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Dokumentation und Würdigung der Anhörung zum Entwurf der Allgemeinen Methoden 6.0 [online]. 05.11.2020 [Accessed: 09.11.2020]. URL: https://www.iqwig.de/download/Allgemeine-Methoden_DWA-Entwurf-fuer-Version-6-0_V1-0.pdf.

The full report (German version) is published under https://www.iqwig.de/en/projects/a20-81.html.