Inavolisib (breast cancer)

Benefit assessment according to §35a SGB V[1]

EXTRACT

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[1] Translation of Sections I 1 to I 6 of the dossier assessment *Inavolisib (Mammakarzinom) – Nutzenbewertung gemäß § 35a SGB V*. Please note: This translation 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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Medical and scientific advice

No advisor on medical and scientific questions was available for the present dossier assessment.

Patient and family involvement

No feedback was received in the framework of the present dossier assessment.

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Part I: Benefit assessment

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

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
AGO	Gynaecological Oncology Group
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-BR23	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Breast Cancer 23
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
ER	oestrogen receptor
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HER2	human epidermal growth factor receptor 2
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MMRM	mixed-effects model with repeated measures
PFS	progression-free survival
PIK3CA	gene for catalytic subunit (p110α) of PI3 kinase (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha)
PR	progesterone receptor
PRO-CTCAE	Patient-Reported Outcomes version of the CTCAE
PT	Preferred Term
RCT	randomized controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SmPC	summary of product characteristics
VAS	visual analogue scale

I 1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book 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 inavolisib. 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 11 August 2025.

Research question

The aim of this report is to assess the added benefit of inavolisib in combination with palbociclib and fulvestrant (hereinafter referred to as 'inavolisib + palbociclib + fulvestrant') compared with the appropriate comparator therapy (ACT) in adult patients with PI3 kinase (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha) (PIK3CA)-mutated, oestrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with a mutation in the gene for the catalytic subunit (p110α), following recurrence during or within 12 months of completing adjuvant endocrine treatment (hereinafter abbreviated to 'patients with PIK3CA-mutated, ER-positive, HER2-negative, locally advanced or metastatic breast cancer').

The research questions presented in Table 2 were defined in accordance with the ACT specified by the G-BA.

Table 2: Research questions for the benefit assessment of inavolisib + palbociclib + fulvestrant (multipage table)

Research question	Therapeutic indication	ACT[a]
1	Women with PIK3CA-mutated, ER-positive, HER2-negative, locally advanced or metastatic breast cancer, following recurrence during or within 12 months of completing adjuvant endocrine treatment[b, c, d, e]	▪ tamoxifen (only for premenopausal women who have not received tamoxifen in previous [neo-]adjuvant endocrine therapy; only for postmenopausal women if aromatase inhibitors are not suitable) or ▪ letrozole or ▪ exemestane (only for women with progression following antioestrogen therapy) or ▪ anastrozole or ▪ fulvestrant or ▪ everolimus in combination with exemestane (only for women without symptomatic visceral metastases who have progressed after a nonsteroidal aromatase inhibitor) or ▪ ribociclib in combination with a nonsteroidal aromatase inhibitor (anastrozole, letrozole) or ▪ abemaciclib in combination with a nonsteroidal aromatase inhibitor (anastrozole, letrozole) or ▪ palbociclib in combination with a nonsteroidal aromatase inhibitor (anastrozole, letrozole) or ▪ ribociclib in combination with fulvestrant or ▪ abemaciclib in combination with fulvestrant or ▪ palbociclib in combination with fulvestrant
2	Men with PIK3CA-mutated, ER-positive, HER2-negative, locally advanced or metastatic breast cancer, following recurrence during or within 12 months of completing adjuvant endocrine treatment[b, e]	▪ tamoxifen or ▪ palbociclib in combination with a nonsteroidal aromatase inhibitor (anastrozole, letrozole)

Table 2: Research questions for the benefit assessment of inavolisib + palbociclib + fulvestrant (multipage table)

Research question	Therapeutic indication	ACT[a]

a. Presented is the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company according to the inclusion criteria in Module 4 Section 4.2.2 is printed in **bold**.
b. Patients previously treated with a CDK4/6 inhibitor in the (neo)adjuvant setting should have had an interval of at least 12 months between termination of CDK4/6 inhibitor treatment and the detection of recurrence.
c. The G-BA assumes that treatment switching has taken place with regard to the drugs used in the initial prior adjuvant endocrine treatment.
d. The G-BA assumes pre/perimenopausal women to receive ovarian suppression with a GnRH analogue.
e. The G-BA assumes that
- the patients in the therapeutic indication have not yet received endocrine therapy in the advanced or metastatic setting,
- an(other) endocrine therapy is indicated for the patients and, in particular, there is no indication for chemotherapy to achieve a necessary, rapid remission, and
- no indication for (secondary) resection or radiotherapy with curative intent.

ACT: appropriate comparator therapy; ER: oestrogen receptor; G-BA: Federal Joint Committee; GnRH: gonadotropin-releasing hormone; HER2: human epidermal growth factor receptor 2; PIK3CA: gene for the catalytic subunit (p110α) of PI3 kinase (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha)

When choosing the ACT, the company did not follow the G-BA's specification. It restricted the ACT in Module 3 A of the dossier to the drug combinations with CDK4/6 inhibitors listed in the table. Furthermore, the company did not differentiate by sex, i.e. it specified an identical ACT for women and men.

The company thus excluded the endocrine monotherapies and the combination of everolimus and exemestane as options for the ACT. As justification, the company stated that endocrine monotherapies were no longer recommended in current guidelines or were only recommended in individual cases and no longer represented a standard treatment for metastatic breast cancer. It added that there were no G-BA assessments for the monotherapies and thus a patient-relevant benefit had not been determined.

The company's reasoning for research question 1 (women) is not commented on further, as the company's deviation from the ACT was of no consequence.

For research question 2 (men), the company argued that, firstly, it is recommended to switch the drug class in the case of endocrine resistance or prior treatment with an aromatase inhibitor, whereby fulvestrant should be used as the preferred combination partner with a cyclin-dependent kinase (CDK)4/6 inhibitor. Secondly, according to the current guidelines, treatment for men is based on the recommendations for women.

In the therapeutic indication at hand, fulvestrant is only approved for women. Accordingly, the use of fulvestrant in the patient group of men represents off-label use. According to the G-BA's notes on the ACT, against the background of an overall poor body of evidence, it cannot be inferred from the guidelines that the off-label use of fulvestrant (+ GnRH analogue) would generally be preferable to the medicinal products previously approved for the patient group of men according to the generally recognized state of medical knowledge, however. The G-BA's view was accepted.

This assessment was conducted in comparison with the ACT specified by the G-BA.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) were used to derive the added benefit. This concurred with the company's inclusion criteria.

Research question 1: women with PIK3CA-mutated, ER-positive, HER2-negative, locally advanced or metastatic breast cancer

Study pool and study design

The INAVO120 study was included in the benefit assessment. INAVO120 is a double-blind RCT comparing the drug combination inavolisib + palbociclib + fulvestrant with placebo + palbociclib + fulvestrant in adult patients with PIK3CA-mutated hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer. Patients must have had a recurrence during adjuvant endocrine treatment or within 12 months of completing this treatment. If a CDK4/6 inhibitor was included as part of neoadjuvant or adjuvant therapy, the progression had to have occurred > 12 months since completion of CDK4/6 inhibitor therapy, however. Patients with type 1 diabetes mellitus and patients with type 2 diabetes mellitus requiring ongoing systemic treatment at the time of study entry were excluded from the study.

A total of 325 patients were enrolled in the study and randomized in a 1:1 ratio to receive either inavolisib + palbociclib + fulvestrant (N = 161) or placebo + palbociclib + fulvestrant (N = 164).

Only 6 men were included in the study. The benefit assessment for research question 1 was based on the total population of the INAVO120 study.

Treatment in both arms was conducted in compliance with the current summaries of product characteristics (SmPCs).

The primary outcome of the study was progression-free survival (PFS), assessed by the investigator using Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 criteria.

Further outcomes were recorded in the categories of morbidity, health-related quality of life and side effects.

The results of the current 2nd data cut from 15 November 2024 were used for this benefit assessment.

Risk of bias

The risk of bias across outcomes was rated as low for INAVO120.

The risk of bias of the result for the outcome overall survival was rated as low.

Due to incomplete observations for potentially informative reasons, the risks of bias for the results of the outcomes in the side effects category were assessed as high, with the exception of discontinuation due to AEs. The planned follow-up period after the end of treatment was 30 days for these outcomes. The observation period was thus determined by the reasons for treatment discontinuation (largely by disease progression), which clearly differed between the treatment arms. Due to a possible association between disease progression and these outcomes, incomplete observations for potentially informative reasons were present.

Although the risk of bias for the outcome discontinuation due to AEs was low, the certainty of results for this outcome was limited. Premature treatment discontinuation for reasons other than AEs is a competing event for the outcome discontinuation due to AEs to be recorded. This means that, although AEs that would have led to discontinuation of therapy may occur after discontinuation for other reasons, the criterion discontinuation is no longer applicable to them. It was impossible to estimate how many AEs this affected.

Results

Mortality

Overall survival

A statistically significant difference between the treatment arms was shown for the outcome overall survival. However, there was an effect modification by the characteristic of age:

A statistically significant difference in favour of inavolisib + palbociclib + fulvestrant was shown between the treatment arms for patients younger than 65 years. There is an indication of an added benefit of inavolisib + palbociclib + fulvestrant compared with palbociclib + fulvestrant.

No statistically significant difference was shown between the treatment arms for patients aged 65 years and older. There is no hint of an added benefit of inavolisib + palbociclib + fulvestrant in comparison with palbociclib + fulvestrant; an added benefit is therefore not proven.

Morbidity

Symptomatic skeletal-related events; symptoms (EORTC QLQ-C30 and EORTC QLQ-BR23, symptom scales); worst pain, recorded using the BPI-SF Item 3; health status, recorded using the EQ-5D VAS

No suitable data were available for the morbidity outcomes. For all outcomes in this outcome category, there is no hint of an added benefit of inavolisib + palbociclib + fulvestrant compared with palbociclib + fulvestrant. An added benefit for these outcomes is therefore not proven.

Health-related quality of life

EORTC QLQ-C30 and EORTC QLQ-BR23 (functional scales)

No suitable data were available for health-related quality of life outcomes. There is no hint of an added benefit of inavolisib + palbociclib + fulvestrant compared with palbociclib + fulvestrant. An added benefit for these outcomes is therefore not proven.

Side effects

SAEs

There was no statistically significant difference between the treatment arms for the outcome SAEs. However, there was an effect modification by the characteristic of menopausal status:

A statistically significant difference to the disadvantage of inavolisib + palbociclib + fulvestrant was shown between the treatment arms for non-postmenopausal women. There is a hint of greater harm of inavolisib + palbociclib + fulvestrant compared with palbociclib + fulvestrant.

There was no statistically significant difference between the treatment arms for postmenopausal women. There is no hint of greater or lesser harm of inavolisib + palbociclib + fulvestrant in comparison with palbociclib + fulvestrant; greater or lesser harm is therefore not proven.

Severe AEs (CTCAE grade ≥ 3)

There was no statistically significant difference between the treatment arms for the outcome of severe AEs. There is no hint of greater or lesser harm of inavolisib + palbociclib + fulvestrant in comparison with palbociclib + fulvestrant; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

A statistically significant difference to the disadvantage of inavolisib + palbociclib + fulvestrant was shown between the treatment arms for the outcome of discontinuation due to AEs. There is a hint of greater harm of inavolisib + palbociclib + fulvestrant compared with palbociclib + fulvestrant.

PRO-CTCAE

No suitable data were available for PRO-CTCAE. There is no hint of greater or lesser harm of inavolisib + palbociclib + fulvestrant compared with palbociclib + fulvestrant. An added benefit for PRO-CTCAE is therefore not proven.

Stomatitis (AEs)

A statistically significant difference to the disadvantage of inavolisib + palbociclib + fulvestrant was shown between the treatment arms for the outcome stomatitis (AEs). There is a hint of greater harm of inavolisib + palbociclib + fulvestrant compared with palbociclib + fulvestrant.

Hyperglycaemia (severe AEs)

A statistically significant difference to the disadvantage of inavolisib + palbociclib + fulvestrant was shown between the treatment arms for the outcome hyperglycaemia (severe AEs). There is a hint of greater harm of inavolisib + palbociclib + fulvestrant compared with palbociclib + fulvestrant.

Other specific AEs

A statistically significant difference to the disadvantage of inavolisib + palbociclib + fulvestrant was shown between the treatment arms for the following outcomes: decreased appetite (AEs), noninfective diarrhoea (AEs), platelet count decreased (severe AEs), metabolism and nutrition disorders (severe AEs) and gastrointestinal disorders (severe AEs). In each case, there is a hint of greater harm of inavolisib + palbociclib + fulvestrant compared with palbociclib + fulvestrant.

For the outcome of metabolism and nutrition disorders (severe AEs), there were effect modifications from the characteristics of visceral disease and menopausal status. However, the subgroup results for this outcome were not interpretable. Therefore, the results for the total population were used for the derivation of the added benefit.

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 the added benefit of the drug inavolisib versus the ACT is assessed as follows:

The INAVO120 study showed an indication of an added benefit of considerable extent for the outcome overall survival in women aged < 65 years. At the same time, there were hints of greater harm of minor to major extent for the overall rate of SAEs (in non-postmenopausal women) and for several specific AEs in the category of severe/serious side effects. Due to the effect modification by age in the outcome overall survival, the added benefit was determined separately by age group.

For women aged < 65 years, the disadvantages in various AE outcomes did not completely call into question the considerable added benefit in overall survival. In summary, there was an indication of a minor added benefit of inavolisib + palbociclib + fulvestrant versus palbociclib + fulvestrant for this age group.

For women aged ≥ 65 years, there were no positive effects of inavolisib + palbociclib + fulvestrant versus placebo + palbociclib + fulvestrant. At the same time, there were several hints of greater harm of minor to major extent, especially in the case of severe/serious specific AEs. However, these were not sufficient to derive a lesser benefit. An added benefit of inavolisib + palbociclib + fulvestrant versus palbociclib + fulvestrant is therefore not proven for women aged ≥ 65 years.

This deviates from the company's assessment, which did not carry out a separate assessment for women and men in its dossier and did not differentiate between age groups, but rather derived an overall indication of a major added benefit.

[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].

Research question 2: men with PIK3CA-mutated, ER-positive, HER2-negative, locally advanced or metastatic breast cancer

Study pool and study design

The company included the INAVO120 study for men with PIK3CA-mutated, ER-positive, HER2-negative, locally advanced or metastatic breast cancer. The study is described in detail under research question 1.

The INAVO120 study compared inavolisib + palbociclib + fulvestrant with placebo + palbociclib + fulvestrant. The G-BA defined tamoxifen or palbociclib in combination with a nonsteroidal aromatase inhibitor (anastrozole, letrozole) as the ACT for research question 2.

The treatment in the comparator arm of INAVO120 did not concur with the ACT, so no data were available on the comparison of inavolisib + palbociclib + fulvestrant with the comparator therapy specified by the G-BA.

Results

No suitable data were available for the assessment of the added benefit of inavolisib + palbociclib + fulvestrant compared with the ACT in men with PIK3CA-mutated, ER-positive, HER2-positive, locally advanced or metastatic breast cancer. There is no hint of an added benefit of inavolisib + palbociclib + fulvestrant in comparison with the ACT; an added benefit is therefore not proven.

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

As the company did not present any data for the assessment of the added benefit of inavolisib + palbociclib + fulvestrant compared with the ACT in men with PIK3CA-mutated, ER-positive, HER2-negative, locally advanced or metastatic breast cancer, an added benefit is not proven.

This deviates from the company's assessment, which did not carry out a separate assessment for women and men in its dossier, but rather derived an overall indication of a major added benefit for both sexes.

Table 3 shows a summary of probability and extent of the added benefit of inavolisib + palbociclib + fulvestrant.

Table 3: Inavolisib + palbociclib + fulvestrant – probability and extent of added benefit (multipage table)

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Women with PIK3CA-mutated, ER-positive, HER2-negative, locally advanced or metastatic breast cancer, following recurrence during or within 12 months of completing adjuvant endocrine treatment[b, c, d, e]	▪ tamoxifen (only for premenopausal women who have not received tamoxifen in previous [neo-]adjuvant endocrine therapy; only for postmenopausal women if aromatase inhibitors are not suitable) or ▪ letrozole or ▪ exemestane (only for women with progression following antioestrogen therapy) or ▪ anastrozole or ▪ fulvestrant or ▪ everolimus in combination with exemestane (only for women without symptomatic visceral metastases who have progressed after a nonsteroidal aromatase inhibitor) or ▪ ribociclib in combination with a nonsteroidal aromatase inhibitor (anastrozole, letrozole) or ▪ abemaciclib in combination with a nonsteroidal aromatase inhibitor (anastrozole, letrozole) or ▪ palbociclib in combination with a nonsteroidal aromatase inhibitor (anastrozole, letrozole) or ▪ ribociclib in combination with fulvestrant or ▪ abemaciclib in combination with fulvestrant or ▪ palbociclib in combination with fulvestrant	▪ Women < 65 years: indication of a minor added benefit[f] ▪ Women ≥ 65 years: added benefit not proven

Table 3: Inavolisib + palbociclib + fulvestrant – probability and extent of added benefit (multipage table)

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
2	Men with PIK3CA-mutated, ER-positive, HER2-negative, locally advanced or metastatic breast cancer, following recurrence during or within 12 months of completing adjuvant endocrine treatment[b, e]	▪ tamoxifen or ▪ palbociclib in combination with a nonsteroidal aromatase inhibitor (anastrozole, letrozole)	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company according to the inclusion criteria in Module 4 Section 4.2.2 is printed in **bold**.
b. Patients previously treated with a CDK4/6 inhibitor in the (neo)adjuvant setting should have had an interval of at least 12 months between termination of CDK4/6 inhibitor treatment and the detection of recurrence.
c. The G-BA assumes that treatment switching has taken place with regard to the drugs used in the initial prior adjuvant endocrine treatment.
d. The G-BA assumes pre/perimenopausal women to receive ovarian suppression with a GnRH analogue.
e. The G-BA assumes that
- the patients in the therapeutic indication have not yet received endocrine therapy in the advanced or metastatic setting,
- an(other) endocrine therapy is indicated for the patients and, in particular, there is no indication for chemotherapy to achieve a necessary, rapid remission, and
- no indication for (secondary) resection or radiotherapy with curative intent.

f. The INAVO120 study included only patients with an ECOG PS of 0 or 1. It remains unclear whether the observed effects are transferable to patients with an ECOG PS ≥ 2.

ACT: appropriate comparator therapy; ER: oestrogen receptor; G-BA: Federal Joint Committee; GnRH: gonadotropin-releasing hormone; HER2: human epidermal growth factor receptor 2; PIK3CA: gene for the catalytic subunit (p110α) of PI3 kinase (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha)

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

I 2 Research question

The aim of this report is to assess the added benefit of inavolisib in combination with palbociclib and fulvestrant (hereinafter referred to as 'inavolisib + palbociclib + fulvestrant') compared with the appropriate comparator therapy (ACT) in adult patients with PI3 kinase (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha) (PIK3CA)-mutated, oestrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with a mutation in the gene for the catalytic subunit (p110α), following recurrence during or within 12 months of completing adjuvant endocrine treatment (hereinafter abbreviated to 'patients with PIK3CA-mutated, ER-positive, HER2-negative, locally advanced or metastatic breast cancer').

The research questions presented in Table 4 were defined in accordance with the ACT specified by the G-BA.

Table 4: Research questions for the benefit assessment of inavolisib + palbociclib + fulvestrant (multipage table)

Research question	Therapeutic indication	ACT[a]
1	Women with PIK3CA-mutated, ER-positive, HER2-negative, locally advanced or metastatic breast cancer, following recurrence during or within 12 months of completing adjuvant endocrine treatment[b, c, d, e]	▪ tamoxifen (only for premenopausal women who have not received tamoxifen in previous [neo-]adjuvant endocrine therapy; only for postmenopausal women if aromatase inhibitors are not suitable) or ▪ letrozole or ▪ exemestane (only for women with progression following antioestrogen therapy) or ▪ anastrozole or ▪ fulvestrant or ▪ everolimus in combination with exemestane (only for women without symptomatic visceral metastases who have progressed after a nonsteroidal aromatase inhibitor) or ▪ ribociclib in combination with a nonsteroidal aromatase inhibitor (anastrozole, letrozole) or ▪ abemaciclib in combination with a nonsteroidal aromatase inhibitor (anastrozole, letrozole) or ▪ palbociclib in combination with a nonsteroidal aromatase inhibitor (anastrozole, letrozole) or ▪ ribociclib in combination with fulvestrant or ▪ abemaciclib in combination with fulvestrant or ▪ palbociclib in combination with fulvestrant
2	Men with PIK3CA-mutated, ER-positive, HER2-negative, locally advanced or metastatic breast cancer, following recurrence during or within 12 months of completing adjuvant endocrine treatment[b, e]	▪ tamoxifen or ▪ palbociclib in combination with a nonsteroidal aromatase inhibitor (anastrozole, letrozole)

Table 4: Research questions for the benefit assessment of inavolisib + palbociclib + fulvestrant (multipage table)

Research question	Therapeutic indication	ACT[a]
a. Presented is the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company according to the inclusion criteria in Module 4 Section 4.2.2 is printed in **bold**. b. Patients previously treated with a CDK4/6 inhibitor in the (neo)adjuvant setting should have had an interval of at least 12 months between termination of CDK4/6 inhibitor treatment and the detection of recurrence. c. The G-BA assumes that treatment switching has taken place with regard to the drugs used in the initial prior adjuvant endocrine treatment. d. The G-BA assumes pre/perimenopausal women to receive ovarian suppression with a GnRH analogue. e. The G-BA assumes that ▫ the patients in the therapeutic indication have not yet received endocrine therapy in the advanced or metastatic setting, ▫ an(other) endocrine therapy is indicated for the patients and, in particular, there is no indication for chemotherapy to achieve a necessary, rapid remission, and ▫ no indication for (secondary) resection or radiotherapy with curative intent. ACT: appropriate comparator therapy; ER: oestrogen receptor; G-BA: Federal Joint Committee; GnRH: gonadotropin-releasing hormone; HER2: human epidermal growth factor receptor 2; PIK3CA: gene for the catalytic subunit (p110α) of PI3 kinase (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha)		

When choosing the ACT, the company did not follow the G-BA's specification. It restricted the ACT in Module 3 A of the dossier to the following drug combinations:

- ribociclib in combination with a nonsteroidal aromatase inhibitor (anastrozole, letrozole)
- abemaciclib in combination with a nonsteroidal aromatase inhibitor (anastrozole, letrozole)
- palbociclib in combination with a nonsteroidal aromatase inhibitor (anastrozole, letrozole)
- ribociclib in combination with fulvestrant
- abemaciclib in combination with fulvestrant
- palbociclib in combination with fulvestrant

Furthermore, the company did not differentiate by sex, i.e. it specified an identical ACT for women and men.

The company thus excluded the endocrine monotherapies and the combination of everolimus and exemestane as options for the ACT. As justification, the company stated in Module 3 A of the dossier that endocrine monotherapies were no longer recommended in current guidelines or were only recommended in individual cases [3-6] and no longer represented a standard

treatment for metastatic breast cancer. It added that there were no G-BA assessments for the monotherapies and thus a patient-relevant benefit had not been determined.

The company's reasoning for research question 1 (women) is not commented on further, as the company's deviation from the ACT was of no consequence. For the G-BA's ACT, no further relevant studies were identified in addition to the INAVO120 study presented by the company for comparison with palbociclib + fulvestrant (see Section I 3.1). Irrespective of this, in the given situation the company would have had the possibility to select an option from the various alternatives of the G-BA.

For research question 2 (men), the company argued that, firstly, it is recommended to switch the drug class in the case of endocrine resistance or prior treatment with an aromatase inhibitor, whereby fulvestrant should be used as the preferred combination partner with a cyclin-dependent kinase (CDK)4/6 inhibitor [5,7-9]. Secondly, according to the current guidelines, treatment for men is based on the recommendations for women [10-14].

In the therapeutic indication at hand, fulvestrant is only approved for women. Accordingly, the use of fulvestrant in the patient group of men represents off-label use. According to the G-BA's notes on the ACT, against the background of an overall poor body of evidence, it cannot be inferred from the guidelines that the off-label use of fulvestrant (+ GnRH analogue) would generally be preferable to the medicinal products previously approved for the patient group of men according to the generally recognized state of medical knowledge, however. The G-BA's view was accepted.

For research question 2 (men), the deviation from the G-BA's ACT resulted in the company assessing the INAVO120 study as relevant and presenting it for the assessment. However, the comparator therapy used in the study did not comply with the G-BA's specification. A relevant study versus the G-BA's ACT was not available (see Section I 4.1).

This assessment was conducted in comparison with the ACT specified by the G-BA.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) were used to derive the added benefit. This concurred with the company's inclusion criteria.

I 3 Research question 1: women with PIK3CA-mutated, ER-positive, HER2-negative, locally advanced or metastatic breast cancer

I 3.1 Information retrieval and study pool

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

Sources used by the company in the dossier:

- Study list on inavolisib (status: 15 May 2025)
- Bibliographical literature search on inavolisib (last search on 15 May 2025)
- Search of trial registries / trial results databases for studies on inavolisib (last search on 15 May 2025)
- Search on the G-BA website for inavolisib (last search on 15 May 2025)

To check the completeness of the study pool:

- Search of trial registries for studies on inavolisib (last search on 22 August 2025); for search strategies, see I Appendix A of the full dossier assessment

The search did not identify any additional relevant studies.

I 3.1.1 Studies included

The study presented in the following table was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: inavolisib + palbociclib + fulvestrant vs. ACT

Study	Study category			Available sources		
	Study for the marketing authorization of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication (yes/no [citation])
WO41554 (INAVO120[c])	Yes	Yes	No	Yes [15,16]	Yes [17,18]	Yes [19,20]

a. Study sponsored by the company.
b. Citation of the trial registry entries and, if available, of the reports on study design and/or results listed in the trial registries.
c. In the tables below, the study will be referred to using this acronym.

CSR: clinical study report; G-BA: Federal Joint Committee; RCT: randomized controlled trial

I 3.1.2 Study characteristics

Table 6 and Table 7 describe the study used for the benefit assessment.

Table 6: Characteristics of the study included – RCT, direct comparison: inavolisib + palbociclib + fulvestrant vs. placebo + palbociclib + fulvestrant (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
INAVO120	RCT, double-blind, parallel	Adult women[b] and men[c] (≥ 18 years) with PIK3CA-mutated[d], HR-positive[e], HER2-negative[f], locally advanced or metastatic breast cancer[g] ▪ with recurrence during or ≤ 12 months of completing adjuvant endocrine treatment ▪ ECOG PS ≤ 1	inavolisib + palbociclib + fulvestrant (N = 161) placebo + palbociclib + fulvestrant (N = 164)	Screening: up to 28 days Treatment: until disease progression, unacceptable toxicity, withdrawal of consent or end of study Follow-up[i]: outcome-specific, at most until death, lost to follow-up, withdrawal of consent or end of study	123 centres in Argentina, Australia, Belgium, Brazil, Canada, China, Denmark, France, Georgia, Germany, Greece, Hong Kong, Italy, Republic of Korea, Malaysia, New Zealand, Poland, Portugal, Russia, Singapore, Spain, Taiwan, Thailand, Turkey, Ukraine, Hungary, United Kingdom, United States 1/2020–ongoing Data cut-offs: 29 September 2023[j] 15 November 2024[k]	Primary: PFS Secondary: overall survival, morbidity, health-related quality of life, AEs

Table 6: Characteristics of the study included – RCT, direct comparison: inavolisib + palbociclib + fulvestrant vs. placebo + palbociclib + fulvestrant (multipage table)

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

a. Primary outcomes include information without taking into account the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b. Women were considered postmenopausal if they met at least one of the following criteria: age ≥ 60 years; age < 60 years and 12 months of amenorrhea plus follicle-stimulating hormone and plasma or serum oestradiol levels within postmenopausal range by local laboratory assessment in the absence of oral contraceptive pills, hormone replacement therapy, or gonadotropin-releasing hormone agonist or antagonist; documented bilateral oophorectomy (≥ 14 days prior to start of study treatment and recovery to baseline). Premenopausal/perimenopausal women must be treated with an LHRH agonist (e.g. goserelin or leuprolide) (beginning ≥ 2 weeks prior to start of treatment and continuing for the duration of study treatment).
c. Male patients are recommended LHRH agonist therapy (e.g. goserelin or leuprolide) (beginning ≥ 2 weeks prior to start of treatment and continuing for the duration of study treatment).
d. Tumours were tested for PIK3CA mutations using the F1LCDx assay from Foundation Medicine, Inc. Blood and tissue samples were tested in a central test laboratory if a local test was not possible.
e. Documented ER+ / PR+ tumour according to ASCO/CAP, defined as ≥ 1% of tumour cells stained positive based on the most recent tumour biopsy and assessed locally. A total of 6 patients (3 patients per study arm) with ER-/PR+ hormone receptor status were included in the study.
f. Documented HER2-negative tumour according to ASCO/CAP, defined as a HER2 IHC score of 0 or 1+, or an IHC score of 2+ accompanied by a negative fluorescence, chromogenic, or silver ISH test indicating the absence of HER2 gene amplification, or a HER2/CEP17 ratio of < 2.0 based on the most recent tumour biopsy and assessed locally.
g. The adenocarcinoma had to be histologically or cytologically confirmed and was not amenable to surgical or radiation therapy with curative intent.
h. If a CDK4/6 inhibitor was included as part of neoadjuvant or adjuvant therapy, the progression had to have occurred > 12 months since completion of CDK4/6 inhibitor therapy.
i. Outcome-specific information is provided in Table 8.
j. Prespecified primary analysis for PFS (planned after 194 PFS events) and interim analysis for overall survival.
k. Prespecified final analysis of overall survival (planned after 153 deaths).

AE: adverse event; ASCO: American Society of Clinical Oncology; CAP: College of American Pathologists; CDK: cyclin-dependent kinase; CEP17: chromosome enumeration probe 17; ECOG PS: Eastern Cooperative Oncology Group Performance Status; ER: oestrogen receptor; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; IHC: immunohistochemistry; ISH: in situ hybridization; LHRH: luteinizing hormone-releasing hormone; N: number of randomized (included) patients; PFS: progression-free survival; PIK3CA: gene for catalytic subunit (p110α) of PI3 kinase (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha); PR: progesterone receptor; RCT: randomised controlled trial

Table 7: Characteristics of the intervention – RCT, direct comparison: inavolisib + palbociclib + fulvestrant vs. placebo + palbociclib + fulvestrant (multipage table)

Study	Intervention	Comparison
INAVO120	inavolisib 9 mg once daily, orally + palbociclib 125 mg once daily, orally on Days 1 to 21 of a 28-day treatment cycle + fulvestrant 500 mg/day, IM on Days 1 and 15 of Cycle 1 and then on Day 1 of each subsequent 28-day treatment cycle	placebo once daily, orally + palbociclib 125 mg once daily, orally on Days 1 to 21 of a 28-day treatment cycle + fulvestrant 500 mg/day, IM on Days 1 and 15 of Cycle 1 and then on Day 1 of each subsequent 28-day treatment cycle
	Dose modifications Allowed ▪ Dose modification of individual components of the study medication independently of the others and at the investigator's discretion[a] ▪ Dose reductions/interruptions for AEs should be taken first with inavolisib unless clearly attributable to palbociclib ▫ Up to 2 dose reductions of inavolisib/placebo for AEs (step 1: 6 mg once daily, step 2: 3 mg once daily)[b] ▪ Dose reduction/interruption of palbociclib according to local marketing authorization (in case of grade ≥ 3 haematologic and non-haematologic toxicities known to be attributable to palbociclib) ▪ Interruption of any component of the study medication up to a maximum of 1 cycle (28 days)[c] Disallowed ▪ Dose reduction of fulvestrant	
	Prior treatment Required ▪ Adjuvant endocrine therapy with an aromatase inhibitor or tamoxifen Disallowed ▪ Systemic therapy for metastatic breast cancer ▪ Fulvestrant and other selective oestrogen receptor degrader[d] ▪ PI3K, AKT or mTOR inhibitors ▪ Chemotherapy, radiotherapy or any other anticancer therapy (≤ 2 weeks before randomization) ▪ Radiotherapy to ≥ 25% of bone marrow ▪ Haematopoietic stem cell or bone marrow transplantation ▪ Chronic corticosteroid therapy of ≥ 10 mg prednisone per day (or equivalent) or immunosuppressants for a chronic disease ▪ strong CYP3A4 inhibitors and inducers (≤ 1 week or 5 drug-elimination half-lives, whichever is longer, prior to initiation of study treatment) ▪ Major surgical procedures / significant traumatic injuries (≤ 28 days prior to initiation of study treatment), minor surgical procedures (≤ 7 days prior to initiation of study treatment)	

Table 7: Characteristics of the intervention – RCT, direct comparison: inavolisib + palbociclib + fulvestrant vs. placebo + palbociclib + fulvestrant (multipage table)

Study	Intervention	Comparison
	Concomitant treatment Required or recommended ▪ Premenopausal or perimenopausal women must receive concomitant treatment with an LHRH agonist (goserelin, leuprolide, triptorelin) beginning ≥ 2 weeks prior to start of study treatment ▪ For male patients, concomitant treatment with an LHRH agonist beginning ≥ 2 weeks prior to start of study treatment is recommended ▪ A compounded alcohol-free mouthwash of dexamethasone (0.5 mg in 5 mL) is recommended for prophylaxis or treatment of stomatitis/mucositis Allowed ▪ Supportive therapy at the discretion of the investigator and per local standard practice ▪ Antihyperglycaemic therapy (metformin) in patients with hyperglycaemia ▪ Bisphosphonates or denosumab for the treatment of bone metastases or osteoporosis/osteopenia Disallowed ▪ Any concomitant anticancer therapy (including chemotherapy, hormonal therapy, immunotherapy, biologic therapy, radiotherapy[e] or herbal preparations) ▪ Hormone replacement therapy, topical oestrogens, megestrol acetate and selective oestrogen receptor modulators ▪ Quinidine or other antiarrhythmics ▪ Radiotherapy for progressive disease[f] ▪ Primary prophylactic use of haematopoietic growth factors ▪ Strong CYP3A4 inhibitors and inducers	

a. For toxicities attributed to the combination of all 3 drugs, initially dose reduction of one drug (i.e. inavolisib or palbociclib), then dose reduction of the other drug in case of persisting toxicity. Further dose reductions are permitted.
b. If certain drug-related AEs continue to occur after 2 dose reductions, inavolisib/placebo should be discontinued. If AEs grade 4 (not life-threatening) occur, dose re-escalation to the starting dose or to a reduced dose is possible. If life-threatening grade 4 AEs occur, treatment with inavolisib/placebo should be permanently discontinued.
c. If the study treatment is interrupted for > 28 days (beyond one treatment cycle), the study treatment should be discontinued.
d. Except in the neoadjuvant setting with a treatment duration ≤ 6 months.
e. Except for the treatment of brain metastases and for the treatment of local symptoms (e.g. impending fractures); for more details, see the text on study design.
f. Palliative radiotherapy for the treatment of new brain metastases with systemic treatment response is allowed. Other local radiotherapy is not permitted, except in circumstances requiring local radiotherapy in which the investigator does not believe that the symptoms are a result of disease progression. In addition, the radiation field does not encompass any lesions.

AE: adverse event; AKT: protein kinase B; CYP: cytochrome P450; IM: intramuscular; LHRH: luteinizing hormone-releasing hormone; mTOR: mammalian target of rapamycin; PI3K: phosphatidylinositol-4,5-bisphosphate 3-kinase; RCT: randomized controlled trial

Study design

INAVO120 is a double-blind RCT comparing the drug combination inavolisib + palbociclib + fulvestrant with placebo + palbociclib + fulvestrant in adult patients with PIK3CA-mutated hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer. Patients must have had a recurrence during adjuvant endocrine treatment or within 12 months of completing this treatment. If a CDK4/6 inhibitor was included as part of neoadjuvant or adjuvant therapy, the progression had to have occurred > 12 months since completion of CDK4/6 inhibitor therapy, however. Patients with type 1 diabetes mellitus and patients with type 2 diabetes mellitus requiring ongoing systemic treatment at the time of study entry were excluded from the study.

A total of 325 patients were enrolled in the study and randomized in a 1:1 ratio to receive either inavolisib + palbociclib + fulvestrant (N = 161) or placebo + palbociclib + fulvestrant (N = 164). Randomization was stratified according to the presence of visceral disease (yes versus no), endocrine resistance (primary versus secondary) and region (North America / Western Europe versus Asia versus other). Only patients with an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1 were included.

Inavolisib is only authorized for patients with ER-positive breast cancer. However, patients with ER-negative, progesterone receptor (PR)-positive breast cancer could also be included in the study. However, only 3 patients with the hormone receptor status ER-/PR+ were included per study arm (see Table 9), so that this deviation from the approval population had no consequences for the benefit assessment.

Only 6 men were included in the study. It was therefore possible to use the total population of the study to address research question 1 (women). In principle, subgroup analyses by sex would have been available as well. The analyses of the total population were used in this situation because it was assumed that the small number of men included did not have a relevant effect on the certainty of conclusions of the analyses for women. In addition, the total population was the basis for the subgroup analyses. Furthermore, a stratified analysis was available for the total population for the outcome overall survival, which corresponded to the prespecified analysis for this outcome. The benefit assessment for research question 1 was therefore based on the total population of the INAVO120 study.

Treatment in both arms was conducted in compliance with the current summaries of product characteristics (SmPCs) [21-23]. Treatment was to be continued until disease progression, unacceptable toxicity or patient withdrawal of consent. It was not allowed to switch from the comparator therapy to treatment with inavolisib + palbociclib + fulvestrant until the final data cut-off.

In the given situation, local radiotherapies play a role in the palliative treatment of bone metastases, for example. According to the study protocol, radiotherapy for the treatment of disease progression was generally not permitted. However, local radiotherapy was allowed under certain circumstances, e.g. to prevent impending bone fractures. In this context, lesions intended to determine disease progression were to be avoided as far as possible. If this was not possible, a tumour assessment was to be conducted before radiotherapy, as the lesions in question would then become unsuitable for determining progression from the time of radiotherapy. Against the background of the protocol specifications, the question arose as to whether local radiotherapies were sufficiently available to patients when required, despite the general ban. Overall, however, it was assumed that the defined exceptions allowed adequate use of radiotherapy.

The primary outcome of the study was progression-free survival (PFS), assessed by the investigator using Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 criteria. Further outcomes were recorded in the categories of morbidity, health-related quality of life and side effects.

Data cut-offs

The INAVO120 study was still ongoing at the time of the benefit assessment. Two data cuts were already available:

- First data cut-off (29 September 2023)

  Prespecified primary analysis for PFS (planned after 194 events in the total population) and interim analysis for overall survival

- Second data cut-off (15 November 2024)

  Prespecified final analysis of overall survival (planned after 153 deaths in the total population)

In Module 4 A, the company presented results from the 2nd data cut to derive the added benefit for all outcomes. In addition, the company presented results on PFS and overall survival for the 1st data cut. The results of the current 2nd data cut from 15 November 2024 were used for this benefit assessment.

Planned duration of follow-up

Table 8 shows the planned duration of patient follow-up for the individual outcomes.

Table 8: Planned duration of follow-up – RCT, direct comparison: inavolisib + palbociclib + fulvestrant vs. placebo + palbociclib + fulvestrant

Study **Outcome category** **Outcome**	**Planned follow-up**
INAVO120	
Mortality	
Overall survival	Until death, lost to follow-up, withdrawal of consent or end of study (whichever occurred first)
Morbidity	
Skeletal-related events	ND
Symptoms (EORTC QLQ-C30, EORTC QLQ-BR23) Worst pain (BPI-SF Item 3)[a] Health status (EQ-5D VAS)	Up to 3 months after disease progression or until the start of subsequent therapy[b], end of study or death (whichever occurred first)
Health-related quality of life	
(EORTC QLQ-C30, EORTC QLQ-BR23)	Up to 3 months after disease progression or until the start of subsequent therapy[b], end of study or death (whichever occurred first)
Side effects	
AEs / SAEs / severe AEs[c]	Up to 30 days after discontinuation of study medication or until initiation of another antitumour treatment (whichever occurred first)[d, e]
PRO-CTCAE	Up to 3 months after disease progression or until the start of subsequent therapy[b], end of study or death (whichever occurred first)

a. No information provided by the company in Module 4; according to the study documents, the BPI-SF is also recorded up to 3 months after progression.
b. In the event of treatment discontinuation for reasons other than disease progression, the recording of patient-reported outcomes was continued until disease progression or the start of subsequent therapy.
c. Operationalized as CTCAE grade ≥ 3.
d. Patients on antihyperglycaemic agents for the treatment of hyperglycaemia during the study treatment period and those patients with events of hyperglycaemia in the 30-day follow-up were observed up to a maximum of 3 months after discontinuation of the study treatment, regardless of the start of a new antitumour treatment.
e. SAEs suspected to be related to the study medication were followed up beyond this period.

AE: adverse event; BPI-SF: Brief Pain Inventory-Short Form; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; ND: no data; PRO-CTCAE: Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; QLQ-BR23: Quality of Life Questionnaire-Breast Cancer 23; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

The observation periods for the outcomes in the categories of morbidity, health-related quality of life and side effects were systematically shortened because they were only recorded up to 3 months after disease progression or for the period of treatment with the study medication (plus 30 days). However, to draw a reliable conclusion on the total study period or

the time to patient death, it would also be necessary to record these outcomes for the total period, as was done for survival.

Patient characteristics at baseline

Table 9 shows the patient characteristics of the included study.

Table 9: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: inavolisib + palbociclib + fulvestrant vs. placebo + palbociclib + fulvestrant (multipage table)

Study **Characteristic** **Category**	**inavolisib + palbociclib + fulvestrant** **N[a] = 161**	**placebo + palbociclib + fulvestrant** **N[a] = 164**
INAVO120		
Age [years], mean (SD)	54 (11)	54 (11)
Age groups, n (%)		
< 65	136 (84)	130 (79)
≥ 65	25 (16)	34 (21)
Sex [F/M], %	97/3	> 99/< 1
Geographic region (IxRS), n (%)		
Asia	58 (36)	62 (38)
North America / Western Europe	62 (39)	63 (38)
Other	41 (25)	39 (24)
ECOG status at baseline		
0	100 (62)	106 (65)
1	60 (37)	58 (35)
Missing	1 (< 1)	0 (0)
Postmenopausal status at randomization, n (%)		
Not postmenopausal	52 (32)	52 (32)
Postmenopausal	104 (65)	111 (68)
Missing[b]	5 (3)	1 (< 1)
Visceral disease (eCRF), n (%)		
No	29 (18)	36 (22)
Yes	132 (82)	128 (78)
Disease status at baseline, n (%)		
Locally advanced	1 (< 1)	2 (1)
Metastatic	160 (> 99)	162 (99)
Bone metastases, n (%)		
No	53 (33)	70 (43)
Yes	108 (67)	94 (57)

Table 9: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: inavolisib + palbociclib + fulvestrant vs. placebo + palbociclib + fulvestrant (multipage table)

Study Characteristic Category	**inavolisib + palbociclib + fulvestrant N[a] = 161**	**placebo + palbociclib + fulvestrant N[a] = 164**
Hormone receptor status, n (%)		
ER+/PR+	113 (70)	113 (69)
ER+/PR-	45 (28)	45 (27)
Other[c]	3 (2)	6 (4)
Disease duration: time between first diagnosis and randomization [months[d]], median [min; max]	49.7 [5.8; 339.0]	47.0 [1.3; 197.3]
Prior (neo)adjuvant chemotherapy, n (%)		
No	29 (18)	27 (16)
Yes	132 (82)	137 (84)
Prior (neo)adjuvant therapy with CDK4/6 inhibitor, n (%)		
No	159 (99)	163 (> 99)
Yes	2 (1)	1 (< 1)
Prior (neo)adjuvant endocrine therapy, n (%)		
Unclear	1 (< 1)	1 (< 1)
Yes	160 (> 99)	163 (> 99)
Treatment discontinuation (all components), n (%)[e]	111 (69)	144 (88)
Disease progression	85 (53)	129 (79)
AE	8 (5)	1 (< 1)
Patient request	4 (2)	4 (2)
Death	7 (4)	4 (2)
inavolisib/placebo	111 (69)	144 (88)
Disease progression	86 (53)	130 (79)
AE	9 (6)	1 (< 1)
Patient request	5 (3)	4 (2)
Death	6 (4)	3 (2)
palbociclib	113 (70)	144 (88)
Disease progression	87 (54)	130 (79)
AE	10 (6)	0 (0)
Patient request	5 (3)	5 (3)
Death	5 (3)	3 (2)

Table 9: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: inavolisib + palbociclib + fulvestrant vs. placebo + palbociclib + fulvestrant (multipage table)

Study Characteristic Category	**inavolisib + palbociclib + fulvestrant N[a] = 161**	**placebo + palbociclib + fulvestrant N[a] = 164**
fulvestrant	111 (69)	144 (88)
Disease progression	89 (55)	130 (79)
AE	6 (4)	0 (0)
Patient request	5 (3)	5 (3)
Death	5 (3)	3 (2)
Study discontinuation, n (%)[f]	86 (53)	99 (60)

a. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. Male patients.
c. A total of 6 patients (3 patients per study arm) with ER-/PR+ hormone receptor status.
d. Institute's calculation from data in days (days x 12 / 365.25).
e. 1 vs. 0 of the randomized patients never started treatment.
f. Frequent reasons for study discontinuation in the intervention arm vs. the control arm (percentages refer to randomized patients): patient request (4% vs. 9%), lost to follow-up (2% vs. 3%). The data additionally include patients who died during the course of the study (intervention arm: 44% vs. control arm: 48%).

AE: adverse event; CDK: cyclin-dependent kinase; ECOG: Eastern Cooperative Oncology Group; eCRF: electronic case report form; ER: oestrogen receptor; F: female; IxRS: interactive voice/web response system; M: male; n: number of patients in the category; N: number of randomized patients; PR: progesterone receptor; RCT: randomized controlled trial; SD: standard deviation

The patient characteristics were largely comparable between the treatment arms. The study population consisted almost entirely of women. In total, only 6 men were included (5 in the intervention arm and 1 in the comparator arm). More than 80% of the study population were under 65 years of age. Just over a third of patients were from Asia and a similar number from North America / Western Europe. Over 60% of the women in the study were postmenopausal. All but 3 patients had metastatic disease at baseline, with just over 60% having bone metastases and 80% having visceral disease. The hormone receptor status was ER-positive in 97%.

Almost all patients had already received adjuvant or neoadjuvant endocrine therapy, with CDK4/6 inhibitors being used in only 3 cases. Over 80% had also received adjuvant or neoadjuvant chemotherapy.

The proportion of patients with premature treatment discontinuation (any component) differed between the treatment arms by around 20 percentage points (69% versus 88%). In most cases, all drugs were discontinued, but it was not clear whether discontinuation was

simultaneous or sequential. The most common reason for discontinuing treatment was disease progression (53% to 55% versus 79% of patients).

Treatment duration and outcome-specific observation period

Table 10 shows the patients' mean/median treatment durations and the mean/median observation periods for individual outcomes.

Table 10: Information on the course of the study – RCT, direct comparison: inavolisib + palbociclib + fulvestrant vs. placebo + palbociclib + fulvestrant (multipage table)

Study **Duration of the study phase** **Outcome category/outcome**	**inavolisib + palbociclib + fulvestrant** **N = 161**	**placebo + palbociclib + fulvestrant** **N = 164**
INAVO120		
Treatment duration [months]		
inavolisib/placebo		
Median [Q1; Q3]	13.1 [7.3; 25.9]	7.5 [3.2; 14.8]
Mean (SD)	16.8 (13.1)	10.9 (10.7)
palbociclib		
Median [Q1; Q3]	13.8 [7.1; 25.8]	7.2 [3.2; 14.7]
Mean (SD)	16.8 (12.9)	10.8 (10.7)
fulvestrant		
Median [Q1; Q3]	14.1 [7.4; 26.3]	7.5 [3.6; 14.9]
Mean (SD)	17.4 (13.0)	11.0 (10.7)
Observation period [months]		
Overall survival[a]		
Median [Q1; Q3]	34.2 [22.6; 42.4]	32.3 [20.6; 40.0]
Mean (SD)	ND	ND
Morbidity (skeletal-related events, EORTC QLQ-C30, EORTC QLQ-BR23, BPI-SF Item 3, EQ-5D VAS)		
Median [min; max]	ND	ND
Mean (SD)	ND	ND
Health-related quality of life (EORTC QLQ-C30, EORTC QLQ-BR23)		
Median [min; max]	ND	ND
Mean (SD)	ND	ND
Side effects		
AEs / SAEs / severe AEs[b, c]		
Median [min; max]	14.5 [0.1; 52.3]	8.1 [0.1; 53.9]
Mean (SD)	17.8 [12.9]	11.5 [10.6]
PRO-CTCAE		
Median [min; max]	ND	ND
Mean (SD)	ND	ND

Table 10: Information on the course of the study – RCT, direct comparison: inavolisib + palbociclib + fulvestrant vs. placebo + palbociclib + fulvestrant (multipage table)

Study **Duration of the study phase** **Outcome category/outcome**	**inavolisib + palbociclib + fulvestrant** **N = 161**	**placebo + palbociclib + fulvestrant** **N = 164**
a. No information is available on how the median observation period (as well as Q1 and Q3) was calculated. The company only states that the individual observation period is defined as the time from randomization to death or to the last timepoint for which the patient was known to be alive, whichever occurred first. b. The data on side effects are based on 161 vs. 163 patients. No information is available on how the median observation period (as well as Q1 and Q3) was calculated. The company only states that the observation period is defined as the time from the first dose of the study medication to the data cut-off, to 30 days after the last dose of the study medication, to withdrawal of consent, to initiation of subsequent therapy or to death, whichever occurred first. c. Patients on antihyperglycaemic agents for the treatment of hyperglycaemia during the study treatment period and those patients with events of hyperglycaemia in the 30-day follow-up were observed up to a maximum of 3 months after discontinuation of the study treatment, regardless of the start of a new antitumour treatment. AE: adverse event; BPI-SF: Brief Pain Inventory-Short Form; EORTC: European Organisation for Research and Treatment of Cancer; max: maximum; min: minimum; N: number of analysed patients; ND: no data; PRO-CTCAE: Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; QLQ-BR23: Quality of Life Questionnaire-Breast Cancer 23; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale		

The company did not provide information on the observation period for all patient-relevant outcomes of the INAVO120 study. It was missing for all patient-reported outcomes on morbidity and health-related quality of life. However, as the recording of these outcomes ended no later than 3 months after disease progression, important differences between the treatment arms were assumed: According to the information in Module 4 A of the dossier, the median time to disease progression or death at the 2nd data cut was 17.2 months versus 7.3 months. The same applied to the observation periods for the side effect outcomes that were recorded up to 30 days after the end of treatment (see Table 8).

Subsequent therapies after discontinuation of the study medication

Table 11 shows the subsequent therapies patients received after discontinuing the study medication. The data refer to the first subsequent therapy after discontinuation of the study medication (second line).

Table 11: Information on subsequent antineoplastic therapies in second-line treatment – RCT, direct comparison: inavolisib + palbociclib + fulvestrant vs. placebo + palbociclib + fulvestrant (multipage table)

Study **Drug class** **Drug**	**Patients with subsequent therapy, n (%)**	
	inavolisib + palbociclib + fulvestrant **N = 161**	**Placebo + palbociclib + fulvestrant** **N = 164**
INAVO120		
Total	83 (51.6)	109 (66.5)
Chemotherapy	46 (55.4)[a]	79 (72.5)[a]
capecitabine	26 (31.3)	37 (33.9)
paclitaxel	12 (14.5)	20 (18.3)
doxorubicin	2 (2.4)	4 (3.7)
carboplatin	2 (2.4)	4 (3.7)
gemcitabine	3 (3.6)	8 (7.3)
eribulin	1 (1.2)	6 (5.5)
vinorelbine	1 (1.2)	3 (2.8)
Anti-hormonal therapy	26 (31.3)	31 (28.4)
aromatase inhibitor	16 (19.3)	20 (18.3)
selective oestrogen-receptor degrader	10 (12.0)	10 (9.2)
LHRH agonist	3 (3.6)	2 (1.8)
tamoxifen	1 (1.2)	1 (0.9)
Antibody-drug conjugate	1 (1.2)	1 (0.9)
trastuzumab deruxtecan	0 (0)	1 (0.9)
DB 1303	1 (1.2)	0 (0)
Cyclin-dependent kinase inhibitor	8 (9.6)	5 (4.6)
abemaciclib	2 (2.4)	0 (0)
ribociclib	1 (1.2)	5 (4.6)
palbociclib	5 (6.0)	0 (0)
mTOR inhibitor	8 (9.6)	10 (9.2)
everolimus	8 (9.6)	10 (9.2)
PI3K inhibitor	5 (6.0)	11 (10.1)
alpelisib	5 (6.0)	9 (8.3)
LOXO-783	0 (0)	1 (0.9)
RLY 2608	0 (0)	1 (0.9)
PARP inhibitor	2 (2.4)	2 (1.8)
olaparib	2 (2.4)	2 (1.8)
Antineovascular agent	3 (3.6)	6 (5.5)
bevacizumab	2 (2.4)	6 (5.5)
rivoceranib	1 (1.2)	0 (0)

Table 11: Information on subsequent antineoplastic therapies in second-line treatment – RCT, direct comparison: inavolisib + palbociclib + fulvestrant vs. placebo + palbociclib + fulvestrant (multipage table)

Study	**Patients with subsequent therapy, n (%)**	
Drug class **Drug**	**inavolisib + palbociclib + fulvestrant** **N = 161**	**Placebo + palbociclib + fulvestrant** **N = 164**
Immunotherapy	2 (2.4)	3 (2.8)
pembrolizumab	1 (1.2)	3 (2.8)
nivolumab	1 (1.2)	0 (0)
Other	6 (7.2)	3 (2.8)
methotrexate	1 (1.2)	0 (0)
unspecified herbal and traditional drugs	4 (4.8)	2 (1.8)
megestrol acetate	1 (1.2)	0 (0)
chidamide	0 (0)	1 (0.9)

a. All percentages provided below are based on the number of patients with subsequent therapy.

LHRH: luteinizing hormone-releasing hormone; mTOR: mammalian target of rapamycin; n: number of patients with subsequent therapy; N: number of analysed patients; PARP: Poly-adenosine diphosphate-ribose-polymerase; PI3K: phosphatidylinositol-3-kinase; RCT: randomized controlled trial

In the INAVO120 study, subsequent antineoplastic therapies were permitted without restrictions in both study arms. In the intervention arm, 83 (51.6%) of the patients received subsequent therapy, compared with 109 (66.5%) in the comparator arm. It was assumed that the majority of patients with disease progression (90 versus 133) received subsequent systemic therapy. Patients in INAVO120 had already been treated with adjuvant endocrine therapy and received both a CDK4/6 inhibitor and fulvestrant in the first line in both study arms. Guidelines do not provide a uniform recommendation on subsequent therapies. Depending on the previous treatment, alpelisib, trastuzumab deruxtecan and other endocrine therapies or chemotherapies with a range of different drugs may be considered [7,11,12]. No precise details are given as to the cases in which chemotherapy is preferable versus endocrine therapy. The ESMO guideline [24] recommends chemotherapy in particular if there is a risk of imminent organ failure and progression after several lines of endocrine therapy.

In INAVO120, the most common subsequent therapies in second line were chemotherapies, although these were administered less frequently in the intervention arm than in the comparator arm (55.4% versus 72.5% of all patients with subsequent therapy). The most frequently used drugs were capecitabine (31.3% versus 33.9%) and paclitaxel (14.5% versus 18.3%). Other chemotherapeutic agents were only used in individual cases. Apart from chemotherapies, antihormonal therapies (31.3% versus 28.4%), in particular aromatase inhibitors and selective oestrogen receptor degraders, were the most common drug groups in

second-line treatment. Other drugs such as CDK4/6 inhibitors, targeted therapies and immunotherapies were only used as subsequent therapy in individual cases.

According to the patient characteristics in Module 4 A of the dossier, aromatase inhibitors were used as adjuvant therapy in around 40% of patients, tamoxifen in just under 50% and a combination of both in 11%. It was therefore understandable that aromatase inhibitors were used in 19% of patients with second-line therapy.

The PIK3CA inhibitor alpelisib was given to 6.0% and 8.3% of all patients with subsequent therapy in the INAVO120 study . According to current guidelines, alpelisib is generally an option in the second line for patients with a PIK3CA mutation, but as one of several treatment options [12,24,25]. The current ESMO guideline points out that, due to its toxicity, the use of alpelisib must be carefully considered based on prior treatment and comorbidities [24]. The benefit assessment procedure for alpelisib determined a lesser benefit of the combination of alpelisib + fulvestrant versus fulvestrant in women with disease progression following endocrine therapy in the advanced stage [26,27]. In view of this, alpelisib was not assumed to be a suitable subsequent therapy for a substantially higher proportion of patients. Regardless of this, alpelisib has not been available in Germany since 2021.

According to the current guideline of the Gynaecological Oncology Group (AGO) on endocrine-based and targeted therapy for metastatic breast cancer, trastuzumab deruxtecan is a treatment option for patients with breast cancer with HER2-low or HER2-ultralow status who have received endocrine therapy in the metastatic setting and for whom endocrine therapy is not an option as the next line of treatment [25,28]. The DESTINY-Breast06 study [29] provided evidence for trastuzumab deruxtecan after endocrine therapy in combination with a CDK4/6 inhibitor, showing advantages in terms of overall survival compared with capecitabine, paclitaxel or nab-paclitaxel (as chosen by the physician) [30]. However, only a few patients in the study had been pretreated with a combination of endocrine therapies and CDK4/6 inhibitors in the first line setting. The INAVO120 study included these patients. However, it was unclear how high the proportion of patients with HER2-low and HER2-ultralow breast cancer was in the INAVO120 study and for how many patients endocrine therapy in the second line was no longer an option. In the INAVO120 study, one patient received trastuzumab deruxtecan as subsequent therapy in the second-line setting. Overall, trastuzumab deruxtecan was assumed to be a suitable subsequent therapy for a higher proportion of patients in both study arms of INAVO120. The number of patients for whom this was the case was unclear, however.

Overall, it was assumed that most patients in INAVO120 received guideline-compliant subsequent therapy.

Risk of bias across outcomes (study level)

Table 12 shows the risk of bias across outcomes (risk of bias at study level).

Table 12: Risk of bias across outcomes (study level) – RCT, direct comparison: inavolisib + palbociclib + fulvestrant vs. placebo + palbociclib + fulvestrant

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	Absence of other aspects	Risk of bias at study level
			Patients	Treating staff			
INAVO120	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes was rated as low for INAVO120.

Transferability of the study results to the German health care context

The company discussed the transferability of the study results to the German health care context based on the patient characteristics of age, family origin, menopausal status, ECOG PS and visceral disease in the INAVO120 study, compared with the German health care context.

It summarized that the INAVO120 study population was sufficiently comparable to the German health care context of patients with PIK3CA-mutated hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer, following recurrence during or within 12 months of completing adjuvant endocrine treatment, with regard to general patient characteristics such as sex, age, ethnicity and menopausal status as well as disease-specific criteria such as ECOG status and metastasis. According to the company, the marginal deviations were due to the selection of a high-risk cohort, which was studied in INAVO120.

The company did not provide any further information on the transferability of the study results to the German health care context.

I 3.2 Results on added benefit

I 3.2.1 Outcomes included

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

- Mortality
  - Overall survival
- Morbidity

- Symptomatic skeletal-related events
- Symptoms, recorded using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) and Quality of Life Questionnaire-Breast Cancer 23 (EORTC QLQ-BR23) (symptom scales)
- Worst pain, recorded using the Brief Pain Inventory-Short Form (BPI-SF) Item 3
- Health status, recorded using the EQ-5D visual analogue scale (VAS)

- Health-related quality of life
  - EORTC QLQ-C30 and EORTC QLQ-BR23 (functional scales)
- Side effects
  - Serious adverse events (SAEs)
  - Severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)
  - Discontinuation due to AEs
  - Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE)
  - Stomatitis (Preferred Term [PT], AEs)
  - Hyperglycaemia (PT, severe AEs)
  - Other specific AEs, if any

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

Table 13 shows for which outcomes data were available in the included study.

Table 13: Matrix of outcomes – RCT, direct comparison: inavolisib + palbociclib + fulvestrant vs. placebo + palbociclib + fulvestrant

Study	Outcomes												
	Overall survival	Symptomatic skeletal-related events	Symptoms (EORTC QLQ-C30, EORTC QLQ-BR23)	Worst pain (BPI-SF Item 3)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30, EORTC QLQ-BR23)	SAEs	Severe AEs[a]	Discontinuation due to AEs	PRO-CTCAE	Stomatitis (PT, AEs)	Hyperglycaemia (PT, severe AEs[a])	Further specific AEs[a, b]
INAVO120	Yes	No[c]	No[c]	No[c]	No[c]	No[c]	Yes	Yes	Yes	No[c]	Yes	Yes	Yes

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. The following events are considered (MedDRA coding): decreased appetite (PT, AEs), noninfective diarrhoea (SMQ, AEs), platelet count decreased (PT, severe AEs), metabolism and nutrition disorders (SOC, severe AEs), gastrointestinal disorders (SOC, severe AEs).
c. No suitable data available; see section 'Notes on individual patient-relevant outcomes' for reasons.

AE: adverse event; BPI-SF: Brief Pain Inventory-Short Form; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; MedDRA: Medical Dictionary for Regulatory Activities; PRO-CTCAE: Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; PT: Preferred Term; QLQ-BR23: Quality of Life Questionnaire-Breast Cancer Module 23; QLQ-C30: Quality of Life Questionnaire-Core 30; SAE: serious adverse event; SMQ: Standardized MedDRA Query; SOC: System Organ Class; VAS: visual analogue scale

Notes on individual patient-relevant outcomes

Symptomatic skeletal-related events

The outcome skeletal-related events of the INAVO120 study is a composite outcome with the following individual components:

- Pathological fracture
- Radiation therapy to bone
- Cancer-related surgery to bone
- Spinal cord compression

In principle, the outcome symptomatic skeletal-related events was relevant for the benefit assessment. However, the company's dossier lacked information on the occurrence of the individual subcomponents in the INAVO120 study. This information would be necessary to assess the results of this outcome, for example to draw conclusions about the direction of effect of the subcomponents.

Furthermore, it was unclear from the available information whether the given operationalization actually represented symptomatic skeletal-related events. For example, the description of the operationalization did not include information as to whether all pathological fractures were symptomatic.

Furthermore, according to the specifications of the study protocol, the use of local radiotherapy was subject to certain conditions or additional consultations. For example, the study protocol stated that further reasons for avoiding local radiotherapy included the difficulty in distinguishing new symptomatic pain or worsening of lytic bone lesions from disease progression. In certain constellations, patients with palliative radiotherapy therefore had to be censored for the outcome skeletal-related events. Ultimately, it remained unclear from these specifications whether all relevant events were included in the analysis.

Due to the uncertainties described, the results on the outcome skeletal-related events were not used for this benefit assessment.

Patient-reported outcomes on morbidity and health-related quality of life

Results on patient-reported outcomes not usable

For the patient-reported outcomes (symptoms and health-related quality of life, [each recorded using the EORTC QLQ-C30 and EORTC QLQ-BR23]; health status [EQ-5D VAS]; worst pain [BPI-SF Item 3]), the company presented both responder analyses for the time to first deterioration and analyses of the change from baseline (mixed-effects model with repeated measures [MMRM] analyses). The outcomes were to be recorded at the beginning of predefined treatment cycles. The results on the patient-reported outcomes in the categories morbidity and health-related quality of life were not used for the benefit assessment, as the response rates were too low at an early stage and showed large differences between the treatment arms. The response rates for the EORTC QLQ-C30, the EQ-5D VAS and the BPI-SF were only above 80% in the first 2 follow-up recordings, i.e. up to 2 months after baseline. From the 3rd follow-up recording after baseline (Month 5), the response rates showed large differences between the study arms and fell below 70% in the comparator arm. For the EORTC QLQ-BR23, this applied from the 1st follow-up recording, which took place in Month 5 after randomization, due to the lower frequency of recording. This was also seen in the Kaplan-Meier curves (time to first deterioration) presented by the company in Module 4 A. In the comparator arm in particular, censoring occurred to a major extent in the first 3 months. Overall, the analyses of the patient-reported outcomes were not usable in the given data situation.

Worst pain (BPI-SF Item 3)

In Module 4 A of the dossier, the company did not present any results for the outcome worst pain, recorded with the BPI-SF Item 3. It justified this by stating that the instrument had been

recorded with an incorrect time reference: 7 days instead of 24 hours, which is described in the BPI-SF user guide. However, this item is also included in the more extensive long form of the BPI, for which the user guide specifies a recall period of 7 days [31,32]. Therefore, the different time reference alone would not be a reason to exclude the data. However, as described above, the data were not usable.

Outcomes on side effects

PRO-CTCAE

As per the study protocol, side effects were also recorded with the PRO-CTCAE instrument in INAVO120. Overall, the PRO-CTCAE system is a valuable addition to the usual recording and analysis of AEs. The system comprises a total of 78 symptomatic AEs of the CTCAE system, which are compiled into a questionnaire adapted to the respective study situation. The selection process is to be planned a priori and carried out transparently. The selection of the individual symptomatic AEs must be transparent, e.g. the recording of all important potential side effects of the drugs in the intervention and the control arm. For a comprehensive description of the PRO-CTCAE system, see the corresponding explanations in benefit assessment A20-87 [33]. According to the study protocol, 7 symptomatic AEs from the PRO-CTCAE system were to be recorded in the INAVO120:

- Diarrhoea
- Nausea
- Vomiting
- Decreased appetite
- Fatigue
- Mouth sores
- Rash

An additional item regarding the overall burden of side effects was also recorded. Occurrence, frequency, severity and/or extent of interference with daily function were recorded for the symptomatic AEs.

The company presented no information on the PRO-CTCAE in Module 4 A. In the study protocol, the selection of these 7 AEs was justified by the fact that they were prominent symptoms for treatment with inavolisib, palbociclib and fulvestrant. The company did not provide more detailed information on its approach, e.g. on the search or the type of documents reviewed. Approaches to selecting the items are described by Tolstrup [34] or Taarnhøj [35] (see also A20-87 [33]). Overall, it was not clear which criteria were used to select

the items, nor whether the side effects of inavolisib, palbociclib or fulvestrant were adequately reflected.

Overall, the outcome of PRO-CTCAE was not used for the benefit assessment due to the untransparent selection process and the inexplicable selection of items for depicting the symptomatic AEs of inavolisib, palbociclib and fulvestrant.

Other side effect outcomes

No information was available on the effect estimation of the time-to-event analyses for side effect outcomes with 0 events in one study arm. One way to obtain point and interval estimates from a time-to-event analysis in such situations is to use the Firth correction to the Cox model [36-39] in combination with profile likelihood methods for the 95% confidence intervals.

I 3.2.2 Risk of bias

Table 14 describes the risk of bias for the results of the relevant outcomes.

Table 14: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: inavolisib + palbociclib + fulvestrant

Study		Outcomes												
	Study level	Overall survival	Symptomatic skeletal-related events	Symptoms (EORTC QLQ-C30, EORTC QLQ-BR23)	Worst pain (BPI-SF Item 3)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30, EORTC QLQ-BR23)	SAEs	Severe AEs[a]	Discontinuation due to AEs	PRO-CTCAE	Stomatitis (PT, AEs)	Hyperglycaemia (PT, severe AEs[a])	Further specific AEs[a, b]
INAVO120	L	L	–[c]	–[c]	–[c]	–[c]	–[c]	H[d]	H[d]	L[e]	–[c]	H[d]	H[d]	H[d]

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. The following events are considered (MedDRA coding): decreased appetite (PT, AEs), noninfective diarrhoea (SMQ, AEs), platelet count decreased (PT, severe AEs), metabolism and nutrition disorders (SOC, severe AEs), gastrointestinal disorders (SOC, severe AEs).
c. No suitable data available; for reasoning, see Section I 3.2.1 of this dossier assessment.
d. Incomplete observations for potentially informative reasons.
e. Despite a low risk of bias, the certainty of results for the outcome of discontinuation due to AEs is assumed to be limited (see text section below).

AE: adverse event; BPI-SF: Brief Pain Inventory-Short Form; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; H: high; L: low; MedDRA: Medical Dictionary for Regulatory Activities; PRO-CTCAE: Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; PT: Preferred Term; QLQ-BR23: Quality of Life Questionnaire-Breast Cancer Module 23; QLQ-C30: Quality of Life Questionnaire-Core 30; SAE: serious adverse event; SMQ: Standardized MedDRA Query; SOC: System Organ Class; VAS: visual analogue scale

The risk of bias of the result for the outcome overall survival was rated as low.

Due to incomplete observations for potentially informative reasons, the risks of bias for the results of the outcomes in the side effects category were assessed as high, with the exception of discontinuation due to AEs. The planned follow-up period after the end of treatment was 30 days for these outcomes. The observation period was thus determined by the reasons for treatment discontinuation (largely by disease progression), which clearly differed between the treatment arms (see Table 9). Due to a possible association between disease progression and these outcomes, incomplete observations for potentially informative reasons were present.

Although the risk of bias for the outcome discontinuation due to AEs was low, the certainty of results for this outcome was limited. Premature treatment discontinuation for reasons other than AEs is a competing event for the outcome discontinuation due to AEs to be recorded. This means that, although AEs that would have led to discontinuation of therapy may occur after discontinuation for other reasons, the criterion discontinuation is no longer applicable to them. It was impossible to estimate how many AEs this affected.

I 3.2.3 Results

Table 15 summarizes the results for the comparison of inavolisib + palbociclib + fulvestrant versus placebo + palbociclib + fulvestrant in women with PIK3CA-mutated, ER-positive, HER2-negative, locally advanced or metastatic breast cancer. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

Kaplan-Meier curves on all outcomes can be found in I Appendix B of the full dossier assessment. Common AEs in INAVO120 are listed in I Appendix C of the full dossier assessment.

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: inavolisib + palbociclib + fulvestrant vs. placebo + palbociclib + fulvestrant (multipage table)

Study **Outcome category** **Outcome**	**inavolisib + palbociclib + fulvestrant**		**placebo + palbociclib + fulvestrant**		**inavolisib + palbociclib + fulvestrant vs. placebo + palbociclib + fulvestrant**
	N	**Median time to event in months [95% CI]** **Patients with event n (%)**	**N**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**HR [95% CI]; p-value[a]**
INAVO120					
Mortality					
Overall survival	161	34.0 [28.4; 44.8] 72 (44.7)	164	27.0 [22.8; 38.7] 82 (50.0)	0.67 [0.48; 0.94]; 0.019
Morbidity					
Symptomatic skeletal-related events	No suitable data[b]				
Symptoms (EORTC QLQ-C30, EORTC QLQ-BR23, symptom scales)	No suitable data[b]				
Worst pain (BPI-SF Item 3)	No suitable data[b]				
Health status (EQ-5D VAS)	No suitable data[b]				
Health-related quality of life					
EORTC QLQ-C30, EORTC QLQ-BR23 (functional scales)	No suitable data[b]				
Side effects					
AEs (supplementary information)	161	ND 161 (100.0)	163	ND 163 (100.0)	–
SAEs	161	ND 44 (27.3)	163	ND 22 (13.5)	1.64 [0.98; 2.74]; 0.058
Severe AEs[c]	161	ND 148 (91.9)	163	ND 140 (85.9)	1.14 [0.90; 1.44]; 0.276
Discontinuation due to AEs[d]	161	ND 14 (8.7)	163	ND 1 (0.6)	12.72 [1.67; 96.95]; 0.002
PRO-CTCAE	No suitable data[b]				
Stomatitis (PT, AEs)	161	ND 57 (35.4)	163	ND 30 (18.4)	2.07 [1.33; 3.22]; 0.001
Hyperglycaemia (PT, severe AEs[c])	161	ND 9 (5.6)	163	ND 0 (0)	–; 0.003

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: inavolisib + palbociclib + fulvestrant vs. placebo + palbociclib + fulvestrant (multipage table)

Study Outcome category Outcome	inavolisib + palbociclib + fulvestrant		placebo + palbociclib + fulvestrant		inavolisib + palbociclib + fulvestrant vs. placebo + palbociclib + fulvestrant
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[a]
Decreased appetite (PT, AEs)	161	ND 44 (27.3)	163	ND 18 (11.0)	2.30 [1.33; 3.99]; 0.002
Noninfective diarrhoea (SMQ, AEs)	161	ND 84 (52.2)	163	ND 26 (16.0)	3.73 [2.40; 5.79]; < 0.001
Platelet count decreased (PT, severe AEs[c])	161	ND 14 (8.7)	163	ND 5 (3.1)	2.95 [1.06; 8.20]; 0.029
Metabolism and nutrition disorders (SOC, severe AEs[c])	161	ND 20 (12.4)	163	ND 5 (3.1)	3.64 [1.36; 9.75]; 0.006
Gastrointestinal disorders (SOC, severe AEsc)	161	ND 18 (11.2)	163	ND 4 (2.5)	4.12 [1.39; 12.21]; 0.006

a. HR and CI: Cox proportional hazards model, p-value: log-rank test; for the outcomes in the categories of mortality, morbidity and health-related quality of life, stratified by visceral disease, endocrine resistance and geographic region; for the outcomes in the category of side effects, unstratified.
b. See Section I 3.2.1 of this dossier assessment for the reasoning.
c. Operationalized as CTCAE grade ≥ 3.
d. Discontinuation of any components of the study medication.

AE: adverse event; BPI-SF: Brief Pain Inventory-Short Form; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; ND: no data; PRO-CTCAE: Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; PT: Preferred Term; QLQ-BR23: Quality of Life Questionnaire-Breast Cancer Module 23; QLQ-C30: Quality of Life Questionnaire-Core 30; SAE: serious adverse event; SMQ: Standardized MedDRA Query; SOC: System Organ Class; VAS: visual analogue scale

On the basis of the available information, at most indications, e.g. of an added benefit, can be determined for the outcome of overall survival and, due to the high risk of bias, at most hints for the side effects outcomes.

Mortality

Overall survival

A statistically significant difference between the treatment arms was shown for the outcome overall survival. However, there was an effect modification by the characteristic of age (see

Section I 3.2.4). For the age group < 65 years, there was an indication of an added benefit of inavolisib + palbociclib + fulvestrant in comparison with palbociclib + fulvestrant, whereas there is no hint of an added benefit for the age group ≥ 65 years.

Morbidity

Symptomatic skeletal-related events; symptoms (EORTC QLQ-C30 and EORTC QLQ-BR23, symptom scales); worst pain, recorded using the BPI-SF Item 3; health status, recorded using the EQ-5D VAS

No suitable data were available for the morbidity outcomes. See Section I 3.2.1 of this benefit assessment for the reasoning. For all outcomes in this outcome category, there is no hint of an added benefit of inavolisib + palbociclib + fulvestrant compared with palbociclib + fulvestrant. An added benefit for these outcomes is therefore not proven.

Health-related quality of life

EORTC QLQ-C30 and EORTC QLQ-BR23 (functional scales)

No suitable data were available for the health-related quality of life outcomes (recorded using the functional scales of EORTC QLQ-C30 and EORTC QLQ-BR23). See Section I 3.2.1 of this benefit assessment for the reasoning. There is no hint of an added benefit of inavolisib + palbociclib + fulvestrant compared with palbociclib + fulvestrant. An added benefit for these outcomes is therefore not proven.

Side effects

SAEs

There was no statistically significant difference between the treatment arms for the outcome SAEs. However, there was an effect modification by the characteristic of menopausal status (see Section I 3.2.4). For non-postmenopausal women, there is a hint of greater harm, whereas for postmenopausal women, there is no hint of greater or lesser harm of inavolisib + palbociclib + fulvestrant compared with palbociclib + fulvestrant.

Severe AEs (CTCAE grade ≥ 3)

There was no statistically significant difference between the treatment arms for the outcome of severe AEs. There is no hint of greater or lesser harm of inavolisib + palbociclib + fulvestrant in comparison with palbociclib + fulvestrant; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

A statistically significant difference to the disadvantage of inavolisib + palbociclib + fulvestrant was shown between the treatment arms for the outcome of discontinuation due to AEs. There is a hint of greater harm of inavolisib + palbociclib + fulvestrant compared with palbociclib + fulvestrant.

PRO-CTCAE

No suitable data were available for PRO-CTCAE. See Section I 3.2.1 of this benefit assessment for the reasoning. There is no hint of greater or lesser harm of inavolisib + palbociclib + fulvestrant compared with palbociclib + fulvestrant. Greater or lesser harm is therefore not proven for PRO-CTCAE.

Stomatitis (AEs)

A statistically significant difference to the disadvantage of inavolisib + palbociclib + fulvestrant was shown between the treatment arms for the outcome stomatitis (AEs). There is a hint of greater harm of inavolisib + palbociclib + fulvestrant compared with palbociclib + fulvestrant.

Hyperglycaemia (severe AEs)

A statistically significant difference to the disadvantage of inavolisib + palbociclib + fulvestrant was shown between the treatment arms for the outcome hyperglycaemia (severe AEs). There is a hint of greater harm of inavolisib + palbociclib + fulvestrant compared with palbociclib + fulvestrant.

Other specific AEs

A statistically significant difference to the disadvantage of inavolisib + palbociclib + fulvestrant was shown between the treatment arms for the following outcomes: decreased appetite (AEs), noninfective diarrhoea (AEs), platelet count decreased (severe AEs), metabolism and nutrition disorders (severe AEs) and gastrointestinal disorders (severe AEs). In each case, there is a hint of greater harm of inavolisib + palbociclib + fulvestrant compared with palbociclib + fulvestrant.

For the outcome of metabolism and nutrition disorders (severe AEs), there were effect modifications from the characteristics of visceral disease and menopausal status. However, the subgroup results for this outcome were not interpretable (see Section I 3.2.4). Therefore, the results for the total population were used for the derivation of the added benefit.

I 3.2.4 Subgroups and other effect modifiers

The following subgroup characteristics were taken into account in this benefit assessment:

- Age (< 65 years versus ≥ 65 years)
- Visceral disease (yes versus no)
- Menopausal status (non-postmenopausal versus postmenopausal; see Table 6 for the operationalization)

The characteristic of visceral disease was considered a measure of disease severity. Consideration of the characteristic of menopausal status was also explicitly included in the

commission of the G-BA. The corresponding analyses were to be presented by the company in the dossier.

Interaction tests are performed when at least 10 patients per subgroup are included in the analysis. For binary data, there must also be at least 10 events in at least one subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are only presented if there is a statistically significant and relevant effect in at least one subgroup. Subgroup results where the extent does not differ between subgroups are not presented.

Kaplan-Meier curves for all subgroup analyses included in the derivation of added benefit are presented in I Appendix B of the full dossier assessment.

Table 16: Subgroups (mortality, side effects) – RCT, direct comparison: inavolisib + palbociclib + fulvestrant vs. placebo + palbociclib + fulvestrant (multipage table)

Study **Outcome** **Characteristic**	**inavolisib + palbociclib + fulvestrant**		**Placebo + palbociclib + fulvestrant**		**inavolisib + palbociclib + fulvestrant vs. placebo + palbociclib + fulvestrant**	
Subgroup	**N**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**N**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**HR [95% CI][a]**	**p-value[b]**
INAVO120						
Overall survival						
Age						
< 65 years	136	36.0 [29.5; NC] 59 (43.4)	130	26.8 [22.3; 36.0] 68 (52.3)	0.65 [0.46; 0.92]	0.015
≥ 65 years	25	14.4 [9.1; NC] 13 (52.0)	34	NA [16.6; NC] 14 (41.2)	1.65 [0.77; 3.51]	0.191
					Interaction[c]:	0.033
SAEs						
Menopausal status						
Not postmenopausal	52	ND 13 (25.0)	52	ND 1 (1.9)	8.45 [1.09; 65.85]	0.016
Postmenopausal	104	ND 29 (27.9)	110	ND 21 (19.1)	1.24 [0.71; 2.19]	0.447
					Interaction[c]:	0.017

Table 16: Subgroups (mortality, side effects) – RCT, direct comparison: inavolisib + palbociclib + fulvestrant vs. placebo + palbociclib + fulvestrant (multipage table)

Study Outcome Characteristic Subgroup	inavolisib + palbociclib + fulvestrant N	 Median time to event in months [95% CI] Patients with event n (%)	Placebo + palbociclib + fulvestrant N	 Median time to event in months [95% CI] Patients with event n (%)	inavolisib + palbociclib + fulvestrant vs. placebo + palbociclib + fulvestrant HR [95% CI][a]	 p-value[b]
Metabolism and nutrition disorders (SOC, severe AEs[d])						
Visceral disease						
No	29	ND 3 (10.3)	36	ND 4 (11.1)	0.71 [0.15; 3.28]	0.658
Yes	132	ND 17 (12.9)	127	ND 1 (0.8)	15.14 [2.01; 113.98]	< 0.001
					Interaction[c]:	0.010
Menopausal status						
Not postmenopausal	52	ND 8 (15.4)	52	ND 0 (0)	–	0.009
Postmenopausal	104	ND 12 (11.5)	110	ND 5 (4.5)	2.32 [0.82; 6.63]	0.104
					Interaction[c]:	0.042

a. HR and CI: Cox proportional hazards model, unstratified.
b. Log-rank test; unstratified.
c. Interaction test: Cox proportional hazards model with corresponding interaction term; likelihood ratio test.
d. Operationalized as CTCAE grade ≥ 3.

AE: adverse event; CI: confidence interval; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; ND: no data; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class

Mortality

Overall survival

Age: < 65 years

A statistically significant difference in favour of inavolisib + palbociclib + fulvestrant was shown between the treatment arms for patients younger than 65 years. There is an indication of an added benefit of inavolisib + palbociclib + fulvestrant compared with palbociclib + fulvestrant.

Age: ≥ 65 years

No statistically significant difference was shown between the treatment arms for patients aged 65 years and older. There is no hint of an added benefit of inavolisib + palbociclib +

fulvestrant in comparison with palbociclib + fulvestrant; an added benefit is therefore not proven.

Side effects

SAEs

Menopausal status: not postmenopausal

A statistically significant difference to the disadvantage of inavolisib + palbociclib + fulvestrant was shown between the treatment arms for non-postmenopausal women. There is a hint of greater harm of inavolisib + palbociclib + fulvestrant compared with palbociclib + fulvestrant.

Menopausal status: postmenopausal

There was no statistically significant difference between the treatment arms for postmenopausal women. There is no hint of greater or lesser harm of inavolisib + palbociclib + fulvestrant in comparison with palbociclib + fulvestrant; greater or lesser harm is therefore not proven.

Metabolism and nutrition disorders (severe AEs)

Visceral disease: no

No statistically significant difference between the treatment arms was shown for patients without visceral disease.

Visceral disease: yes

A statistically significant difference to the disadvantage of inavolisib + palbociclib + fulvestrant was shown between the treatment arms for patients with visceral disease.

Menopausal status: not postmenopausal

A statistically significant difference to the disadvantage of inavolisib + palbociclib + fulvestrant was shown between the treatment arms for non-postmenopausal women.

Menopausal status: postmenopausal

There was no statistically significant difference between the treatment arms for postmenopausal women.

As there was an effect modification by 2 subgroup characteristics for the outcome of metabolism and nutrition disorders (severe AEs), a separate analysis for each severity grade according to menopausal status would be necessary for the interpretation. Such an analysis was not available in the company's dossier. Thus, the available results on subgroup analyses for this outcome were not interpretable. The results of the total population were therefore used for the derivation of the added benefit (see Section I 3.2.3). The subgroup results for the outcome are not further presented in the tables on the derivation of the added benefit.

I 3.3 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the IQWiG General Methods [1].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

I 3.3.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level was assessed based on the results presented in Section I 3.2 (see Table 17).

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

For the outcome discontinuations due to AEs, insufficient severity data were available for a classification as serious/severe. The outcome of discontinuation due to AEs was therefore assigned to the outcome category of non-serious/non-severe side effects.

Table 17: Extent of the added benefit at outcome level: inavolisib + palbociclib + fulvestrant vs. placebo + palbociclib + fulvestrant (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**inavolisib + palbociclib + fulvestrant vs. placebo + palbociclib + fulvestrant** **Median time to event (months)** **Proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Outcomes with observation over the entire study duration		
Mortality		
Overall survival Age < 65 years	36.0 vs. 26.8 43.4% vs. 52.3% HR: 0.65 [0.46; 0.92]; p = 0.015 Probability: indication	Outcome category: mortality $0.85 \leq CI_u < 0.95$ Added benefit, extent: considerable
≥ 65 years	14.4 vs. NA months 52.0% vs. 41.2% HR: 1.65 [0.77; 3.51]; p = 0.191	Lesser benefit/added benefit not proven

Table 17: Extent of the added benefit at outcome level: inavolisib + palbociclib + fulvestrant vs. placebo + palbociclib + fulvestrant (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**inavolisib + palbociclib + fulvestrant vs. placebo + palbociclib + fulvestrant** **Median time to event (months)** **Proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Outcomes with shortened observation period		
Morbidity	No suitable data[c]	Lesser benefit/added benefit not proven
Health-related quality of life	No suitable data[c]	Lesser benefit/added benefit not proven
Side effects		
SAEs Menopausal status Not postmenopausal	ND vs. ND 25.0% vs. 1.9% HR: 8.45 [1.09; 65.85]; HR: 0.12 [0.02; 0.92][d]; p = 0.016 Probability: hint	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ Greater harm, extent: minor
Postmenopausal	ND vs. ND 27.9% vs. 19.1% HR: 1.24 [0.71; 2.19]; p = 0.447	Greater/lesser harm not proven
Severe AEs	ND vs. ND 91.9% vs. 85.9% HR: 1.14 [0.90; 1.44]; p = 0.276	Greater/lesser harm not proven
Discontinuation due to AEs	ND vs. ND 8.7% vs. 0.6% HR: 12.72 [1.67; 96.95]; HR: 0.08 [0.01; 0.60][d]; p = 0.002 Probability: hint	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ Greater harm, extent: considerable
PRO-CTCAE	No suitable data[c]	Greater/lesser harm not proven
Stomatitis (AEs)	ND vs. ND 35.4% vs. 18.4% HR: 2.07 [1.33; 3.22]; HR: 0.48 [0.31; 0.75][d]; p = 0.001 Probability: hint	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ Greater harm, extent: considerable

Table 17: Extent of the added benefit at outcome level: inavolisib + palbociclib + fulvestrant vs. placebo + palbociclib + fulvestrant (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**inavolisib + palbociclib + fulvestrant vs. placebo + palbociclib + fulvestrant** **Median time to event (months)** **Proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Hyperglycaemia (severe AEs)	ND vs. ND 5.6% vs. 0% HR: – p = 0.003 Probability: hint	Outcome category: serious/severe side effects Greater harm, extent: non-quantifiable
Decreased appetite (AEs)	ND vs. ND 27.3% vs. 11.0% HR: 2.30 [1.33; 3.99]; HR: 0.43 [0.25; 0.75][d]; p = 0.002 Probability: hint	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ Greater harm, extent: considerable
Noninfective diarrhoea (AEs)	ND vs. ND 52.2% vs. 16.0% HR: 3.73 [2.40; 5.79]; HR: 0.27 [0.17; 0.42][d]; p < 0.001 Probability: hint	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ Greater harm, extent: considerable
Platelet count decreased (severe AEs)	ND vs. ND 8.7% vs. 3.1% HR: 2.95 [1.06; 8.20]; HR: 0.34 [0.12; 0.94][d]; p = 0.029 Probability: hint	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ Greater harm, extent: minor
Metabolism and nutrition disorders (severe AEs)	ND vs. ND 12.4% vs. 3.1% HR: 3.64 [1.36; 9.75]; HR: 0.27 [0.10; 0.74][d]; p = 0.006 Probability: hint	Outcome category: serious/severe side effects $CI_u < 0.75$ and risk ≥ 5% Greater harm, extent: major
Gastrointestinal disorders (severe AEs)	ND vs. ND 11.2% vs. 2.5% HR: 4.12 [1.39; 12.21]; HR: 0.24 [0.08; 0.72][d]; p = 0.006 Probability: hint	Outcome category: serious/severe side effects $CI_u < 0.75$ and risk ≥ 5% Greater harm, extent: major

Table 17: Extent of the added benefit at outcome level: inavolisib + palbociclib + fulvestrant vs. placebo + palbociclib + fulvestrant (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**inavolisib + palbociclib + fulvestrant vs. placebo + palbociclib + fulvestrant** **Median time to event (months)** **Proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
a. Probability provided if there is a statistically significant and relevant effect. b. Depending on the outcome category, the effect size is estimated using different limits based on the upper limit of the confidence interval (CI_u). c. See Section I 3.2.1 for reasoning. d. Institute's calculation; reversed direction of effect to enable the use of limits to derive the extent of added benefit. AE: adverse event; CI: confidence interval; CI_u: upper limit of the confidence interval; HR: hazard ratio; NA: not achieved; NC: not calculated: PRO-CTCAE: Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; SAE: serious adverse event		

I 3.3.2 Overall conclusion on added benefit

Table 18 summarizes the results taken into account for the overall conclusion on the extent of the added benefit.

Table 18: Positive and negative effects from the assessment of inavolisib + palbociclib + fulvestrant in comparison with placebo + palbociclib + fulvestrant

Positive effects	**Negative effects**
Outcomes with observation over the entire study duration	
Mortality ▪ Overall survival ▫ Age (< 65 years) indication of an added benefit – extent: considerable	–
Outcomes with shortened observation period	
–	Serious/severe side effects ▪ SAEs ▫ Menopausal status (not postmenopausal) hint of greater harm – extent: minor ▪ Hyperglycaemia: hint of greater harm – extent: non-quantifiable ▪ Platelet count decreased: hint of greater harm – extent: minor ▪ Metabolism and nutrition disorders: hint of greater harm – extent: major ▪ Gastrointestinal disorders: hint of greater harm – extent: major
–	Non-serious/non-severe side effects ▪ Discontinuation due to AEs: hint of greater harm – extent: considerable ▪ Stomatitis: hint of greater harm – extent: considerable ▪ Decreased appetite: hint of greater harm – extent: considerable ▪ Noninfective diarrhoea: hint of greater harm – extent: considerable
There are no suitable data on the outcomes of morbidity, health-related quality of life and PRO-CTCAE.	
AE: adverse event; PRO-CTCAE: Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; SAE: serious adverse event	

The INAVO120 study showed an indication of an added benefit of considerable extent for the outcome overall survival in women aged < 65 years. At the same time, there were hints of greater harm of minor to major extent for the overall rate of SAEs (in non-postmenopausal women) and for several specific AEs in the category of severe/serious side effects. Due to the effect modification by age in the outcome overall survival, the added benefit was determined separately by age group.

For women aged < 65 years, the disadvantages in various AE outcomes did not completely call into question the considerable added benefit in overall survival. In summary, there was an indication of a minor added benefit of inavolisib + palbociclib + fulvestrant versus palbociclib + fulvestrant for this age group.

For women aged ≥ 65 years, there were no positive effects of inavolisib + palbociclib + fulvestrant versus placebo + palbociclib + fulvestrant. At the same time, there were several hints of greater harm of minor to major extent, especially in the case of severe/serious specific AEs. However, these were not sufficient to derive a lesser benefit. An added benefit of inavolisib + palbociclib + fulvestrant versus palbociclib + fulvestrant is therefore not proven for women aged ≥ 65 years.

This deviates from the company's assessment, which did not carry out a separate assessment for women and men in its dossier and did not differentiate between age groups, but rather derived an overall indication of a major added benefit.

I 4 Research question 2: men with PIK3CA-mutated, ER-positive, HER2-negative, locally advanced or metastatic breast cancer

I 4.1 Information retrieval and study pool

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

Sources used by the company in the dossier:

- Study list on inavolisib (status: 15 May 2025)
- Bibliographical literature search on inavolisib (last search on 15 May 2025)
- Search of trial registries / trial results databases for studies on inavolisib (last search on 15 May 2025)
- Search on the G-BA website for inavolisib (last search on 15 May 2025)

To check the completeness of the study pool:

- Search of trial registries for studies on inavolisib (last search on 22 August 2025); for search strategies, see I Appendix A of the full dossier assessment

The review did not identify any relevant studies.

Evidence provided by the company

The company included the INAVO120 study for men with PIK3CA-mutated, ER-positive, HER2-negative, locally advanced or metastatic breast cancer. The study is described in detail in Section I 3.1.2.

The INAVO120 study compared inavolisib + palbociclib + fulvestrant with placebo + palbociclib + fulvestrant. However, as described in Chapter I 2, the G-BA defined tamoxifen or palbociclib in combination with a nonsteroidal aromatase inhibitor (anastrozole, letrozole) as the ACT for research question 2.

The treatment in the comparator arm of INAVO120 did not concur with the ACT, so no data were available on the comparison of inavolisib + palbociclib + fulvestrant with the comparator therapy specified by the G-BA. Regardless of this, only 6 men were included in the INAVO120 study (5 in the intervention arm and 1 in the comparator arm).

I 4.2 Results on added benefit

No suitable data were available for the assessment of the added benefit of inavolisib + palbociclib + fulvestrant compared with the ACT in men with PIK3CA-mutated, ER-positive, HER2-positive, locally advanced or metastatic breast cancer. There is no hint of an added

benefit of inavolisib + palbociclib + fulvestrant in comparison with the ACT; an added benefit is therefore not proven.

I 4.3 Probability and extent of added benefit

As the company did not present any data for the assessment of the added benefit of inavolisib + palbociclib + fulvestrant compared with the ACT in men with PIK3CA-mutated, ER-positive, HER2-negative, locally advanced or metastatic breast cancer, following recurrence during or within 12 months of completing adjuvant endocrine treatment, an added benefit is not proven.

This deviates from the company's assessment, which did not carry out a separate assessment for women and men in its dossier, but rather derived an overall indication of a major added benefit for both sexes.

I 5 Probability and extent of added benefit – summary

The result of the assessment of the added benefit of inavolisib + palbociclib + fulvestrant in comparison with the ACT is summarized in Table 19.

Table 19: Inavolisib + palbociclib + fulvestrant – probability and extent of added benefit (multipage table)

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Women with PIK3CA-mutated, ER-positive, HER2-negative, locally advanced or metastatic breast cancer, following recurrence during or within 12 months of completing adjuvant endocrine treatment[b, c, d, e]	▪ tamoxifen (only for premenopausal women who have not received tamoxifen in previous [neo-]adjuvant endocrine therapy; only for postmenopausal women if aromatase inhibitors are not suitable) or ▪ letrozole or ▪ exemestane (only for women with progression following antioestrogen therapy) or ▪ anastrozole or ▪ fulvestrant or ▪ everolimus in combination with exemestane (only for women without symptomatic visceral metastases who have progressed after a nonsteroidal aromatase inhibitor) or ▪ ribociclib in combination with a nonsteroidal aromatase inhibitor (anastrozole, letrozole) or ▪ abemaciclib in combination with a nonsteroidal aromatase inhibitor (anastrozole, letrozole) or ▪ palbociclib in combination with a nonsteroidal aromatase inhibitor (anastrozole, letrozole) or ▪ ribociclib in combination with fulvestrant or ▪ abemaciclib in combination with fulvestrant or ▪ palbociclib in combination with fulvestrant	▪ Women < 65 years: indication of a minor added benefit[f] ▪ Women ≥ 65 years: added benefit not proven

Table 19: Inavolisib + palbociclib + fulvestrant – probability and extent of added benefit (multipage table)

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
2	Men with PIK3CA-mutated, ER-positive, HER2-negative, locally advanced or metastatic breast cancer, following recurrence during or within 12 months of completing adjuvant endocrine treatment[b, e]	▪ tamoxifen or ▪ palbociclib in combination with a nonsteroidal aromatase inhibitor (anastrozole, letrozole)	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company according to the inclusion criteria in Module 4 Section 4.2.2 is printed in **bold**.
b. Patients previously treated with a CDK4/6 inhibitor in the (neo)adjuvant setting should have had an interval of at least 12 months between termination of CDK4/6 inhibitor treatment and the detection of recurrence.
c. The G-BA assumes that treatment switching has taken place with regard to the drugs used in the initial prior adjuvant endocrine treatment.
d. The G-BA assumes pre/perimenopausal women to receive ovarian suppression with a GnRH analogue.
e. The G-BA assumes that
- the patients in the therapeutic indication have not yet received endocrine therapy in the advanced or metastatic setting,
- an(other) endocrine therapy is indicated for the patients and, in particular, there is no indication for chemotherapy to achieve a necessary, rapid remission, and
- no indication for (secondary) resection or radiotherapy with curative intent.

f. The INAVO120 study included only patients with an ECOG PS of 0 or 1. It remains unclear whether the observed effects are transferable to patients with an ECOG PS ≥ 2.

ACT: appropriate comparator therapy; ER: oestrogen receptor; G-BA: Federal Joint Committee; GnRH: gonadotropin-releasing hormone; HER2: human epidermal growth factor receptor 2; PIK3CA: gene for the catalytic subunit (p110α) of PI3 kinase (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha)

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

I 6 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.

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