Medicinrådet

Bilag til Medicinrådets vurdering af inavolisib til behandling af PIK3CA-muteret ER+/HER2-negativ lokalt fremskreden eller metastatisk brystkræft

Patienter med tilbagefald under eller inden for 12 måneder efter afsluttet adjuverende endokrin behandling

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. inavolisib
2. Forhandlingsnotat fra Amgros vedr. inavolisib
3. Ansøgers endelige ansøgning vedr. inavolisib

24. oktober 2025

Roche Pharmaceuticals A/S
Flaskehalsen 17, 4. Sal
1799 København V
www.roche.dk

Til Medicinrådet,

Høringssvar fra Roche Pharmaceuticals A/S vedrørende Medicinrådets anbefaling vedr. Itovebi (inavolisib) til behandling af PIK3CA-positiv brystkræft.

Roche takker for det fremsendte udkast til Medicinrådets vurderingsrapport af Itovebi (inavolisib) til behandling af PIK3CA-positiv brystkræft. Roche ønsker at kommentere på enkelte dele i Medicinrådets tilgang; både i den kliniske samt den sundhedsøkonomiske vurdering..

- Medicinrådet nævner flere gange i vurderingsrapporten, at palbociclib er dårligere end abemaciclib og ribociclib på samlet overlevelse. Denne konklusion er imidlertid ikke evidensbaseret, men bygger snarere på en fortolkning uden direkte videnskabelig dokumentation.

  Der er ikke udført studier der dokumenterer at palbociclib i kombination med fulvestrant er dårligere end ribociclib og abemaciclib på overlevelse. Samtidig viser den indirekte sammenligning som Medicinrådet behandlingsvejledning baserer sig på, at der ikke er en statistisk signifikant forskel mellem de tre CDK4/6-hæmmer i kombination med fulvestrant.

  Dette understøttes af fagudvalgets vurdering, som konkluderer, at der ud fra effektestimaterne for både de relative og absolutte forskelle ikke er dokumenteret nogen forskel i samlet overlevelse mellem de tre CDK4/6-hæmmere i analyserne. Fagudvalget fremhæver desuden, at studieforskellene betyder, at de indirekte sammenligninger skal tolkes med forsigtighed.

  Danske RWD har heller ikke kunne påvise en forskel en statistisk forskel på overlevelse mellem palbociclib og de to andre CDK4/6-i (2). Medicinrådets tilgang, hvor ekstrapoleringen af komparatorarmen justeres baseret på dette, er derfor ikke evidensbaseret.

- I Medicinrådets analyse er QALY-gevinsten lig med LY-gevinsten. Dette skyldes, at Medicinrådet antager, at patienter i hhv. PD1 og specielt PD2 progredierer hurtigere, hvis de har fået inavolisib + palbociclib + fulvestrant i første behandlingslinje end hvis de får palbociclib + fulvestrant. Der er absolut intet evidens, der tyder på, at dette skulle være tilfældet. Vi opfordrer derfor Medicinrådet til at antage, at progressionen på de efterfølgende linjer sker ved samme hastighed. Der er intet der tyder på, at andet skulle være tilfældet.

(1) Medicinrådets lægemiddelrekommandation vedrørende CDK4/6- hæmmere til ER+/HER2- lokalt fremskreden eller metastatisk brystkræft. 2023
https://medicinraadet.dk/media/c0bd0iyw/medicinr%C3%A5dets-l%C3%A6gemiddelrek-vedr-cdk4-6-h%C3%A6mmere-til-er-her2-lokalt-fremskreden-eller-metastatisk-brystkr%C3%A6ft-vers-2-0.pdf

(2) Gehrchen, M.L., Berg, T., Garly, R. et al. Real-world effectiveness of CDK 4/6 inhibitors in estrogen-positive metastatic breast cancer. BJC Rep 2, 44 (2024). https://doi.org/10.1038/s44276-024-00070-w

Amgros I/S
Dampfærgevej 22
2100 København Ø
Danmark

T +45 88713000
F +45 88713008

Medicin@amgros.dk
www.amgros.dk

22.10.2025

MBA/DBS

Forhandlingsnotat

Dato for behandling i Medicinrådet	19.11.2025
Leverandør	Roche
Lægemiddel	Itovebi (inavolisib)
Ansøgt indikation	I kombination med palbociclib og fulvestrant til patienter med PIK3CA-muteret ER+/HER2-negativ, lokalt fremskreden eller metastatisk brystkræft efter tilbagefald under eller inden for 12 måneder efter afsluttet adjuverende endokrin behandling
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel

Prisinformation

Amgros har forhandlet følgende priser på Itovebi (inavolisib):

Tabel 1: Forhandlingsresultat – betinget pristilbud

Lægemiddel	Styrke, pakningsstørrelse	AIP (DKK)	Forhandlet SAIP (DKK)	Forhandlet rabat ift. AIP
Itovebi	9 mg, 28 tabletter	95.000	[redacted]	[redacted]
Itovebi	3 mg, 28 tabletter	47.500	[redacted]	[redacted]

Prisen er betinget af Medicinrådets anbefaling.

Hvis Itovebi ikke anbefales af Medicinrådet, har Amgros aftalt følgende pris med leverandøren (jævnfør tabel 2):

Tabel 2: Forhandlingsresultat – ubetinget pristilbud

Lægemiddel	Styrke (pakningsstørrelse)	AIP (DKK)	Forhandlet SAIP (DKK)	Forhandlet rabat ift. AIP
Itovebi	9 mg, 28 tabletter	95.000	[redacted]	[redacted]
Itovebi	3 mg, 28 tabletter	47.500	[redacted]	[redacted]

Aftaleforhold

[redacted] Leverandøren har mulighed for at sætte prisen ned i hele aftaleperioden.

Informationer fra forhandlingen

[redacted]

Konkurrencesituationen

[redacted]

Tabel 3 viser lægemiddeludgifter i relation til andre lægemidler til brystkræft med PIK3CA-mutation.

*Tabel 3: Sammenligning af lægemiddeludgifter pr. patient per år**

Lægemiddel	Styrke (pakningsstørrelse)	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. år (SAIP, DKK)
Itovebi	9 mg, 28 tabletter	9 mg (p.o.) dagligt	[redacted]	[redacted]
Ibrance	125 mg, 21 tabletter	125 mg (p.o.) dagligt i 21 dage og herefter 7 dages pause	[redacted]	[redacted]
Itovebi + Ibrance				[redacted]
Truqap**	200 mg x 64 tabletter	400 mg (p.o.) to gange dagligt (800 mg i alt) i fire dage efterfulgt af tre dages pause	[redacted]	[redacted]
Piqray***	150 mg x 56 tabletter	300 mg (p.o.) en gang dagligt	[redacted]	[redacted]

*Både Itovebi, Truqap og Piqray er i kombination med fulvestrant. Fulvestrant er derfor ikke inkluderet i ovenstående tabel.

[redacted]

Status fra andre lande

Tabel 2: Status fra andre lande

Land	Status	Kommentar	Link
Norge	Under evaluering	Afventer indsendelse af dokumentationen fra leverandøren	Link til vurderingen
England	Under evaluering		Link til vurderingen
Sverige	Ikke vurderet nationalt		Link til anbefalingen

Opsummering

[redacted]

Application for the assessment of inavolisib for PIK3CA-mutated, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer, following recurrence on or within 12 months of completing adjuvant endocrine treatment

Color scheme for text highlighting	
Color of highlighted text	Definition of highlighted text
	Confidential information

Contact information

Contact information	
Marianne Botoft	**Roche Pharmaceuticals A/S**
Title	Medical Science Partner
Phone number	+45 2657 8420
E-mail	Marianne.botoft@roche.com
Christian Graves Beck	**Roche Pharmaceuticals A/S**
Title	Nordic HTA Enabler
Phone number	+45 2344 2083
E-mail	Christian_graves.beck@roche.com
Simone Kjeldbæk	**Roche Pharmaceuticals A/S**
Title	Medical Writer
Phone number	+45 2121 6075
E-mail	Simone.kjeldbaek@roche.com
Andreas Fanø	**Roche Pharmaceuticals A/S**
Title	Medical Science Partner
Phone number	+45 4214 2988
E-mail	andreas.fanoe@roche.com
Patrik Hillring	**Roche Pharmaceuticals A/S**
Titel	Nordic HEOR Partner
Phone number	+46 8726 1118
E-mail	patrik.hillring@roche.com

Table of contents

Tables

Figures

Abbreviations

ABEMA	Abemaciclib
Adj.	Adjuvant
AE	Adverse Event
AIC	Akaike Information Criteria
ASCO	American Society of Clinical Oncology
BC	Breast Cancer
BIC	Bayesian Information Criterion
BMI	Body-Mass Index
BOR	Best Overall Response
BPI-SF	Brief Pain Inventory-Short Form
CBR	Clinical Benefit Rate
CCOD	Clinical Cutoff Date
CCOD1	CCOD September 29, 2023
CCOD2	CCOD November 15, 2024
CDK4/6i	Cyclin-dependent kinase 4 and 6 inhibitor
CEACs	Cost-effectiveness acceptability curves
CI	Confidence Interval
COR	Confirmed Objective Response
Covid-19	Coronavirus disease 2019
CR	Complete Response
ctDNA	Circulating tumor DNA
CUA	Cost-Utility Analysis
DBCG	Danish breast cancer group
DMC	Danish Medicines Council
DoR	Duration of Response
DRG	Diagnose Relative Group

DSA	Deterministic Sensitivity Analyses
eBC	Early breast cancer
ECOG	Eastern Cooperative Oncology Group
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 Questionnaire
ESMO	European Society for Medical Oncology
ER	Estrogen Receptors
ET	Endocrine Therapy
EQ-5D-5L	European Quality of Life 5-Dimension, 5-Level questionnaire
FULV	Fulvestrant
GHS	Global Health Status
HER2	Human epidermal growth factor receptor 2
HER2-	Human epidermal growth factor receptor 2-negative
HR	Hazard Ratio
HR+	Hormone receptor-positive
HRQoL	Health-Related Quality of Life
HSUV	Health State Utility Value
ICER	Incremental Cost-Effectiveness Ratio
IM	Intramuscular
INAVO	Inavolisib
INAVO120	Study WO41554 (NCT05646862)
ITT	Intent-to-treat
KM	Kaplan-Meier (curve)
LA	Locally advanced
LHRH	Luteinising hormone-releasing hormone
LMEM	Linear mixed effects models
LY	Life-year
mBC	Metastatic Breast Bancer
neo. Adj.	Neo-Adjuvant
NGS	Next generation sequencing
NICE DSU	National Institute for Health and Care Excellence Decision Support Unit
ORR	Objective Response Rate
OS	Overall Survival
PALBO	Palbociclib
Pbo	Placebo
PCR	Polymerase chain reaction
PD	Progressive disease
PD1	First Progressive Disease
PD2	Second Progressive Disease
PFS	Progression-Free Survival
PFS2	Second progression
PH	Proportional Hazard
PI3K	Phosphatidylinositol 3-kinase
PI3K/AKT/mTOR	Phosphoinositide 3-kinase/Protein Kinase B/ mammalian Target of Rapamycin

PIK3CA	Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit Alpa
PO QD	Orally once daily
PR	Partial Response
PRO	Patient-Reported Outcome
PRO-CTCAE	PRO Common Terminology Criteria for Adverse Events
PSA	Probabilistic Sensitivity Analysis
QALY	Quality-Adjusted Life-Year
QLQ-BR23	QLQ-Breast Cancer Module 23
QoL	Quality of Life
RECIST v1.1	Response Evaluation Criteria in Solid Tumors, Version 1.1
Ribo	Ribociclib
RWD	Real World data
RWE	Real World Evidence
SAE	Serious Adverse Event
SD	Stable Disease
SE	Standard Error
SEER	Surveillance, Epidemiology, and End Results
SLR	Systematic Literature Review
SoC	Standard of Care
TAE	Therapeutic Area Expert
TTD	Time-to-disease
TTOT	Time-to-off treatment
UDSA	Univariate Deterministic Sensitivity Analysis
VAS	Visual Analogue Scale
1L	First line
2L	Second line
3L	Third line

1. Regulatory information on the medicine

Overview of the medicine	
Proprietary name	Itovebi
Generic name	Inavolisib
Therapeutic indication as defined by EMA	Inavolisib, in combination with palbociclib and fulvestrant, is indicated for the treatment of adult patients with Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha -mutated (PIK3CA), hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-), locally advanced (LA) or metastatic breast cancer (mBC), following recurrence on or within 12 months of completing adjuvant (adj.) endocrine treatment (ET).
Marketing authorization holder in Denmark	Roche Pharmaceuticals A/S
ATC code	L01EM06
Combination therapy and/or co-medication	Palbociclib and fulvestrant
(Expected) Date of EC approval	July 15 2025
Has the medicine received a conditional marketing authorization?	No
Accelerated assessment in EMA	No
Orphan drug designation	No
Other therapeutic indications approved by EMA	No
Other indications that have been evaluated by the DMC (yes/no)	No
Joint Nordic assessment (JNHB)	Not relevant for JNHB as there are different treatment practices across the Nordic countries.
Dispensing group	BEGR
Packaging – types, sizes/number of units and concentrations	Itovebi 3 mg: Red, round, film-coated tablet (approx. 6 mm diameter) with "INA3" imprinted. Itovebi 9 mg: Pink, oval, film-coated tablet (approx. 13 mm length, 6 mm width) with "INA9" imprinted Itovebi is available in 28-day cartons (4 x 7 blister cards).

2. Summary table

Summary	
Indication relevant for the assessment	Inavolisib, in combination with palbociclib and fulvestrant, for the treatment of adult patients with PIK3CA-mutated, HR+/HER2-, LA or mBC, following recurrence on or within 12 months of completing adj. ET
Dosage regiment and administration	Inavolisib 9-mg tablet taken orally once daily (PO QD) on Days 1–28 of each 28-day cycle. Fulvestrant 500 mg administered by intramuscular (IM) injection on Days 1 and 15 of Cycle 1 and then on Day 1 of each subsequent 28-day cycle. Palbociclib 125-mg capsule or tablet taken PO QD on Days 1–21 of each 28-day cycle. Luteinising hormone-releasing hormone (LHRH) antagonist for pre/peri-menopausal patients.
Choice of comparator	Palbociclib + fulvestrant
Prognosis with current treatment (comparator)	Patients with PIK3CA-mutated and endocrine-resistant ER+/HER2- BC account for a small patient population in Denmark. Currently, no data on the prognosis for Danish patients with PIK3CA-mutated endocrine resistance ER+/HER2- mBC is available. For patients with ER+/HER2-, endocrine-resistant mBC, SoC in first line (1L) is a cyclin-dependent kinase 4 and 6 inhibitor (CDK4/6i) in combination with fulvestrant (1). Data from a Danish Real world evidence (RWE) study shows that endocrine-resistant patients treated in 1L with palbociclib in combination with fulvestrant has a significant lower median Overall Survival (OS) than the endocrine-sensitive patient group. The median OS was 28.8 months for endocrine-resistant patients, significantly lower than 43.6 months observed in the endocrine-sensitive patient group. The PIK3CA status was not included in the analysis in the study (2). Data indicates that PIK3CA-mutated, endocrine-resistant patients with ER+/HER2- breast cancer generally exhibit poorer outcomes compared to endocrine-sensitive patients without a PIK3CA mutation. This includes an approximate 8.4-month reduction in median OS for patients with a PIK3CA mutation (3, 4).
Type of evidence for the clinical evaluation	Study WO41554 (INAVO120) is a head-to-head study and provides a direct comparison of Inavolisib in combination with a CDK4/6i + fulvestrant and CDK4/6i + fulvestrant.
Most important efficacy endpoints (Difference/gain compared to comparator)	*Progression-Free Survival (PFS)* Inavolisib: 17.2 months (95% CI: 11.6, 22.2) Placebo: 7.3 months (95% CI: 5.9, 9.2) Hazard Ratio (HR): 0.42 (95% CI: 0.32, 0.55)

Summary	
	24-month rate Inavolisib: 41.8% [redacted] Placebo: 16.7% [redacted] *Median Overall Survival (OS)* Inavolisib: 34.0 months (95% CI: 28.4, 44.8) Placebo: 27.0 months (95% CI: 22.8, 38.7) Hazard Ratio (HR): 0.67 (95% CI: 0.48, 0.94) *30-month rate* Inavolisib: 56.5% [redacted] Placebo: 46.3% [redacted] *Duration of Response (DOR)* Inavolisib: 19.2 months (95% CI: 14.7, 28.3) Placebo: 11.1 months (95% CI: 8.5, 20.2) Hazard Ratio (HR): 0.60 (95% CI: 0.37, 0.97)
Most important serious adverse events for the intervention and comparator	*Febrile neutropenia* Inavolisib: 2.5% Placebo: 0,0% *Pyrexia* Inavolisib: 2.5% Placebo: 0% *Coronavirus disease 2019 (Covid-19)* Inavolisib: 2.5% Placebo: 0.6%
Impact on health-related quality of life	Clinical documentation: EQ-5D-5L utility values. Progressions-free inavolisib: 0.861 (0.841; 0.880) Progressions-free placebo: 0.857 (0.836; 0.877) During first progression inavolisib: 0.774 (0.745; 0.803) During first progression placebo: 0.762 (0.736; 0.788) No significant direct effect on HRQoL (thus assumed equal), but indirect through extending the life and progression of patients.
Type of economic analysis that is submitted	Type of analysis: Cost-utility Analysis Type of model: Partitioned survival model
Data sources used to model the clinical effects	Study WO41554 (INAVO120)
Data sources used to model the health-related quality of life	Study WO41554 (INAVO120)

Summary	
Life years gained	Life year gained: 0.46
QALYs gained	0.57 QALY
Incremental costs	2.352.810810 DKK
ICER (DKK/QALY)	4.125.791791 DKK/QALY
Uncertainty associated with the ICER estimate	Extrapolation Price of drugs Subsequent treatment
Number of eligible patients in Denmark	Incidence: 33 new patients a year Prevalence: 0 patients
Budget impact (in year 5)	92.7 mil DKK

3. The patient population, intervention, choice of comparator and relevant outcomes

3.1 The medical condition

Breast cancer (BC) is the most common type of cancer in women and represents approximately 26% of all newly diagnosed cancers (5). BC is the leading cause of cancer-related death among women, accounting for 14.4% of all female cancer deaths — equivalent to around 1,100 deaths annually in Denmark (6-8).

In 2023, 5.412 Danish women were diagnosed with BC (6). The 5-year survival rate is around 90%, varying depending on the BC subtype (6, 7).

BC is a heterogeneous disease comprising four major molecular subtypes of BC, classified based on the expression of estrogen receptors (ER), progesterone receptors, and human epidermal growth factor receptor 2 (HER2). HR+ BC is the most prevalent type of all BC,

accounting for approximately 70% of all BC cases and around 3,200 Danish patients are diagnosed annually with ER+/HER2- BC (9).

The most common initial symptom of BC is a painless lump in the breast, either self-detected or found during screening. Other symptoms may include changes in breast shape or skin appearance, nipple inversion or discharge, and in rare cases, skin ulceration or signs of inflammation (10).

Despite a high 5-year relative survival rate for early breast cancer (eBC), the prognosis remains poor for patients diagnosed with HR+/HER2- LA or mBC. According to SEER (Surveillance, Epidemiology, and End Results) data, the 5-year relative survival rate for this subgroup is around 36,5 % (9). Around 20–30% of patients with eBC eventually develop distant metastases during their diseases and 40-50 % of these patients are classified as endocrine-resistant (11, 12). Each year, approximately 350 patients with HR+/HER2- experience disease recurrence after prior treatment for eBC (13).

Multiple studies have shown a decline in Health-Related Quality of Life (HRQoL) and health utilities with disease progression, particularly in relation to pain, anxiety, and reduced daily functioning, the decline was observed even before documented progression (14-16). Findings highlight the substantial burden associated with advanced HR+/HER2– BC and reinforce the need for treatments that can delay progression and maintain quality of life.

3.2 Patient population

The population for this submission concerns a small and well-defined subsegment of patients with PIK3CA-mutated, endocrine-resistant, HR+/HER2-, LA/mBC who experience disease progression during or within 12 months of completion of adj. ET.

While eBC is generally associated with high 5-year survival rates, the prognosis significantly worsens in advanced stages. Furthermore, the presence of endocrine resistance and a PIK3CA-mutation is independently associated with a poorer prognosis compared to the endocrine-sensitive patients without a PIK3CA-mutation (3, 4, 11).

Within the HR+/HER2- BC patient group, a PIK3CA mutation is one of the most common somatic mutations affecting the PIK3CA-gene, which encodes for Phosphatidylinositol 3-kinase (PI3K) (9, 17). Activating PIK3CA mutations lead to the dysregulation of the PI3K signaling pathway, a critical pathway involved in cellular growth, proliferation, and survival (17-19). These activating mutations have been identified as a potential mechanism driving intrinsic resistance to standard-of-care (SoC) ET when combined with CDK4/6i (20). Specifically, the upregulation of the Phosphoinositide 3-kinase/Protein Kinase B/mammalian Target of Rapamycin (PI3K/AKT/mTOR) pathway promotes both ER-dependent and ER-independent transcription, fostering endocrine resistance and enabling tumor cell survival and proliferation. BC cells notably exhibit increased reliance on PI3K signaling when adapting to hormone deprivation. Ultimately, PI3K pathway activation contributes to estrogen-independent activation of the ER, through phosphorylation of ER and subsequent upregulation of ER-regulated genes (21). Consequently, patients whose tumors harbor PIK3CA mutations derive less benefit from standard treatment options

that do not directly target the PI3K pathway, compared to patients with wild-type tumors (3, 4). Several studies have highlighted *PIK3CA*-mutuation as a mediator of endocrine resistance and being associated with worse clinical outcome (22, 23).

PIK3CA mutations are present in approximately 35–40% of patients with HR+/HER2- BC and an international meta-analysis by Fillbrunn et al., have demonstrated that patients with PIK3CA-mutated HR+/HER2- mBC experience an approximate 8,4-month reduction in median OS compared to BC patients with wild-type tumors (4, 24, 25). Further as described endocrine resistance is also a poor prognostic factor in HR+ BC and patients who experience disease progression on, or soon after, adj. ET have worse survival outcomes compared with those with endocrine-sensitive disease (11).

Table 1 Incidence and prevalence of the general population diagnosed with HR+/HER2- BC in the past 5 years*

Year	[2019]	[2020]	[2021]	[2022]	[2023]
Incidence in Denmark	3 618	3 430	3 569	3 639	3 820
Prevalence in Denmark	50.874	52.049	53.221	54.370	55.661
Global prevalence	*N/A*	*N/A*	*N/A*	*N/A*	*N/A*

*The incidence and prevalence estimates are derived from annual cancer statistics published by the Danish Health and Medicines Authority (26-31). To estimate the number of patients with HR+/HER2− BC in Denmark, the total number of BC cases is multiplied by the subtype distribution reported in SEER data, where HR+/HER2− accounts for approximately 70% of all cases (9). Abbreviations: Not Applicable – N/A; Breast cancer – BC; Hormone receptor - HR; Human epidermal growth factor receptor 2 - HER2.

Based on estimates by the Danish Medicines Council (DMC), approximately 350 patients with ER+/HER2- mBC are diagnosed annually in Denmark following prior treatment for eBC (13). Of these, an estimated 16% are considered ineligible for treatment with ET combined with a CDK4/6i due to factors such as age or comorbidities. This leaves to approximately 300 patients per year with recurrent mBC following earlier treatment for localized BC, that are potential candidates for ET combined with CDK4/6i. Within this cohort of patients eligible for fulvestrant combined with CDK4/6i treatment, approximately 40-50% are classified as endocrine-resistant, which equates to an estimated 120 Danish patients per year (13). Of these endocrine-resistant patients, around 35-40% are anticipated to harbor a PIK3CA mutation, which equates to around 42-48 Danish patients per year (24). However, Roche has conducted an analysis in collaboration with DBCG on the number of candidates for inavolisib which amounted to 31-35 patients. This was calculated by counting the number of patients with relapse on current treatment or within the first 12 months of adjuvant endocrine treatment. This was 88 patients in 2024. Of them 35%-40% would be PIK3CA mutated, which accounts to 31-35 patients. Thus we assume an average of 35 patients.

Table 2 Estimated number of patients eligible for treatment

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients in Denmark who are eligible for treatment in the coming years	33	33	33	33	33

The estimated patient number is based on numbers previously assessed by the DMC (13). Abbreviations: Danish Medicines Council – DMC.

3.3 Current treatment options

Currently, no targeted therapies are available for Danish patients with HR+/HER2- LA or mBC whose tumors harbor a PIK3CA mutation. Consequently, this PIK3CA-mutated sub-group has not been recognized as a distinct population in Danish clinical practice, and thus, their therapeutic options have been identical to those for patients with wild-type tumors. For this patient group current treatment options in Danish clinical practice are detailed in the guidelines issued by the Danish Breast Cancer Group (DBCG) (1) and in the DMC's treatment guideline (32). The current standard of care (SoC) for 1L endocrine-resistant HR+/HER2- mBC is a CDK4/6i in combination with fulvestrant.

The tumor's sensitivity to ET, also referred to as endocrine sensitivity or resistance, varies depending on whether the patient has previously received adj. ET, and if so, when the recurrence occurred in relation to this treatment. The disease is considered endocrine-resistant if recurrence occurs during treatment or within 12 months after the completion of adj. ET (33). The clinical definition of endocrine resistance is described in the DBCG guideline and are aligned with the definition in the INAVO120 study (1, 34).

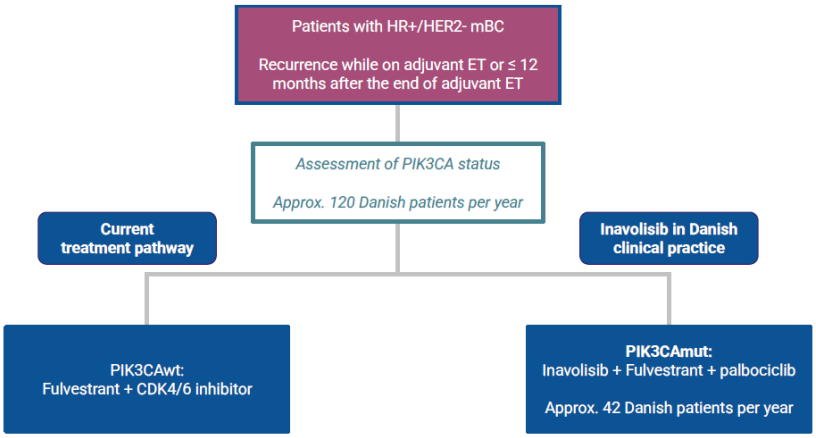


Figure 1 Current treatment pathway and proposed positioning of inavolisib in Danish clinical practice for patients with PIK3CA-mutated endocrine-resistant HR+/HER2- locally advanced or metastatic BC (13, 35).

Abbreviations: Endocrine therapy - ET; Breast cancer - BC; Hormone receptor - HR; Human epidermal growth factor receptor 2 - HER2; Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha – PIK3CA.

Expected Prognosis with Current Treatments

As described in section 3.2, endocrine-resistant patients having a tumor harboring a

PIK3CA mutation may derive less benefit from current treatment options that do not directly target the PI3K pathway, compared to patients with wild-type tumors. This includes an approximate 8.4-month reduction in median OS for patients with a PIK3CA-mutation (3, 4).
No Danish prognostic data for this patient groups is available, however, international clinical trial data from the SOLAR-1 trial, underscored, in alignment with findings from the INAVO120 study the poorer prognosis associated with PIK3CA-mutated tumors and highlighted the potential for targeted therapies to improve outcomes in this specific subgroup (36). This group of patients has a less favorable prognosis compared to those with wild-type tumors, and there is a need for targeted treatment. A critical need acknowledged and articulated by the expert committee in 2022 during their assessment of alpelisib (13). At present, there is no preferred standard second line (2L) treatment following progression on ET and a CDK4/6i. Consequently, the management of patients after disease progression on CDK4/6i and ET presents a significant challenge (1). This challenge underscores the importance of maintaining patients on CDK4/6i and ET for the longest possible duration, to maximize the benefits of 1L therapy.

3.4 The intervention

Inavolisib is a highly potent and selective PI3Kα inhibitor that also promotes the degradation of mutant p110α (encoded by the PIK3CA gene). Experimental and clinical evidence suggests that upregulation of the PI3K/AKT/mTOR pathway promotes ER-dependent and ER-independent transcription, contributing to endocrine resistance and leading to tumor cell survival and proliferation (37). With the dual mechanisms of action, inavolisib inhibits the activation of downstream PI3K pathway components, including AKT, resulting in reduced cellular proliferation and induction of apoptosis in PIK3CAmut BC cell lines (38) Inavolisib is the first targeted treatment to demonstrate OS-benefit in 1L treatment for patients with HR+/HER2- mBC (39).

Overview of intervention	
Indication relevant for the assessment	Itovebi, in combination with palbociclib and fulvestrant, is indicated for the treatment of adult patients with PIK3CAmutated HR+/HER2-, LA or mBC, following recurrence on or within 12 months of completing adj. ET. In pre/perimenopausal women and in men, ET should be combined with a LHRH agonist.
ATMP	N/A
Method of administration	Oral
Dosing	Drug: Inavolisib 9-mg tablet taken PO QD on Days 1−28 of each 28-day cycle, beginning on Day 1 of Cycle 1. Drug: Fulvestrant 500 mg administered by IM injection on Days 1 and 15 of Cycle 1 and then on Day 1 of each subsequent 28-day cycle, or approximately every 4 weeks. Drug: Palbociclib 125-mg capsule/tablet taken PO QD on Days 1−21 of each 28-day cycle, beginning on Day 1 of Cycle 1.

Overview of intervention	
Dosing in the health economic model (including relative dose intensity)	***Inavolisib + palbociclib + fulvestrant*** Dosing as described above. Relative dose intensity: Inavolisib - 84.35%; Palbociclib - 85.22%; Fulvestrant - 95.63% ***Placebo + palbociclib + fulvestrant*** Dosing as described above. Relative dose intensity: Palbociclib - 83.17%; Fulvestrant - 93.5%
Should the medicine be administered with other medicines?	Inavolisib is administered in combination with palbociclib and fulvestrant.
Treatment duration / criteria for end of treatment	Until disease progression or unacceptable toxicity. Dose reductions as per SmPC.
Necessary monitoring, both during administration and during the treatment period	***Screening before initiating treatment:*** Test for fasting glucose levels (FPG or FBG) and HbA 1C levels ***After treatment initiation:*** Monitor/self-monitor fasting glucose once every 3 days for the first week (Day 1 to 7), then once every week for the next 3 weeks (Day 8 to 28), then once every 2 weeks for the next 8 weeks, then once every 4 weeks thereafter, and as clinically indicated.
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	For patient selection validated PCR (Polymerase chain reaction) or NGS (Next generation sequencing) assays are needed. The test is not currently applied in Danish clinical practice. For inclusion in the model see section 11.
Package size(s)	28 film-coated tablets in blister package

3.4.1 Description of ATMP

N/A.

3.4.2 The intervention in relation to Danish clinical practice

SoC for 1L endocrine-resistant HR+/HER2- mBC is a CDK4/6i in combination with fulvestrant. Inavolisib will be an add-on treatment to existing SoC for this small and well-defined patient group with *PIK3CA*-mutated and endocrine resistant HR+/HER2-mBC (see section 3.3).

Patient selection for Inavolisib treatment requires the identification of an eligible PIK3CA mutation. In the DBCG guidelines and European Society for Medical Oncology (ESMO) guidelines among others, genomic profiling for biomarkers like PIK3CA mutation status is recommended at initial mBC diagnosis when findings will influence the treatment pathway (35). PIK3CA mutation testing is not yet routinely applied throughout Danish clinical practice, primarily because no treatment specifically targeting PIK3CA mutations previously has been available for Danish BC patients (1).

Notably, in anticipation of alpelisib's recommendation from the DMC in 2022, National pathology guidelines were updated to include PIK3CA analysis, indicating that nationwide implementation of PIK3CA testing is feasible at short notice (13). In that regards the Danish Society of Pathology has undertaken comprehensive quality assurance procedures, enabling fast national implementation of the PIK3CA mutation analysis (13).

For patient selection and eligibility for enrollment in the INAVO120 study, PIK3CA mutation status was prospectively determined using either centrally performed NGS analysis on plasma-derived circulating tumor DNA (ctDNA) (87.4% of cases), or by local laboratories (12.6% of cases) using validated PCR or NGS assays on tumor tissue or plasma. The testing in the INAVO120 study encompassed a broad range of PIK3CA alterations, including hotspot and non-hotspot mutations (34). Validated tests using either NGS or PCR methodology on both tumor tissue and ctDNA samples can be used to identify patients harboring PIK3CA mutation (40). Both PCR and NGS laboratory techniques are established at hospitals across Denmark (41). As described in section 3.1 it is anticipated that 120 patients will be eligible for a PIK3CA mutation test per year. Given a PIK3CA mutation prevalence of 35-40% (25), approximately 2-3 patients would require testing to identify one eligible patient.

3.5 Choice of comparators

Current SoC for 1L endocrine-resistant HR+/HER2- mBC in Danish clinical practice is a CDK4/6i in combination with fulvestrant. Palbociclib was the initial CDK4/6i to receive approval. The INAVO120 study was designed using palbociclib as its comparator, reflecting its position as the first approved agent in this class. In August 2023, the DMC updated the treatment guideline for CDK4/6i in ER+/HER2- LA/mBC based on longer follow-up data from the pivotal PALOMA-3, MONALEESA-3, and MONARCH-2 studies (42-44). Abemaciclib (ABEMA) and ribociclib, when used in combination with fulvestrant, is now considered to be clinically equivalent for the treatment of ER+/HER2- LA/mBC, palbociclib is no longer regarded as clinically equivalent (45). The assessment done by the DMC indicates that palbociclib provides inferior OS outcomes compared to ABEMA and ribociclib. Despite this, the expert committee (fagudvalget) notes that analyses of effect estimate for relative and absolute differences, based on the secondary endpoint OS from the three studies, do not demonstrate any statistically significant distinctions between the three drugs (45). Nonetheless, results from individual studies suggest that palbociclib may have inferior efficacy compared to ribociclib and ABEMA (42-44). This assessment primarily stems from the PALOMA-3 study, which showed a clinically meaningful improvement in OS but did not achieve a statistically significant OS benefit for palbociclib + fulvestrant compared to placebo + fulvestrant (46).

The efficacy assessment is further supported by real world evidence (RWE). A large international real-world data (RWD) study suggests no significant OS differences between 1L ribociclib, ABEMA, and palbociclib when combined with an aromatase inhibitor for patients with HR+/HER2- mBC (47). Similarly, a Danish RWD study examining the effectiveness of the three CDK4/6i could not definitively confirm a specific ranking among them (48). Based on guidelines, RWE and advice from DMC the three CDK4/6i´s could in this

application be considered equivalent and the intervention in this assessment are therefore compared solely to palbociclib in combination with fulvestrant.

Overview of comparator	
Generic name	Palbociclib (49)
ATC code	L01EF01
Mechanism of action	Reversible inhibitor of cyclin-dependent kinase 4 and 6.
Method of administration	Oral
Dosing	125 mg tablet taken PO QD on Days 1−21 of each 28-day cycle
Dosing in the health economic model	*Inavolisib arm:* Palbociclib: 125 mg per day on days 1-21 of each 28-day cycle Relative dose intensity: 85.22% *Placebo arm:* Palbociclib: 125 mg per day on days 1-21 of each 28-day cycle Relative dose intensity: 83.17%
Should the medicine be administered with other medicines?	Palbociclib is administered in combination with fulvestrant
Treatment duration/ criteria for end of treatment	Treatment until objective disease progression, symptomatic deterioration, unacceptable toxicity or death whichever occurs first.
Need for diagnostics or other tests	No
Package size(s)	21 film-coated tablets in blisters, 63 film-coated tablets in blisters

Overview of comparator	
Generic name	Fulvestrant (50)
ATC code	L02BA03
Mechanism of action	Fulvestrant is a competitive estrogen receptor antagonist.
Method of administration	Fulvestrant is administered as IM injection.
Dosing	The recommended dose is 500 mg at intervals of one month, with an additional 500 mg dose given two weeks after the initial dose.
Dosing in the health economic model (including relative dose intensity)	Inavolisib arm: Fulvestrant: 500 mg (2 vials of 250 mg) on days 1,14, 28 and then every 28 days thereafter Relative dose intensity: 95.63% Placebo arm: Fulvestrant: Se description above Relative dose intensity: 93.5%

Overview of comparator	
Should the medicine be administered with other medicines?	Fulvestrant is administered in combination with palbociclib.
Treatment duration/ criteria for end of treatment	Treatment until objective disease progression, symptomatic deterioration, unacceptable toxicity or death whichever occurs first.
Need for diagnostics or other tests	No
Package size(s)	Available as 250 mg/5 mL pre-filled syringe (single or twin pack)

3.6 Cost-effectiveness of the comparators

In the INAVO120 study, the combination of inavolisib, palbociclib, and fulvestrant was compared with palbociclib and fulvestrant. As CDK4/6i in combination with fulvestrant is considered SoC in clinical practice in Denmark and recommended by the DMC, it is reasonable to assume its cost-effectiveness. Therefore, no additional cost-effectiveness analysis for the comparator arm is provided.

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

Table 3 Efficacy outcome measures relevant for the application for the INAVO120 study (34)

Outcome measure	Time point	Definition	How was the measure investigated/method of data collection
Primary Endpoint			
Progression free survival (PFS) INAVO120	The median duration of follow was 34,2 months in the inavolisib group and 32.3 months in the placebo group (39)	Time from randomization to the first occurrence of disease progression or death from any cause (whichever occurred first), as determined by the investigator according to RECIST v1.1	Response was assessed by the investigator on the basis of physical examinations, CT scans, and other imaging modalities as clinically indicated, which may include brain imaging (CT or MRI), MRI scans, and/or bone scans, using RECIST v1.1 criteria (34)
Secondary Endpoints			
Overall survival (OS) INAVO120	See timepoint for primary endpoint	OS is defined as the time from randomization to death from any cause.	See collection of primary endpoints
OOR	See timepoint for	Proportion of patients with a CR or PR on	See collection of primary endpoints

Outcome measure	Time point	Definition	How was the measure investigated/method of data collection
INAVO120	primary endpoint	two consecutive occasions ≥ 4 weeks apart, as determined by the investigator according to RECIST v1.1	
Best Overall Response (BOR) rate INAVO120	See timepoint for primary endpoint	Proportion of patients with a CR or PR, as determined by the investigator according to RECIST v1.1	See collection of primary endpoints
DOR INAVO120	See timepoint for primary endpoint	Time from the first occurrence of a CR or PR to the first occurrence of disease progression or death from any cause (whichever occurred first), as determined by the investigator according to RECIST v1.1	See collection of primary endpoints
CBR INAVO120	See timepoint for primary endpoint	Proportion of patients with a CR, PR, and/or stable disease for at least 24 weeks, as determined by the investigator according to RECIST v1.1	See collection of primary endpoints

Validity of outcomes

The primary and secondary endpoints in the INAVO120 study are well-defined and golden standard endpoint within oncologic research (51). PFS and OS have been used in prior DMC submissions for mBC and treatment guideline protocol (32, 52). Therefore, the clinical efficacy data derived from the INAVO120 study is considered as relevant for Danish clinical practice.

4. Health economic analysis

A cost-utility analysis (CUA) was conducted from the perspective of the Danish healthcare system. Cost-effectiveness results are expressed as incremental costs per quality-adjusted of life years (QALYs) gained and per life-years (LYs) gain. The model was created in Microsoft Office 365. The base-case and all scenario analyses weighed all outcomes equally for all patients regardless of the characteristics of those receiving or affected by the interventions (i.e., all QALYs are equal).

4.1 Model structure

The model consists of four mutually exclusive health states: PFS, first progressive disease (PD1), second progressive disease (PD2) and death (Figure 2). Based on the time-to-events observed in the INAVO120 study at November 15, 2024 (CCOD2), all patients enter the model in the PFS state and transition throughout the model until they reach the death state (absorbing state).

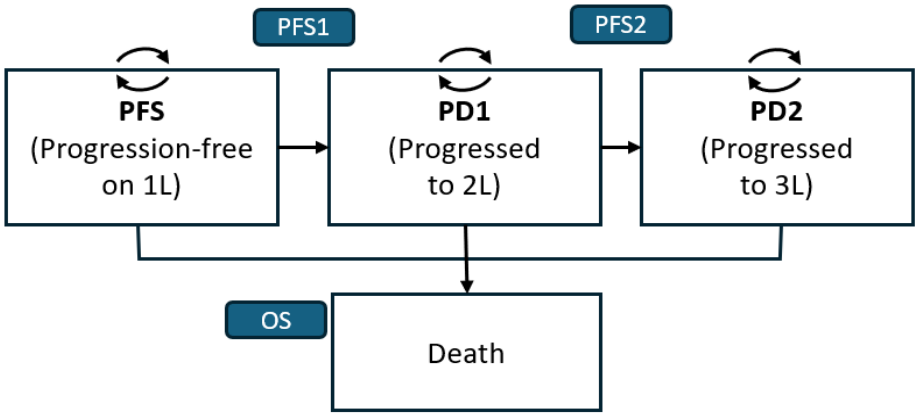


Figure 2 Model structure.

Abbreviations: Overall survival - OS; Progression free survival - PFS; Progressive disease - PD.

PFS

PFS is the initial state in which all patients enter the model. Based on the PFS survival curve derived from the INAVO120 study, in each model cycle, patients either remain in the PFS state or transition to PD1 or Death.

PD1

Patients enter PD1 once they experience a first progression. In each model cycle, patients either remain in PD1, or transition to PD2 or Death, but they cannot return to PFS. At any given point in time, the proportion of patients in the PD1 state is calculated as the difference between the proportion of patients who are alive and had a first progression, and the proportion of patients who are still progression-free (i.e., proxy to PFS2-PFS).

PD2

From PD1, patients transition to PD2 upon experiencing a second progression. In each model cycle, patients either remain in PD2 or move to Death, but they cannot return to PFS or PD1. The proportion of patients in the PD2 state is calculated as the difference between the proportion of patients who are alive and the proportion of patients who had a first progression (i.e., OS-proxy to PFS2).

Death

Death is modelled as an absorbing state which indicates that all patients eventually enter this state and cannot leave it. The proportion of patients who reside in the death state in each model cycle is determined by the OS curve derived from the INAVO120 study (i.e., 1-OS).

Model Validation

Key model inputs were validated by therapeutic area expert (TAEs) in Denmark during an

advisory board held in December 2024 These included whether the model structure and assumptions reflect the natural history of the disease. Since there were no clear 2L treatment guidelines in Denmark, an interview with a Swedish expert (part of the Swedish INAVO120 Tandvårds- och läkemedelsförmånsverket submission) was used.

4.2 Model features

A partitioned survival model was selected to allow the PFS, proxy to PFS2 and OS data derived from the INAVO120 study to be fully incorporated. As described in section 4.1, the proportion of patients who reside in each health state was calculated based on the study-observed events in the INAVO120 study, which is expected to accurately reflect disease progression during the study duration period. Thus, the partitioned survival modelling framework assumes that all endpoints (PFS, proxy to PFS2, OS) are modelled and extrapolated independently, which implies that trends in the hazards of each endpoint as well as treatment effects on the hazards observed during the trial period can be generalized long-term.

The main limitation of the partitioned survival modelling approach is that PFS, proxy to PFS2, and OS are modelled as independent endpoints. Since transitions are not explicitly modelled, the model structure is rigid and does not allow for sensitivity analysis to be explored by altering the transition probability in specific health states. Nevertheless, the proportion of patients in each health state is driven by parametric survival curves which are varied in scenario analysis to evaluate the impact on the incremental cost-utility ratio. It is also worth noting that partitioned survival modelling is common in oncology and it has previously been accepted in other health-technology assessments in HR+/HER2-, PIK3CA-mutated LA or mBC (53).

Table 4 Features of the economic model

Model features	Description	Justification
Patient population	1L HR+/HER2-, PIK3CA-mutated endocrine-resistant LA or mBC	N/A
Perspective	Limited societal perspective	According to DMC guidelines
Time horizon	Lifetime (46 years)	To capture all health benefits and costs in line with DMC guidelines. Based on mean age at diagnosis in the population (54 years).
Cycle length	7 days	Consistent with length of treatment cycle
Half-cycle correction	Yes	
Discount rate	3.5 %	The DMC applies a discount rate of 3.5 % for all years
Intervention	Inavolisib + Palbociclib + Fulvestrant	

Model features	Description	Justification
Comparator(s)	Placebo + palbociclib + fulvestrant	INAVO120 study
Outcomes	PFS, OS, Time to end of next-line of treatment (proxy to PFS2)	PFS2 is an exploratory endpoint

5. Overview of literature

5.1 Literature used for the clinical assessment

The only study relevant for this application is the INAVO120 study, therefor a systematic literature review has not been performed (39, 54). INAVO120 is a phase III, double-blind, randomized, placebo-controlled trial comparing 1L inavolisib plus palbociclib-fulvestrant with placebo plus palbociclib-fulvestrant in patients with *PIK3CA*-mutated, HR+/HER2- LA or mBC who had had disease recurrence during or within 12 months after the completion of adj. ET. The trial was enriched for patients with clinicopathologic characteristics associated with a poor prognosis (39, 54).

Table 5 Relevant literature included in the assessment of efficacy and safety for inavolisib.

Reference	Trial name	NCT identifier	Dates of study (55)	Used in comparison of
Full paper: Turner et al. Inavolisib-Based Therapy in *PIK3CA*-Mutated Advanced BC (INAVO120): a phase III, double-blind, randomized, placebo-controlled trial comparing first-line inavolisib plus palbociclib–fulvestrant (inavolisib arm) with placebo plus palbociclib–fulvestrant (placebo arm) in patients with PIK3CA-mutated, hormone receptor–positive, HER2-negative locally advanced or metastatic breast cancer who had had disease recurrence during or within 12 months after the completion of adj. endocrine therapy. N Engl J Med 2024;391:1584-96. (54)	INAVO120	NCT04191499	Start: 29/01/2020 Completion: 17/01/28 Data cut-off: 29/09/23	Inavolisib plus palbociclib–fulvestrant (inavolisib arm) with placebo plus palbociclib–fulvestrant (placebo arm) in patients with PIK3CA-mutated, HR+/HER2- LA or mBC who had had disease recurrence during or within 12 months after the completion of adj. ET
Full paper: Jhaveri et al. Overall Survival with Inavolisib in *PIK3CA*-Mutated Advanced Breast Cancer (INAVO120): a phase III, double-blind, randomized, placebo-controlled trial comparing first-line inavolisib plus palbociclib–fulvestrant (inavolisib arm) with placebo plus palbociclib–fulvestrant (placebo arm) in patients with PIK3CA-mutated, hormone receptor–positive, HER2-negative locally advanced or metastatic breast cancer who had had disease recurrence during or within 12 months after the completion of adj. endocrine therapy. N Engl J Med 2025. (39)	INAVO120	NCT04191499	Start: 29/01/2020 Completion: 17/01/28 Data cut-off: 15/11/24	Inavolisib plus palbociclib–fulvestrant (inavolisib arm) with placebo plus palbociclib–fulvestrant (placebo arm) in patients with PIK3CA-mutated, HR+/HER2- LA or mBC who had had disease recurrence during or within 12 months after the completion of adj. ET
Data on file Unpublished data 2024.: Inavolisib Clinical Study Report. (56)	INAVO120	NCT04191499	Start: 29/01/2020 Completion: 17/01/28 Data cut-off: 29/09/23	Inavolisib plus palbociclib–fulvestrant (inavolisib arm) with placebo plus palbociclib–fulvestrant (placebo arm) in patients with PIK3CA-mutated, HR+/HER2- LA or mBC who had had disease recurrence during or within 12 months after the completion of adj. ET
Data on file Unpublished data 2025.: Inavolisib Clinical Study Report. (57)	INAVO120	NCT04191499	Start: 29/01/2020 Completion: 17/01/28 Data cut-off: 15/11/24	Inavolisib plus palbociclib–fulvestrant (inavolisib arm) with placebo plus palbociclib–fulvestrant (placebo arm) in patients with PIK3CA-mutated, HR+/HER2- LA or mBC who had had disease recurrence during or within 12 months after the completion of adj. ET

5.2 Literature used for the assessment of health-related quality of life

Table 6 Relevant literature included for documentation of health-related quality of life.

Reference	Health state/Disutility	Reference to where in the application the data is described/applied
Full paper: Turner et al. Inavolisib-Based Therapy in *PIK3CA*-Mutated Advanced Breast Cancer (INAVO120): a phase III, double-blind, randomized, placebo-controlled trial comparing first-line inavolisib plus palbociclib–fulvestrant (inavolisib arm) with placebo plus palbociclib–fulvestrant (placebo arm) in patients with PIK3CA-mutated, hormone receptor–positive, HER2-negative locally advanced or metastatic breast cancer who had had disease recurrence during or within 12 months after the completion of adj. endocrine therapy. N Engl J Med 2024;391:1584-96. (54)	Used for health states: PFS1, PFS2, PD	Section 10
Full paper: Jhaveri et al. Overall Survival with Inavolisib in *PIK3CA*-Mutated Advanced Breast Cancer (INAVO120): a phase III, double-blind, randomized, placebo-controlled trial comparing first-line inavolisib plus palbociclib–fulvestrant (inavolisib arm) with placebo plus palbociclib–fulvestrant (placebo arm) in patients with PIK3CA-mutated, hormone receptor–positive, HER2-negative locally advanced or metastatic breast cancer who had had disease recurrence during or within 12 months after the completion of adj. endocrine therapy. N Engl J Med 2025. (39)	Used for health states: PFS1, PFS2, PD	Section 10
Data on file Unpublished data 2024.: Inavolisib Clinical Study Report. (20)	Used for health states: PFS1, PFS2, PD	Section 10
Data on file Unpublished data 2025.: Inavolisib Clinical Study Report. (57)	Used for health states: PFS1, PFS2, PD	Section 10

5.3 Literature used for inputs for the health economic model

Table 7 Relevant literature used for input to the health economic model

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
Data on file Unpublished data 2025.: Inavolisib Clinical Study Report. (57)	OS, PFS, safety and utility	Head-to-head study	Section 8 for OS and PFS, section 9 for safety and section 10 for utility

6. Efficacy

6.1 Efficacy of inavolisib plus palbociclib and fulvestrant compared to placebo for patients with PIK3CA-mutated, HR+/HER2 LA or mBC who had had relapse during or within 12 months after the completion of adj. ET

6.1.1 Relevant studies

INAVO120 is a Phase III, randomized, double-blind, placebo-controlled, multicenter, global study designed to compare the efficacy, as measured by PFS as the primary endpoint, OS as one of the secondary endpoints and safety of the triplet combination of inavolisib plus palbociclib and fulvestrant versus placebo plus palbociclib and fulvestrant in patients with PIK3CA-mutant, HR+/HER2- LA or mBC whose disease progressed during treatment or within 12 months of completing adj. ET and who have not received prior systemic therapy for LA or mBC (34).

Patients eligible for enrollment included premenopausal, perimenopausal, or postmenopausal women, as well as men, all of whom presented with PIK3CA-mutated, HR+/HER2- LA or mBC Additional eligibility criteria included disease recurrence or progression during or within 12 months after the completion of adj. ET (patients with de novo mBC were excluded), a fasting glucose level of less than 126 mg per deciliter, a glycated hemoglobin level of less than 6.0%, and measurable disease according to Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) (54).

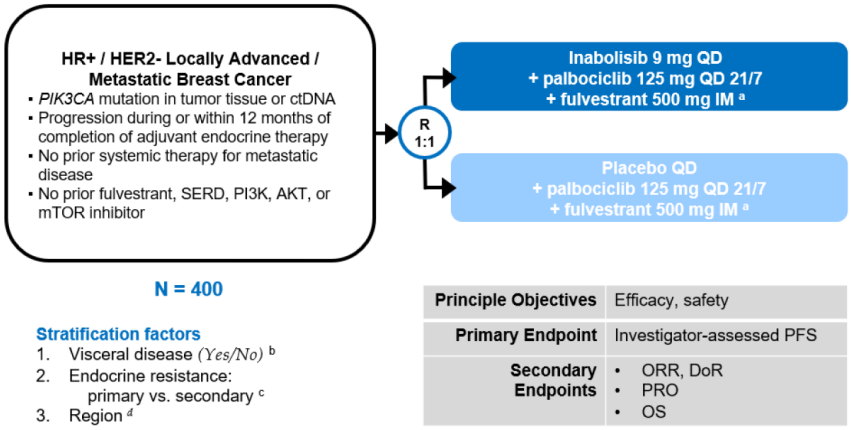


Figure 3 Overview of study design in the INAVO120 study (34).

Abbreviations: HR+ - Hormone receptor positive; HER2 - Human epidermal growth factor receptor 2; PIK3CA - Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PD - Progressive disease; ctDNA - Circulating tumor DNA; PI3K - Phosphatidylinositol 3-kinase - PI3K; PFS - Progression-free survival; ORR – Objective response rate; DoR - Duration of Response; PRO - Patient-reported outcomes-PRO; OS - Overall Survival; PO QD – Orally Once daily.

Patients were assigned in the ratio 1:1 by permuted-block randomization (to ensure a balanced assignment to each treatment arm) to receive 9 mg inavolisib PO QD on days 1 to 28 of each 28-day cycle or placebo once daily (Figure 38). Both inavolisib and placebo

were given with 125 mg palbociclib PO QD on days 1 to 21 of each 28-day cycle and 500 mg IM fulvestrant on days 1 and 15 of cycle 1 and approximately every 28 days thereafter (Figure 3 and Figure 39). Randomization was stratified according to (34, 54):

- Visceral disease (yes or no)
- Resistance to ET (primary or secondary according to ESMO ABC4 guidelines) (58). Primary resistance to ET was defined as relapse during the first 2 years of adj. ET, and secondary resistance to ET was defined as relapse after the start of year 2 of adj. ET or relapse within 12 months after the completion of adj. ET.
- Geographic region (North America and western Europe, Asia, or other).

Premenopausal or perimenopausal women plus all men received a LHRH agonist for hormone suppression for the duration of the trial intervention. The administration of the trial agents continued until disease progression, unacceptable toxicity, withdrawal of consent, or death. Patients who discontinued any trial agent because of unacceptable side effects could continue to receive the other trial agents in their assigned regimen (54). Dose modifications for adverse events (AE)s were taken first with inavolisib rather than palbociclib (unless palbociclib clearly caused the AEs based on known toxicity profile and the investigator's assessment). For toxicities caused by the combination of inavolisib, palbociclib and fulvestrant, it was preferred to initially modify the dosage of one drug (inavolisib or palbociclib), dose reductions for fulvestrant were not allowed (34).

The median durations of follow-up in both treatment arms were comparable with 21.3 months in the inavolisib group and 21.5 months in the placebo group for CCOD September 29, 2023 (CCOD1) (54).

Patient overview of CCOD2 (39)

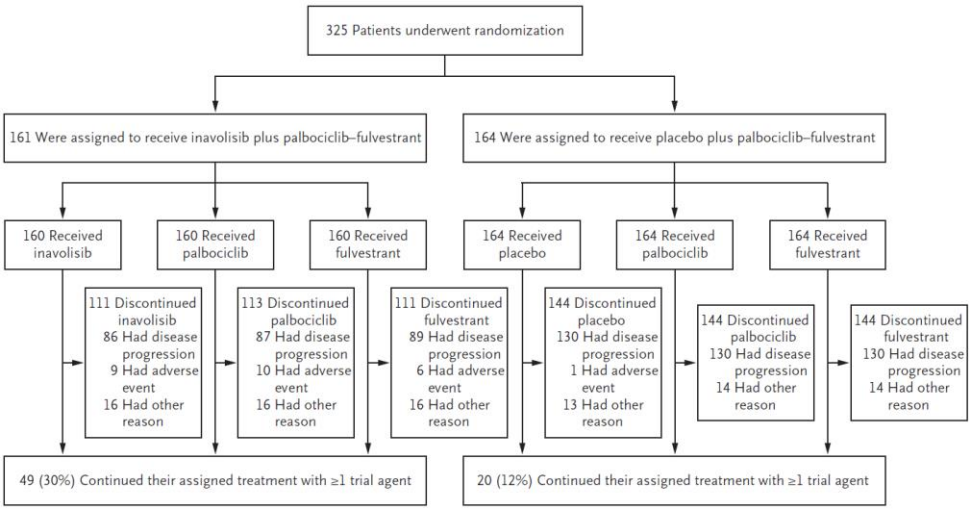


Figure 4 Overview of randomization and follow-up in the INAVO120 study (39).

The median follow-up duration were of 34.2 months in the inavolisib arm and 32.3 months in the placebo arm at CCOD2 (39).

Post-progression therapies are detailed in Table 54 in Appendix C. After treatment discontinuation, the percentage of patients who received chemotherapy in the second line of treatment was lower in the inavolisib group than in the placebo group (46 of 83 patients [55%] vs. 79 of 109 [72%]). Similarly, the percentage of patients who received antibody–drug conjugates in the third or later line of treatment was lower in the inavolisib group than in the placebo group (8 of 48 patients [17%] vs. 20 of 56 [36%]). Moreover, although the number of patients who received a PI3Kα inhibitor as subsequent therapy was low in both trial groups (7 patients in the inavolisib group and 14 in the placebo group), fewer patients in the inavolisib group than in the placebo group received a PI3K inhibitor in either the second line or the third or later line of treatment (5 of 83 patients [6%] vs. 11 of 109 [10%] in the second line of treatment and 2 of 48 patients [4%] vs. 3 of 56 [5%] in the third or later line of treatment) (39, 59).

The primary efficacy endpoint was PFS. Secondary efficacy endpoints included OS; confirmed objective response (COR), best overall response (BOR), clinical benefit rate (CBR), and duration of response (DoR) using RECIST v1.1. Other secondary endpoints included patient-reported outcomes and safety (54).

More information on the study included can be found in Table 8.

Table 8 Overview of study design for studies included in the comparison

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
INAVO120, NCT04191499 (34, 39, 54, 57)	A Phase III, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Inavolisib Plus Palbociclib and Fulvestrant Versus Placebo Plus Palbociclib and Fulvestrant in Patients With PIK3CA-Mutant, Hormone Receptor-Positive, HER2-Negative, LA or mBC	The administration of the trial agents continued until disease progression, unacceptable toxic effects, withdrawal of consent, or death. CCOD1: Median follow-up was 21.3 months for inavolisib and 21.5 months for placebo. CCOD2: The median follow-up were of 34.2 months for inavolisib and 32.3 months for placebo.	Premenopausal, perimenopausal, or postmenopausal women or men with PIK3CA-mutated, HR+/HER2- LA or mBC.	Inavolisib 9 mg PO QD, on days 1 to 28 of each 28-day cycle) given with palbociclib 125 mg PO QD, on days 1 to 21 of each 28-day cycle) and fulvestrant (IM), 500 mg on days 1 and 15 of cycle 1 and approximately every 28 days thereafter).	Placebo PO QD on days 1 to 28 of each 28-day cycle) given with palbociclib 125 mg PO QD, on days 1 to 21 of each 28-day cycle) and fulvestrant (IM), 500 mg on days 1 and 15 of cycle 1 and approximately every 28 days thereafter).	Outcomes: The primary efficacy endpoint was PFS. Secondary efficacy endpoints included OS; COR, BoR, CB, and DoR using RECIST v1.1. Other secondary endpoints included PROs and safety, see Appendix A for further details. Follow-up: All patients would subsequently move onto the survival follow-up period until death, patient withdrawal of consent, loss to follow-up, or study termination. Following study treatment discontinuation, patients would be followed for safety for 30 days after final study treatment (30-day safety follow-up, including a 30-day follow-up visit), or until the initiation of another anti-cancer therapy, whichever occurs first.

6.1.2 Comparability of studies

N/A.
This section is not relevant as efficacy and safety are compared directly in the INAVO120 study.

6.1.2.1 Comparability of patients across studies

Baseline characteristics of patients in the INAVO120 study are listed in Table 9. Patient disposition between the two arms in INVAO120 are presented in Figure 38. Generally, baseline characteristics were well balanced between the inavolisib and the placebo arms (54). Median patient age was 53.0 years in the inavolisib arm and 54.5 years in the placebo arm. The proportion of females was 96.9% and 99.4% in the inavolisib arm and the placebo arm, respectively. Black or African American patients were underrepresented in both arms.

The majority of the intent-to-treat (ITT) population had an ECOG score of 0 in both arms (100 patients in each arm). The proportion of patients with an ECOG score of 1 was 37.3% (60 patients) and 35.4% (58 patients) in the inavolisib arm and in the placebo arm, respectively. The number of patients who were premenopausal was 65 (40.4%) and 59 (36.0%) in the inavolisib arm and placebo arm, respectively.

The number of patients who were postmenopausal was 91 (56.5%) and 104 (63.4%) in the inavolisib arm and placebo arm, respectively (54). The median weight in the inavolisib arm was 62.5 kg and, in the placebo, arm it was 64.0 kg. The Body-Mass Index (BMI) in the inavolisib arm were the following: <18.5 (5.0% [8 patients]), ≥18.5 to <25.0 (48.4% [78 patients]), ≥25.0 to <30.0 (27.3% [44 patients]), ≥30.0 (18.0% [29 patients]), and missing data (1.2% [2 patients]). The BMI in the placebo arm were the following: <18.5 (6.1% [10 patients]), ≥18.5 to <25.0 (45.7% [75 patients]), ≥25.0 to <30.0 (30.5% [50 patients]), ≥30.0 (17.1% [28 patients]), and missing data (0.6% [1 patient] (54). The distribution of relevant risk factors was well balanced between the two arms.

There was an overall high disease burden with 50.3% (81 patients) in the inavolisib arm and 52.4% (86 patients) in the placebo arm having metastases in at least 3 organs. The proportion of patients who had metastases in 1 or 2 organs in the inavolisib arm was 13.0% (21 patients) and 36.6% (59 patients), respectively. The proportion of patients who had metastases in 1 or 2 organs in the placebo arm was 19.5% (32 patients) and 28.0% (46 patients), respectively. Sites of metastases were visceral (inavolisib: 82.0% [132 patients], placebo: 78.0% [128 patients]), liver (inavolisib: 47.8% [77 patients], placebo: 55.5% [91 patients]), lung (inavolisib: 41.0% [66 patients], placebo: 40.2% [66 patients]) and bone only (inavolisib: 3.1% [5 patients], placebo: 3.7% [6 patients]) (54).

The number of patients with ER-positive and PR-positive hormone-receptor status were 113 (70.2%) and 113 (68.9%) patients in the inavolisib arm and placebo arm, respectively. The number of patients with ER-positive and PR-negative hormone-receptor status were 45 (28.0%) and 45 (27.4%) patients in the inavolisib arm and placebo arm, respectively. Proportion of patients who had primary or secondary resistance to ET in the

inavolisib arm was 32.9% (53 patients) and 67.1% (108 patients), respectively. The proportion of patients who had primary or secondary resistance to ET in the placebo arm was 35.4% (58 patients) and 64.0% (105 patients), respectively. Most of the patients had previously received neo. adj. or adj. chemotherapy (inavolisib: 82.0% [132 patients], placebo: 83.5% [137 patients]) and had not previously received a CDK4/6i (inavolisib: 98.1% [158 patients], placebo: 99.4% [163 patients]). 47.7% of the patients had previously received neo. adj. or adj. tamoxifen only (54).

Table 9 Baseline characteristics of patients in the INAVO120 study*.

	INAVO120	
	Inavolisib N=161	**Placebo N=164**
Age – Median age, years (min-max)	53.0 (27-77)	54.5 (29-79)
Female sex – n (%)	156 (96.9)	163 (99.4)
Race – n (%)[a]		
Asian	61 (37.9)	63 (38.4)
Black or African American	1 (0.6)	1 (0.6)
White	94 (58.4)	97 (59.1)
ECOG Performance Status score – n (%)		
0	100 (62.1)	106 (64.6)
1	60 (37.3)	58 (35.4)
Menopausal status at randomization – n (%)		
Premenopausal	65 (40.4)	59 (36.0)
Postmenopausal	91 (56.6)	104 (63.4)
Median Weight – kg (min-max)	62.5 (39-124)	64.0 (38-111)
BMI – n (%)		
<18.5	8 (5.0)	10 (6.1)
≥18.5 to <25.0	78 (48.4)	75 (45.7)
≥25.0 to <30.0	44 (27.3)	50 (30.5)
≥30.0	29 (18.0)	28 (17.1)
Missing data	2 (1.2)	1 (0.6)
Number of organs with metastases – n (%)		
1	21 (13.0)	32 (19.5)

	INAVO120	
	Inavolisib N=161	**Placebo N=164**
2	59 (36.6)	46 (28.0)
≥3	81 (50.3)	86 (52.4)
Site of metastases – n (%)		
Visceral[b]	132 (82.0)	128 (78.0)
Liver	77 (47.8)	91 (55.5)
Lung	66 (41.0)	66 (40.2)
Bone only[c]	5 (3.1)	6 (3.7)
Hormone-receptor status – n (%)[d]		
ER-positive, Progesterone receptor-positive	113 (70.2)	113 (68.9)
ER-positive, Progesterone receptor-negative	45 (28.0)	45 (27.4)
Other	3 (1.9)	6 (3.7)
Resistance to endocrine therapy – n (%)[e]		
Primary resistance	53 (32.9)	58 (35.4)
Secondary resistance	108 (67.1)	105 (64.0)
Missing data	0	1 (0.6)
Previous neo. Adj. or adj. chemotherapy – n (%)	132 (82.0)	137 (83.5)
Previous neo. Adj. or adj. endocrine therapy – n (%)		
Overall	160 (99.4)	163 (99.4)
Aromatase inhibitor only	60 (37.3)	71 (43.3)
Tamoxifen only	82 (50.9)	73 (44.5)
Aromatase inhibitor and tamoxifen	18 (11.2)	19 (11.6)
Previous neo. Adj. or adj. CDK4/6i – n (%)	3 (1.9)	1 (0.6)

*Patient data are for the full analysis population, which included all the patients who had undergone randomization (54).
Abbreviations: ECOG - Eastern Cooperative Oncology Group (ECOG) performance-status (scores range from 0 [no disability] to 5 [death]); BMI - Body-mass index (calculated as the weight in kilograms divided by the square of the height in meters); CDK4/6 - cyclin-dependent kinase 4 and 6; estrogen receptor – ER.

[a] Race was reported by the patient.

[b] Visceral disease is defined as lung, liver, brain, pleural, or peritoneal involvement.

[c] Patients with evaluable bone-only disease were not eligible; patients with disease that was limited to bone but had lytic lesions or both lytic lesions and blastic lesions and at least one measurable soft-tissue component (as defined according to RECIST v1.1) were eligible.

[d] Tumors were considered to be positive if at least 1% of tumor cells expressed estrogen receptor (ER) or progesterone receptor, according to guidelines of the American Society of Clinical Oncology (ASCO) and the CAP.
[e] Resistance to ET was defined as primary resistance (relapse during the first 2 years of adj. ET) or secondary resistance (relapse after the start of year 2 of adj. ET or relapse within 12 months after the completion of adj. ET) according to the 4th ESMO International Consensus Guidelines for Advanced Breast Cancer.

6.1.3 Comparability of the study population with Danish patients eligible for treatment

Table 10 Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population (2, 60)	Value used in health economic model (39, 54)
Age (years), range	66.8 (27.6-92.3)	54 years
Age		
Gender	~1% male ~99% female	3.10% male. 96.90% female
Sites of metastases (%)		
Visceral	65.3	N/A
Liver	25.0	
Lung	25.0	

Currently, there is no specific description available for the Danish real-world patient population with endocrine-resistant, PIK3CA-mutated HR+/HER2- mBC. However, insights into patient characteristics are provided by a Danish retrospective, non-interventional, population-based study by Garly et al. (2). This study reflects the characteristics of 1L patients with endocrine-resistant metastatic HR+/HER2-BC who received palbociclib in combination with fulvestrant. The PIK3CA mutation status in this patient population is unknown. The median age in the INAVO120 study is lower than observed in the Danish patient population (54). A large study by Lambertini et al. also demonstrates that the median age for the endocrine-resistant patient group is generally lower than that in the endocrine-sensitive patient group (11). In the current subgroup analysis (see appendix A Figure 40 and Figure 41), the efficacy of inavolisib in combination with palbociclib and fulvestrant was evaluated in patients aged ≥65 years. These subgroup analyses were not powered to detect statistically significant differences, and the number of patients in this subgroup was limited. The results should therefore be interpreted with caution. The observed outcomes in older patients may be influenced by several factors, including small sample size, variability, and wide confidence intervals. The age distribution between treatment arms was comparable, and currently there is no biological rationale or mechanistic evidence suggesting that the efficacy of inavolisib would be diminished solely due to age. Additional exploratory analyses are ongoing to better understand treatment effect in underrepresented subpopulations, including older patients. Further, it is worth noting that in the Garly et al. study, the group of patients receiving an aromatase inhibitor as an endocrine backbone was significantly younger than the fulvestrant group. The precise patient selection criteria for the choice of endocrine backbone are unknown, and

there may be unaddressed confounders contributing to this substantial difference in median age between the two subgroups, thereby introducing some uncertainty regarding the generalizability of median age observations in this patient population.

The number of patients with visceral metastasis is significantly higher in the INAVO120 study with 82.0% and 78.0% in the inavolisib arm and the placebo arm, respectively, compared to the Danish patient population where 65.3% of the patient population had visceral metastasis. Concerning ECOG performance status, the study by Garly et al. does not explicitly describe it. However, earlier assessments by the DMC have described the patient group eligible for alpelisib as generally having a good performance status. This patient group can, to some extent, be compared to the patient group eligible for inavolisib. This aligns well with the INAVO120 study patients, where 62.1% had an ECOG score of 0 and 37.3% had a score of 1 (54).

Despite some numerical differences in median age and incidence of visceral metastases, the Danish patient population is considered broadly comparable to the INAVO120 study cohort. Key patient characteristics, such as age distribution within treatment arms and good performance status, align well, suggesting the study's findings are representative for Danish clinical practice.

6.1.4 Efficacy – results per INAVO120

In this section, results on the following outcomes are presented from the INAVO120 (WO41554) study:

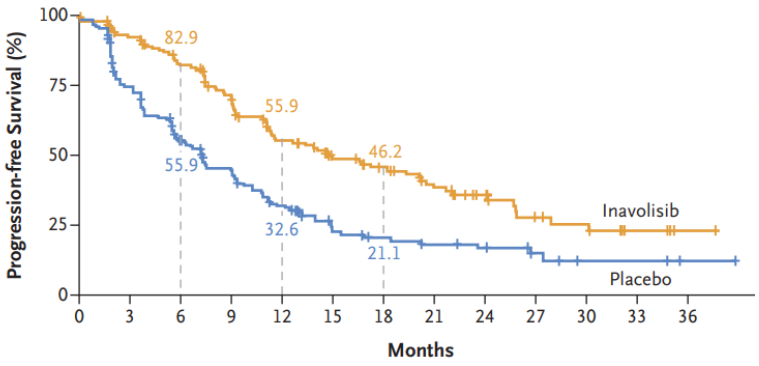
- Primary endpoint:
  - PFS
- Secondary endpoints
  - OS
  - ORR
  - DOR
  - CBR

Results for the secondary endpoints BOR and CBR can be found in Appendix B. For all efficacy outcomes data will be described for the two different data cuts: 1) data cutoff, September 29, 2023 (CCOD1) and 2) data-cutoff date, November 15, 2024 (CCOD2).

Progression-free survival (PFS)

The primary efficacy analysis population is used for all secondary endpoints unless otherwise specified. The primary efficacy endpoint in the INAVO120 study was PFS and defined as the time from randomization to the first occurrence of disease progression (assessed by the investigator according to RECIST v1.1) or death from any cause, whichever occurred first (34). Patients without disease progression or death from any cause were censored at the time of the last tumor assessment (or at the time of randomization if no tumor assessment was performed after the baseline visit) (54). The treatment arms were compared using a two-sided stratified log-rank test with the same stratification factors as used for randomization (section 6.1.1). Survival curves in each treatment arm were estimated using KM estimates providing a visual description of the survival curves and the difference across treatment arms. The KM approach was also used to estimate median PFS for each treatment arm. The treatment effect was quantified via a HR, computed from a stratified Cox proportional-hazards regression, including a 95% CI (34).

PFS at CCOD1 (54)



No. at Risk

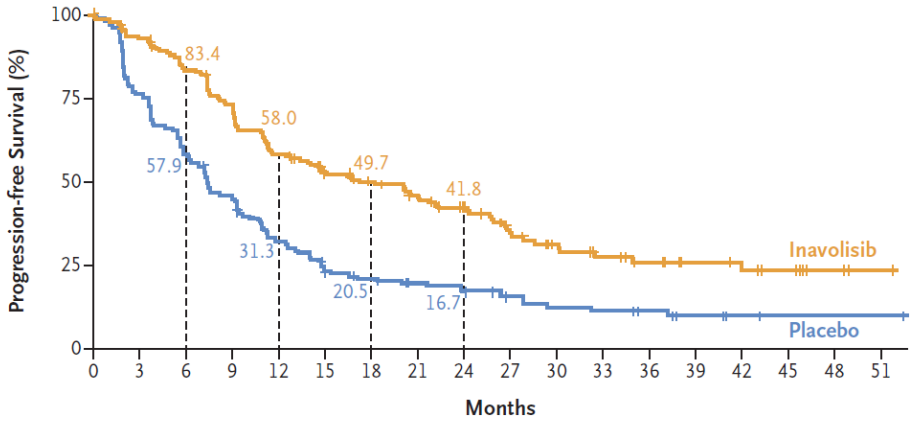
Inavolisib	161	134	111	92	66	48	41	31	22	13	11	5	1
Placebo	164	113	77	59	40	23	19	16	12	6	3	3	1

Figure 5 KM plot for PFS in the full analysis population in INVAO120 (CCOD1) (54).

Tick marks indicate censored data. Abbreviation: Progression free survival - PFS

In the full analysis population (inavolisib: N=161, placebo: N=164), the median PFS was 15.0 months (95% CI: 11.3, 20.5) for inavolisib and 7.3 months (95% CI: 5.6, 9.3) for placebo (Figure 5). The stratified HR for disease progression or death was 0.43 (95% CI: 0.32, 0.59) with a P-value of <0.001. In the landmark survival analysis, the probability of PFS was 82.9% [redacted] at 6 months, 55.9% [redacted] at 12 months, and 46.2% [redacted] at 18 months in the inavolisib arm. In the placebo arm, the probability of PFS was 55.9% [redacted] at 6 months, 32.6% [redacted] at 12 months, and 21.1% [redacted] at 18 months. Events occurred in 82 (50.9%) of 161 patients in the inavolisib arm and in 113 (68.9%) of 164 patients in the placebo arm (20, 54).

PFS at CCOD2 (39)



No. at Risk

Inavolisib	161	146	129	112	89	73	65	57	46	32	25	19	15	11	10	7	3	1
Placebo	164	125	95	74	50	34	30	24	21	14	11	10	8	4	2	1	1	1

Figure 6 KM plot for PFS in the full analysis population in INVAO120, which included all the patients who had undergone randomization (39).

Tick marks indicate censored data (CCOD1). Abbreviation: Progression free survival - PFS

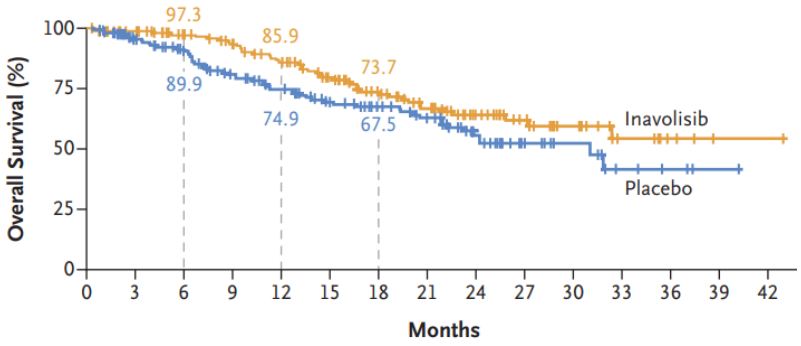
The analysis of the primary endpoint of investigator-assessed PFS was final at the initial CCOD1 (Figure 6). For the descriptive results at the updated CCOD2, a median PFS of 17.2

months (95% CI: 11.6, 22.2) was observed for the inavolisib arm and 7.3 months (95% CI: 5.9, 9.2) for the placebo arm. The stratified HR for disease progression or death was 0.42 (95% CI: 0.32, 0.55) with a P-value of <0.0001. In the updated landmark analysis of the full analysis population, the probability of PFS was 83.4% [redacted] at 6 months, 58.0% [redacted] at 12 months, 49.7% [redacted] at 18 months, and 41.8% [redacted] at 24 months in the inavolisib arm. In the placebo arm, the probability of PFS was 57.9% [redacted] at 6 months, 31.3% [redacted] at 12 months, 20.5% [redacted] at 18 months, and 16.7% [redacted] at 24 months. Events occurred in 103 (64%) of 161 patients in the inavolisib arm and in 141 (86%) of 164 patients in the placebo arm at CCOD2 (39, 57).

Overall Survival (OS)

OS after randomization was defined as the time from randomization to death from any cause (34). Data for patients who are alive at the time of the analysis CCOD was censored at the last date they were known to be alive. Data from patients without post baseline information was censored at the date of randomization plus 1 day. Analysis methodology for OS was the same as for PFS. OS was not met at the time of the primary analysis because a sufficient number of events not being available.

OS at CCOD1 (54)



No. at Risk

Inavolisib	161	143	127	114	101	85	69	56	38	26	17	8	4	1	1
Placebo	164	139	120	98	87	72	61	52	33	19	11	5	3	1	0

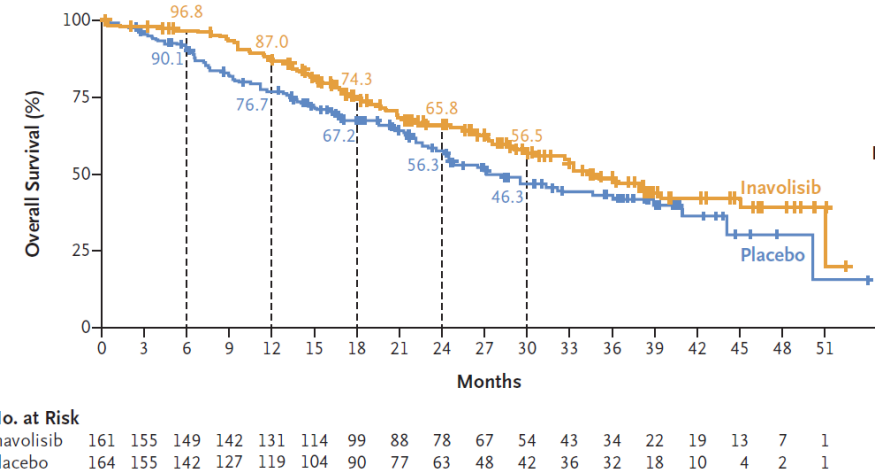
Figure 7 KM plot for OS in the full analysis population at CCOD1 (54).

Abbreviation: Overall survival - OS

At the time of the interim analysis of OS, the median OS in the inavolisib arm was not reached yet at the time of the interim analysis and the median OS in the placebo arm was 31.1 months (95% CI: 22.3, NR). The landmark survival analysis showed that the survival probability in the inavolisib arm at 6, 12, 18, and [redacted] was 97.3% [redacted], 85.9% [redacted] 73.7% [redacted] and [redacted] respectively. For the placebo arm, the survival probability at 6, 12, 18, and [redacted] was 89.9% [redacted] 74.9% [redacted], 67.5% [redacted] and [redacted] respectively. There were reported 42 (26.1%) deaths of 161 patients in the inavolisib arm and 55 (33.5%) deaths of 164 patients in the placebo arm. The stratified HR for death was 0.64 (95% CI: 0.43, 0.97)

with a P-value of 0.03 (did not cross the predefined boundary for significance of <0.0098) (Figure 7)(54).

OS at CCOD2 (39)



No. at Risk

Inavolisib	161	155	149	142	131	114	99	88	78	67	54	43	34	22	19	13	7	1
Placebo	164	155	142	127	119	104	90	77	63	48	42	36	32	18	10	4	2	1

Figure 8 KM plot for OS in the full analysis population, which included all the patients who had undergone randomization (39).

Tick marks indicate censored data (CCOD2). Abbreviation: Overall survival - OS

At CCOD2, median OS was 34.0 months (95% CI: 28.4, 44.8) and 27.0 months (95% CI: 22.8, 38.7) in the placebo arm (Figure 8). The HR for death was 0.67 (95% CI: 0.48, 0.94) with a P-value of <0.02. [redacted]

Objective Response Rate (ORR)

ORR is defined as the proportion of patients with a Complete Response (CR) and/or Partial Response (PR) on at least two consecutive occasions ≥4 weeks apart, according to RECIST v1.1 (34). Patients who did not achieve a confirmed response and patients with no response assessments (for whatever reason) were considered non-responders. An estimate of the response rate and its 95% CI was calculated using the Blyth-Still-Casella method for each treatment arm. Response rates in the treatment arms were compared using the stratified Mantel-Haenszel test. Confidence intervals (CI) for the difference in ORRs between the two arms were determined using the normal approximation to the binomial distribution (34).

ORR at CCOD1 (20, 54)

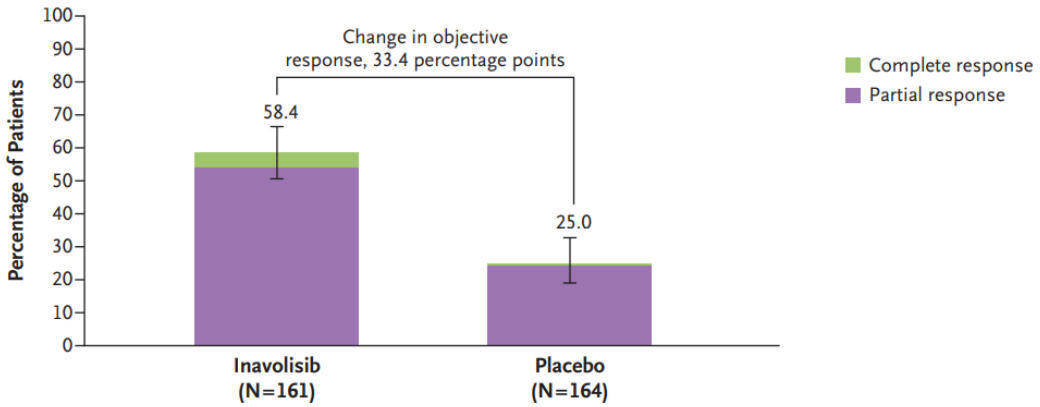


Figure 9 Percentage of patients with an objective response at CCOD1 (54).

ORR occurred in 58.4% of the patients in the inavolisib arm and in 25.0% of the patients in the placebo arm with a difference 33.4% (95% CI: 23.3, 43.5) between the two treatment arms (Figure 9) (54). In the inavolisib arm, 7 (4.3%) [redacted] patients had a CR, 87 (54.0%) [redacted] had a PR, 46 (28.6%) [redacted] had stable disease (SD), 7 (4.3%) [redacted] had progressive disease (PD), and 14 (8.7%) [redacted] had missing data. In the placebo arm, 1 (0.6%) [redacted] patient had a CR, 40 (24.4%) [redacted] patients had a PR, 79 (48.2%) [redacted] patients had SD, 34 (20.7%) [redacted] patients had PD, and 10 (6.1%) [redacted] patients had missing data (Table 11) [redacted]

ORR at CCOD2 (39, 57)

At the updated CCOD, ORR occurred in 62.7% of the patients in the inavolisib arm and in 28.0% of the patients in the placebo arm with a difference of 34.7% (95% CI: 24.5, 44.8) between the two treatment arms and a P-value of <0.001. [redacted]

Table 11 Objective Response Rate (ORR) (20, 39, 54, 57).

	Inavolisib N=161		Placebo N=164	
	CCOD1 (20)	**CCOD2 (39, 57)**	**CCOD1 (20)**	**CCOD2 (39, 57)**
Responders, n (%)	94 (58.4%) (95% CI: 50.4, 66.1)	101 (62.7%) (95% CI: 54.8, 70.2)	41 (25.0%) (95% CI: 18.6, 32.3)	41 (28.0%) (95% CI: 21.3, 35.6)
CR, n (%)	7 (4.3%) [redacted]	[redacted]	1 (0.6%) [redacted]	[redacted]

Partial Response, n (%)	87 (54.0%)	[redacted]	40 (24.4%)	[redacted]
Stable Disease, n (%)	46 (28.6%)	[redacted]	79 (48.2%)	[redacted]
Progressive Disease, n (%)	7 (4.3%)	[redacted]	34 (20.7%)	[redacted]
Missing, n (%)	14 (8.7%)	[redacted]	10 (6.1%)	[redacted]

Duration of Response (DoR)

DoR was defined as the time from the first occurrence of a PR or CR to the first occurrence of disease progression or death from any cause (whichever occurs first), as determined according to RECIST v1.1 (34). Data for patients without the occurrence of disease progression or death was censored at the time of the last tumor assessment. Analysis methodology was the same as for the primary endpoint, PFS. Comparisons between treatment arms using stratified and unstratified log rank tests were made for descriptive purposes. The analysis of DoR included only patients who achieved an objective response to study treatment (34).

DoR at CCOD1 (54)

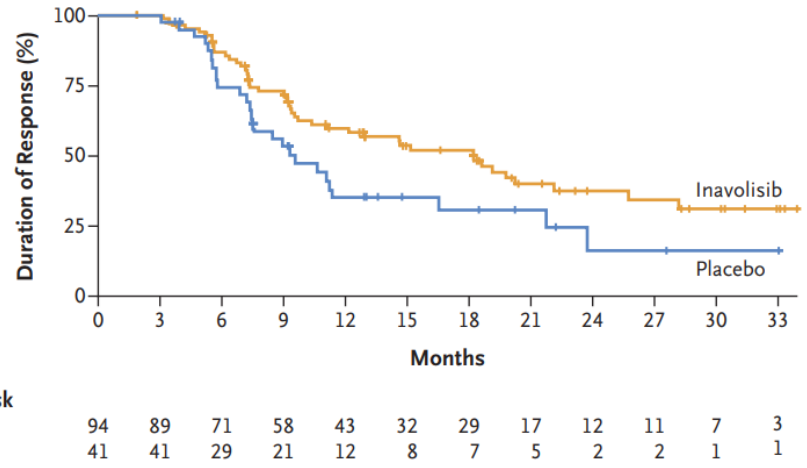


Figure 10 KM plot for DoR at CCOD1 (54).

Abbreviation: Duration of response - DoR

DoR events occurred in 46 (48.9%) of patients in the inavolisib arm and in 27 (65.9%) of the patients in the placebo arm. The median DoR was 18.4 months (95% CI: 10.4, 22.2) in the inavolisib arm and 9.6 months (95% CI: 7.4, 16.6) in the placebo arm, with a stratified HR of 0.57 (95% CI: 0.33, 0.99) (Figure 10)(54).

DoR at CCOD2 (39)

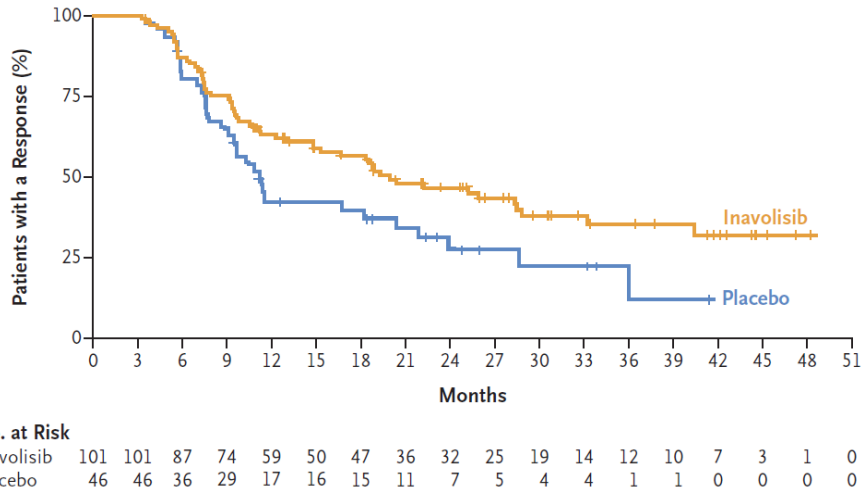


Figure 11 KM plot for DoR at CCOD (39).

Tick marks indicate censored data (CCOD2) Abbreviation: Duration of response – DoR; Confirmed objective response - COR; Clinical response – CR; Partial response – PR; Disease progression – DP.

DoR events occurred in 58 (57.4%) patients out of 101 patients in the inavolisib arm and in 33 (71.7%) patients out of 46 patients in the placebo arm. The median DoR was 19.2 months (95% CI: 14.7, 28.3) in the inavolisib arm and 11.1 months (95% CI: 8.5, 20.2) in the placebo arm, with a stratified HR of [redacted] (Figure 11)(39, 57).

7. Comparative analyses of efficacy

7.1.1 Differences in definitions of outcomes between studies

N/A.

7.1.2 Method of synthesis

N/A.

7.1.3 Results from the comparative analysis

Table 12 Results from the comparative analysis of inavolisib vs. placebo for patients with PIK3CA-Mutated Advanced BC (20, 39, 54, 57).

Outcome measure	Inavolisib (N=161)	Placebo (N=164)	Result	Inavolisib (N=161)	Placebo (N=164)	Result
	CCOD1 (20, 54)			CCOD2 (39, 57)		

Outcome measure	Inavolisib (N=161)	Placebo (N=164)	Result	Inavolisib (N=161)	Placebo (N=164)	Result
Median PFS, months	15.0 months (95% CI: 11.3, 20.5)	7.3 months (95% CI: 5.6, 9.3)	Difference: 7.7 HR: 0.43 (95% CI: 0.32, 0.59) P-value: <0.0001	17.2 months (95% CI: 11.6, 22.2)	7.3 months (95% CI: 5.6, 9.2)	Difference: 9.5 HR: 0.42 (95% CI: 0.32, 0.55) P-value: <0.0001
PFS, 6-months (%)	82.9%	55.9%	Difference: 27.01	83.4%	57.9%	Difference: 25.45
PFS, 12-months (%)	55.9%	32.6%	Difference: 23.28	58.0%	31.3%	Difference: 26.67
PFS, 18-months (%)	46.2%	21.1%	Difference: 25.14	49.7%	20.5%	Difference: 29.19
PFS, 24-months (%)	NE	NE	NE	41.8%	16.7%	Difference: 25.12
Median OS, months	NR (95% CI: 27.3, NR)	31.1 months (95% CI: 22.3, NR)	HR: 0.64 (95% CI: 0.43, 0.97)	34.0 months (95% CI: 28.4, 44.8)	27.0 months (95% CI: 22.8, 38.7)	Difference: 7.0 HR: 0.67 (95% CI: 0.48, 0.94)
OS, 6-months (%)	97.3%	89.9%	Difference: 7.4%	96.8%	90.1%	Difference: 6.7%
OS, 12-months (%)	86.0%	74.9%	Difference: 11.1%	87.0%	76.7%	Difference: 10.3%

Outcome measure	Inavolisib (N=161)	Placebo (N=164)	Result	Inavolisib (N=161)	Placebo (N=164)	Result
OS, 18-months (%)	73.7%	67.5%	Difference: 6.2%	74.3%	67.2%	Difference: 7.2%
OS, 24-months (%)				65.8%	56.3%	Difference: 9.5%
OS, 30-months (%)	NE	NE	NE	56.5%	46.3%	Difference: 10.3%
OOR	58.4%	25.0%	Difference: 33.4% (95% CI: 23.3, 43.5) P-value: <0.0001	62.7% (95% CI: 54.8, 70.2)	28.0% (95% CI: 21.3, 35.6)	Difference: 34.7% (95% CI: 24.5, 44.8) P-value: <0.0001
Complete Response	4.3%	0.6%	Difference: 3.7%			
Partial Response	54.0%	24.4%	Difference: 29.6%			
Stable disease	28.6%	48.2%	Difference: -19.6%			
Progressive Disease	4.3%	20.7%	Difference: -16.4%			
Missing	8.7%	6.1%	Difference: 2.6%			
BOR						

Outcome measure	Inavolisib (N=161)	Placebo (N=164)	Result	Inavolisib (N=161)	Placebo (N=164)	Result
CR						
Partial Response						%
Stable Disease						
Progressive Disease						
Missing						
CBR						
Median DoR	18.4 months (95% CI: 10.4, 22.2)	9.6 months (95% CI: 7.4, 16.6)	Difference: 8.8 HR: 0.57 (95% CI: 0.33, 0.99)	19.2 months (95% CI: 14.7, 28.3)	11.1 months (95% CI: 8.5, 20.2)	Difference: 8.1 HR: 0.60 (95% CI: 0.37, 0.97)
DoR, 6-months (%)						
DoR, 12-months (%)						
DoR, 18-months (%)						
DoR, 24-months (%)						

Outcome measure	Inavolisib (N=161)	Placebo (N=164)	Result	Inavolisib (N=161)	Placebo (N=164)	Result
				[redacted]	[redacted]	

Abbreviations: NR – Not Reached, NE – Not Estimated

7.1.4 Efficacy – results per [efficacy outcome]

N/A.

8. Modelling of efficacy in the health economic analysis

8.1 Presentation of efficacy data from the clinical documentation used in the model

8.1.1 Extrapolation of efficacy data

8.1.1.1 Extrapolation of PFS

As illustrated in Figure 5, the PFS1 KM data in the INAVO120 study is only available for 50 months. To estimate the clinical benefits of inavolisib beyond the INAVO120 study follow-up, the observed data for PFS1 was extrapolated over a lifetime horizon. The process of selecting the best fit parametric survival extrapolation for PFS1 was based on DMC guidance as seen in Table 13.

Table 13 Summary of assumptions associated with extrapolation of PFS.

Method/approach	Description/assumption
Data input	INAVO120
Model	Full parametrization
Assumption of proportional hazards between intervention and comparator	No. More details in Appendix D section D.1.3
Function with best AIC fit	Intervention: Log-Logistic Comparator: Log-normal
Function with best BIC fit	Intervention: Log-Logistic Comparator: Log-normal
Function with best visual fit	Intervention: Log-Logistic Comparator: Log-Logistic
Function with best fit according to evaluation of smoothed hazard assumptions	Intervention: Log-Logistic Comparator: Log-Logistic
Validation of selected extrapolated curves (external evidence)	Flat-Iron US-RWD.

Method/approach	Description/assumption
Function with the best fit according to external evidence	Intervention: Log-Logistic Comparator: Log-Logistic
Selected parametric function in base case analysis	Intervention: Log-Logistic Comparator: Log-Logistic
Adjustment of background mortality with data from Statistics Denmark	Yes
Adjustment for treatment switching/cross-over	Not applicable
Assumptions of waning effect	No
Assumptions of cure point	No

The goodness-of-fit of the selected parametric distributions (Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) statistics was evaluated and can be seen in Appendix D section D.1.4.

Figure 12 and Figure 13 present the visual fit of all parametric distributions to the KM PFS1 data for both treatment arms. All parametric distributions provided a relatively good fit for the observed KM data for both treatment arms. However, log-logistic was the only distribution which provided an excellent fit for both treatment arms. It is worth noting that the same independent parametric model was chosen for both treatment arms since the proportional hazard assumption does not hold (See Appendix D section D.1.3), in line with NICE DSU 14 guidelines (61).

Figure 12 Visual fit of the PFS1 extrapolations to KM for Inavolisib + palbociclib + fulvestrant.
Abbreviation: First progression free survival - PFS1

Figure 13 Visual fit of the PFS1 extrapolations to KM for Placebo + palbociclib + fulvestrant.

Abbreviation: First progression free survival - PFS1

The long-term projections for PFS1 for the placebo arm were validated for clinical robustness using real-world data (RWD) from the Flatiron Health database. This database is a US-based, longitudinal, observational database containing electronic health record data from over 265 cancer clinics including more than 2 million active U.S. cancer patients. Although this is an entirely US-based cohort, the baseline characteristics were restricted to reflect the INAVO120 study in terms of patients' clinical characteristics. In addition, the cohort only included patients who received Palbo+fulv as 1L treatment. More details about the selection criteria can be found in the poster presented at ASCO (62).

Table 14 presents the PFS1 estimates generated using all distributions against the Flatiron RWD. All distributions yielded lower PFS1 estimates than the RWD. However, the PFS1 estimates generated by log-normal, log-logistic and generalized gamma were very similar and were the closest to the RWD. Log-normal was excluded from the base-case analysis as upon visual inspection it underestimates the KM curve for the Inavolisib arm beyond month 26. Whereas generalized gamma provided a good fit to both treatment arms, its AIC/Bayesian Information Criterion (BIC) scores were higher than those for log-logistic. Therefore, log-logistic was selected in the base-case scenario as it provided an excellent fit to the KM data for both treatment arms and it had the best statistical fit (Figure 14).

Table 14 Long-term parametric PFS1 estimates for Placebo + palbociclib + fulvestrant compared to RWD

PFS1 estimates	Exponential	Weibull	Log-normal	Gen Gamma	Log-logistic	Gompertz	Gamma	Flatiron RWD
2-years	15%	16%	16%	17%	15%	17%	15%	22%
3-years	6%	7%	9%	10%	9%	10%	6%	14%
4-years	2%	3%	6%	6%	6%	7%	2%	10%
5-years	1%	1%	4%	4%	4%	5%	1%	7%

Figure 14 Log-logistic extrapolation of PFS1 for both treatment arms.
Abbreviation: First progression free survival - PFS1

8.1.1.2 Extrapolation of Proxy to PFS2

As shown in section 7, the time-to-event data for proxy to PFS2 was only available for 50 months. To estimate the clinical benefits of Inavolisib beyond the INAVO120 study follow-up, the KM data for proxy to PFS2 was extrapolated over a lifetime horizon. The same process based on guidance from the DMC guidance was followed for selecting the parameter distribution to model proxy to PFS2.

Table 15 Summary of assumptions associated with extrapolation of PFS2.

Method/approach	Description/assumption
Model	Full parametrization
Assumption of proportional hazards between intervention and comparator	No. More details in Appendix D section D.1.3
Function with best AIC fit	Intervention: Log-Logistic Comparator: Log-Logistic
Function with best BIC fit	Intervention: Log-Logistic Comparator: Log-Logistic
Function with best visual fit	Intervention: Log-Logistic Comparator: Log-Logistic
Function with best fit according to evaluation of smoothed hazard assumptions	Intervention: Log-Logistic Comparator: Log-Logistic
Validation of selected extrapolated curves (external evidence)	Flat-Iron US-RWD

Method/approach	Description/assumption
Function with the best fit according to external evidence	Intervention: Log-Logistic Comparator: Log-Logistic
Selected parametric function in base case analysis	Intervention: Log-Logistic Comparator: Log-Logistic
Adjustment of background mortality with data from Statistics Denmark	Yes
Adjustment for treatment switching/cross-over	Not applicable
Assumptions of waning effect	No
Assumptions of cure point	No

The goodness-of-fit of the selected parametric distributions (Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) statistics was evaluated and can be seen in Appendix D section D.1.4.

Figure 15 and Figure 16 illustrate the visual fit of all parametric distributions to the observed proxy of PFS2 data in the Inavolisib and placebo arms, respectively. As shown, all parametric distributions provided a relatively good fit to the observed KM data for both treatment arms.

Figure 15 Visual fit of proxy to PFS2 extrapolations to KM for inavolisib + palbociclib + fulvestrant.

Abbreviation: Second progression free survival – PFS2

Figure 16 Visual fit of proxy to PFS2 extrapolations for Placebo + palbociclib + fulvestrant.

Abbreviation: Second progression free survival – PFS2

It is worth noting that the same definition for "proxy to PFS2" as the one used in the INAVO120 study was used to select the RWD data (62, 63). A RWD cohort, similar to the one used to assess the clinical plausibility of the PFS1 extrapolation, was generated from the Flatiron Health Database. The only difference between cohorts is that the data used for proxy to PFS2 was not restricted to patients who had a PIK3CA-mutation. This is due to the very low sample size. Since PIK3CA-mutated patients have a worse prognosis than patients without the PIK3CA mutation, the proxy to PFS2 estimates from the INAVO120 study are expected to be slightly lower than the RWD estimates.

Table 16 shows the proxy to PFS2 estimates over time using various parametric distributions compared to RWD. It can be observed that log-logistic and gamma yielded the closest but slightly lower estimates compared to the RWD. Log-logistic was chosen in the base-case analysis as it provided a good fit to the observed KM data and it had the best statistical fit (Figure 17).

Table 16 Long-term proxy to PFS2 estimates for Placebo + palbociclib + fulvestrant compared to RWD.

Proxy to PFS2 estimates	Exponential	Weibull	Log-normal	Gen Gamma	Log-logistic	Gompertz	Gamma	Flatiron RWD
2-years	36%	35%	35%	34%	33%	36%	34%	35%
3-years	21%	18%	22%	20%	20%	20%	18%	22%
4-years	12%	9%	15%	12%	14%	11%	9%	15%
5-years	7%	4%	11%	7%	10%	6%	4%	12%
6-years	4%	2%	8%	5%	6%	3%	2%	8%

Figure 17 Log-logistic extrapolation of proxy to PFS2 for both treatment arms.

Abbreviation: Second progression free survival – PFS2

8.1.1.3 Extrapolation of Proxy to OS

As shown in Figure 7, the observed OS data was only available until month 50, hence the KM was extrapolated over a lifetime horizon to estimate the clinical benefits of inavolisib beyond the INAVO120 study follow-up. Similarly to the extrapolations of PFS1 and proxy to PFS2, the process of selecting the best fit parametric survival extrapolation for OS was based on guidance from the DMC.

Table 17 Summary of assumptions associated with extrapolation of OS

Method/approach	Description/assumption
Model	Full parametrization
Assumption of proportional hazards between intervention and comparator	No. More details in Appendix D section D.1.3
Function with best AIC fit	Intervention: Weibull Comparator: Exponential
Function with best BIC fit	Intervention: Weibull Comparator: Exponential
Function with best visual fit	Intervention: Gamma Comparator: Gamma
Function with best fit according to evaluation of smoothed hazard assumptions	Intervention: Gamma Comparator: Gamma
Validation of selected extrapolated curves (external evidence)	Flat-Iron US-RWD.

Method/approach	Description/assumption
Function with the best fit according to external evidence	Intervention: Gamma Comparator: Gamma
Selected parametric function in base case analysis	Intervention: Gamma Comparator: Gamma
Adjustment of background mortality with data from Statistics Denmark	Yes
Adjustment for treatment switching/cross-over	Not applicable
Assumptions of waning effect	No
Assumptions of cure point	No

The goodness-of-fit of the selected parametric distributions (Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) statistics was evaluated and can be seen in Appendix D section D.1.4.

The visual fit of all parametric distributions to the OS data for both treatment arms is presented in Figure 18 and Figure 19. Upon visual inspection, exponential and log-normal were excluded as they did not fit the KM data well for either treatment arm.

Figure 18 Visual fit of OS extrapolations for Inavo+palbo+fulv.

Abbreviation: Overall survival – OS

Figure 19 Visual fit of OS extrapolations for Placebo + palbociclib + fulvestrant

Abbreviation: Overall survival – OS

The clinical plausibility of the OS extrapolation was performed based on the same cohort of patients from the Flatiron dataset used to determine the extrapolation for PFS1(62, 63). As shown in

Table 18, all distributions projected similar OS estimates for the first 3 years. However, beyond year 3, the highest long-term survival was provided by the log-logistic distribution, followed by generalized gamma, gamma and Weibull. Compared to RWD, Weibull, generalized gamma and gamma yielded similar OS estimates. Log-logistic overestimated OS long-term, whereas Gompertz slightly underestimated it.

The generalized gamma was excluded from the base-case analysis as its OS extrapolations cross between treatment arms from year 5, which was deemed clinically implausible. In the base-case analysis, the gamma distribution was selected to extrapolate OS (Figure 20) as it fits the observed OS hazard better (i.e., hazard first increases and then decreases) than a Weibull distribution which assumes a monotonic underlying hazard.

Table 18 Long-term parametric OS estimates for Placebo + palbociclib + fulvestrant compared to RWD

OS estimates	Weibull	Gen gamma	Log-logistic	Gompertz	Gamma	Flatiron RWD
2-years	58%	57%	57%	58%	58%	54%
3-years	42%	42%	43%	42%	42%	40%
4-years	29%	30%	33%	29%	30%	28%
5-years	21%	22%	27%	19%	21%	23%
6-years	14%	16%	22%	12%	15%	15%

Figure 20 Gamma extrapolations for OS for both treatment arms

Abbreviation: Overall survival – OS

8.1.1.4 Extrapolation of Treatment duration

Treatment duration for both treatments arms was calculated in the model based on the time-to-off treatment (TTOT) data collected within the INAVO120 study to accurately report the costs associated with the resulting efficacy. Since patients in the INAVO120 study could discontinue inavolisib, palbociclib or fulvestrant independently, and those who discontinued inavolisib were allowed to continue receiving palbociclib or fulvestrant, TTOT for inavolisib, palbociclib and fulvestrant was estimated separately within each treatment arm. Since all treatments can be administered until disease progression only, it was assumed that Time-to-disease (TTD) cannot exceed PFS (i.e., PFS is used as a ceiling for TTD).

Figure 21 and Figure 22 illustrate the KM TTOT data in the INAVO120 study for both treatment arms. The KM TTOT curves for inavolisib, palbociclib and fulvestrant in the inavolisib arm overlap which suggests that inavolisib was well tolerated by patients. A similar overlap can be observed for the KM TTOT curves for palbociclib and fulvestrant in the placebo arm. For both treatment arms, the individual KM TTOT curves for each drug were very similar, the same parametric distribution was selected to model the TTOT drug curves. In addition, in line with NICE DSU 14 guidelines, this parametric distribution was chosen for both treatment arms (61).

The goodness-of-fit of the selected parametric distributions, AIC and BIC statistics, was evaluated and can be seen in Appendix D section D.1.4.

Figure 21 KM plot for TTOT – Inavolisib arm.

Abbreviation. Time to off-treatment – TTOT

Figure 22 KM plot for TTOT – Placebo arm.

Abbreviation: Time to off-treatment - TTOT

As shown in Figure 23, Figure 24 and Figure 25, all distributions seemed to fit the KM TTOT curves well apart from log-normal and log-logistic which overestimated TTOT. In the placebo arm, all distributions provided a good visual fit for the KM curves (Figure 26 and Figure 27).

Figure 23 Visual fit of extrapolations of TTOT – Inavolisib (inavolisib arm).

Abbreviation: Time to off-treatment – TTOT

Figure 24 Visual fit of extrapolations of TTOT – Palbociclib (inavolisib arm).

Abbreviation: Time to off-treatment – TTOT

Figure 25 Visual fit of extrapolations of TTOT – Fulvestrant (inavolisib arm).

Abbreviation: Time to off-treatment - TTOT

Figure 26 Visual fit of extrapolations of TTOT – Palbociclib (placebo arm).

Abbreviation: Time to off-treatment - TTOT

Figure 27 Visual fit of extrapolations of TTOT – Fulvestrant (placebo arm).

Abbreviation: Time to off-treatment – TTOT

Since PFS1 is used as a ceiling for TTOT, log-normal, log-logistic and gompertz were excluded from the base-case analysis because they projected TTOT estimates higher than the PFS1 estimates. Table 19 provides the TTOT estimates for inavolisib compared to PFS1 over time. Based on clinical experts' opinion at the UK ad board held in April 2025, gamma (Figure 28 and Figure 29) was selected in the base-case analysis.

Table 19 TTOT estimates for inavolisib compared to PFS1 estimates over time

	PFS estimates	TTOT estimates (inavolisib)			
	Base-case (log-logistic)	Exponential	Weibull	Gamma	Generalized Gamma
5-years	15%	9%	11%	10%	13%
7-years	10%	3%	5%	4%	7%
10-years	6%	0%	1%	1%	3%

Figure 28 Gamma extrapolation for TTOT for the inavolisib arm.

Abbreviation: Time to off-treatment - TTOT

Figure 29 Gamma extrapolation for TTOT for the placebo arm.

Abbreviation: Time to off-treatment - TTOT

8.1.2 Calculation of transition probabilities

We applied a partitioned survival model so the transition probabilities are based on the PFS and OS curves from INAVO120 study. Extrapolation beyond the clinical follow-up period was performed by fitting parametric distributions to the observed time to event data from the trial.

Table 20 Transitions in the health economic model

Health state (from)	Health state (to)	Description of method	Reference
PFS	Recurrence	Extrapolation with log-logistic distribution	INAVO120
PFS2	Recurrence	Extrapolation with log-logistic distribution	INAVO120
OS	Death	Extrapolation with Gamma distribution	INAVO120

The results subject to long-term treatment effect and survival assumptions are demonstrated in Figure 30 and Figure 31. These Markov trace figures are based on the model and show the proportion of patients who are in the progression-free, PD1, PD2 and death state. The figures support the chosen lifetime perspective of 46 years.

Figure 30 Markov trace inavolisib arm.

Figure 31 Markov trace placebo arm.

8.2 Presentation of efficacy data from [additional documentation]

N/A.

8.3 Modelling effects of subsequent treatments

See Section 11.6.

8.4 Other assumptions regarding efficacy in the model

N/A.

8.5 Overview of modelled average treatment length and time in model health state

Table 21 Estimates in the model

	Modelled average [effect measure] (reference in Excel)	Modelled median [effect measure] (reference in Excel)	Observed median from relevant study
Inavolisib	25.0	16.8	16.8
Palbociclib	24.5	16.6	16.6
Fulvestrant	24.9	17.2	17.2
	Model inputs G-I118	Model inputs G-I117	
Palbociclib	12.4	8.5	8.5 Months
Fulvestrant	12.6	9.0	9.0 Months
	Model inputs G-H124	Model inputs G-H123	

Table 22 Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction

Treatment	Treatment length [months]	Health state 1 [months]	Health state 2 [months]
Inavolisib + palbociclib + fulvestrant	45.06	31.64	5.88
Placebo + palbociclib + fulvestrant	38.86	15.25	10.67

9. Safety

9.1 Safety data from the clinical documentation

All analyses of safety are descriptive in nature, as no formal statistical hypothesis testing was performed. Safety analyses described in this section were conducted for patients exposed to any study treatment, with patients assessed according to the trial agents they received.

At CCOD1, this population included 162 patients in each study arm. Patients in the inavolisib arm received inavolisib for a median of 9.2 months; palbociclib, for 9.1 months; and fulvestrant, for 8.6 months (54). The median relative dose intensities were 95.8%, 87.3%, and 100.0%, respectively. Patients in the placebo arm received placebo for a median of 5.6 months; palbociclib, for 5.6 months; and fulvestrant, for 5.6 months. The median relative dose intensities were 88.4% for palbociclib and 100.0% for fulvestrant (54).

At CCOD2, the safety-evaluable patient population included 161 patients in the inavolisib arm and 163 patients in the placebo arm (39). Patients in the inavolisib arm received inavolisib for a median of 13.1 months; palbociclib, for 13.8 months; and fulvestrant, for 14.1 months. The median relative dose intensities were 95.4%, 83.8%, and 94.7%, re-

spectively. Patients in the placebo arm received placebo for a median of 7.5 months; palbociclib, for 7.2 months; and fulvestrant, for 7.5 months. The median relative dose intensities were 86.7% for palbociclib and 94.1% for fulvestrant (39).
Patients were monitored for AEs throughout the study treatment, following informed consent until 30 days after the final dose of study treatment or until initiation of another anti-cancer therapy, whichever occurred first (20). Table 23 provides an overview of safety events.

Table 23 Overview of safety events in the INAVO120 study for CCOD1 and CCOD2. See text above for median treatment duration.

	Inavolisib (N=162)	Placebo (N=162)	Difference, % (95 % CI)	Inavolisib (N=161)	Placebo (N=163)	Difference, % (95 % CI)
	CCOD1 (20, 54, 64)			CCOD2 (39, 57, 59)		
Number of adverse events, n	[redacted]					
Number and proportion of patients with ≥1 adverse events, n (%)	160 (98.8%)	162 (100%)		161 (100%)	163 (100%)	
Number of serious adverse events, n	[redacted]					
Number and proportion of patients with ≥ 1 serious adverse events*, n (%)	39 (24.1%)	17 (10.5%)		44 (27.3%)	22 (13.5%)	
Number of CTCAE grade ≥ 3 events, n	N/A	N/A		N/A	N/A	
Number and proportion of patients with ≥ 2 CTCAE grade ≥ 1 events*, n (%)	149 (92.0%)	135 (83.3%)		152 (94.4%)	140 (85.9%)	
Number of adverse reactions, n	NR	NR		NR	NR	
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

	Inavolisib (N=162)	Placebo (N=162)	Difference, % (95 % CI)	Inavolisib (N=161)	Placebo (N=163)	Difference, % (95 % CI)
	CCOD1 (20, 54, 64)			CCOD2 (39, 57, 59)		
Inavolisib/Placebo	[redacted]					
Palbociclib	[redacted]					
Fulvestrant	[redacted]					
Number and proportion of patients who had a dose reduction, n (%)	[redacted]					
Inavolisib/placebo	23 (14.2%)	5 (3.1%)		24 (14.9%)	6 (3.7%)	
Palbociclib	61 (37.7%)	49 (30.2%)		65 (40.4%)	56 (34.4%)	
AE leading to dose modification/interruption of treatment	134 (82.7%)	121 (74.7%)		140 (87.0%)	126 (77.3%)	
Inavolisib/Placebo	113 (69.8%)	57 (35.2%)		117 (72.7%)	67 (41.1%)	
Palbociclib	125 (77.2%)	116 (71.6%)		130 (80.7%)	121 (74.2%)	
Fulvestrant	52 (32.1%)	34 (21.0%)		55 (34.2%)	40 (24.5%)	
AE leading to interruption of treatment	[redacted]					
Inavolisib/placebo	112 (69.1%)	56 (34.6%)		116 (72.0%)	66 (40.5%)	
Palbociclib	115 (71.0%)	99 (61.1%)		119 (73.9%)	106 (65.0%)	
Fulvestrant	52 (32.1%)	34 (21.0%)		55 (34.2%)	40 (24.5%)	
Number and proportion of patients who discontinue	NR	NR		NR	NR	

	Inavolisib (N=162)	Placebo (N=162)	Difference, % (95 % CI)	Inavolisib (N=161)	Placebo (N=163)	Difference, % (95 % CI)
	CCOD1 (20, 54, 64)			CCOD2 (39, 57, 59)		
treatment regardless of reason, n (%)						
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	11 (6.8%)	1 (0.6%)		14 (8.7%)	1 (0.6%)	
Inavolisib/Placebo	10 (6.2%)	1 (0.6%)		11 (6.8%)	1 (0.6%)	
Palbociclib	8 (4.9%)	0		10 (6.2%)	0	
Fulvestrant	5 (3.1%)	0		6 (3.7%)	0	

* Grade 3-4+5.

Adverse Events (AEs)

CCOD1

In the safety analysis population, 160 patients (98.8%) of 162 patients in the inavolisib arm experienced at least one AE (54). In the placebo arm, 162 patients (100.0%) of 162 patients experienced at least one AE (Table 23) (54). Inavolisib in combination with palbociclib and fulvestrant in patients with PIK3CA mutated, HR+/HER2-, LA or mBC demonstrated manageable safety and tolerability profile as shown by the high median relative dose intensity of inavolisib and low treatment discontinuation rate at 6.8% in the inavolisib arm (20). The safety profile of the inavolisib treatment regimen was consistent with the known safety profile of each individual study drug component and the underlying disease. The addition of inavolisib did not compromise the dose intensity of palbociclib and fulvestrant. Overall, the triplet combination showed good tolerability. No new safety signals were identified (20). Some of the AEs in the stated time period, which occurred in at least 20% of the patients of any grade, were selected and are presented in Table 24 (54).

CCOD2

At CCOD2, the inavolisib arm continued to demonstrate manageable safety and good tolerability and remained consistent with that observed at the time of the CCOD1 and with the known risks of each individual study drug component and the underlying disease (39). All patients (100%) in both treatment arms reported at least one AE of any grade (39). While some differences were noted between treatment arms for specific AEs, the incidence and severity of these events were consistent with the anticipated safety profile of inavolisib and the respective safety profiles of palbociclib and fulvestrant (57). No new safety signals were identified (Table 23)(39).

Selected AEs (grouped terms)

CCOD1

Selected AEs of any grade that occurred in ≥20% of the patients in either study arm are presented in Table 24 (54). Data are for the safety analysis population, which included all the patients who had received at least one dose of any trial agent, with patients assessed according to the trial agents they received. Neutropenia, thrombocytopenia, stomatitis and mucosal inflammation, anemia, hyperglycemia, diarrhea, nausea, rash, and ocular toxic effects were assessed as grouped terms (i.e., AE´s grouped according to medical concept) and used to assess selected AEs on the basis of the known safety profile of inavolisib (39, 54). The selected AEs of any grade included neutropenia (inavolisib: 88.9%; placebo: 90.7%), thrombocytopenia (inavolisib: 48.1%; placebo: 45.1%), stomatitis or mucosal inflammation (inavolisib: 51.2%; placebo: 26.5%), anemia (inavolisib: 37.0%; placebo: 36.4%), hyperglycemia (inavolisib: 58.6%; placebo: 8.6%), diarrhea (inavolisib: 48.1%; placebo: 16.0%), nausea (inavolisib: 27.8%; placebo: 16.7%), rash (inavolisib: 25.3%; placebo: 17.3%), decreased appetite (inavolisib: 23.5%; placebo: 8.6%), fatigue (inavolisib: 23.5%; placebo: 13.0%), covid-19 (inavolisib: 22.8%; placebo: 10.5%), headache (inavolisib: 21.0%; placebo: 13.6%), leukopenia (inavolisib: 17.3%; placebo: 24.7%), and ocular toxic effects (inavolisib: 22.2%; placebo: 13.0%) (Table 24) (54). The majority of selected AEs were of Grade 1 or 2 in severity except for neutropenia in which Grade 3-4 neutropenia was reported in 130 patients (80.2%) and 127 patients (78.4%) in the inavolisib arm and the placebo arm, respectively. There were no Grade 5 selected AEs in either arm (20). Febrile neutropenia occurred in 2.5% of the patients in the inavolisib arm and 0.6% in the placebo arm (54). Hyperglycemia (known on-target, reversible toxicity associated with PI3K pathway inhibition) in the inavolisib arm were mainly Grade 1 (16.0%) or Grade 2 (37.0%), and reversible. 2 (1.2%) patients discontinued from the study due to hyperglycemia and Type 2 diabetes mellitus) (20). All events were non-serious, and manageable with oral anti-hyperglycemic agents and dose reductions (2.5%) or interruptions (27.8%) in all patients, including pre-diabetic patients in the inavolisib arm. Grade 3 hyperglycemia events were reported in 9 (5.6%) patients in the inavolisib arm and no Grade 4 or Grade 5 hyperglycemia events were reported in either arm (20). The incidence of hyperglycemia was 65.5% among patients in the inavolisib group with a BMI of ≥30.0 and 56.8% among those with a BMI of ≤30.0 (54).

CCOD2

At CCOD2, a comparable proportion of patients experienced selected AEs in the inavolisib (98.1%) and the placebo arm (96.3%) (39, 57). Selected AEs (grouped terms) occurring at any grade were more common in the inavolisib group than in the placebo group (39). These events included hyperglycemia (inavolisib: 63.4%; placebo: 13.5%), stomatitis or mucosal inflammation (inavolisib: 55.3%; placebo: 28.8%), diarrhea (inavolisib: 52.2%; placebo: 16.0%), rash (inavolisib: 26.7%; placebo: 19.6%), thrombocytopenia (inavolisib: 49.7%; placebo: 46.0%), anemia (inavolisib: 39.8%; placebo: 38.0%), nausea (inavolisib: 29.2%; placebo: 19.6%), ocular toxic effects (inavolisib: 29.2%; placebo: 16.0%), increased Aspartate Aminotransferase or Alanine Aminotransferase level (inavolisib: 21.1%; placebo: 22.7%), vomiting (inavolisib: 16.1%; placebo: 6.1%), lymphopenia (inavolisib: 3.7%; placebo: 9.2%), and pneumonitis (inavolisib: 3.1%; placebo: 1.2%). In both study arms, neutropenia of any grade occurred in more than 90% of the patients (Table 24)(39).

The majority of selected AEs continued to be of Grade 1 or 2 in severity at the updated CCOD, except for neutropenia in which reports on Grade 3-4 were increased to 133 (82.6%) and 131 (80.4%) patients in the inavolisib arm and the placebo arm, respectively. There were no Grade 5 selected AEs in either arm at the updated CCOD (57).

Hyperglycemia were reported in the inavolisib arm, where 17.4% patients experienced Grade 1 and 39.1% patients experienced Grade 2 hyperglycemia (57). All events of hyperglycemia continued to be non-serious, and manageable with oral anti-hyperglycemic agents and dose reductions (2.5%) or interruptions (29.2%) in all patients including pre-diabetic patients in the inavolisib arm (57). Grade 3 hyperglycemia were reported in 11 (6.8%) patients in the inavolisib arm, no Grade 4 or Grade 5 hyperglycemia events were reported in either arm at the updated CCOD (57). Grade 2 events of diarrhea occurred in 29 (18.0%) patients in the inavolisib group and 7 (4.3%) patients in the placebo group (39). The most common ocular toxic effects that were observed were dry eye (in 14 patients [8.7%] in the inavolisib group and 7 patients [4.3%] in the placebo group) and blurred vision (in 8 [5.0%] and 2 [1.2%], respectively). All were grade 1 or 2 events (39). The event of covid-19 occurred more frequently in the inavolisib arm (24.2%) in comparison to the placebo arm (11.0%). This was anticipated to be related to the longer AE collection and observation period in the inavolisib arm due to the longer treatment exposure (39, 57).

Table 24 Selected AEs (grouped terms) of any grade that occurred ≥20% of the patients in either trial group.

Adverse events	Inavolisib (N=162)		Placebo (N=162)		Inavolisib (N=161)		Placebo (N=163)	
	CCOD1 (54)				CCOD2 (39)			
	Any Grade AE	Grade 3 or 4	Any Grade AE	Grade 3 or 4	Any Grade AE	Grade 3 or 4	Any Grade AE	Grade 3 or 4
Neutropenia, n (%)	144 (88.9)	130 (80.2)	147 (90.7)	127 (78.4)	147 (91.3)	133 (82.6)	148 (90.8)	131 (80.4)
Thrombocytopenia, n (%)	78 (48.1)	23 (14.2)	73 (45.1)	7 (4.3)	80 (49.7)	22 (13.7)	75 (46.0)	8 (4.9)
Stomatitis and mucosal inflammation, n (%)	83 (51.2)	9 (5.6)	43 (26.5)	0	89 (55.3)	9 (5.6)	47 (28.8)	0
Anemia, n (%)	60 (37.0)	10 (6.2)	59 (36.4)	3 (1.9)	64 (39.8)	11 (6.8)	62 (38.0)	3 (1.8)
Hyperglycemia, n (%)	95 (58.6)	9 (5.6)	14 (8.6)	0	102 (63.4)	11 (6.8)	22 (13.5)	0
Diarrhea, n (%)	78 (48.1)	6 (3.7)	26 (16.0)	0	84 (52.2)	6 (3.7)	26 (16.0)	0
Nausea, n (%)	45 (27.8)	1 (0.6)	27 (16.7)	0	47 (29.2)	0	32 (19.6)	0
Rash, n (%)	41 (25.3)	0	28 (17.3)	0	43 (26.7)	0	32 (19.6)	1 (0.6)
Decreased appetite, n (%)	38 (23.5)	0	14 (8.6)	0	NR	NR	NR	NR
Fatigue, n (%)	38 (23.5)	0	21 (13.0)	2 (1.2)	NR	NR	NR	NR
Covid-19, n (%)	37 (22.8)	3 (1.9)	17 (10.5)	1 (0.6)	NR	NR	NR	NR
Headache, n (%)	34 (21.0)	0	22 (13.6)	0	NR	NR	NR	NR
Leukopenia, n (%)	28 (17.3)	11 (6.8)	40 (24.7)	17 (10.5)	NR	NR	NR	NR
Ocular toxic effects, n (%)	36 (22.2)	0	21 (13.0)	0	47 (29.2)	1 (0.6)	26 (16.0)	0

Abbreviations: NR – Not Reported; Covid-19 - coronavirus disease 2019.

Grade 3-4 AEs

CCOD1
The percentage of reported grade 3-4 AE´s were comparable between the inavolisib arm (88.3%) and placebo arm (82.1%) (65). The grade 3 or 4 incidence rates were driven by neutropenia (inavolisib: 80.2%; placebo: 8.4%), stomatitis or mucosal inflammation (inavolisib: 5.6%; placebo: 0%), hyperglycemia (inavolisib: 5.6%; placebo: 0%), and diarrhea (inavolisib: 3.7%; placebo: 0%). No grade 3 or 4 rash was reported (54).

CCOD2
At CCOD2, grade 3 or 4 AE´s were reported in a higher percentage of patients in the inavolisib arm than in the placebo arm (90.7% vs. 84.7%) (39, 59). Specifically, the most common grade 3 or 4 selected hematologic AE´s included neutropenia (inavolisib: 82.6%; placebo: 80.4%), thrombocytopenia (inavolisib:13.7%; placebo:4.9%), and anemia (inavolisib: 6.8%; placebo: 1.8%). The most common grade 3 or 4 selected nonhematologic AEs included hyperglycemia (inavolisib: 6.8%; placebo: 0%), stomatitis or mucosal inflammation (inavolisib: 5.6%; placebo: 0%), elevated aspartate aminotransferase or alanine aminotransferase level (inavolisib: 4.3%; placebo: 2.5%), and diarrhea (inavolisib: 3.7%; placebo: 0%) (39).

Serious Adverse Events (SAEs)

CCOD1
No SAEs with a frequency of ≥5% were reported in the INAVO120 study (Table 25) (20). SAEs occurred in 39 (24.1%) patients in the inavolisib arm and in 17 (10.5%) patients in the placebo arm (54). All SAEs reported in the INAVO120 study can be found in Appendix E (20). Grade 5 (fatal) AE´s were reported in 6 (3.7%) patients in the inavolisib arm and in 2 (1.2%) patients in the placebo arm (54). In the inavolisib group, grade 5 AE´s were acute coronary syndrome, covid-19, cerebral hemorrhage, cerebrovascular accident, and gastrointestinal hemorrhage in one patient each; no information was available for the sixth patient who died (54). In the placebo group, grade 5 AE´s included cardiac arrest and covid-19 pneumonia in one patient each. None of the deaths were considered by the investigator to be related to the trial agents (54).

CCOD2
No SAEs with a frequency of ≥5% were reported in the INAVO120 study at CCOD2 (Table 25) no new Grade 5 AEs were reported since CCOD1 (39, 57). The proportion of patients with SAEs was higher in the inavolisib arm than in the placebo arm (in 44 (27.3%) patients vs. 22 (13.5%) patients) which was consistent with what was observed at the time of primary analysis (Appendix E) (39).

Table 25 Serious adverse events with frequency of ≥ 5% in the INAVO120 study*(20).

Adverse events	Inavolisib (N=162)		Placebo (N=162)		Inavolisib (N=161)		Placebo (N=163)	
	CCOD1				CCOD2			
	Number of AEs	Number of patients with AEs	Number of AEs	Number of patients with AEs	Number of AEs	Number of patients with AEs	Number of AEs	Number of patients with AEs

Adverse events	Inavolisib (N=162)		Placebo (N=162)		Inavolisib (N=161)		Placebo (N=163)	
	CCOD1				CCOD2			
AE, n (%)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

*No SAEs with a frequency of ≥5% were reported in the INAVO120 study. SAEs were reported at a frequency of <2.5% (Appendix E).

AEs leading to treatment discontinuation or dose reduction

CCOD1

AEs led to the discontinuation of any trial agent in 11 (6.8%) patients in the inavolisib arm (inavolisib: 10 (6.2%) patients; palbociclib: 8 (4.9%) patients; fulvestrant: 5 (3.1%) patients) and in 1 (0.6%) patient in the placebo arm (no patients discontinued palbociclib or fulvestrant because of AEs) (Table 23) (54). AEs led to a dose reduction in 23 (14.2%) patients in the inavolisib arm and in 5 (3.1%) patients in the placebo arm. Hyperglycemia led to a reduction in 4 (2.5%) patients in the inavolisib arm and was the only AE leading to a reduction in the inavolisib dose in ≥2% of the patients (54).

CCOD2

At CCOD2, AEs led to the discontinuation of inavolisib in 6.8% of the patients and to the discontinuation of placebo in 0.6% (Table 23) (39). AEs led to inavolisib dose interruptions in 72.0% of the patients in the inavolisib group and to placebo dose interruptions in 40.5% of those in the placebo group. AEs led to a dose reduction in 24 (14.9%) patients in the inavolisib arm and in 6 (3.7%) patients in the placebo arm (39).

Table 26 Adverse events used in the health economic model (Treatment-Emergent Adverse Events (TEAEs))

Adverse events	Intervention	Comparator		
	Frequency used in economic model for intervention	Frequency used in economic model for comparator	Source	Justification
Anemia	11 (6.8%)	5 (3%)	As seen in INAVO120 (57)	
Leukopenia	11 (6.8%)	18 (11%)		
Neutropenia	79 (49.1%)	81 (49.4%)		
Thrombocytopenia	8 (5%)	3 (1.8%)		
Diarrhea	6 (3.7%)	3 (1.8%)		
Neutrophils count decreased	58 (36%)	54 (32.9%)		
Platelet count decreased	14 (8.7%)	5 (3%)		
White blood cell count decreased	22 (13.7%)	18 (11%)		
Hyperglycemia	9 (5.6%)	0		

Adverse events	Intervention	Comparator
Alanine aminotransferase increased	7 (4.3%)	0
Infection	0	0
Hepatobiliary toxicity	0	0
QT interval prolongation	0	0

9.2 Safety data from external literature applied in the health economic model

Table 27 Adverse events that appear in more than X % of patients

Adverse events	Intervention (N=x)	Comparator (N=x)	Difference, % (95 % CI)
		N/A	

10. Documentation of health-related quality of life (HRQoL)

Table 28 Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
European Quality of Life 5-Dimension, 5-Level questionnaire (EQ-5D-5L)	INAVO120 (WO41554)	EQ-5D-5L was used to assess health status.
European Organisation for Research and Treatment of Cancer Quality of Life-Core 30 Questionnaire (EORTC QLQ-C30)	INAVO120 (WO41554)	The EORTC QLQ-C30 assessed disease and treatment-related symptoms often experienced by patients with LA or metastatic cancer including fatigue, pain, depression/anxiety, and any limitations in function. Completion and results can be found in Appendix F.
Brief Pain Inventory-Short Form (BPI-SF)	INAVO120 (WO41554)	The “worst pain” item from the BPI-SF was used to evaluate an increase in pain severity. Completion and results can be found in Appendix F.

10.1 Presentation of the health-related quality of life

10.1.1 Study design and measuring instruments

PRO data were collected with the EORTC QLQ-C30, BPI-SF and EQ-5D-5L to more fully characterize the clinical profile of inavolisib in combination with palbociclib and fulvestrant compared with placebo plus palbociclib and fulvestrant (34).

The EORTC QLQ-C30 is a validated and reliable self-reported measure. It consists of 30 questions that assess 5 aspects of patient functioning (physical, emotional, role, cognitive, and social), eight symptom scales (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, and diarrhea), financial difficulties, and Global Health Status (GHS)/HRQoL with a recall period of the previous week (34, 66-68).

The BPI-SF is a widely used patient-reported outcome measure for assessing pain, and the “worst pain” item is frequently recommended for evaluating increases in the severity of pain. The item asks patients to rate their pain at its worst in the last week on a scale from 0 to 10 (34, 69, 70).

The EQ-5D-5L is a validated self-report health status questionnaire that is used to calculate a health status utility score for use in health economic analyses. Two components to the EQ-5D-5L were utilized: a five-item health state profile that assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, as well as a VAS that measures health state. Published weighting systems allowed for creation of a single composite score of the patient's health status (34, 71-74).

MBC is not curable with currently approved and available therapies, and the primary focus for patients is on living as long as possible and delaying the progression of cancer while maintaining their quality of life and the ability to carry out daily activities (58). Disease-related pain may be an important variable to assess during treatment, and a higher proportion of HR+ patients develops bone metastases, which is often associated with pain (75, 76). It is hypothesized that progression of disease would be associated with an increase in pain symptoms, and examining and measuring patients’ disease-related pain and interference with functioning is important to capture. These issues will be assessed using abovementioned validated PRO assessments in patients enrolled in the study (34).

10.1.2 Data collection

HRQoL data were collected at multiple predefined time points throughout the INAVO120 study to capture patient-reported outcomes across the treatment and follow-up phases. Assessments were conducted at baseline (prior to treatment initiation), and on Day 1 of each 28-day treatment cycle, starting from Cycle 2 and continuing until treatment discontinuation. Further assessments were performed at the time of treatment discontinuation, during the 30-day safety follow-up, and throughout the post-treatment and survival follow-up period, with measurement points extending up to month 57 (57).

Summary statistics (mean, standard deviation, median, and range) of linear transformed scores were reported for all scales (symptoms, functional domains GHS/Quality of Life (QoL)) of the EORTC QLQ-C30 for each assessment time point, and the “worst pain” item of the BPI-SF. The mean change of the linear transformed scores from baseline (and 95% CI using the normal approximation) was reported independently for each treatment arm. Line charts depicting the mean and mean changes from the baseline assessment (and 95% CIs) of items and scales over time will be provided for each treatment arm. In the event of incomplete data, for all questionnaire scales, if more than 50% of the constituent items were completed, a pro-rated score was computed consistent with the scoring manuals and validation papers. For scales with less than 50% of the items completed, the

scale was considered as missing in accordance with the EORTC scoring manual guidelines. PRO completion, compliance rates, and reasons for missing data were summarized at each time point by treatment arm for each measure in ITT patients. The compliance rate was based on the total number of patients expected to complete the questionnaire at a particular time point (34). The questionnaire completion rates for each measure are defined as the proportion of patients who answered at least one question out of the total number of patients expected at each visit (57).Pattern of missing data and completion for EORTC QLQ-C30 and BPI-SF at CCOD1 are listed in Table 61 and Table 62, respectively in Appendix F. Pattern of missing data and completion for EORTC QLQ-C30 and BPI-SF at CCOD2 are listed in Table 63 and Table 64, respectively in Appendix F. Treatment Discontinuation, 30 Day Safety Follow-up, Post-Treatment Follow Up and Survival Follow-up for EQ-5D-5L at CCOD are listed in Table 65 in Appendix F. Pattern of missing data and completion for EQ-5D-5L at CCOD2 are listed in Table 29.

Table 29 Pattern of missing data and completion for EQ-5D-5L at CCOD2. All tests were performed on Day 1 in the cycle (77).

Time point	HRQoL population N		Missing N (%)		Expected to complete N		Completion N (%)	
	Number of patients at randomization		Number of patients for whom data is missing (% of patients at randomization)		Number of patients "at risk" at time point X		Number of patients who completed (% of patients expected to complete)	
	Inavolisib	Placebo	Inavolisib	Placebo	Inavolisib	Placebo	Inavolisib	Placebo
[redacted]								

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
[redacted]				

Abbreviations: NR – Not Reported.

Completion rates for the EORTC QLQ-C30 (Table 63) and BPI-SF (Table 68) were high at baseline in both treatment arms: 92.5% (EORTC QLQ-C30) and 93.1% (BPI-SF) in the inavolisib arm, and 92.7% (EORTC QLQ-C30) and 94.5% (BPI-SF) in the placebo arm. The completion rate remained >75% through Cycle 37 (for almost all time points) in both treatment arms. Rates remained above 75% at the treatment discontinuation and 30-day safety follow-up visits, but were difficult to interpret at subsequent tumor assessment visits during the follow-up period as few patients were included at CCOD, and dropped off at the 3-month survival follow-up (<25%) (57). Missing responses at certain time points were primarily attributable to disease progression, deterioration in general condition or treatment discontinuation.

10.1.3 HRQoL results

PRO Scores and Change from Baseline by Visit for EORTC QLQ-C30 at CCOD1 are listed in Table 66 in Appendix F. PRO Scores and Change from Baseline by Visit for EORTC QLQ-C30 and BPI-SF at CCOD2 are listed in Table 67 and Table 68, respectively in Appendix F. Treatment Discontinuation, Post-Treatment Follow Up, 30 Day Safety Follow-up and Survival Follow-up for EQ-5D-5L at CCOD2 are listed in Table 69 in Appendix F.

Figure 32 Mean Change from Baseline with 95%CI in EORTC QLQ–C30 GHS/QoL at CCOD2 (57).

The observations are based on data from up to 305 unique patients (149 in the inavolisib arm and 156 in the placebo arm) who completed at least one EORTC QLQ-C30 GHS/QoL assessment.
PRO completed (n): Number of patients who completed the HRQoL questionnaire at the respective cycle. PRO not completed (n): Number of patients who were expected to respond but did not. Missing responses at certain time points were primarily attributable to disease progression, deterioration in general condition or treatment discontinuation. PRO expected (n): Total number of patients who were on study at the specific time point and therefore expected to provide a response.

Table 30 PRO Scores and Change from Baseline by Visit for EQ-5D-5L at CCOD2. All tests were performed on Day 1 in the cycle (77).

	Inavolisib (N=15161)		Placebo (N=164)		Inavolisib vs. placebo
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
[redacted]					

	Inavolisib (N=15161)	Placebo (N=164)	Inavolisib vs. placebo
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			

Abbreviations: Not Applicable – N/A.

The addition of inavolisib did not contribute to increased treatment burden in patients, as indicated by the majority of patients in both arms reporting levels of selected symptoms from the PRO Common Terminology Criteria for Adverse Events (PRO-CTCAE) and overall bother from treatment side effects at moderate levels or less (20).

10.2 Health state utility values (HSUVs) used in the health economic model

10.2.1 HSUV calculation

Patients' HRQoL was measured in the INAVO120 study by administering the EQ-5D-5L questionnaire. By applying Danish EQ-5D-5L (78) tariff value in accordance to the DMC guidance, the EQ-5D-5L data was converted to utilities.

To estimate the utility data collected within the INAVO120 study, a linear mixed effects model (LMEM) with normal random subject effects was performed which included the following covariates: health state, time from randomization, treatment arm baseline utility, age, gender, baseline ECOG and study stratification factors (i.e., visceral disease, endocrine-resistance status and geography). The model was fitted on the change from baseline utility value as this distribution is closer to normal than the skewed absolute values. The utility values can be seen in Figure 33.

It is worth noting that in LMEMs, handling missing data operates under the assumption that data are missing at random, which means that the likelihood of missingness depends on observed values rather than unobserved values. The model does not explicitly impute missing data, but rather leverages all available data points, including incomplete cases, to provide unbiased fixed effect estimates. Covariates play a crucial role in this process, as the model assumes that for a time point with missing data for a patient, the

unobserved values would behave similarly to those of anyone with the same covariate values, with the addition of the estimated random subject effect for that patient. By including random effects for subjects and other grouping factors, LMEMs account for missingness within the hierarchical structure of the data, ensuring robust estimates from the observed data.

HSUVs have been age-adjusted by applying a multiplicative adjustment index from a Danish perspective in accordance with section 7.3 of the methods guide.

Figure 33 Graphical Display of Utilities per (Jensen et al 2021) (78)

Table 31 Utility estimates using the Danish tariff, in accordance with DMC guidance, for PFS, PD1 and PD2 – Separated treatment arms

Health state	Inavo+p+f		Placebo+p+f	
	Mean estimate	SE	Mean estimate	SE
PFS	0.861	0.010	0.857	0.011
PD1	0.774	0.015	0.762	0.013
PD2	0.728	0.032	0.811	0.047

The utility for PD2 derived from the INAVO120 study is based on very small number of observations (n=30) and it is much higher than other values used in the literature. Clinical experts in an ad-board held in the UK for Inavolisib also confirmed that the utility for PD2 seems too high and did not recommend its use in the base-case analysis.

To circumvent this issue, the treatment arms were pooled and external literature was used in the PD2 health state (79). Results can be seen in Table 32. This approach removes the utility gain from inavolisib in PFS and PD1 compared to the control arm and should be seen as conservative. The back-transform estimates were obtained by adding the mean baseline value to the marginal mean estimate.

Table 32 Utility estimates using the Danish tariff, in accordance with DMC guidance, for PFS, PD1 and PD2 – treatment arms pooled

Health state	N of observations	Mean estimate	SE
PFS	2044	0.859	0.007
PD1	278	0.767	0.010
PD2(79)	100	0.505	0.002

10.2.1.1 Mapping

N/A.

10.2.2 Disutility calculation

Disutilities have not been used in the health economic analysis.

10.2.3 HSUV results

HSUVs have been age-adjusted by applying a multiplicative adjustment index from a Danish perspective in accordance with section 7.3 of the methods guide.

Table 33 Overview of health state utility values

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUVs				
PFS	0.859 [0.844-0.873]	EQ-5D-5L	DK	Estimate is based on mean of both trial arms.
PD1	0.767 [0.748-0.787]	EQ-5D-5L	DK	Estimate is based on mean of both trial arms.
PD2	0.505 [0.502-0.507]	EQ-5D-3L	UK	External source Lloyd et al. (2006) (79)

10.3 Health state utility values measured in other trials than the clinical trials forming the basis for relative efficacy

10.3.1 Study design

N/A.

10.3.2 Data collection

N/A.

10.3.3 HRQoL Results

N/A.

10.3.4 HSUV and disutility results

N/A.

Table 34 Overview of health state utility values [and disutilities]

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
N/A				

Table 35 Overview of literature-based health state utility values

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
N/A				

11. Resource use and associated costs

Costs and resource use vary depending on the administered treatment and health states. The model includes drug costs, administration costs, subsequent therapy costs, Disease management costs, and AE costs. The costs included are consistent with the limited societal perspective as described in the DMC guidelines. Drug costs are estimated from Medicinpriser.dk, where administration costs, disease management costs, and AE costs are based on the Danish diagnose relative group (DRG) tariffs 2025.

For all pharmaceuticals administered in the model, pharmacy purchase prices (PPP) have been used. Drug acquisition costs are applied to patients in each health state, including subsequent therapies not captured in the study and uses the cheapest price per treatment.

11.1 Medicines - intervention and comparator

The model includes functionality which includes an indirect treatment comparison (NMA) to ABEMA and Ribociclib at the DMCs discretion by applying a NMA-derived HRs of ABEMA + fulvestrant and ribociclib + fulvestrant to the PFS and OS survival estimates of the Placebo arm. More information can be provided, if needed. However, this is not the analysis and comparison that we are conducting. We compare only to palbociclib+ fulvestrant. This is in line with DMCs treatment guidelines for CDK4/6i´s stating that they have similar efficacy (45) and in agreement with the DMC. This is also supported by the literature (79).

Table 42 presents the dosing schedule of all treatments included in the model which was in line with the INAVO120 study. Inavolisib is given PO QD at a dose of 9 mg on days 1-21 of each 28-days cycle. Similarly, palbociclib is administered PO QD at a dose of 125 mg on days 1-21 of each 28-days cycle. However, fulvestrant is administered as an IM injection at a dose of 500 mg on days 0, 14, 28 and every 28 days thereafter. Relative dose intensity has been applied to the recommended dose according to the study.

Table 36 Medicines used in the model. See Section 3 for more details

Medicine	Dose	Relative dose intensity		Frequency	Price (DKK)	Vial sharing
Inavolisib	9.0	84.35%	Daily	102,500		No
Palbociclib	125.0	85.22%	Daily week 1-3 of 4-week cycle	22,351		No
Fulvestrant	500.0	95.63%	Weekly following start-up	462		No
Palbociclib	125.0	83.17%	Daily week 1-3 of 4-week cycle	22,351		No
Fulvestrant	500.0	93.50%	Weekly following start-up	462		No

11.2 Medicines– co-administration

N/A.

11.3 Administration costs

The unit costs for the mode of administration were obtained from DRG tariffs 2025 and are applied to the administration cost in the model and presented in Table 37

Table 37 Administration costs used in the model

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference
Oral	28-day cycle	0	N/A	Assumption
Intramuscular injection	28-day cycle	1,578.00	09MA98	DRG2025

11.4 Disease management costs

All patients included in the INAVO120 study tested positively for the PIK3CA-mutation. Since the PIK3CA- mutation testing is not yet routinely performed in the clinical setting in Denmark, its cost was only applied to the inavolisib arm to capture the additional costs which will be incurred by the healthcare system once Inavolisib is introduced to the market.

Since not all patients who get tested for the PIK3CA-mutation will be positive, the total cost of PIK3CA-mutation testing (Table 38) was estimated by dividing the cost of one PIK3CA-mutation diagnostic test to the probability of being positive for the PIK3CA mutation as per Martínez-Sáez et al (2020) (25).

Table 38 PIK3CA-mutation testing costs

	Cost (DKK)	Reference
PIK3CA-mutation diagnostic test	3105	DRG2025 31PR03
Probability of positive test	35.7%	(25)
Total cost	**8,697.48**	-

Disease management costs assumption is presented in Table 39. The same interventions and frequencies are assumed for each health state (PFS, PD1 & PD2).

Table 39 Disease management costs used in the model

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
Outpatient visit	0.33	1,578.00	DRG2025 09MA98	Assumption
Computer temography scan - chest	0.33	2,401.00	DRG2025 30PR07	Assumption
Echocardiography	0.33	2,111.00	DRG2025 05PR04	Assumption
Complete clood count	1	0.00		Included in the DRG Tarif

11.5 Costs associated with management of adverse events

Treatment-emergent AEs with a severity grade of 3 and higher observed in more than 5% of patients irrespective of treatment arm were included in this CUA.

The cost per patient associated with each AE was estimated by multiplying the unit costs (Table 40) to the probability of experiencing the AE, which was calculated as the number of patients who experienced the AE per treatment arm (Table 26) divided by the patients' sample size. The costs per AE per patient were then summed up to generate the total costs associated with AEs for each treatment arm (

Table 41). The AEs costs were applied as a one-time cost in the model.

Table 40 Cost associated with management of AEs (AE unit cost based on Danish DRG)

Adverse event	Unit cost (DKK)	Reference
Anaemia	4,221	DRG2025 16PR02
Leukopenia	2,208	DRG2025 16MA98
Neutropenia	45,920	DRG2025 04MA07
Thrombocytopenia	37,482	DRG2025 16MA03
Diarrhea	2,208	DRG2025 16MA98
Neutrophils count decreased	2,208	DRG2025 17MA98

Platelets count decreased	2,208	DRG2025 17MA98
White blood cell count decreased	2,208	DRG2025 17MA98
Hyperglycemia	2,208	DRG2025 10MA98
Alanine aminotransferase increased	35,206	DRG2025 07MA14
Infection	2,208	DRG2025 10MA98
Hepatobiliary toxicity	46,506	DRG2025 07MA06
QT interval prolongation	21,047	DRG2025 05MA07

Table 41 Total AE costs per patient

	Inavolisib + Palbociclib + fulvestrant	Placebo + Palbociclib + fulvestrant
Total AE cost per patient (DKK)	27,859.43	24,773.36

11.6 Subsequent treatment costs

The post-progression landscape in Denmark is very complex and no treatment guidelines are available. Information for each line of treatment after progression is an assumption based on information gathered from clinical experts and local opinions and may vary from hospital to hospital. To simplify the same subsequent treatment options are used across trial arms.

PD1

The PD1 state includes patients who had one progression and started 2L treatment (Table 42). Table 4 summarizes the 2L post-progression treatments and their respective for all comparators included in the model. The assumption is that the 2L post-progression treatments are given until patients transition to PD2. Testing for the PIK3CA mutation is not currently routinely provided in the 1L setting, therefore the treatment pathway from 2L+ is likely to change in the future if patients start to be tested for the PIK3CA mutation in the 1L setting.

PD2

Patients in the PD2 state experienced a second progression and started 3L+ treatment (Table 42) The assumption is that patients are given 3L+ post-progression treatments until they die. Treatment options in PD2 are an assumption based on information gathered in Sweden from a clinical expert for the Swedish Inavolisib application.

Table 42 Medicines of subsequent treatments

Medicine	Share	Dose	Relative dose intensity	Frequency	Vial sharing	Price per pack (AIP)
2L treatment						
Capecitabine		80%	1250mg/m2 100%	Twice daily for 14 days per 21 day cycle	No	542 DKK
Exemestane	20%	25 mg	100%	Daily	No	3680 DKK
Thirde line (3L) treatment						
Enhertu	45.0%	5,4 mg/kg	100%	Once per 21-day cycle	No	11089,9 DKK
Paclitaxel	15.0%	175mg/m2	100%	Every 3. weeks	No	110,5 DKK
Eribulin	40.0%	1,23mg/m2	100%	Week 1 and week 2 of 21day cycle	No	2050 DKK

Body surface area based on Statens Institut for Folkesundhed 2021 (Women: 1.8 m2 (166.7cm, 71.4kg))
All doses are taken from https://pro.medicin.dk/, https://pro.medicin.dk/Medicin/Praeparater/7326, https://pro.medicin.dk/Medicin/Praeparater/6484, https://pro.medicin.dk/Medicin/Praeparater/9736 https://pro.medicin.dk/Medicin/Praeparater/10868 https://pro.medicin.dk/Medicin/Praeparater/5984

11.7 Patient costs

Patient costs were added to the model in line with the DMC guidance (80). Travel cost assumes an average of 20km total distance to the hospital costing an average of 3.73DKK per kilometer. One trip to the hospital was assumed to happen every three weeks in all health states.

Table 43 Travel cost

Activity	Distance	Cost (DKK/km)	Frequency
Hospital visit	20km	3.73DKK	Every 3 weeks in each health state

Informal care costs assume 203DKK cost per hour for informal care each week in line the DMC guidance.

Table 44 Informal care cost

Activity	Rate (DKK/Hour)	Time spent [minutes, hours, days]
Informal care	203DKK	1h every week

11.8 Other costs

N/A.

12. Results

12.1 Base case overview

Table 45 Base case overview

Feature	Description	
Comparator	Placebo + Palbociclib + Fulvestrant	
Type of model	Partitioned survival model	
Time horizon	46 years (life time)	
Treatment line	LA or mBC (1L)	
Measurement and valuation of health effects	Health-related quality of life measured with EQ-5D-5L in the INAVO120 study. Danish population weights were used to estimate health-state utility values	
Costs included	Medicine costs, hospital costs, diagnostic test, Costs of AE´s Patient costs of AEs, patient costs and post-progression treatment cost	
Dosage of medicine	Fixed	
Average time on treatment	Intervention: 25.0 months Comparator: 11.7 months	
Parametric function for PFS	Intervention: Log-logistic Comparator: Log-logistic	
Parametric function for OS	Intervention: Gamma Comparator: Gamma	
Inclusion of waste	N/A	
Average time in model health state	Inavo+Palbo+Fulv	Pbo+Palbo+fulv
PFS	2.64	1.2727
PD1	0.49	0.8989

Feature	Description	
PD2	0.63	1.0808

12.1.1 Base case results

Table 46 Base case results, discounted estimates

	Inavolisib palbociclib fulvestrant	Placebo palbociclib fulvestrant	Difference
Medicine costs	2,754,389	259,527	2,494,863
Diagnostic test	8,697	0	8,697
Administration	42,744	23,337	19,407
Disease management costs	58,241	28,683	29,558
Costs associated with management of adverse events	27,859	24,773	3,086
Subsequent treatment costs	290.826	499.655	-208.830
Patient costs	45,450	39,421	6,029
Palliative care costs	0	0	0
Total costs	**3,228,208**	**875.397**	**2.352.810**
Life years gained (PFS)	2.4242	1.19	1.23
Life years gained (PD1)	0.46	0.82	-0.36
Life years gained (PD2)	0.57	0.98	-0.41
Total life years	**3.44**	**2.99**	**0.46**
QALYs (PFS)	2.07	1.02	1.05
QALYs (PD1)	0.35	0.63	-0.28
QALYs (PD2)	0.29	0.49	-0.21
Total QALYs	**2.71**	**2.14**	**0.57**
Incremental costs per life year gained			**5,146,067**
Incremental cost per QALY gained (ICER)			**4,125,791**

12.2 Sensitivity analyses

To identify key model drivers and the influence of parameter uncertainty, one-way deterministic sensitivity analyses (DSA) are conducted using alternate values for model parameters. To test the impact of applying different assumptions, scenario analyses are conducted for the key model parameters.

To test the robustness of results with respect to uncertainty in the model input parameters, a probabilistic sensitivity analysis (PSA) is performed using a Monte Carlo simulation. In this analysis, each parameter subject to parameter uncertainty is assigned a probability distribution, and cost-effectiveness results associated with the simultaneous selection of random values from the distribution of each of these parameters were generated. The process was repeated for 1,000 iterations and results of the PSA were plotted on the cost-effectiveness plane (or scatter plot) and were used to calculate cost-effectiveness acceptability curves (CEACs), highlighting the probability of cost-effectiveness over various willingness to pay thresholds.

12.2.1 Deterministic sensitivity analyses

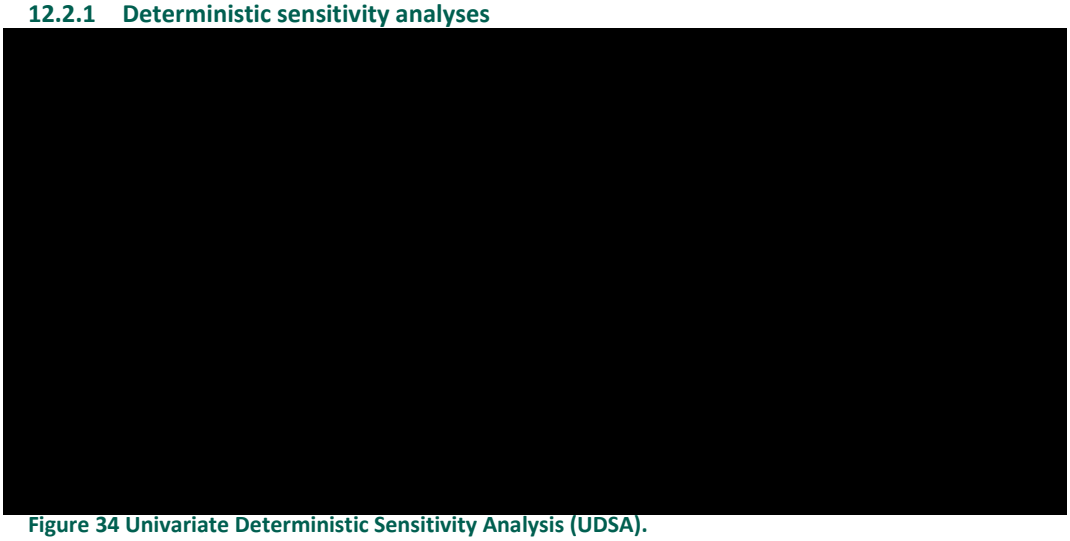


Figure 34 Univariate Deterministic Sensitivity Analysis (UDSA).

Table 47 One-way sensitivity analyses results (10 percentile variation)

Parameter	Lower value	Lower input result	Higher value	Higher input result
Utility in PFS - Inavo+p+f				
Utility in PD1 - Pbo+p+f				
Utility in PFS - Pbo+p+f				
Utility in PD1 - Inavo+p+f				
Second progression treatments - Cost Per model cycle - Pbo+p+f				
Utility in PD2 - Pbo+p+f				

Second progression treatments - Cost Per model cycle - Inavo+p+f	[redacted]
Utility in PD2 - Inavo+p+f	[redacted]
Supportive care cost in PFS	[redacted]
AE management cost per patient - Pbo+p+f	[redacted]
AE management cost per patient - Inavo+p+f	[redacted]
Cost per IM administration	[redacted]
Cost of diagnostic test	[redacted]
Cost per informal care hour	[redacted]
Supportive care cost in PD2	[redacted]
First progression treatments - Cost Per model cycle - Pbo+p+f	[redacted]
Supportive care cost in PD1	[redacted]
First progression treatments - Cost Per model cycle - Inavo+p+f	[redacted]
Cost per IM administration, loading	[redacted]

12.2.2 Probabilistic sensitivity analyses

Figure 35 Cost-Effectiveness Plane

Figure 36 Incremental Cost-Effectiveness Plane

Figure 37 Cost-Effectiveness Acceptability Curve

13. Budget impact analysis

Number of patients (including assumptions of market share)

Table 48 Number of new patients expected to be treated over the next five-year period if the medicine is introduced (adjusted for market share)

	Year 1	Year 2	Year 3	Year 4	Year 5
			Recommendation		
Inavolisib + Palbociclib + Fulvestrant	33	33	33	33	33
Placebo + Palbociclib + Fulvestrant	0	0	0	0	0
			Non-recommendation		
Inavolisib + Palbociclib + Fulvestrant	0	0	0	0	0
Placebo + Palbociclib + Fulvestrant	33	33	33	33	33

Budget impact

Table 49 Expected budget impact of recommending the medicine for the indication

	Year 1	Year 2	Year 3	Year 4	Year 5
The medicine under consideration is recommended	41.1 mio	65.2 mio.	81.6 mio.	92.5 mio.	99.6 mio
The medicine under consideration is NOT recommended	9.0 mio	15.1 mio.	19.8 mio.	23.2 mio.	25.6 mio
Budget impact of the recommendation	32.2 mio	50.2 mio.	61.8 mio.	69.3 mio.	74.0 mio

14. List of experts

N/A.

15. References

1. DBCG. Kliniske retningslinjer kræft – Systemisk behandling af brystkræft III - palliativ og systemisk behandling af metastaserende brystkræft (MBC), Version 2. 2024 [Available from: https://www.dmcg.dk/globalassets/generel-overflytning/dmcg/kliniske-retningslinjer---skabeloner-ogvejledninger/brug-ikke-kliniske-retningslinjer-opdelt-pa-dmcg/dbcg/dbcg_pall-syste-bhmbc_v.2.0_admgodk__150124.pdf.
2. Garly R, Berg T, Jensen M-B, Knoop A, Volmer L, Glavicic V, et al. A retrospective, non-interventional study of breast cancer patients diagnosed with ER+/HER2 negative, locally advanced or metastatic breast cancer treated with palbociclib in Denmark. Acta Oncologica. 2023;62(3):290-7.
3. Mosele F, Stefanovska B, Lusque A, Dien AT, Garberis I, Droin N, et al. Outcome and molecular landscape of patients with PIK3CA-mutated metastatic breast cancer. Annals of Oncology. 2020;31(3):377-86.
4. Fillbrunn M, Signorovitch J, André F, Wang I, Lorenzo I, Ridolfi A, et al. PIK3CA mutation status, progression and survival in advanced HR+/HER2-breast cancer: a meta-analysis of published clinical trials. BMc cancer. 2022;22(1):1002.
5. Kvalitetsinstitut S. DBCG Kvalitetsdatabase for Brystkræft - National årsrapport 2024 2024 [Available from: https://sundk.dk/media/l2rp4h4c/dbcg-a-rsrapport-2024_offentliggjort-version-20250627.pdf.
6. Bekæmpelse K. Kræft i Danmark 2025 2025 [Available from: https://www.cancer.dk/om-os/udgivelser-og-rapporter/viden-om-kraeft/kraeft-i-danmark-2025/.
7. NORDCAN. Cancer fact sheets 2022 [Available from: https://gco.iarc.fr/media/nordcan/factsheets/92/en/countries/208/breast-180-denmark-208.pdf.

8. Sundhedsstyrelsen. Screening for brystkræft 2023 [Available from: https://www.sst.dk/da/Borger/Sygdomme-og-lidelser/Kr%C3%A6ftsygdom/Screening-for-kraeft/Brystkraeft.
9. Institute NC. Cancer Stat Facts: Female Breast Cancer Subtypes 2022 [Available from: https://seer.cancer.gov/statfacts/html/breast-subtypes.html.
10. Sundhed.dk - Ann Søegaard Knop s. Brystkræft 2024 [Available from: https://www.sundhed.dk/borger/patienthaandbogen/brystsygdomme/sygdomme/brystkraeft/brystkraeft/.
11. Lambertini M, Blondeaux E, Bisagni G, Mura S, De Placido S, De Laurentiis M, et al. Prognostic and clinical impact of the endocrine resistance/sensitivity classification according to international consensus guidelines for advanced breast cancer: an individual patient-level analysis from the Mammella InterGruppo (MIG) and Gruppo Italiano Mammella (GIM) studies. EClinicalMedicine. 2023;59.
12. O'Shaughnessy J. Extending survival with chemotherapy in metastatic breast cancer. The oncologist. 2005;10(S3):20-9.
13. Medicinrådet. Bilag til Medicinrådets anbefaling vedrørende alpelisib i kombination med fulvestrant til behandling af lokalt fremskreden eller metastatisk ER+/HER2-brystkræft med PIK3CAmutation 2022 [Available from: https://filer.medicinraadet.dk/media/cr2ku0gl/bilag_til_medicinr%C3%A5dets_anbefaling_vedr-_alpelisib_i_komb-_m-_fulvestrant_til_metastatisk_brystkr%C3%A6ft-vers-_1-0_adlegacy.pdf.
14. Harbeck N, Franke F, Villanueva-Vazquez R, Lu Y-S, Tripathy D, Chow L, et al. Health-related quality of life in premenopausal women with hormone-receptor-positive, HER2-negative advanced breast cancer treated with ribociclib plus endocrine therapy: results from a phase III randomized clinical trial (MONALEESA-7). Therapeutic Advances in Medical Oncology. 2020;12:1758835920943065.
15. Davie A, Carter GC, Rider A, Pike J, Lewis K, Bailey A, et al. Real-world patient-reported outcomes of women receiving initial endocrine-based therapy for HR+/HER2− advanced breast cancer in five European countries. BMC cancer. 2020;20:1-15.
16. Lambert-Obry V, Gouault-Laliberté A, Castonguay A, Zanotti G, Tran T, Mates M, et al. Real-world patient-and caregiver-reported outcomes in advanced breast cancer. Current Oncology. 2018;25(4):e282.
17. Elgene Lim M, Metzger-Filho O, Winer EP. The natural history of hormone receptor-positive breast cancer. Oncology. 2012;26(8):688.
18. Dong C, Wu J, Chen Y, Nie J, Chen C. Activation of PI3K/AKT/mTOR pathway causes drug resistance in breast cancer. Frontiers in pharmacology. 2021;12:628690.
19. Thorpe LM, Yuzugullu H, Zhao JJ. PI3K in cancer: divergent roles of isoforms, modes of activation and therapeutic targeting. Nature Reviews Cancer. 2015;15(1):7-24.
20. Anderson EJ, Mollon LE, Dean JL, Warholak TL, Aizer A, Platt EA, et al. A systematic review of the prevalence and diagnostic workup of PIK3CA mutations in HR+/HER2− metastatic breast cancer. International Journal of Breast Cancer. 2020;2020(1):3759179.
21. Skolariki A, D'Costa J, Little M, Lord S. Role of PI3K/Akt/mTOR pathway in mediating endocrine resistance: Concept to clinic. Exploration of Targeted Anti-tumor Therapy. 2022;3(2):172.
22. Araki K, Miyoshi Y. Mechanism of resistance to endocrine therapy in breast cancer: the important role of PI3K/Akt/mTOR in estrogen receptor-positive, HER2-negative breast cancer. Breast cancer. 2018;25:392-401.
23. Presti D, Quaquarini E. The PI3K/AKT/mTOR and CDK4/6 pathways in endocrine resistant HR+/HER2− metastatic breast cancer: biological mechanisms and new treatments. Cancers. 2019;11(9):1242.
24. Fox EM, Arteaga CL, Miller TW. Abrogating endocrine resistance by targeting ERα and PI3K in breast cancer. Frontiers in oncology. 2012;2:145.

25. Martínez-Sáez O, Chic N, Pascual T, Adamo B, Vidal M, González-Farré B, et al. Frequency and spectrum of PIK3CA somatic mutations in breast cancer. Breast cancer research. 2020;22:1-9.
26. Sundhedsdatastyrelsen. Nye kræfttilfælde i Danmark 2023 2024 [Available from: https://sundhedsdatastyrelsen.dk/media/16526/Kraefttilfaelde%202023.pdf.
27. Sundhedsdatastyrelsen. Nye kræfttilfælde i Danmark 2022 2023 [Available from: https://sundhedsdatastyrelsen.dk/media/16528/Kraefttilfaelde%202022.pdf.
28. Sundhedsdatastyrelsen. Nye kræfttilfælde i Danmark 2021 2023 [Available from: https://sundhedsdatastyrelsen.dk/media/16529/Kraefttilfaelde%202021.pdf.
29. Sundhedsdatastyrelsen. Nye kræfttilfælde i Danmark 2020 2022 [Available from: https://sundhedsdatastyrelsen.dk/media/16530/Kraefttilfaelde%202020.pdf.
30. Sundhedsdatastyrelsen. Nye kræfttilfælde i Danmark 2019 2021 [Available from: https://sundhedsdatastyrelsen.dk/media/16531/Kraefttilfaelde%202019.pdf.
31. Bekæmpelse K. Statistik om brystkræft hos mænd 2025 [Available from: https://www.cancer.dk/brystkraeft-maend-mammacancer/fakta/statistik/?utm_source=chatgpt.com.
32. Medicinrådet. Medicinrådets behandlingsvejledning vedrørende CDK4/6-hæmmere til ER+/HER2-lokalt fremskreden eller metastatisk brystkræft. 2023.
33. Gennari A, André F, Barrios C, Cortes J, de Azambuja E, DeMichele A, et al. ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer☆. Annals of oncology. 2021;32(12):1475-95.
34. Turner NC, Im S-A, Saura C, Juric D, Loibl S, Kalinsky K, et al. Protocol for: Inavolisib-based therapy in PIK3CA-mutated advanced breast cancer. New England Journal of Medicine. 2024;391(17):1584-96.
35. ESMO. HR+/HER2– MBC: Recurrence While on Adjuvant ET or ≤12 Months After the End of Adjuvant ET (Primary or Secondary ET-Resistance) 2025 [Available from: https://www.esmo.org/guidelines/living-guidelines/esmo-living-guideline-metastatic-breast-cancer/hr-positive-her2-negative-metastatic-breast-cancer/hr-her2-mbc-recurrence-while-on-adjuvant-et-or-12-months-after-the-end-of-adjuvant-et-primary-or-secondary-et-resistance.
36. André F, Ciruelos E, Juric D, Loibl S, Campone M, Mayer I, et al. Alpelisib plus fulvestrant for PIK3CA-mutated, hormone receptor-positive, human epidermal growth factor receptor-2–negative advanced breast cancer: final overall survival results from SOLAR-1. Annals of Oncology. 2021;32(2):208-17.
37. Hong R, Edgar K, Song K, Steven S, Young A, Hamilton P, et al. Abstract PD4-14: GDC-0077 is a selective PI3Kalpha inhibitor that demonstrates robust efficacy in PIK3CA mutant breast cancer models as a single agent and in combination with standard of care therapies. Cancer research. 2018;78(4_Supplement):PD4-14-PD4-.
38. Schmid P, Bedard P, Jhaveri K, Cervantes A, Gambardella V, Hamilton E, et al. A phase I/Ib study evaluating GDC-0077 (inavolisib)+ palbociclib (palbo)+ fulvestrant in patients (pts) with PIK3CA-mutant (mut), hormone receptor-positive/HER2-negative metastatic breast cancer (HR+/HER2-mBC). Senologie-Zeitschrift für Mammadiagnostik und-therapie. 2021;18(02):85.
39. Jhaveri KL, Im S-A, Saura C, Loibl S, Kalinsky K, Schmid P, et al. Overall Survival with Inavolisib in PIK3CA-Mutated Advanced Breast Cancer. New England Journal of Medicine. 2025.
40. Röth A, Ichikawa S, Ito Y, Kim JS, Nagy Z, Obara N, et al. Crovalimab treatment in patients with paroxysmal nocturnal haemoglobinuria: Long-term results from the phase I/II COMPOSER trial. European journal of haematology. 2023;111(2):300-10.
41. Patologiselskab D. ANBEFALINGER FOR MOLEKYLÆRPATOLOGISKE ANALYSER 2022 [Available from: https://danskpatologi.org/udvalg/udvalg-for-molekylaerpatologi/anbefalinger-for-molekylaerpatologiske-analyser/.

42. Cristofanilli M, Turner NC, Bondarenko I, Ro J, Im S-A, Masuda N, et al. Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. The Lancet Oncology. 2016;17(4):425-39.
43. Slamon DJ, Neven P, Chia S, Fasching PA, De Laurentiis M, Im S-A, et al. Overall survival with ribociclib plus fulvestrant in advanced breast cancer. New england Journal of medicine. 2020;382(6):514-24.
44. Goetz M, Toi M, Huober J, Sohn J, Tredan O, Park I, et al. LBA15 MONARCH 3: Interim overall survival (OS) results of abemaciclib plus a nonsteroidal aromatase inhibitor (NSAI) in patients (pts) with HR+, HER2-advanced breast cancer (ABC). Annals of oncology. 2022;33:S1384.
45. Medicinrådet. Opsummering af Medicinrådets evidensgennemgang vedrørende CDK4/6-hæmmere til ER+/HER2- lokalt fremskreden eller metastatisk brystkræft. 2025.
46. Cristofanilli M, Rugo HS, Im S-A, Slamon DJ, Harbeck N, Bondarenko I, et al. Overall survival with palbociclib and fulvestrant in women with HR+/HER2− ABC: updated exploratory analyses of PALOMA-3, a double-blind, phase III randomized study. Clinical Cancer Research. 2022;28(16):3433-42.
47. Rugo H, Layman R, Lynce F, Liu X, Li B, McRoy L, et al. Comparative overall survival of CDK4/6 inhibitors plus an aromatase inhibitor in HR+/HER2− metastatic breast cancer in the US real-world setting. ESMO open. 2025;10(1):104103.
48. Gehrchen ML, Berg T, Garly R, Jensen M-B, Eßer-Naumann S, Rønlev JD, et al. Real-world effectiveness of CDK 4/6 inhibitors in estrogen-positive metastatic breast cancer. BJC reports. 2024;2(1):44.
49. EMA. IBRANCE - SmPC [Available from: https://www.ema.europa.eu/en/documents/product-information/ibrance-epar-product-information_en.pdf.
50. EMA. Faslodex - SmPC [Available from: https://www.ema.europa.eu/en/documents/product-information/faslodex-epar-product-information_en.pdf.
51. Pazdur R. Endpoints for assessing drug activity in clinical trials. The oncologist. 2008;13(S2):19-21.
52. Medicinrådet. Medicinrådets anbefaling vedrørende sacituzumab govitecan til behandling af lokalt fremskreden eller metastatisk triple-negativ brystkræft 2025 [Available from: https://filer.medicinraadet.dk/media/qsvdxgwl/medicinradets-anbefaling-vedr-sacituzumab-govitecan-til-brystkraeft-vers-2-0-x.pdf.
53. NICE. Alpelisib with fulvestrant for treating hormone receptor-positive, HER2-negative, PIK3CA-mutated advanced breast cancer. 2022.
54. Turner NC, Im S-A, Saura C, Juric D, Loibl S, Kalinsky K, et al. Inavolisib-based therapy in PIK3CA-mutated advanced breast cancer. New England Journal of Medicine. 2024;391(17):1584-96.
55. Clinicaltrials.gov. A Study Evaluating the Efficacy and Safety of Inavolisib + Palbociclib + Fulvestrant vs Placebo + Palbociclib + Fulvestrant in Participants With PIK3CA-Mutant, Hormone Receptor-Positive, HER2-Negative, Locally Advanced or Metastatic Breast Cancer (INAVO120) 2025 [Available from: https://clinicaltrials.gov/study/NCT04191499.
56. Röth A, He G, Brodsky A, Chai-Adisaksopha CC, Dumagay T, Demichelis R, et al. S181: THE PHASE III, RANDOMIZED COMMODORE 2 TRIAL: RESULTS FROM A MULTICENTER STUDY OF CROVALIMAB VS ECULIZUMAB IN PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH) PATIENTS NAIVE TO COMPLEMENT INHIBITORS. HemaSphere. 2023;7(Suppl).
57. Update Clinical Study Report, Study WO41554 (Data on file). 2024.

58. Cardoso F, Senkus E, Costa A, Papadopoulos E, Aapro M, André F, et al. 4th ESO–ESMO international consensus guidelines for advanced breast cancer (ABC 4). Annals of Oncology. 2018;29(8):1634-57.
59. Jhaveri KL, Im S-A, Saura C, Loibl S, Kalinsky K, Schmid P, et al. Supplement to: Overall Survival with Inavolisib in PIK3CA-Mutated Advanced Breast Cancer. New England Journal of Medicine. 2025.
60. kvalitetsinstitut S. DBCG Kvalitetsdatabase for Brystkræft 2025 [Available from: https://sundk.dk/media/l2rp4h4c/dbcg-a-rsrapport-2024_offentliggjort-version-20250627.pdf.
61. NICE. ICE DSU TECHNICAL SUPPORT DOCUMENT 14: SURVIVAL ANALYSIS FOR ECONOMIC EVALUATIONS ALONGSIDE CLINICAL TRIALS - EXTRAPOLATION WITH PATIENT-LEVEL DATA. 2013.
62. Lambert P, E. Thanopoulou, and P. Dhillon. Abstract P4-07-27: Real-world observational study of patients with endocrine-resistant, hormone receptor+, HER2- metastatic breast cancer in the first-line setting: Patient characteristics, PIK3CA mutation prevalence, treatments, and clinical outcomes. Clinical Cancer Research. 2025;31(12_Supplement)(p. P4-07-27-P4-07-27).
63. Lambert P, Thanopoulou E, Dhillon P. Abstract P4-07-27: Real-world observational study of patients with endocrine-resistant, hormone receptor+, HER2-metastatic breast cancer in the first-line setting: Patient characteristics, PIK3CA mutation prevalence, treatments, and clinical outcomes. Clinical Cancer Research. 2025;31(12_Supplement):P4-07-27-P4-07-27.
64. Turner NC, Im S-A, Saura C, Juric D, Loibl S, Kalinsky K, et al. Supplement to: Inavolisib-based therapy in PIK3CA-mutated advanced breast cancer. New England Journal of Medicine. 2024;391(17):1584-96.
65. . !!! INVALID CITATION !!! {Turner, 2024 #18;Turner, 2024 #18}.
66. Fitzsimmons D, Johnson C, George S, Payne S, Sandberg AA, Bassi C, et al. Development of a disease specific quality of life (QoL) questionnaire module to supplement the EORTC core cancer QoL questionnaire, the QLQ-C30 in patients with pancreatic cancer. European journal of cancer. 1999;35(6):939-41.
67. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. JNCI: Journal of the National Cancer Institute. 1993;85(5):365-76.
68. Sprangers M, Groenvold M, Arraras JI, Franklin J, te Velde A, Muller M, et al. The European Organization for Research and Treatment of Cancer breast cancer-specific quality-of-life questionnaire module: first results from a three-country field study. Journal of clinical oncology. 1996;14(10):2756-68.
69. Shi Q, Wang XS, Mendoza TR, Pandya KJ, Cleeland CS. Assessing persistent cancer pain: a comparison of current pain ratings and pain recalled from the past week. Journal of pain and symptom management. 2009;37(2):168-74.
70. Cleeland CS, Ryan K. The brief pain inventory. Pain Research Group. 1991;20(20):143-7.
71. Brooks R, Group E. EuroQol: the current state of play. Health policy. 1996;37(1):53-72.
72. Group TE. EuroQol-a new facility for the measurement of health-related quality of life. Health policy. 1990;16(3):199-208.
73. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Quality of life research. 2011;20:1727-36.
74. Janssen M, Pickard AS, Golicki D, Gudex C, Niewada M, Scalone L, et al. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. Quality of life research. 2013;22:1717-27.

75. Irvin Jr W, Muss HB, Mayer DK. Symptom management in metastatic breast cancer. The oncologist. 2011;16(9):1203-14.
76. Wood R, de Courcy J, Mitra D, Iyer S. Patient reported pain severity and interference in HR+/HER2-advanced/metastatic breast cancer in real world settings. Annals of Oncology. 2016;27:vi88.
77. Roche F-H-L. Data on file (EQ-5D-5L). 2025.
78. Jensen CE, Sørensen SS, Gudex C, Jensen MB, Pedersen KM, Ehlers LH. The Danish EQ-5D-5L value set: a hybrid model using cTTO and DCE data. Applied Health Economics and Health Policy. 2021;19:579-91.
79. Lloyd A, Nafees B, Narewska J, Dewilde S, Watkins J. Health state utilities for metastatic breast cancer. British journal of cancer. 2006;95(6):683-90.
80. Medicinrådet. Værdisætning af enhedsomkostninger 2024 [Available from: https://filer.medicinraadet.dk/media/lemjycrd/vaerdisaetning-af-enhedsomkostninger-vers-1-8.pdf.

Appendix A. Main characteristics of studies included

Table 50 Main characteristics of studies included

Trial name: INAVO120	**NCT number: NCT04191499**
Objective	The objective of the study is to evaluate the efficacy, safety, and pharmacokinetics of inavolisib in combination with palbociclib and fulvestrant compared with placebo plus palbociclib and fulvestrant in patients with *PIK3CA*-mutant, hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer whose disease progressed during treatment or within 12 months of completing adjuvant endocrine therapy and who have not received prior systemic therapy for locally advanced or metastatic disease.
Publications – title, author, journal, year	Inavolisib-Based Therapy in PIK3CA-Mutated Advanced Breast Cancer., Turner NC, Im SA, Saura C, et al**.,** The New England Journal of Medicine., 2024. Overall Survival with Inavolisib in PIK3CA-Mutated Advanced Breast Cancer., Jhaveri KL, Im SA, Saura C, et al., The New England Journal of Medicine
Study type and design	[State the phase of the trial and describe the method of randomization, degree of blinding, extent of crossover, status (ongoing or completed), etc. A Phase III, randomized, double-blind, placebo-controlled, multicenter, global study. The study is currently active. Patients were randomly assigned to one of two treatment arms: inavolisib plus palbociclib and fulvestrant or placebo plus palbociclib and fulvestrant. Randomization occurred in a 1:1 ratio using a permuted-block randomization method to ensure a balanced assignment to each treatment arm. Randomization was stratified according to the following factors: • Visceral disease (yes or no) • Endocrine resistance (primary or secondary according to ESMO ABC4 guidelines [Cardoso et al. 2018]) • Geographic region (North America/Western Europe, Asia, other) No crossover was allowed. Study site personnel and patients were blinded to treatment assignment during the study. The Sponsor and its agents were also blinded to treatment assignment, with the exception of individuals who required access to patient treatment assignments to fulfill their job roles during the clinical trial.

Trial name: INAVO120		NCT number: NCT04191499
Sample size (n)	325	
Main inclusion criteria	• Confirmed diagnosis of HR+/HER2- breast cancer • Metastatic or locally advanced disease not amenable to curative therapy • Progression of disease during adjuvant endocrine treatment or within 12 months of completing adjuvant endocrine therapy with an aromatase inhibitor or tamoxifen • Receiving LHRH agonist therapy for at least 2 weeks prior to Day 1 of Cycle 1 if pre/peri-menopausal • Confirmation of biomarker eligibility (detection of specified mutation(s) of PIK3CA via specified test) • Consent to provide fresh or archival tumor tissue specimen • Measurable disease per Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1); evaluable "bone-only" disease is not eligible; "bone-only" disease with at least one measurable, soft-tissue component, even if considered disease that is limited to bone but has lytic or mixed lytic/blastic lesions and at least one measurable soft-tissue component per RECIST v1.1 may be eligible • Eastern Cooperative Oncology Group Performance Status of 0 or 1 • Life expectancy of > 6 months • Adequate hematologic and organ function within 14 days prior to initiation of study treatment	
Main exclusion criteria	• Metaplastic breast cancer • Any history of leptomeningeal disease or carcinomatous meningitis • Any prior systemic therapy for metastatic breast cancer • Prior treatment with fulvestrant or any selective estrogen-receptor degrader, with the exception of participants that have received fulvestrant or any selective estrogen-receptor degrader as part of neoadjuvant therapy only and with treatment duration of no longer than 6 months • Prior treatment with any PI3K, AKT, or mTOR inhibitor, or any agent whose mechanism of action is to inhibit the PI3K-AKT-mTOR pathway	

Trial name: INAVO120	NCT number: NCT04191499
	• Type 2 diabetes requiring ongoing systemic treatment at the time of study entry; or any history of Type 1 diabetes • Known and untreated, or active CNS metastases. Patients with a history of treated CNS metastases may be eligible • Active inflammatory or infectious conditions in either eye, or any eye conditions expected to require surgery during the study treatment period • Symptomatic active lung disease, or requiring daily supplemental oxygen • History of inflammatory bowel disease or active bowel inflammation • Anti-cancer therapy within 2 weeks before study entry • Investigational drug(s) within 4 weeks before randomization • Prior radiotherapy to >= 25% of bone marrow, or hematopoietic stem cell or bone marrow transplantation • Chronic corticosteroid therapy or immunosuppressants • Pregnant, lactating, or breastfeeding, or intending to become pregnant during the study or within 2 weeks after the final dose of study treatment • Major surgical procedure, or significant traumatic injury, within 28 days prior to Day 1 of Cycle 1
Intervention	**Inavolisib:** Administered PO QD on Days 1−28 of each 28-day cycle at a starting dose of 9 mg, in combination with palbociclib administered PO QD on Days 1−21 of each 28-day cycle (21 days on; 7 days off) at a starting dose of 125 mg and fulvestrant 500 mg administered as two IM injections of 250 mg each on day 1 and 15 of Cycle 1. For subsequent cycles, patients received fulvestrant 500 mg (two IM injections of 250 mg each) in the clinic on day 1 of each cycle, or approximately every 4 weeks. 161 patients were assigned to the intervention group
Comparator(s)	**Placebo:** Administered PO QD on Days 1−28 of each 28-day cycle. **Palbociclib:** Administered PO QD on Days 1−21 of each 28-day cycle (21 days on; 7 days off) at a starting dose of 125 mg. **Fulvestrant:** 500 mg was administered as two IM injections of 250 mg each on day 1 and 15 of Cycle 1. For subsequent cycles, patients received fulvestrant 500 mg (two IM injections of 250 mg each) in the clinic on day 1 of each cycle, or approximately every 4 weeks. 164 patients were assigned to the placebo group

Trial name: INAVO120	NCT number: NCT04191499
Follow-up time	Median follow-up of 34.2 months in the inavolisib group Median follow-up of 32.3 months in the placebo group
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** **Primary Efficacy Objectives:** The primary endpoint for this study is progression-free survival (PFS), as determined by the investigator according to Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1). **Secondary Efficacy Objectives:** The secondary endpoints in this study are overall survival (OS), Objective response rate (ORR), Confirmed objective response (COR), Best overall response rate (BOR), clinical benefit rate (CBR) and duration of response (DOR). **Safety Objectives:** The safety objective for this study is to evaluate the safety of inavolisib plus palbociclib and fulvestrant compared with placebo plus palbociclib and fulvestrant on the basis of the following endpoints: Incidence and severity of adverse events, with severity determined according to NCI CTCAE v5.0, change from baseline in targeted vital signs and change from baseline in targeted clinical laboratory test results. **Patient-reported Outcome Objectives:** The patient-reported outcome (PRO) objective for this study was TTD in Global Health Status/Quality of Life (GHS/QoL). **Other endpoints not included in this application:** The secondary efficacy objectives for this study are TTD in GHS/HRQoL, TTD in pain, TTD in physical functioning (PF) and TTD in role functioning (RF). The exploratory efficacy objectives for this study are time to end of next-line treatment (proxy for time to second objective disease progression [PFS2]) and time to first skeletal-related event (SRE). Mean and mean change-from-baseline scores in all functions (Physical, Role, Cognitive, Emotional, and Social), GHS/HRQoL, and disease- or treatment-related symptom scores, as measured by the scales of the EORTC QLQ-C30 and EORTC QLQ-Breast Cancer Module 23 Questionnaire (EORTC QLQ-BR23). The exploratory safety objective for this study is to evaluate tolerability of inavolisib plus palbociclib and fulvestrant compared with placebo

	plus palbociclib and fulvestrant from the patient's perspective, based on the following endpoints: Presence, frequency of occurrence, severity, and/or degree of interference with daily function of selected symptomatic treatment toxicities as assessed through use of the NCI PRO-CTCAE and the "bother from side effects" item Change from baseline in symptomatic treatment toxicities, as assessed through use of the PRO-CTCAE and the "bother from side effects" item.
Method of analysis	All efficacy analyses were intention-to-treat analysis. **<u>Primary Efficacy Analysis:</u>** **PFS** The primary efficacy analysis population consists of all randomized patients grouped according to their assigned treatment at randomization. The primary analysis of the study tested the equality of PFS distributions in the inavolisib plus palbociclib and fulvestrant and placebo plus palbociclib and fulvestrant arms, as follows: **H0**: PFS inavolisib plus palbociclib and fulvestrant = PFS placebo plus palbociclib and fulvestrant versus **H1**: PFS inavolisib plus palbociclib and fulvestrant ≠ PFS placebo plus palbociclib and fulvestrant The treatment arms were compared using a two-sided stratified log-rank test. The stratification factors that were used are the same as those for randomization: - Visceral disease (yes or no) - Endocrine resistance (primary or secondary according to ESMO ABC4 guidelines [Cardoso et al. 2018]) - Geographic region (North American/Western Europe, Asia, or other) Survival curves in each treatment arm were estimated using KM estimates. The treatment effect was quantified via a HR, computed from a stratified Cox proportional-hazards regression, including 95% CI constructed with the Brookmeyer–Crowley method. The prespecified boundary for statistical significance with respect to overall survival was P<0.0469.

Secondary Efficacy Analysis:

The primary efficacy analysis population is used for all secondary endpoints unless
otherwise specified.

OS
The final analysis of overall survival was event driven and planned to take place after approximately 153 deaths had occurred. Analysis methodology is as outlined for the primary endpoint, PFS.

OOR and COR
An estimate of the response rate and its 95% CI were calculated using the Blyth-Still-Casella method for each treatment arm. Response rates in the treatment arms were compared using the stratified Mante Haenszel test. Confidence intervals for the difference in ORRs and CORs between the two arms were determined using the normal approximation to the binomial distribution.

BoR and CBR
Analysis methodology as outlined for ORR and COR.

DOR
Analysis methodology is as outlined for the primary endpoint, PFS. Comparisons
between treatment arms using stratified and unstratified log rank test was made for
descriptive purposes. Because the determination of DOR is based on a non-randomized
subset of patients, formal hypothesis testing was not performed.

Safety Analysis
The safety analysis population consists of all patients who received at least one dose of
study drug and is based on the treatment the patients actually received. Safety was assessed through summaries of exposure to study treatment, adverse
events, changes in laboratory test results, and changes in vital signs and ECGs.
Study treatment exposure (such as treatment duration, total dose received, and number
of cycles and dose modifications) and dose intensity was summarized with descriptive
statistics.

Patient-reported Outcome Objectives:
Summary statistics (mean, standard deviation, median, and range) of linear transformed scores were reported for all scales (symptoms, functional domains GHS/QoL) of the EORTC QLQ-C30 for each assessment time point, and the “worst pain” item of the BPI-SF. The mean change of the linear transformed scores from baseline (and 95% CI using the

Trial name: INAVO120	NCT number: NCT04191499
	normal approximation) was reported independently for each treatment arm.
Subgroup analyses	No subgroup analysis was performed.
Other relevant information	*N/A*

Patient overview of CCOD1 (64)

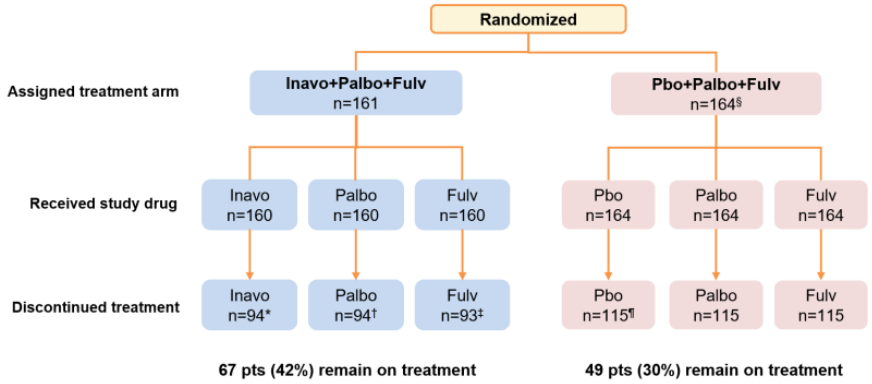


Figure 38 Patient disposition in the INAVO120 study (64).

*n=11 due to adverse events, †n=8 due to adverse events, ‡n=5 due to adverse events, §Two patients received at least one dose of inavolisib meaning that for the Safety Analysis Set n=162, ¶n=1 due to adverse events (64). Abbreviation: Palbo - palbociclib; Pbo - placebo; Fulv – fulvestrant.

Dosing Schedule

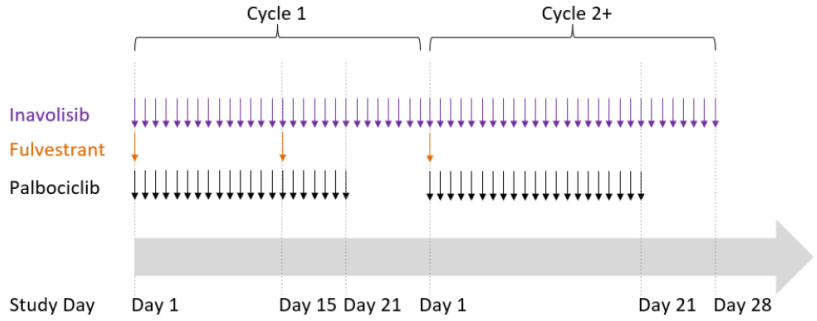


Figure 39 Illustration of dosing schedule in the INAVO120 study (34).

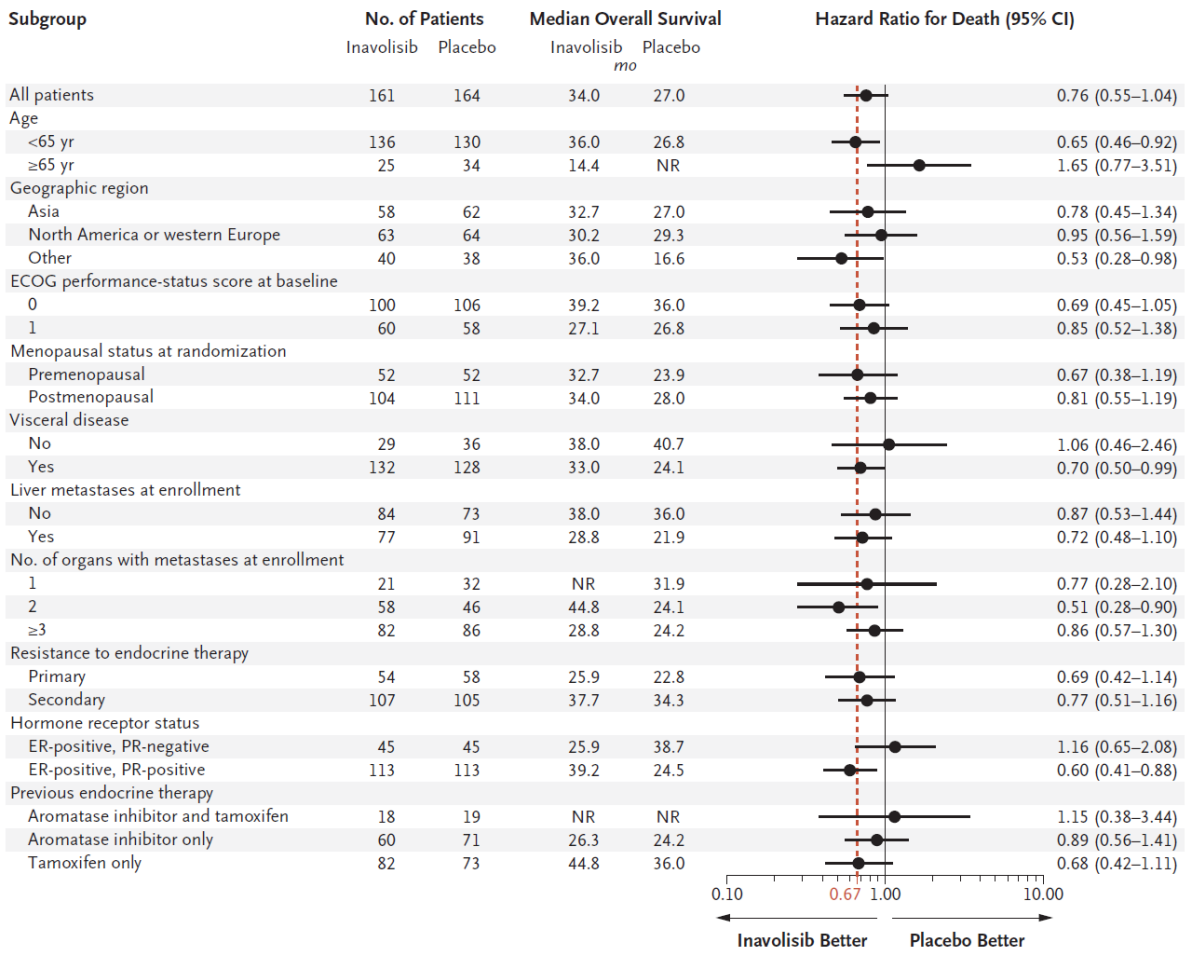


Figure 40 Analysis of Overall Survival in Key Subgroups (39)

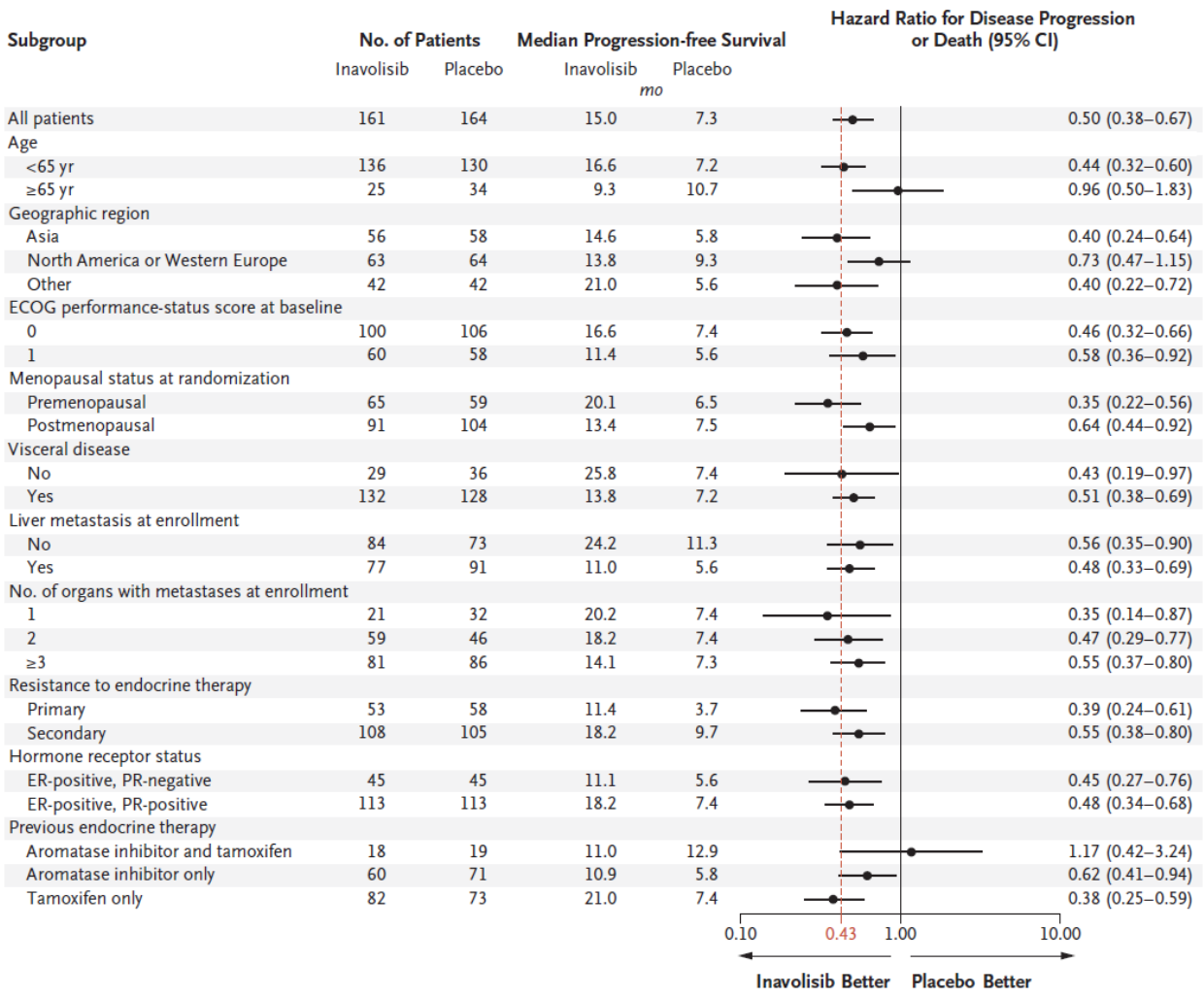


Figure 41 Analysis of Progression-free Survival in Key Subgroups (54)

Appendix B. Efficacy results per study

Results per study

[Complete the table for all studies included, regardless of whether they have been used in the health economic model. Explain how all estimates, such as CIs and p-values, have been estimated, this includes the method used, adjustment variables, stratification variables, weights, corrections (in cases with 0 counts), correlation structure (mixed effects model for repeated measurements) and methods used for imputation. Specify how assumptions were checked. Survival rates: state at which time point these are reported for.]

Table 51 Results per study

Results of INAVO120 (NCT04191499)												
					Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm		N	Result (CI)	Difference	95% CI	P value	Difference	95% CI	P value		
Median Progression-free survival (PFS)	CCOD1	Inavolisib	161	15.0 months (11.3-20.5)	7.7 months	N/A	N/A	HR: 0.43	0.32-0.59	<0.0001	Survival curves in each treatment arm were estimated using KM estimates providing a visual description of the survival curves and the difference across treatment arms. The KM approach was also used to estimate median PFS for each treatment arm. The treat-	(34, 39, 54)
		Placebo	164	7.3 months (5.6-9.3)								
		Inavolisib	161	17.2 months (11.6-22.2)	9.5 months	N/A	N/A	HR: 0.42	0.32-0.55	<0.0001		

	CCOD2	Placebo	164	7.3 months (5.9-9.2)						ment effect was quantified via a HR, computed from a stratified Cox proportional-hazards regression, including a 95% CI.	
PFS 6-months rate	CCOD1	Inavolisib	161	82.9% [redacted]	N/A	N/A	N/A	27.01	[redacted]	Survival curves in each treatment arm were estimated using KM estimates providing a visual description of the survival curves and the difference across treatment arms. The KM approach was also used to estimate median PFS for each treatment arm. The treatment effect was quantified via a HR, computed from a stratified Cox proportional-hazards regression, including a 95% CI.	(34, 39, 54)
		Placebo	164	55.9% [redacted]							
	CCOD2	Inavolisib	161	83.4% [redacted]	N/A	N/A	N/A	25.45	[redacted]		
		Placebo	164	57.9% [redacted]							
PFS 12-months rate	CCOD1	Inavolisib	161	55.9% [redacted]	N/A	N/A	N/A	23.28	[redacted]	Survival curves in each treatment arm were estimated using KM estimates providing a visual description of the survival curves and the difference across treatment arms. The KM approach was also used to estimate median PFS for each treatment arm. The treatment effect was quantified via a HR, computed from a stratified Cox proportional-hazards regression, including a 95% CI.	(34, 39, 54)
		Placebo	164	32.6% [redacted]							
	CCOD2	Inavolisib	161	58.0% [redacted]	N/A	N/A	N/A	26.67	[redacted]		
		Placebo	164	31.3% [redacted]							
		Inavolisib	161	46.2% [redacted]	N/A	N/A	N/A	25.14	[redacted]	Survival curves in each treatment arm were estimated using KM estimates providing a	(34, 39, 54)

PFS 18-months rate	CCOD1	Placebo	164	21.1% [redacted]							visual description of the survival curves and the difference across treatment arms. The KM approach was also used to estimate median PFS for each treatment arm. The treatment effect was quantified via a HR, computed from a stratified Cox proportional-hazards regression, including a 95% CI.	
	CCOD2	Inavolisib	161	49.7% [redacted]	N/A	N/A	N/A	29.19	[redacted]	[redacted]		
		Placebo	164	20.5% [redacted]								
PFS 24-months rate	CCOD1	Inavolisib	161	NE	NE	NE	NE	NE	NE	NE	Survival curves in each treatment arm were estimated using KM estimates providing a visual description of the survival curves and the difference across treatment arms. The KM approach was also used to estimate median PFS for each treatment arm. The treatment effect was quantified via a HR, computed from a stratified Cox proportional-hazards regression, including a 95% CI.	(34, 39, 54)
		Placebo	164	NE								
	CCOD2	Inavolisib	161	41.8% [redacted]	N/A	N/A	N/A	25.12	[redacted]	[redacted]		
		Placebo	164	16.7% [redacted]								
Median overall survival (OS)	CCOD1	Inavolisib	161	NR (95% CI: 27.3, NR)	N/A	N/A	N/A	0.64	0.43-0.97	N/A	Survival curves in each treatment arm were estimated using KM estimates providing a visual description of the survival curves and the difference across treatment arms. The KM approach was also used to estimate median PFS for each treatment arm. The treatment effect was quantified via a HR, computed from a stratified Cox proportional-hazards regression, including a 95% CI.	(34, 39, 54)
		Placebo	164	31.1 months (95% CI: 22.3, NR)								
	CCOD2	Inavolisib	161	34.0 months (95% CI: 28.4, 44.8)	7.0	N/A	N/A	0.67	0.48, 0.94	N/A		

		Placebo	164	27.0 months (95% CI: 22.8, 38.7)								
OS 6-months rate	CCOD1	Inavolisib	161	97.3% [redacted]	N/A	N/A	N/A	7.4	[redacted]	[redacted]	Survival curves in each treatment arm were estimated using KM estimates providing a visual description of the survival curves and the difference across treatment arms. The KM approach was also used to estimate median PFS for each treatment arm. The treatment effect was quantified via a HR, computed from a stratified Cox proportional-hazards regression, including a 95% CI.	(34, 39, 54)
		Placebo	164	89.9% [redacted]								
	CCOD2	Inavolisib	161	96.8% [redacted]	N/A	N/A	N/A	6.7	[redacted]	[redacted]		
		Placebo	164	90.1% [redacted]								
OS 12-months rate	CCOD1	Inavolisib	161	86.0% [redacted]	N/A	N/A	N/A	11.1	[redacted]	[redacted]	Survival curves in each treatment arm were estimated using KM estimates providing a visual description of the survival curves and the difference across treatment arms. The KM approach was also used to estimate median PFS for each treatment arm. The treatment effect was quantified via a HR, computed from a stratified Cox proportional-hazards regression, including a 95% CI.	(34, 39, 54)
		Placebo	164	74.9% [redacted]								
	CCOD2	Inavolisib	161	87.0% [redacted]	N/A	N/A	N/A	10.3	[redacted]	[redacted]		

		Placebo	164	76.7% [redacted]							
OS 18-months rate	CCOD1	Inavolisib	161	73.7% [redacted]	N/A	N/A	N/A	6.2	[redacted]	[redacted]	Survival curves in each treatment arm were estimated using KM estimates providing a visual description of the survival curves and the difference across treatment arms. The KM approach was also used to estimate median PFS for each treatment arm. The treatment effect was quantified via a HR, computed from a stratified Cox proportional-hazards regression, including a 95% CI. (34, 39, 54)
		Placebo	164	67.5% [redacted]							
	CCOD2	Inavolisib	161	74.3% [redacted]	N/A	N/A	N/A	7.2	[redacted]	[redacted]	
		Placebo	164	67.2% [redacted]							
OS 24-months rate	CCOD1	Inavolisib	161	[redacted]	N/A	N/A	N/A	[redacted]	[redacted]	[redacted]	Survival curves in each treatment arm were estimated using KM estimates providing a visual description of the survival curves and the difference across treatment arms. The KM approach was also used to estimate median PFS for each treatment arm. The treatment effect was quantified via a HR, computed from a stratified Cox proportional-hazards regression, including a 95% CI. (34, 39, 54)
		Placebo	164	[redacted]							
	CCOD2	Inavolisib	161	65.8% [redacted]	N/A	N/A	N/A	9.5	[redacted]	[redacted]	

		Placebo	164	56.3% [redacted]								
OS 30-months rate	CCOD1	Inavolisib	161	NE	NE	NE	NE	NE	NE	NE	Survival curves in each treatment arm were estimated using KM estimates providing a visual description of the survival curves and the difference across treatment arms. The KM approach was also used to estimate median PFS for each treatment arm. The treatment effect was quantified via a HR, computed from a stratified Cox proportional-hazards regression, including a 95% CI.	(34, 39, 54)
		Placebo	164	NE								
	CCOD2	Inavolisib	161	56.5% [redacted]	N/A	N/A	N/A	10.3	[redacted]	[redacted]		
		Placebo	164	46.3% [redacted]								
Confirmed Objective Response (COR) Responders	CCOD1	Inavolisib	161	58.4% [redacted]	N/A	N/A	N/A	33.4	23.3-43.5	<0.0001	An estimate of the response rate and its 95% CI was calculated using the Blyth-Still-Casella method for each treatment arm. Response rates in the treatment arms were compared using the stratified Mantel-Haenszel test. Confidence intervals (CI) for the difference in ORRs between the two arms were determined using the normal approximation to the binomial distribution.	(34, 39, 54)
		Placebo	164	25.0% [redacted]								
	CCOD2	Inavolisib	161	62.7% (95% CI: 54.8, 70.2)	N/A	N/A	N/A	34.7	24.5-44.8	<0.0001		
		Placebo	164	28.0% (95% CI: 21.3, 35.6)								

Complete Response (CR)	CCOD1	Inavolisib	161	4.3%	N/A	N/A	N/A	3.7	N/A	N/A	An estimate of the response rate and its 95% CI was calculated using the Blyth-Still-Casella method for each treatment arm. Response rates in the treatment arms were compared using the stratified Mantel-Haenszel test. Confidence intervals (CI) for the difference in ORRs between the two arms were determined using the normal approximation to the binomial distribution.	(34, 39, 54)
		Placebo	164	0.6%								
	CCOD2	Inavolisib	161		N/A	N/A	N/A		N/A	N/A		
		Placebo	164									
Partial Response (PR)	CCOD1	Inavolisib	161	54.0%	N/A	N/A	N/A	29.6	N/A	N/A	An estimate of the response rate and its 95% CI was calculated using the Blyth-Still-Casella method for each treatment arm. Response rates in the treatment arms were compared using the stratified Mantel-Haenszel test. Confidence intervals (CI) for the difference in ORRs between the two arms were determined using the normal approximation to the binomial distribution.	(34, 39, 54)
		Placebo	164	24.4%								
	CCOD2	Inavolisib	161		N/A	N/A	N/A		N/A	N/A		
		Placebo	164									

Stable disease (SD)	CCOD1	Inavolisib	161	28.6%	N/A	N/A	N/A	-19.6	N/A	N/A	An estimate of the response rate and its 95% CI was calculated using the Blyth-Still-Casella method for each treatment arm. Response rates in the treatment arms were compared using the stratified Mantel-Haenszel test. Confidence intervals (CI) for the difference in ORRs between the two arms were determined using the normal approximation to the binomial distribution.	(34, 39, 54)
		Placebo	164	48.2%								
	CCOD2	Inavolisib	161	[redacted]	N/A	N/A	N/A	[redacted]	N/A	N/A		
		Placebo	164	[redacted]								
Progressive Disease (PD)	CCOD1	Inavolisib	161	4.3%	N/A	N/A	N/A	-16.4	N/A	N/A	An estimate of the response rate and its 95% CI was calculated using the Blyth-Still-Casella method for each treatment arm. Response rates in the treatment arms were compared using the stratified Mantel-Haenszel test. Confidence intervals (CI) for the difference in ORRs between the two arms were determined using the normal approximation to the binomial distribution.	(34, 39, 54)
		Placebo	164	20.7%								
	CCOD2	Inavolisib	161	[redacted]	N/A	N/A	N/A	[redacted]	N/A	N/A		
		Placebo	164	[redacted]								

Missing	CCOD1	Inavolisib	161	8.7%	N/A	N/A	N/A	2.6	N/A	N/A	An estimate of the response rate and its 95% CI was calculated using the Blyth-Still-Casella method for each treatment arm. Response rates in the treatment arms were compared using the stratified Mantel-Haenszel test. Confidence intervals (CI) for the difference in ORRs between the two arms were determined using the normal approximation to the binomial distribution.	(34, 39, 54)
		Placebo	164	6.1%								
	CCOD2	Inavolisib	161	[redacted]	N/A	N/A	N/A	[redacted]	N/A	N/A		
		Placebo	164	[redacted]								
Best Overall Response (BOR) Responders	CCOD1	Inavolisib	161	[redacted]	N/A	N/A	N/A	[redacted]			An estimate of the response rate and its 95% CI was calculated using the Blyth-Still-Casella method for each treatment arm. Response rates in the treatment arms were compared using the stratified Mantel-Haenszel test. Confidence intervals (CI) for the difference in ORRs between the two arms were determined using the normal approximation to the binomial distribution.	(34, 39, 54)
		Placebo	164	[redacted]								
	CCOD2	Inavolisib	161	[redacted]	N/A	N/A	N/A	[redacted]				
		Placebo	164	[redacted]								

Complete Response (CR)	CCOD1	Inavolisib	161	[redacted]	N/A	N/A	N/A	[redacted]	N/A	N/A	An estimate of the response rate and its 95% CI was calculated using the Blyth-Still-Casella method for each treatment arm. Response rates in the treatment arms were compared using the stratified Mantel-Haenszel test. Confidence intervals (CI) for the difference in ORRs between the two arms were determined using the normal approximation to the binomial distribution.	(34, 39, 54)
		Placebo	164	[redacted]								
	CCOD2	Inavolisib	161	[redacted]	N/A	N/A	N/A	[redacted]	N/A	N/A		
		Placebo	164	[redacted]								
Partial Response (PR)	CCOD1	Inavolisib	161	[redacted]	N/A	N/A	N/A	[redacted]	N/A	N/A	An estimate of the response rate and its 95% CI was calculated using the Blyth-Still-Casella method for each treatment arm. Response rates in the treatment arms were compared using the stratified Mantel-Haenszel test. Confidence intervals (CI) for the difference in ORRs between the two arms were determined using the normal approximation to the binomial distribution.	(34, 39, 54)
		Placebo	164	[redacted]								
	CCOD2	Inavolisib	161	[redacted]	N/A	N/A	N/A	[redacted]	N/A	N/A		
		Placebo	164	[redacted]								

Stable disease (SD)	CCOD1	Inavolisib	161	[redacted]	N/A	N/A	N/A	[redacted]	N/A	N/A	An estimate of the response rate and its 95% CI was calculated using the Blyth-Still-Casella method for each treatment arm. Response rates in the treatment arms were compared using the stratified Mantel-Haenszel test. Confidence intervals (CI) for the difference in ORRs between the two arms were determined using the normal approximation to the binomial distribution.	(34, 39, 54)
		Placebo	164	[redacted]								
	CCOD2	Inavolisib	161	[redacted]	N/A	N/A	N/A	[redacted]	N/A	N/A		
		Placebo	164	[redacted]								
Progressive Disease (PD)	CCOD1	Inavolisib	161	[redacted]	N/A	N/A	N/A	[redacted]	N/A	N/A	An estimate of the response rate and its 95% CI was calculated using the Blyth-Still-Casella method for each treatment arm. Response rates in the treatment arms were compared using the stratified Mantel-Haenszel test. Confidence intervals (CI) for the difference in ORRs between the two arms were determined using the normal approximation to the binomial distribution.	(34, 39, 54)
		Placebo	164	[redacted]								
	CCOD2	Inavolisib	161	[redacted]	N/A	N/A	N/A	[redacted]	N/A	N/A		
		Placebo	164	[redacted]								

Missing	CCOD1	Inavolisib	161	[redacted]	N/A	N/A	N/A	[redacted]	N/A	N/A	An estimate of the response rate and its 95% CI was calculated using the Blyth-Still-Casella method for each treatment arm. Response rates in the treatment arms were compared using the stratified Mantel-Haenszel test. Confidence intervals (CI) for the difference in ORRs between the two arms were determined using the normal approximation to the binomial distribution.	(34, 39, 54)
		Placebo	164	[redacted]								
	CCOD2	Inavolisib	161	[redacted]	N/A	N/A	N/A	[redacted]	N/A	N/A		
		Placebo	164	[redacted]								
Clinical Benefit Rate (CBR) Responders	CCOD1	Inavolisib	161	[redacted]	N/A	N/A	N/A	[redacted]			An estimate of the response rate and its 95% CI was calculated using the Blyth-Still-Casella method for each treatment arm. Response rates in the treatment arms were compared using the stratified Mantel-Haenszel test. Confidence intervals (CI) for the difference in ORRs between the two arms were determined using the normal approximation to the binomial distribution.	(34, 39, 54)
		Placebo	164	[redacted]								
	CCOD2	Inavolisib	161	[redacted]	N/A	N/A	N/A	[redacted]				
		Placebo	164	[redacted]								

Median Duration of Response (DoR)	CCOD1	Inavolisib	161	18.4 months (95% CI: 10.4, 22.2)	8.8	N/A	N/A	0.57	0.33-0.99	N/A	An estimate of the response rate and its 95% CI was calculated using the Blyth-Still-Casella method for each treatment arm. Response rates in the treatment arms were compared using the stratified Mantel-Haenszel test. Confidence intervals (CI) for the difference in ORRs between the two arms were determined using the normal approximation to the binomial distribution.	(34, 39, 54)
		Placebo	164	9.6 months (95% CI: 7.4, 16.6)								
	CCOD2	Inavolisib	161	19.2 months (95% CI: 14.7, 28.3)	8.1	N/A	N/A	0.60	0.37-0.97	N/A		
		Placebo	164	11.1 months (95% CI: 8.5, 20.2)								
DoR, 6-months	CCOD1	Inavolisib	161	[redacted]	N/A	N/A	N/A	[redacted]	N/A	N/A	An estimate of the response rate and its 95% CI was calculated using the Blyth-Still-Casella method for each treatment arm. Response rates in the treatment arms were compared using the stratified Mantel-Haenszel test. Confidence intervals (CI) for the difference in ORRs between the two arms were determined using the normal approximation to the binomial distribution.	(34, 39, 54)
		Placebo	164	[redacted]								
	CCOD2	Inavolisib	161	[redacted]	N/A	N/A	N/A	[redacted]	N/A	N/A		
		Placebo	164	[redacted]								

DoR, 12-months	CCOD1	Inavolisib	161	[redacted]	N/A	N/A	N/A	[redacted]	N/A	N/A	An estimate of the response rate and its 95% CI was calculated using the Blyth-Still-Casella method for each treatment arm. Response rates in the treatment arms were compared using the stratified Mantel-Haenszel test. Confidence intervals (CI) for the difference in ORRs between the two arms were determined using the normal approximation to the binomial distribution.	(34, 39, 54)
		Placebo	164	[redacted]								
	CCOD2	Inavolisib	161	[redacted]	N/A	N/A	N/A	[redacted]	N/A	N/A		
		Placebo	164	[redacted]								
DoR, 18-months	CCOD1	Inavolisib	161	[redacted]	N/A	N/A	N/A	[redacted]	N/A	N/A	An estimate of the response rate and its 95% CI was calculated using the Blyth-Still-Casella method for each treatment arm. Response rates in the treatment arms were compared using the stratified Mantel-Haenszel test. Confidence intervals (CI) for the difference in ORRs between the two arms were determined using the normal approximation to the binomial distribution.	(34, 39, 54)
		Placebo	164	[redacted]								
	CCOD2	Inavolisib	161	[redacted]	N/A	N/A	N/A	[redacted]	N/A	N/A		
		Placebo	164	[redacted]								

DoR, 24-months	CCOD1	Inavolisib	161	[redacted]						An estimate of the response rate and its 95% CI was calculated using the Blyth-Still-Casella method for each treatment arm. Response rates in the treatment arms were compared using the stratified Mantel-Haenszel test. Confidence intervals (CI) for the difference in ORRs between the two arms were determined using the normal approximation to the binomial distribution.	(34, 39, 54)
		Placebo	164	[redacted]							
	CCOD2	Inavolisib	161	[redacted]	N/A	N/A	N/A	[redacted]	N/A	N/A	
		Placebo	164	[redacted]							

Abbreviations: NE - Not Estimated; N/A – Not applicable.

Secondary efficacy outcomes

Best Overall Response (BOR)

BOR is defined as the proportion of patients with a CR or PR, as determined according to RECIST v1.1 (34). Patients who did not achieve a CR or PR and patients with no response assessments (for whatever reason) were considered non-responders. Analysis methodology was the same as for ORR (34).

BOR at CCOD1 (20)

[redacted]

[redacted]

Table 52 Best Overall Response Rate (BOR).

	Inavolisib N=161		Placebo N=164	
	CCOD1 (20)	CCOD2 (57)	CCOD1 (20)	CCOD2 (57)
Responders, n (%)	[redacted]			
CR, n (%)	[redacted]			
Partial Response, n (%)	[redacted]			
Stable Disease, n (%)	[redacted]			
Progressive Disease, n (%)	[redacted]			
Missing, n (%)	[redacted]			

Clinical Benefit Rate (CBR)

CBR is defined as the proportion of patients with a CR, PR, and/or SD for at least 24 weeks, as determined according to RECIST v1.1 (34). Patients who did not achieve clinical benefit and patients with no response assessments (for whatever reason) were considered non-responders. Analysis methodology was the same as for ORR (34).

[redacted]

[redacted]

Appendix C. Comparative analysis of efficacy

N/A.

INAVO120 is a head-to-head study – i.e. no need for an indirect comparison.

Comparative analysis of efficacy

BOR at CCOD1

The proportion of patients with a best overall response of CR or PR, assessed by investigator per RECIST v1.1, was more than doubled in the inavolisib arm with [redacted] compared to the placebo arm [redacted] An increase of [redacted] in favor of the inavolisib arm was considered clinically meaningful. The proportion of patients achieving a best response of CR consistently showed higher benefit for patients in the inavolisib arm [redacted] compared with the placebo arm [redacted] There were [redacted] with a best response of PR in the inavolsib arm compared with [redacted] partial responders in the placebo arm (Table 12)(20).

BOR at CCOD2

[redacted]

CBR at CCOD1

The proportion of patients with a CR, PR, and/or SD sustained for ≥24 weeks, assessed by investigator per RECIST v1.1, was higher in the inavolisib arm ([redacted] as compared with the placebo arm [redacted] with an increase of [redacted] in favor of the inavolisib arm (Table 12)(20).

CBR at CCOD2

[redacted]

[redacted]

Table 53 Comparative analysis of studies comparing [intervention] to [comparator] for patients with [indication]

Outcome		Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value		
N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Table 54 Key Post-progression Therapies (59).

Patients – n (%)	Inavolisib		Placebo	
	Second line	Third line or later	Second line	Third line or later
Discontinued treatment	111/161 (68.9%)		144/164 (87.8%)	

[redacted]

Patients – n (%)	Inavolisib		Placebo	
	Second line	Third line or later	Second line	Third line or later
No subsequent therapy - death	17/161 (10.6%)		22/164 (13.4%)	
Received subsequent therapy*	83/111 (74.8%)	48/111 (43.2%)	109/144 (75.7%)**	56/144 (38.9%)
Chemotherapy (any)	46/83 (55.4%)	41/48 (85.4%)	79/109 (72.5%)	49/56 (87.5%)
Capecitabine	26/83 (31.3%)	14/48 (29.2%)	37/109 (33.9%)	24/56 (42.9%)
Paclitaxel	12/83 (14.5%)	17/48 (35.4%)	20/109 (18.3%)	16/56 (28.6%)
Eribulin	1/83 (1.2%)	11/48 (22.9%)	6/109 (5.5%)	17/56 (30.4%)
Antibody–drug conjugate (any)	1/83 (1.2%)	8/48 (16.7%)	1/109 (0.9%)	20/56 (35.7%)
Trastuzumab deruxtecan	0	6/48 (12.5%)	1/109 (0.9%)	16/56 (28.6%)
Sacituzumab govitecan	0	2/48 (4.2%)	0	8/56 (14.3%)
PI3K inhibitor (any)	5/83 (6.0%)	2/48 (4.2%)	11/109 (10.1%)	3/56 (5.4%)
Alpelisib	5/83 (6.0%)	2/48 (4.2%)	9/109 (8.3%)	2/56 (3.6%)
mTOR kinase inhibitor (everolimus)	8/83 (9.6%)	4/48 (8.3%)	10/109 (9.2%)	9/56 (16.1%)
CDK4/6 inhibitor (any)	8/83 (9.6%)	3/48 (6.2%)	5/109 (4.6%)	3/56 (5.4%)

Patients – n (%)	Inavolisib		Placebo	
	Second line	Third line or later	Second line	Third line or later
Ribociclib	1/83 (1.2%)	1/48 (2.1%)	5/109 (4.6%)	0
ABEMA	2/83 (2.4%)	2/48 (4.2%)	0	2/56 (3.6%)
Other (any)	6/83 (7.2%)	0	3/109 (2.8%)	5/56 (8.9%)

* Twenty-eight of 111 patients (20.7%) did not receive subsequent therapy in the inavolisib group due to progressive disease (12 patients), death/censored (7), adverse events (2), loss to follow-up (1), non-compliance with study drug (1), physician decision (1), symptomatic deterioration (1), or withdrawal by subject (3). Eleven patients in the inavolisib group had not received subsequent treatment but were documented being alive as of the clinical cutoff date. Thirty-four of 144 patients (23.6%) did not receive subsequent therapy in the placebo group due to progressive disease (24 patients), death/censored (4), withdrawal by subject (3), symptomatic deterioration (2), or adverse events (1). Twelve patients in the placebo group had not received subsequent treatment but were documented being alive as of the clinical cutoff date.
** One hundred-ten patients in this group received post-progression therapies but one patient was excluded as they were listed as “not applicable” in the database. CDK4/6 denotes cyclin-dependent kinase 4 and 6, mTOR mammalian target of rapamycin, and PI3K phosphatidylinositol 3-kinase.

Appendix D. Extrapolation

[Describe in detail how extrapolation is performed in accordance with sections 6.4.2 and 6.4.3 of the methods guide and the online appendix "Anvendelse af forløbsdata i sundhedsøkonomiske analyser".

- Specify which parametric function was selected for the intervention and comparator, respectively. All standard parametric models (exponential, Weibull, Gompertz, gamma, log normal, log logistic and generalized gamma) and other considered extrapolations must be available in the Excel model.
- Specify if the extrapolation models for the intervention and comparator are fitted in a joint model or independently.
- The section must include a discussion about using the same or different parametric function to extrapolate data for the intervention and comparator.
- A graphical representation of the time-to-event data curves where both the KM estimate and the parametric distributions are shown in the same figure must be presented in this section (for both intervention and comparator). The figure must include a graph with the general population's mortality rate and must display the entire time horizon of the model.
- Describe whether (and how) adjustments have been made for treatment switching/cross-over (intervention and/or comparator).
- Describe and explain how the extrapolations have been validated and present the results. When relevant, present a graphical representation of the validation.]

D.1 Extrapolation of [effect measure 1]

D.1.1 Data input

See Section 8

D.1.2 Model

See Section 8

D.1.3 Proportional hazards

PFS1

The proportional hazards assumption must be demonstrated to justify fitting an unstratified parametric function. The proportional hazard assumption implies that even though the hazard may vary over time, the HR between two treatment arms remains constant. To assess whether the proportional hazard assumption holds, a diagnostic plot of the log cumulative hazard for PFS1 over the log of time for the INAVO120 treatment arms was used.

The log cumulative hazard plot in Figure 42 shows that the hazard curves cross which indicates that the proportional hazard assumption is violated. In addition, Figure 43 illustrates the non-random pattern of the Schoenfeld residuals against time which further supports that the proportional hazards assumption does not hold ($p<0.05$). Therefore, to address the non-proportionality of the hazards, independent parametric models for PFS1 across treatment arms were used. It is worth noting that the same independent parametric model was chosen for both treatment arms, in line with NICE DSU 14 guidelines (61).

Figure 42 Log-cumulative hazard plot for PFS1

Figure 43 Schoenfeld residuals plot for PFS1

Proxy to PFS2

The log cumulative hazard plot for proxy to PFS2 in Figure 44 shows that the hazard curves cross which indicates that the proportional hazard assumption is violated. This is also supported by the Schoenfeld residuals plot in Figure 45 which suggests that the pro-

portional hazards assumption does not hold based on the non-random pattern of the residuals (p=0.05). Hence, to address the non-proportionality of the hazards, the same independent parametric model for proxy to PFS2 was selected for both treatments, as per the NICE DSU 14 guidance (61).

Figure 44 Log-cumulative hazard plot for proxy to PFS2

Figure 45 Schoenfeld Residuals plot for proxy to PFS2

Overall Survival

The log cumulative hazard plot in Figure 46 illustrates that the hazard curves cross over time which indicates that the proportional hazard assumption is violated. Moreover, the Schoenfeld residuals plot in Figure 47 indicates that the proportional hazards assumption

does not hold due to the non-random pattern of the residuals against time, although this is not statistically significant (p>0.05). As per the NICE DSU 14 guidance, the same independent parametric model was fitted for OS for both treatment arms to account for the non-proportionality of the hazards (61).

Figure 46 Log-cumulative hazard plot for OS

Figure 47 Schoenfeld residuals plot for OS

D.1.4 Evaluation of statistical fit (AIC and BIC)

Table 55 AIC and BIC statistics – PFS1

	Inavolisib + Palbociclib + fulvestrant		Placebo + palbociclib + fulvestrant	
Distribution	**AIC (Rank)**	**BIC (Rank)**	**AIC (Rank)**	**BIC (Rank)**
Exponential	[redacted]			
Weibull	[redacted]			
Log-normal	[redacted]			
Gen Gamma	[redacted]			
Log-logistic	[redacted]			
Gompertz	[redacted]			
Gamma	[redacted]			

Table 56 AIC and BIC statistics – proxy to PFS2

	Inavolisib + palbociclib + fulvestrant		Placebo + palbociclib + fulvestrant	
Distribution	**AIC (Rank)**	**BIC (Rank)**	**AIC (Rank)**	**BIC (Rank)**
Exponential	[redacted]			
Weibull	[redacted]			
Log-normal	[redacted]			
Gen Gamma	[redacted]			
Log-logistic	[redacted]			
Gompertz	[redacted]			
Gamma	[redacted]			

Table 57 AIC and BIC statistics - OS

	Inavolisib + palbociclib + fulvestrant		Placebo + palbociclib + fulvestrant	
Distribution	**AIC (Rank)**	**BIC (Rank)**	**AIC (Rank)**	**BIC (Rank)**
Exponential	[redacted]			
Weibull	[redacted]			
Log-normal	[redacted]			
Gen Gamma	[redacted]			
Log-logistic	[redacted]			
Gompertz	[redacted]			
Gamma	[redacted]			

Table 58 AIC and BIC statistics for TTOT – Inavo+palbo+fulv arm

	Inavolisib		Palbociclib		Fulvestrant	
Distribution	**AIC (Rank)**	**BIC (Rank)**	**AIC (Rank)**	**BIC (Rank)**	**AIC (Rank)**	**BIC (Rank)**
Exponential	[redacted]					
Weibull	[redacted]					
Log-normal	[redacted]					
Gen Gamma	[redacted]					
Log-logistic	[redacted]					
Gompertz	[redacted]					
Gamma	[redacted]					

Table 59 AIC and BIC statistics for TTOT – Placebo arm

	Palbociclib		Fulvestrant	
Distribution	AIC (Rank)	BIC (Rank)	AIC (Rank)	BIC (Rank)
Exponential	[redacted]			
Weibull				
Log-normal				
Gen gamma				
Log-logistic				
Gompertz				
Gamma				

D.1.5 Evaluation of visual fit

See Section 0

D.1.6 Evaluation of hazard functions

The smooth hazard plots for PFS1, PFS2, and OS reveal a common pattern observed in oncology: an initial upward trend in the hazard function, followed by a subsequent decline. This "humped" shape often indicates a mixed patient population. The initial rise in hazard likely corresponds to patients who do not respond to treatment, experiencing an early increase in risk. Conversely, the subsequent decrease in hazard suggests a subset of patients who do respond, leading to a reduced risk over time. Given this distinct hazard profile, only a limited number of standard statistical distributions can accurately model such behavior for extrapolation. Specifically, the **log-normal**, **log-logistic**, and **Gamma** distributions are capable of producing this humped hazard function.

For our base-case analysis, we've selected the **log-logistic** distribution for modeling PFS1 and PFS2. For OS, the **Gamma** distribution has been chosen. These choices were made because they not only align with the observed smooth hazard trends but also yield plausible outcomes for long-term predictions.

Figure 48: Smooth hazard function PFS1

Figure 49: Smooth hazard function PFS2

Figure 50: Smooth hazard function OS

Figure 51: Smooth hazard PFS1 for inavolisib

Figure 52: Smooth hazard PFS1 for placebo

Figure 53: Smooth hazard PFS2 for inavolisib

Figure 54: Smooth hazard PFS2 for placebo

Figure 55: Smooth hazard OS for inavolisib

Figure 56: Smooth hazard OS for inavolisib

D.1.7 Validation and discussion of extrapolated curves

See Section 8

D.1.8 Adjustment of background mortality

Adjustment of background mortality is done with Danish life tables in line with DMC guidance.

D.1.9 Adjustment for treatment switching/cross-over

N/A.

D.1.10 Waning effect

See Section 8.2

D.1.11 Cure-point

N/A.

Appendix E. Serious adverse events

Table 60 Serious Adverse Events, Safety Analysis Set (20, 57).

Adverse events	Inavolisib (N=162)	Placebo (N=162)	Inavolisib (N=161)	Placebo (N=163)
	CCOD1		CCOD2	
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				

Adverse events	Inavolisib (N=162)	Placebo (N=162)	Inavolisib (N=161)	Placebo (N=163)
	CCOD1		CCOD2	
[redacted]				

Adverse events	Inavolisib (N=162)	Placebo (N=162)	Inavolisib (N=161)	Placebo (N=163)
	CCOD1		CCOD2	
[redacted]				

Adverse events	Inavolisib (N=162)	Placebo (N=162)	Inavolisib (N=161)	Placebo (N=163)
	CCOD1		CCOD2	
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				

Adverse events	Inavolisib (N=162)	Placebo (N=162)	Inavolisib (N=161)	Placebo (N=163)
	CCOD1		CCOD2	
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				

Adverse events	Inavolisib (N=162)	Placebo (N=162)	Inavolisib (N=161)	Placebo (N=163)
	CCOD1		CCOD2	
[redacted]				

Abbreviations: NR – Not Reported.

Appendix F. Health-related quality of life

Pattern of missing data and completion for EORTC QLQ-C30 and BPI-SF at CCOD1 are listed in Table 61 and Table 62, respectively.

Table 61 Pattern of missing data and completion for EORTC QLQ-C30 at CCOD1 (20).

Time point	HRQoL population N		Missing N (%)		Expected to complete N		Completion N (%)	
	Number of patients at randomization		Number of patients for whom data is missing (% of patients at randomization)		Number of patients "at risk" at time point X		Number of patients who completed (% of patients expected to complete)	
	Inavolisib	Placebo	Inavolisib	Placebo	Inavolisib	Placebo	Inavolisib	Placebo
[redacted]								

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				

Time point	HRQoL population N	Missing N (%)		Expected to complete N	Completion N (%)	
[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]		[redacted]		
[redacted]	[redacted]	[redacted]		[redacted]		
[redacted]	[redacted]			[redacted]		
[redacted]	[redacted]			[redacted]		
[redacted]	[redacted]			[redacted]		
[redacted]	[redacted]			[redacted]		
[redacted]	[redacted]			[redacted]		

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	

Abbreviations: NR – Not Reported

Table 62 Pattern of missing data and completion for BPI-SF Worst Pain Item at CCOD1 (20).

Time point	HRQoL population N		Missing N (%)		Expected to complete N		Completion N (%)	
	Number of patients at randomization		Number of patients for whom data is missing (% of patients at randomization)		Number of patients "at risk" at time point X		Number of patients who completed (% of patients expected to complete)	
	Inavolisib	Placebo	Inavolisib	Placebo	Inavolisib	Placebo	Inavolisib	Placebo
[redacted]								

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]			[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Time point	HRQoL population N	Missing N (%)		Expected to complete N	Completion N (%)
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					

Abbreviations: NR – Not Reported

Pattern of missing data and completion for EORTC QLQ-C30, BPI-SF and EQ-5D-5L at CCOD2 are listed in Table 63, Table 64 and Table 65, respectively.

Table 63 Pattern of missing data and completion for EORTC QLQ-C30 CCOD2 (57). All tests were performed on Day 1 in the cycle.

Time point	HRQoL population N		Missing N (%)		Expected to complete N		Completion N (%)	
	Number of patients at randomization		Number of patients for whom data is missing (% of patients at randomization)		Number of patients "at risk" at time point X		Number of patients who completed (% of patients expected to complete)	
	Inavolisib	Placebo	Inavolisib	Placebo	Inavolisib	Placebo	Inavolisib	Placebo
	[redacted]							

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				

Abbreviations: NR – Not Reported.

Table 64 Pattern of missing data and completion for BPI-SF Worst Pain Item at CCOD2 (57).

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)

Time point	HRQoL population N		Missing N (%)		Expected to complete N		Completion N (%)	
	Inavolisib	Placebo	Inavolisib	Placebo	Inavolisib	Placebo	Inavolisib	Placebo
[redacted]								

Time point	HRQoL population N	Missing N (%)		Expected to complete N	Completion N (%)	
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				

Time point	HRQoL population N	Missing N (%)		Expected to complete N	Completion N (%)	
[redacted]						
[redacted]	[redacted]	[redacted]		[redacted]		
[redacted]	[redacted]	[redacted]		[redacted]		
[redacted]	[redacted]	[redacted]		[redacted]		
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: NR – Not Reported.

Table 65 Pattern of missing data and completion for EQ-5D-5L at CCOD2 (77).

Time point	HRQoL population N		Missing N (%)		Expected to complete N		Completion N (%)	
	Number of patients at randomization		Number of patients for whom data is missing (% of patients at randomization)		Number of patients “at risk” at time point X		Number of patients who completed (% of patients expected to complete)	
	Inavolisib	Placebo	Inavolisib	Placebo	Inavolisib	Placebo	Inavolisib	Placebo

Time point	HRQoL population N	Missing N (%)		Expected to complete N	Completion N (%)
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					

Time point	HRQoL population N	Missing N (%)		Expected to complete N	Completion N (%)
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
[redacted]				

Abbreviations: NR – Not Reported

HRQoL Results – continued

PRO Scores and Change from Baseline by Visit for EORTC QLQ-C30 at CCOD1 are listed in Table 66.

Table 66 PRO Scores and Change from Baseline by Visit for EORTC QLQ-C30 - Global health status/QoL at CCOD1 (20).

	Inavolisib		Placebo		Inavolisib vs. placebo
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
[redacted]					

	Inavolisib	Placebo	Inavolisib vs. placebo
[redacted]			

	Inavolisib	Placebo	Inavolisib vs. placebo
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			

Abbreviations: NA – Not Applicable; NE – Not Estimated

PRO Scores and Change from Baseline by Visit for EORTC QLQ-C30, BPI-SF and EQ-5D-5L at CCOD2 are listed in Table 67 and Table 68, respectively. Treatment Discontinuation, Post-Treatment Follow Up, 30 Day Safety Follow-up and Survival Follow-up for and EQ-5D-5L at CCOD2 are listed in Table 69.

Table 67 PRO Scores and Change from Baseline by Visit for EORTC QLQ-C30. Global health status/QoL (CCOD2) All tests were performed on Day 1 in the cycle (57).

	Inavolisib (N=161)	Placebo (N=164)	Inavolisib vs. placebo
[redacted]			
[redacted]			
[redacted]			
[redacted]			

	Inavolisib (N=161)	Placebo (N=164)	Inavolisib vs. placebo
[redacted]			

	Inavolisib (N=161)	Placebo (N=164)	Inavolisib vs. placebo
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			

Abbreviations: N/A – Not Applicable

Table 68 PRO Scores and Change from Baseline by Visit for BPI-SF Worst Pain Item at CCOD2 (57).

	Inavolisib (N=161)	Placebo (N=164)	Inavolisib vs. placebo
[redacted]			

	Inavolisib (N=161)	Placebo (N=164)	Inavolisib vs. placebo
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			

Abbreviations: N/A – Not Applicable.

Table 69 PRO Scores and Change from Baseline by Visit for EQ-5D-5L at CCOD2 (77).

	Inavolisib (N=161)	Placebo (N=164)	Inavolisib vs. placebo
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			

Abbreviations: N/A – Not Applicable.

Appendix G. Probabilistic sensitivity analyses

Table 70. Overview of parameters in the PSA

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Disc Inc. life years				
PFS – Inavolisib	[redacted]	Decomposition cholesky	Decomposition cholesky	Log-logistic
	[redacted]	Decomposition cholesky	Decomposition cholesky	
PFS – Placebo	[redacted]	Decomposition cholesky	Decomposition cholesky	
	[redacted]	Decomposition cholesky	Decomposition cholesky	
PFS2 – Inavolisib	[redacted]	Decomposition cholesky	Decomposition cholesky	Log-logistic
	[redacted]	Decomposition cholesky	Decomposition cholesky	Log-logistic
PFS2 – Placebo	[redacted]	Decomposition cholesky	Decomposition cholesky	Log-logistic
	[redacted]	Decomposition cholesky	Decomposition cholesky	Log-logistic
OS – Inavolisib	[redacted]	Decomposition cholesky	Decomposition cholesky	Gamma
	[redacted]	Decomposition cholesky	Decomposition cholesky	Gamma
OS – Placebo	[redacted]	Decomposition cholesky	Decomposition cholesky	Gamma

	[redacted]	Decomposition cholesky	Decomposition cholesky	Gamma
TTOT – Inavolisib	[redacted]	Decomposition cholesky	Decomposition cholesky	Gamma
	[redacted]	Decomposition cholesky	Decomposition cholesky	Gamma
TTOT – Placebo	[redacted]	Decomposition cholesky	Decomposition cholesky	Gamma
	[redacted]	Decomposition cholesky	Decomposition cholesky	Gamma
PD2	[redacted]			Log-logistic
HSUV				
PFS	[redacted]			Beta
PD1	[redacted]			Beta
PD2	[redacted]			Beta
Costs				
Administration cost injection	[redacted]			Log-normal
Supportive care costs	[redacted]			Log-normal
Post-progres-sion treatment costs – PD1	[redacted]			Log-normal Log-normal
Post-progres-sion treatment costs – PD2	[redacted]			Log-normal Log-normal
AE management cost	[redacted]			Log-normal Log-normal
Diagnostic test	[redacted]			Log-normal

AE		[redacted]	[redacted]		Log-normal
RDI:					
Inavolisib + palbocilib + fulvestrant	Inavolisib	84.35%	*82%*	*86%*	Beta
	Palbociclib	85.22%	*82%*	*88%*	Beta
	Fulvestrant	95.63%	*95%*	*97%*	Beta
Palbociclib	Palbociclib	83,17%	*84%*	*82%*	Beta
	Fulvestrant	93,50%	*95%*	*93%*	Beta

Appendix H. Literature searches for the clinical assessment

H.1 Efficacy and safety of the intervention and comparator(s)

N/A.

Table 71 Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	N/A	N/A	N/A
Medline	N/A	N/A	N/A
CENTRAL	N/A	N/A	N/A

Abbreviations:

Table 72 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
e.g. NICE	N/A	N/A	N/A
e.g. EMA website	N/A	N/A	N/A

Abbreviations:

Table 73 Conference material included in the literature search

Conference	Source of ab-stracts	Search strategy	Words/terms searched	Date of search
Conference name	N/A	N/A	N/A	N/A

H.1.1 Search strategies

N/A.

Table 74 of search strategy table for [name of database]

No.	Query	Results
#1	N/A	N/A

H.1.2 Systematic selection of studies

N/A.

Table 75 Inclusion and exclusion criteria used for assessment of studies

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Changes, local adaption
Population	N/A	N/A	N/A
Intervention	N/A	N/A	N/A
Comparators	N/A	N/A	N/A
Outcomes	N/A	N/A	N/A
Study design/publication type	N/A	N/A	N/A
Language restrictions	N/A	N/A	N/A

Table 76 Overview of study design for studies included in the analyses

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
Study 1	N/A	N/A	N/A	N/A	N/A	N/A

H.1.3 Excluded full text references

N/A.

H.1.4 Quality assessment

N/A.

H.1.5 Unpublished data

N/A.

Appendix I. Literature searches for health-related quality of life

I.1 Health-related quality-of-life search

N/A.

Table 77 Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
Embase	N/A	N/A	N/A
Medline	N/A	N/A	N/A
Specific health economics data-bases[1]	N/A	N/A	N/A

Abbreviations:

Table 78 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
e.g. NICE	N/A	N/A	N/A
CEA Registry	N/A	N/A	N/A

Table 79 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
Conference name	N/A	N/A	N/A	N/A
	N/A	N/A	N/A	N/A

[1] Papaioannou D, Brazier J, Paisley S. Systematic searching and selection of health state utility values from the literature. Value Health. 2013;16(4):686-95.

I.1.1 Search strategies

N/A.

Table 80 Search strategy for [name of database]

No.	Query	Results
#1	N/A	N/A
#2	N/A	N/A
#3	N/A	N/A
#4	N/A	N/A
#5	N/A	N/A
#6	N/A	N/A
#7	N/A	N/A
#8	N/A	N/A
#9	N/A	N/A
#10	N/A	N/A

I.1.2 Quality assessment and generalizability of estimates

N/A.

I.1.3 Unpublished data

N/A.

Appendix J. Literature searches for input to the health economic model

J.1 External literature for input to the health economic model

N/A.

J.1.1 Example: Systematic search for […]

N/A.

Table 51 Sources included in the search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	N/A	N/A	N/A
Medline	N/A	N/A	N/A
CENTRAL	N/A	N/A	N/A

Abbreviations:

J.1.2 Example: Targeted literature search for [estimates]

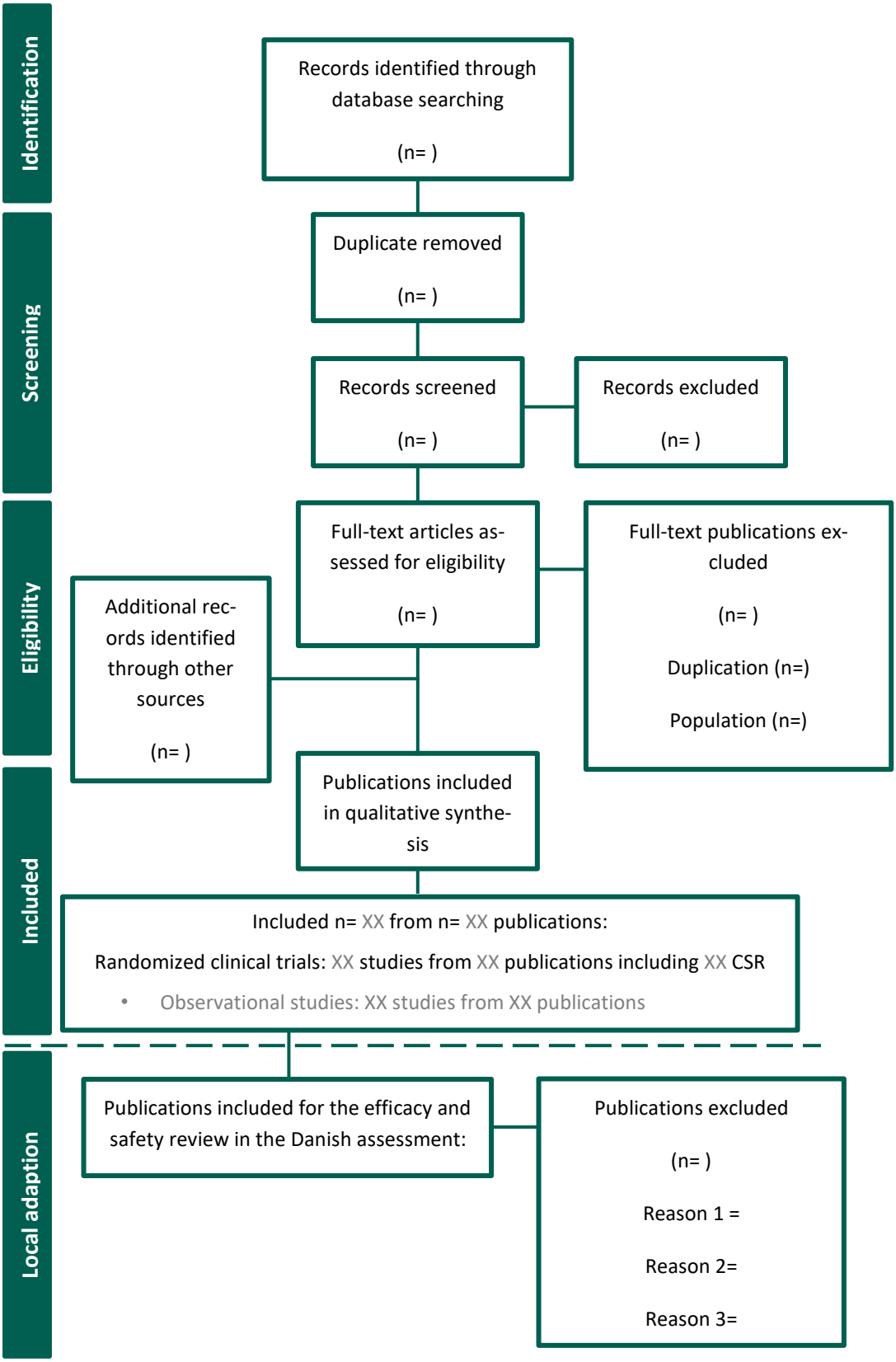
N/A.

Table 52 Sources included in the targeted literature search

Source name/ database	Location/source	Search strategy	Date of search
e.g. NICE	N/A	N/A	N/A
	N/A	N/A	N/A

Abbreviations:

Example of PRISMA diagram. The diagram is editable and may be used for recording the records flow for the literature searches and for the adaptation of existing SLRs.



Medicinrådet

Danish Medicines Council
Secretariat
Dampfærgevej 21-23, 3rd floor
DK-2100 Copenhagen Ø

+ 45 70 10 36 00
medicinraadet@medicinraadet.dk

www.medicinraadet.dk