# Cost-effectiveness of inavolisib in combination with palbociclib and fulvestrant versus palbociclib and fulvestrant alone for the first-line treatment of PIK3CA-mutated, hormone receptor-positive, HER2-negative advanced breast cancer in the Netherlands

*A cost-effectiveness analysis from the Dutch societal perspective*

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Rotterdam
May 2026

*Word count (main text only): approximately 14,600*

# Abstract

**Background.** Inavolisib, a PI3Kα inhibitor, was approved for PIK3CA-mutated, hormone receptor-positive, HER2-negative advanced breast cancer after the INAVO120 trial showed it markedly prolonged progression-free and overall survival when added to palbociclib and fulvestrant. Its list price is high and no Dutch cost-effectiveness estimate exists. This study assessed the cost-effectiveness and budget impact of inavolisib combination therapy for the Dutch setting and derived both a value-based threshold price and a cost-based access price.

**Methods.** A partitioned survival model with a 20-year horizon estimated costs and quality-adjusted life years (QALYs) from the Dutch societal perspective, with a healthcare payer scenario. Survival was extrapolated from INAVO120 using parametric models. Costs followed the 2024 Dutch costing guideline, expressed in 2025 prices. Uncertainty was assessed through probabilistic and one-way deterministic sensitivity analyses and thirteen cost-utility scenarios. An access-based price was derived using the ASCERTAIN pricing model, and a five-year budget impact analysis was conducted from the payer perspective.

**Results.** Inavolisib produced 0.394 additional QALYs at an incremental cost of €437,407 per patient, giving an incremental cost-effectiveness ratio of €1,109,246 per QALY, about fourteen times the €80,000 per QALY threshold. The conclusion was robust across perspective, probabilistic, and scenario analyses (range €759,775 to €1,111,376 per QALY). To meet the threshold, the price would need to fall by approximately 96%, to about €516 per cycle (the value-based threshold price). The cost-based access price was €6,800 per cycle. Reimbursement at list price was estimated to add €105.0 million to the Dutch drug budget over five years.

**Conclusion.** At its list price inavolisib combination therapy is not cost-effective for the Dutch setting, and the shortfall is too large to be closed by a conventional discount. These Dutch-specific estimates can inform the forthcoming Zorginstituut Nederland appraisal and price negotiations.

# Table of contents

Abstract ..... 2
Table of contents ..... 3
1. Introduction ..... 5
1.1 Research question ..... 6
2. Theoretical framework ..... 8
2.1 Economic evaluation and resource allocation ..... 8
2.2 Key methodological concepts in cost-utility analysis ..... 8
2.2.1 Perspective ..... 8
2.2.2 Quality-adjusted life years ..... 8
2.2.3 Cost-effectiveness thresholds ..... 9
2.2.4 Discounting ..... 9
2.2.5 Time horizon ..... 9
2.3 Health economic modelling ..... 9
2.3.1 The need for modelling ..... 9
2.3.2 Modelling approaches ..... 9
2.3.3 Addressing uncertainty ..... 10
2.4 From value to price: access-based pricing ..... 10
2.4.1 The price-determination gap ..... 10
2.4.2 The access-based pricing model ..... 10
2.4.3 Rationale for combining CUA and ABP ..... 11
2.5 Evidence base and positioning of the study ..... 11
2.5.1 Clinical effectiveness evidence ..... 11
2.5.2 Existing economic evaluations of inavolisib ..... 11
2.5.3 Dutch pharmacoeconomic evidence on advanced breast cancer ..... 11
2.5.4 Knowledge gap and scientific contribution ..... 12
2.6 Conceptual model ..... 12
3. Methods ..... 13
3.1 Study design and decision-analytic model ..... 13
3.2 Treatment effect ..... 14
3.3 Health-related quality of life ..... 18
3.4 Resource use and costs ..... 19
3.4.1 Perspective and indexation ..... 20
3.4.2 Stable disease costs ..... 20
3.4.3 Progressed disease costs ..... 23
3.4.4 End-of-life costs ..... 24
3.5 Sensitivity and scenario analyses ..... 24
3.6 Access-based pricing model ..... 26
3.7 Budget impact analysis ..... 28

4. Results ..... 30
4.1 Base-case results ..... 30
4.2 Probabilistic sensitivity analysis ..... 31
4.3 Access-based price ..... 34
4.4 Scenario analyses ..... 35
Access-based price scenario analyses ..... 35
Cost-utility analysis scenario analyses ..... 36
4.5 Budget impact ..... 37
5. Discussion and conclusion ..... 38
5.1 Summary of key findings ..... 38
5.2 Comparison with the existing literature ..... 38
5.3 Strengths and limitations ..... 39
5.4 Recommendations for further research ..... 42
5.5 Policy implications ..... 42
5.6 Conclusion ..... 43
References ..... 45
Appendix A. Detailed cost derivations ..... 51
Appendix B. AIC values for parametric survival distributions ..... 54
Appendix C. NZa primary-care diagnostic tariff codes applied ..... 55
Appendix D. Full screening of adverse events from the INAVO120 safety analysis ..... 56
Appendix E. Adverse event disutility values and management costs ..... 57
Appendix F. Access-based pricing model parameter specification ..... 58
Appendix G. Probabilistic sensitivity analysis: distributions and parameterisation ..... 60
Appendix H. Access-based price: full scenario analysis ..... 62
Appendix I. Cost-utility analysis: full scenario results ..... 63

# 1. Introduction

Breast cancer is the most commonly diagnosed cancer in women worldwide, accounting for 11.6% of all cancer cases and an estimated 670,000 deaths globally in 2022 [1,2]. In the Netherlands, 15,400 women were diagnosed and 3,062 died from breast cancer in 2024 [3,4]. Beyond this clinical burden, breast cancer imposes a substantial economic burden on the Dutch healthcare system: in 2019, breast cancer care totalled €813 million, representing 12.5% of all cancer care expenditure and 0.84% of total national healthcare spending [5,6].

Approximately 65–75% of newly diagnosed breast cancer cases are classified as hormone-receptor-positive/HER2-negative (HR+/HER2−), making this the most common molecular subtype [7,8]. While five-year relative survival exceeds 99% for localised HR+/HER2− disease, it drops to approximately 36% once the disease has metastasised [9]. The therapeutic landscape for metastatic HR+/HER2− breast cancer in the Netherlands has evolved considerably over the past decade. Historically, endocrine monotherapy with aromatase inhibitors or fulvestrant formed the backbone of palliative treatment [10]. Following the reimbursement of CDK4/6 inhibitors in 2017 and the results of the Dutch SONIA trial, clinical practice shifted towards giving these patients an aromatase inhibitor first and reserving the fulvestrant plus CDK4/6-inhibitor combination for afterwards [11,12].

A note on terminology is useful here, because "line of treatment" can be counted in two ways. The first counts the order of hormone-based treatments overall: in the Netherlands the fulvestrant plus CDK4/6-inhibitor combination comes after an aromatase inhibitor, so it is sometimes called a second-line treatment [11,12]. The second counts only treatments given once the cancer has become advanced or metastatic. This study uses the second meaning, following the INAVO120 trial and the European Medicines Agency registration: the trial patients had only been treated at an earlier, curable stage of their disease, so the inavolisib combination is the first treatment they receive for advanced disease. For this reason, "first-line" in this thesis always means the first treatment for advanced or metastatic disease.

A persistent clinical challenge in this population is resistance to endocrine therapy. Approximately 40% of patients with HR+/HER2− advanced breast cancer harbour activating mutations in the PIK3CA gene, which contribute to endocrine therapy resistance and earlier therapeutic failure [13]. Inavolisib, a recently approved selective PI3Kα inhibitor, specifically targets this resistance mechanism. In the pivotal phase III INAVO120 trial (NCT04191499), the addition of inavolisib to palbociclib and fulvestrant significantly improved progression-free survival (PFS) (median 15.0 versus 7.3 months; hazard ratio 0.43, 95% CI 0.32 to 0.59) and overall survival (OS) (median 34.0 versus 27.0 months; hazard ratio 0.67, 95% CI 0.48 to 0.94) in 325 patients with PIK3CA-mutated, HR+/HER2− advanced breast cancer who had progressed on prior endocrine therapy [14,15]. These results met the positive recommendation criteria of the PASKWIL 2023 framework for palliative oncology studies [13].

Inavolisib's clinical promise, however, comes at a considerable price. At a list price of €13,695 per 28-day cycle, the estimated drug acquisition cost alone amounts to roughly €195,151 per patient for the median treatment duration [13,16]. This figure substantially exceeds the

€52,709 average total lifetime treatment cost reported for advanced breast cancer patients in the Netherlands during 2010–2014 [17], illustrating the continuing escalation of oncology drug costs over the past decade. Within a publicly financed healthcare system with a fixed budget, additional spending on one intervention displaces resources that could have produced health elsewhere [18,19], raising pressing questions about whether the added clinical benefit of inavolisib justifies its added costs.

A sizeable Dutch pharmacoeconomic literature on breast cancer exists, covering trastuzumab, CDK4/6 inhibitors, and end-of-life cost patterns [11,12,17,20,21]. However, no economic evaluation of inavolisib has yet been conducted for the Dutch setting. The only published evaluations were carried out by Huang et al. (2025) and Zhu et al. (2026) for the Chinese and United States settings, both of which concluded that inavolisib is not cost-effective at its current list price [22–24]. These findings cannot be transferred directly to the Dutch setting, where the cost-effectiveness thresholds, procurement prices, and analytic perspective differ substantially. The published evaluations applied per-capita-GDP-based or United States thresholds and a healthcare-payer perspective, whereas the Dutch reference case uses severity-dependent thresholds and, in the base case, the broader societal perspective [22,23,25,26]. A Netherlands-specific evaluation is therefore both absent and non-trivially different.

Moreover, a standard cost-effectiveness analysis establishes what a treatment is worth relative to its alternatives at a given price, but does not directly address what the price itself should be. A complementary approach is the recently proposed Access-Based Pricing (ABP) model, developed within the ASCERTAIN consortium by Xander and colleagues. It derives a defensible price by combining four components: capitalised research and development costs, a value-based reward, operational costs, and an operational profit margin [27,28]. To date, the ABP model has not been applied to a Dutch oncology case.

This thesis therefore contributes to the existing literature on three fronts. First, it provides the first country-specific economic evaluation of inavolisib for the Dutch setting, filling an evidence gap directly relevant to an impending Dutch reimbursement decision. Second, it operationalises the ABP model in an oncology context for the first time in the Netherlands, complementing the cost-utility analysis with a supply-side pricing estimate. Third, by jointly comparing the current list price, the threshold prices implied by the Dutch cost-effectiveness thresholds, and the ABP-derived price, it offers a triangulated pricing framework that can inform negotiations, both for inavolisib specifically and, more broadly, for the growing class of high-cost targeted oncology therapies entering reimbursement review.

## 1.1 Research question

The primary research question addressed in this thesis is: Is inavolisib in combination with palbociclib and fulvestrant cost-effective compared with palbociclib and fulvestrant alone as afirst-line treatment for PIK3CA-mutated, HR+/HER2− locally advanced or metastatic breast cancer in the Dutch setting, and what pricing scenarios balance clinical value with healthcare affordability?

This primary question is operationalised through the following sub-questions:

1) What are the incremental costs of inavolisib + palbociclib + fulvestrant compared with palbociclib + fulvestrant for this indication?

2) What are the incremental health effects of the intervention compared with the comparator, based on the available clinical evidence?

3) What is the incremental cost-effectiveness ratio (ICER) of the intervention at the current list price of €13,695 per cycle?

4) What are the key drivers of cost-effectiveness, as identified through deterministic and probabilistic sensitivity analyses?

5) What is the access-based price of inavolisib under the ABP model, and how does it compare with the current list price and with the threshold-based prices implied by the cost-utility analysis?

6) Would the intervention be cost-effective at the access-based price?

7) What is the budget impact of introducing inavolisib combination therapy on the Dutch healthcare budget over a 3 to 5-year horizon?

# 2. Theoretical framework

## 2.1 Economic evaluation and resource allocation

Healthcare resources are finite while demand for health-improving interventions is essentially unlimited, so funding one intervention necessarily means forgoing others. This trade-off is captured by the concept of opportunity cost: the health benefit that the displaced resources would otherwise have generated for other patients [18,19]. In a budget-constrained system, this forgone benefit is conventionally expressed in quality-adjusted life years (QALYs). The true cost of adopting a new technology is therefore the QALYs that the same expenditure could have produced elsewhere in the system [18,19]. Economic evaluations provide a structured framework for comparing costs and consequences of alternative interventions, thereby informing reimbursement decisions [18,29]. Economic evaluations are conventionally distinguished by how they measure consequences: a cost-minimisation analysis (CMA) compares only costs when effects are assumed equivalent; a cost-effectiveness analysis (CEA) expresses outcomes in natural clinical units such as life-years gained; a cost-benefit analysis (CBA) values both costs and consequences in monetary terms; and a cost-utility analysis (CUA) expresses outcomes in quality-adjusted life years, allowing comparison across disease areas [18]. The last of these is required by the Dutch guideline as the reference case [25]. A related but distinct tool is the budget impact analysis (BIA), which estimates the financial consequences of adopting an intervention within a specific healthcare budget [25,30].

## 2.2 Key methodological concepts in cost-utility analysis

### 2.2.1 Perspective

The perspective determines which costs and effects are included. The healthcare payer perspective restricts the scope to direct medical costs. The societal perspective additionally aims to capture all costs and effects regardless of where they fall or who bears them, both within and outside the healthcare sector. Examples include productivity losses, informal care, and patient out-of-pocket costs [18]. The Dutch guideline requires the societal perspective as the reference case, with the healthcare payer perspective reported as a secondary analysis [25].

### 2.2.2 Quality-adjusted life years

QALYs combine quantity and quality of life by weighting life-years by a utility score measured on a scale from 0 (death) to 1 (full health) [18,31]. Health-related quality of life can be measured using generic preference-based instruments such as the EQ-5D, which allow cross-disease comparisons, or disease-specific instruments that require validated mapping algorithms to generate utilities [32]. The EQ-5D-5L extends the original three-level version to five severity levels across five dimensions, and the Dutch guideline requires the EQ-5D-5L scored using the Dutch tariff developed by Versteegh et al. (2016) [25,33].

### 2.2.3 Cost-effectiveness thresholds

The cost-effectiveness threshold represents the maximum acceptable incremental cost per additional QALY. The demand-side threshold reflects society's willingness to pay for health gains, while the supply-side threshold reflects the health foregone elsewhere when resources are reallocated [19,34]. The Netherlands adopts a demand-side approach with thresholds of €20,000, €50,000 or €80,000 per QALY for proportional-shortfall severity ranges of 0.10–0.40, 0.41–0.70 and 0.71–1.00 respectively, as set by Zorginstituut Nederland and applied in its package appraisals (*pakketadviezen*) [25,26]. Advanced oncological disease such as metastatic HR+/HER2− breast cancer carries a very high disease burden: the proportional shortfall of metastatic breast cancer has been estimated at 0.86, which falls in the highest severity class (0.71–1.00) and therefore corresponds to the €80,000 per QALY reference value [25,26,35].

### 2.2.4 Discounting

Costs and health outcomes occurring in the future are valued less than those occurring today. The rationale for discounting costs (reflecting the social consumption interest rate) differs from that for discounting health (reflecting the social rate of time preference for health). The latter has been argued to be lower, particularly if the willingness to pay for a QALY grows in real terms over time [36]. Applying a single rate to both would risk disproportionately undervaluing distant health gains. The Dutch guideline therefore prescribes differential discounting: 3.0% per year for costs and 1.5% per year for health outcomes [25].

### 2.2.5 Time horizon

The time horizon should capture all relevant differences in costs and health effects. For chronic or life-threatening conditions the Dutch guideline recommends a lifetime horizon as the reference case [25,26].

## 2.3 Health economic modelling

### 2.3.1 The need for modelling

A cost-effectiveness analysis requires costs and health outcomes to be estimated over a patient's lifetime, but the INAVO120 trial followed patients for a median of only 34 months [15]. This is too short to observe the full survival of patients with advanced breast cancer, a proportion of whom live for several years, with a small fraction surviving well beyond a decade [6]. The costs and survival beyond the trial's follow-up therefore have to be estimated rather than observed. Economic modelling addresses this by combining the observed trial data with external evidence to extrapolate lifetime costs and health outcomes [18,37].

### 2.3.2 Modelling approaches

Partitioned survival models (PSMs) derive state occupancy directly from the survival curves reported in trials. In a typical oncology-specific PSM, the area under the PFS curve represents time in the progression-free state, the area between the PFS and OS curves represents time in progressed disease, and the complement of the OS curve represents death [38,39]. PSMs have become the dominant structure in oncology health technology assessment submissions,

accounting for 77% of NICE oncology submissions between 2013 and 2016 [39,40], largely because they align naturally with the primary endpoints reported in oncology trials. An alternative would be a Markov state-transition model, but this requires patient-level data to estimate transition probabilities between health states [18,37], which were not available for INAVO120. The partitioned survival approach was therefore preferred, as it can be built directly from the published progression-free and overall survival curves.

### 2.3.3 Addressing uncertainty

Health economic models are subject to three kinds of uncertainty [18]. Parameter uncertainty arises from imprecision in the input estimates, and is addressed through probabilistic sensitivity analysis (PSA), which samples all uncertain inputs simultaneously from probability distributions using Monte Carlo simulation. Structural and methodological uncertainty arise from model design choices (such as the parametric survival distribution selected) and analytical conventions (such as the discount rates), and are explored through scenario analyses. In addition, deterministic sensitivity analysis varies one parameter at a time to identify those that drive the result, that is, those whose variation changes the ICER most. The Dutch guideline requires PSA as the primary means of characterising decision uncertainty [25].

## 2.4 From value to price: access-based pricing

### 2.4.1 The price-determination gap

A cost-utility analysis establishes whether an intervention offers good value at a given price, but it does not indicate what that price should be. Existing pricing approaches each capture only part of the picture. Cost-plus pricing derives a price from production costs but largely ignores therapeutic value, whereas value-based pricing anchors the price to incremental health gains but ignores capitalised development costs. Value-based pricing also faces a further difficulty in oncology: the added therapeutic value of a novel treatment is often uncertain at the time of pricing, because pivotal trials frequently rely on surrogate endpoints, single-arm or open-label designs, and short follow-up relative to the disease course [28]. The incremental health gain on which a value-based price depends is therefore itself imprecisely estimated. Together with the escalating list prices of novel targeted oncology therapies, this has sharpened the need for a more integrated pricing framework [27].

### 2.4.2 The access-based pricing model

The ABP model, developed within the ASCERTAIN consortium by Xander and colleagues, derives a price per patient by integrating four components: (i) capitalised research and development costs distributed across the expected patient population; (ii) a value-based reward reflecting added therapeutic benefit; (iii) operational costs; and (iv) an operational profit margin [27,28]. The aim of the model is to provide a transparent, defensible reference price for a newly authorised medicine that simultaneously rewards genuine innovation and protects patient access, thereby offering payers and manufacturers a common, cost- and value-

grounded starting point for price negotiations rather than a price set by either production cost or therapeutic value alone [27,28].

### 2.4.3 Rationale for combining CUA and ABP

The CUA yields a threshold price; the price at which the ICER equals the willingness-to-pay threshold. The ABP model yields an access-based price reflecting defensible capitalised costs and a calibrated value-based reward. Together with the current list price, these form a triangulated pricing framework for evidence-informed pricing negotiations [27]. This integration is particularly valuable for high-cost targeted therapies in small-population indications such as PIK3CA-mutated HR+/HER2− advanced breast cancer.This triangulation presents decision-makers with three reference points side by side: the list price, the value-based threshold price, and the cost-based access-based price. By making clear what a pricing or reimbursement decision is based on, it reduces reliance on a single, assumption-sensitive figure and supports more transparent and better-informed resource-allocation decisions [27,28].

## 2.5 Evidence base and positioning of the study

### 2.5.1 Clinical effectiveness evidence

The clinical efficacy of inavolisib for PIK3CA-mutated HR+/HER2− advanced breast cancer is established by the phase III INAVO120 trial, the results of which supported its authorisation and its positive recommendation under the PASKWIL 2023 framework [13–15]. A detailed description of the trial population and endpoints is provided in Chapter 3.

### 2.5.2 Existing economic evaluations of inavolisib

At the time of completion of this study, two economic evaluations of inavolisib have been published. Zhu et al. (2026) compared inavolisib plus palbociclib and fulvestrant with palbociclib plus fulvestrant as a first-line treatment in patients with HR+/HER2− advanced breast cancer in both China and the United States [22]. Huang et al. (2026) evaluated the same comparison in the Chinese setting [23]. Both concluded that inavolisib is not cost-effective at the current local list price. These findings cannot be directly extrapolated to the Netherlands for three reasons. First, the cost-effectiveness thresholds differ. China sets its willingness-to-pay threshold as a multiple of per-capita GDP, and the United States commonly references USD 100,000 to 150,000 per QALY, neither of which corresponds to the Dutch severity-dependent thresholds of €20,000, €50,000 and €80,000 per QALY [25,26]. Second, both the prices of the drugs themselves and the cost of the surrounding hospital care (consultations, scans, admissions) differ substantially between these countries and the Netherlands [22,23]. Third, the analytic perspective differs: the published Chinese and United States analyses were conducted from a healthcare-payer or health-system perspective, whereas the present analysis adopts the broader Dutch societal perspective, which additionally captures informal care, productivity losses, and patient costs [22,23,25].

### 2.5.3 Dutch pharmacoeconomic evidence on advanced breast cancer

A small body of Dutch pharmacoeconomic research provides context for the present analysis. On the cost side, Schneider et al. estimated the direct medical costs of advanced breast

cancer in the Netherlands at a mean of €52,709 per patient over the 2010–2014 period [17], and Seferina et al. (2017) evaluated adjuvant trastuzumab in a real-world Dutch setting [21]. On the treatment side, the Dutch SONIA trial showed that deferring CDK4/6 inhibitors to a later line did not compromise outcomes [11], and Wortelboer et al. (2025) examined the cost-effectiveness of giving them later rather than first [12]. Together, these studies characterise the cost levels and current treatment pathway against which inavolisib is evaluated, but none addresses inavolisib itself.

### 2.5.4 Knowledge gap and scientific contribution

Three gaps emerge from the existing literature. First, no economic evaluation of inavolisib has been conducted for the Dutch setting. Second, the ABP model has not been applied to an oncology case in the Netherlands. Third, existing evaluations have not combined a CEA with an explicit access-based pricing analysis. The present study addresses all three gaps simultaneously.

## 2.6 Conceptual model

Patients with PIK3CA-mutated HR+/HER2− advanced breast cancer enter the model in the progression-free state. The structure of the partitioned survival model is shown schematically in Figure 1, and the partitioning of state membership from the PFS and OS curves is described above. Because membership is derived from the two curves rather than from explicit transition probabilities, the model does not impose a fixed ordering of states: death is taken from the overall survival curve and therefore occurs from both the progression-free and the progressed-disease state. Both living health states accumulate costs and QALYs, weighted by state-specific utility values and adjusted for treatment-related adverse events. The ICER is obtained by dividing the difference in discounted cumulative costs between the two strategies by the difference in their discounted cumulative QALYs over the time horizon.

In parallel, the ABP model derives an access-based price from capitalised R&D expenditure, a calibrated innovation reward (driven principally by the product's added therapeutic benefit), operational costs, and a profit margin. This price is then compared with the list price and the threshold prices from the CUA.

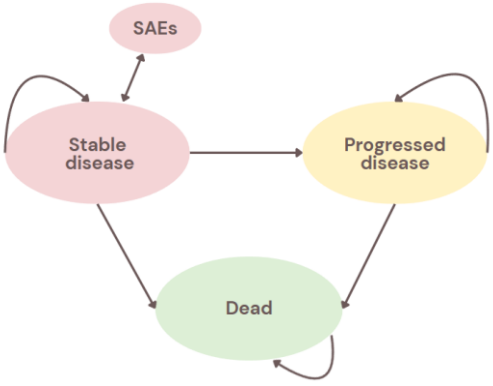


***Figure 1. Schematic of the conceptual model.***

*SAEs= Serious Adverse Events*

# 3. Methods

## 3.1 Study design and decision-analytic model

A cost-utility analysis was conducted to evaluate the cost-effectiveness of inavolisib in combination with palbociclib and fulvestrant versus palbociclib and fulvestrant alone in PIK3CA-mutated, HR+/HER2− locally advanced or metastatic breast cancer. Consistent with the INAVO120 trial and the European Medicines Agency registration, the regimen is evaluated as first-line treatment of advanced disease, in patients whose disease progressed during or within twelve months of completing adjuvant endocrine therapy. (The line-of-treatment terminology is set out in Section 1.) The trial's relative treatment-effect estimates are applied directly to the Dutch setting, an assumption discussed in the limitations (Section 5.3). The analysis was conducted from the Dutch societal perspective as the base case, in accordance with the reference case of the 2024 Dutch guideline for economic evaluations in healthcare [26] and the *Kostenhandleiding* 2024, the Dutch costing guideline [41]. The healthcare payer perspective, restricted to direct medical costs, was reported as a secondary analysis (Section 3.6). The outcome measure was the incremental cost-effectiveness ratio (ICER), expressed as cost per quality-adjusted life year (QALY) gained. Cost-effectiveness was evaluated against the Dutch reference willingness-to-pay threshold of €80,000 per QALY, applicable to conditions classified as having a high burden of disease [26].

A partitioned survival model was constructed in Microsoft Excel®, comprising three mutually exclusive health states: progression-free (stable disease), progressed disease, and death. At model entry all simulated patients (n = 1,000) were in the progression-free state. The proportion of patients in each state at each cycle was derived from parametric extrapolations of the PFS and OS curves from the INAVO120 trial, as described in Section 3.2. A 28-day cycle length was applied, consistent with the dosing schedule of the trial regimens (palbociclib 125 mg days 1–21 of a 28-day cycle; inavolisib 9 mg daily continuously; fulvestrant 500 mg every 28 days from cycle 2 onwards). Costs were discounted at 3.0% per annum and effects at 1.5% per annum [26,41].

A half-cycle correction was applied to costs and effects that accrue continuously throughout a cycle, because the precise timing of these events within a cycle is unknown. The corrected categories were the healthcare resource use and monitoring costs in both the stable disease and progressed disease states, the ongoing palliative and supportive care costs in the progressed disease state, the societal informal-care and patient-time costs in both health states, and the QALYs accumulated in each health state. For each of these, the model averaged the state occupancy at the start and end of the cycle. The half-cycle correction was not applied to costs incurred at a known, fixed point. Drug acquisition and drug administration costs were applied to the proportion of patients in the relevant health state at the start of the cycle, because medication for a full cycle is dispensed and administered at the beginning of that cycle. One-off costs at transition (second-line capecitabine acquisition and DPYD genotyping at the cycle of progression) and the one-off end-of-life cost at the moment of death were likewise applied without half-cycle correction, as these occur at a defined event rather

than continuously. Adverse-event management costs and disutilities, and the one-off productivity loss, were applied as a single lump-sum at the first model cycle, consistent with the approach of Zhu et al. (2026) and Huang et al. (2026) [22,23].

A lifetime time horizon of 20 years was used to ensure that virtually all simulated patients had died by the end of the simulation. Median overall survival in the INAVO120 inavolisib arm was 34.0 months (comparator 27.0 months) [15]; Dutch SONABRE registry data show that fewer than 5% of advanced breast cancer patients survive beyond 10 years after diagnosis [17], and long-term follow-up of metastatic breast cancer cohorts confirms that very few patients survive beyond 15 years [42]. A 20-year horizon therefore captures the full cost and outcome trajectory with a large margin.

## 3.2 Treatment effect

Treatment effect inputs were derived from the phase III INAVO120 trial (NCT04191499), a double-blind randomised controlled trial that randomised 325 patients with PIK3CA-mutated, HR+/HER2− advanced breast cancer in a 1:1 ratio to inavolisib + palbociclib + fulvestrant (n = 161) or placebo + palbociclib + fulvestrant (n = 164) [14,15]. Both the PFS and OS curves were taken from the OS update by Jhaveri et al. (2025), which reported a median follow-up of 34 months [15]. This longer follow-up reduced censoring in the tail of both curves and ensured internal consistency between PFS and OS within the same data cut-off.

Because individual patient data were not available, the published Kaplan–Meier curves were digitised using WebPlotDigitizer version 5 and reconstructed into pseudo-individual patient data using the algorithm of Guyot et al. (2012) [43]. This algorithm preserves the reported number of events and number of patients at risk at each published time point. All subsequent analyses were performed in R version 4.5.3 (R Foundation for Statistical Computing) using RStudio version 2026.01.1+403. The reconstruction and survival modelling relied principally on the IPDfromKM package, a published R implementation of the Guyot algorithm that converts digitised Kaplan–Meier coordinates and numbers-at-risk into individual-level time-to-event data. Parametric models were fitted using the survival package, while readxl, ggplot2, dplyr, gridExtra, and readbitmap were used for data handling and plotting.

Six candidate parametric distributions were fitted to the reconstructed data per endpoint per arm, following the recommendations of the NICE Decision Support Unit Technical Support Document 14 [44]: exponential, Weibull, log-normal, log-logistic, Gompertz, and generalised gamma. The preferred distribution was selected on the basis of (i) the Akaike Information Criterion (AIC), (ii) visual inspection of the fitted curves against the observed Kaplan–Meier data, and (iii) clinical plausibility of the long-term extrapolation. For both endpoints, a single distribution was selected and applied to both treatment arms to ensure internal model consistency [44]. Differences in AIC of less than two units were treated as providing no meaningful evidence in favour of one model over another, while differences exceeding ten units were treated as essentially decisive [45]. Full AIC and BIC values for all candidate distributions are reported in Appendix B; the visual fits are shown in the main text (Figures 2 to 5).

**PFS distribution selection.** The generalised gamma distribution was selected for PFS extrapolation, weighing the three criteria together rather than AIC alone. Statistically, it achieved the best pooled AIC across both arms (1,810.70), ahead of the next-best candidate (log-logistic, 1,817.16). The placebo arm was the most discriminating, because the candidate distributions diverged most there (an AIC range of 34 units). In that arm the generalised gamma ranked first (945.33) and was the only distribution that tracked the observed Kaplan-Meier curve through the tail on visual inspection, while the exponential, Weibull, and Gompertz distributions fell away too steeply (Figure 3). In the inavolisib arm the log-logistic had a marginally lower AIC (860.93 versus 865.37), but this difference of about four units provides only weak evidence in its favour and is well below the threshold for a decisive difference. A single distribution must be applied to both arms to avoid structural bias in the treatment comparison. Clinically, the extrapolated progression-free survival at 20 years (approximately 1 to 4%) was consistent with the expectation that virtually all patients with advanced HR+/HER2− breast cancer eventually progress, so distributions implying a larger long-term progression-free fraction were judged implausible. Log-logistic was pre-specified as the alternative for the scenario analysis 10 (S10). The labels S1 to S13 used throughout this thesis refer to the pre-specified scenario analyses listed in Table 4 (Section 3.6).

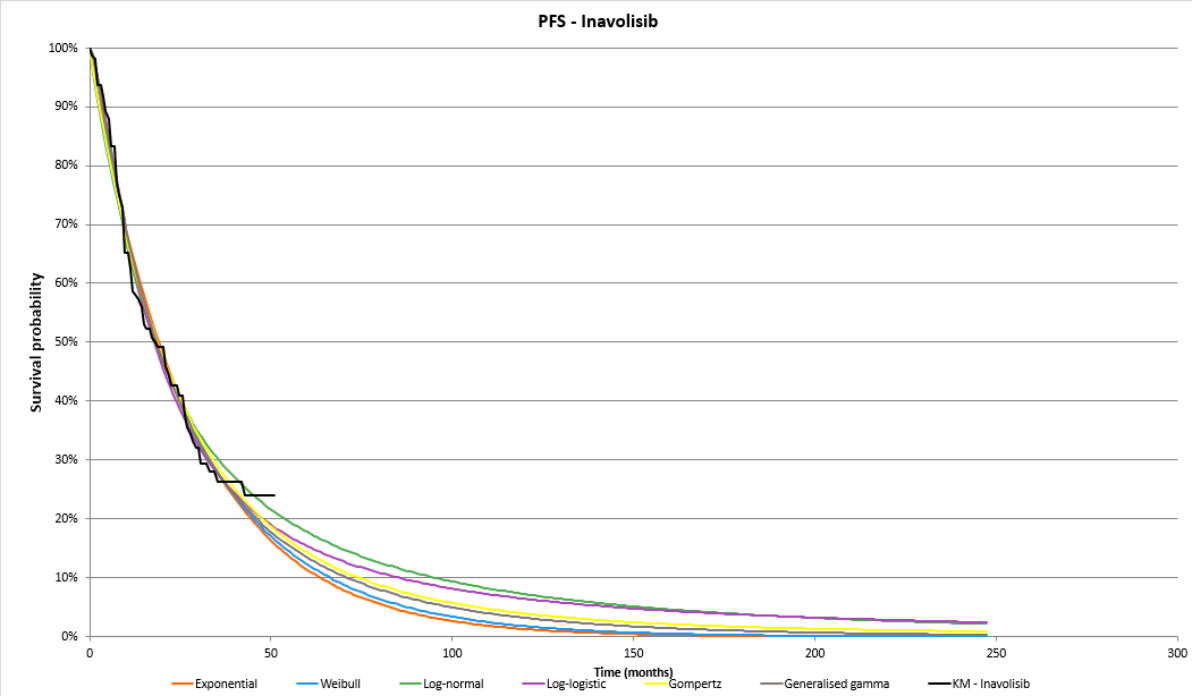


***Figure 2. Progression-free survival, inavolisib arm: observed Kaplan-Meier estimate versus six fitted parametric distributions.***

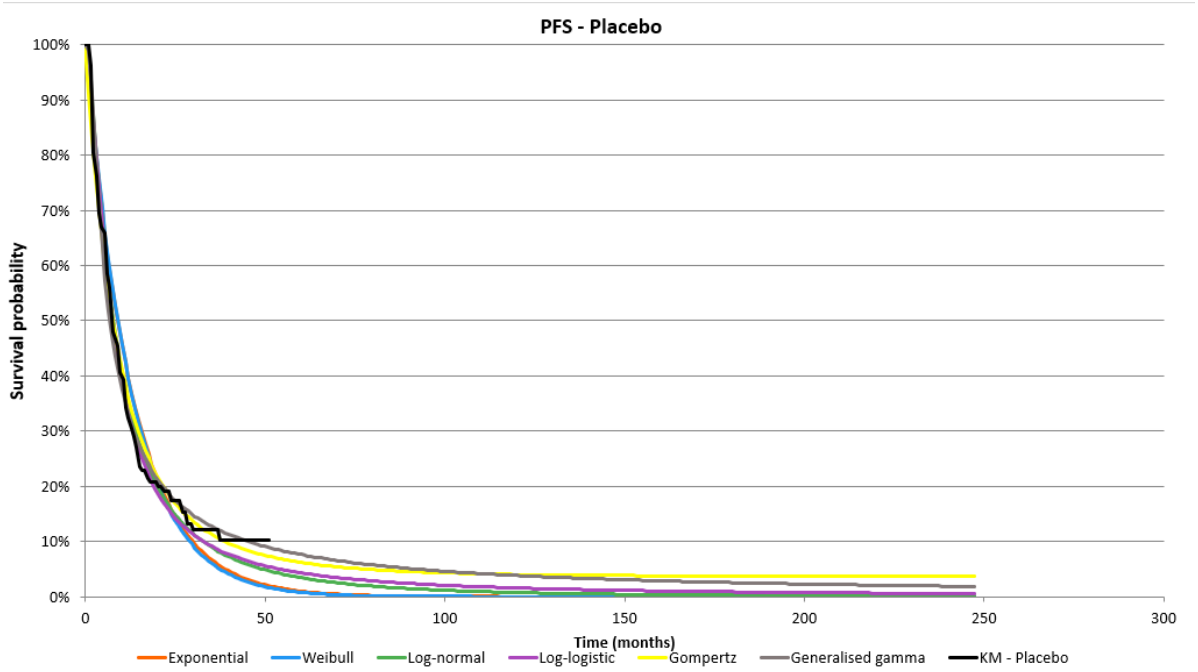


***Figure 3. Progression-free survival, placebo arm: observed Kaplan-Meier estimate versus six fitted parametric distributions.***

**OS distribution selection.** The log-logistic distribution was selected for OS extrapolation, again weighing statistical fit, visual inspection, and clinical plausibility together. It ranked first by AIC in both treatment arms individually (678.85 inavolisib; 753.51 placebo) and achieved the best pooled AIC overall (1,432.36), ahead of Weibull (1,434.27). On visual inspection it tracked the Kaplan-Meier estimate closely throughout the observed period in both arms (Figures 4 and 5). The selected distribution produced a clinically plausible tail of approximately 6 to 7% at 20 years, consistent with published long-term survival in advanced HR+/HER2− breast cancer [6]. Two distributions were rejected primarily on clinical plausibility, despite acceptable statistical fit. The Gompertz distribution produced grossly implausible extrapolations in both arms. In the placebo arm it flattened into a permanent plateau at approximately 80% survival, implying that most patients would never die of the disease even at a metastatic stage. In the inavolisib arm it collapsed to zero survival by approximately 33 months. Both behaviours are incompatible with the natural history of metastatic breast cancer [6]. The exponential distribution visibly overestimated long-term survival in the inavolisib arm, because its constant-hazard assumption cannot capture the declining hazard seen in the data. Log-normal was pre-specified as an optimistic-tail scenario (S11) and Gompertz as a pessimistic-tail scenario (S12) for the sensitivity analysis

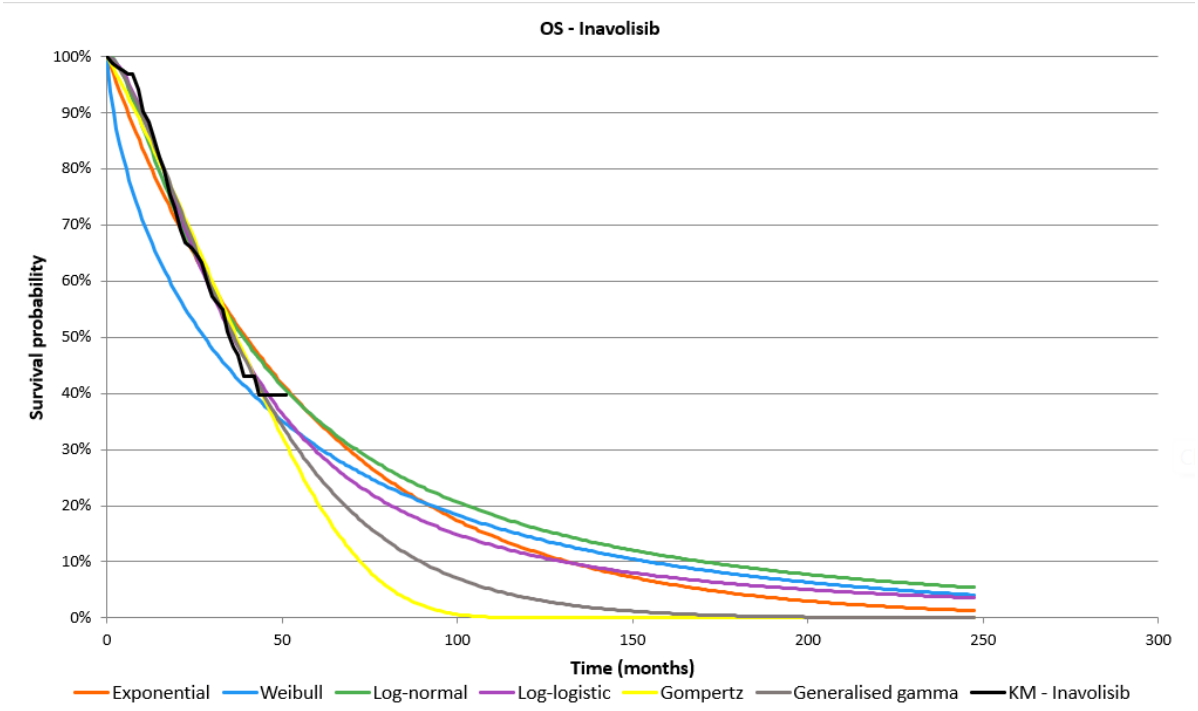


***Figure 4. Overall survival, inavolisib arm: observed Kaplan-Meier estimate versus six fitted parametric distributions.***

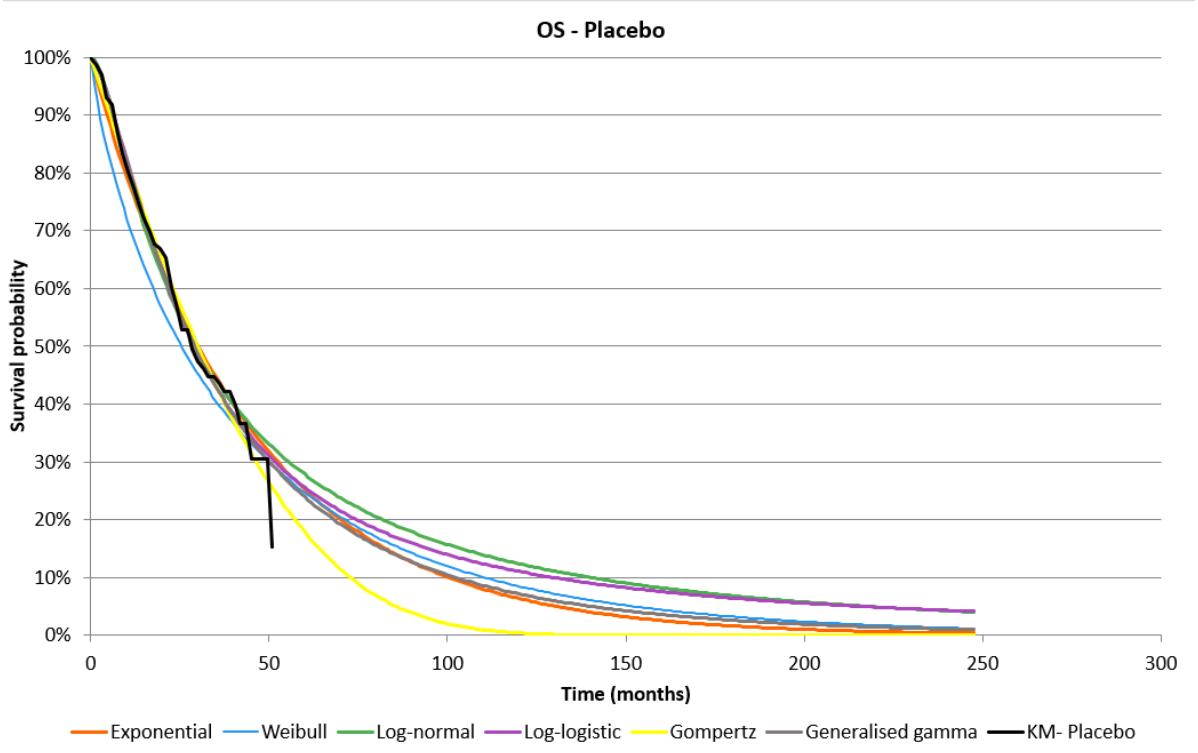


***Figure 5. Overall survival, placebo arm: observed Kaplan-Meier estimate versus six fitted parametric distributions.***

At each model cycle, the proportion of patients in stable disease was set equal to the estimated PFS probability, and the proportion in the death state to 1 minus the estimated OS probability. The proportion in progressed disease was then obtained as the difference between the two, that is, the estimated OS probability minus the estimated PFS probability. This is the standard partitioned survival approach, in which state membership is read from the two survival curves rather than from explicit transitions between states [26,37]. Because deaths are taken directly from the OS curve, they occur from both the stable and the progressed disease states; the model does not require patients to pass through progressed disease before death. The number of newly progressed patients per cycle was calculated as the decrease in the stable-disease count between consecutive cycles, and the number of newly deceased patients as the increase in the death count. The one-off cost of second-line treatment initiation (Section 3.4.3) was applied to the newly progressed patients, and the one-off end-of-life cost (Section 3.4.4) to the newly deceased patients. Progressed-disease occupancy was obtained as the difference between the overall survival and progression-free survival curves (equivalently, as the cohort minus the stable-disease and death counts). Because the overall survival curve remained at or above the progression-free survival curve in every cycle, this occupancy was non-negative throughout, and a maximum function in the first cycle ensured it could not fall below zero. Treatment-effect waning beyond the observed 34-month follow-up was not applied in the base case; both survival curves were extrapolated under their selected parametric distributions.

## 3.3 Health-related quality of life

Health-state utility values were not collected via EQ-5D in the INAVO120 trial. Utility inputs were therefore taken from Lloyd et al. (2006), a standard-gamble preference study in which 100 members of the UK general public valued vignette-based health states for metastatic breast cancer [46]. This source was selected for three reasons: (i) it is the only published study that provides an internally consistent set of stable-disease utility, progression decrement, and adverse-event disutilities specifically for metastatic breast cancer within a single study design; (ii) it has been used as the base-case utility source in the two published cost-effectiveness analyses of inavolisib (Zhu et al. (2026) and Huang et al. 2026) [22,23]; and (iii) it has been accepted in multiple NICE technology appraisals for CDK4/6-inhibitor regimens in HR+/HER2− advanced breast cancer [46].

The following base-case utility values were applied: stable disease (progression-free) 0.72, with a treatment-response gain of +0.07 yielding an effective on-treatment PFS utility of 0.72 for the base case; progressed disease 0.443 (stable disease minus a progression-related utility decrement of 0.27); death 0.00 [46]. The same health-state utilities were applied to both treatment arms, consistent with the *Kostenhandleiding* 2024 recommendation to use health-state-specific rather than treatment-specific utilities in the absence of trial-derived utility data [26,41].

QALYs were calculated by multiplying the half-cycle-corrected proportion of patients in each health state by the cycle length in years (28/365.25) and by the assigned utility weight, summed across all health states and all model cycles, and discounted at 1.5% per annum [41]. The death state contributed zero QALYs.

**Adverse event disutilities.** Quality-of-life decrements for the grade 3/4 adverse events included in the model (selected per the criteria in Section 3.4 and Appendix D) were sourced primarily from Lloyd et al. (2006) [46]. Lloyd does not cover hyperglycaemia and rash, which are characteristic side effects of PI3K inhibitors. The decrements for these two events were therefore taken from Wu et al. (2023) [47]. The total QALY loss per adverse event was calculated as the product of the per-arm incidence rate (from the INAVO120 safety population [14]), the disutility weight, and the mean event duration converted to years. The corresponding management cost per episode was taken from the *Kostenhandleiding 2024* [41] and, where guideline unit costs were unavailable, from Gambardella et al. [48]. These per-event QALY losses and costs were summed across all included AEs to obtain a total QALY loss and management cost per arm, applied as a lumpsum at the first model cycle. Detailed values are reported in Appendix D and Appendix E.

Scenario analyses using alternative utility values (Mistry et al. (2018) from MONALEESA-2 and Dutch SONABRE registry real-world EQ-5D) were pre-specified to test the influence of the utility source (Section 3.6).

## 3.4 Resource use and costs

Costs were estimated from the Dutch societal perspective in 2025 prices, in accordance with the 2024 Dutch guideline and the *Kostenhandleiding* 2024 [26,41]. The societal perspective comprises three cost categories: costs within the healthcare sector (direct medical costs and future unrelated medical costs in life-years gained), costs of patients and family (informal care, patient travel, and patient time), and costs in other sectors (productivity losses). Direct medical cost components consisted of drug-related costs (drug acquisition, administration, premedication, and concomitant medications), healthcare resource use (outpatient consultations, monitoring tests, and pre-treatment diagnostics), and end-of-life costs (a one-off cost applied at the model transition to the death state). Cost components were enumerated separately for the stable disease and progressed disease health states. Drug acquisition prices were obtained from *Farmacotherapeutisch Kompas* and *medicijnkosten.nl*, both denominated in 2025 prices [16,49]. Diagnostic laboratory tariffs were taken from the NZa primary-care diagnostic tariff list as published by Starlet-DC for 2025 [50]. All other reference prices were drawn from the *Kostenhandleiding* 2024, denominated in 2022 prices, and indexed to 2025 prices using the cumulative CBS Consumer Price Index factor 1.1076 (2022→2025) [51]. Table 1 summarises the indexation. Where multiple reimbursed formulations were available for a drug, the cheapest reimbursed product was selected as the cost input.

### 3.4.1 Perspective and indexation

The Dutch societal perspective was applied in the base case, as required by the reference case of the 2024 Dutch guideline [26]. In addition to direct medical costs reimbursed under the basic health insurance package, the base case included informal care, productivity losses, patient travel, and patient time costs, valued according to the *Kostenhandleiding* 2024 [41]. Capturing all costs and consequences regardless of who bears them does not affect the access-based price derivation, because the pricing-model application depends only on the incremental cost and QALY estimates.

Three societal cost categories beyond direct medical costs were valued according to the *Kostenhandleiding* 2024 [41]. Productivity losses from paid work were estimated using the friction-cost method, which counts only the production lost during the friction period needed to replace an absent worker rather than all time until recovery or death; a friction period of approximately 85 working days was applied, with the average gross labour cost per hour indexed to 2025 prices and weighted by the proportion of patients of working age. Because the model assumes the same age distribution and working-age proportion in both arms, the productivity loss enters as an equal lump-sum and does not differ between treatments in the base case. Patient and family out-of-pocket costs consisted of patient travel to and from outpatient visits (valued per kilometre plus parking and public-transport allowances) and patient time spent receiving care (valued at the recommended reference rate per hour), both applied per outpatient visit through the model trace. Informal care provided by family members was valued using the proxy-good method at the *Kostenhandleiding* reference rate per hour, applied to an assumed number of informal-care hours per week that differs by health state (more hours in progressed disease than in stable disease); the underlying hours assumption and its uncertainty are described in Section 3.6 and Section 5.3. Finally, future unrelated medical costs in life-years gained were included in the societal base case using the PAID 3.0 methodology [52]. All four societal categories are reported as separate line items in the disaggregated results (Table 5), and the healthcare payer perspective (Section 3.6, scenario S13) removes them to isolate their effect on the ICER.

***Table 1. Consumer Price Index factors applied to 2022 reference prices***

| Period | Annual CPI change (%) | Index factor | Source |
|---|---|---|---|
| 2022 → 2023 | 3.8 | 1.038 | CBS [51] |
| 2023 → 2024 | 3.3 | 1.033 | CBS [51] |
| 2024 → 2025 | 3.3 | 1.033 | CBS [51] |
| **Cumulative 2022 → 2025** | – | **1.1076** | Calculated |

*CPI = Consumer Price Index; CBS = Statistics Netherlands.*

### 3.4.2 Stable disease costs

In the stable disease state, both arms received palbociclib 125 mg orally on days 1–21 of each 28-day cycle and fulvestrant 500 mg by intramuscular injection on day 1 (with an additional

loading dose on day 15 of cycle 1). The inavolisib arm received inavolisib 9 mg orally on days 1–28; the comparator arm received placebo. Premenopausal patients in both arms received concomitant goserelin 3.6 mg by subcutaneous injection every 28 days, weighted by the proportion of premenopausal patients at randomisation (40.4% in the inavolisib arm, 36.0% in the comparator arm) [14]. No scheduled premedication was applied in the stable disease state because none of the regimen drugs requires routine pharmacological premedication per their Summaries of Product Characteristics [49].

Inavolisib and palbociclib are oral self-administered tablets and incurred no administration cost. Fulvestrant was administered at home by a home-care nurse rather than at the hospital, in line with current Dutch practice [53]. The *Kostenhandleiding* 2024 does not publish a dedicated reference price for home-based intramuscular oncological drug administration; the reference price for hospital subcutaneous oncological drug administration was therefore used as a proxy (€75.28 in 2022 prices, indexed to €83.38 in 2025) [41,54]. A scenario applying half of this proxy is included in the sensitivity analysis to test the assumption (Section 3.6).

Community-pharmacy dispensing fees (*terhandstelling*) were added for the agents dispensed through a community pharmacy under the extramural reimbursement system, namely palbociclib and goserelin. A first-dispensing fee (*eerste uitgifte*, €11.87 in 2020 prices) was applied in the first cycle and a repeat-dispensing fee (*standaardterhandstelling*, €6.45 in 2020 prices) in subsequent cycles, indexed to 2025 using the cumulative CBS Consumer Price Index factor, with the goserelin fee weighted by the arm-specific premenopausal proportion. Inavolisib is supplied as an intramural (hospital) add-on and was therefore not assigned a community-pharmacy dispensing fee. Fulvestrant is administered by a home-care nurse rather than dispensed to the patient, so its handling cost is captured within the administration cost rather than as a separate dispensing fee, avoiding double-counting. The same repeat-dispensing fee was applied to second-line capecitabine in the progressed-disease state, once per capecitabine cycle over the expected number of cycles and weighted by the proportion of patients receiving second-line chemotherapy. Dispensing tariffs were obtained from the *Stichting Farmaceutische Kengetallen* [55].

Healthcare resource use in the stable disease state consisted of outpatient oncology consultations, complete blood count (CBC) monitoring, and HbA1c monitoring. The palbociclib SmPC mandates a CBC at the start of each cycle, with an additional CBC on day 15 of cycles 1 and 2. HbA1c was monitored every three months in the inavolisib arm only, as mandated by the inavolisib Prescribing Information [56]. Fasting plasma glucose monitoring was also mandated by the inavolisib label but specified as either home self-monitoring or in-clinic; the home self-monitoring option (using patient-purchased glucose strips) was assumed in the base case, generating no payer cost. Two outpatient consultations were costed in cycle 1 (cycle-start review on day 1 and a combined day-15 toxicity review and CBC) and one consultation per cycle from cycle 2 onwards.

Per-cycle drug costs were calculated as follows. Inavolisib was costed at €489.10 per 9 mg tablet × 28 tablets per cycle = €13,694.80. Palbociclib was costed at €58.18 per 125 mg tablet

× 21 tablets per cycle = €1,221.78. Fulvestrant was costed at €126.44 per pre-filled syringe (Mylan, cheapest reimbursed formulation); the loading-dose schedule required 4 syringes (€505.76) in cycle 1 and 2 syringes (€252.88) in subsequent cycles. Goserelin 3.6 mg was costed at €115.39 per implant × the arm-specific premenopausal proportion (40.4% inavolisib, 36.0% comparator). The outpatient consultation reference price was €120.00 (2022 prices, Kostenhandleiding 2024 §4.3) indexed to €132.91 (2025); the CBC consisted of four NZa primary-care diagnostic tariffs summing to €9.25 per panel [50]. HbA1c was costed at €8.05 per test (NZa code 74065) applied once per three cycles, giving €2.68 per cycle [50]. Step-by-step derivations for administration costs, CBC component summation, and HbA1c per-cycle amortisation are reported in Appendix A. Table 2 reports the resulting per-cycle cost components.

***Table 2. Stable disease per-cycle cost components (2025 prices, €/cycle)***

| Component | Inavolisib arm | Comparator | Δ | Source |
|---|---|---|---|---|
| Inavolisib (9 mg × 28 days) | 13,694.80 | 0.00 | **+13,694.80** | FK code L01EM06 [49] |
| Palbociclib (125 mg × 21 days) | 1,221.78 | 1,221.78 | 0.00 | FK code L01EF01 [49] |
| Fulvestrant (cycle 1: 4 syringes; cycles 2+: 2 syringes) | 505.76 (C1) / 252.88 (C2+) | 505.76 (C1) / 252.88 (C2+) | 0.00 | FK code L02BA03; medicijnkosten.nl [16,49] |
| Goserelin 3.6 mg (weighted by premenopausal %) | 46.62 | 41.54 | **+5.08** | FK code L02AE03 [49]; Turner et al. [14] |
| Fulvestrant administration (cycle 1: 2 occasions; cycles 2+: 1) | 166.77 (C1) / 83.38 (C2+) | 166.77 (C1) / 83.38 (C2+) | 0.00 | *Kostenhandleiding* §4.2 [41]; Blommestein et al. [54] |
| Outpatient consultation (C1: 2; C2+: 1) | 265.82 (C1) / 132.91 (C2+) | 265.82 (C1) / 132.91 (C2+) | 0.00 | *Kostenhandleiding* §4.3 [41] |
| CBC monitoring (C1–C2: 2/cycle; C3+: 1/cycle) | 18.50 (C1–C2) / 9.25 (C3+) | 18.50 (C1–C2) / 9.25 (C3+) | 0.00 | NZa codes; Starlet-DC [50] |
| HbA1c monitoring (every 3 cycles; inavolisib only) | 2.68 | 0.00 | **+2.68** | NZa code 74065; Starlet-DC [50]; Genentech [56] |
| **Cycle 1 total** | **15,922.73** | **2,220.17** | **+13,702.56** | – |
| **Cycles 3+ total** | **15,444.30** | **1,741.74** | **+13,702.56** | – |

*FK = Farmacotherapeutisch Kompas; CBC = complete blood count; SmPC = Summary of Product Characteristics; C1, C2, C3+ = cycle 1, cycle 2, cycles 3 onwards; Δ = arm difference. Detailed component-level derivations are reported in Appendix A.*

### 3.4.3 Progressed disease costs

Both arms were modelled as transitioning to capecitabine monotherapy as the representative second-line regimen, dosed at 1,250 mg/m² twice daily on days 1–14 of a 21-day cycle, in line with the Dutch breast cancer guideline NABON/NIV 2020 and observational evidence from PRAEGNANT [57,58]. Arm-specific second-line chemotherapy administration rates were applied as a one-off weight at the cycle of transition: 55% in the inavolisib arm and 72% in the comparator arm, taken from the INAVO120 OS update [15]. Adverse event management costs for the second-line regimen were not modelled because (i) capecitabine was applied at identical dose and schedule in both arms, so per-patient AE incidence was equal across arms, and (ii) the only arm-level imbalance (the 55%/72% administration difference) was already captured in the drug acquisition cost.

Pre-treatment DPYD genotyping for dihydropyrimidine dehydrogenase deficiency was applied as a one-off cost (€84) at the cycle of transition, in line with EMA recommendations and standard Dutch oncology practice [59–61]. Capecitabine was costed at €1.55 per 500 mg tablet (Capecitabine Accord, cheapest formulation) × 112 tablets per 21-day cycle (assuming mean BSA 1.72 m², dose 2,150 mg/day rounded to 2,000 mg, 14 treatment days) = €173.60 per capecitabine cycle. The base case assumed six cycles per treated patient, the lower bound of the NABON/NIV 2020 guideline range ("niet meer dan 6-9 kuren") and consistent with the real-world median progression-free survival of approximately 3.5 months on capecitabine after CDK4/6-inhibitor failure (equivalent to roughly five 21-day cycles) reported in the PRAEGNANT registry [57,58]. This gave a total one-off acquisition cost of €1,041.60, weighted by the arm-specific administration rate (55% inavolisib, 72% comparator). Two scenario analyses bracket this assumption: five cycles (the real-world median, S5) and nine cycles (the guideline maximum, S6). Per-cycle monitoring (CBC, liver and renal function tests, and an outpatient consultation) was denominated per 21-day capecitabine cycle (€153.55) and converted to per-28-day-model-cycle using the ratio 28/21 = €204.73. Ongoing palliative care was modelled as a quarterly outpatient consultation (€132.91 per 3 cycles = €44.30 per cycle) applied to all patients in the progressed disease state [41]. Bone-targeted therapy with zoledronic acid 4 mg every 12 weeks was modelled for the proportion of patients with bone metastases at INAVO120 baseline (3.1% inavolisib, 3.7% comparator) [14,62]. No premedication or concomitant medication costs were applied, as capecitabine is classified as low-emetic-risk by MASCC/ESMO 2023 [63]. Step-by-step derivations including BSA assumption and cycle-length conversion are reported in Appendix A. Table 3 reports the components.

***Table 3. Progressed disease cost components (2025 prices, €/cycle unless stated)***

| Component | Inavolisib arm | Comparator | Δ | Source |
|---|---|---|---|---|
| Capecitabine acquisition (one-off at transition) | 572.88 | 749.95 | **−177.07** | FK code L01BC06 [49]; medicijnkosten.nl [16]; Jhaveri et al. [15] |
| DPYD genotyping (one-off at transition) | 84.00 | 84.00 | 0.00 | Henricks et al. [61]; EMA [59] |
| HCRU (CBC, LFT, renal, outpatient) | 204.73 | 204.73 | 0.00 | *Kostenhandleiding* [41]; NZa codes; Starlet-DC [50] |
| Palliative care consultation (every 3 cycles) | 44.30 | 44.30 | 0.00 | *Kostenhandleiding* §4.3 [41] |
| Bone-targeted therapy (weighted by bone-mets %) | 2.94 | 3.51 | **−0.57** | Coleman et al. [62]; medicijnkosten.nl [16]; Turner et al. [14] |
| **Per-cycle ongoing total** | **251.97** | **252.54** | **−0.57** | – |

*CBC = complete blood count; LFT = liver function tests; HCRU = healthcare resource use; FK = Farmacotherapeutisch Kompas; Δ = arm difference. The two one-off costs (capecitabine acquisition and DPYD genotyping) are applied once at the cycle of transition into progressed disease and are not part of the ongoing per-cycle total. Ongoing HCRU is denominated per 28-day model cycle (€153.55 per 21-day capecitabine cycle × 28/21).*

### 3.4.4 End-of-life costs

End-of-life costs were applied as a one-off cost at the model transition into the death state, equally in both arms. The base-case value was taken from Schneider et al. (2020), the only Dutch study reporting end-of-life costs specifically in advanced breast cancer (n = 558, SONABRE Registry, 2010–2017 cohort) [20]. The reported mean cost over the last 12 months before death was €21,641 in 2017 prices. This was indexed to 2025 using the cumulative CBS Consumer Price Index factor of 1.3239 (2017 to 2025), giving €28,651 per patient [51]. The approach to incorporating end-of-life costs in a Dutch cost-effectiveness analysis followed the template of De Kok et al. (2009) [64]. As a scenario analysis (Section 3.6), the value from Van Dijk et al. (2025), the most recent Dutch end-of-life cost study and the only one including long-term care under the Wlz, was used in place of the base-case estimate [65].

Future unrelated medical costs in the life-years gained were included in the societal base case using the PAID 3.0 methodology [52], and were excluded in the healthcare payer perspective.

## 3.5 Sensitivity and scenario analyses

Three layers of sensitivity analysis were pre-specified: a probabilistic sensitivity analysis (PSA), one-way deterministic sensitivity analyses (DSA) for individual parameters, and structural and perspective scenarios. In the PSA, each uncertain parameter was assigned a probability distribution following standard practice [18,44]: a beta distribution for proportions, probabilities, and utilities (bounded between 0 and 1); a gamma distribution for costs and for

the societal time inputs (informal-care hours and patient-time hours) (non-negative and right-skewed); and a log-normal distribution for the hazard ratios. Resource-use frequencies and adverse-event durations were held fixed at their point estimates rather than sampled, because they are determined by the treatment protocol rather than estimated with statistical uncertainty, and their contribution to total cost is small relative to drug acquisition. Probabilistic sampling was instead applied to the unit costs and utilities, which carry the uncertainty most relevant to the result. The distribution parameters (alpha and beta) were derived by the method of moments from each parameter's mean and standard error. The source of the standard error differed by parameter and is documented in full in Appendix G. Where the source reported a count, the standard error was calculated from the binomial formula, $SE = \sqrt{(p(1-p)/n)}$; where the source reported a 95% confidence interval, the standard error was derived from the interval width (on the log scale for the hazard ratios); the end-of-life cost was the only parameter for which the source reported a standard deviation directly. For some inputs, no measure of dispersion was reported. This was the case for the unit costs, utilities, and disutilities. For these, a standard error was assumed as a fixed proportion of the mean: 10% for utilities and disutilities, 15 to 25% for direct medical costs, and 30% for the societal inputs. For the direct medical costs, the lower end was applied to well-established reference-price and tariff-based unit costs and the upper end to costs that were derived or based on assumptions. This follows the convention in standard health-economic guidance, under which costs are typically assigned a coefficient of variation in this range when no measure of dispersion is reported [66–68]. Adverse event disutilities were sampled on their absolute value using a beta distribution and subtracted from the relevant health-state utility. The survival-curve parameters were sampled jointly from the variance–covariance matrix of the flexsurv (an R package for fitting parametric survival models, which returns each fitted distribution together with the variance–covariance matrix of its parameters) fits using Cholesky decomposition rather than the method of moments. The PSA was run with 1,000 Monte Carlo iterations, and the cost-effectiveness plane and cost-effectiveness acceptability curve were plotted from the simulation output. The DSA varied each parameter individually within its 95% confidence interval (or, where a confidence interval was unavailable, by ±25% around the point estimate. This deterministic ±25% bound is independent of the standard error assumed for the same parameter in the probabilistic analysis; it was applied uniformly for comparability across parameters, except for the societal informal-care hours, which were varied over the wider plausible bounds reported in Section 5.3 (±100% in the progression-free state and ±50% in the progressed disease state) rather than ±25%) and reported a tornado diagram of the resulting ICER changes. Table 4 summarises the pre-specified scenario analyses; those whose ICER differs meaningfully from the base case are reported in the Results section, and the full set of results for all scenarios is reported in Appendix I.

***Table 4. Pre-specified scenario analyses***

| Scenario | Parameter change | Rationale (one phrase) |
|---|---|---|
| S1. Pricing model - 25% discount | Inavolisib acquisition × 0.75 | Lower bound MEA simulation |
| S2. Pricing model - 40% discount | Inavolisib acquisition × 0.60 | Central MEA simulation |
| S3. Pricing model - 60% discount | Inavolisib acquisition × 0.40 | Upper bound MEA simulation |
| S4. End-of-life - broader scope | Replace Schneider (2020) €28,651 with Van Dijk (2025) €63,914 | Test EoL data source [20,65] |
| S5. Second-line capecitabine - 5 cycles | Reduce capecitabine course from 6 to 5 cycles (real-world median PFS ~3.5 months post-CDK4/6i) | Test second-line duration, lower bound [58] |
| S6. Second-line capecitabine - 9 cycles | Increase capecitabine course from 6 to 9 cycles (NABON/NIV guideline maximum) | Test second-line duration, upper bound [57] |
| S7. Palbociclib formulation | 125 mg capsule (€76.76/day) vs base-case tablet (€58.18/day) | Test cheapest-formulation choice |
| S8. Bone-metastasis proportion | Real-world ~45% (SONABRE) instead of INAVO120 trial 3.1%/3.7% | Test trial-to-real-world generalisability |
| S9. Fulvestrant administration cost | SC reference price × 0.5 (closer to true IM injection time) | Test conservative proxy |
| S10. PFS alternative distribution | Log-logistic for PFS instead of generalised gamma | Test structural uncertainty [44] |
| S11. OS optimistic tail | Log-normal for OS instead of log-logistic (~9% at 180 mo) | Test OS extrapolation upper bound |
| S12. OS pessimistic tail | Gompertz for OS instead of log-logistic (forced to 0% by ~100 mo) | Test OS extrapolation lower bound |
| S13. Healthcare payer perspective | Restrict to direct medical costs only; exclude informal care, productivity losses, patient time, and future unrelated medical costs | Test healthcare vs societal perspective [26,41] |

*AE = adverse event; MEA = managed entry agreement; PD = progressed disease; PSA = probabilistic sensitivity analysis; PAID = Practical Application to Include future Disease costs; SC = subcutaneous; IM = intramuscular. S13 (healthcare payer perspective) is presented in italics to indicate that it is a structural perspective change, not a parameter variation.*

## 3.6 Access-based pricing model

To complement the cost-utility analysis with a supply-side pricing estimate, the access-based price (ABP) of inavolisib was derived using the ASCERTAIN pricing model [34,36]. The model estimates a defensible per-patient price by integrating four components: the capitalised research and development cost allocated across the eligible patient population, a value-based innovation reward, operational costs (cost of goods sold plus sales, general, and administrative expenses), and an operational profit margin. The model was implemented in R using the published ASCERTAIN function set [36].

Inputs were specified as follows. The patient population was derived from the annual incidence of PIK3CA-mutated HR+/HER2− advanced breast cancer (0.71 per 100,000 population, derived from the epidemiological figures cited in the EMA Risk Management Plan), applied over the model 10-year horizon at the European Economic Area level. As a cross-check on this incidence, the French *Haute Autorité de Santé* assessment of inavolisib reported approximately 1,450 incident eligible patients per year in France; relative to a French population of about 68.4 million this implies an incidence of roughly 2.1 per 100,000, higher

than the 0.71 per 100,000 derived from the EMA figures [69]. A larger eligible population spreads the fixed capitalised research-and-development cost across more patients, which lowers the access-based price. The EMA-based figure is therefore the more conservative (higher-price) assumption, and it was retained for the base case. The higher HAS-derived incidence is examined in the access-based-price scenario analysis (Section 4.5 and Appendix H). Drug-specific inputs reflected inavolisib as an orally administered small-molecule kinase inhibitor: a daily dose of 9 mg given as a single 9 mg film-coated tablet, classified as a standard specialised chemical compound, with the median duration of treatment of 9.2 months reported in the EMA European Public Assessment Report used as the treatment duration. Research and development costs, the cost of capital, treatment rate, market competition, and relative utilisation were set to the model default values, in line with the model developers' guidance for cases without firm-specific data. The value-based innovation reward combined the added-therapeutic-benefit premium, for which the minor tier (a 10% premium) was selected. This tier was anchored to the assessment of the French Haute Autorité de Santé. It graded inavolisib in this exact indication as offering a minor improvement in medical benefit (ASMR IV, “amélioration mineure”) relative to the palbociclib and fulvestrant doublet, the same comparator used here [69]. This external, formally graded benchmark was preferred to the PASKWIL framework, which establishes whether a palliative treatment meets a benefit threshold but does not discriminate between minor, moderate, and major improvement. No quality-of-evidence penalty was applied. INAVO120 is a phase III, double-blind, randomised, placebo-controlled trial with mature and statistically significant overall-survival data (hazard ratio 0.67). It was accepted as the pivotal registration trial by the European Medicines Agency and the French authorities, so a substandard-evidence discount was not considered warranted. The residual uncertainty regarding the comparator and the relative effect size is already reflected in the minor benefit tier. The unmet-medical-need and societal-value premiums were applied at their preset values (35% and 30% respectively), and the return-on-public-investment adjustment at its preset (15%). The choice of benefit tier was varied in the scenario analysis (Section 4.5 and Appendix H) [12,69]. The operational parameters used the model preset values for sales, general, and administrative expenses (82.75% of cost of goods sold) and the default operational profit margin (29.4%).

The model returns an access-based price per treatment cycle, which was aligned to the 28-day cycle length of the cost-utility model before substitution. The ABP was then used in two ways: first, it was compared directly with the current list price and with the threshold price implied by the cost-utility analysis (the price at which the ICER would equal €80,000 per QALY); second, it was substituted for the inavolisib acquisition cost in the cost-utility model to estimate the ICER at the access-based price, addressing the question of whether inavolisib would be cost-effective at a cost-based price. The sensitivity of the ABP to the value-based parameters (added therapeutic benefit, quality of evidence, societal value, profit margin, and market competition) was explored in a set of scenario analyses, as these are the most discretionary inputs. The detailed parameter specification is reported in Appendix F.

## 3.7 Budget impact analysis

A budget impact analysis was conducted from the Dutch healthcare payer perspective over a five-year horizon, with annual increments and no discounting. This follows the ISPOR Good Practice II recommendations and the 2024 Dutch guideline, and is distinct from the lifetime societal cost-utility analysis [6,26,30]. The healthcare payer perspective is the standard scope for a budget impact analysis in the Netherlands [70]. Alongside the incremental cost-effectiveness ratio, the budget impact is a distinct and decision-relevant consideration in Dutch reimbursement, since affordability at the population level can influence reimbursement and placement in the sluis even when an intervention is judged cost-effective [71]. The budget impact was calculated as the difference between a world in which a growing share of eligible patients receive inavolisib combination therapy and a world in which all eligible patients receive the comparator. Consistent with the budget impact scope, only the incremental drug acquisition, administration, and monitoring costs over the treatment course were included; progressed-disease and end-of-life costs are broadly common to both arms over this short horizon and are captured in the lifetime cost-utility analysis rather than the budget impact analysis [30].

The eligible population was estimated at approximately 293 incident patients per year and was held constant across the five-year budget impact horizon. This reflects the assumption of a stable annual incidence, which is appropriate over such a short horizon. The underlying incidence of HR+/HER2− advanced breast cancer and of PIK3CA mutations is not expected to change meaningfully over five years. Holding the eligible population fixed also isolates the budget impact of changing market uptake from confounding demographic trends, in line with standard budget impact analysis practice. No direct Dutch count of the PIK3CA-mutated, endocrine-resistant, HR+/HER2− advanced breast cancer population is published. This figure was therefore derived from registry data and the European Medicines Agency assessment of inavolisib, rather than from an official Zorginstituut Nederland estimate. It is therefore an approximation, as is common for the population input of a budget impact analysis. The derivation applied a series of restrictions to the annual Dutch advanced or metastatic breast cancer flow of approximately 2,750 patients [6]: multiplied by the HR+/HER2− share (65%) [72], the endocrine-resistant share (45%) [15], and the PIK3CA-mutated share (36.4%) [72], giving $2{,}750 \times 0.65 \times 0.45 \times 0.364 \approx 293$ patients per year. To reflect the uncertainty in these literature-based proportions, a sensitivity range of 205 to 508 eligible patients per year was carried into the scenario analysis.

Market uptake of inavolisib was modelled as a gradual S-shaped increase from 15% in year 1 to 35%, 55%, 70%, and 80% in years 2 to 5, reflecting the typical diffusion pattern for a new oncology agent and a plateau constrained by the companion-diagnostic requirement and the diabetes exclusion of INAVO120 [30,73,74]. Per-patient treatment costs (drug acquisition, administration, and monitoring) were taken from the cost-utility analysis described in Section 3.4, using the same 2025 unit prices [16,49–51]. These were applied over the mean time on treatment of 9.2 months for inavolisib [72] and 7.3 months for the comparator [15]. The robustness of the result was tested in scenario analyses varying the eligible population (low

and high bounds), the uptake trajectory (conservative and aggressive), and the inavolisib price (list versus the access-based price derived in Section 3.5).

# 4. Results

The structure follows the analysis plan: base-case cost-effectiveness from the societal perspective (Section 4.1), probabilistic sensitivity analysis (Section 4.2), deterministic sensitivity analysis (Section 4.3), the access-based price and its comparison with the list and threshold prices (Section 4.4), and the scenario analyses including the healthcare payer perspective (Section 4.5).

## 4.1 Base-case results

Over the 20-year time horizon and from the Dutch societal perspective, inavolisib plus palbociclib and fulvestrant yielded 2.578 discounted QALYs and 4.317 discounted life-years at a total discounted cost of €592,861 per patient, compared with 2.183 discounted QALYs and 3.930 discounted life-years at €156,039 per patient for palbociclib plus fulvestrant. The addition of inavolisib therefore produced 0.394 incremental QALYs (and 0.387 incremental life-years) at an incremental cost of €437,407, giving a base-case incremental cost-effectiveness ratio of €1,109,246 per QALY gained (€1,129,537 per life-year). As a check on internal consistency, the discounted life-years exceed the discounted QALYs in each arm (4.317 versus 2.578 for inavolisib; 3.930 versus 2.183 for the comparator). This is expected, because each life-year is weighted by a utility below one. The incremental QALY gain (0.394) is marginally larger than the incremental life-year gain (0.387), because inavolisib shifts survival time towards the higher-utility progression-free state. This is plausible for a therapy that prolongs progression-free survival. At the €80,000 per QALY threshold applicable to a high-burden indication, the incremental net monetary benefit was −€405,861 per patient. Inavolisib combination therapy is therefore not cost-effective at its current list price; the base-case ICER exceeds the threshold by a factor of approximately fourteen.

The incremental cost was driven almost entirely by drug acquisition in the stable disease state, which accounted for €437,102 of the incremental cost, effectively the whole of it, reflecting the inavolisib list price of €13,695 per 28-day cycle. All other cost categories were minor by comparison and several were cost-saving for inavolisib: stable-disease healthcare resource use and monitoring added €1,901, adverse-event management €81, and stable-disease administration €869 to the incremental cost, while the second-line treatment lump-sum (−€177), ongoing progressed-disease care (−€1,411), and end-of-life costs (−€233) were marginally lower in the inavolisib arm because its patients spend less time in, and reach, the progressed and death states later. Among the societal cost categories, productivity loss was equal across arms (€0 incremental), informal care in the stable disease state added €3,544 while informal care in the progressed disease state was €7,507 lower for inavolisib, patient time added €135, and future unrelated medical costs under PAID 3.0 added €2,517. The societal categories therefore partially offset one another and did not meaningfully alter the conclusion, as confirmed by the healthcare payer perspective reported in Section 4.5. Table 5 reports the disaggregated cost components.

***Table 5. Disaggregated discounted cost components, per patient (societal perspective, 2025 prices)***

| Component | Inavolisib € | Comparator € | Increment € |
|---|---|---|---|
| Drug acquisition — SD | €468,184 | €31,082 | €437,102 |
| Administration — SD | €2,648 | €1,779 | €869 |
| HCRU / monitoring — SD | €4,943 | €3,042 | €1,901 |
| AE management lump-sum | €245 | €163 | €81 |
| PD lump-sum (2L chemo) | €610 | €787 | −€177 |
| PD ongoing (HCRU in PD) | €5,711 | €7,123 | −€1,411 |
| End-of-life | €24,576 | €24,809 | −€233 |
| **HEALTHCARE PAYER SUBTOTAL** | **€506,916** | **€68,784** | **€438,247** |
| Productivity loss (lump-sum) | €13,289 | €13,289 | €0 |
| Informal care SD | €11,379 | €7,835 | €3,544 |
| Informal care PD | €30,726 | €38,233 | −€7,507 |
| Patient time (SD + PD) | €2,489 | €2,354 | €135 |
| PAID 3.0 unrelated medical (×LY) | €28,061 | €25,544 | €2,517 |
| **SOCIETAL TOTAL** | **€592,861** | **€156,039** | **€437,407** |

*SD = stable disease; PD = progressed disease; HCRU = healthcare resource use; AE = adverse event; PAID = Practical Application to Include future Disease costs. All costs are discounted at 3.0% per annum and expressed per patient over the 20-year time horizon. The healthcare payer subtotal comprises all direct medical costs; the societal total additionally includes informal care, productivity loss, patient time, and future unrelated medical costs. Negative increments indicate the component is lower in the inavolisib arm. Components may not sum exactly to subtotals because of rounding. Source: model output (Analysis sheet).*

## 4.2 Probabilistic sensitivity analysis

The probabilistic analysis confirmed the deterministic result. On the cost-effectiveness plane (Figure 6), the great majority of simulations fell in the north-east quadrant, where inavolisib was more effective and more costly, with the point cloud centred on an incremental cost of approximately €440,000 and an incremental QALY gain of approximately 0.4, closely matching the deterministic estimate. The incremental costs clustered between roughly €330,000 and €650,000 and the incremental QALYs between roughly −0.4 and 1.3; a small minority of iterations produced a marginally negative QALY increment, reflecting parameter draws in which the survival difference narrowed. No iteration approached the €80,000 per QALY threshold line.

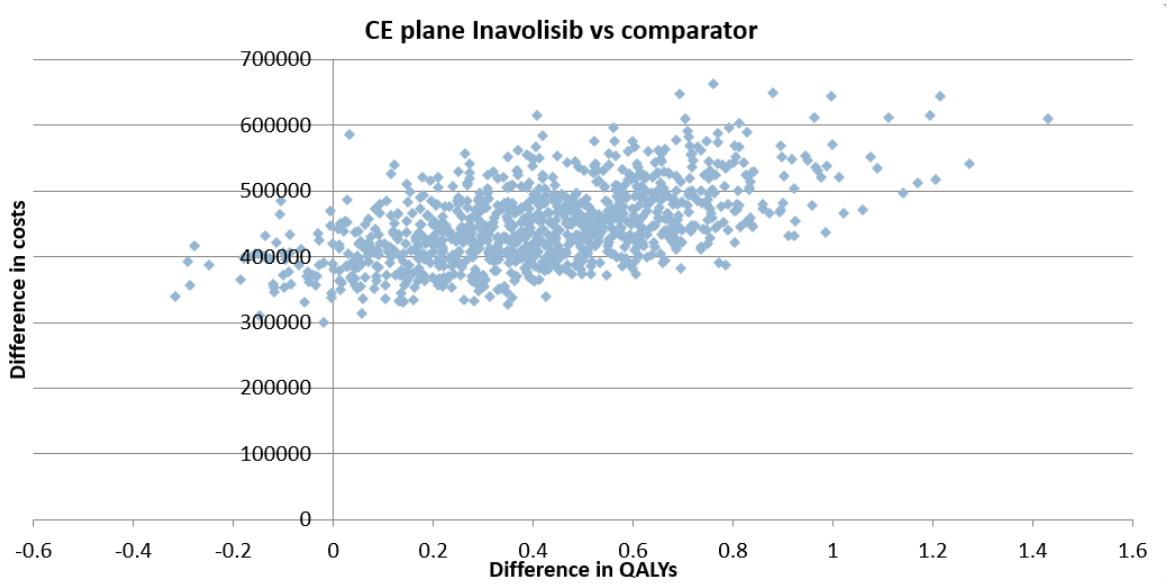


**Figure 6.** ***Cost-effectiveness plane, inavolisib versus comparator (probabilistic sensitivity analysis, 1,000 iterations, societal perspective).***

The cost-effectiveness acceptability curve (Figure 7) shows that the probability of inavolisib being cost-effective is effectively zero up to a willingness-to-pay of approximately €500,000 per QALY, and remains zero at the €80,000 per QALY threshold. The probability rises only once the threshold approaches the region of the deterministic ICER. It reaches approximately 0.40 at €900,000 per QALY, 0.50 at €1,000,000 per QALY, and exceeds 0.60 at approximately €1,250,000 per QALY. It continues to rise to about 0.79 at €2,000,000 per QALY, the upper limit of the analysed willingness-to-pay range. The gradient remained positive at this point and the curve had not reached a plateau. This is the expected behaviour of a cost-effectiveness acceptability curve for an intervention with a positive incremental QALY gain. Such a curve approaches a probability of one only asymptotically as the willingness-to-pay threshold increases, rather than levelling off at a finite value [75]. The PSA therefore reinforces the base-case finding: at any plausible Dutch willingness-to-pay threshold the probability that inavolisib combination therapy is cost-effective at its current list price is essentially nil, and the decision uncertainty around this conclusion is negligible.

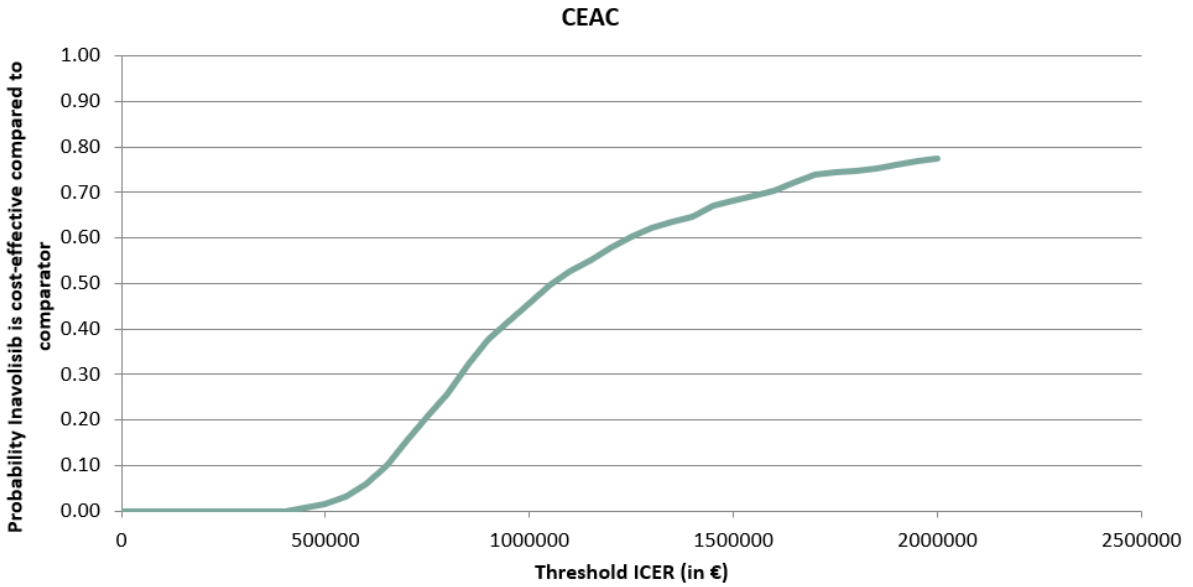


***Figure 7. Cost-effectiveness acceptability curve (societal perspective).***

In the one-way deterministic sensitivity analysis, the ICER was most sensitive to the progression-free health-state utility, which moved the ICER between €860,284 (utility 0.861) and €1,557,739 per QALY (utility 0.579) across its 95% confidence interval, and to the inavolisib acquisition cost, which moved the ICER between €842,243 and €1,375,699 per QALY across a ±25% variation. The progressed-disease utility was the third-ranked driver (€1,014,555 to €1,221,434 per QALY). All remaining parameters, including the informal-care hours in the progressed disease state, future unrelated medical costs, and the end-of-life cost, changed the ICER by less than €20,000 per QALY and are negligible by comparison. Critically, no single one-way variation brought the ICER below €840,000 per QALY; the base-case conclusion that inavolisib is not cost-effective at its list price is therefore robust to plausible variation in every individual parameter. Table 6 reports the full results and Figure 8 presents the tornado diagram.

**Table 6. One-way deterministic sensitivity analysis (societal perspective)**

| Parameter | Low input | High input | ICER at low | ICER at high |
|---|---|---|---|---|
| Utility, progression-free | 0.579 | 0.861 | €1,557,739 | €860,284 |
| Inavolisib price/tablet | €366.83 | €611.38 | €841,149 | €1,375,699 |
| Utility, progressed disease | 0.356 | 0.530 | €1,014,555 | €1,221,434 |
| Informal-care hours/week, PD | 9 | 27 | €1,117,943 | €1,098,905 |
| PAID future medical /LY | €4,875 | €8,125 | €1,106,828 | €1,110,020 |
| End-of-life cost | €28,651 | €63,916 | €1,108,424 | €1,107,696 |

*Low and high inputs are the bounds applied in the one-way analysis: utilities at their 95% confidence interval (point estimate ± 1.96 standard errors); the inavolisib price, informal-care hours, future medical costs, and the end-of-life cost at ± 25% or the alternative source value. Rows are sorted by the width of the ICER range.*

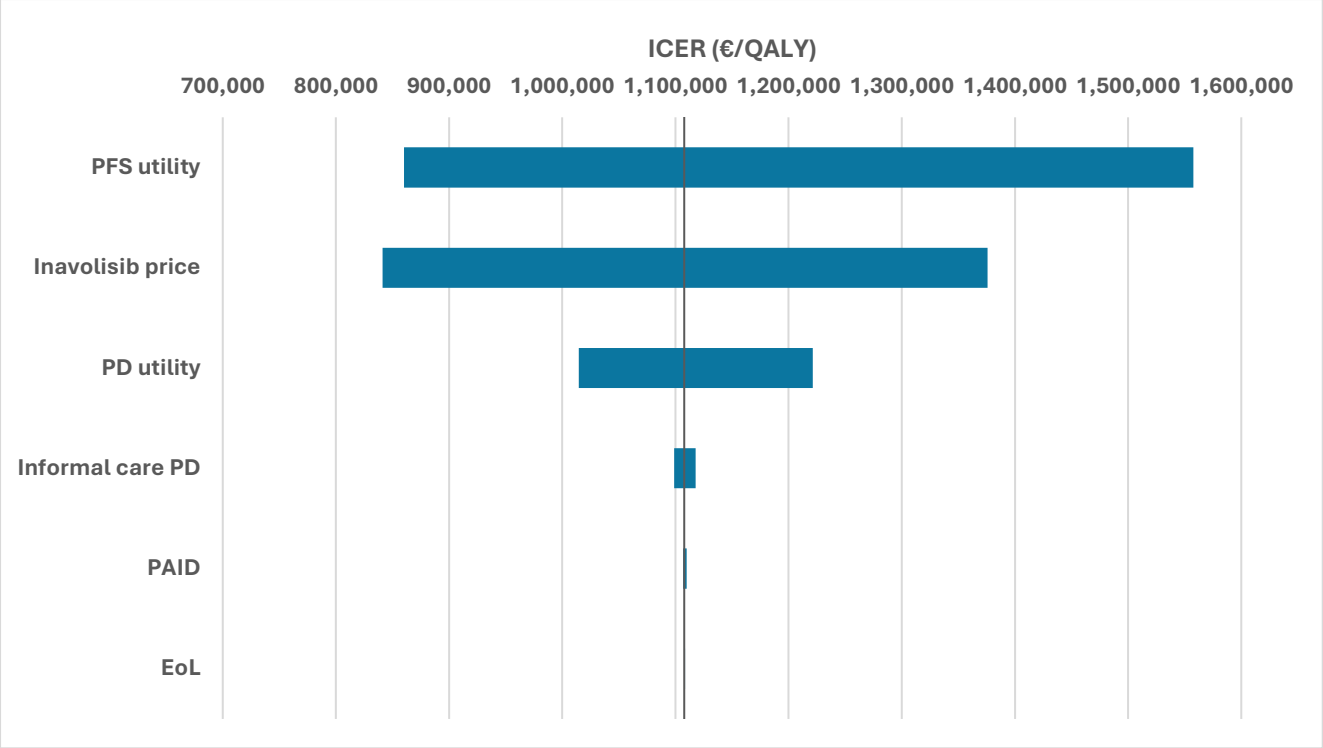


***Figure 8.*** *Tornado diagram of the one-way deterministic sensitivity analysis (societal perspective). The vertical line marks the base-case ICER of €1,109,246 per QALY.*

## 4.3 Access-based price

The ASCERTAIN pricing model returned a base-case access-based price of €242.87 per day, equivalent to €6,800.38 per 28-day cycle once aligned to the cost-utility model cycle length. This is approximately 50% below the current list price of €13,695 per 28-day cycle. The price was built from four components per treatment course (total €68,004): a capitalised research-and-development cost of €49,533 per patient, a value-based innovation reward of €14,117, operational costs of €3,364, and an operational profit of €989. The dominant component is therefore the capitalised R&D cost, allocated across an estimated 11,406 patients treated across the European Economic Area over the ten-year horizon. Operational manufacturing costs and profit together account for less than 6% of the price. The total value-based premium was 28.5%, reflecting a minor added therapeutic benefit (10%), raised by the unmet-medical-need (35%) and societal-value (30%) premiums and reduced by the return-on-public-investment adjustment (15%), with no quality-of-evidence penalty applied (Section 3.5). Substituting this access-based price for the inavolisib acquisition cost in the cost-utility model yielded an ICER of €571,572 per QALY from the societal perspective, still approximately seven times the €80,000 per QALY threshold, confirming that the regimen would remain well above the cost-effectiveness threshold even if priced at the cost-based access level.

The access-based price thus sits between the list price and the threshold price implied by the cost-utility analysis. The threshold price, defined as the inavolisib acquisition cost at which the regimen would just meet the €80,000 per QALY threshold from the societal perspective, is approximately €516 per 28-day cycle (€18.43 per tablet), equivalent to roughly 4% of the

current list price (a discount of approximately 96%). The access-based price of €6,800 per cycle is therefore about fourteen times the threshold price of €516 per cycle. The consequence for cost-effectiveness can be seen by substituting the access-based price into the cost-utility model. At the threshold, the 0.394 incremental QALYs gained would justify a total incremental cost of about €31,500 per patient (0.394 × €80,000). At the access-based price, however, the total incremental cost per patient remains an order of magnitude higher than this, so the resulting ICER stays far above €80,000 per QALY. This confirms that the gap between price and health gain is structural rather than attributable to the manufacturer's margin alone.

## 4.4 Scenario analyses

This section reports two distinct sets of scenario analyses in turn: first the scenario analyses for the access-based price (the ABP model), and then the scenario analyses for the cost-utility analysis. The access-based price was most sensitive to the parameters governing the size of the treated patient population, because the capitalised R&D cost is fixed and is spread across that population. Varying the treatment rate had the largest effect of any single parameter: a low treatment rate (12%) raised the price to €29,427 per 28-day cycle, while a high treatment rate (75%) lowered it to €5,075. The assumed incidence had a similarly large effect; the lower-bound incidence of 0.44 per 100,000 (counting *de novo* metastatic disease only, the more conservative of the two source-based derivations) raised the price to €11,665 per cycle. Market competition was modelled as competitors entering in years 5 and 7 and sharing the patient pool. This raised the price to €13,833 per cycle, because a smaller share of patients receiving inavolisib concentrates the fixed R&D cost over fewer patients. This is a feature of the supply-side cost-allocation logic rather than a market-price effect. Faster market uptake reduced the price modestly (€6,598 for fast uptake; €6,186 for breakthrough uptake).

### Access-based price scenario analyses

Among the value-based parameters, the societal-value premium was the most influential: removing it lowered the price to €5,314 per cycle (a fall of about 22%), which shows how much of the price rests on that component. Raising the added-therapeutic-benefit tier from minor to moderate increased the price to €8,138 per cycle, and to major increased it to €9,475 per cycle. Re-applying the quality-of-evidence penalty to the minor base case reduced the price to €6,553 per cycle (the value floor), while combining that penalty with a moderate tier reproduced the price of €7,395 per cycle that a moderate, quality-of-evidence-adjusted specification would yield. Removing the return-on-public-investment adjustment raised the price to €7,543 per cycle. Varying the profit margin had a negligible effect (within 1% of the base case), confirming that profit is a minor component of the price. The full set of fourteen pricing scenarios is reported in Appendix H. Across every scenario tested, the access-based price remained substantially above the threshold price required for cost-effectiveness at €80,000 per QALY, reinforcing that the central finding is robust to the pricing-model assumptions.

### Cost-utility analysis scenario analyses

The material cost-utility scenario analyses are summarised in Table 7; the full set of thirteen pre-specified scenarios is reported in Appendix I. The two survival-extrapolation scenarios moved the ICER most: substituting log-normal for the overall-survival curve (S11, optimistic tail) reduced the ICER to €759,775 per QALY, and substituting log-logistic for the progression-free survival curve (S10) reduced it to €835,926 per QALY, both through a larger modelled QALY gain. The Gompertz overall-survival scenario (S12) gave €1,070,405 per QALY. All remaining scenarios, namely the end-of-life cost source (S4), the second-line and cost-component variations (S5 to S9), and the healthcare payer perspective (S13), changed the ICER by less than 1% and are immaterial, because the inavolisib acquisition cost dominates the incremental cost. The pricing-discount scenarios isolate the effect of price directly: a 25%, 40%, and 60% discount reduced the ICER to €842,243, €682,040, and €468,437 per QALY respectively (S1 to S3). Across every scenario the ICER remained well above the €80,000 per QALY threshold, so no structural, cost, or perspective assumption alters the conclusion that inavolisib is not cost-effective at its list price; the price reduction required to reach the threshold is quantified in Section 4.4.

The healthcare payer perspective (S13) is reported here because it is a structural perspective change rather than a parameter variation. Removing the four societal cost categories (informal care, productivity loss, patient time, and future unrelated medical costs) reduced the total cost of inavolisib to €506,916 and of the comparator to €68,784 per patient, while leaving the health outcomes unchanged at 0.394 incremental QALYs and 0.387 incremental life-years. The incremental cost from the healthcare payer perspective was €438,247, giving an ICER of €1,111,376 per QALY (€1,131,706 per life-year) and an incremental net monetary benefit of −€406,700 at the €80,000 threshold. The payer ICER is therefore within 0.3% of the societal base-case ICER (€1,109,246 per QALY), confirming that the choice of perspective does not meaningfully affect the conclusion: the societal cost categories partially offset one another between arms, and inavolisib is not cost-effective at its list price under either perspective.

**Table 7. Scenario analysis results (deterministic ICER, societal perspective unless noted)**

| Scenario | Change applied | Tests | ICER (€/QALY) |
|---|---|---|---|
| **Base** | Deterministic, societal perspective | Reference | **€1,109,246** |
| **S10** | PFS log-logistic instead of generalised gamma | PFS structural uncertainty | €835,926 |
| **S11** | OS log-normal instead of log-logistic (optimistic tail) | OS extrapolation, upper bound | €759,775 |
| **S12** | OS Gompertz instead of log-logistic (pessimistic tail) | OS extrapolation, lower bound | €1,070,405 |
| **S13** | Healthcare payer perspective (excludes societal costs) | Perspective | €1,111,376 |

*Per the analysis plan, only scenarios whose ICER differs substantially from the base case are discussed in the text. All ICER values are taken from the model output (deterministic, societal perspective unless stated); the payer row (S13) is the healthcare payer perspective.*

## 4.5 Budget impact

Over a five-year horizon, reimbursing inavolisib at its list price was estimated to increase the Dutch drug budget by approximately €105.0 million cumulatively, rising from €6.2 million in year 1 to €32.9 million in year 5 as uptake increased from 15% to 80% (Table 8). At the access-based price of €6,800.38 per cycle derived in Section 3.5, the cumulative five-year impact fell to €53.49 million, a reduction of 49%.

**Table 8. Base-case budget impact by year (Dutch healthcare payer perspective, undiscounted)**

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|---|---|---|---|---|
| Eligible patients (incident) | 293 | 293 | 293 | 293 | 293 |
| Uptake (% on inavolisib) | 15% | 35% | 55% | 70% | 80% |
| Patients on inavolisib | 44 | 103 | 161 | 205 | 234 |
| Patients on comparator | 249 | 190 | 132 | 88 | 59 |
| Cost with inavolisib (€) | 10,400,904 | 18,634,742 | 26,868,580 | 33,043,959 | 37,160,878 |
| Cost without (all comparator) (€) | 4,225,526 | 4,225,526 | 4,225,526 | 4,225,526 | 4,225,526 |
| **Budget impact (€)** | **6,175,378** | **14,409,216** | **22,643,054** | **28,818,433** | **32,935,352** |
| **Cumulative (5-yr) (€)** | | | | | **104,981,434** |

*Cost with inavolisib reflects the modelled mix of patients on inavolisib and on the comparator in each year; cost without reflects all eligible patients on the comparator. All figures are undiscounted, per the budget impact convention. Source: budget impact model (base case, list price).*

In the scenario analyses (Table 9), the cumulative five-year impact ranged from €73.5 million under the low eligible-population assumption (205 patients per year) to €182.0 million under the high assumption (508 patients per year), and from €76.2 million under conservative uptake to €131.7 million under aggressive uptake. The eligible population size and the uptake trajectory were therefore the dominant drivers of budget impact, consistent with the literature on oncology budget impact analyses [74]. Because the eligible-population estimate is itself an approximation derived from literature-based proportions rather than a direct Dutch count, these scenario bounds should be read as the plausible range rather than a precise forecast.

**Table 9. Sensitivity of the cumulative five-year budget impact across scenarios**

| Scenario | Cumulative 5-year impact (€) | vs base case |
|---|---|---|
| **Base case (list price)** | **104,981,434** | **reference** |
| Population low (205/yr) | 73,451,174 | −30% |
| Population high (508/yr) | 182,015,592 | +73% |
| Uptake conservative | 76,163,001 | −27% |
| Uptake aggressive | 131,741,407 | +25% |
| Access price | 53,489,051 | −49% |

*Percentages are relative to the base case. The access-price row applies the access-based price of €6,800.38 per cycle from Section 3.5; all other rows apply the list price. Source: budget impact model.*

# 5. Discussion and conclusion

## 5.1 Summary of key findings

This is the first economic evaluation of inavolisib plus palbociclib and fulvestrant conducted for the Dutch setting. From the societal perspective, the regimen produced 0.394 additional QALYs at an incremental cost of €437,407 per patient, giving a base-case ICER of €1,109,246 per QALY gained. This is approximately fourteen times the €80,000 per QALY willingness-to-pay threshold applicable to a high-burden indication, and the incremental net monetary benefit at that threshold is strongly negative (−€405,861). The conclusion is robust to the choice of perspective: the healthcare payer ICER (€1,111,376 per QALY) is almost identical, because the societal cost categories largely offset one another between arms. It is robust to structural uncertainty: across all scenario analyses the ICER remained between €759,775 and €1,111,376 per QALY. It is also robust in the one-way deterministic analysis, in which the progression-free utility and the inavolisib acquisition cost were the largest drivers yet no single parameter brought the ICER below €840,000 per QALY. The incremental cost is driven almost entirely by the inavolisib acquisition cost; the threshold price at which the regimen would become cost-effective is approximately €516 per 28-day cycle, a reduction of about 96% from the current list price and well below even the cost-based access-based price of €6,800 per cycle. The gap between price and health gain is therefore structural rather than a matter of the manufacturer's margin. The three reference prices considered in this thesis can be placed side by side: the current list price of €13,695 per 28-day cycle, the cost-based access-based price of €6,800 per cycle, and the value-based threshold price of approximately €516 per cycle. The access-based price lies roughly midway between the list price and the threshold price, but it remains about fourteen times the threshold price, so the regimen would still not be cost-effective at the access-based price. Finally, reimbursement at the list price was estimated to add approximately €105.0 million to the Dutch drug budget over five years, falling to €53.49 million at the access-based price (a reduction of about 49%), for an eligible population of roughly 293 patients per year. Taken together, these findings answer each of the seven sub-questions and converge on the overall conclusion set out in Section 5.6.

## 5.2 Comparison with the existing literature

Three economic evaluations of inavolisib have been published to date, all in non-European settings. Zhu et al. (2026) evaluated first-line inavolisib plus palbociclib and fulvestrant in HR+/HER2− advanced breast cancer from Chinese and United States healthcare payer perspectives, and Huang et al. (2026) evaluated the same regimen in the Chinese setting; both concluded that inavolisib is not cost-effective at the current list price [22,23]. Huang et al. (2025) reached a similar conclusion for the male breast cancer subpopulation [24]. All three relied on the Lloyd et al. (2006) utility values and identified the same dominant ICER drivers found here (Section 5.1) [22–24,46].

The comparison with these studies is constrained by three structural differences that prevent direct transfer of their conclusions to the Netherlands. First, the willingness-to-pay thresholds

differ markedly. China applies thresholds derived from per-capita GDP multipliers and the United States commonly references $100,000 to $150,000 per QALY. Neither corresponds to the Dutch severity-dependent structure of €20,000, €50,000, and €80,000 per QALY. Second, drug acquisition and healthcare resource-use costs differ substantially across jurisdictions. Third, the analytic perspective differs: the published Chinese and United States evaluations adopted a healthcare-payer or health-system perspective, whereas the present analysis adopts the broader Dutch societal perspective, which additionally captures informal care, productivity losses, and patient costs [22,23]. Notwithstanding these differences, the qualitative conclusion of the present analysis aligns with all three published evaluations: inavolisib is not cost-effective at its list price.

## 5.3 Strengths and limitations

**Strengths.** This study is the first economic evaluation of inavolisib conducted for the Dutch setting, directly addressing an evidence gap relevant to an impending Zorginstituut Nederland reimbursement decision. The analysis follows the 2024 Dutch guideline for economic evaluations [25,26]. This includes the societal perspective as the base case (with the healthcare payer perspective as a secondary analysis), the updated 3.0%/1.5% differential discount rates, and probabilistic sensitivity analysis as the primary characterisation of decision uncertainty. Costs are transparently indexed from the *Kostenhandleiding* 2024 reference prices to 2025 levels using a single CBS CPI factor, with all source-level derivations documented in Appendix A. The scenario analysis spans thirteen pre-specified variations covering perspective, pricing, survival extrapolation, utility source, and cost-component scope, allowing the reader to identify which assumptions drive the cost-effectiveness conclusion. The triangulated pricing framework combining CUA threshold prices with ABP-derived prices is methodologically novel in the Dutch oncology context.

**Limitations.** Several limitations should be considered when interpreting the results. These are discussed below with an assessment of the likely direction of bias on the ICER (downward = more favourable to inavolisib; upward = less favourable; unknown = ambiguous).

**Utility source (direction: downward).** The base-case utility values were taken from Lloyd et al. (2006) [46], a vignette-based standard-gamble study in the UK general public rather than EQ-5D collected from trial patients. This is the most consequential limitation. The PFS-to-PD utility decrement in Lloyd (0.27) is larger than the decrements observed in modern EQ-5D-5L data from CDK4/6-inhibitor trials (typically 0.10–0.18), which means the QALY gain from delaying progression is likely overstated in the base case. The net effect is a downward bias on the ICER, making inavolisib appear more cost-effective than it would under trial-derived EQ-5D utilities. This limitation is shared with all three published INAVO120 CEAs [22–24] and reflects the absence of EQ-5D data from the INAVO120 trial itself. Additionally, the Lloyd utilities are not valued with the Dutch Versteegh (2016) tariff [33] as required by the ZIN reference case; the direction of this tariff mismatch is unknown.

**Treatment-effect extrapolation (direction: downward).** The base case extrapolates the inavolisib treatment effect beyond the 34-month observed follow-up over a 20-year time

horizon using generalised gamma (PFS) and log-logistic (OS) distributions. This implicitly assumes that the treatment benefit persists indefinitely. If the effect wanes over time, the incremental QALY gain would be smaller and the ICER would increase. This durability assumption is a recognised limitation of survival extrapolation in oncology and could not be tested directly because the trial follow-up (34 months) is short relative to the 20-year horizon.

**Single-trial evidence base (direction: unknown).** The analysis relies entirely on the INAVO120 trial. No corroborating trials exist for this specific regimen in this population. The external validity of the trial to the broader Dutch PIK3CA-mutated HR+/HER2− advanced breast cancer population is uncertain, particularly given that INAVO120 enrolled a relatively young cohort (median age 54 years) and excluded patients with poorly controlled diabetes.

**Progressed disease cost simplifications (direction: downward).** Both arms were modelled as receiving capecitabine monotherapy as the representative second-line regimen, with arm-specific administration rates (55% inavolisib, 72% comparator). In practice, second-line treatment is heterogeneous and may include antibody-drug conjugates (trastuzumab deruxtecan, sacituzumab govitecan) at substantially higher cost. The exclusion of these high-cost alternatives from the base case underestimates absolute PD costs. However, because the comparator arm has a higher administration rate for subsequent therapy, the incremental cost may be understated, modestly favouring inavolisib. Adverse-event management costs in the progressed disease state were not modelled (Section 3.4.3), which similarly underestimates PD costs but has a negligible incremental effect because capecitabine dose and schedule are identical across arms.

**Partitioned survival model structure (direction: downward, negligible).** The partitioned survival structure derives the occupancy of the three health states directly and independently from the extrapolated PFS and OS curves, rather than from explicit transition probabilities between states [26,37]. Two consequences follow. First, because the number of newly progressed patients in each cycle is taken as the decrease in stable-disease occupancy, it includes patients who leave the stable state by dying as well as those who progress. These patients are therefore credited with the one-off second-line treatment cost. Because the comparator arm has a higher second-line treatment administration rate (72% versus 55%), this very slightly inflates comparator costs relative to inavolisib, biasing the ICER marginally downward, although the effect is negligible. Second, where the independently extrapolated curves would imply a negative progressed-disease occupancy, this was constrained to zero; this did not occur in the base-case extrapolations. A state-transition (Markov) structure with explicit transition probabilities would avoid these issues but requires patient-level transition data that were not available from the published trial.

**Fulvestrant administration proxy (effect on ICER: none; affects absolute costs only, equal in both arms).** The *Kostenhandleiding* 2024 does not publish a reference price for home-based intramuscular drug administration. The hospital subcutaneous administration reference price was used as a proxy, which likely overestimates the true cost of a brief home-

care nurse visit for an intramuscular injection. Because this cost is equal for both arms, it inflates absolute costs but does not affect the incremental cost or the ICER.

**Bone-metastasis proportion (effect on ICER: none; affects absolute costs only, equal in both arms).** The trial-derived bone-metastasis proportions (3.1% inavolisib, 3.7% comparator) are substantially lower than the approximately 40–50% observed in real-world Dutch registries, likely because INAVO120 excluded patients with bone-only disease not measurable by RECIST. This underestimates bone-targeted therapy costs equally in both arms.

**End-of-life cost source (effect on ICER: none; affects absolute costs only, equal in both arms).** The base-case end-of-life cost (Schneider et al. (2020), €28,651) reflects a hospital-only perspective and excludes general practitioner, hospice, and home-care nursing costs. The true payer-perspective end-of-life cost is therefore underestimated. Because end-of-life costs are equal in both arms, this does not affect the incremental cost but does underestimate absolute total costs per arm. A broader-scope scenario using Van Dijk et al. (2025) (€63,914) is included in the sensitivity analysis (S4).

**Informal care and productivity inputs in the societal base case (direction: unknown).** Because the societal perspective is the base case, the analysis includes informal care hours, productivity losses, patient time, and future unrelated medical costs. Two of these inputs rest on weak evidence. First, the informal care hours (5 hours per week in the progression-free state and 18 hours per week in the progressed disease state) are not derived from a disease-specific source for HR+/HER2− advanced breast cancer; no such Dutch estimate exists. They are modelling assumptions, contextualised by the Dutch median of approximately 15 hours per week of informal care across all conditions and by international cancer-caregiver estimates of 29 to 33 hours per week across all stages. Breast cancer has among the lowest informal care costs of all cancer types. These hours were varied widely in one-way sensitivity analysis (±100% in the progression-free state, ±50% in the progressed disease state). Second, the future unrelated medical cost was applied using the PAID 3.0 methodology with an indicative value; the exact age- and sex-specific value should be drawn from the live PAID 3.0 tool. The direction of bias is unknown: informal care and productivity costs accrue in both arms, and because inavolisib extends the progression-free period (lower-intensity care) but also extends overall survival (longer total care), the net effect on the incremental cost is ambiguous. This is the principal limitation specific to the societal base case and is the main reason the healthcare payer perspective is reported alongside it (scenario S13).

**Hyperglycaemia disutility (direction: unknown).** The disutility for inavolisib-specific hyperglycaemia was sourced from Wu et al. (2023) [47], which is not derived from a metastatic breast cancer population. No breast-cancer-specific hyperglycaemia disutility has been published. The value used (−0.006) is small and its impact on the ICER is minimal, but the direction of any bias is unknown.

**Severity weighting and the willingness-to-pay threshold (direction: unknown).** The €80,000 per QALY threshold applied here follows from a proportional shortfall of 0.86, which

places the indication in the highest Dutch severity class (0.71 to 1.00) [35]. This estimate, however, was derived for metastatic breast cancer in general rather than specifically for the PIK3CA-mutated, HR+/HER2− subgroup after progression on endocrine therapy, and a subgroup-specific proportional shortfall has not been published. Because this subgroup has a comparably poor prognosis, its proportional shortfall would be expected to remain within the highest severity class, so the €80,000 per QALY threshold is unlikely to change. Nevertheless, a formally calculated subgroup-specific shortfall would strengthen the severity classification. Given that the base-case ICER exceeds the threshold by more than an order of magnitude, plausible variation in the threshold does not alter the cost-effectiveness conclusion.

**Additional data that could affect the conclusion.** Several types of additional data could meaningfully alter the results. First, if EQ-5D-5L data from INAVO120 become available (expected as part of the Zorginstituut Nederland inavolisib assessment), they would replace the Lloyd utility inputs and likely narrow the PFS-PD decrement, increasing the ICER. Second, real-world Dutch data on second-line treatment patterns after inavolisib (including ADC uptake rates and costs) would refine the progressed disease cost estimates. Third, longer-term follow-up from INAVO120 would reduce the structural uncertainty around survival extrapolation and treatment-effect durability. Fourth, Dutch-specific data on informal care hours and productivity losses for patients on oral targeted therapy would strengthen the societal-perspective scenario. The net expected direction from these additional data sources is an increase in the ICER (less favourable to inavolisib), primarily driven by the expected narrowing of the utility decrement from Lloyd to EQ-5D.

## 5.4 Recommendations for further research

Four lines of further research would strengthen the evidence base. First, prospective collection of EQ-5D-5L data in patients receiving inavolisib, valued with the Dutch Versteegh (2016) tariff, would replace the Lloyd et al. (2006) utilities that are the single most influential and most uncertain input in the model. Second, analysis of Dutch real-world registry data (for example, the SONABRE registry) on second-line treatment sequencing after inavolisib, including the uptake and cost of antibody-drug conjugates, would refine the progressed disease cost estimates. Third, extended follow-up of the INAVO120 trial would reduce the structural uncertainty around survival extrapolation and allow a direct test of the treatment-effect waning assumption. Fourth, a value-of-information analysis could formally quantify the expected value of collecting each of these additional data types, helping to prioritise future data collection. Finally, the access-based pricing framework applied here could be extended to other high-cost targeted oncology therapies entering Dutch reimbursement review, building a methodological template for transparent, evidence-informed pricing.

## 5.5 Policy implications

This study is positioned to inform an impending Zorginstituut Nederland assessment of inavolisib. The policy relevance lies in three areas. First, the base-case ICER from the societal perspective (€1,109,246 per QALY) provides a Dutch-specific cost-effectiveness estimate

where none previously existed. It can be compared directly against the €80,000 per QALY threshold applicable to this high-burden indication, and on this comparison the regimen is not cost-effective at its list price. Second, the analysis quantifies the price at which the regimen would become cost-effective. The threshold price implied by the cost-utility analysis is approximately €516 per 28-day cycle, a reduction of about 96% from the list price, and the access-based price derived from the ASCERTAIN pricing model is €6,800 per cycle. These two independent reference points, one value-based and one cost-based, bracket the range relevant to the confidential price negotiations between the manufacturer and the Minister of Health, and the gap between them is itself informative for that negotiation. The present analysis reports these figures as evidence; whether any particular price is attainable or acceptable is a matter for the negotiating parties. Third, the analysis identifies which Dutch real-world data would most reduce decision uncertainty, namely trial-derived EQ-5D utilities, second-line treatment patterns, and longer-term survival follow-up. These implications are presented as evidence to inform the decision; the desirability of reimbursement at any given price is a societal and political judgement beyond the scope of this analysis. On the basis of these results, the most defensible policy option would be to make reimbursement conditional on a substantial, confidentially negotiated price reduction rather than to reimburse at the list price or to reject the drug outright. Because the shortfall is too large to be closed by a conventional discount alone (the threshold price is roughly 4% of the list price), a financial-based managed entry agreement would be the most direct instrument to bring net spending closer to a cost-effective level while preserving patient access. Such an agreement could combine a confidential net-price discount with an expenditure cap or a price–volume arrangement. This is consistent with Dutch and wider European practice, in which financial-based agreements predominate; earlier performance-based schemes were largely discontinued in oncology because of their administrative burden [76]. Given that the largest single source of decision uncertainty is the absence of trial-derived EQ-5D utilities and mature survival data, an outcomes-based or coverage-with-evidence-development agreement would be a complementary, though secondary, option. Linking continued reimbursement to the prospective collection of Dutch real-world effectiveness and utility data would allow access while the evidence base matures. In the Netherlands, however, the formal coverage-with-evidence-development programme is generally reserved for orphan products and drugs with conditional or exceptional marketing authorisation, so its formal applicability to a fully authorised product such as inavolisib may be limited. Such an agreement would also align with the Zorginstituut Nederland practice of advising conditional inclusion (the *sluis* procedure) for high-cost drugs whose cost-effectiveness is not established at the list price. Whichever instrument is chosen, the triangulated price range reported here provides a transparent, evidence-based anchor for that negotiation.

## 5.6 Conclusion

At its current list price, inavolisib plus palbociclib and fulvestrant is not cost-effective for PIK3CA-mutated HR+/HER2− advanced breast cancer from the Dutch societal perspective.

The regimen produced 0.394 additional QALYs at an incremental cost of €437,407 per patient, giving a base-case ICER of €1,109,246 per QALY. This exceeds the €80,000 per QALY threshold by more than an order of magnitude, and the conclusion is insensitive to perspective and to parameter uncertainty. For the regimen to meet the threshold, the inavolisib price would need to fall by approximately 96%, to around €516 per 28-day cycle, far below even the cost-based access-based price, indicating that the shortfall is structural and cannot be closed by a conventional confidential discount alone. Because the base-case analysis, if anything, flatters inavolisib (the Lloyd utility decrement and the exclusion of high-cost second-line agents both bias the ICER downward), the true ICER is likely somewhat higher still. These findings suggest that, at the list price, reimbursement would require either a very substantial price reduction or a managed-entry agreement, particularly given an estimated budget impact of approximately €105.0 million over five years, and they provide a quantified Dutch-specific basis for the forthcoming Zorginstituut Nederland appraisal.

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## Appendix A. Detailed cost derivations

This appendix documents the step-by-step derivation of each cost component used in the model. All drug prices are 2025 list prices from *Farmacotherapeutisch Kompas* and medicijnkosten.nl [16,46]. All *Kostenhandleiding* 2024 reference prices are at 2022 price level and indexed to 2025 using the CBS CPI factor 1.1076 [48].

**Table A1. Stable disease drug acquisition cost derivations**

| Drug | Unit price | Units/cycle | Cost/cycle | Derivation |
|---|---|---|---|---|
| Inavolisib 9 mg | 489.10 | 28 tabs | 13,694.80 | 489.10 x 28 = 13,694.80 |
| Palbociclib 125 mg | 58.18 | 21 tabs | 1,221.78 | 58.18 x 21 = 1,221.78. Tablet formulation selected (cheapest); capsule = 76.76/day (scenario S7) |
| Fulvestrant 250mg/5ml (Mylan) | 126.44 | C1: 4 syr; C2+: 2 syr | C1: 505.76; C2+: 252.88 | Mylan = cheapest reimbursed formulation. C1 loading: day 1 + day 15 (2 x 2 syr = 4 syr). C2+: day 1 only (2 syr) |
| Goserelin 3.6 mg | 115.39 | 1 implant | Inav: 46.62; Comp: 41.54 | Weighted by premenopausal %: 115.39 x 0.404 = 46.62 (inav); 115.39 x 0.360 = 41.54 (comp) |

*C1 = cycle 1; C2+ = cycles 2 onwards; syr = pre-filled syringe; tabs = tablets. Source: FK [46]; medicijnkosten.nl [16]; Turner et al. (2024) [14] for premenopausal proportions.*

**Table A2. Fulvestrant administration cost derivation**

| Step | Value | Year | Source |
|---|---|---|---|
| SC oncological drug admin reference | 75.28 | 2022 | *Kostenhandleiding* 2024 Section 4.2 [40] |
| CPI indexation 2022 to 2025 | x 1.1076 | | CBS StatLine [48] |
| **Indexed unit cost per occasion** | **83.38** | 2025 | Calculated |
| C1: 2 occasions (day 1 + day 15) | 166.77 | 2025 | 83.38 x 2 |
| C2+: 1 occasion | 83.38 | 2025 | 83.38 x 1 |

*SC = subcutaneous (used as proxy for IM home administration). No dedicated NZa or Kostenhandleiding tariff exists for home-based IM oncological drug administration. Scenario S9 tests half this proxy.*

**Table A3. Outpatient consultation cost derivation**

| Step | Value | Year | Source |
|---|---|---|---|
| Outpatient visit reference price | 120.00 | 2022 | *Kostenhandleiding* 2024 Section 4.3 [40] |
| CPI indexation | x 1.1076 | | CBS StatLine [48] |
| **Indexed unit cost** | **132.91** | 2025 | Calculated |

**Table A4. Capecitabine acquisition cost derivation**

| Step | Value | Unit | Source / derivation |
|---|---|---|---|
| Unit price (Capecitabine Accord 500 mg) | 1.55 | EUR/tab | Cheapest reimbursed formulation [16] |
| Mean BSA (Dutch female) | 1.72 | m2 | RIVM Dutch average |
| Prescribed dose (1,250 mg/m2 BID) | 2,150 | mg/day | 1.72 x 1,250 = 2,150; rounded to 2,000 mg/day |
| Tablets per day | 4 | tabs | 2,000 / 500 = 4 tablets BID not separately modelled |
| Treatment days per 21-day cycle | 14 | days | Days 1-14 of 21-day cycle; 7 days off |
| Cost per 21-day capecitabine cycle | 173.60 | EUR | 1.55 x 4 x 2 (BID) x 14 = 173.60 |
| Cycles assumed per treated patient | 6 | cycles | Standard 6-cycle capecitabine course |
| **Total acquisition per treated patient** | **1,041.60** | EUR | 173.60 x 6 = 1,041.60 |
| Weighted by 2L administration proportion (inavolisib) | 572.88 | EUR | 1,041.60 x 0.55 = 572.88 |
| Weighted by 2L administration proportion (comparator) | 749.95 | EUR | 1,041.60 x 0.72 = 749.95 |

*BSA = body surface area; BID = twice daily. 2L administration proportion rates from Jhaveri et al. (2025) [15]. Applied as one-off cost at the model cycle of transition to progressed disease.*

**Table A5. Progressed disease HCRU cycle-length conversion**

| Step | Value | Unit | Derivation |
|---|---|---|---|
| Per-capecitabine-cycle HCRU (21 days) | 153.55 | EUR | Outpatient 132.91 + CBC 9.25 + ALT 2.50 + AST 2.38 + bilirubin 1.97 + alk phos 2.39 + creatinine 2.15 |
| Conversion ratio (28/21) | 1.333 | | Model cycle 28 days / capecitabine cycle 21 days |
| **Per-model-cycle HCRU (28 days)** | **204.73** | EUR | 153.55 x 1.333 = 204.73 |

*Preserves the clinical monitoring frequency of one full panel per capecitabine cycle while expressing costs in the 28-day model cycle.*

**Table A6. End-of-life cost CPI indexation**

| Parameter | Value | Year | Source |
|---|---|---|---|
| Schneider (2020) reported cost | 21,641 | 2017 | Schneider et al. (2020) [18] |
| Cumulative CPI 2017 to 2025 | x 1.3239 | | CBS StatLine [48] |
| **Indexed EoL cost (base case)** | **28,651** | 2025 | Calculated |
| Van Dijk (2025) reported cost | 50,423 | 2019 | Van Dijk et al. (2025) [59] |
| Cumulative CPI 2019 to 2025 | x 1.2676 | | CBS StatLine [48] |
| **Indexed EoL cost (scenario S4)** | **63,914** | 2025 | Calculated |

*EoL = end-of-life. Schneider: hospital-perspective only (SONABRE Registry, advanced breast cancer). Van Dijk: includes long-term care under Wlz (all-cause, not cancer-specific). Both applied equally in both arms.*

## Appendix B. AIC values for parametric survival distributions

Tables B1 and B2 present the Akaike Information Criterion (AIC) values for all six candidate parametric distributions fitted to the reconstructed progression-free survival and overall survival data from the INAVO120 trial. The pooled AIC is the sum of the arm-specific AIC values; a single distribution was applied to both arms, so the pooled value is the relevant selection criterion. The values are the exact output of the survival analysis performed in R using the flexsurv and survival packages.

**Table B1. AIC values and rankings - PFS, by treatment arm**

| Distribution | AIC inavolisib | Rank | AIC placebo | Rank | Pooled AIC | Pooled rank |
|---|---|---|---|---|---|---|
| **Gen. gamma** | 865.37 | 2 | **945.33** | **1** | **1,810.70** | **1** |
| Log-logistic | **860.93** | **1** | 956.23 | 3 | 1,817.16 | 2 |
| Log-normal | 866.64 | 4 | 951.59 | 2 | 1,818.23 | 3 |
| Gompertz | 867.07 | 6 | 970.46 | 4 | 1,837.53 | 4 |
| Exponential | 865.57 | 3 | 977.75 | 5 | 1,843.32 | 5 |
| Weibull | 867.01 | 5 | 979.57 | 6 | 1,846.58 | 6 |

*AIC = Akaike Information Criterion (lower values indicate better fit). Bold indicates the best-fitting distribution in each column. Rows are sorted by pooled rank. The generalised gamma achieved the lowest pooled AIC (1,810.70) and was selected for the base case; log-logistic (pooled AIC 1,817.16) was the closest alternative and is used in scenario analysis S10.*

**Table B2. AIC values and rankings - OS, by treatment arm**

| Distribution | AIC inavolisib | Rank | AIC placebo | Rank | Sum AIC | Pooled rank |
|---|---|---|---|---|---|---|
| **Log-logistic** | **678.85** | **1** | **753.51** | **1** | **1,432.36** | **1** |
| Weibull | 680.04 | 2 | 754.23 | 3 | 1,434.27 | 2 |
| Gen. gamma | 681.81 | 3 | 754.78 | 4 | 1,436.59 | 3 |
| Gompertz | 684.31 | 4 | 756.47 | 6 | 1,440.78 | 4 |
| Log-normal | 687.47 | 5 | 753.92 | 2 | 1,441.39 | 5 |
| Exponential | 688.29 | 6 | 756.21 | 5 | 1,444.50 | 6 |

*AIC = Akaike Information Criterion (lower values indicate better fit). Bold indicates the best-fitting distribution in each column. Rows are sorted by pooled rank. The log-logistic distribution achieved the lowest AIC in both arms individually and the lowest pooled AIC (1,432.36); it was selected for the base case. Log-normal (optimistic tail, S11) and Gompertz (pessimistic tail, S12) are used in scenario analyses.*

## Appendix C. NZa primary-care diagnostic tariff codes applied

Table D1 lists the NZa primary-care diagnostic tariff codes and their 2025 prices used to cost the laboratory monitoring in the stable disease and progressed disease states.

**Table D1. NZa diagnostic tariff codes (2025 prices)**

| NZa code | Description | Price (EUR) | Panel / state |
|---|---|---|---|
| 70101 | Erythrocytes with haematocrit and indices | 2.72 | CBC (SD + PD) |
| 70107 | Leukocyte count | 1.62 | CBC (SD + PD) |
| 70718 | Automated differential count | 2.32 | CBC (SD + PD) |
| 70103 | Platelet count | 2.59 | CBC (SD + PD) |
| | **CBC panel total** | **9.25** | |
| 74891 | ALT (alanine aminotransferase) | 2.50 | LFT (PD only) |
| 70489 | AST (aspartate aminotransferase) | 2.38 | LFT (PD only) |
| 70303 | Bilirubin total | 1.97 | LFT (PD only) |
| 70102 | Alkaline phosphatase | 2.39 | LFT (PD only) |
| 70419 | Creatinine with eGFR | 2.15 | Renal (PD only) |
| 74065 | HbA1c (glycated haemoglobin) | 8.05 | Every 3 cycles, inavolisib only |

*CBC = complete blood count; LFT = liver function tests; SD = stable disease; PD = progressed disease; eGFR = estimated glomerular filtration rate. Source: Starlet-DC Tarievenlijst Eerstelijnsdiagnostiek 2025 [47].*

## Appendix D. Full screening of adverse events from the INAVO120 safety analysis

Table E1 reports all Grade 3/4 adverse events from the INAVO120 safety population with an incidence of 2% or higher in at least one arm. The inclusion threshold for the base-case model was set at 5% in at least one arm. Two AEs (diarrhoea and elevated AST or ALT) fell within 1.3 percentage points of this threshold; their exclusion from the base case has a negligible effect on the incremental result because their incidence is similar across arms.

**Table E1. Grade 3/4 adverse events from INAVO120 (safety population)**

| Adverse event | Inavolisib (%) | Placebo (%) | Meets 5%? | Inclusion decision |
|---|---|---|---|---|
| Neutropenia | 82.6 | 80.4 | Yes | Base case |
| Thrombocytopenia | 13.7 | 4.9 | Yes | Base case |
| Anaemia | 6.8 | 1.8 | Yes | Base case |
| Hyperglycaemia | 6.8 | 0.0 | Yes | Base case |
| Stomatitis / mucosal inflammation | 5.6 | 0.0 | Yes | Base case |
| *Elevated AST or ALT* | *4.3* | *2.5* | *No (4.3%)* | *Borderline* |
| *Diarrhoea* | *3.7* | *0.0* | *No (3.7%)* | *Borderline* |
| Leukopenia | 3.1 | 4.3 | No | Excluded |
| Fatigue | 1.9 | 1.8 | No | Excluded |
| Rash | 1.9 | 0.0 | No | Excluded |

*Safety population: inavolisib arm N = 161; placebo arm N = 163. Italic rows denote borderline AEs (within 1.3 percentage points of the 5% inclusion threshold) that were screened but not included in the base-case model. Source: Jhaveri et al. (2025), Table 1 [15].*

## Appendix E. Adverse event disutility values and management costs

Table F1 reports the disutility weight, mean episode duration, and management cost per episode for each Grade 3/4 adverse event included in the base-case model. Table F2 presents the resulting lump-sum QALY loss and cost per arm.

**Table F1. AE disutility weights, durations, and management costs per episode**

| Adverse event | Disutility | Duration (d) | Cost/episode | Source |
|---|---|---|---|---|
| Neutropenia | -0.150 | 7 | 175.13 | Lloyd [44]; Gambardella [62]; KH2024 [40] |
| Thrombocytopenia | -0.030 | 7 | 142.16 | Wu [45]; Gambardella [62]; KH2024 [40] |
| Anaemia | -0.070 | 14 | 632.28 | Lloyd [44]; Gambardella [62]; KH2024 [40] |
| Hyperglycaemia | -0.006 | 28 | 270.02 | Wu [45]; Gambardella [62]; KH2024 [40] |
| Stomatitis | -0.151 | 18 | 204.30 | Lloyd [44]; Gambardella [62]; KH2024 [40]; medicijnkosten.nl 2026 |

*d = days; KH2024 = Kostenhandleiding 2024. Neutropenia cost is weighted: 99% outpatient management + 1% febrile neutropenia hospitalisation (FN incidence <1% in INAVO120). Hyperglycaemia managed with metformin initiation and extra outpatient visits. Costs in 2025 EUR.*

**Table F2. Lump-sum AE cost and QALY loss per arm (per patient)**

| | Inavolisib arm | Comparator arm | Incremental |
|---|---|---|---|
| Total AE management cost | 244.62 | 159.15 | **+85.47** |
| Total AE QALY loss | -0.00307 | -0.00239 | **-0.00068** |

*Applied as a one-off lump-sum at the first model cycle. QALY loss = incidence x disutility x (duration / 365.25). The incremental AE QALY loss is trivially small and does not meaningfully affect the ICER.*

## Appendix F. Access-based pricing model parameter specification

Table G1 documents the inputs to the ASCERTAIN access-based pricing model for inavolisib. Parameters set to model defaults or presets follow the model developers' guidance for cases without firm-specific data. Value-based parameters marked for scenario analysis are the most discretionary inputs and are varied in the sensitivity analysis.

**Table G1. ASCERTAIN pricing-model inputs for inavolisib**

| Parameter | Setting | Basis |
|---|---|---|
| Prevalence input | 0 | Incidence-based population used at launch |
| Incidence | 0.71 / 100,000/yr | Derived from EMA RMP: SEER metastatic HR+/HER2- 3.9/100k women x 0.503 x 36.4% PIK3CA. De novo only (lower bound) |
| Treatment rate | Default | Model default (coordinator guidance) |
| Competition | No | Only approved PI3Kalpha inhibitor in this combination |
| Relative utilisation index | Normal | Model default uptake |
| Dose per day | 9 mg | Genentech Prescribing Information; INAVO120 |
| Compound type | Specialised chemical | Oral small-molecule kinase inhibitor (oncology) |
| Container type | Tablet (n=1) | One 9 mg tablet per daily dose (FDA label: 3 mg & 9 mg strengths) |
| Treatment duration | 9.2 months | Median duration of Itovebi treatment, EMA EPAR (range 0-38.8) |
| Days in cycle | 1 (daily) | Daily oral administration |
| R&D cost | Default | EUR 889,484,725 (Wouters et al. 2020) |
| Cost of capital | Default (10.5%) | Model default |
| Return on public investment | Preset (0.15) | 15% reduction for public R&D contribution |
| *Added therapeutic benefit* | *Moderate (0.3)* | *PASKWIL 2023 positive recommendation; scenario-varied* |
| *Quality-of-evidence adj.* | *Preset (0.5)* | *Single-trial evidence, surrogate PFS; scenario-varied* |
| *Unmet-medical-need adj.* | *Preset (0.35)* | *Endocrine-resistant PIK3CA-mut disease; scenario-varied* |
| *Societal value* | *Preset (0.3)* | *Most discretionary value parameter; scenario-varied* |
| SGA expenses | Preset (82.75%) | Proportion of COGS (Dolon 2023) |

| | | |
|---|---|---|
| *Profit margin* | *Default (29.4%)* | *Ledley et al. (2020); scenario-varied* |

*ABP = access-based price; COGS = cost of goods sold; SGA = sales, general and administrative; EPAR = European Public Assessment Report; RMP = Risk Management Plan. Italic rows are value-based parameters varied in scenario analysis. The model returns an access-based price per treatment cycle, aligned to the 28-day model cycle before substitution into the cost-utility model. Sources: ASCERTAIN pricing model [33,34]; inavolisib dose, tablet strength and treatment-until-progression from the FDA Prescribing Information and EMA EPAR; treatment duration (9.2 months) from the EMA EPAR; incidence derivation from the EMA Risk Management Plan.*

## Appendix G. Probabilistic sensitivity analysis: distributions and parameterisation

This appendix documents how the probability distribution for each uncertain parameter was parameterised for the probabilistic sensitivity analysis. The method-of-moments formulas (Table H1) convert a mean and a standard error into the shape parameters of the assigned distribution. Table H2 records, for each group of parameters, the source of the standard error: whether it was reported by or directly calculable from the source, or assumed. The distinction is important for transparency: only a minority of parameters carry a dispersion measure from their source, and the remainder rely on assumed standard errors that are themselves tested in the deterministic sensitivity analysis.

**Table H1. Method-of-moments formulas used to derive distribution parameters**

| Distribution | Applied to | Shape parameters from mean (m) and standard error (SE) |
|---|---|---|
| **Beta** | Proportions, probabilities, utilities (0-1) | alpha = $m \cdot [(m(1-m)/SE^2) - 1]$ ; beta = $(1-m) \cdot [(m(1-m)/SE^2) - 1]$ |
| **Gamma** | Costs; societal time inputs (informal-care and patient-time hours) | alpha = $m^2 / SE^2$ ; beta = $SE^2 / m$ |
| **Log-normal** | Hazard ratios | mu = ln(m) ; sigma = SE on the log scale = (ln(upper) − ln(lower)) / (2 × 1.96) |
| **Fixed** | List prices, tariffs, structural constants | Not sampled (SE = 0) |

*Adverse-event disutilities were parameterised with a beta distribution fitted to the absolute (positive) value of the decrement and subtracted from the health-state utility in the model. Survival-curve parameters were not parameterised by the method of moments; they were sampled jointly from the variance–covariance matrix of the flexsurv fits using Cholesky decomposition.*

**Table H2. Source of the standard error, by parameter group**

| Parameter group | Distribution | Standard error: source and method |
|---|---|---|
| Hazard ratios (PFS, OS) | Log-normal | CALCULATED from the reported 95% CI on the log scale [14] |
| AE incidences (Gr 3/4) | Beta | CALCULATED from the reported count n/N, binomial SE = $\sqrt{(p(1-p)/n)}$ [14] |
| Baseline proportions (premenopausal, bone mets, 2L chemo) | Beta | CALCULATED from the reported count n/N, binomial SE [6,14] |
| End-of-life cost | Gamma | FROM SOURCE: standard deviation reported directly by Schneider (2020) [18] (the only parameter with a source-reported SD) |

| | | |
|---|---|---|
| Utilities (PFS, PD) | Beta | ASSUMED: SE = 10% of the mean (no dispersion reported) [44] |
| AE disutilities | Beta (on \|value\|) | ASSUMED: SE = 10% of the absolute value [44,45] |
| Unit costs, AE management, resource use | Gamma | ASSUMED: SE = 15–25% of the mean (no dispersion reported) [40] |
| Societal inputs (informal care, productivity, PAID) | Gamma / Beta | ASSUMED: SE = 30% of the mean; informal-care hours a data gap, tested widely in the DSA [40] |
| Survival-curve parameters | Multivariate normal | FROM SOURCE: variance–covariance matrix of the flexsurv fits (Cholesky), not method of moments [43] |
| Drug list prices, NZa tariffs, structural constants | Fixed | Not sampled (administered prices and model constants) |

*CALCULATED = the standard error was computed from a count or interval reported in the source; FROM SOURCE = a dispersion measure was reported directly; ASSUMED = no dispersion was reported and a standard error was assumed as a fixed proportion of the mean, consistent with standard practice and tested in the deterministic sensitivity analysis. Full numerical values of every parameter, its standard error, and its alpha/beta are provided in the model parameter workbook.*

## Appendix H. Access-based price: full scenario analysis

This appendix reports all fourteen scenarios run on the ASCERTAIN pricing model. Each scenario changes a single input relative to the base case; all other inputs are held at the base-case values reported in Appendix F. The access-based price is reported per 28-day cycle (the cost-utility model cycle length), obtained by multiplying the model's per-day output by 28. The base-case price is €6,800.38. The scenarios are grouped by the type of input varied: the value-based premium parameters, the operational profit margin, and the parameters that determine the size of the treated patient population.

**Table I1. Access-based price under all pricing-model scenarios (per 28-day cycle)**

| ID | Scenario (change vs base case) | ABP per 28-day cycle | Direction vs base (€6,800) |
|---|---|---|---|
| — | Base case (minor ATB; no quality-of-evidence penalty; all other value premiums preset; default profit, treatment rate, uptake; no competition; incidence 0.71) | **€6,800.38** | — |
| P1 | Moderate added therapeutic benefit (0.3) | €8,137.78 | Higher (+20%) |
| P2 | Major added therapeutic benefit (0.5) | €9,475.00 | Higher (+39%) |
| P3 | Minor ATB with quality-of-evidence penalty (value floor) | €6,552.71 | Lower (−4%) |
| P4 | No societal-value premium | €5,314.38 | Lower (−22%) |
| P5 | No return-on-public-investment adjustment | €7,543.38 | Higher (+11%) |
| P6a | Low profit margin (10%) | €6,735.11 | Lower (−1%) |
| P6b | High profit margin (50%) | €6,869.69 | Higher (+1%) |
| P7 | Competition (competitors enter years 5 and 7) | €13,832.69 | Much higher (+103%) |
| P8a | Low treatment rate (12%) | €29,427.02 | Much higher (+333%) |
| P8b | High treatment rate (75%) | €5,074.70 | Much lower (−25%) |
| P9a | Fast market uptake | €6,597.86 | Lower (−3%) |
| P9b | Breakthrough market uptake | €6,185.80 | Lower (−9%) |
| P10 | Lower-bound incidence (0.44 per 100,000) | €11,664.55 | Much higher (+72%) |

*ATB = added therapeutic benefit. The P-prefixed scenario labels (P1 to P10) denote the access-based pricing scenarios and are numbered independently of the cost-utility scenarios (S1 to S13). All prices are per 28-day*

*cycle (the model's per-day output multiplied by 28); the list price is €13,695 per 28-day cycle for comparison. Scenarios P1–P6 vary the value-based premium and profit parameters and move the price within a relatively narrow band; scenarios P7, P8, and P10 vary the parameters that determine the size of the treated patient population and have the largest effect, because the fixed capitalised R&D cost is spread across that population. The competition scenario (P7) raises the price because a smaller share of patients receiving inavolisib concentrates the fixed R&D cost; this reflects the model's cost-allocation logic, not a market-price effect. In every scenario the access-based price remains above the threshold price required for cost-effectiveness at €80,000 per QALY.*

## Appendix I. Cost-utility analysis: full scenario results

This appendix reports the deterministic incremental cost-effectiveness ratio (ICER) for every pre-specified scenario (Table 4), from the societal perspective unless otherwise stated. Consistent with the analysis plan, only the scenarios whose ICER differs substantially from the base case (S10, S11, and S12) are discussed in the main text and reported in Table 7; the remaining scenarios are reported here for completeness. Across all thirteen scenarios the ICER ranged from €468,437 (S3, a 60% price discount) to €1,118,735 (S7, palbociclib capsule formulation), and in no scenario did the ICER fall below the €80,000 per QALY threshold. The cost-component scenarios (S4 to S9) changed the ICER by less than 1% because the inavolisib acquisition cost dominates the incremental cost; the pricing-discount scenarios (S1 to S3) and the survival-extrapolation scenarios (S10 to S12) produced the largest movements.

**Table J1. Deterministic ICER for all pre-specified scenarios**

| Scenario | Description | ICER (€/QALY) | vs base |
|---|---|---|---|
| **Base** | Deterministic, societal perspective | **€1,109,246** | reference |
| S1 | Pricing model, 25% discount on inavolisib acquisition | €841,149 | -24% |
| S2 | Pricing model, 40% discount on inavolisib acquisition | €682,040 | -39% |
| S3 | Pricing model, 60% discount on inavolisib acquisition | €466,965 | -58% |
| S4 | End-of-life cost: Van Dijk (€63,914) instead of Schneider | €1,107,696 | -0% |
| S5 | Second-line capecitabine reduced to 5 cycles | €1,108,466 | +0% |
| S6 | Second-line capecitabine increased to 9 cycles | €1,108,168 | +0% |
| S7 | Palbociclib 125 mg capsule instead of tablet | €1,118,735 | +1% |
| S8 | Bone-metastasis proportion 45% (real-world) instead of trial 3.1/3.7% | €1,108,947 | +0% |
| S9 | Fulvestrant administration cost at half the subcutaneous reference | €1,107,429 | -0% |
| S10 | Progression-free survival log-logistic instead of generalised gamma | €835,926 | -25% |
| S11 | Overall survival log-normal instead of log-logistic (optimistic tail) | €759,775 | -32% |
| S12 | Overall survival Gompertz instead of log-logistic (pessimistic tail) | €1,070,405 | -4% |
| S13 | Healthcare payer perspective (excludes societal costs) | €1,111,376 | +0% |

*ICER = incremental cost-effectiveness ratio. All values are deterministic and from the societal perspective except S13 (healthcare payer). Percentages are relative to the base-case ICER of €1,109,246 per QALY. All scenario ICERs are computed from the model by changing the relevant input (price multiplier, end-of-life cost source, capecitabine cycle count, palbociclib formulation, bone-metastasis proportion, fulvestrant administration cost, survival distribution, or perspective) and reading the resulting ratio.*