Strengthening the national Health Technology Assessment framework for Greece

Economic Assessment – Pilot

WHO Europe and SAG

14 January 2025

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HELLENIC REPUBLIC
Ministry of Health

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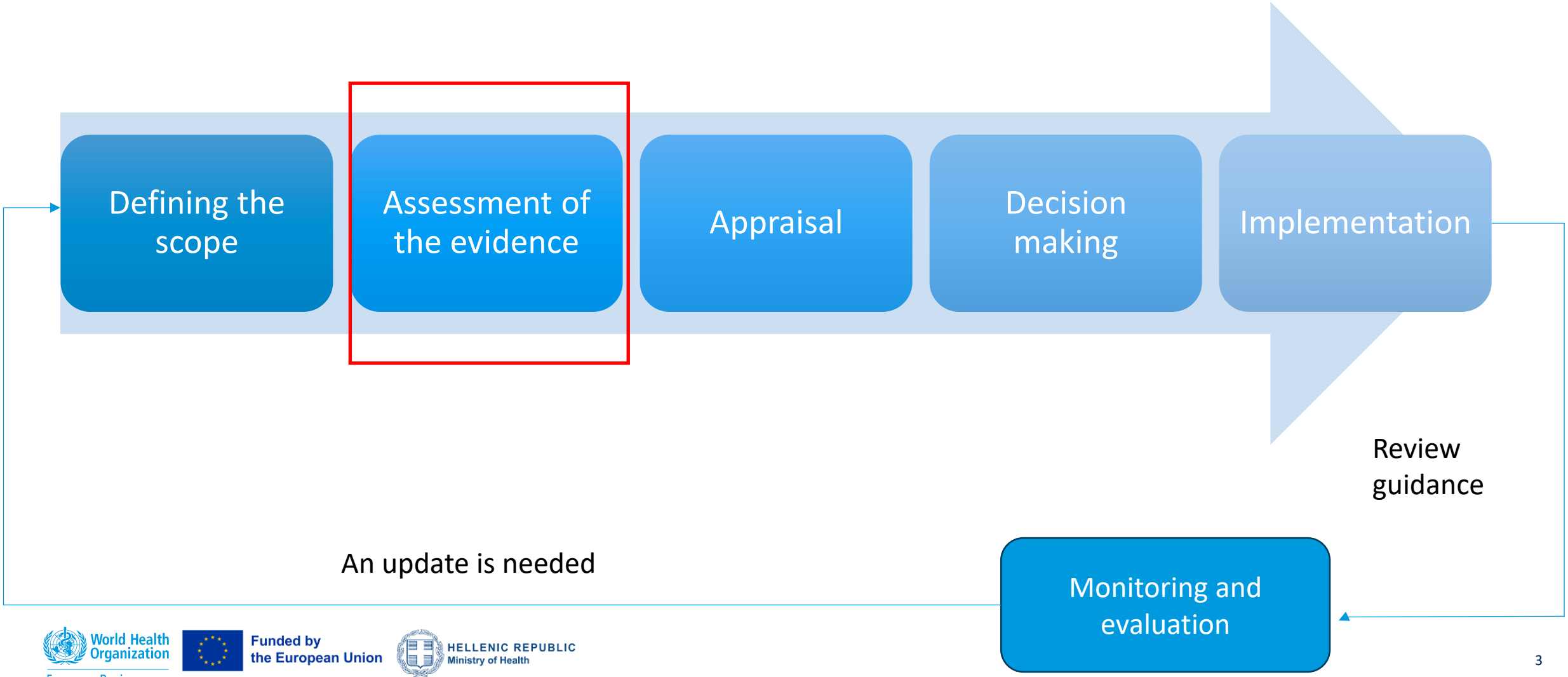
Agenda (Greek timings)

16:00-16:10	**Welcome, agenda, and objectives**
16:10-16:20	**Overview of economic assessment process and methods**
16:20-16:50	**Pilot: Understanding the model and inputs**
16:50-17:20	**Pilot: Understanding the extrapolation and sensitivity analyses**
17:20-17:50	**Pilot: Budget impact and other considerations**
17:50-18:00	**Next steps**

The process of all Health technology assessments (HTAs)



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Objectives

To apply the new HTA economic assessment guidance to the Truqap (capivasertib) submission, critically assessing relevance and accuracy in the Greek context.

By the end of this session, participants will be able to:

- Have an insight into the economic evidence available for capivasertib for treatment of ER-positive, HER2-negative locally advanced or metastatic breast cancer in the public domain.
- Review the economic evidence dossier submitted:
  - For the cost-effectiveness of capivasertib; and
  - For the budget impact of capivasertib if approved/ considered for reimbursement.

Economic assessment process: Recap

Process overview

- **Purpose**: Objective, research-based evaluation of economic evidence for efficient and appropriate resource use.
- **Methodology**:
  - Based on draft Greek HTA methods guidance.
  - Emphasizes transparency, independence, and traceability of evidence and in line with EU HTAR guidance.
- **Economic Assessment**:
  - After clinical assessment determines added therapeutic value:
    - If **Major/Substantial/Moderate/ minor added value** → triggers full cost-effectiveness analysis.
    - If **No added value** → cost-minimization approach.
- **Stakeholder Involvement**:
  - Economic assessment conducted by the HTA body
  - Clinical and patient experts consulted during draft report and review final assessment report.

HTA Process Guidance- medicinal products – National HTA framework
DRAFT

Technical Validation: Checks completeness of application, references, and whether the health economic analysis has been submitted in Excel format with the possibility to change relevant parameters.

- All inputs in the model must be fully editable, and in the event of changes, the model must automatically update all the results, sensitivity analyses

Final summary of report published with plain-language summary (confidential info redacted).

Economic assessment methods: Recap

Methods overview

Purpose: Ensure new medicinal products provide good value for money for the Greek healthcare system.

When Required:

- Full cost-effectiveness evaluation for products with ***added therapeutic value***.
- Cost-minimization analysis for products with ***no added therapeutic value*** (requires robust non-inferiority trials).

Role in Decision-Making: Supports pricing and reimbursement negotiations alongside other mechanisms (e.g., rebates, clawbacks).

Reference Case: Standardized approach for consistency across evaluations.

Informed by EU best practices and adapted to Greek context.

HTA Methods Guidance for Greece-medicinal products *DRAFT*

Key Components of Economic Evaluation

Type of Analysis:

- **Cost-comparison**: For equivalent health outcomes.
- **Cost-utility**: For differences in outcomes (measured in QALYs).

Perspective: Greek health system (pharmaceutical budget + broader healthcare perspective).

Model Specifications:

- Use Excel-based models; transparent, adaptable to Greek data.
- Lifetime time horizon; QALYs preferred (EQ-5D-5L instrument).

Costs & Thresholds:

- Use Greek-specific costs; adjust foreign data if needed.
- Base threshold: €27,117/QALY (range €10,000–€100,000/QALY).

Discount Rate: 3.5% (base case).

Uncertainty Handling:

- Deterministic & probabilistic sensitivity analyses

Budget Impact:

- 5-year forecast of financial consequences for adoption vs. non-adoption

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Economic Assessment: Pilot

Framing the economic assessment – extrapolating survival curves

- Starting point for the economic evaluation (based on a partitioned survival model) is the extrapolation of clinical outcomes beyond the trial evidence.
- Company estimated long-term progression free survival by fitting parametric curves to the patient level data in the placebo + fulvestrant arm from CAPitello-291
- Note this is in line with the company's global model, where ***fulvestrant is the reference*** against other comparator treatments in the network meta-analysis
- The following base-case extrapolation models were selected for the post-CDK4/6 inhibitor AKT-altered population:

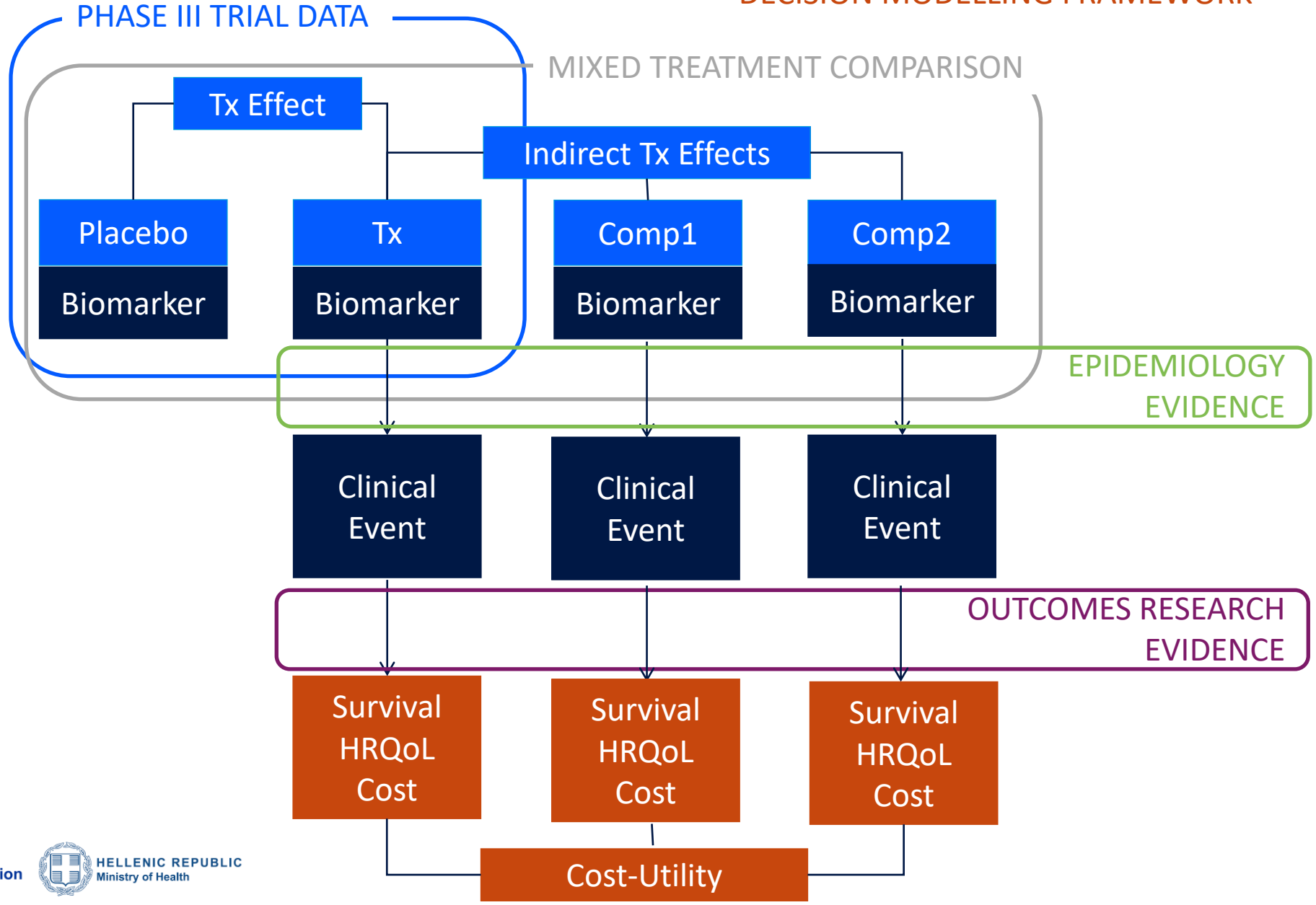
--> Overall Survival (OS): Weibull distribution

--> Progression-Free Survival (PFS): Log-normal distribution

- *"These models provided the most appropriate balance between fit to the observed Kaplan–Meier (KM) curves and clinically plausible long-term behaviour."*
- *"More flexible or heavy-tailed models (e.g., log-logistic, generalised gamma) were excluded due to implausible long-term predictions."* (NICE preferred log-logistic model for progression free survival)
- **NOTE**: SOLAR-1 not included in NMA evidence network - alpelisib + fulvestrant efficacy estimated using an anchored indirect treatment comparison (ITC) involving fulvestrant as the common comparator to derive HRs for PFS and OS in the PIK3CA-mutated population
- **NOTE**: Proportional hazards assumption retained (no time-varying HR options) (also no treatment waning assumed)

Recall: in the CAPitello-291 trial, in the PI3K/AKT-altered population, capivasertib plus fulvestrant significantly improved **progression-free survival** (median 7.3 months; 95% confidence interval [CI] 5.5 to 9.0) compared with placebo plus fulvestrant (median 3.1 months; 95% CI 2.0 to 3.7), but **OS improvement not statistically significant** (hazard ratio 0.69; 95% CI 0.45 to 1.05)

DECISION MODELLING FRAMEWORK



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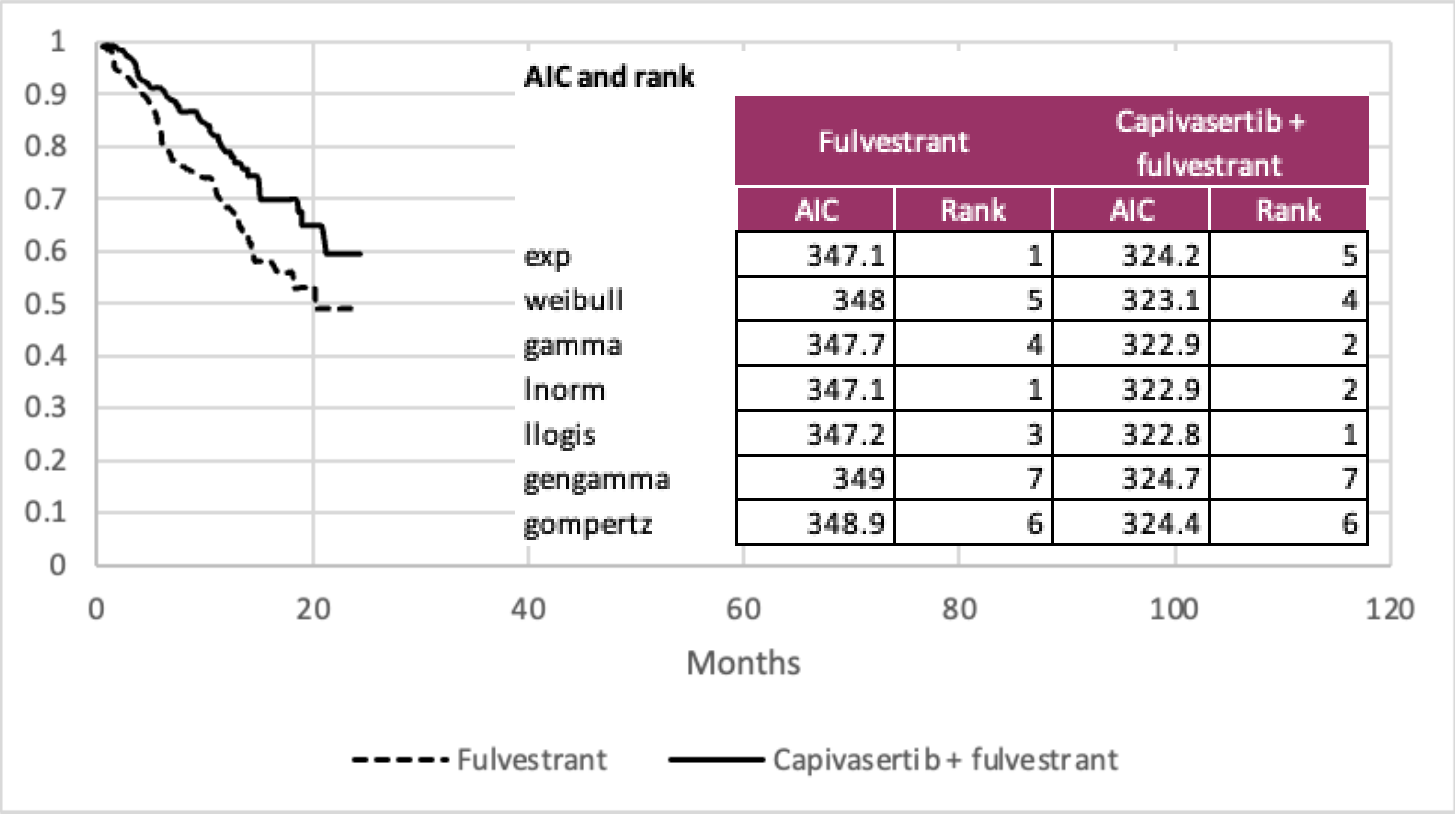
Overall survival – model fitting



AIC and rank

	Fulvestrant		Capivasertib + fulvestrant	
	AIC	Rank	AIC	Rank
exp	347.1	1	324.2	5
weibull	348	5	323.1	4
gamma	347.7	4	322.9	2
lnorm	347.1	1	322.9	2
llogis	347.2	3	322.8	1
gengamma	349	7	324.7	7
gompertz	348.9	6	324.4	6

Very small differences in model fit based on Akaike's Information Criterion (AIC)

AIC is a statistical measure used for assessing models. It balances goodness-of-fit with the number of variables used. Smaller AIC values indicate better model fitting.

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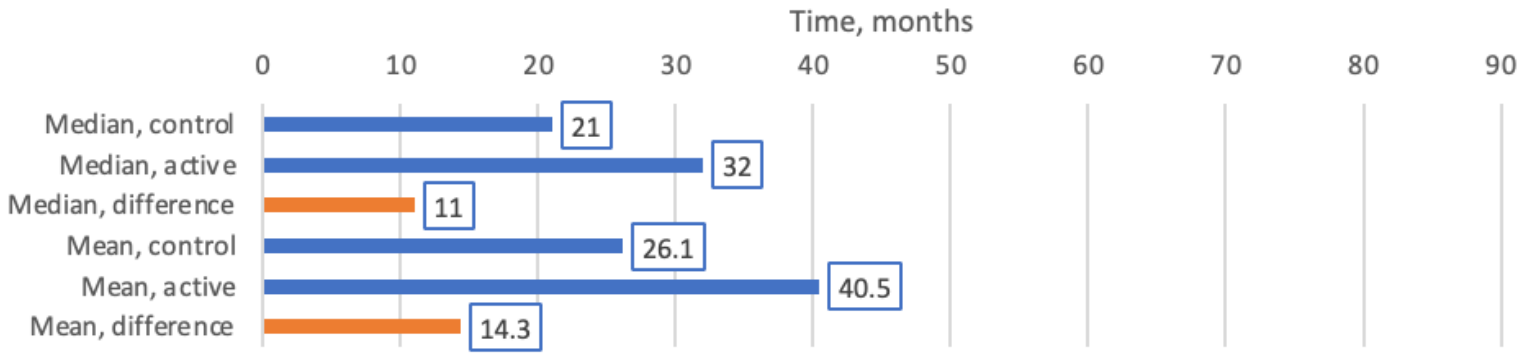
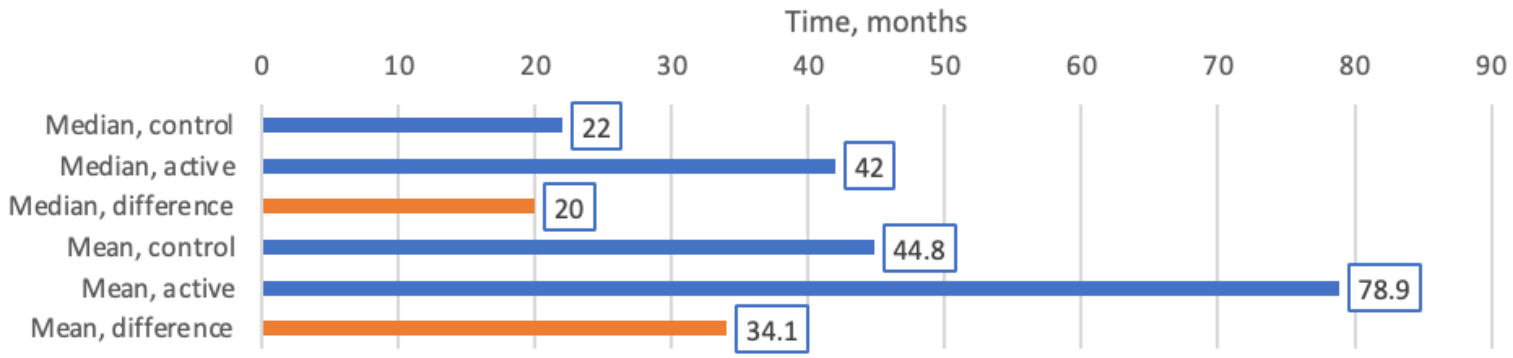
Overall survival – Weibull versus log-normal

Weibull



Log-normal



Huge differences in OS estimates between Weibull and log-normal curves due to behaviour in the tail. Fully support the company's choice of curve in this context.

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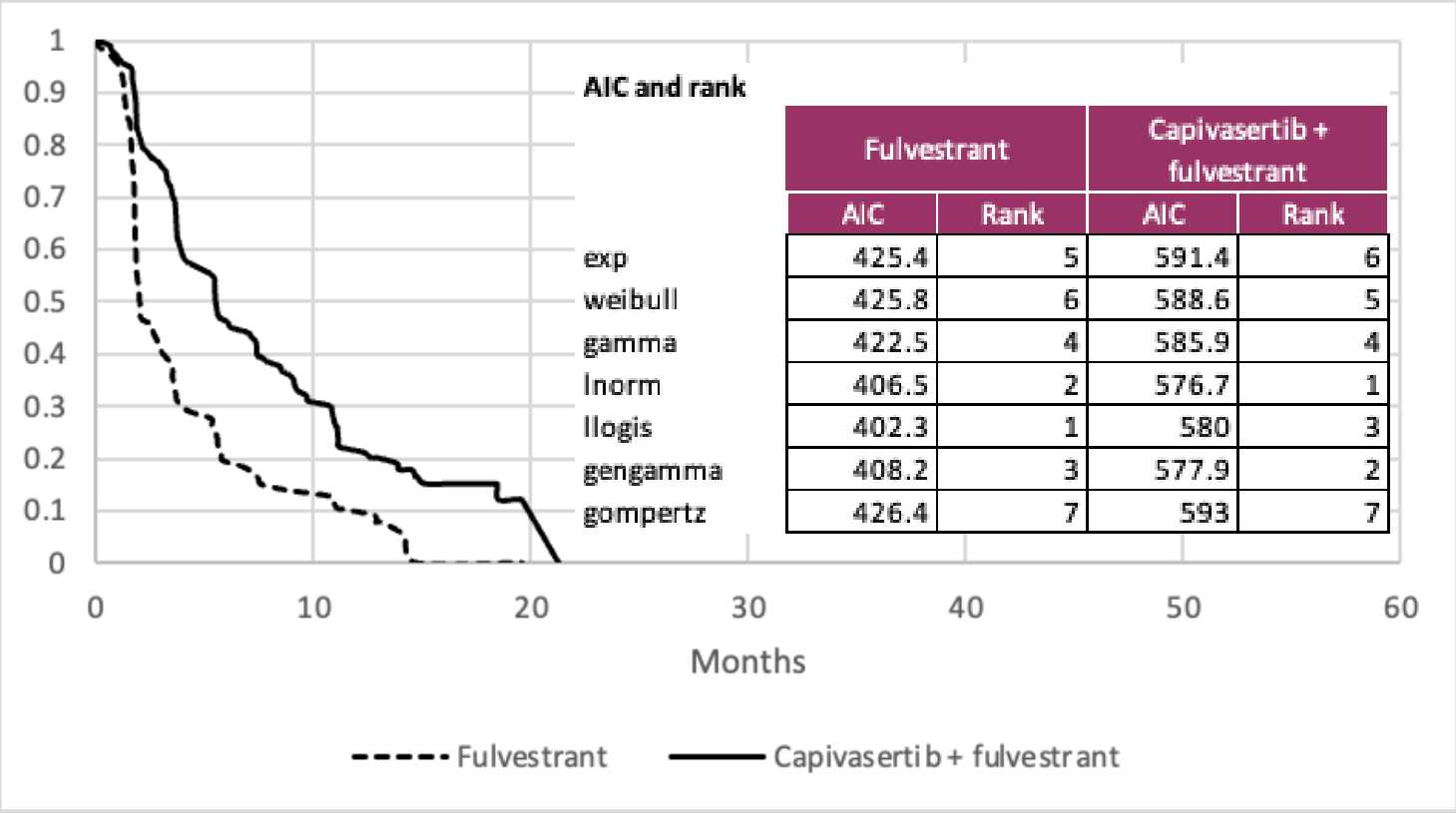
Progression free survival – model fitting



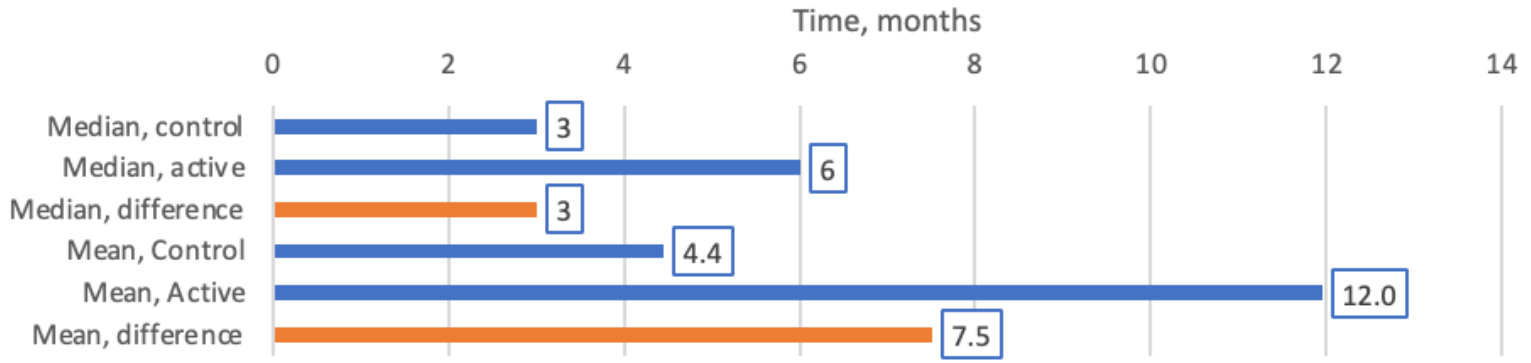
AIC and rank

	Fulvestrant		Capivasertib + fulvestrant	
	AIC	Rank	AIC	Rank
exp	425.4	5	591.4	6
weibull	425.8	6	588.6	5
gamma	422.5	4	585.9	4
lnorm	406.5	2	576.7	1
llogis	402.3	1	580	3
gengamma	408.2	3	577.9	2
gompertz	426.4	7	593	7

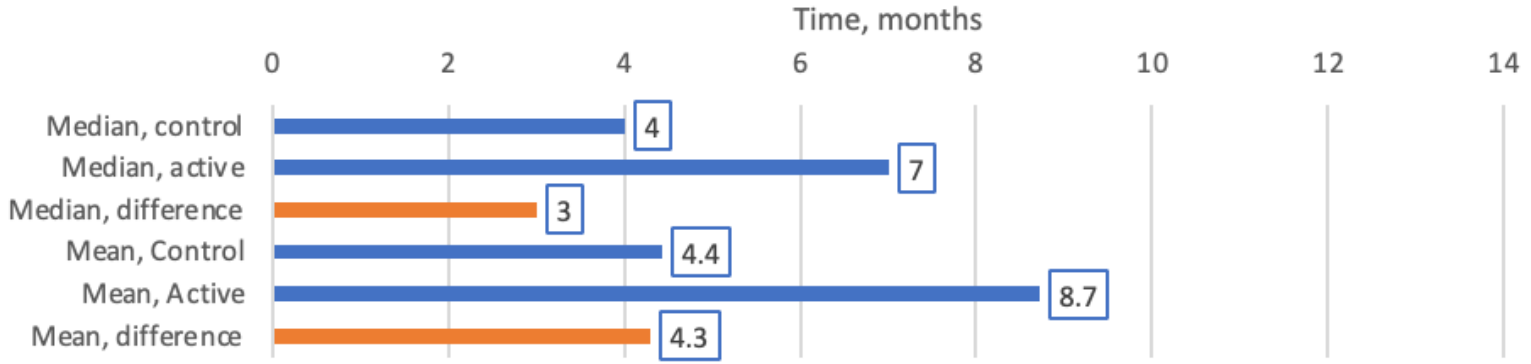
Difference in AIC are less minor for PFS?

Progression free survival – log-normal versus Weibull

Log-normal



Weibull



Differences between log-normal and Weibull are much less profound for PFS. This is due to the maturity of the curves. **(Why not just use the KM curves?)**

Partitioned survival models: an overview

- **A partitioned survival model** is an economic model used to follow a **theoretical cohort over time.**
- The cohort is distributed across **exhaustive and mutually exclusive health states**
- Unlike a **Markov model**, state membership is **not determined by transition probabilities**
- The proportion of patients in each state is estimated using **parametric survival equations**
- These models are frequently used to evaluate **advanced cancer treatments**

Key inputs:

- OS curve
- PFS curve
- Costs and utilities assigned to each health state
- Time horizon
- Cycle length

Survival curves are usually derived from:

- Clinical trial data
- Parametric survival extrapolations

Model details and structure

- The model consists of three health states for progression-free, progressed disease and death.
- Movements across health states are determined by the underlying PFS and OS survival curves rather than by explicit transition matrices.
- The cycle length used is 1 month. Half cycle correction is applied.
- A discount rate of 3.5% was applied to both costs and health outcomes.
- In the base case, a time horizon of 20 years is used.
- At each model cycle:
  - The PF proportion is taken from the log-normal PFS curve.
  - The alive proportion is taken from the Weibull OS curve.
  - The PD proportion is calculated as the difference between OS and PFS.
  - The death proportion accumulates according to the decline in OS.
- No additional structural assumptions (e.g., treatment waning, cure fractions, post-progression adjustments, or tunnel states) are applied in the base case.
- For comparator treatments (e.g., alpelisib + fulvestrant, everolimus + exemestane), transition probabilities are generated in the same manner.

- **Objective**: to determine the cost-effectiveness of capivasertib in combination with fulvestrant for treating patients with HR+ / HER2- locally advanced or metastatic breast cancer (aBC) and one or more PIK3CA/AKT1/PTEN-alterations, following recurrence or progression on or after an endocrine-based regimen.
- The base-case analysis considers costs and health effects from the perspective of the health care payer (EOPYY) in Greece.

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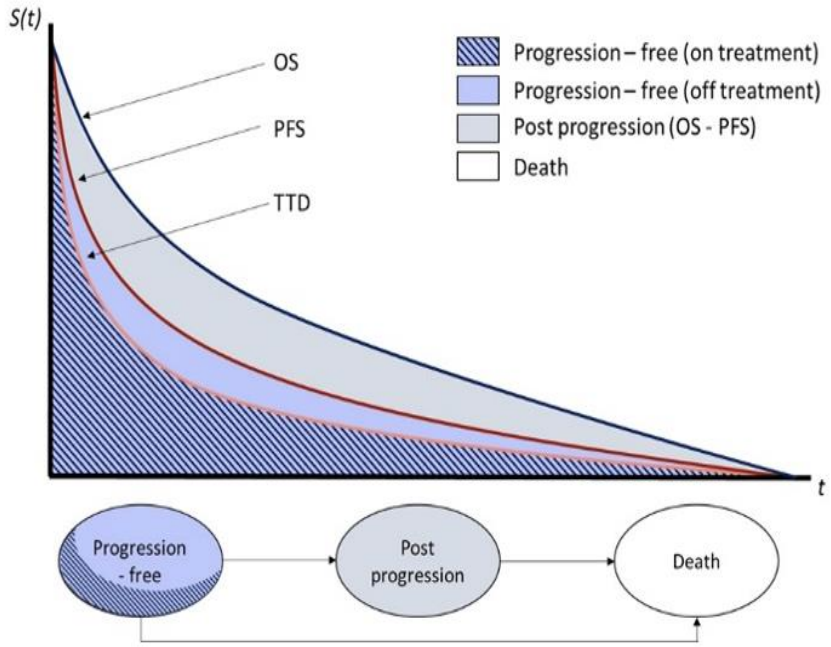
Overview of the model



- PFS and OS curves are extrapolated to the model time horizon.
- These survival curves are used to **partition the patient cohort** across three health states (progression-free, post-progression, death).
- **Progression-free state occupancy** is calculated as the **area under the PFS curve**
- **Post-progression state occupancy** is calculated as the **area between the OS and PFS curves**
- **Health state proportions per cycle** are calculated as:
  - Progression-free = **PFS**
  - Post-progression = **OS – PFS**
  - Death = **1 – OS**

Findings (Altered prior CDK population)

Outcome	Capivasertib + Fulvestrant	Fulvestrant	Everolimus + Exemestane
Life-years (LYs)			
Progression-free LYs	0.95	0.37	0.61
Progressed-disease LYs	2.17	1.71	1.29
Total LYs	3.12	2.08	1.90
QALYs			
Progression-free QALYs	0.73	0.29	0.47
Progressed-disease QALYs	1.57	1.25	0.94
Total QALYs	2.30	1.54	1.41
Costs by health state (€)			
Costs in PF state	€68,370	€1,663	€15,031
Costs in PD state	€10,120	€7,732	€7,615
Costs by category (€)			
Drug acquisition costs (total)	€67,825	€1,588	€14,837
Administration costs	€266	€49	€155
Disease management/ resource use	€1,170	€899	€699
Biomarker testing costs	€171	€0	€0
Subsequent treatment costs	€7,981	€5,789	€5,878
Adverse event management costs	€46	€2	€0
End-of-life (terminal care) costs	€1,030	€1,068	€1,077
Total healthcare costs	€78,489	€9,394	€22,646

Comparison	Incremental Costs (€)	Incremental QALYs	ICER (€ / QALY)	Incremental LYs	ICER (€ / LY)
vs Fulvestrant	+€69,095	+0.77	€89,930 / QALY	+1.04	€66,667 / LY
vs Everolimus + Exemestane	+€55,843	+0.89	€62,779 / QALY	+1.22	€45,875 / LY

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Findings (PIK3CA prior CDK population)

Outcome	Capivasertib + Fulvestrant	Alpelisib + Fulvestrant
Life-years (LYs)		
Progression-free LYs	0.74	0.55
Progressed-disease LYs	2.09	1.65
Total LYs	2.84	2.20
QALYs		
Progression-free QALYs	0.57	0.43
Progressed-disease QALYs	1.52	1.20
Total QALYs	2.09	1.63
Costs by health state (€)		
Costs in PF state	€54,136	€19,905
Costs in PD state	€10,155	€9,940
Costs by category (€)		
Drug acquisition costs (total)	€53,647	€19,498
Administration costs	€210	€153
Disease management / resource use (excl. testing)	€1,119	€884
Biomarker testing costs	€171	€171
Subsequent treatment costs	€8,042	€8,025
Adverse event management costs	€60	€47
End-of-life (terminal care) costs	€1,041	€1,065
Total healthcare costs	€64,291	€29,845

Comparison	Incremental Costs (€)	Incremental QALYs	ICER (€ / QALY)	Incremental LYs	ICER (€ / LY)
Vs Alpelisib + Fulvestrant	+€34,446	+0.46	€74,369/ QALY	+0.63	€54,489/ LY

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Input parameters in pharmacoeconomic models – overview and key points

- Key input parameters in a pharmacoeconomics model
  - Efficacy and safety data (AND assumptions) for the intervention + comparators
  - Health-Related Quality of Life: measurement, utility values, adjustments for age
  - Resource use data (i.e. types of resources used for the management of patients under each alternative + the quantity of each resource, across time). Typically, these will refer, among others, to:
    - Pharmaceuticals, or other health technologies used for the treatment or monitoring of patients
    - Treatment administration
    - Laboratory work and/or health care professional visits/consultations throughout the time horizon of the model
    - Hospitalizations or other interventions for the management of the disease or the adverse effects of treatment
    - Supportive care, palliative care or other forms of care
  - Unit costs for resources – these need to reflect the third-party payer, as per the preferred approach for the Greek HTA submissions

- Key input parameters must reflect the local setting to the greatest possible extent
- In most (if not all) cases, MAHs will adapt a global model to the local setting. Making sure that the parameters have been adjusted to the local setting (and not just carried forward from the global model) is essential
- This is especially important for parameters such as resource use elements, which can sometimes be overlooked

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Input parameters in pharmacoeconomic models – overview and key points

- Things to consider when reviewing the pharmacoeconomics model (this particular one as well as any submission model in general):
  - Does the choice of intervention and comparators reflect the PICOs of the clinical part of the submission? (remember that this includes not just the choice of treatment(s) but also elements like patient populations, dosage, previous treatments etc.)
  - In many cases, hypotheses must be made even in the clinical part of the model (e.g. extrapolations, as discussed by Andy later on). Don't take them at face value. Do they seem reasonable? Are they supported by the literature or previous empirical work?
  - Utility estimates: as country-specific value sets for the EQ-5D are not currently available for Greece, utilities will be typically estimated using value sets from other countries. Is the country choice justified by relevance (rather than chosen by convenience)? This also applies to disutilities of events etc. The absence of a country-specific dataset for Greece renders the sensitivity analysis on HRQoL data a highly important aspect
  - Drug acquisition costs: those should reflect the perspective of the third-party payer, i.e., the costs that the 3PP actually pays, in principle (as final paybacks or confidential discounts cannot be assessed at this stage – the latter, however, can be evaluated under certain conditions). Questions to ask: are all mandatory discounts uniformly applied across the intervention and comparators? (as legally mandated for each case of drug, e.g. hospital or community based). Are administration costs properly considered? Is the dosage according to the label for the PICO? For treatments where a generic is available, was its price used in the model?

- The models typically utilize scenario approaches for some of the variables used (i.e. alternative baseline values can be used, either as built-in choice, or user input)
- In case the evaluator of the model wishes to test alternative baseline values (i.e. alternative approaches or hypotheses) this can be done in the model, without "damaging" the file or creating irreversible changes
- This approach can be really useful to sense-check consistency

Input parameters in pharmacoeconomic models – overview and key points (continued)

- Things to consider when reviewing the pharmacoeconomics model (this particular one as well as any submission model in general):
  - Does the resource use pattern reflect the local setting? Adapting a global model to a country setting may present challenges such as differences in the modes of service delivery (e.g. roles of health professionals, services that are available or not etc.) or even treatment approaches
  - Regarding treatment patterns (e.g. percentages of patients in a given treatment regimen: how was this calculated? Market shares? Published literature? Expert opinion?)
  - Consider if the resource use presented in the model (a) is appropriate for Greece [e.g. are there missing elements of care?] (b) has been evaluated correctly [e.g. how was the volume of each resource measured or sourced?]
  - Do the unit costs of resources reflect the third-party payer? Was this properly documented (i.e. did the developers use the official price lists and reference the respective elements). This can be influential and result to changes in the results model if not done correctly
  - Costs for interventional procedures or adverse events should also reflect the 3PP. Official tariffs should be used in priority (as in most cases these represent episodes of care that have been costed by the system – e.g. through DRGs) and, if not available, complemented by literature data
  - Are price adjustments for different time periods done correctly?

- The models typically utilize scenario approaches for some of the variables used (i.e. alternative baseline values can be used, either as built-in choice, or user input)
- In case the evaluator of the model wishes to test alternative baseline values (i.e. alternative approaches or hypotheses) this can be done in the model, without “damaging” the file or creating irreversible changes
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Deterministic sensitivity analysis

- Assesses how **model results change** when **specific input parameters are varied**
- Parameters are varied using **pre-defined ranges**
  - Often based on **published uncertainty** (e.g. confidence intervals)
- **Univariate DSA**: one parameter varied at time
- **Multivariate DSA**: two or more parameters varied simultaneously
- Results are commonly presented in Tornado diagrams

Key considerations and limitations of DSA

- Limited ability to vary **many parameters simultaneously**
- Univariate DSA should be interpreted **with caution when parameters are correlated**
- Does not fully capture overall parameter uncertainty
- Used primarily for exploratory and structured checks

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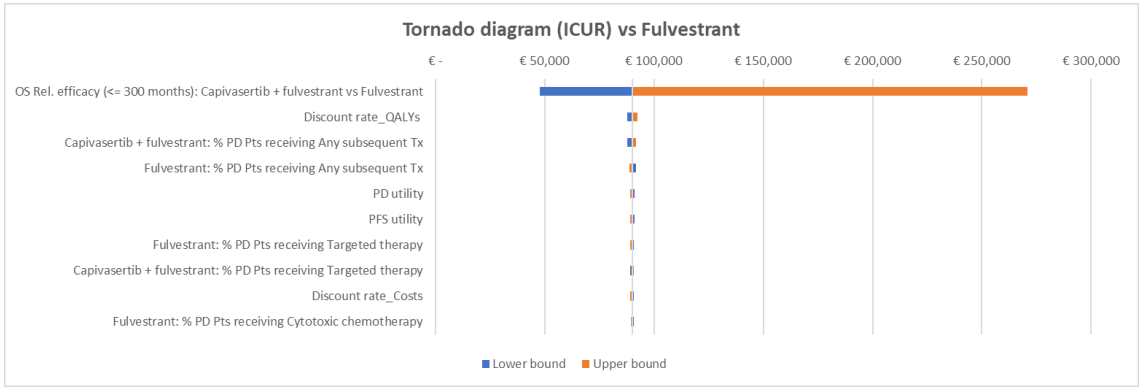
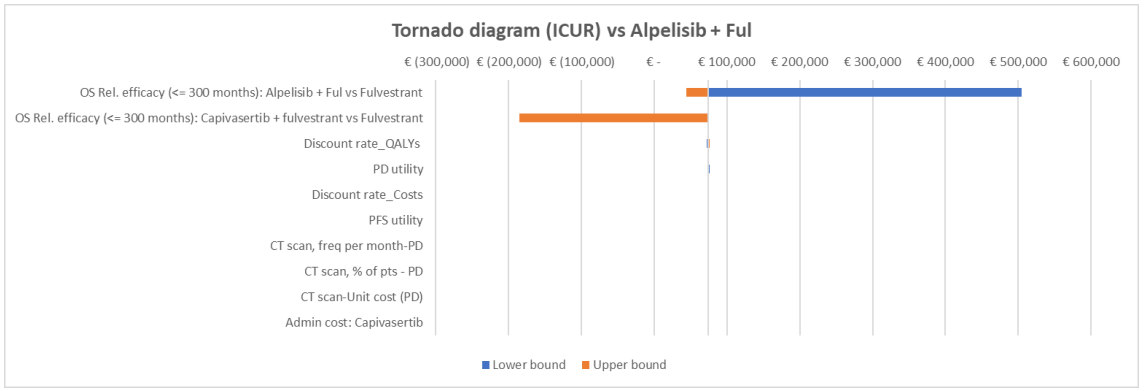
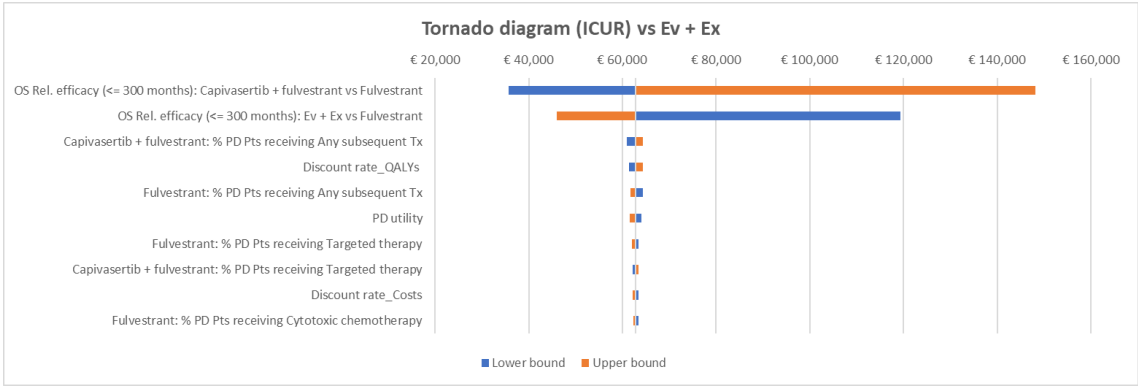
Deterministic sensitivity analysis







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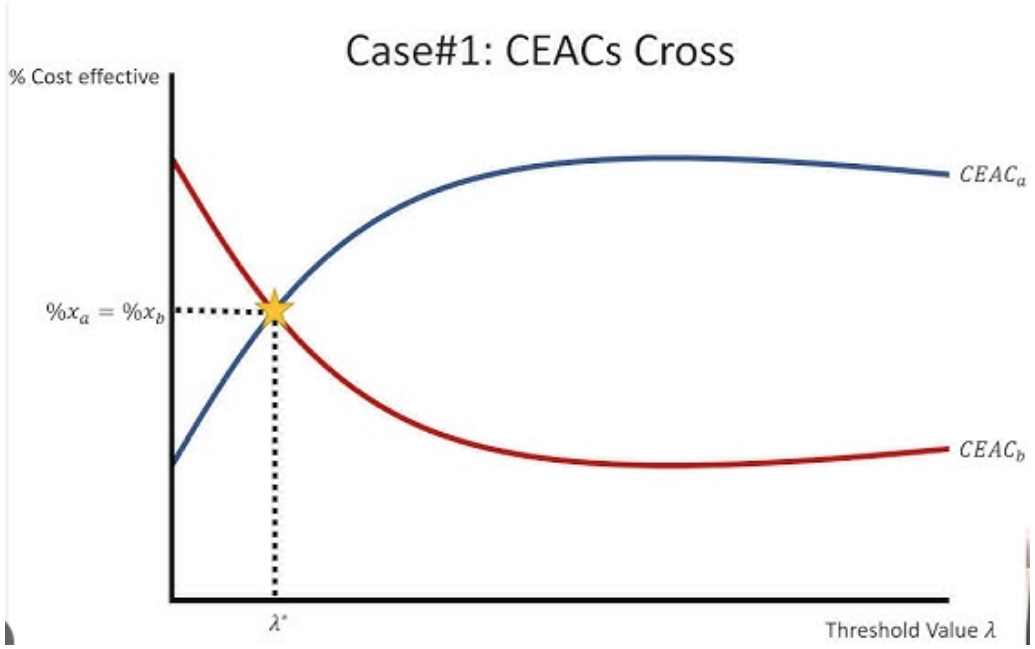
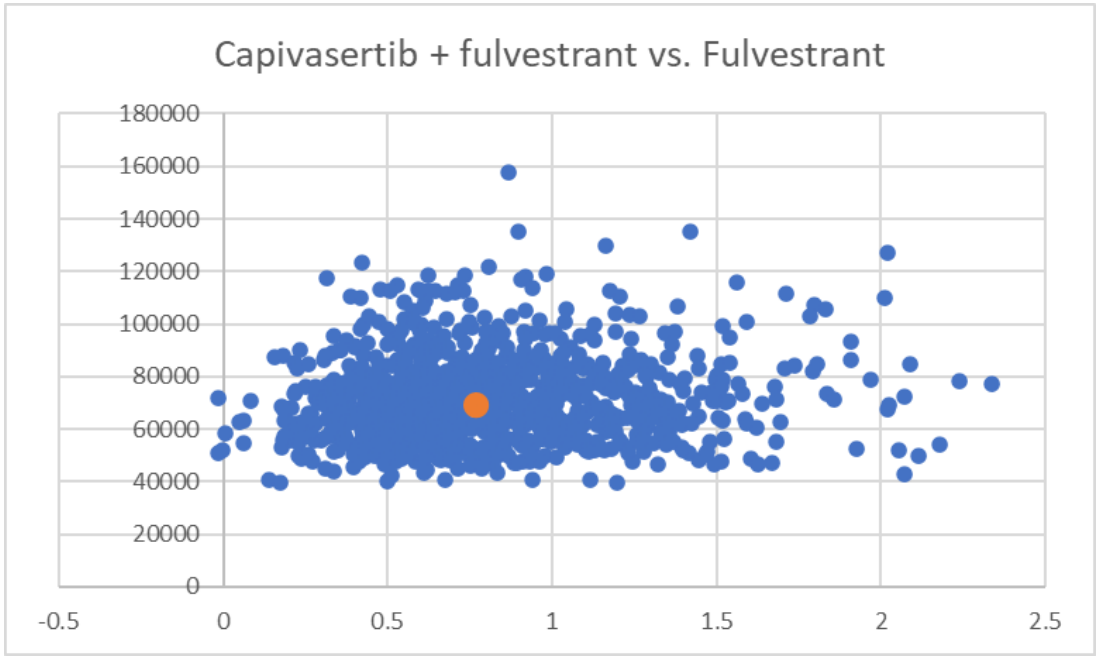
Probabilistic sensitivity analysis

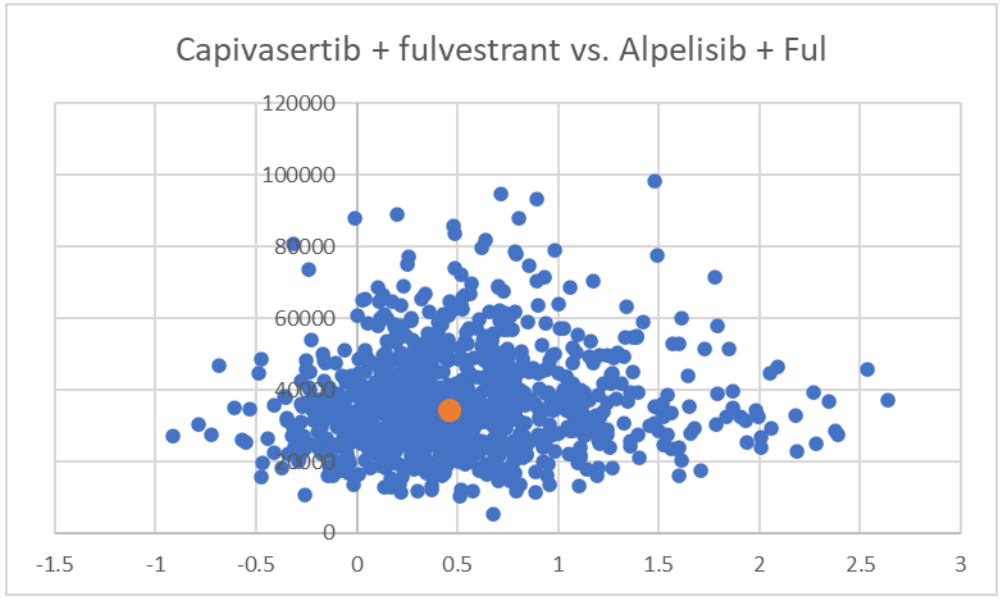
- Quantifies **overall uncertainty** in model results due to **uncertain input parameters**
- Input parameters are represented as **probability distributions**, not fixed values
- **Distributions** reflect uncertainty around point estimates
- **Values** for each parameter are **randomly sampled** from their distributions
- The model is run **many times** (simulations)
- Each run generates costs and health outcomes
- Results form a distribution of outcomes and plotted on a cost-effectiveness plane

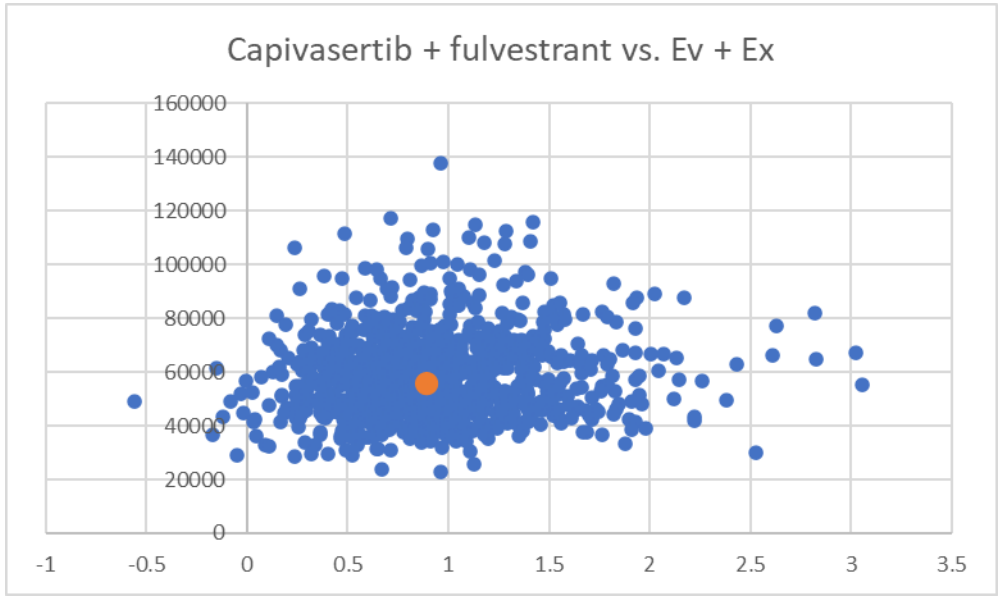
A CEAC shows the **probability that a treatment is cost-effective** compared with an alternative, **across different willingness-to-pay thresholds**.



Probabilistic sensitivity analysis







Budget impact

	Year 1	Year 2	Year 3	Year 4	Year 5
	Recommendation				
Capivasertib + Fulvestrant	64	172	258	258	258
Placebo + Fulvestrant	32	52	57	57	57
Alpelisib + Fulvestrant	64	107	143	143	143
Everolimus + Exemestane	54	99	115	115	115
Total number	215	430	573	573	573
	Non-recommendation				
Capivasertib + Fulvestrant	0	0	0	0	0
Placebo + Fulvestrant	32	43	57	57	57
Alpelisib + Fulvestrant	129	301	401	401	401
Everolimus + Exemestane	54	86	115	115	115
Total number	215	430	573	573	573

Budget Impact Analysis

- Estimates the **change in healthcare spending** from adopting a new intervention
- Assesses **affordability** for the budget holder
- Typically conducted over a **3–5 year time horizon**
- **Key drivers** include population size and eligibility, uptake rate and market share, treatment and health costs,
- Used by decision-makers for **budget planning and resource allocation**

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Budget impact

	Year 1	Year 2	Year 3	Year 4	Year 5
Capivasertib is recommended	€4,350,917	€10,143,731	€14,596,971	€14,714,665	€14,802,550
Capivasertib is NOT recommended	€2,563,776	€5,525,421	€7,456,390	€7,577,771	€7,662,216
Budget impact of the recommendation	€1,787,141	€4,618,310	€7,140,581	€7,136,894	€7,140,334

- This BIM uses the same sources and unit cost assumptions as the CEA for all inputs related to drug acquisition costs, administration, adverse event management, end-of-life care, and biomarker testing.

Discussion

- Is the choice of model and the base case evidence/ analysis & the sensitivity analyses sufficient for decision-making?
- Is there meaningful gain in **survival and QALY gains** across the PICOS or for some of the comparisons to warrant the budget impact/ value for money?
- Is the therapy is considered cost-effective and clinically valuable within the Greek setting for any of the circumstances?

Other considerations

Purpose: Explore non-clinical factors influencing HTA decisions.

Domains to Assess:

- Ethical: Potential benefits and harms for patients, families, and society.
- Legal: Rules and regulations impacted by implementation.
- Social: Equity of access; financial, cultural, and demographic barriers.
- Feasibility: Resource requirements (staff, premises, equipment, IT systems).
- Organizational: Impact on healthcare delivery processes and system structure.

Importance: Provides contextual insights beyond cost-effectiveness and clinical benefit.

Key Frameworks & Guidance

Equity Considerations: Use PROGRESS-Plus framework for systematic stratification (e.g., rural vs. urban, vulnerable groups).

Acceptability: Assess patient and provider perspectives on adoption.

Capacity & Infrastructure: Evaluate readiness for advanced therapies (e.g., ATMPs).

Decision Frameworks: Apply GRADE Evidence-to-Decision (EtD) for integrating values, preferences, and feasibility. Transparent pathway towards appraisal.

Social Value Judgments: Currently absent in Greece; should be developed for future HTA processes.

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Other considerations

Domain	Aspects to consider
Ethical	What are the potential benefits and harms from adopting or not adopting the medicinal product for patients, family, health professionals, society as a whole and other groups?
Legal	Which rules and regulations may influence or be influenced, and in what way, by the implementation of the medicinal product?
Social	Are there groups of patients who currently don't have good access to similar (types of) health technologies? Are there factors – e.g., financial, cultural, socio-demographic – that could prevent a group or person from gaining access to the medicinal product?
Feasibility	What are the requirements for using the medicinal product in terms of human resources (staff mix and skills), premises, equipment and consumables, information systems and maintenance? How do these requirements differ relative to the comparator(s)? To what extent is the health technology likely to be deemed acceptable to patients, healthcare providers and society at large?
Organizational	How may implementing the medicinal product influence or be influenced by the existing healthcare delivery processes and health system structure? What healthcare management challenges and opportunities may the medicinal product bring?

PROGRESS-Plus

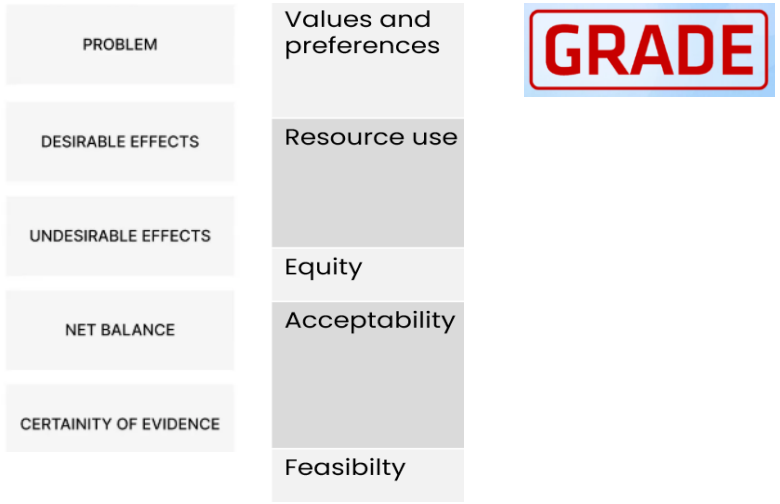
Cochrane Methods Equity

Trusted evidence.
Informed decisions.
Better health.

PROGRESS-Plus is an acronym used to identify characteristics that stratify health opportunities and outcomes.

- **PROGRESS** refers to:
  - Place of residence - where someone lives (e.g. the country, region, city, community and their characteristics, or urban vs. rural settings) comm
  - Race/ethnicity/culture/language
  - Occupation - e.g. unemployment, underemployment, informal employment, and unsafe working condition, as well as type of occupation
  - Gender/sex
  - Religion
  - Education
  - Socioeconomic status
  - Social capital - e.g. social relationships and networks

- **Plus** refers to:
  1) personal characteristics associated with discrimination (e.g. age, disability)
  2) features of relationships (e.g. smoking parents, excluded from school
  3) time-dependent relationships (e.g. leaving the hospital, respite care, other instances where a person may be temporarily at a disadvantage)



HTD – Other considerations

Beyond the clinical and economic evidence, the assessment also explored broader ethical, legal, social, feasibility and organisational factors that may influence the implementation of capivasertib in Greece. These considerations help contextualise the potential impact of introducing or not introducing the technology within the Greek healthcare system. The table below summarises key points across each domain, following the structure proposed in the HTA methodological guidance.

Table 19. **Other considerations relevant to the implementation of capivasertib in Greece**

Domain	Considerations
Ethical	Adoption of capivasertib provides an additional option with clinically meaningful benefit for patients who have progressed after CDK4/6 inhibitors, potentially improving survival and quality of life for patients and their families. Non-adoption may limit access to an effective therapy. Potential harms relate mainly to treatment-related toxicity and the risk that some patients may not derive benefit despite increased costs. Overall, no specific ethical concerns for health professionals or society are anticipated beyond the usual balance between benefit, risk and resource use in oncology.
Legal	The medicinal product fits within existing Greek rules and regulations on reimbursement of oncology medicines and biomarker-guided treatments, including hospital-only provision and use of molecular diagnostics. No changes in legislation are required, and implementation is not expected to conflict with current regulatory frameworks.
Social	Patients in remote or rural areas, or on islands, may have more limited access to molecular testing and specialised oncology centres, which could reduce access to capivasertib compared with patients treated in large urban hospitals. Financial barriers are minimal because hospital oncology medicines are reimbursed without co-payment; however, organisational or geographic factors may still affect equity of access. No specific cultural barriers are anticipated.
Feasibility	Capivasertib is administered orally in combination with intramuscular fulvestrant, requiring no additional premises, equipment or specialist staff beyond current practice. Monitoring and AE management are similar to existing targeted therapies and can be handled within current information systems. Requirements do not materially differ from comparators, and the regimen is expected to be acceptable to both patients and healthcare professionals, given familiarity with endocrine-based treatments.
Organisational	Implementation is not expected to disrupt established care pathways in metastatic breast cancer. The main organisational implication is the need to ensure sufficient molecular testing capacity (AKT/PIK3CA/PTEN) and coordination between oncology and pathology services. This may create some management challenges in centres with limited diagnostic infrastructure but also offers an opportunity to strengthen precision oncology services more broadly within the health system.

Next steps

- Pilot assessment group currently working on the clinical assessment, which will be followed by the economic & other considerations.
- Upcoming final stakeholder workshop, funded through TAEIX/ EC planned for 9th February 2026 – hybrid with Zoom and at the Athens Mariott Hotel.

NICE's Treatment pathway

NICE guidance for HR+ HER2- advanced breast cancer

HR+/HER2- advanced breast cancer

Life threatening/ organ involvement/ organ failure → Chemotherapy (CG81)

First line

Tamoxifen [+ ovarian suppression if pre/peri menopause] (CG81 published 2009)

CDK4/6 inhibitor* + AI:
palbociclib (TA495)
ribociclib (TA496)
abemaciclib (TA563)

Disease progression

Life threatening/ organ involvement /organ failure → Chemotherapy (CG81)

PIK3CA mutation

PIK3CA pathway altered

Second line

Other comparators in NICE scope:
- CDK4/6i + fulvestrant [only if not had previously]
- Exemestane
- Fulvestrant
- Tamoxifen

Everolimus + exemestane (TA421)

Alpelisib + fulvestrant (TA816)

Capivasertib + fulvestrant

Comparators in company submission

Disease progression

Chemotherapy (CG81) or other 3rd line+ treatment

*__Company__: endocrine therapy alone superseded by CDK4/6i + AI in all but small proportion of patients with comorbidities/poor performance status

Adapted from company submission figure 1

NICE

AI, aromatase inhibitor; CDK4/6i, cyclin-dependent kinase 4 and 6 inhibitor; CG, clinical guideline; HER2-, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive; TA, technology appraisal

Patient characteristics

Table 1. Characteristics of the Patients at Baseline.*

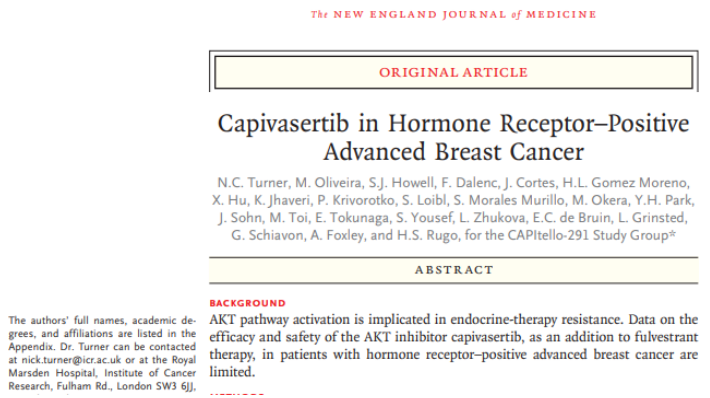
Characteristic	Overall Population		Patients with AKT Pathway–Altered Tumors	
	Capivasertib–Fulvestrant (N=355)	Placebo–Fulvestrant (N=353)	Capivasertib–Fulvestrant (N=155)	Placebo–Fulvestrant (N=134)
Median age (range) — yr	59 (26–84)	58 (26–90)	58 (36–84)	60 (34–90)
Female sex — no. (%)	352 (99.2)	349 (98.9)	153 (98.7)	134 (100)
Race — no. (%)†				
White	201 (56.6)	206 (58.4)	75 (48.4)	76 (56.7)
Asian	95 (26.8)	94 (26.6)	48 (31.0)	35 (26.1)
Black	4 (1.1)	4 (1.1)	2 (1.3)	1 (0.7)
Other	55 (15.5)	49 (13.9)	30 (19.4)	22 (16.4)
Postmenopausal or menopausal status — no. (%)	287 (80.8)	260 (73.7)	130 (83.9)	105 (78.4)
ECOG performance-status score — no. (%)‡				
0	224 (63.1)	241 (68.3)	93 (60.0)	97 (72.4)
1	131 (36.9)	111 (31.4)	62 (40.0)	36 (26.9)
2	0	1 (0.3)	0	1 (0.7)
Site of metastases — no. (%)				
Bone only	51 (14.4)	52 (14.7)	25 (16.1)	16 (11.9)
Liver	156 (43.9)	150 (42.5)	70 (45.2)	53 (39.6)
Viscera	237 (66.8)	241 (68.3)	103 (66.5)	98 (73.1)
No. of previous therapies for advanced breast cancer — no. (%)§				
0	37 (10.4)	52 (14.7)	12 (7.7)	20 (14.9)
1	235 (66.2)	208 (58.9)	107 (69.0)	79 (59.0)
2	73 (20.6)	77 (21.8)	31 (20.0)	29 (21.6)
3	10 (2.8)	16 (4.5)	5 (3.2)	6 (4.5)
Hormone-receptor status — no. (%)¶				
ER-positive, PR-positive	255 (71.8)	246 (69.7)	116 (74.8)	101 (75.4)
ER-positive, PR-negative	94 (26.5)	103 (29.2)	35 (22.6)	31 (23.1)
ER-positive, with unknown PR status	5 (1.4)	4 (1.1)	4 (2.6)	2 (1.5)
Endocrine status — no. (%)‖				
Primary resistance	127 (35.8)	135 (38.2)	60 (38.7)	55 (41.0)
Secondary resistance	228 (64.2)	218 (61.8)	95 (61.3)	79 (59.0)
No. of previous endocrine therapies for advanced breast cancer — no. (%)				
0	39 (11.0)	54 (15.3)	13 (8.4)	20 (14.9)
1	287 (80.8)	252 (71.4)	131 (84.5)	96 (71.6)
2	29 (8.2)	47 (13.3)	11 (7.1)	18 (13.4)
Previous CDK4/6 inhibitor — no. (%)				
As neoadjuvant or adjuvant therapy	2 (0.6)	5 (1.4)	0	2 (1.5)
As therapy for advanced breast cancer	245 (69.0)	244 (69.1)	113 (72.9)	91 (67.9)
Previous chemotherapy — no. (%)				
As neoadjuvant or adjuvant therapy	180 (50.7)	170 (48.2)	79 (51.0)	67 (50.0)
As therapy for advanced breast cancer	65 (18.3)	64 (18.1)	30 (19.4)	23 (17.2)

CAPItello-291 Trial Summary

The CAPItello-291 was a Phase III, randomized, double-blind trial evaluating the efficacy and safety of capivasertib + fulvestrant versus placebo + fulvestrant in patients with hormone receptor-positive (HR+), HER2-negative advanced breast cancer who had progressed on or after endocrine therapy.

Key Trial Details

- **Population**: 708 patients (pre-, peri-, and postmenopausal women and men)
- **Biomarker subgroup**: 289 patients (40.8%) had **AKT pathway alterations** (PIK3CA, AKT1, PTEN)
- **Prior CDK4/6i therapy**: 69.1% of patients
- **Primary Endpoints**
- **Progression-Free Survival (PFS)**:
  - **Overall population**:
    - Capivasertib + fulvestrant: **7.2 months**
    - Placebo + fulvestrant: **3.6 months**
    - **Hazard Ratio (HR)**: 0.60 (95% CI: 0.51–0.71), **P < 0.001**
  - **AKT pathway–altered subgroup**:
    - Capivasertib + fulvestrant: **7.3 months**
    - Placebo + fulvestrant: **3.1 months**
    - **HR**: 0.50 (95% CI: 0.38–0.65), **P < 0.001**



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Capivasertib in Hormone Receptor–Positive Advanced Breast Cancer

N.C. Turner, M. Oliveira, S.J. Howell, F. Dalenc, J. Cortes, H.L. Gomez Moreno, X. Hu, K. Jhaveri, P. Krivorotko, S. Loibl, S. Morales Murillo, M. Okera, Y.H. Park, J. Sohn, M. Toi, E. Tokunaga, S. Yousef, L. Zhukova, E.C. de Bruin, L. Grinsted, G. Schiavon, A. Foxley, and H.S. Rugo, for the CAPItello-291 Study Group*

ABSTRACT

BACKGROUND

AKT pathway activation is implicated in endocrine-therapy resistance. Data on the efficacy and safety of the AKT inhibitor capivasertib, as an addition to fulvestrant therapy, in patients with hormone receptor–positive advanced breast cancer are limited.

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Turner can be contacted at nick.turner@icr.ac.uk or at the Royal Marsden Hospital, Institute of Cancer Research, Fulham Rd., London SW3 6JJ.

Safety Profile

Most frequent Grade ≥3 adverse events:

Rash: 12.1% (vs. 0.3% in placebo group)

Diarrhea: 9.3% (vs. 0.3%)

World Health Organization European Region

Funded by the European Union

HELLENIC REPUBLIC Ministry of Health

Survival curves

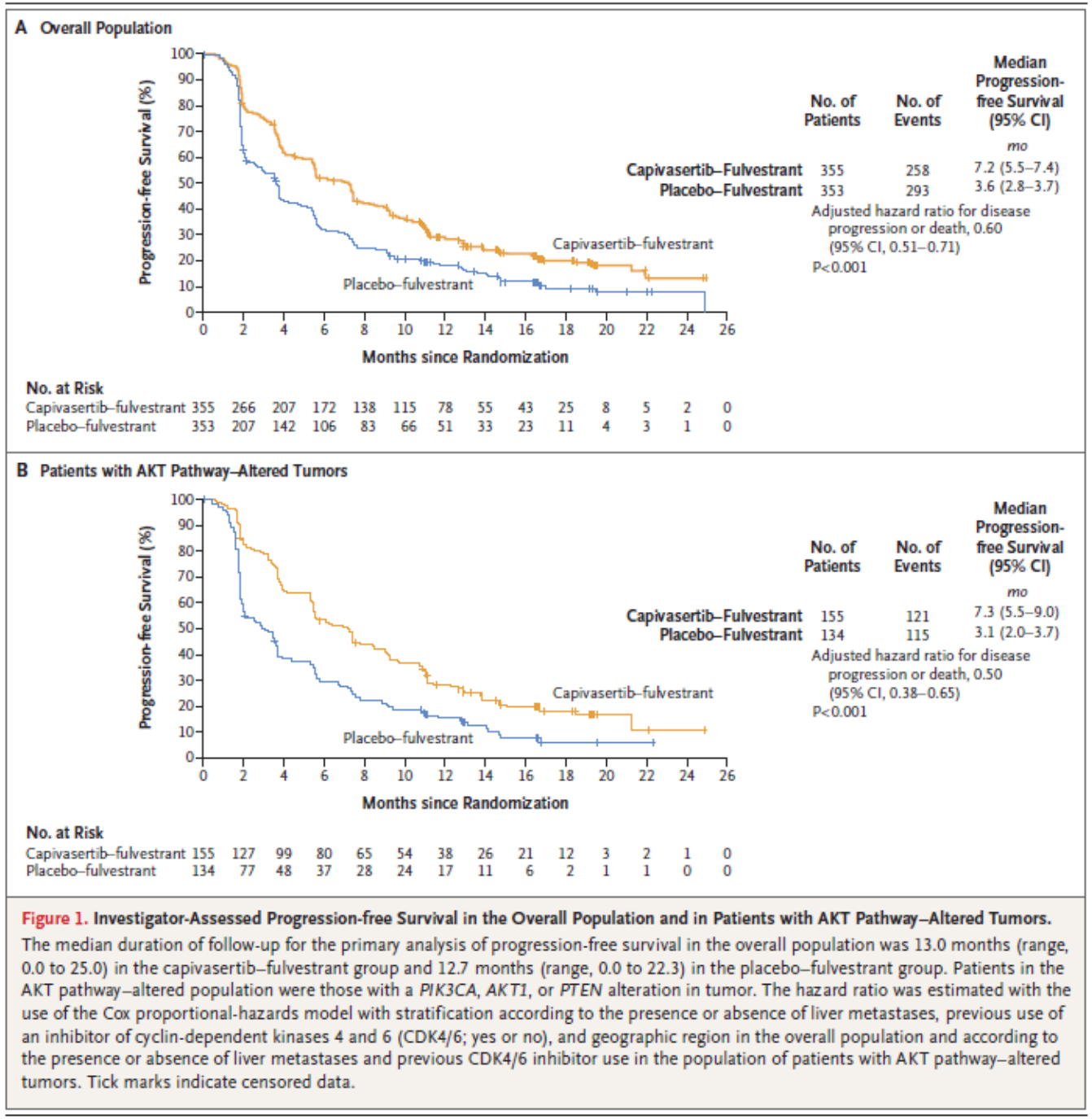


Figure 1. Investigator-Assessed Progression-free Survival in the Overall Population and in Patients with AKT Pathway–Altered Tumors.
The median duration of follow-up for the primary analysis of progression-free survival in the overall population was 13.0 months (range, 0.0 to 25.0) in the capivasertib–fulvestrant group and 12.7 months (range, 0.0 to 22.3) in the placebo–fulvestrant group. Patients in the AKT pathway–altered population were those with a *PIK3CA*, *AKT1*, or *PTEN* alteration in tumor. The hazard ratio was estimated with the use of the Cox proportional-hazards model with stratification according to the presence or absence of liver metastases, previous use of an inhibitor of cyclin-dependent kinases 4 and 6 (CDK4/6; yes or no), and geographic region in the overall population and according to the presence or absence of liver metastases and previous CDK4/6 inhibitor use in the population of patients with AKT pathway–altered tumors. Tick marks indicate censored data.

Overall survival estimates

	1 years	2 years	3 years	5 years	10 years	20 years
Capivasertib + Fulvestrant KM	78.9%	59.4%	0.0%*	0.0%	0.0%	0.0%
Capivasertib + Fulvestrant KM (PIK3CA prior cdk)	*80.9%*	*57.3%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*
Capivasertib + Fulvestrant	78.9%	59.4%	43.5%	22.3%	3.5%	0.1%
Capivasertib + Fulvestrant (PIK3CA prior cdk)	*77.9%*	*56.6%*	*39.6%*	*17.9%*	*1.8%*	*0.0%*
Placebo + Fulvestrant KM	69.3%	48.8%	0.0%*	0.0%	0.0%	0.0%
Placebo + Fulvestrant KM (PIK3CA prior cdk)	*69.8%*	*44.4%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*
Fulvestrant	67.3%	41.9%	25.0%	8.2%	0.4%	0.0%
Fulvestrant (PIK3CA prior cdk)	*66.8%*	*39.9%*	*22.3%*	*6.2%*	*0.2%*	*0.0%*
Alpelisib + Fulvestrant *(PIK3CA prior cdk)*	70.7%	45.4%	27.6%	9.1%	0.4%	0.0%
Everolimus + Exemestane	64.2%	37.8%	21.2%	6.1%	0.2%	0.0%

Note: KM values beyond 2 years appear as 0% because follow-up in CAPItello-291 did not extend sufficiently to observe survival events at later timepoints. These values do not represent true survival but reflect censoring of the KM curve. CDK: cyclin-dependent kinase; KM: Kaplan–Meier; OS: overall survival; PI3Ki: phosphoinositide 3-kinase inhibitors.

For capivasertib + fulvestrant, the base-case OS HR was applied to the extrapolated fulvestrant curve to generate modelled OS probabilities.

Progression free survival estimates

	1 years	2 years	3 years	5 years	10 years	20 years
Capivasertib + Fulvestrant KM	22.3%	0.0%	0.0%	0.0%	0.0%	0.0%
Capivasertib + Fulvestrant KM (PIK3CA prior cdk)	*23.3%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*
Capivasertib + Fulvestrant	25.8%	11.4%	6.3%	2.7%	0.7%	0.1%
Capivasertib + Fulvestrant (PIK3CA prior cdk)	*19.9%*	*7.3%*	*3.5%*	*1.2%*	*0.2%*	*0.0%*
Placebo + Fulvestrant KM	10.3%	0.0%	0.0%	0.0%	0.0%	0.0%
Placebo + Fulvestrant KM (PIK3CA prior cdk)	*12.4%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*	*0.0%*
Fulvestrant	5.6%	1.0%	0.3%	0.0%	0.0%	0.0%
Fulvestrant (PIK3CA prior cdk)	*4.3%*	*0.6%*	*0.1%*	*0.0%*	*0.0%*	*0.0%*
Alpelisib + Fulvestrant *(PIK3CA prior cdk)*	12.9%	3.6%	1.4%	0.4%	0.0%	0.0%
Everolimus + Exemestane	15.4%	5.0%	2.2%	0.7%	0.1%	0.0%

CDK: cyclin-dependent kinase; KM: Kaplan–Meier; PFS: progression-free survival; PI3Ki: phosphoinositide 3-kinase inhibitors.
Note: KM values beyond ~12 months reflect censoring due to limited follow-up.

For capivasertib + fulvestrant, the base-case PFS HR was applied to the fulvestrant curve, ensuring consistency with the relative effect observed in the post-CDK4/6i AKT-altered subgroup.