Strengthening the national Health Technology Assessment framework for Greece

Clinical Assessment – Pilot

Tarang Sharma
Krista Kruja

10 December 2025

Funded by the European Union

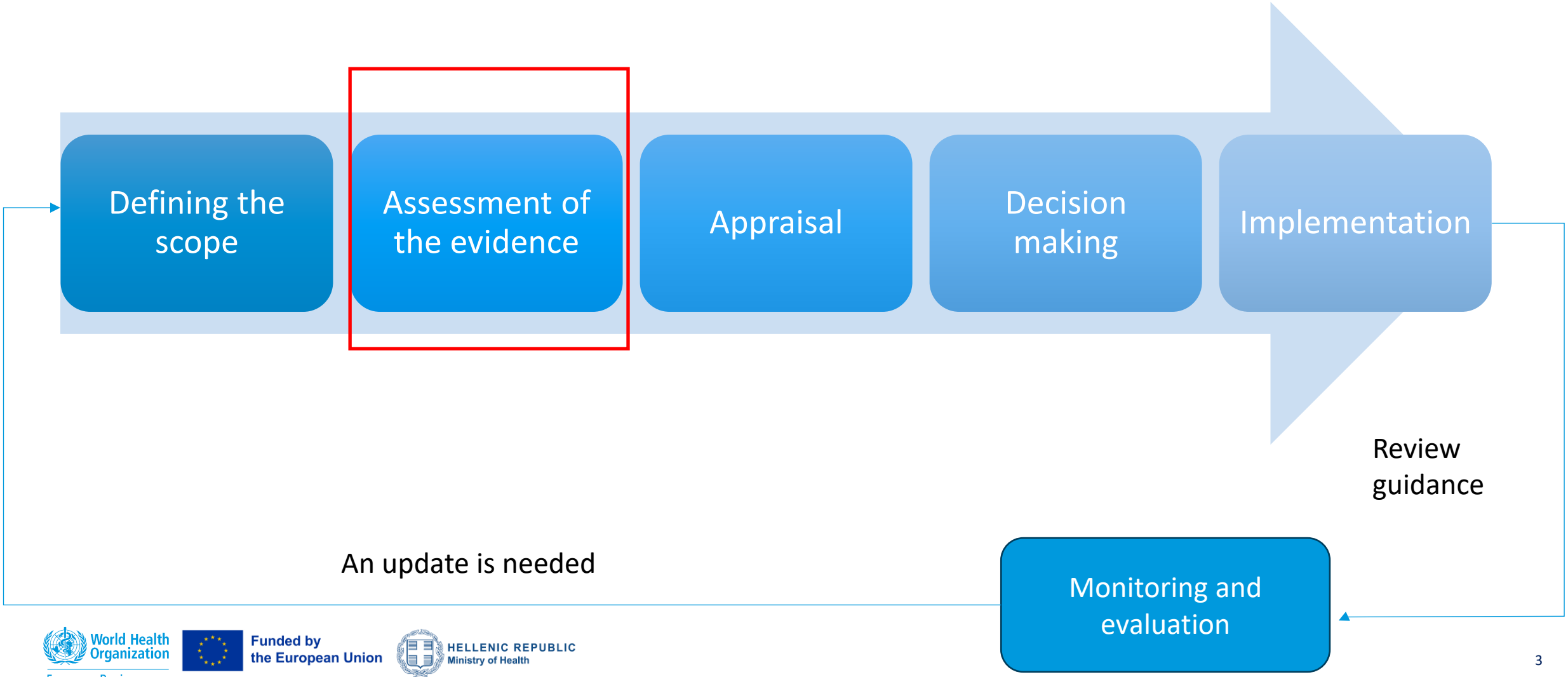
HELLENIC REPUBLIC
Ministry of Health

World Health Organization
European Region

Agenda

14:00-14:10	**Welcome, agenda, and objectives**
14:10-14:20	**Overview of clinical assessment process and methods**
14:20-14:40	**Pilot product summary and consolidated PICO**
14:40-15:20	**Clinical data from the public domain and discussion**
15:20-15:30	**Next steps**

The process of all Health technology assessments (HTAs)



World Health Organization European Region
Funded by the European Union
HELLENIC REPUBLIC Ministry of Health

Objectives

To apply the new HTA clinical assessment guidance to the Truqap (capivasertib) submission, critically assessing what is relevant to the Greek context.

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

- Have an in-sight into the clinical evidence available for capivasertib for treatment of ER-positive, HER2-negative locally advanced or metastatic breast cancer in the public domain.
- Review the clinical evidence dossier submitted:
  - For inclusion of required elements for validation;
  - Apply the new clinical assessment methods and process guidance to critically appraise the capivasertib dossier when submitted for clinical evidence assessment in line with EU HTAR guidance within the Greek context.

World Health Organization European Region
Funded by the European Union
HELLENIC REPUBLIC Ministry of Health

Clinical assessment process: Recap

Process overview

- **Purpose**: Objective, research-based evaluation of clinical 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.
- **Clinical Assessment**:
  - Conducted first; determines added therapeutic value.
  - **Major/Substantial/Moderate added value** → triggers full cost-effectiveness analysis.
  - **No or minor added value** → cost-minimization approach.
- **Stakeholder Involvement**:
  - 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 etc.

Validation within 7 business days; clock stops for additional information if requested.

Assessment Report: Draft reviewed by HTD and patient and clinical experts.

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

Clinical assessment methods: Recap

Methods overview

HTA Methods Guidance for Greece-medicinal products *DRAFT*

Purpose: Evaluate additional clinical benefit vs. comparators using systematic, transparent methods.

Evidence Sources:
•Prefer **high-quality RCTs** (direct head-to-head comparisons).
•Include systematic reviews and meta-analyses.
•Non-randomized studies only with justification (rare/ultra-rare conditions).

Real-World Evidence (RWE):
•Complements trial data for long-term outcomes, rare AEs, and diverse populations.
•Useful for HRQoL, resource use, and implementation context.

Literature Search:
•Follow PRISMA/MOOSE standards.
•Search ≥2 databases (e.g., MEDLINE, CENTRAL).
•Include pivotal trials; justify time frame.
•Provide flowchart of included/excluded studies.

Preferred Methods: Direct comparisons → conventional meta-analysis.

Indirect/mixed comparisons → Network Meta-Analysis (NMA). Advanced Techniques: Bucher's method for indirect comparisons. NMA using frequentist or Bayesian frameworks.

Adjust for heterogeneity with MAIC, STC, etc if IPD available.

Multiplicity & Subgroup Analyses: Pre-specify hypotheses and statistical plans.

Post-hoc analyses → exploratory only.

Sensitivity Analyses: Test robustness under alternative assumptions. Report impact vs. primary analysis.

Quality of Evidence & Added Value

Quality Assessment:

- Use **GRADE** for conventional meta-analysis (risk of bias, inconsistency, imprecision, indirectness, publication bias).
- Use **CiNeMA** for NMAs (bias, heterogeneity, incoherence).

Added Clinical Benefit:

- Based on severity, efficacy, safety, therapeutic role, public health impact.
- Categorized into 5 levels (I: major → V: no improvement).

Therapeutic Value:

- Supports the reimbursement and pricing negotiations.

Category of ATV	Description of the category
I: major	A major therapeutic improvement may be recognized for drugs with a new mechanism of action, demonstrated with a high level of evidence and a superiority associated with a clinically relevant effect in terms of mortality or morbidity, compared to the clinically relevant comparator, in the context of an under-covered medical need for a serious disease.
II: substantial/ important	Important therapeutic progress may be recognized for drugs that have demonstrated superiority associated with clinical efficacy in terms of mortality or morbidity in the context of an under-covered medical need. The value of this efficacy can be positively modulated by a substantial gain in quality of life and/or safety.
III: moderate	Moderate therapeutic progress may be recognized for drugs that have demonstrated superiority associated with clinical efficacy in terms of mortality or morbidity in the context of an under-covered medical need. The value of this efficacy can be positively modulated by a substantial gain in quality of life and/or safety.
IV: minor	Small progress compared to the existing therapeutic/preventive/diagnosis procedures. It reflects a demonstration and/or quantity of effect (efficacy, quality of life, tolerance) that is not optimal in view of the medical context. It may be a drug that has demonstrated relevant efficacy with a slight and acceptable reduction in quality of life or safety. Conversely, it may be a drug with little additional efficacy or demonstrated nonoptimal efficacy but associated with a gain in terms of quality of life or tolerance. It may also be a major improvement in conditions of care demonstrated or expected.
V: no improvement	A demonstration based on a non-inferiority study, a generic or a biosimilar medicinal product. In the absence of a therapeutic alternative or when alternatives are limited, it may also reflect a deficiency or uncertainty related to the choice of comparator, the quality of the proof of effect, the quantity of effect, or its clinical relevance. A suspected or established loss of opportunity for patients with respect to clinically relevant comparators.

World Health Organization European Region
Funded by the European Union
HELLENIC REPUBLIC Ministry of Health

Thresholds for effect size

	Comment	Outcome category		
Category		All cause mortality	Serious or severe adverse effects as well as HRQoL#	Non-serious or non-severe adverse effects
I Major	Large effect (e.g., large reduction in risk mortality) or large improvement in HRQoL	0.5-0.85	0.70 and risk ≥ 5%*	Not applicable
II Moderate	Moderate effect seen	0.85	0.75 and risk ≥ 5%*	Not applicable
III Considerable	Considerable effect seen	0.95	0.90	0.80
IV - Minor	Small or minor reduction in risk of non-serious adverse effects	1.00	1.00	0.90

Overview of Pilot Product & PICO

Truqap (capivasertib) – EMA indication

Medicine: TRUQAP (capivasertib) + fulvestrant

Target Patients:

Adults with ER-positive, HER2-negative locally advanced or metastatic breast cancer with PIK3CA, AKT1, or PTEN alterations

Treatment Context:

- After recurrence or progression on or after an endocrine-based regimen

Special Considerations:

- Pre-/Perimenopausal women: Combine with LHRH agonist
- Men: LHRH agonist as per standard clinical practice standards

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EMA/220840/2024
EMEA/H/C/006017

Truqap (*capivasertib*)
An overview of Truqap and why it is authorised in the EU

What is Truqap and what is it used for?

Truqap is a cancer medicine used in adults to treat breast cancer that is locally advanced (has spread nearby) or metastatic (has spread to other parts of the body) when the cancer has come back or worsened after hormonal treatment. It is used when the cancer cells have receptors (targets) for certain hormones on their surface (ER-positive) and do not have large quantities of another receptor called HER2 (HER2-negative). The cancer cells must also have been shown to have one or more mutations (changes) in the *PIK3CA, AKT1* or *PTEN* genes. Truqap is used in combination with fulvestrant (an anti-oestrogen medicine).

If Truqap is used in women before the menopause or around the time of menopause (pre-menopausal or peri-menopausal), it should also be given in combination with a luteinising hormone-releasing hormone (LHRH) agonist (a medicine that lowers blood levels of the hormones oestrogen and progesterone).

Truqap contains the active substance capivasertib.

How is Truqap used?

Truqap can only be obtained with a prescription and treatment should be started by a doctor experienced in the use of cancer treatments.

Truqap is available as tablets to be taken twice a day, approximately 12 hours apart. The tablets are taken for four consecutive days, followed by three days with no treatment. Fulvestrant is given on days 1, 15 and 29, and once monthly thereafter.

Treatment with Truqap should continue for as long as the patient benefits from it; treatment may be stopped, or the dose reduced, if the patient has unacceptable side effects.

For more information about using Truqap, see the package leaflet or contact your doctor or pharmacist.

How does Truqap work?

The active substance in Truqap, capivasertib, blocks the activity of enzymes known as serine/threonine kinase (AKT) 1, 2 and 3. These enzymes play an important role in the growth and division of cancer

The recommended dose is 400 mg (two 200 mg tablets) twice daily (total daily dose of 800 mg), for 4 days followed by 3 days off treatment.

In case of adverse reactions, the dose modification guidance is as follows:

- *First dose reduction: 320 mg (two 160 mg tablets) twice daily (total daily dose of 640 mg), for 4 days followed by 3 days off treatment*
- *Second dose reduction: 200mg twice daily (total daily dose of 400 mg), for 4 days followed by 3 days off treatment and second.*

Medicine background

Target: Serine/threonine kinase AKT (protein kinase B) – a target in HR+/HER2– breast cancer.

Capivasertib: First available AKT inhibitor for second-line treatment of unresectable or metastatic HR+/HER2– breast cancer. Indicated after progression on endocrine therapy (ET) (with or without CDK4/6 inhibitor).

Mode of Action as proposed by HTD

- Significant crosstalk between estrogen receptor (ER) and AKT pathways → AKT activation linked to ET resistance.
- Capivasertib + fulvestrant: Dual inhibition of ER and AKT pathway.
- Goal: Overcome ET resistance and restore ET sensitivity.

World Health Organization European Region
Funded by the European Union
HELLENIC REPUBLIC Ministry of Health

Epidemiology and context in Greece

Global Impact of Breast Cancer

Breast cancer is the fifth leading cause of cancer death worldwide with 670,000 deaths recorded in 2022.

Breast Cancer Subtypes

HR-positive HER2-negative breast cancer accounts for 70% of cases, showing disease heterogeneity.

Metastatic Breast Cancer Challenges

Metastatic breast cancer remains incurable but treatable, with significant progression from early-stage cases.

Genetic Alterations and Targets

Alterations in PI3K/AKT/PTEN pathways in ER+/HER2– lead to rapid progression and poor outcomes.

Claims by HTD

- No clear Standard of Care (SoC) for HR+/HER2− advanced breast cancer after progression on endocrine therapy (ET).
- Limitations of existing options:
  - *Second-line PFS: 3–5 months.*
  - *Prior CDK4/6 inhibitor use → weaker PFS/OS*.
- Declining benefit with later lines for first-line fulvestrant or aromatase inhibitors:
  - *Clinical benefit rate: 70% (1st line) → 30% (2nd line).*
- Resistance issues:
  - *ET and CDK4/6 inhibitor resistance common.*
  - *Chemotherapy option → high toxicity.*

Quality of Life and Economic Burden

Patient Symptom Burden

Patients experience pain, fatigue, nausea, anxiety, and depression, impacting daily functioning and work capacity.

Caregiver Emotional and Financial Stress

Family caregivers face emotional stress and financial strain due to the demands of metastatic breast cancer care.

Economic Cost Burden

Annual costs in Greece reach €89.9 million, with drug acquisition as the largest expense in patient care.

Financial Toxicity and Quality of Life

Financial toxicity strongly correlates with reduced quality of life, emphasizing the need for effective treatments.

World Health Organization European Region
Funded by the European Union
HELLENIC REPUBLIC Ministry of Health

	Overarching	Sub-populations		
Population	Estrogen receptor (ER)-positive, HER2-negative locally advanced or metastatic breast cancer **with one or more PIK3CA/AKT1/PTEN-alterations** following recurrence or progression on or after an endocrine-based regimen **(with or without CDK4/6i)**.	Sub-population **with CDK4/6i**	Sub-population **without CDK4/6i**	Sub-population **with PIK3CA alteration (with or without CDK4/6i).**
Intervention	Oral capivasertib (at a dose of 400 mg twice daily for 4 days, followed by 3 days off) plus **fulvestrant** (500 mg, administered intramuscularly (IM) every 14 days for the first three injections and every 28 days thereafter)			
Comparison*	**Fulvestrant** 500 mg IM on Day 1, 15 and 29 and once monthly thereafter (**Overarching comparison**)	**Overarching** and Everolimus 10 mg + exemestane 25 mg once daily	**Overarching**	Alpelisib 300 mg orally once daily in combination with **Overarching** (in cases where a PIK3CA mutation has been detected)
Outcome	*Comparative measures of effectiveness and safety on subsequent slides*			

World Health Organization European Region
Funded by the European Union
HELLENIC REPUBLIC Ministry of Health

*Chemotherapy has not been considered as a relevant competitor for this analysis

PICO A

ATTRIBUTE	DETAILS
Population	**Pre-/perimenopausal women** with ER+, HER2– advanced breast cancer with one or more PIK3CA/AKT1/PTEN alterations after endocrine therapy progression: Additional subgroups analyses: a) by gender b) by recurrence or disease progression c) locally advanced or metastatic disease
Intervention	TRUQAP + fulvestrant + LHRH agonist
Comparators	Using the “or” Boolean function 1. CDK4/6 inhibitor + fulvestrant + LHRH agonist; 2. fulvestrant + LHRH agonist; 3. Aromatase inhibitor + LHRH agonist

Fulvestrant: 500mg IM every 28 days with a loading dose on days 1 & 15
LHRH: luteinising hormone releasing hormone

World Health Organization European Region
Funded by the European Union
HELLENIC REPUBLIC Ministry of Health

PICO B

ATTRIBUTE	DETAILS
Population	**Postmenopausal women** with ER+, HER2– advanced breast cancer with one or more PIK3CA/AKT1/PTEN alterations after endocrine therapy progression: Additional subgroups analyses: a) by gender b) by recurrence or disease progression c) locally advanced or metastatic disease
Intervention	TRUQAP + Fulvestrant
Comparators	Using the "or" Boolean function 1. fulvestrant; 2. everolimus plus aromatase inhibitor (anastrazole, letrozole, exemestane), fulvestrant or tamoxifen; 3. everolimus plus exemestane; 4. CDK 4/6 & fulvestrant (for naïve CDK 4/6 patients); 5. everolimus plus fulvestrant

Fulvestrant: 500mg IM every 28 days with a loading dose on days 1 & 15

PICO C

ATTRIBUTE	DETAILS
Population	Adults (men and women) with ER+, HER2– advanced breast cancer **with PIK3CA alteration** following recurrence or progression on or after an endocrine-based regimen. • In pre- or perimenopausal women, TRUQAP plus fulvestrant should be combined with a LHRH agonist. • For men, administration of LHRH agonist according to current clinical practice standards should be considered. Additional subgroups analyses: a) by gender b) by recurrence or disease progression c) locally advanced or metastatic disease
Intervention	TRUQAP + Fulvestrant
Comparators	alpelisib in combination with fulvestrant

Fulvestrant: 500mg IM every 28 days with a loading dose on days 1 & 15
LHRH: luteinising hormone releasing hormone

World Health Organization European Region
Funded by the European Union
HELLENIC REPUBLIC Ministry of Health

Outcomes

Measures of effectiveness

Evaluation measures	Score*	Classification of importance of the measures*
PFS: was defined as the time from the date of randomization until the date of objective disease progression, as defined by Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 criteria, or death (by any cause in the absence of progression) regardless of whether the patient withdraws from randomized therapy or receives another anti-cancer therapy prior to progression	8	Critical (robust available data)
OS: the length of time from randomization until the date of death due to any cause	9	Critical (available data but limited/immature)
PFS2: the time from randomization until second progression on next-line treatment, as assessed by the investigator at the local site, or death due to any cause	8	Critical (robust available data)
ORR: the percentage of patients with at least one complete response (CR) or partial response (PR) per RECIST v1.1 criteria, as assessed by the investigator at the local site	6	Important (robust available data)
Duration and onset of response: the time from the date of first documented response until date of documented progression or death in the absence of disease progression	6	Important (robust available data)

Measures of effectiveness continued

Evaluation measures	Score*	Classification of the importance of the measures*
Clinical benefit rate: the percentage of patients who have CR, PR or stable disease (SD) per RECIST v1.1 criteria (without subsequent cancer therapy) maintained ≥ 24 weeks after randomization	6	Important (available data but limited/immature)
Time to response (TTR): Time from randomisation to first CR/PR	6	Important (available data but limited/immature)
HRQoL: Evaluation of EORTC QLQ-C30, EORTC QLQ-BR23, scale/item score, including change from baseline and time to deterioration	8	Critical (robust available data)
Plasma concentration of capivasertib: plasma concentration of capivasertib pre-dose and post-dose (C1h and C4h)	6	Important (no data available)
Time to definitive deterioration of the ECOG (Eastern Cooperative Oncology Group) performance	6	Important (no data available)
Time to first subsequent chemotherapy or death: time from randomization to the earlier of start date of subsequent chemotherapy after discontinuation of randomized treatment or death due to any cause	2	Low importance (available data)
Healthcare resource use	2	Low importance (no data available)

Consolidated PICO - Outcomes

Evaluation measures	Classification of the importance of the measures	Score
Overal survival (OS)	Critical	9
Progression free survival (PFS)	Critical	8
HRQoL: EORTC QLQ-C30 and QLQ -BR23*	Critical	8
Objective Response Rate (ORR)	Important	6
Duration and onset of response	Important	6
Time to response (TTR)	Important	6
Deaths related to treatment	Critical	9
Adverse Events: Patients ≥ 1	Important	6
Adverse events grade ≥ 3	Important	6
AE responsible for treatment discontinuation	Important	6
AE responsible for treatment alteration	Important	6

World Health Organization European Region
Funded by the European Union
HELLENIC REPUBLIC Ministry of Health

**The EQ-5D will be needed for the pharmacoeconomic analysis.*

Clinical evidence

Approach

- To cover this aspect of the training, the focus will be on publicly available data from the pivotal RCT, and the evidence evidence submitted to NICE
- Key trial: CAPItello-291 (Turner et al, NEJM, 2023)
- NICE Appraisal – TA 1063 (Published 15 May 2025)
- Additional input from HAS, France (published 25 June 2025)
- Additional input from IQWiG and G-BA, Germany (published 3 April 2025)
- Additional input from AIFA, Italy (published 11 October 2024, published 11 October 2024, board decision 28 October 2025)
- Additional input from INFARMED, Portugal (HTD, withdrew in May 2025)

Key issues to explore

Relevance and robustness of the clinical evidence

Consider:

- Decision problem and evidence submission by the company vs preferred PICO (e.g. see NICE)
  - Aligned?
- Need for indirect comparisons / Network meta-analysis
  - validity of the indirect comparison requires that different randomised trials to be similar → Transitivity

NICE Recommendation

Capivasertib plus fulvestrant is recommended as an option for treating hormone receptor (HR)-positive HER2-negative (defined as immunohistochemistry [IHC]0 or IHC1 positive, or IHC2 positive and in situ hybridisation [ISH]1 negative) locally advanced or metastatic breast cancer in adults that has:

- 1 or more PIK3CA, AKT1 or PTEN gene alterations
- recurred or progressed after a cyclin-dependent kinase (CDK) 4 and 6 inhibitor plus an aromatase inhibitor.

Capivasertib plus fulvestrant is only recommended if the company provides it according to the commercial arrangement.

Key trial: CAPItello-291

- Randomised, double-blind, placebo-controlled

Phase 3 trial

Subgroup: PI3K and AKT pathway-altered (PIK3CA, AKT1 or PTEN) tumours

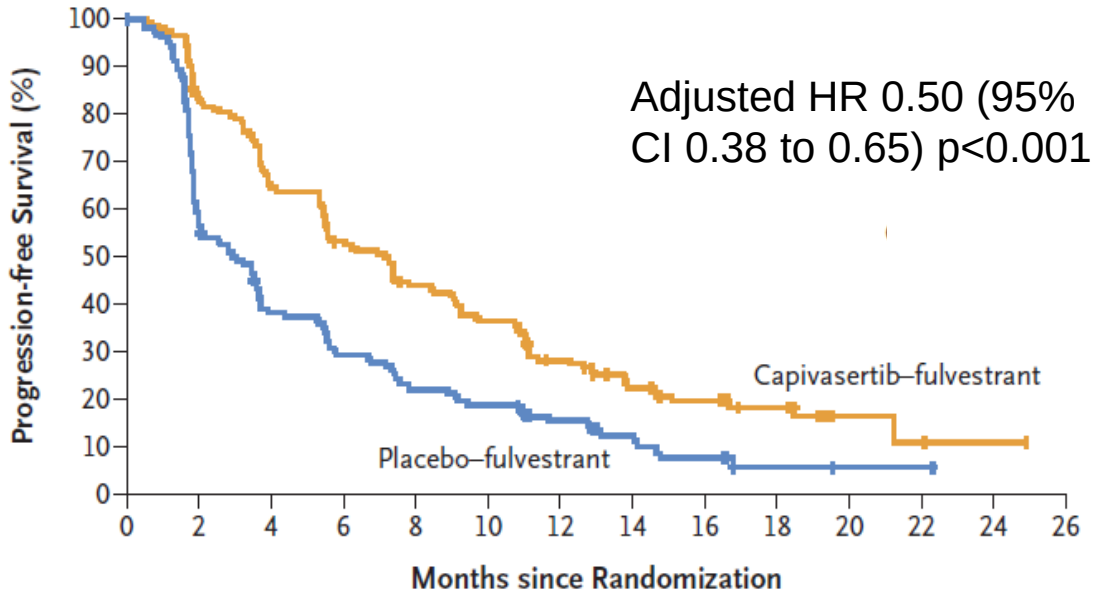
- capivasertib plus fulvestrant significantly improved progression-free survival
  - (median 7.3 months; 95% confidence interval [CI] 5.5 to 9.0) compared with placebo plus fulvestrant (median 3.1 months; 95% CI 2.0 to 3.7)
- OS improvement not statistically significant (hazard ratio 0.69; 95% CI 0.45 to 1.05)

CAPItello-291 trial: Kaplan–Meier plots of PFS

CAPItello-291 background

Capivasertib + fulvestrant significantly improves PFS compared with placebo + fulvestrant in PI3K/AKT-altered patients; results similar in prior CDK4/6i group

Primary endpoint: PI3K/AKT-altered population (FAS)



Adjusted HR 0.50 (95% CI 0.38 to 0.65) p<0.001

No. at Risk													
Capivasertib–fulvestrant	155	127	99	80	65	54	38	26	21	12	3	2	1	0
Placebo–fulvestrant	134	77	48	37	28	24	17	11	6	2	1	1	0	0

Median PFS (95% CI): capivasertib + fulvestrant 7.3 (5.5 to 9.0); placebo + fulvestrant 3.1 (2.0 to 3.7)

EAG: little difference between subgroups but less effect with no prior CDK4/6i and in pre/peri-menopausal group

PI3K/AKT-altered population, prior CDK4/6 inhibitor (FAS)

[redacted]

Median PFS (95% CI): capivasertib + fulvestrant [redacted]; placebo + fulvestrant [redacted]

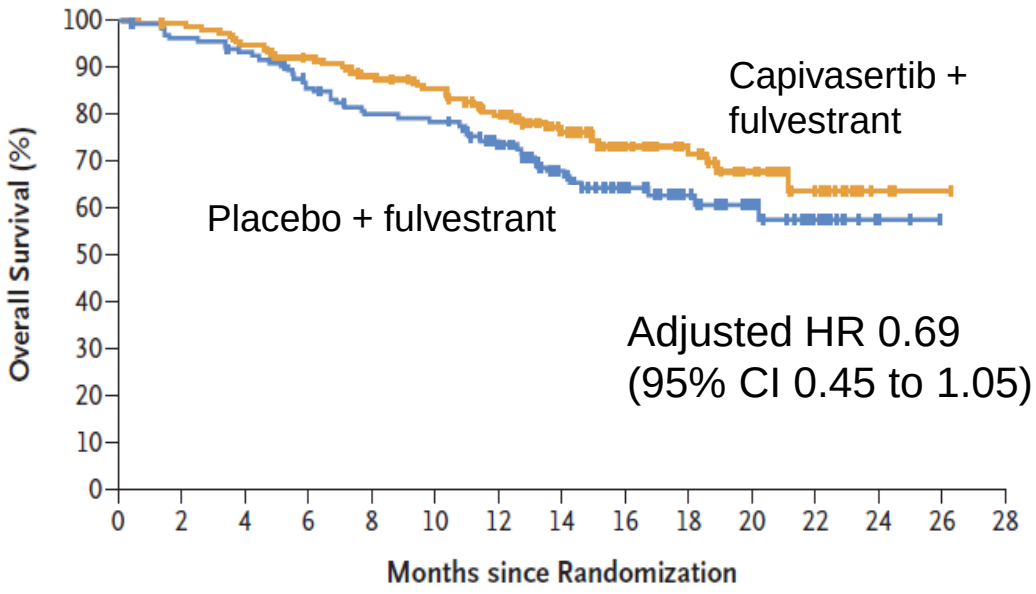
CDK4/6, cyclin-dependent kinase 4 and 6; CI, confidence interval; FAS, full analysis set; HR, hazard ratio; PFS, progression-free survival

CAPItello-291 background

CAPItello-291 trial: Kaplan–Meier plots of OS

Capivasertib + fulvestrant improves OS compared with placebo + fulvestrant in PI3K/AKT-altered patients; results similar in prior CDK4/6i group

PI3K/AKT-altered population (FAS)



No. at Risk

Capivasertib–fulvestrant	155	153	144	139	131	125	111	83	60	45	30	14	3	1	0
Placebo–fulvestrant	134	127	122	112	101	99	87	62	46	31	22	13	3	0	0

Treatment	Median OS (months; 95% CI)
Capi + fulvestrant	Not reached
Placebo + fulvestrant	Not reached

PI3K/AKT-altered population, prior CDK4/6 inhibitor (FAS)

[redacted]

Treatment	Median OS (months; 95% CI)
Capi + fulvestrant	[redacted]
Placebo + fulvestrant	[redacted]

NICE

CDK, cyclin-dependent kinase; CI, confidence interval; HR, hazard ratio; FAS, full analysis set; OS, overall survival

Questions for consideration

Need for indirect comparisons / network meta-analysis

- What are other relevant comparisons based on the agreed Greek PICO?

- Note: NICE accepted company evidence for two comparators only:
  - alpelisib plus fulvestrant
  - everolimus plus exemestane
  - This does not include everyone who it is licensed for!

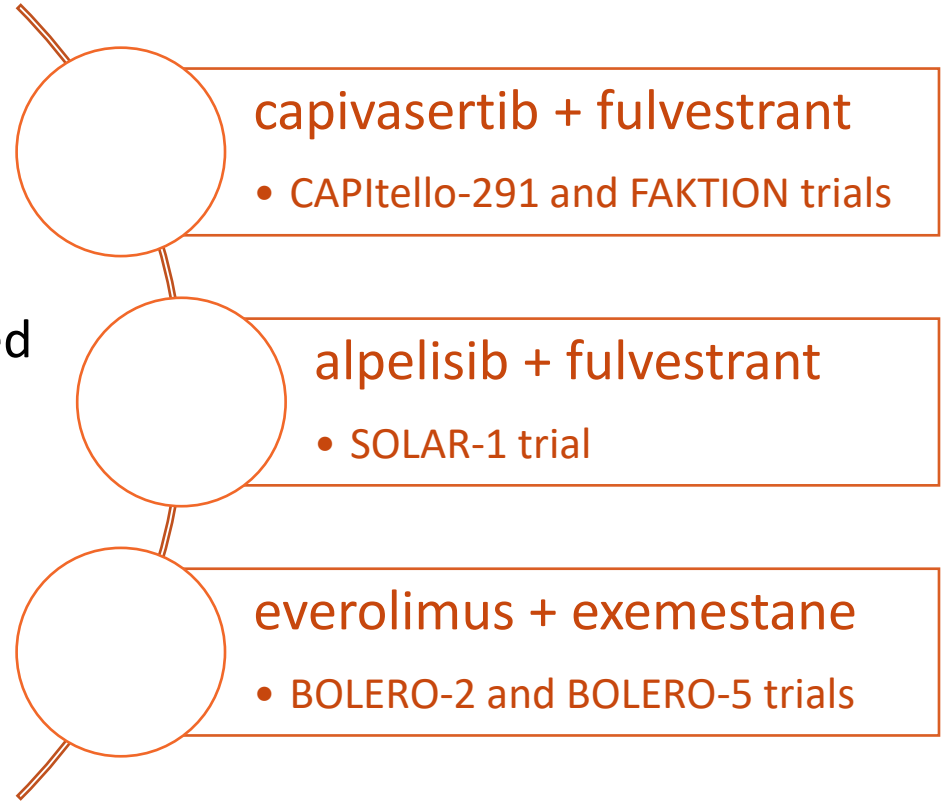
Trial outcomes

- PFS (surrogate endpoint) vs OS (median follow up for primary analysis – about 13 months)

- Note: In CAPItello-291, the dual primary end point was investigator-assessed progression-free survival in the overall population and among patients with AKT pathway–altered tumours (overall survival was a secondary endpoint)

Indirect comparisons

NICE company submission included a network meta-analysis with 10 randomized trials



- NMA used data from subgroups of people in **CAPItello-291** and **FAKTION** who had PI3K and AKT pathway-altered tumours, and the PIK3CA-altered subgroup from SOLAR-1.
  - BUT **other trials did not report who had PI3K and AKT pathway-altered tumours**

- Other sources of heterogeneity:
  - HER2 status
  - prior treatment with prior endocrine and CDK4/6i treatment
    - 8 trials had endocrine but no CDK4/6i
  - different proportions with ECOG PS status 1

Questions for consideration

Suitability indirect comparisons / network meta-analysis

- Enough evidence to support the exchangeability of the trials? Likely impact?

Note – in NICE appraisal:

- Company → No evidence prior CDK4/6i or HER2 status would bias NMA and all studies included people with a low PS score (≤2 ECOG
- Clinical experts → BOLERO-2 (everolimus) and SOLAR-1 (alpelisib) were before CDK4/6 was adopted (cannot be compared to CAPItello-291)

Safety

- In CAPItello-291, the most common adverse events of any grade that were reported in the capivasertib–fulvestrant group were:
  - diarrhoea (in 72.4% of the patients, vs. 20.0% of those in the placebo–fulvestrant group);
  - rash (as a grouped term; in 38.0% and 7.1%, respectively); and
  - nausea (in 34.6% and 15.4%)
- Hyperglycaemia of any grade occurred in 16.3% of the patients who received capivasertib–fulvestrant (vs 3.7% in placebo arm)
- Discontinuation due to adverse events occurred in 46 patients (13.0%) receiving capivasertib and in 8 (2.3%) receiving placebo.

Questions for consideration

Safety profile of the technology

- How does the safety profile of the technology compare to relevant alternative treatments?

Note: Clinical experts for the NICE TA explained that the toxicity is much lower with capivasertib plus fulvestrant than alpelisib plus fulvestrant and that hyperglycaemia, rash and stomatitis are more significant with alpelisib plus fulvestrant or everolimus plus exemestane

Modelling

- Company developed a partitioned survival model to undertake the economic evaluation (more on this in the next session)
- Need an estimate of *long-term progression free survival* – fitting (parametric) survival curves to the patient level data in placebo plus fulvestrant arm from CAPitello-291
  - Common comparator in the NMA
  - Log-logistic model seemed the best fit for the data – good balance of "goodness to fit' and complexity (based on Akaike information criterion [AIC] and Bayesian information criterion [BIC]
- Modelling *long-term relative treatment effects (PFS and OS)* for the treatments (hazard ratios from NMA)
  - Concern about proportional hazards assumption (relative hazards remain constant over time for each treatment comparison)
  - Time varying analysis required – NICE committee concluded that "the fractional polynomial approach was appropriate for decision making and reduced the uncertainty around the estimates of long-term treatment effect"

Review of the clinical evidence by HAS, France

Reimbursement Approval

HAS granted full reimbursement for TRUQAP combined with fulvestrant in specific breast cancer patients.

Clinical Benefit Assessment

Clinical benefit was rated low with no added therapeutic value over existing treatments.

Trial Data Highlights

CAPItello-291 trial showed modest progression-free survival improvement, but no established overall survival benefit yet.

Public Health Impact

HAS concluded the treatment's impact on public health is negligible due to limited evidence beyond PFS.

Indication: TRUQAP (capivasertib) + fulvestrant for ER+, HER2– locally advanced/metastatic breast cancer with PIK3CA/AKT1/PTEN alterations after progression on endocrine therapy.

Reimbursement: 100% coverage for outpatient and inpatient use.

Clinical Benefit (SMR): Low

Clinical Added Value (ASMR): None (CAV - V).

Basis: CAPItello-291 trial → modest PFS benefit while, OS and QoL not demonstrated.

the Committee deems that TRUQAP 160 mg and 200 mg (capivasertib) film-coated tablets in combination with fulvestrant provides no clinical added value (CAV V) compared to fulvestrant alone in the treatment of adult patients with oestrogen receptor (ER)-positive, HER2-negative locally advanced or metastatic breast cancer with one or more PIK3CA/AKT1/PTEN-alterations following recurrence or progression on or after an endocrine-based regimen.

Review of the clinical evidence by HAS, France (contd.)

- **Methodological Concerns**:
  - Subgroup (PIK3CA/AKT1/PTEN) defined post-inclusion; no stratification at randomization.
  - Control arm (fulvestrant alone) considered **non-optimal** vs. other available alternatives.
- **Evidence Gaps**:
  - **OS**: No significant benefit yet; final analysis expected Q1 2026.
  - **QoL**: No formal improvement (exploratory endpoint only).
  - **Public Health Impact**: Considered negligible.
- **Safety Profile**:
  - Grade ≥3 AEs: 39.7% vs. 14.9%.
  - Serious AEs: 18% vs. 8.6%.
  - Discontinuations: 14.4% vs. 2.3%.
  - AE-related deaths: 1.7% vs. 0.3%.

    Increased Toxicity Risk

    Capivasertib combined with fulvestrant significantly increased toxicity compared to fulvestrant alone.

    Adverse Event Statistics

    Both the grade ≥3 adverse events SAEs were higher.

    Treatment Discontinuations and Deaths

    Treatment discontinuations due to adverse events were also higher.

    Hyperglycemia Risk

    Hyperglycemia identified as an important risk requiring further study through post-authorization safety studies.
- **Positioning**: Role vs. second-line alternatives was inadequately established.

Clinical and Methodological Concerns

Subgroup Analysis Limitations

Subgroup of patients with genetic alterations was defined post-inclusion, raising concerns about analysis robustness.

Non-Optimal Control Arm

Control arm used fulvestrant monotherapy, despite better second-line treatment options being available but excluded.

Generalizability and Evidence Gaps

30% patients lacked prior standard care; immature overall survival data and missing quality of life measures limit conclusions.

World Health Organization European Region
Funded by the European Union
HELLENIC REPUBLIC Ministry of Health

IQWiG, review in Germany

Scope: Adults with ER+, HER2− locally advanced/metastatic breast cancer with **PIK3CA/AKT1/PTEN alterations** after recurrence/progression on endocrine therapy.
Comparator: Fulvestrant or other endocrine-based therapies per G-BA specification.
Evidence Base: CAPItello-291 Phase III trial.

Result:

- ***Added benefit not proven*** *for most subgroups (women after recurrence during/after adjuvant ET; men).*
- *For women with progression during/after ET in metastatic stage: concluded* ***added benefit****.*
- **Reasoning**:
- *OS data immature.*
- *QoL improvement not demonstrated.*
- *Safety concerns: higher grade ≥3 AEs (39.7% vs 14.9%), serious AEs (18% vs 8.6%), discontinuations (14.4% vs 2.3%).*

In summary, the additional benefit of capivasertib is assessed as follows:

a1) Women with oestrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with PIK3CA/AKT1/PTEN alteration(s), following disease recurrence on or after (neo-)adjuvant endocrine therapy, no previous treatment in locally advanced or metastatic stage

An additional benefit is not proven.

a2) Men with oestrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with PIK3CA/AKT1/PTEN alteration(s), following disease recurrence on or after (neo-)adjuvant endocrine therapy, no previous treatment in locally advanced or metastatic stage

An additional benefit is not proven.

b1) Women with oestrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with PIK3CA/AKT1/PTEN alteration(s), with disease progression on or after endocrine therapy which occurred in locally advanced or metastatic stage

Indication of a considerable additional benefit.

b2) Men with oestrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with PIK3CA/AKT1/PTEN alteration(s), with disease progression on or after endocrine therapy which occurred in locally advanced or metastatic stage

An additional benefit is not proven.

G-BA Final Decision (April 3, 2025)

Outcome:

Significant added benefit confirmed only for women with progression during/after ET in locally advanced/metastatic stage.

Other subgroups: **no added benefit**.

Basis: Improved OS signal and PFS benefit in CAPItello-291 for this subgroup.

Price: Truqap 200 mg (64 tablets) = €7,064.17; Fulvestrant 250 mg = €160.91.

World Health Organization European Region
Funded by the European Union
HELLENIC REPUBLIC Ministry of Health

AIFA, review in Italy

Reimbursement Status:

•***Approved for reimbursement*** *by the Italian Medicines Agency (AIFA) in* ***October 2025****.*

•*Classified under* ***Class H*** *(hospital use, fully reimbursed by the National Health Service).*

Indication:

•*Adult patients with* ***ER-positive, HER2-negative locally advanced or metastatic breast cancer*** *with* ***PIK3CA/AKT1/PTEN alterations****, after recurrence or progression on or after an endocrine-based regimen.*

•*Pre-/perimenopausal women: combine with* ***LHRH agonist****.*

Basis for Decision:

•*Evidence from* ***CAPItello-291 Phase III trial*** *(PFS benefit: 7.3 vs 3.1 months; HR=0.50).*

•*OS data immature; QoL improvement not demonstrated.*

•*Safety concerns: higher grade ≥3 AEs and discontinuations.*

Innovation Status & Fund

Innovation Evaluation:

AIFA assessed **therapeutic need**, **added clinical value**, and **quality of evidence** for innovation status.

Capivasertib + fulvestrant was NOT granted full innovation status, mainly due to:

- OS data immature.
- Limited QoL evidence.
- Safety profile concerns.

Therefore, **not eligible for the Innovation Fund** (which provides immediate access and dedicated budget).

Criteria for Innovation:

High unmet need, significant added therapeutic value, robust evidence.

Capivasertib met unmet need but failed on added value and evidence robustness.

INFARMED, review in Portugal

Status:
•The marketing authorization holder **withdrew the request for prior evaluation** for reimbursement in Portugal (May 2025).
•This means **no positive reimbursement decision has been issued yet**.

Indication under evaluation:
•Adult patients with **ER-positive, HER2-negative locally advanced or metastatic breast cancer** with **PIK3CA/AKT1/PTEN alterations**, after recurrence or progression on endocrine therapy

Public report:
•The **assessment report is available on the infomed (**INFARMED's portal) for transparency.

Reasons:

- OS data immature.
- QoL improvement not demonstrated.
- Safety concerns (high grade ≥3 AEs).

Innovation Status: Not granted

Next steps

- Dossier expected from HTD by 18 December 2025 – 7 days for validation – to happen over Christmas break?
- Economic dossier expected a few weeks afterwards.
- Upcoming training on economic assessments and other considerations: 14 January 2026 (dependent on economic dossier).

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

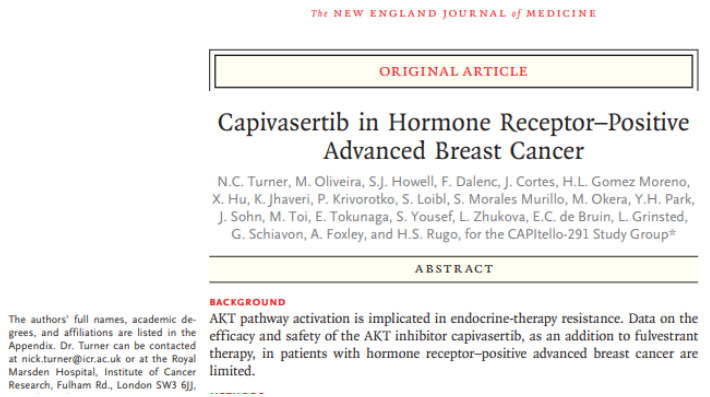
AI, aromatase inhibitor; CDK4/6i, cyclin-dependent kinase 4 and 6 inhibitor; CG, clinical guideline; HER2-, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive; TA, technology appraisal

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

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)

Survival curves

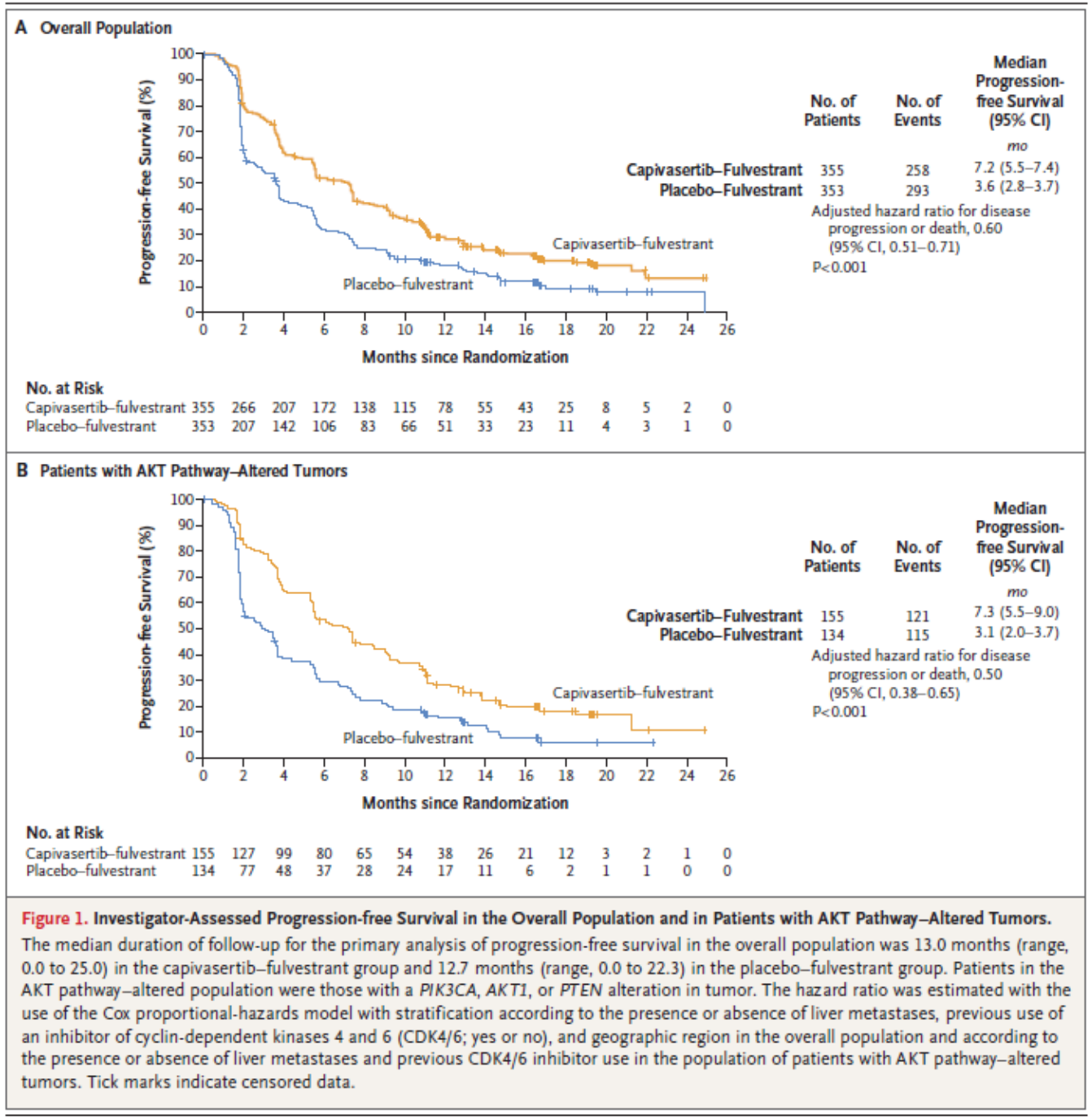


Figure 1. Investigator-Assessed Progression-free Survival in the Overall Population and in Patients with AKT Pathway–Altered Tumors.
The median duration of follow-up for the primary analysis of progression-free survival in the overall population was 13.0 months (range, 0.0 to 25.0) in the capivasertib–fulvestrant 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.