Capivasertib (Truqap®) with fulvestrant for the treatment ER-positive, HER2-negative locally advanced or metastatic breast cancer

General information [1]

Drug description

The active substance of Truqap® is capivasertib, an antineoplastic agent and other protein kinase inhibitor. The serine/threonine kinase AKT is a pivotal node in the phosphatidylinositol 3-kinase (PI3K) signalling cascade regulating multiple cellular processes, including cellular survival, proliferation, cell cycle, metabolism, gene transcription and cell migration. Capivasertib selectively inhibits all isoforms of AKT (AKT1, AKT2 and AKT3), hampering downstream proliferation signalling and thereby reducing the growth of tumour cells.

Indication

Capivasertib (Truqap®) is indicated in combination with fulvestrant for the treatment of adult patients with 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.
In pre- or perimenopausal women, Truqap® plus fulvestrant should be combined with a luteinising hormone-releasing hormone (LHRH) agonist. For men, the administration of LHRH agonists should be considered according to current clinical practice standards.

Incidence [2]

In Austria, in 2022, a total of 6,096 women and 65 men were newly diagnosed with breast cancer. The age-standardised[1] incidence rate was 122.4 per 100,000 women and 1.5 per 100,000 men.

Current treatment [3]

The ESMO treatment recommendation for the treatment of ER-positive HER2-negative breast cancer is displayed in Figure 1 of the Appendix.

Regulatory status

EMA [1]	FDA [4]
Approval status for this indication: On 25 April 2024, the CHMP adopted a positive opinion, recommending granting a marketing authorisation for Truqap®. The full indication is: ❖ Truqap® is indicated in combination with fulvestrant for the treatment of adult patients with 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. ❖ 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. ❖ Truqap will be available as 160 and 200 mg film-coated tablets. **Other indications**: none	**Approval status for this indication**: On 16 November 2023, the FDA approved capivasertib (Truqap®) with fulvestrant for adult patients with HR-positive, HER2-negative locally advanced or metastatic breast cancer with one or more PIK3CA/AKT1/PTEN-alterations, as detected by an FDA-approved test, following progression on at least one endocrine-based regimen in the metastatic setting or recurrence on or within 12 months of completing adjuvant therapy. FDA also approved the FoundationOne®CDx assay as a companion diagnostic device to identify patients with breast cancer for treatment with capivasertib with fulvestrant. ✓ Priority review **Other indications**: none

Manufacturer

The manufacturer of Truqap® is AstraZeneca.

Costs

[1] European Standard Population 2013.

Currently, there is no cost information available.

Warnings and precautions[2] [5]

- **Hyperglycemia**
  - Evaluate blood glucose levels prior to starting and at regular intervals during treatment.
  - Withhold, reduce dose, or permanently discontinue Truqap® based on severity.
- **Diarrhoea**
  - Truqap® caused diarrhoea in most patients. Advise patients to increase oral fluids, start antidiarrheal treatment, and consult with a healthcare provider if diarrhoea occurs while taking Truqap®.
  - Withhold, reduce dose, or permanently discontinue Truqap® based on severity.
- **Cutaneous adverse reactions**
  - Monitor for signs and symptoms of cutaneous adverse reactions.
  - Withhold, reduce dose, or permanently discontinue Truqap® based on severity.
- **Embryo-foetal toxicity**
  - Truqap® can cause foetal harm.
  - Advise patients of potential risks to a foetus and to use effective contraception.

Study characteristics [6-9]

Trial name	*n*	Intervention (I)	Comparator (C)	Dual PE	Median follow-up	Characteristics	Biomarker	Funding	Publication(s)
CAPItello-291 NCT04305496	708 (1:1)	oral capivasertib (400 mg twice daily for 4 days, followed by 3 days off) + fulvestrant (500 mg intramuscularly every 14 days for the first three injections and every 28 days thereafter	placebo + fulvestrant	investigator-assessed PFS both in the overall population and among patients with AKT pathway–altered (PIK3CA, AKT1, or PTEN) tumours	13.0 vs. 12.7 months	**ongoing**[3], randomised, double-blind, placebo-controlled, phase 3 trial,	HER2	AstraZeneca and the National Cancer Institute	CAPItello-291 trial [8]

Inclusion criteria	Exclusion criteria	Patient characteristics at baseline (patients with AKT pathway-altered tumours, n=155 vs. n=134)
❖ Adult females, pre- and/or post-menopausal, and adult males. Pre-menopausal (and peri-menopausal) women can be enrolled if amenable to treatment with an LHRH agonist. Patients are to have commenced concomitant treatment with LHRH agonist prior to or on Cycle 1, Day 1 and must be willing to continue it for the duration of the study. ❖ Histologically confirmed HR+/HER2- breast cancer determined from the most recent	❖ Symptomatic visceral disease or any disease burden that makes the patient ineligible for endocrine therapy per the investigator's best judgment. ❖ More than two lines of endocrine therapy for inoperable locally advanced or metastatic disease. ❖ More than 1 line of chemotherapy for inoperable locally advanced or metastatic disease. Adjuvant and neoadjuvant chemotherapy are not classed as lines of chemotherapy for advanced breast cancer ❖ Prior treatment with any of the following: • AKT, PI3K and mTOR inhibitors • Fulvestrant, and other SERDs	❖ Median age (range): 58 (36–84) vs. 60 (34–90) ❖ Female sex: 98.7% vs. 100% ❖ Race • White: 48.4% vs. 56.7% • Asian: 31.0% vs. 26.1% • Black: 1.3% vs. 0.7% • Other: 19.4% vs. 16.4% ❖ Post-menopausal or menopausal status: 83.9% vs. 78.4%

[2] Since there is no EMA EPAR available yet, chapter "Warnings and precautions" refers to the FDA label information.
[3] The CAPItello-291 trial is currently ongoing; the estimated study completion date is June 2024.

tumour sample (primary or metastatic), as per the American Society of Clinical Oncology and College of American Pathologists guideline recommendations. To fulfil the requirement of HR+ disease, breast cancer must express ER with or without co-expression of progesterone receptor. ❖ Metastatic or locally advanced disease with radiological or objective evidence of recurrence or progression (the cancer should have shown progression during or after most recent therapy); locally advanced disease must not be amenable to resection with curative intent (patients who are considered suitable for surgical or ablative techniques following potential down-staging with study treatment are not eligible). ❖ ECOG/WHO PS: 0-1 ❖ Patients are to have received treatment with an AI containing regimen (single agent or in combination) and have: • Radiological evidence of breast cancer recurrence or progression while on or within 12 months of the end of (neo)adjuvant treatment with an AI, OR • Radiological evidence of progression while on prior AI administered as a treatment line for locally advanced or metastatic breast cancer (this does not need to be the most recent therapy). ❖ Patients must have measurable disease according to RECIST 1.1 and/or at least 1 lytic or mixed (lytic + sclerotic) bone lesion that can be assessed by CT or MRI; patients with sclerotic/osteoblastic bone lesions only in the absence of measurable disease are not eligible. ❖ FFPE tumour sample from primary/recurrent cancer for central testing.	• Any other chemotherapy, immunotherapy, immunosuppressant medication (other than corticosteroids) or anticancer agents within 3 weeks prior to study treatment initiation. • Potent inhibitors or inducers of CYP3A4 within 2 weeks prior to the first dose of study treatment (3 weeks for St John's wort) or drugs that are sensitive to CYP3A4 inhibition within 1 week prior to study treatment initiation. ❖ Radiotherapy with a wide field of radiation up to 4 weeks before study treatment initiation (capivasertib/placebo) and/or radiotherapy with a limited field of radiation for palliation up to 2 weeks before study treatment initiation (capivasertib/placebo). ❖ Except for alopecia, any unresolved toxicities from prior therapy greater than CTCAE grade 1 at the time of starting study treatment. ❖ Spinal cord compression or brain metastases unless asymptomatic, treated and stable and not requiring steroids up to 4 weeks before study treatment initiation. ❖ Any of the following cardiac criteria: • Mean resting QT interval corrected by Fridericia's formula >470 msec obtained from 3 consecutive ECGs. • Any clinically important abnormalities in rhythm, conduction or morphology of resting ECG. • Any factors that increase the risk of corrected QT interval prolongation or risk of arrhythmic events such as heart failure, hypokalaemia, potential for torsades de pointes, congenital long QT syndrome, family history of long QT syndrome or unexplained sudden death under 40 years of age or any concomitant medication known to prolong the QT interval. • Experience of any of the following procedures or conditions in the preceding 6 months: coronary artery bypass graft, angioplasty, vascular stent, myocardial infarction, angina pectoris, congestive heart failure NYHA grade ≥2. • Uncontrolled hypotension - systolic blood pressure <90 mmHg and/or diastolic blood pressure <50 mmHg. • Cardiac ejection fraction outside institutional range of normal or <50% (whichever is higher) as measured by echocardiogram (or MUGA scan if an echocardiogram cannot be performed or is inconclusive). ❖ Clinically significant abnormalities of glucose metabolism as defined by any of the following: • Patients with diabetes mellitus type 1 or diabetes mellitus type 2 requiring insulin treatment • HbA1c ≥8.0% (63.9 mmol/mol).	❖ ECOG performance-status score: • 0: 60.0% vs. 72.4% • 1: 40.0% vs. 26.9% • 2: 0 vs. 0.7% ❖ Site of metastases: • Bone only: 16.1% vs. 11.9% • Liver: 45.2% vs. 39.6% • Viscera: 66.5% vs. 73.1% ❖ No. of previous therapies for advanced breast cancer: • 0: 7.7% vs. 14.9% • 1: 69.0% vs. 59.0% • 2: 20.0% vs. 21.6% • 3: 3.2% vs. 4.5% ❖ Hormone-receptor status: • ER-positive, PR-positive: 74.8% vs. 75.4% • ER-positive, PR-negative: 22.6% vs. 23.1% • ER-positive, with unknown PR status: 2.6% vs. 1.5% ❖ Endocrine status: • Primary resistance: 38.7% vs. 41.0% • Secondary resistance: 61.3% vs. 59.0% ❖ No. of previous endocrine therapies for advanced breast cancer: • 0: 8.4% vs. 14.9% • 1: 84.5% vs. 71.6% • 2: 7.1% vs. 13.4% ❖ Previous CDK4/6 inhibitor: • As neoadjuvant or adjuvant therapy: 0 vs. 1.5% • As therapy for advanced breast cancer: 72.9 vs. 67.9% ❖ Previous chemotherapy: • As neoadjuvant or adjuvant therapy: 51.0% vs. 50.0% • As therapy for advanced breast cancer: 19.4% vs. 17.2%

	❖ Known abnormalities in coagulation such as bleeding diathesis, or treatment with anticoagulants precluding intramuscular injections of fulvestrant or LHRH agonist (if applicable). ❖ Currently pregnant (confirmed with positive pregnancy test) or breast-feeding.	

Efficacy (I vs. C)	**Safety** (I vs. C, n=355 vs. n=350)
Primary analysis (data-cutoff date, August 15, 2022) **Overall population:** **Median PFS** according to the investigator's assessment: 7.2 months vs. 3.6 months; HR for progression or death 0.60 (95%CI, 0.51-0.71); p<0.001 **Estimated OS at 18 months:** 73.9% (95% CI, 68.3-78.7) vs. 65.0% (95% CI, 58.7-70.6); HR for death 0.74 (95% CI, 0.56-0.98) **AKT pathway–altered population:** **Median PFS**: 7.3 months vs. 3.1 months; HR 0.50 (95% CI, 0.38-0.65); p<0.001 **Estimated OS at 18 months**: 73.2% (95% CI, 64.8-80.0) vs. 62.9% (95% CI, 53.1-71.2); HR 0.69 (95% CI, 0.45-1.05)	**Any AE grade 3≥:** 41.7% vs. 15.5% **Serious AEs:** 16.1% vs. 8.0% **Death due to AEs[4]:** n=4 vs. n=1 **Discontinuation due to AEs:** 13.0% vs. 2.3%

Patient-reported outcomes

- ❖ Global health status and QoL were maintained in both the capivasertib–fulvestrant group and the placebo-fulvestrant group (mean overall change from baseline in the QLQ-C30 score at visits during the treatment period, −2.52 points and −5.62 points, respectively; difference, 3.10 points; 95% CI, 0.21 to 5.98).
- ❖ Global health status and QoL were maintained for longer with capivasertib–fulvestrant than with placebo-fulvestrant.
- ❖ The median time to deterioration (defined as a sustained decrease of ≥10 points in the score from baseline) was 24.9 months in the capivasertib–fulvestrant group, as compared with 12.0 months in the placebo-fulvestrant group (HR 0.70; 95% CI, 0.53-0.92).
- ❖ The results in the AKT pathway–altered population were similar to those in the overall population.

ESMO-MCBS version 1.1 [10]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	2B	≤6 months	PFS: + 4.2 months	0.50 (0.38-0.65)	HR ≤0.65 AND gain ≥1.5 months	3	-	-	-	3
Adapted	NC	2B	≤6 months	PFS: + 4.2 months	0.50 (0.38-0.65)	HR ≤0.65 AND gain ≥1.5 months	3	+10.7% discontinuations due to AEs	-	-1[5]	2

Risk of bias (RCT) [11]

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
yes low risk	yes low risk	yes low risk	unclear[6] unclear risk	yes[7] high risk	unclear

Ongoing trials [12]

NCT number/trial name	Description	Estimated study completion date
NCT04305496 / CAPItello-291	Please see above.	06/2024
NCT04862663 / CAPItello-292	A phase Ib/III open-label, randomised study of capivasertib plus CDK4/6 inhibitors and fulvestrant vs. CDK4/6 inhibitors and fulvestrant in HR-positive and HER2-negative locally advanced, unresectable or metastatic breast cancer.	08/2029

[4] None of the deaths were considered by the local investigators to be related to capivasertib or fulvestrant.
[5] Toxicity adjustment due to + 10.7% discontinuations due to AEs.
[6] Due to the ongoing status of the trial, the risk of bias is currently considered unclear.
[7] The trial was designed and overseen by a steering group of medical oncology experts, including representatives from AstraZeneca (the sponsor). Data analyses were performed by a clinical research organization and paid for by the sponsor. Editorial and medical writing assistance with subsequent drafts was provided by paid representatives of the sponsor who are not authors.

Available assessments

- In June 2023, NIHR published a Health Technology Briefing "Capivasertib with fulvestrant for HR+/HER2- locally advanced or metastatic breast cancer "[13].
- No further assessments were identified via NICE, ICER, CADTH and G-BA.

Other aspects and conclusions

- In April 2024, the **CHMP adopted a positive opinion**, recommending the granting of a marketing authorisation for Truqap®, indicated in combination with fulvestrant for the treatment of adult patients with 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. In November 2023, the **FDA approved Truqap®** with fulvestrant for adult patients with HR-positive, HER2-negative locally advanced or metastatic breast cancer with one or more PIK3CA/AKT1/PTEN-alterations, as detected by an FDA-approved test, following progression on at least one endocrine-based regimen in the metastatic setting or recurrence on or within 12 months of completing adjuvant therapy.
- **CAPItello-291** (NCT04305496) is an **ongoing**, phase 3, randomised, double-blind trial assessing the efficacy and safety of capivasertib–fulvestrant therapy in patients with hormone receptor-positive, HER2-negative advanced breast cancer whose disease had progressed during or after aromatase inhibitor therapy, with or without a CDK4/6 inhibitor. Premenopausal, perimenopausal, or post-menopausal women or men ≥18 years with locally advanced or metastatic HR-positive, HER2-negative breast cancer who had progression on aromatase inhibitor-based treatment and could have received up to two prior lines of endocrine therapy and up to 1 line of chemotherapy for locally advanced or metastatic disease, were eligible.
- The **dual primary endpoint** was investigator-assessed **PFS** both in the overall population and among patients with AKT pathway–altered (PIK3CA, AKT1, or PTEN) tumours. In the overall population, the median PFS was 7.2 months in the capivasertib–fulvestrant group, as compared with 3.6 months in the placebo–fulvestrant group (HR for progression or death 0.60; 95% CI, 0.51-0.71; p<0.001). In the AKT pathway–altered population, the median PFS was 7.3 months in the capivasertib–fulvestrant group, as compared with 3.1 months in the placebo–fulvestrant group (HR 0.50; 95% CI, 0.38-0.65; p<0.001).
- Global health status and QoL were **maintained** in both the capivasertib–fulvestrant and placebo-fulvestrant groups (for longer with capivasertib–fulvestrant than with placebo-fulvestrant).
- The **original and adapted ESMO-MCBS** were applied, resulting in a final adjusted magnitude of benefit **grade 3 and 2**, respectively.
- Due to the ongoing status of the trial, the **risk of bias was considered unclear**. However, it is **increased** by the industry-funded background of the trial.
- Besides the CAPItello-291 trial, one phase Ib/III open-label, randomised study of capivasertib plus CDK4/6 inhibitors and fulvestrant vs. CDK4/6 inhibitors and fulvestrant in HR-positive and HER2-negative locally advanced, unresectable or metastatic breast cancer, was identified via ClinicalTrials.gov.
- Final analysis data from the CAPItello -291 trial and further robust phase 3 data in patients with AKT pathway-altered tumours are required to substantiate the first results of the CAPItello trial.

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Abbreviations: AE=adverse event, AI=aromatase inhibitor, AJ=adjustment, C=comparator, CADTH=Canada's Drug and Health Technology Agency, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CT=computed tomography, ECG=Electrocardiogram, ECOG= Eastern Cooperative Oncology Group, EMA=European Medicines Agency, ER=oestrogen receptor, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FFPE=Formalin-fixed paraffin-embedded, FM=final magnitude of clinical benefit grade, G-BA=Gemeinsamer Bundesausschuss, HER=human epidermal growth factor receptor, HR=hormone receptor, HR=hazard ratio, I=intervention, ICER=Institute for Clinical and Economic Review, Int.=intention, LHRH=Luteinising hormone-releasing hormone, MG=median gain, MRI=magnetic resonance tomography, MUGA=multiple-gated acquisition, n=number of patients, NICE=National Institute for Health Care Excellence, NIHR=National Institute for Health and Research, NYHA=New York Heart Association, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, QoL=quality of life, RECIST=Response Evaluation Criteria in Solid Tumours, SAE=serious adverse event, SERD=Selective oestrogen receptor degrader, ST=standard treatment, WHO=World Health Organisation

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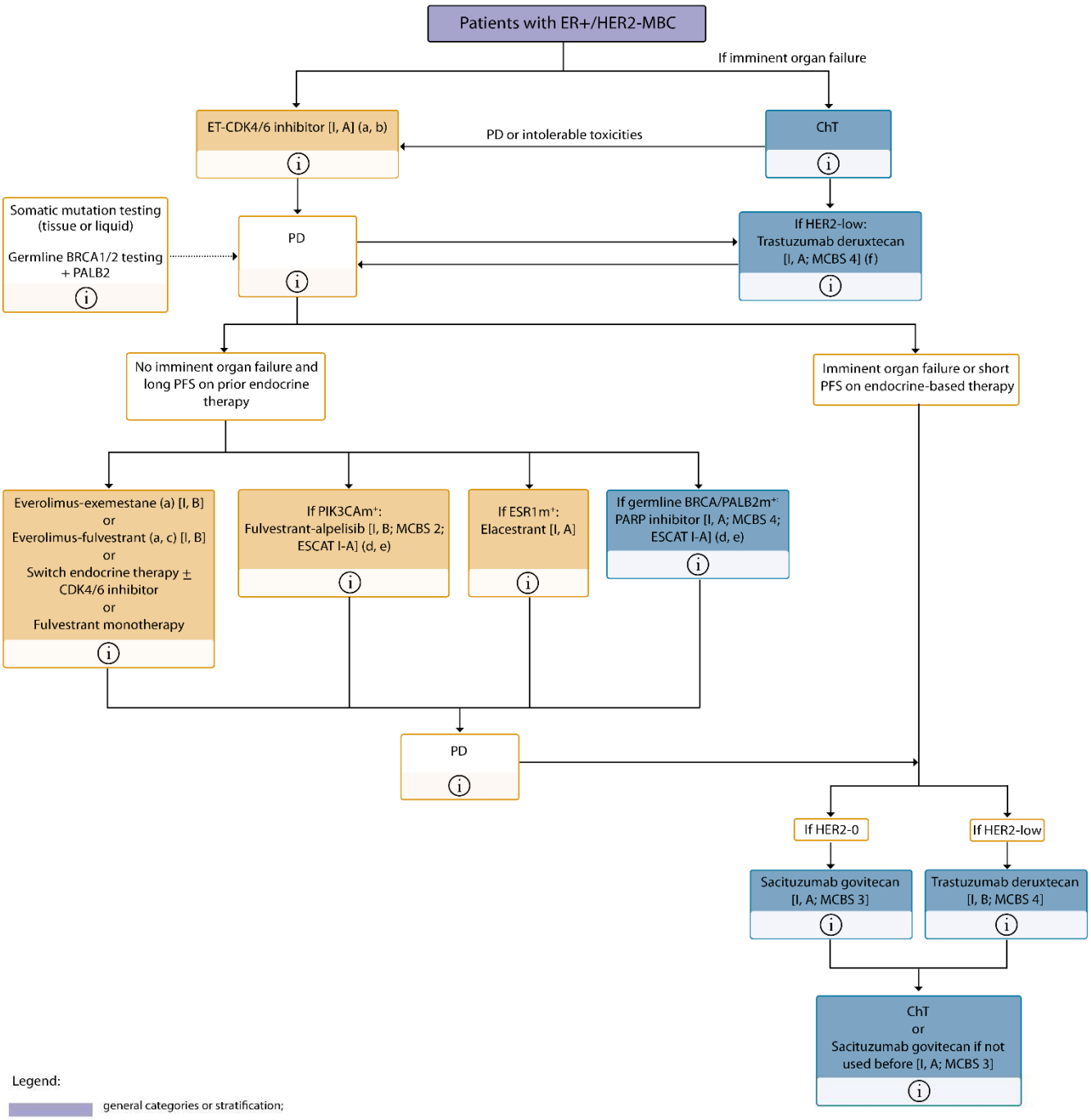
Appendix – Figure 1: ESMO treatment recommendation for ER-positive HER2-negative breast cancer



AI, aromatase inhibitor; CDK4/6, cyclin-dependent kinase 4 and 6; ChT, chemotherapy; EMA, European Medicines Agency; ER, estrogen receptor; ESCAT, ESMO Scale for Clinical Actionability of Molecular Targets; ESR1, estrogen receptor 1; ET, endocrine therapy; FDA, Food and Drug Administration; HER2, human epidermal growth factor receptor 2; m, mutation; MBC, metastatic breast cancer; MCBS, ESMO-Magnitude of Clinical Benefit Scale; OFS, ovarian function suppression; PALB2, partner and localiser of BRCA2; PARP, poly (ADP-ribose) polymerase; PD, progressive disease; PFS, progression-free survival; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

(a) OFS if the patient is premenopausal.

(b) If relapse <12 months after end of adjuvant AI: fulvestrant–CDK4/6 inhibitor (a); if relapse >12 months after end of adjuvant AI: AI–CDK4/6 inhibitor (a).

(c) Preferred if the patient is ESR1 mutation positive [ESCAT score: II-A]. (d)

(d) ESMO-MCBS v1.1 (Cherny, 2017) was used to calculate scores for new therapies/indications approved by the EMA or FDA. The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee (https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms).

(e) ESCAT scores apply to genomic alterations only. These scores have been defined by the guideline authors and validated by the ESMO Translational Research and Precision Medicine Working Group. (Mateo, 2018)

(f) Trastuzumab deruxtecan can also be given following adjuvant ChT in the setting of fast progression (DESTINY-Breast04/EMA indication)