Advanced breast cancer resistance to SoC therapies

- More than two-thirds of patients with advanced breast cancer have hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2−) tumors.
- Endocrine therapy (ET) is the core treatment for patients with HR+/HER2− advanced breast cancer, most commonly in the form of an aromatase inhibitor (AI), tamoxifen (a selective estrogen receptor modulator) or fulvestrant (a selective estrogen receptor degrader; SERD).
- Many patients additionally receive a cyclin-dependent kinase (CDK) 4/6 inhibitor in combination with ET, which prolongs benefits compared to ET-alone.
- Patients eventually develop resistance to ET plus CDK4/6 inhibitor combination therapy, which results in disease progression.

Study rationale for triple combination therapy

- The phosphoinositide 3-kinase (PI3K)/protein kinase (AKT)/phosphatase and tensin homologue (PTEN) signaling pathway regulates cell growth, proliferation, survival, and proliferation.
- Altered activation of the PI3K/AKT/PTEN pathway is a key compensatory mechanism driving multi-drug resistance in cancers receiving ET with a CDK4/6 inhibitor.2,3
- Because AKT is downstream of PI3K and PTEN, AKT inhibitors can suppress pathway hyperactivity caused by PI3KCA, AKT1 or PTEN alterations.
- Capivasertib is a potent selective inhibitor of AKT1, AKT2 and AKT3 that has demonstrated synergistic antitumor activity with fulvestrant in vitro and in vivo experimental models.4
- This Phase II FAKTION trial showed that patients with HR+/HER2− advanced breast cancer had significantly longer progression-free survival (PFS) when treated with capivasertib plus fulvestrant compared with fulvestrant alone (hazard ratio [HR] 0.39; 95% confidence interval [CI] 0.23, 0.69).5

Molecular targets of the triple combination therapy

- PIK3CA, AKT1, AKT2, AKT3, PTEN, CDK4, CDK6, cyclin D-CDK4/6, cyclin E-CDK2, cyclin A-CDK2, cyclin A-CDK4, cyclin B-CDK1, cyclin D1-CDK4/6, cyclin E-CDK2, cyclin E-CDK4, cyclin A-CDK4, cyclin B-CDK1, cyclin D1-CDK4/6.

Objectives

- To assess the safety and tolerability of capivasertib plus palbociclib and fulvestrant when dosed concomitantly in patients with HR+/HER2− advanced breast cancer.
- To confirm the recommended Phase III dose and/or maximum tolerated dose of the triple-dose combination.

Patient population

- Study participants must be aged ≥ 18 years.
- Women or men aged ≥ 18 years at the time of screening.
- Histologically confirmed HR+/HER2− breast cancer determined from the most recent tumor sample as per the American Society of Clinical Oncology and College of American Pathologists guidelines.6,7
- Previous treatment with an ET (tamoxifen or an AI) on an as a single agent or in combination with:
  - radiological evidence of breast cancer recurrence in progression within 6 months of completing a definitive ET regimen.
  - radiological evidence of progressive disease while on or within 12 months of completing a definitive ET regimen.
  - OR radiological evidence of progression while receiving the ET for locally advanced or metastatic breast cancer (this does not need to be the most recent therapy).

Dosing schedule for the triple combination therapy

- Capivasertib + fulvestrant + palbociclib will be administered with an intermittent schedule based on a 28-day dosing cycle.

Study drugs will be administered with an intermittent schedule based on a 28-day dosing cycle

- Each cycle consists of 21 treatment days and 7 non-treatment days.
- The dosing schedule is as follows:
  - Capivasertib 300 mg on days 1, 8 and 15 of each cycle.
  - Fulvestrant 250 mg (as a single intramuscular injection) on day 1 of each cycle.
  - Palbociclib 210 mg on days 1–21 of each cycle.
  - Treatment can be repeated for up to 12 cycles or until disease progression.

References

4. Capivasertib was discovered by AstraZeneca subsequent to a collaboration with Astex Therapeutics (and its collaboration with the Institute of Cancer Research, UK) in 2008.
5. Capivasertib is a potent selective inhibitor of AKT1, AKT2 and AKT3 that has demonstrated synergistic antitumor activity with fulvestrant in vitro and in vivo experimental models.

Acknowledgments and disclosures

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- More than one line of ET for inoperable locally advanced or metastatic disease.
- More than one line of chemotherapy for inoperable locally advanced or metastatic disease.
- Any previous treatment with a SERD (including unlicensed SERDs), allosteric mechanistic target of rapamycin (mTOR) inhibitors (e.g. everolimus), FAK inhibitors (e.g. apatinib) or AKT inhibitors.
- Previous CDK4/6 inhibitor treatment of metastatic cancer; patients who received a CDK4/6 inhibitor as (neo)adjuvant therapy remain eligible, provided that it was completed at least 12 months before enrolment.
- A disease burden that makes the patient ineligible for ET according to the investigator’s local judgement (e.g. symptomatic secondary disease that is potentially life-threatening in the short term).

Phase III key inclusion criteria

- Women or men aged ≥ 18 years at the time of screening.
- Histologically confirmed HR+/HER2− breast cancer determined from the most recent tumor sample as per the American Society of Clinical Oncology and College of American Pathologists guidelines.
- Previous treatment with an ET (tamoxifen or an AI) on an as a single agent or in combination with:
  - radiological evidence of breast cancer recurrence in progression within 6 months of completing a definitive ET regimen.
  - radiological evidence of progressive disease while on or within 12 months of completing a definitive ET regimen.
  - OR radiological evidence of progression while receiving the ET for locally advanced or metastatic breast cancer (this does not need to be the most recent therapy).

Phase III key exclusion criteria

- Women on or aged ≥ 18 years at the time of screening.
- Histologically confirmed HR+/HER2− breast cancer determined from the most recent tumor sample as per the American Society of Clinical Oncology and College of American Pathologists guidelines.
- Previous treatment with an ET (tamoxifen or an AI) on an as a single agent or in combination with:
  - radiological evidence of breast cancer recurrence in progression within 6 months of completing a definitive ET regimen.
  - radiological evidence of progressive disease while on or within 12 months of completing a definitive ET regimen.
  - OR radiological evidence of progression while receiving the ET for locally advanced or metastatic breast cancer (this does not need to be the most recent therapy).

Phase III study endpoints

- PFS, defined as the time from patient randomization until investigator-assessed disease progression (per Response Evaluation Criteria in Solid Tumors v1.1) or death due to any cause.
- Overall survival.
- PFS of the subgroup of patients with tumors carrying an alteration in PIK3CA, AKT1 and/or PTEN.
- Second progression-free survival (PFS2; objective response rate, duration of response, clinical benefit rate at 24 weeks, health-related quality-of-life measures (EORTC QLQ-C30 and EORTC QLQ-BR23) scores and time to definitive debulking (World Health Organization/Eastern European Oncology Group performance status).
- Pharmacokinetics of capivasertib administered with palbociclib and fulvestrant.
- Safety and tolerability of combined capivasertib, palbociclib and fulvestrant therapy relative to placebo, palbociclib and fulvestrant, evaluated in terms of adverse and serious adverse events, vital signs, clinical chemistry/hematology/glucose metabolism parameters and cardiac parameters.

CAPItello-292 will enroll patients globally, including from sites in Australia, Belgium, Canada, Denmark, France, Japan, Sweden and the USA.