A prospective, direct-to-patient study to evaluate clinical and molecular mechanisms of resistance to capivasertib in estrogen receptor-positive metastatic breast cancer

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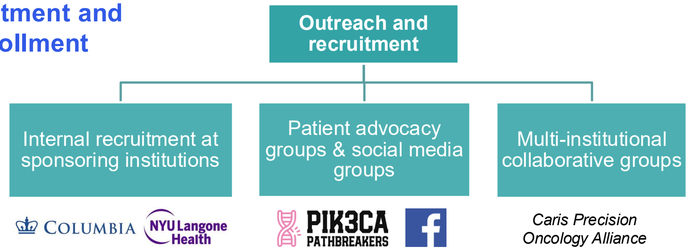
Background

- The AKT inhibitor capivasertib was FDA approved in November 2023 for patients with estrogen receptor-positive (ER+) metastatic breast cancer (MBC) harboring mutations in *PIK3CA*, *AKT1*, and/or *PTEN*.
- In the CAPItello-291 trial, capivasertib combined with fulvestrant more than doubled progression free survival to 7.3 months versus 3.1 months with fulvestrant alone, and exhibited a favorable toxicity profile. However, almost all patients eventually progress on therapy.
- Preclinical studies have identified several resistance mechanisms to AKT inhibitors including reactivated PI3K pathway signaling and increased compensatory signaling of parallel pathways. However, there are no validated clinical biomarkers of resistance to capivasertib.
- Liquid biopsies can facilitate comprehensive genomic analyses of drug resistance mechanisms, with greater ease of use and broader accessibility compared to tissue biopsies.
- We are conducting a prospective, liquid biopsy-based study to characterize clinical mechanisms of capivasertib resistance in patients.

Study Overview

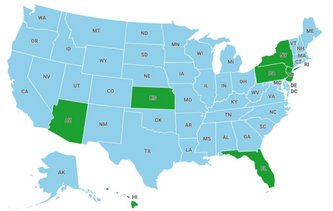
- **Study Design:** prospective, decentralized, direct-to-patient study open to patients treated anywhere in the United States who are starting capivasertib (n = 20).
- **Major eligibility criteria:** 1) ER+ MBC with mutations in *PIK3CA*, *AKT1*, and/or *PTEN*, 2) planned to initiate capivasertib as next line of therapy.
- **Study procedures:**
  - Circulating tumor DNA (ctDNA) will be collected at two time points: 1) before or within 2 weeks after starting capivasertib and 2) after progression on or discontinuation of capivasertib.
  - Remote participants will be mailed liquid biopsy kits to their homes and collect blood samples locally.
  - Whole exome and whole transcriptome sequencing of paired samples will be performed using Caris Assure.

Recruitment and Enrollment



Enrollment to date

- Patient recruitment was initiated in January 2025.
- As of November 20 2025, 12 patients from 8 medical institutions in 7 states have been enrolled in the study.
- 9 patients have come off study due to disease progression or treatment-related toxicity; of these, 5 have had paired pre- and post-treatment samples collected.



Study Schema

INCLUSION CRITERIA:

- ≥ 18 years of age
- Diagnosed with estrogen receptor-positive metastatic breast cancer
- Known mutation(s) in *PIK3CA, AKT1,* and/or *PTEN*
- Planned to start capivasertib as next line of therapy

Before or up to 2 weeks after starting capivasertib	On treatment with capivasertib	Upon discontinuation of capivasertib	After collection of 20 paired samples
Collect baseline ctDNA sample using Caris Assure kit Mail ctDNA to Caris Life Sciences	Clinical management as per primary oncologist Study team collects local records every 2-3 months	Collect post-treatment ctDNA sample using Caris Assure kit (*for patients who have received ≥2 months of capivasertib) Mail ctDNA to Caris Life Sciences	Whole exome and whole transcriptome sequencing of paired ctDNA samples by Caris Life Sciences

Sequencing and Analysis

- Paired pre- and post-treatment samples will be analyzed using whole exome and whole transcriptome sequencing via the Caris Assure platform, then compared to identify acquired genomic and transcriptomic alterations on capivasertib.
- Hypotheses: alterations in negative regulators of mTORC1 and parallel pathways such as PIM signaling will drive clinical resistance to capivasertib.

This study is currently recruiting! For more information, please contact the study team:

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