Investigators in the Division of Gynecologic Oncology at Penn Medicine are conducting a clinical trial to investigate combination therapy with olaparib and AZD6738 in women with high grade serous ovarian cancer (including germline or somatic BRCA mutations), or primary peritoneal and/or fallopian tube cancer. [ClinicalTrials.gov Identifier: NCT03462342]. Known as CAPRI, this trial is currently enrolling at Penn Medicine.1

CAPRI is a clinical trial that was developed by using a preclinical drug development platform developed by the Simpkins lab in the Ovarian Cancer Research Center (OCRC) within the Division of Gynecology Oncology. The goal of this platform is to identify new drug combinations with strong scientific rationale in the laboratory, with the ultimate goal of moving these regimens to the clinic for patients with ovarian cancer.

Background
Platinum-based chemotherapies (carboplatin and paclitaxel) are the first-line treatment for ovarian cancer at this time. Like radiotherapy and other chemotherapies, these drugs interfere with DNA repair, causing apoptosis in cancer cells. Because their use is limited by drug resistance, finding alternative therapeutic strategies has been a long-time objective for cancer researchers.

The majority of ovarian malignancies (and most ovarian cancer deaths) are attributable to high-grade serous ovarian cancers (HGSOC), which are known to have a high incidence of DNA repair defects in women both with and without germline BRCA mutations.

Olaparib, a targeted poly (ADP ribose) polymerase inhibitor (PARPi), is currently indicated for maintenance therapy in women (with germline or somatic BRCA gene mutations) after front line and second line therapy. In addition, olaparib is indicated in the recurrent setting for germline and somatic BRCA mutations after three prior therapies. Olaparib induces apoptosis in cancer cells by preventing them from repairing damaged DNA.

Historically, olaparib monotherapy has demonstrated modest clinical activity in recurrent BRCA-mutant high-grade serous ovarian cancers. Recent studies suggest, however, that the efficacy of PARP inhibitors improves substantially when combined with agents that inhibit the DNA damage checkpoint kinase ATR.2

One such agent, AZD6738, an investigational potent selective oral ATR inhibitor, works by blocking cancer cell enzymes that control the cell cycle checkpoints (G2-M) and DNA repair.

The goal of combination therapy is to improve response rates to PARPi monotherapy and overcome PARPi resistance. By targeting two alternative DNA repair pathways, dual inhibition of PARP and ATR will lead to increased DNA double strand breaks and cell death.

OCRC researchers have shown that combination olaparib/AZD6738 results in synergistic tumor regression in PARPi-resistant OVCA patient-derived xenograft (PDX) models from BRCA mutant patients. This drug combination will now be evaluated in a clinical trial (CAPRI) for ovarian cancer patients. Patients may enroll in a companion trial evaluating [18F]FTT PARPi tracer as a potential biomarker of response to treatment.

About CAPRI
CAPRI will determine the safety and tolerability of combination olaparib/AZD6738 and the objective response rate and progression free survival of the combined regimen in women with recurrent ovarian cancer in distinct patient cohorts.

Women with recurrent platinum sensitive and resistant high grade serous ovarian cancer may be enrolled in CAPRI. Patients also with a germline or somatic BRCA mutation who have progressed on a prior PARPi are eligible. If found eligible to participate following

(Continued on back)
screening, they will be given olaparib to be taken on all 28 days of the cycle and investigational AZD6738 from days 1–7.

For the first cycle, patients will come in every week; after this, patients are expected to come in each month at the end of each 28-day cycle. Patients will undergo scans for tumor assessments every 2 cycles, and if stable disease or response to therapy is documented after cycle 4, imaging will continue every 3 cycles thereafter.

Patients may also enroll in a companion clinical trial called the [18F]FTT Ovarian Cancer Trial. This study is testing a novel PARPi molecular tracer ([18F]FTT) developed by Penn Nuclear Medicine scientists as a non-invasive imaging modality as a biomarker predictive of response to PARPi treatments.

Persons interested in CAPRI or FTT may contact Katie Elkins, MEd, at 215–615–6740 (Research Coordinator), Sangeeta Shenoy, (Project Manager) at 215–614–0234, or Fiona Simpkins, MD (Study PI), at 215–662–3318.

References
1. Combination ATR and PARP Inhibitor (CAPRI) Trial With AZD6738 and Olaparib in Recurrent Ovarian Cancer (CAPRI) [ClinicalTrials.gov Identifier: NCT03462342]

FACULTY TEAM
Established in 2007, the Penn Ovarian Cancer Research Center (OCRC) serves as a catalyst to promote comprehensive and interdisciplinary research on ovarian cancer in collaboration with the Jordan Center for Gynecologic Cancer, the Abramson Cancer Center, the Basser Center for BRCA, the Wistar Institute and the Penn Immunotherapy Program, as well as numerous local, national and international investigators and clinicians.

The ultimate goal of the OCRC and its programs is to improve the quality of life for women with ovarian cancer and provide support and guidance to their families.

Ovarian Cancer Research Center Faculty
Robert A. Burger, MD
Ron Drapkin, MD, PhD
Andrea Facciabene, PhD
Wei-Ting Hwang, PhD
Chunsheng Li, PhD
Mark A. Morgan, MD
Daniel J. Powell, Jr., PhD
Fiona Simpkins, MD
Janos Tanyi, MD, PhD
Lin Zhang, MD

ACCESS
Department of Obstetrics and Gynecology
Biomedical Research Building
421 Curie Blvd., Rm. 1215
Philadelphia, PA 19104