**Background and Hypothesis**

PARPi can induce a senescence-like phenotype in cancer cells with cell survival dependent on anti-apoptotic proteins.

In PARPi therapy-induced HGSC and TNBC senescence cell survival depends on the Bcl-2 family member Bcl-XL. Increased expression of Bcl-XL occurs in 88% of HGSC.

Olaparib and navitoclax, a Bcl-2/Bcl-XL inhibitor, are synergistic in pre-clinical models of HGSC and TNBC.

**Hypothesis:** Olaparib increases tumor cell survival dependence on inhibition of cell death by Bcl-2/Bcl-XL. Thus, navitoclax will augment apoptosis induced by PARP inhibition with olaparib.

**Study Design**

- **Primary Objective**
  To define a dose of Navitoclax that can be combined safely with Olaparib in women with HGSC and triple negative breast cancer (BRCA ½ or PALB2 mutation) for Phase II study

- **Secondary Objectives**
  To determine the pharmacokinetic (PK) profile of Olaparib and Navitoclax

- **Exploratory Objectives**
  - To determine if anti-apoptotic, pro-apoptotic effector proteins and pro-apoptotic BH3-only proteins in baseline tumor biopsies are potential predictive biomarkers
  - Evaluate cell fate decision biomarkers including senescence biomarkers in biopsy tissues, liquid biopsies (senescence secretome), and ex-vivo micro-dissected tumor (MDT) predict response to treatment
  - To determine if ex vivo 3D organoids derived from biopsy samples prior to treatment can provide data on sequencing drug sequencing

**Key Eligibility Criteria**

- Recurrent metastatic HGSC with progression > 6 months from last platinum OR metastatic TNBC with germline or somatic BRCA1, BRCA2 or PALB2 pathogenic mutations
- Life expectancy ≥16 wks, ECOG PFS ≤ 2
- No limit on # of prior lines of treatment for HGSC . TNBC ≤ 2 lines
- Prior maintenance, or treatment, with a PARP inhibitor is allowed provided progression did not occur on or within 6 months of discontinuing the drug
- Willing/able to undergo study related procedures and biopsies
- Adequate hepatic, bone marrow, coagulation and renal function.
- Able to tolerate Olaparib

**Future directions**

- Identification of RP2D and potential phase II
- Analysis of correlative studies to identify optimal sequencing, potential biomarkers and new senolytic targets

**Acknowledgements**

Janet D. Cottrelle Foundation;, Astra Zeneca and Abbvie (drug supply)