

NOW Feasibility Study of Neoadjuvant Olaparib for Frontline BRCA Mutant Ovarian Cancer

Victoria Michael¹, Shannon N. Westin², Michaela Onstad Grinsfelder², Larissa Meyer³, Nicole Fleming³, Ying Yuan⁴
 Department of Gynecologic Oncology, The University of Texas MD Anderson Cancer Center¹
 McGovern Medical School, The University of Texas Health Science Center at Houston¹

Background

- Studies suggest primary ovarian cancer is a chemo-sensitive disease with measurable response in up to 70% of patients [1]
- Response to NACT is rare (4-6%) [1]
- Recurrence after clinical complete response is ~75% likely [1]
- The data suggests the need for better frontline therapy
- The standard of care treatment for platinum sensitive ovarian cancer is a platinum-based doublet with or without bevacizumab [2]
- For breast cancer, chemotherapy has been replaced in the BRCA mutant population with PARP Inhibition with impressive response rates[3]
- Majority of high grade serous ovarian cancers are BRCA wildtype, while 20% have somatic or germline BRCA mutations[4]
- Approximately 50% of the tumors evaluated had homologous recombination (HR) repair deficiencies [4]
- Olaparib is a potent Polyadenosine 5'diphosphoribose PARP inhibitor. PARP enzymes are involved in repairing DNA SSBs. Inhibition allows SSBs to progress to more serious DSBs [5]
- Tumors with HR deficiencies such as BRCA 1/2, RAD51 C/D, and PALB2, cannot repair the DNA damage causing cell apoptosis.
- Olaparib may offer efficacious and less toxic cancer treatment compared to available chemotherapy treatment regimens

Figure 1. Mechanism of sensitivity to olaparib in cells with HR deficiencies [6]

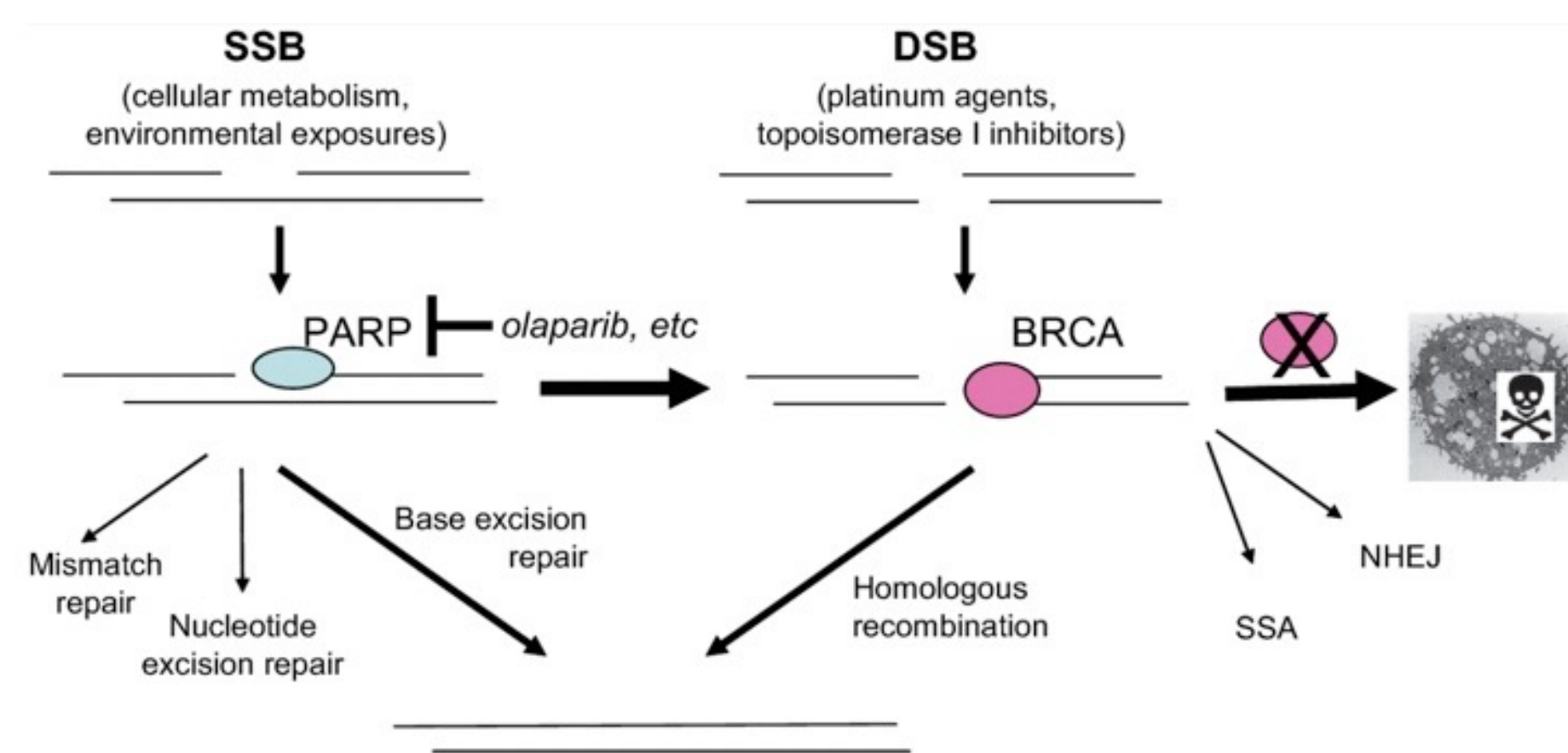
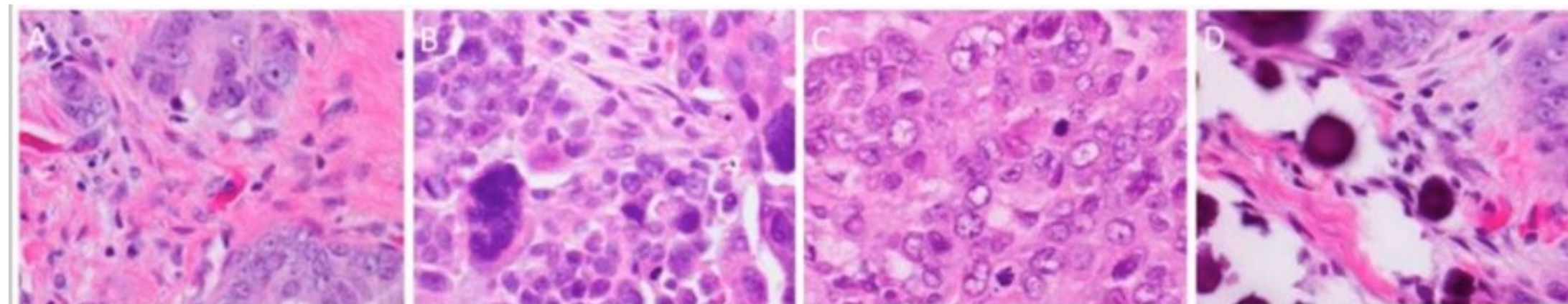


Figure 2. Cytology of High Grade Serous Ovarian Cancer [7]



Cytological features of high-grade serous cancer. (A): Multinucleated tumor giant cells; (B): severe pleomorphism and prominent nucleoli; (C): frequent mitotic figures; (D): psammoma bodies. All original magnifications × 40.

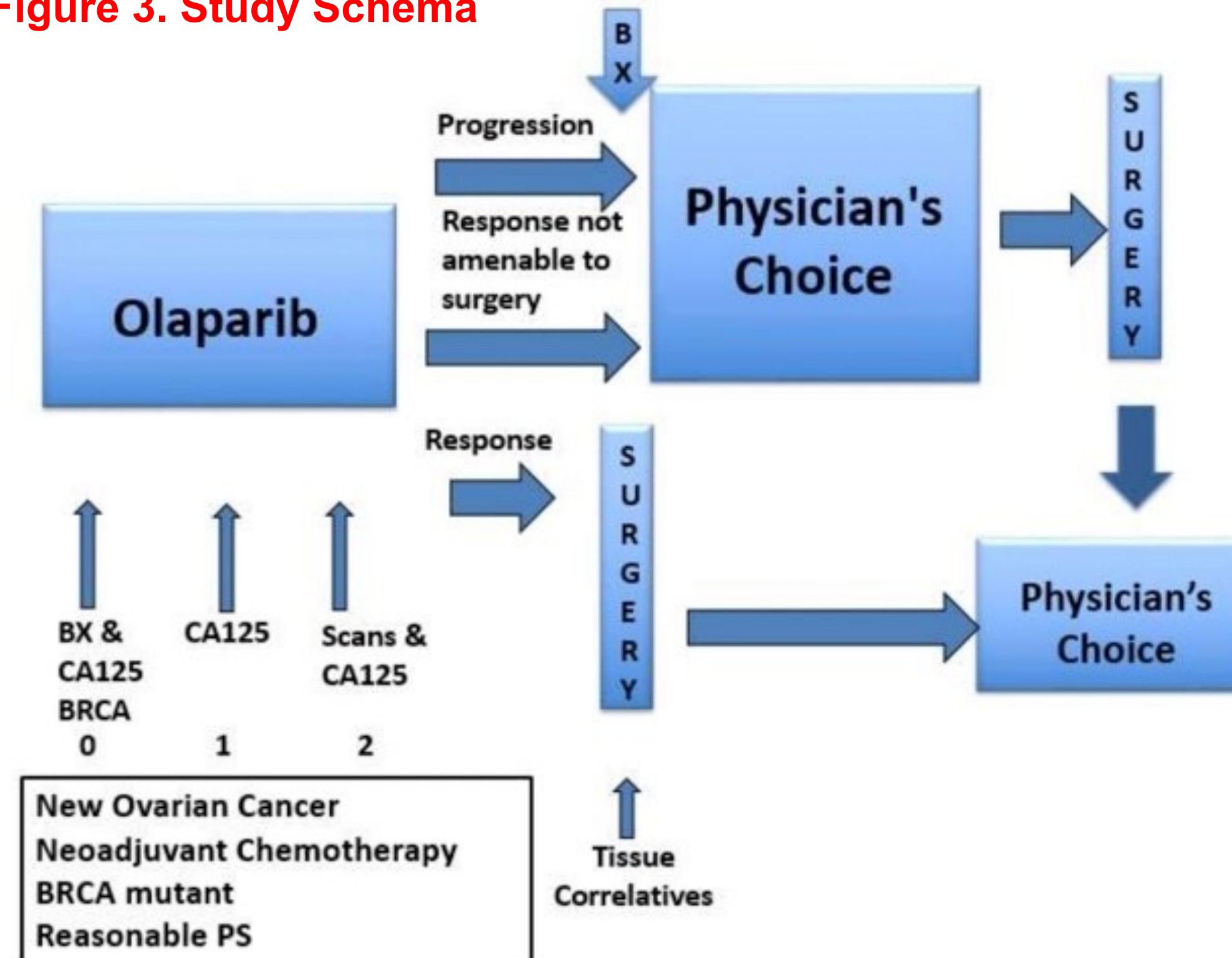
Objectives

- **Primary Objective:**
- To determine feasibility of daily olaparib given in neoadjuvant setting in women with primary advanced high grade non-mucinous epithelial ovarian, fallopian tube, or primary peritoneal cancer
- **Secondary Objectives:**
 1. Efficacy of neoadjuvant olaparib by using response rate,
 2. Proportion of subjects able to proceed to TRS (tumor reductive surgery) without chemotherapy
 3. Determine progression free survival (PFS),
 4. Complete pathologic response at interval TRS,
 5. Toxicity of olaparib in neoadjuvant setting,
 6. Toxicity of chemotherapy after neoadjuvant Olaparib, and
 7. Longitudinal symptom burden of patients treated with neoadjuvant olaparib and adjuvant chemotherapy
- **Exploratory Objectives:**
 1. Explore genetic material and protein expression in HR related pathways before and after treatment with olaparib
 2. Correlate molecular results with clinical endpoints including response and survival

Trial Design

- This is a single-arm, open-label, pilot study to assess the impact of olaparib in women with advanced stage, metastatic BRCA mutant ovarian cancer undergoing neoadjuvant chemotherapy. Patients who are to proceed with NACT will be approached for enrollment
- A total of 15 evaluable patients with untreated, advanced stage ovarian cancer undergoing neoadjuvant chemotherapy will be treated with olaparib 300mg (tablet formation) by mouth twice a day (PO BID) for 2 cycles. Each cycle will be 28 days long. Following 2 cycles of Olaparib, patients with no evidence of tumor progression will have tumor reductive surgery and then receive standard cytotoxic chemotherapy within 3-6 weeks of surgery according to provider discretion. Patients with tumor progression or responsive disease not amenable to surgery will undergo tumor biopsy then proceed to standard cytotoxic chemotherapy with goal of getting patients to a respectable state.
- Patients will have their laparoscopic tumor evaluation after receiving 2 cycles of neoadjuvant therapy. Patients scored as <10 by the validated scoring system (ability to resect to no gross residual disease) will proceed to primary tumor reductive surgery followed by physician's choice cytotoxic chemotherapy. Patients scored ≥ 10 will receive physician's choice cytotoxic chemotherapy with the goal of subsequent tumor reductive surgery (Figure 3)

Figure 3. Study Schema



PS, Performance Status; Bx, Biopsy; CA125, Cancer Antigen 125; BRCA, Breast Cancer Susceptibility Gene; Physician's Choice, Adjuvant therapy at the discretion of the treating physician

Patient Selection

Inclusion criteria:

- Age ≥ 18 years at time of signing informed consent
- Histology showing high-grade epithelial non-mucinous ovarian, primary peritoneal, or fallopian tube cancer
- Documented germline, or somatic testing by ctDNA, BRCA 1/2, RAD51C/D, PALB2
- No prior treatment for primary advanced (Stage III or IV) epithelial ovarian, primary peritoneal, or fallopian tube carcinoma such as irradiation, chemotherapy, hormonal therapy, immunotherapy, investigational therapy, surgery, and/or other concurrent agents or therapies
- A disposition to neoadjuvant chemotherapy with planned interval tumor reductive surgery after 3 complete cycles of treatment
- Have measurable disease based on RECIST 1.1. Evaluable disease includes nonmeasurable lesions, ascites, pleural effusion
- Peripheral neuropathy Grade 0 or 1 by CTCAE v5.0
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- Life expectancy of ≥ 16 weeks
- Postmenopausal or evidence of non-childbearing status. Women of childbearing potential must utilize acceptable contraception for two weeks before the first dose of Olaparib, the duration of the study, and at least for six months after the last dose of olaparib
- Adequate normal organ and marrow function

Patient Selection

- **Exclusion criteria:**
 - Prior treatment for ovarian, fallopian tube, or primary peritoneal cancer
 - Histology showing mucinous or low-grade epithelial carcinoma
 - Presence of other active invasive cancers
 - Resting electrocardiogram (ECG) indicating uncontrolled, potentially reversible cardiac conditions, as judged by the investigator
 - Any unresolved toxicity (>CTCAE grade 2) from previous anti-cancer therapy, excluding alopecia
 - History of hypersensitivity to olaparib or its excipients
 - Uncontrolled intercurrent illnesses
 - Subjects who are pregnant and/or breast-feeding
 - History of leptomeningeal carcinomatosis, uncontrolled or symptomatic brain metastasis or uncontrolled seizures
 - Patients with Myelodysplastic Syndrome (MDS)/Acute Myeloid Leukemia (AML) or with features suggestive of MDS/AML
 - Previous treatment with PARP inhibitor, including olaparib
 - Patients unable to swallow orally administered medication or patients with GI disorders likely to interfere with absorption of study drug
 - Concomitant use of known strong or moderate CYP3A inhibitors or inducers
 - Major surgery within two weeks of starting study treatment
 - Previous allogenic bone marrow transplant, double umbilical cord blood transplant
 - Whole blood transfusions in the last 120 days prior to entry to the study

Table 1. Patient Demographics and Clinical Features

Characteristic	Olaparib/Total (n=14)
Age, median (range)	58.3 (44-88)
Ethnicity, n (%)	
Hispanic/Latina	3 (21.4)
Not Hispanic/Latina	10 (71.4)
Unknown	1 (7.1)
Race, n (%)	
White/Caucasian	10 (71.4)
Asian	0 (0)
Black	1 (7.1)
Native American/Pacific Islander	0 (0)
Other	3 (21.4)
Stage, n (%)	
III	6 (42.9)
IV	2 (14.3)
N/A	6 (42.9)
Histology, n (%)	
High grade serous	14 (100)
Mutation, n (%)	
BRCA1	10 (71.4)
BRCA2	2 (14.3)
RAD51C	1 (7.1)
RAD51D	0 (0)
PALB2	1 (7.1)

Future Directions

The results of this study will help researchers and clinicians in their approach to find efficacious treatment for high grade primary epithelial ovarian cancer. The results will provide new insight on ways to personalize treatment for primary epithelial ovarian cancer by different strata, in this case genetic mutations in HR repair. Because little substantive progress has been made in the treatment and management of primary epithelial ovarian cancer in the last 30 years, it is crucial for researchers to use this data to reshape the necessary scientific models so that cancer medicine can take a step in the right direction in innovating new treatment regimens for this subset of gynecologic malignancies.