

PARP Inhibition after Preoperative Chemotherapy in Patients with Triple-Negative Breast Cancer (TNBC) or Known BRCA 1/2 Mutations: Hoosier Oncology Group BRE09-146



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ABSTRACT

Background: TNBC patients who do not achieve pathologic complete response (pCR) have an extremely high risk of disease recurrence. Based on recently reported I-SPY trial, TNBC patients who had residual disease category II or III had 2-year disease free survival (DFS) of only ~40% (*J Clin Oncol* 2009;27:18s). Currently, no standard systemic therapy exists for this high-risk group who represent a real opportunity to explore the potential impact of novel therapies. Recent laboratory and early clinical studies (*Nature* 2005;434:913, *NEJM* 2011;10:1056) identified a unique sensitivity to DNA-damaging chemotherapy and PARP inhibition. We initiated a randomized phase II trial of DNA-damaging chemotherapy (cisplatin) or PARP-inhibition + cisplatin in TNBC patients with residual invasive disease after standard anthracycline and/or taxane containing neoadjuvant chemotherapy. **Methods:** To ensure a high-risk population, patients must have residual disease category 0-2 based on the Miller-Payne classification system, residual cancer burden classification II or III, residual lymph node involvement, or at least 2 cm of residual invasive disease in the breast. After completion of standard radiation therapy, patients will be randomized 1:1 to cisplatin (75 mg/m² IV Day 1 every 3 weeks x 4 cycles) alone or in combination with PARP inhibition (PF-01367338 - 24 mg IV D1, 2, 3 of each 3 week cycle with a single dose escalation to 30 mg in the absence of significant toxicity in cycle 1 followed by maintenance PARP inhibition weekly x 24 weeks). The **primary objective** is 2-year DFS. To detect an improvement in 2-year DFS from 40% with cisplatin alone to 63.2% in the cisplatin + PF-01367338 arm (corresponding to HR=0.5), with 80% power using a one-side log-rank test with 0.10 level of significance, 102 patients are required in the primary analysis. **Secondary objectives** include safety, 1-year DFS, overall survival, and biomarkers of tumor recurrence, resistance to chemotherapy and/or PARP inhibition. Two dose escalation safety cohorts (N=13) were completed without dose limiting toxicity; the randomized portion began enrollment in 11/2010 and enrolled 6 patients as of 01/2011

METHODS

PRIMARY OBJECTIVE:

- To evaluate 2-year disease-free survival (DFS), in patients with TNBC or ER/PR + HER2- & known BRCA1/2 mutations treated with single agent cisplatin with or without PF-01367338 following preoperative chemotherapy

SECONDARY OBJECTIVES:

- Effects and tolerability of the combination
- One (1) year DFS
- Five (5) year overall survival
- Pharmacokinetic data
- Explore correlative studies of PARP inhibition

DESIGN

TRIPLE negative or ER+ with BRCA 1/2 mutation breast cancer patients with significant residual invasive disease after neoadjuvant chemotherapy

N=135

RANDOMIZATION

Cisplatin 75 mg/m² IV
D1 every 3 weeks
x 4 cycles

Cisplatin 75 mg/m² IV
D1 every 3 weeks
+
PF-01367338 24 mg* IV
D1, 2, 3
every 3 weeks
x 4 cycles
(* 30 mg from cycle 2)

PF-01367338 30 mg IV
maintenance
every week
x 24 weeks

Follow up for DFS

ACCRUAL STATUS

- Two dose escalation safety cohorts (N=13) were completed without dose limiting toxicity
- Randomized portion began enrollment in 11/2010 and enrolled 19 patients as of 04/30/2011

AVAILABLE SITES

CALIFORNIA
University of California, Los Angeles
Central Coast Medical Oncology Corporation (TORI), Santa Maria
West Valley Hematology Oncology (TORI), Northridge

COLORADO
University of Colorado Cancer Center, Clinical Investigations Core, Aurora

FLORIDA
Memorial Cancer Institute Breast Cancer Center (TORI), Hollywood
University of Miami, Sylvester Comprehensive Cancer Center, Miami

INDIANA
Fort Wayne Oncology & Hematology, Inc., Fort Wayne
Community Regional Cancer Center, Indianapolis
Indiana University Melvin and Bren Simon Cancer Center
Horizon Oncology Center, Lafayette
Community Hospital, Monroe Medical Associates, Munster
Northern Indiana Cancer Research Consortium, South Bend

MISSOURI
Siteman Cancer Center, St. Louis

NEVADA
Comprehensive Cancer Centers of Nevada (TORI), Las Vegas

NEW MEXICO
Presbyterian Medical Group (NMCCA), Albuquerque

NORTH CAROLINA
Hope: A Women's Cancer Center (TORI), Asheville

OHIO
University Hospitals, Case Medical Center, Cleveland

PENNSYLVANIA
PinnacleHealth Fox Chase Regional Cancer Center, Harrisburg
Bux-Mont Oncology Hematology Associates (FCCC) at Grand View Hospital, Sellersville

TENNESSEE
ACORN: The West Clinic, Memphis

VIRGINIA
Virginia Oncology Associates, Norfolk

INTRODUCTION

- Triple negative breast cancer (TNBC) patients with residual disease after neoadjuvant chemotherapy have poor outcomes.¹
- Targeting DNA repair with PARP inhibition in patients with BRCA pathway dysfunction leads to cell death in breast cancer models based on landmark preclinical studies.^{2,3}
- PARP inhibitors when used alone or in combination with chemotherapy in metastatic TNBC and BRCA mutant patients have shown promising results.^{4,5}
- The rationale for our randomized phase 2 study was to assess the benefit of using cisplatin with or without a new PARP inhibitor PF-01367338 in TNBC or BRCA deficient patients with residual disease after standard neoadjuvant chemotherapy.

ELIGIBILITY CRITERIA

- Age ≥ 18 years at the time of consent
- ECOG Performance Status 0 or 1
- Histologically or cytologically confirmed triple negative (ER-/PR-/HER2-) invasive breast cancer, stage I-III at diagnosis
- Patients with ER+ and/or PR+ should have known deleterious mutation in BRCA1 or BRCA2
- Must have completed preoperative (neoadjuvant) chemotherapy with an anthracycline or a taxane or both)
- Must have completed definitive resection of primary tumor with negative margins
- Must have significant residual invasive disease at the time of definitive surgery following preoperative chemotherapy
 - Significant residual disease is defined at least one of the following:
 - Miller-Payne response in the breast of 0-2⁶
 - Residual Cancer Burden (RCB) classification II or III⁷
 - Residual carcinoma in one or more regional lymph nodes that would meet AJCC 6th edition criteria for N1 - N3 disease
- Must have completed adjuvant radiation therapy, if indicated

CONTACT INFORMATION

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