TBCRC030: A randomized phase II study of preoperative cisplatin versus paclitaxel in patients (pts) with BRCA1/2-proficient triple negative breast cancer (TNBC): Evaluating the Homologous Recombination Deficiency (HRD) Biomarker

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Background and Rationale

Both platinum and taxane chemotherapy have activity in TNBC, however biomarkers predictive of benefit from specific agents are lacking.

Defects in the HR pathway may result in detectable DNA damage. The HRD assay quantifies DNA damage; may identify tumors in non-BRCA1/2 mutation carriers with 'BRCA-like' phenotype which may benefit from DNA repair-targeted treatment strategies.

HRD Score = Count of the number of loss of heterozygosity regions of intermediate size (> 15 Mb and < whole chromosome) observed in the tumor genome

HRD Score Predicts Response in TNBC to Agents Targeting HR pathway

PrECOG 0105: preoperative carboplatin/gemcitabine/iniparib for TNBC		
Mean HRD Scores: All patients (n=77)		
Responders	16.2	P=.0003
Non-Responders	11.2	
Mean HRD Scores: BRCA1/2 intact (n=58)		
Responders	16.6	P=.0006
Non-Responders	11.1	
28/58 of the non BRCA1/2 carriers were responders; 26/28 had an HRD score ≥ 10		

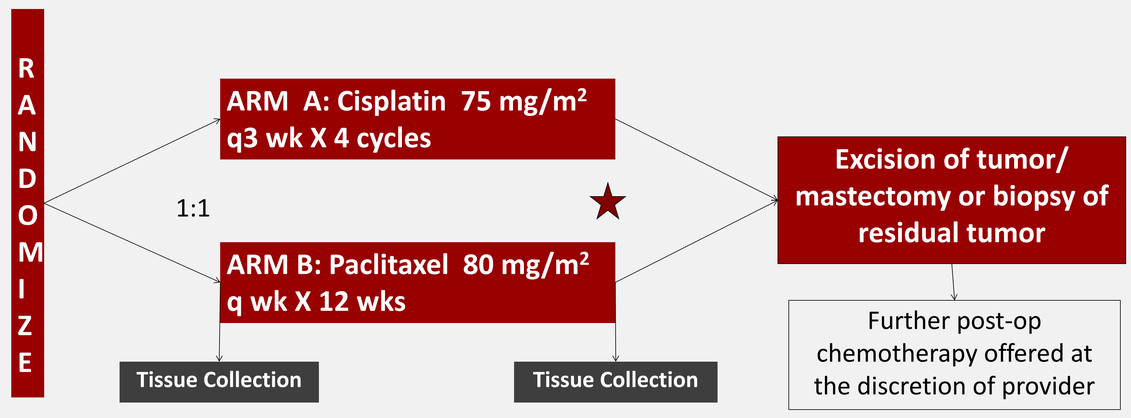
Abkevich V, et al. British Journal of Cancer, 2012 *Telli et al, SABCS 2012*

Objectives

This trial will prospectively determine the association between HRD score and response to platinum or taxane preoperative chemotherapy in TNBC, as well as explore other potential novel biomarkers of response.

- **Primary objectives:**
  - To determine the association of the HRD score with pathologic response to neoadjuvant platinum-based chemotherapy in TNBC.
  - To determine the association of the HRD score with pathologic response to neoadjuvant taxane-based therapy in TNBC
- **Secondary objectives:**
  - To compare the positive predictive value of HRD score for cisplatin vs taxane.
  - To determine the association of the HRD score with pathologic complete response (pCR) to neoadjuvant platinum or taxane--based chemotherapy.
  - To evaluate clinical and pathologic responses treated with preoperative cisplatin and paclitaxel.
  - To compare the performance of the HRD-TAI assay, the HRD LST assay, and the HRD combined assay (HRD-LOH, HRD-TAI, and HRD-LST) to predict pathologic response to cisplatin or taxane therapy.

Methods



Eligibility:
- No known BRCA germline mutation
- ER/PR/HER2 negative
- Invasive breast cancer: T1 (>1.5cm only), stage II or stage III
- Willing to undergo mandatory research biopsies

Key correlative analyses:
- 25 gene hereditary cancer panel (HCP) assay
- Number of subchromosomal regions with allelic imbalance extending to the telomere (N(tAI)) and Large Scale Transition (LST) assays.
- Signatures of taxane response
- Whole exome sequencing and copy number findings to determine total number of mutations, proportion of mutational processes, and identify specific mutations or deletions in a panel of DNA repair genes.
- RNA-seq to evaluate predictive gene expression signatures including BRCA1/BLM+FANCI levels
- Chromosome 15q26 copy number
- Chromosome 5 LOH, loss of Rad17 and PAM 50 subtypes
- Lehmann molecular TNBC subtypes
- Intratumoral and stromal lymphocytes
- Genomic alterations in circulating tumor DNA

Statistical considerations:
The primary clinical endpoint of the study is pathologic response: using Symmans residual cancer burden (RCB) score, patients with RCB-0/1 are considered to have good response, and patients with RCB-2/3 are considered to have poor response.

Target accrual- 160 patients. Assuming response rates of 40% to cisplatin and 30% to taxane and a drop-out rate of 12%, there will be 91% and 87% power, respectively, to detect a difference of 0.75 standard deviations in HRD score by pCR. Interim analysis of tissue quality and HRD score distribution is planned, to allow option of increasing accrual if below goal for samples to meet primary endpoint

Current Status: Opened on 01/29/2014, Current accrual: 3/160 patients

Participating centers: Dana-Farber/ Harvard Cancer Center, Baylor University, Duke University, Johns Hopkins University, Indiana University, University of Pittsburgh, University of Alabama Birmingham, University of North Carolina, Vanderbilt University Memorial Sloan-Kettering Cancer Center. **Study contacts: Overall PI:** Erica Mayer, MD, MPH: emayer@partners.org, **Coordinating Center contact for TBCRC sites:** Susan Barry and Kasey Componeschi, Project Manager CTOPM@dfci.harvard.edu **Clinical trial information: NCT01982448**

Companion trial for pts with BRCA germline mutations: Cisplatin vs. Doxorubicin/Cyclophosphamide in BRCA- NCT01670500

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