FAIRLANE: A Phase II Randomized, Double-Blind, Study Of the Akt Inhibitor Ipatasertib (GDC-0068) In Combination With Paclitaxel As Neoadjuvant Treatment For Early Stage Triple-Negative Breast Cancer

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BACKGROUND

PI3K/Akt Activation in Triple-Negative Breast Cancer (TNBC)

- TNBC often exhibits activation of PI3K/Akt signaling, associated with loss of PTEN expression, low INPP4B expression, and/or increased *PIK3CA* amplification (TCGA database)
- Inhibition of the PI3K/Akt pathway in diverse preclinical breast cancer models leads to radiosensitization and/or chemosensitization

Inhibition of PI3K/Akt Signaling in TNBC with Ipatasertib Combined with Chemotherapy

- Ipatasertib is an oral, potent ATP-competitive small molecule inhibitor of all three isoforms of Akt (Lin et at., Sci Signal 2012)
- The combination of ipatasertib with taxanes in preclinical breast cancer models resulted in enhanced efficacy relative to either ipatasertib or chemotherapy alone
- In a Phase Ib clinical study, the combination of ipatasertib with docetaxel or paclitaxel chemotherapy was well-tolerated and resulted in RECIST responses, particularly in patients with breast cancers having PI3K/Akt activation (Figure 1) (Isakoff et al., SABCS 2014)

STUDY DESIGN

- FAIRLANE is a randomized, double-blind, placebo controlled, multicenter, neoadjuvant Phase II study designed to estimate the efficacy of ipatasertib combined with paclitaxel versus placebo combined with paclitaxel in women with Stage Ia-IIIa TNBC (Figure 2)
- Approximately 150 patients will be enrolled, randomized in a 1:1 ratio, and stratified by PTEN status, node involvement, and tumor size
- All patients will undergo pretreatment and Day 8 tumor tissue acquisition to evaluate pathway biomarkers
- Following three cycles of treatment, patients will undergo surgery
- Following surgical resection of primary tumor, patients are expected to continue post-operative treatment with a standard adjuvant chemotherapy regimen at physician's discretion

Global FAIRLANE Study Sites

- US, Spain, Portugal

Study Endpoints

- **Primary efficacy endpoint:** pCR within the breast and axilla (ypT0/ Tis ypN0) in all patients and in patients with PTEN low tumors, will be assessed by local pathology evaluation following completion of neoadjuvant therapy and surgery
- **Secondary endpoints:** Objective response rate, safety, breast-conserving surgery rate, pharmacokinetics, and pathway biomarkers

Key Inclusion Criteria

- Premenopausal or postmenopausal women, age ≥ 18 years
- Eastern Cooperative Oncology Group (ECOG) performance status of 0-1
- Histologically documented TNBC, Stage I to operable Stage IIIa breast cancer
- Primary tumor ≥ 1.5 cm in largest diameter (cT1-3) by MRI. In the case of a multifocal tumor the largest lesion must be ≥ 1.5 cm
- Adequate archival or newly obtained fresh tissue samples

Key Exclusion Criteria

- Known HER2-positive, ER-positive, or PgR-positive breast cancer
- Patients with cT4 or cN3 stage breast tumors
- Bilateral invasive breast cancer
- Multicentric breast cancer (the presence of ≥ 1 tumor in different quadrants)
- Any prior treatment for the current primary invasive breast cancer
- Patients who have undergone excisional biopsy of primary tumor and/or axillary lymph nodes

Study Treatment

- Patients will receive 3 cycles of ipatasertib 400 mg or placebo orally once daily on Days 1 to 21 of each 28-day cycle, along with paclitaxel 80 mg/m^2 every 7 days for a total of 12 doses

Figure 1. Anti-Tumor Activity of Ipatasertib in Combination with Taxanes (Docetaxel or Paclitaxel) in Breast Cancer Patients (Phase Ib Study PAM4983g): Percentage SLD Change from Baseline by RECIST v1.1.

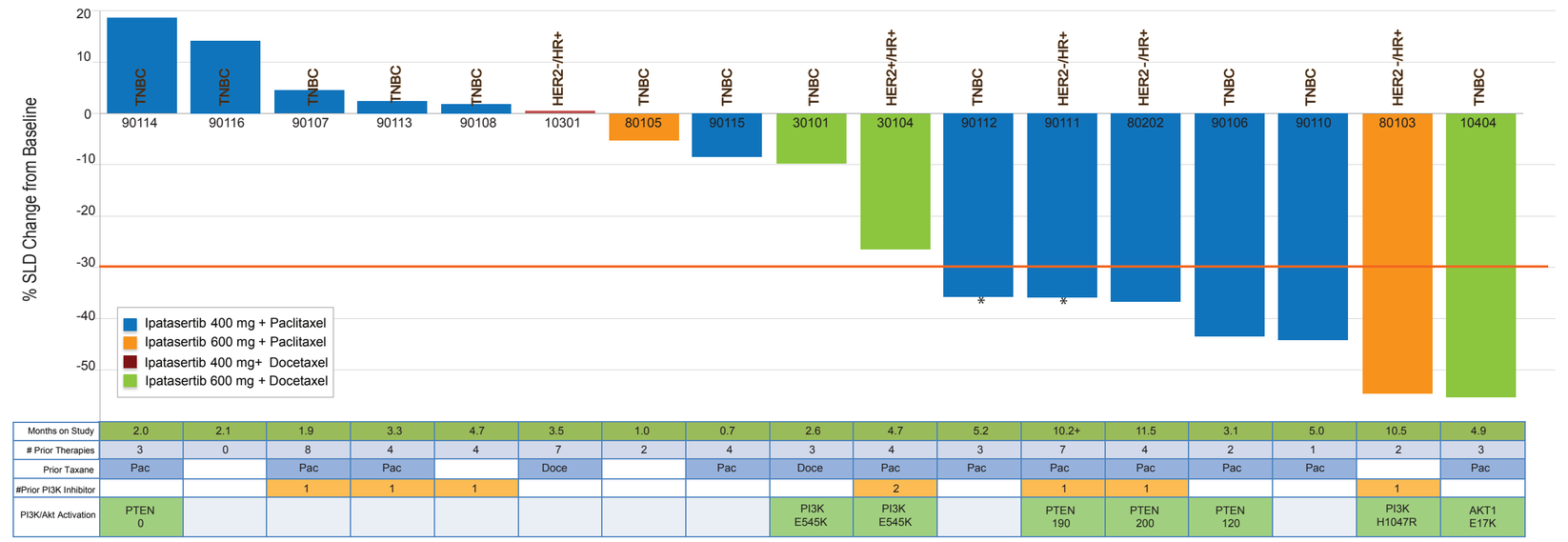
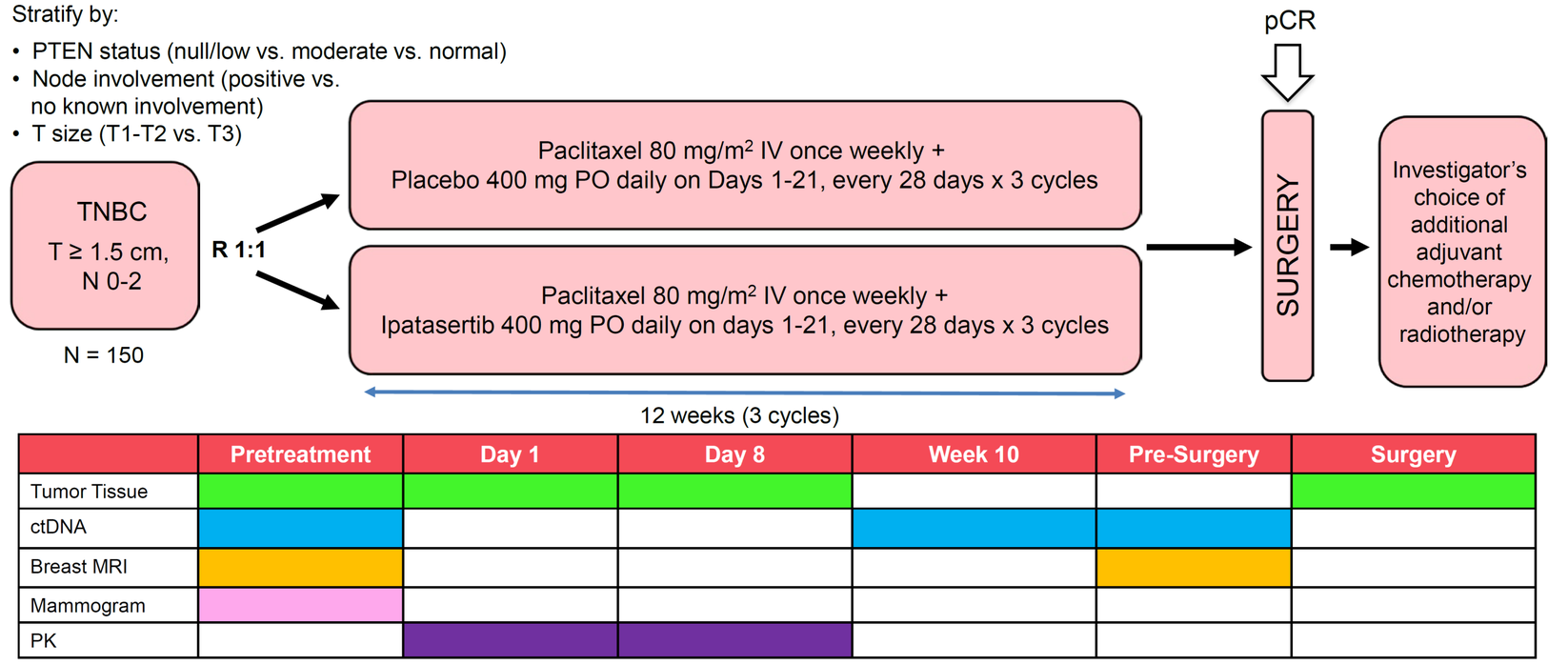


Figure 2. Study Design.



Study Statistical Methods

- Primary and secondary efficacy analyses based on randomized patients, allocated to the treatment arm to which they were randomized
- pCR rate and 90% confidence interval (CI; Blyth-Still-Casella method) for each treatment arm and by PTEN status
- Stratified Cochran-Mantel-Haenszel tests will be used to compare treatment arms

PREDICTIVE BIOMARKERS

- This study will try to define a biomarker of sensitivity to the combination of ipatasertib and paclitaxel
- The lead biomarker for ipatasertib is evaluation of PTEN by IHC

SUMMARY

- There is robust scientific rationale to inhibit PI3K/Akt signaling with ipatasertib combined with paclitaxel in TNBC
- FAIRLANE is a Phase II trial to test the safety and efficacy of ipatasertib in combination with paclitaxel in the neoadjuvant TNBC setting
- The study is currently enrolling ~150 patients in US and EU. ClinicalTrials.gov identifier: NCT02301988.
- FAIRLANE is a sister study to LOTUS, a randomized Phase II study evaluating the benefit of adding ipatasertib to paclitaxel in first line metastatic TNBC

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