LOTUS: A Randomized, Phase II Study of Ipatasertib (GDC-0068), an Inhibitor of Akt, in Combination with Paclitaxel as Front-Line Treatment for Patients with Metastatic Triple-Negative Breast Cancer

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BACKGROUND

PI3K/Akt Activation in Triple-Negative Breast Cancer (TNBC)
- Approximately 80% of basal-like breast cancers lack protein expression for HER2 and hormone receptors (referred to as TNBC) by immunohistochemistry (IHC)
- Currently, there are no approved targeted therapies for TNBC
- The PI3K/Akt pathway is often activated in TNBC, through loss of the tumor suppressor PTEN, activating mutations or amplifications of PI3KCA, or loss of INPP4B
- Complete lack of PTEN expression as measured by IHC is observed in ~20% of TNBC, and low levels of PTEN expression have been observed in approximately 60% of TNBC (Genentech, data on file)

Inhibition of PI3K/Akt Signaling in TNBC with Ipatasertib
- Single-agent ipatasertib is well-tolerated with down-regulation of Akt, in combination with paclitaxel, showing increased efficacy (Figure 1)
- In a Phase Ib study (PMA4983g), ipatasertib at the recommended Phase II dose of 400 mg oral (PO) daily for 21 days on with 7 days off with weekly paclitaxel 90 mg/m² was well-tolerated and resulted in radiographic responses³

Preliminary data from LOTUS-1 (NCT02162719) suggests a radiographic response rate of 43% in TNBC patients with PTEN-low tumors.

STUDY DESIGN
- Randomized, double-blinded, placebo controlled, international, multicenter, Phase II study designed to estimate the efficacy of ipatasertib/placebo combined with paclitaxel in patients with previously untreated locally-advanced or metastatic TNBC
- Treatment will continue until disease progression, intolerable toxicity, elective withdrawal, or study completion
- Tumor assessments will be performed at screening, during the last week of Cycle 2, and every 8 weeks thereafter
- Patients will then be followed every 3 months for survival

Study Endpoints
- The primary objective is progression-free survival (PFS), defined as time from randomization to radiographic disease progression or death within 30 days of last dose of study treatment, in all TNBC patients and TNBC patients with PTEN-low tumors
- Secondary objectives include estimation of overall survival (OS), objective response rate (ORR), duration of ORR, safety, pharmacokinetics (PK), patient-reported outcomes (PROs), and correlative biomarkers

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Study Treatment
- Ipatasertib (400 mg) or placebo administered PO once daily, beginning on Cycle 1, Day 1 through Day 21 of each 28-day cycle
- Paclitaxel 80 mg/m² administered by IV on Days 1, 8, and 15 of each cycle

Study Statistical Methods
- Primary and secondary efficacy analyses will include all randomized patients, grouped by treatment at randomization
- Kaplan-Meier curves will be produced for analyses of PFS, OS, and duration of response, and stratified log-rank tests will be used to compare treatments

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
- All patients will have prospective PTEN tumor testing

Figure 1. Ipatasertib + Chemotherapy Shows Efficacy In Vitro and In Vivo.

Figure 2. Study Design.

N=120
- Screen patients with inoperable, locally advanced or metastatic triple-negative breast cancer
- Stratify by prior adjuvant/neoadjuvant treatment, disease-free interval from last dose of chemotherapy, and tumor PTEN status

Arm 1, N=60
- Paclitaxel 80 mg/m² (IV Days 1, 8, and 15 of 28-day cycle)
- Ipatasertib 400 mg daily (3 weeks on/1 week off)

Arm 2, N=60
- Paclitaxel (IV Days 1, 8, and 15 of 28-day cycle)
- Placebo 400 mg daily (3 weeks on/1 week off)

Key Inclusion Criteria
- Age ≥ 18 years, ECOG 0-1, with histologically documented locally advanced or metastatic TNBC not amenable to curative resection
- Archival tumor specimens, measurable disease per RECIST v1.1, and adequate hematologic/organ function within 14 days of study

Key Exclusion Criteria
- Prior adjuvant/neoadjuvant chemotherapy and/or radiation completed 6 months prior to study
- Known HER2+, ER+, or PR+ breast cancer (ER+ and PR+ defined as > 1% of cells expressing hormonal receptors via IHC)
- Brain or spinal cord metastasis, determined by CT or MRI

Stratification Factors
- Prior adjuvant/neoadjuvant treatment including chemotherapy and/or radiation (yes vs. no)
- Disease-free interval from last dose of adjuvant/neoadjuvant chemotherapy (≤ 12 mo. vs. > 12 mo.)
- Tumor PTEN status (null, low, medium)

SUMMARY
- There is robust scientific rationale to inhibit PI3K/AKT signaling with ipatasertib combined with paclitaxel in frontline metastatic TNBC
- This global Phase II study will evaluate the safety and efficacy of ipatasertib/placebo combined with paclitaxel in all TNBC patients and in TNBC patients with PTEN-low tumors
- This is a sister study to FAIRLANE, a randomized Phase II study evaluating the benefit of adding ipatasertib to paclitaxel in neoadjuvant TNBC
- The study is currently enrolling ~120 patients worldwide. ClinicalTrials.gov identifier: NCT02162719.

REFERENCES

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