**LORELEI: A Phase II Randomized Double-Blind Study of Neoadjuvant Letrozole Plus Taselisib (GDC-0032) Versus Letrozole Plus Placebo in Postmenopausal Women with ER+/HER2- Early Stage Breast Cancer**

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**STUDY DESIGN**

- **LORELEI** is a Phase II, two-arm, randomized, double-blind, multicenter, neoadjuvant study of letrozole and taselisib versus letrozole and placebo in postmenopausal women with newly diagnosed ER+HER2-, untreated, Stage I-II operable breast cancer.

- **Patients** will be randomized (1:1) to receive continuous daily letrozole (2.5 mg) with either placebo or taselisib (4 mg tablet dose on a 5 days on/2 days off schedule) for a maximum of 16 weeks. Stratification at randomization is based on tumor size and nodal status.

- **During the treatment period, tumor tissue will be collected for analysis purposes at Day 15 and at surgery.**

- **MRI, ultrasound, and mammogram will be performed baseline. Ultrasound will be repeated at Week 9 to ensure no progressive disease and all the radiographic evaluations will be repeated before surgery to assess efficacy of treatment and for surgical planning (see Figure 2).**

- **Study treatment is followed by surgery.**

- **Adverse treatment will be given as per physician’s discretion.**

- **The study will finish at the 30-day safety follow-up visit. Information about potential residual toxicities of treatment, surgery performed, pathologic results and adverse treatment plan will be collected in this visit.**

**Figure 2: LORELEI Study Schema.**

**Figure 1. Taselisib (GDC-0032) is a PI3K Inhibitor that Spares the p110 Beta Isoform.**

**Key Inclusion Criteria**

- **Histologically confirmed invasive breast carcinoma which is ≥ 2 cm in largest diameter (cT1-3) by MRI; largest lesion in multifocal tumor must be ≥ 2 cm**

- **Documentation confirming the absence of distant metastases (M0) as determined by institutional practice**

- **Breast cancer eligible for primary surgery**

- **Available pre-treatment core biopsy (FFPE and fresh frozen tissue) or biopsy tissue for all patients at baseline and must be evaluable for PIK3CA mutation status**

- **Any prior treatment for primary invasive breast cancer**

- **Patients with cT4 or cN3 stage breast tumors**

- **Changes in enhancing tumor volume from baseline to surgery as measured by breast MRI via central assessment**

- **Patients who have undergone excisional biopsy of primary tumor and/or axillary lymph nodes**

- **Type 1 or 2 diabetes requiring insulin therapy**

- **Other Secondary Endpoints**

- **ORR using breast ultrasound, clinical breast exam (i.e. palpation) and mammography**

- **Changes in enhancing tumor volume from baseline to surgery as measured by breast MRI via central assessment**

- **Tumor ORR, assessed by centrally assessed breast MRI via modified RECIST criteria in all enrolled patients and PIK3CA mutant patients**

- **Pathologic complete response (pCR) rate in breast and axilla at time of surgery in all enrolled patients and PIK3CA mutant patients (total pCR- ypT0/Tis ypN0) by local evaluation**

**Secondary Endpoints**

- **Determination of Sample Size**

- **The sample size was also determined to detect an absolute percentage increase of 18% in pCR rate (1% in the letrozole-plascebo arm vs 19% in the letrozole-taselisib arm in the PIK3CA mutant cohort) with 80% power at 1% two-sided significance level.**

**Efficacy**

- **Response via breast MRI will be centrally assessed and all measurements will be based on modified RECIST criteria. pCR rate in breast and axilla at time of surgery assessed (total (pCR- ypT0/Tis ypN0) by local evaluation.**

**Safety and Tolerability**

- **Safety will be evaluated through monitoring of all serious and non-serious adverse events, and laboratory abnormalities defined and graded according to NCICTC.” Observation of safety assessments will include physical exams, vital sign assessments, PIS evaluation, electrocardiograms, laboratory evaluations (including fasting glucose monitoring), and DLCO.**

**Pharmacokinetic and Biomarker Assessments**

- **Blood samples for PK assessment will be collected at Weeks 1, 3 and 9**

- **Biopsy tissue is mandatory for all patients at baseline and must be evaluable for PIK3CA mutation status.**

**ACKNOWLEDGEMENTS**

- **An Independent Data Monitoring Committee will monitor accumulating patient safety data at a minimum of once every 6 months until the last patient has completed study treatment.**

**REFERENCES**

1. Olivero et al., AACR 2013 Annual Meeting.


**Figure 1.** Taselisib (GDC-0032) is a PI3K Inhibitor that Spares the p110 Beta Isoform.