Radiant study: Phase 1b study of pre-op radiation with abemaciclib and letrozole in early-stage hormone-receptor positive breast cancer

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BACKGROUND

The advantages of preoperative breast radiation include accurate tumor site identification, better target volume delineation and tumor down staging with increased rates of breast conserving surgery. Preoperative radiation therapy can overcome treatment planning challenges seen in patients who have had reconstructive surgery such as tissue expander, implant and flap irradiation issues.

There is increasing pre-clinical data showing synergism between CDK 4/6 inhibitors and radiation. All three CDK4/6 inhibitors (abemaciclib, ribociclib and palbociclib) have been shown to radiosensitize ER+ cell lines leading to the decrease in the surviving fraction of cell.

This study proposes that pre-operative radiation with CDK4/6 inhibitor abemaciclib is safe and tolerable treatment regimen for patients with early-stage hormone receptor positive (HR+) /HER2- breast cancer.

TRIAL DESIGN

This is a single arm phase 1b study evaluating the combination of letrozole, abemaciclib and preoperative breast radiation. Patients will be identified using Oncotype DX Breast Recurrence score, a multi-gene assay that is predictive of response to chemotherapy in the adjuvant setting.

Post-menopausal women with node-negative primary breast cancers are eligible for the study. Tumors should have low-risk and intermediate risk Oncotype DX Breast Recurrence score (≤25). The study is divided into 4 parts- PART A (pre-radiation), PART B (Radiation), PART C (post-radiation) and PART D (breast surgery).

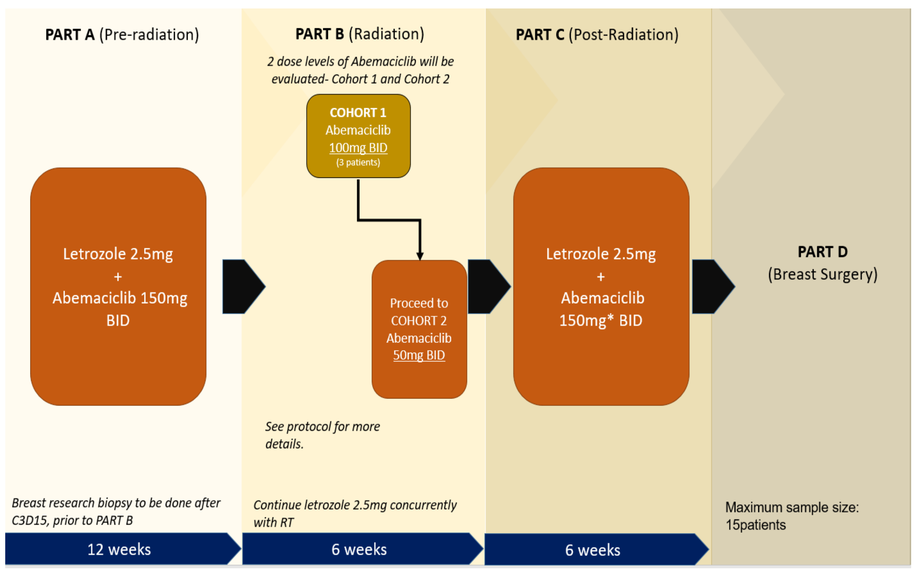
PART A: All patients will start pre-op systemic therapy at the recommended dose of Abemaciclib 150mg BID (Part A). Patient will take letrozole 2.5mg daily and Abemaciclib 150mg twice a day for 3 cycles prior to radiation. Towards the end of PART A, patients will have on-treatment biopsy

PART B: In PART B, patients will receive concurrent breast radiation, in addition to systemic therapy (abemaciclib and Letrozole). While getting concurrent radiation, we will use a streamlined Bayesian Optimal Interval (BOIN) design to determine the dose of abemaciclib. Enrollment will be in cohorts of 3 patients to 2 dose levels of abemaciclib --- 100mg BID and 50mg BID. Patients will receive 4500-5400 cGy in 25-30 fractions. Patients will undergo standard CT simulation and be treated with tangential fields to the whole breast which typically will include the level one lymph nodes. They will receive comprehensive whole breast radiation without regional nodal radiation (patients with suspicious nodes or biopsy proven nodes would not be eligible).

PART C: Following the completion of radiation, patients will continue on systemic therapy for up to 2 cycles with letrozole and abemaciclib prior to primary breast surgery.

PART D: Patients will have breast surgery (breast conserving surgery or mastectomy) along with sentinel lymph node biopsy following completion of systemic therapy.

Patients will be monitored for post-op complications for up to 30 days.



ENDPOINTS

Primary Objectives:

- To evaluate safety and tolerability of the combination of abemaciclib and radiation as assessed by adverse events (AEs)
- To evaluate changes in cell cycle as evident by immunohistochemistry

Secondary Objectives:

- To determine the clinical efficacy of combination of pre-operative radiation and radiation

Exploratory Objectives:

- To study changes to DNA repair mechanism
- To assess breast cosmesis

STATISTICAL DESIGN

We will use a streamlined Bayesian Optimal Interval (BOIN) design, enrolling cohorts of three patients to evaluate two abemaciclib dose levels while targeting a 0.33 toxicity rate and applying an overdose-control threshold of 0.85. The BOIN rules guide cohort expansion or dose de-escalation based on the number of observed DLTs, ensuring systematic and adaptive dose evaluation during concurrent radiation therapy. Under this design, enrollment begins at 100 mg BID, with de-escalation to 50 mg BID only if dose-limiting toxicities (DLTs) meet predefined BOIN decision rules.

DLTs include grade 4 skin or hematologic toxicities (white blood cells only), grade ≥2 pneumonitis/ILD, or any unexpected clinically significant toxicity, assessed from the start of radiation through 28 days post-radiation.

ACCRUAL

The study will enroll up to 15 patients at Rutgers Cancer Institute (RCI) and Robert Wood Johnson Barnabas Health (RWJBH) network sites

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