Phase IB/II-Open Label Single Arm Study to Evaluate Safety and Efficacy of Tucatinib in Combination with Letrozole and Palbociclib in Subjects with Hormone Receptor Positive and HER2 Positive Metastatic Breast Cancer (TULIP Trial)

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Background

Breast cancers overexpressing HER2-oncogene and hormone receptors (HR) represent therapeutic challenges because of high expression of HER2 oncoprotein and its role in breast cancer tumorigenesis. In combination with HER2, mutations in HR are also associated with adverse outcomes in breast cancer [1-2]. However, the combined HR/HER2 studies have shown synergies in the growth of HER2+ tumors [2-3]. Several phase I/II clinical trials combining HER2 inhibitors and hormone therapy have been performed [4-5]. However, these trials were not practice changing because no overall survival benefit was observed. There is a need for rationalization for evaluation of novel targeted drug combinations in HR+/HER2+ breast cancer.

Activation of cdk4 and CDK4/6 complexes plays an important role in the transformation of HR+/HER2- breast cancers, but not HR+/HER2+ breast cancers. Preclinical studies of HR+/HER2- breast cancer and HR receptors converges at cell cycle checkpoints and results in the increased cdk4 CD1 expression. The breast cancer cell cycle is more sensitive to inhibition of CDK4 oncoprotein and higher in HR+/HER2- breast cancer compared to other breast cancer subtypes [4]. Consistent with these results, palbociclib showed activity against luminal B (HR+/HER2-) tumors, and synergy between both CDK4 and HER2-targeted agents and ER antagonists (fulvestrant) have been reported in retrospective PHOC guidelines. Early results over prior endocrine therapy in the metastatic setting are allowed. Prior adjuvant and/or endocrine approach endocrine agents are not counted against this study:

1. Adipose organ and bone marrow.

2. For any prior use of HER2-targeted agents for HR+/HER2- breast cancers that have significant high impact to the breast cancer field.

We hypothesized that in HR+/HER2+ metastatic breast cancer treatment with a novel HER2-inhibitor, tucatinib, combined with a CDK4 inhibitor palbociclib and an aromatase inhibitor letrozole would result in improved PFS. Tucatinib in a patient oral small-molecule inhibitor highly selective for HER2 receptor tyrosine kinase with a 500 fold increase in potency for HER2 simulation compared to CDK4/6. Tucatinib inhibits HER2 signaling without significant EGFR-related side effects (skin rash and gastrointestinal toxicity) typical of less selective inhibitors [10]. Tucatinib showed significant antitumor activity and favorable toxicity profile in phase I/II clinical trials, including activity in patients with brain metastases [11, 12]. Non-overlapping toxicity profiles and metabolic pathways targeted together with synergistic mechanism of action of palbociclib and tucatinib provide rationale for combining these agents with letrozole in HR+/HER2+ metastatic breast cancer. This novel combination of three oral agents, if well tolerated, will be highly patient-centered as an effective non-chemotherapy based regimen for treatment of HR+/HER2+ breast cancer.

Study objectives and End-points

- **Primary endpoint:** objective assessment of the safety of combination therapy
  - Primary end-point: dose limiting toxicities (DLTs), adverse events (AEs) and serious adverse events (SAEs) by CTCAE v4.3
  - Secondary objectives: (1) primary efficacy of combination therapy.
  - Secondary end-points: (1) PK parameters, (2) ORR, CBR, DOR.

- **Phase I:**
  - Primary objective: efficacy of combination therapy assessed by PFS

- **Phase II:**
  - Primary objective: efficacy of combination therapy assessed by PFS

References:

1. ORR: CBR, DOR (2) summary of AEs, SAEs and DLTs

Research/consultative studies

Identification of molecular predictors of response and resistance to therapy. This will be done using archival and prospective analyses of CTILCs, genomic analysis of cDNA, and analysis of expression in serial biopsies, as it will reflect changes that occur over time.

Study Funding

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Study Contact Information

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Eligibility:

- **Criteria:**
  - **Age:** 18 years and older
  - **Gender:** women
  - **Histology:** invasive ductal carcinoma of the breast
  - **Performance Status (PS):** 0-1
  - **Comorbidities:** no severe organ dysfunction, no HIV infection
  - **Other medications:** all medications must be discontinued 24 hours prior to first cycle of study

- **Inclusion:**
  - **Metastatic breast cancer patients** who have received
  - **Tumor characteristics:** HER2 positive with baseline brain metastases
  - **Pregnancy/Amenorrhea:** females of childbearing potential must have a negative pregnancy test and must be compliant with the use of contraception while participating in study and for at least 4 weeks after treatment discontinuation.

- **Exclusion:**
  - **Breast cancer patients** with previous treatment with tucatinib
  - **Tumor characteristics:** patients with non-HR/HER2 breast cancer
  - **Pregnancy/Amenorrhea:** patients with childbearing potential are not allowed to participate

Conclusion

This is a multicenter, single arm, open-label trial phase 1b/2 clinical trial designed to evaluate the safety and efficacy of a novel combination of tucatinib, letrozole and palbociclib in HR+/HER2+ breast cancer. The study will evaluate the efficacy of this novel drug combination in subjects with metastatic HER2+ breast cancer. The trial will be conducted in compliance with all applicable regulations and regulations and will be evaluated by CTDI 11 and RAB001-MM.