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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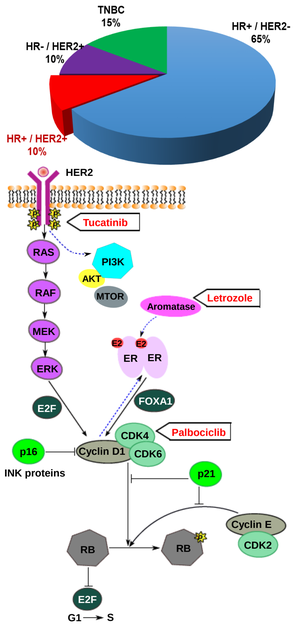
BACKGROUND

Breast cancers overexpressing HER2-oncogene and hormone receptors (HR) represent therapeutic challenge because of a bi-directional cross-talk between HR and HER2 pathways leading to tumor progression and drug resistance [1, 2]. In preclinical experiments, HER2-targeted agents combined with endocrine therapy showed synergy in suppressing the growth of HR+/HER2+ tumors [2, 3]. Several phase III clinical trials combining anti-hormonal and HER2-targeted agents have been performed [4, 5]. However, these trials were not practice changing because no overall survival benefits were demonstrated. Therefore, there is a strong rationale for evaluation of novel targeted drug combinations in HR+/HER2+ breast cancer subtype.

Activation of cyclin D1 and CDK4/6 complex plays an important role in the tumorigenesis of HR+/HER2+ breast tumors [6]. Mitogenic signaling from HER2 and HR receptors converges at cell cycle checkpoints and results in the increased cyclin D1 expression. The frequency of cyclin D1 amplification and CDK4 gain are higher in HR+/HER2+ breast cancer comparing to other breast cancer subtypes [7]. Consistent with these data, preclinical studies of CDK4/6 inhibitor palbociclib showed its activity against luminal B (HR+/HER2+) tumors, and synergy with both tamoxifen and HER2-targeted agents trastuzumab, lapatinib, and TDM-1 [6, 8, 9]. Therefore, testing the combination of anti-endocrine, CDK4/6-targeted and HER2-targeted agents for HR+/HER2+ breast cancer is a rational approach with potential 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 CDK4/6 inhibitor palbociclib and an aromatase inhibitor letrozole will result in improved PFS. Tucatinib is a potent oral small-molecule inhibitor highly selective for HER2 receptor tyrosine kinase. With a 500-fold increase in potency for HER2 inhibition compared to EGFR, 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 clinical trials, including activity in patients with brain metastases [11, 12]. Non-overlapping toxicity profiles and metabolic pathways taken 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

Phase IB:

- Primary objective: assessment of the safety of combination therapy
- Primary end-point: dose limiting toxicities (DLTs), adverse events (AEs) and serious adverse events (SAEs) by CTCEA v.4.3
  - Secondary objectives: (1) pharmacokinetic (PK) analysis (2) preliminary efficacy of combination therapy
  - Secondary endpoints: (1) PK parameters; (2) ORR, CBR, DOR

Phase II:

- Primary objective: efficacy of combination therapy assessed by PFS
- Primary end-point: PFS
  - Secondary objectives: (1) additional efficacy assessment by response rate; (2) additional safety analysis
  - Secondary end-points: (1) ORR, CBR, DOR (2) summary of AEs, SAEs and DLTs

Research / correlative studies objectives:

Identification of molecular predictors of response and resistance to therapy.
This will be done via genomic and proteomic analysis of CTCs, genomic analysis of ctDNA, and analysis of exosomes in serial blood samples, as well as total mRNA sequencing in paired tumor biopsy samples.

MAIN ELIGIBILITY CRITERIA

Inclusion Criteria:

- Histologically confirmed HR+/HER2+ locally advanced unresectable or metastatic breast cancer
- Measurable and/or evaluable disease per RECIST 1.1 and/or RANO-BM criteria. Bone only disease is allowed
- Subjects with untreated asymptomatic CNS metastases not needing immediate local therapy are eligible
- Subjects with stable brain metastases treated with radiation therapy or surgery are allowed to enroll, provided that they are off corticosteroids or on stable/tapering dose of corticosteroids and stability of CNS metastatic disease for at least 4 weeks has been demonstrated, with the last MRI taken within 2 weeks prior to cycle 1 day 1 (C1D1) of the study
- Age ≥ 18 years
- ECOG performance status 0-1
- Life expectancy of more than 6 months, in the opinion of the investigator
- Post-menopausal status (premenopausal women are eligible if they are on mandatory ovarian function suppression)
- At least two approved HER2-targeted agents at any time in the course of the disease
- At least one HER2-targeted agent in metastatic setting, with exception of asymptomatic subjects with oligometastatic or bone/soft tissue only disease, who, otherwise, would be appropriate for a single agent anti-endocrine therapy per NCCN guidelines
- Up to two lines of prior endocrine therapy in the metastatic setting are allowed. Prior adjuvant and/or neoadjuvant endocrine regimens are allowed and not counted towards this limit
- Adequate organ and bone marrow function
- LVEF ≥ 50% (as assessed by ECHO or MUGA) within 4 weeks prior to first dose of study treatment
- Serum or urine pregnancy test (for women of childbearing potential) negative ≤ 7 days of starting treatment
- Ability to understand and the willingness to sign a written informed consent and comply with the study procedures

Exclusion Criteria:

- Subjects with previously treated progressing brain metastases are excluded
- Subjects with known brain metastases and contraindications for contrast MRI imaging of the brain are excluded
- Pregnancy or breast feeding
- Current active treatment with an investigational agent
- Known history of hypersensitivity to aromatase inhibitor drugs
- Any toxicity related to prior cancer therapies not resolved to ≤ Grade 1, except peripheral neuropathy, which must have resolved to ≤ Grade 2, and alopecia
- Previous treatment with lapatinib, neratinib, afatinib, tucatinib, or other investigational EGFR tyrosine kinase inhibitors or HER2 tyrosine kinase inhibitors
- Previous treatment with palbociclib, abemaciclib, ribociclib or other investigational CDK4/6 inhibitors
- Systemic anti-cancer therapy (including hormonal therapy), radiation, or experimental agent ≤ 2 weeks of C1D1
- Active bacterial, fungal or viral infections requiring treatment with IV antibiotic, IV anti-fungal, or IV anti-viral drugs
- Known active hepatitis B, hepatitis C or HIV infections
- Inability to swallow pills or any significant gastrointestinal disease which would preclude adequate oral absorption
- Use of strong CYP3A4 or CYP2C8 inducers or inhibitors, or moderate CYP2C8 inhibitor trimethoprim within 3 elimination half-lives of the inducer or inhibitor prior to first dose of the study treatment
- Uncontrolled clinically significant cardiovascular conditions, or any history of symptomatic CHF
- Other severe acute or chronic medical or psychiatric conditions or laboratory abnormalities that may increase the risk associated with study participation, or may interfere with the interpretation of study results

See complete eligibility criteria at https://clinicaltrials.gov/ct2/show/NCT03054363

STUDY FUNDING

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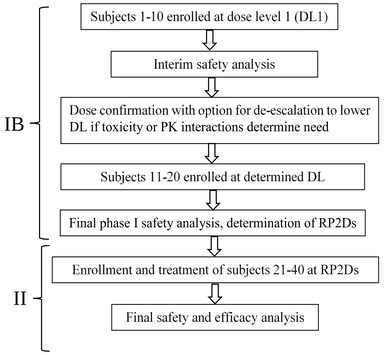
STUDY DESIGN

This is a multicenter, single arm, open-label, run-in phase IB safety cohort with immediate roll over to a phase II clinical trial.

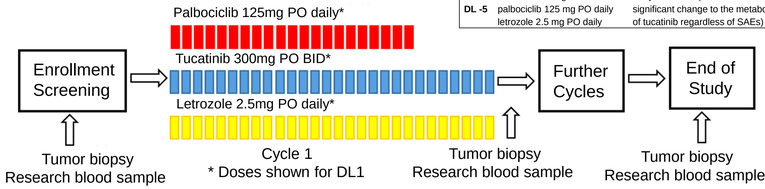
During phase IB, we will evaluate the tolerability of tucatinib given at maximum tolerated dose (300 mg PO BID) with standard doses of palbociclib (125 mg daily for 21 days on, 7 days off) and letrozole (2.5 mg PO daily). Safety assessment will be based on evaluation of toxicities of tucatinib and palbociclib; it will not depend on letrozole toxicities, as they are relatively mild and not life threatening. Safety will be considered clinically meaningfully altered if ≥60% of subjects experience DLTs secondary to palbociclib, or ≥20% of subjects experience DLTs secondary to tucatinib, or ≥50% of subjects develop DLTs that can be attributed to both drugs. If prespecified safety boundaries are crossed at the first interim safety analysis, enrollment will continue at lower dose levels. Discontinuation of either palbociclib, or letrozole for toxicities is allowed. If both palbociclib and letrozole are discontinued, patient will be removed from the study. If tucatinib is discontinued for toxicities, patient will be removed from the study. Additional dose de-escalation levels may be used if PK analysis shows significant interaction between palbociclib and tucatinib.

In phase II part of this trial, we will expand the testing of this drug combination in subjects with metastatic HR+/HER2+ breast cancer to evaluate efficacy by PFS rate. Additional evaluation of efficacy will be done by ORR, CBR and DOR. Tumor response will be evaluated by RECIST 1.1 and RANO-BM.



DLs	Drug doses	Subjects treated
DL1	tucatinib 300 mg PO BID palbociclib 125 mg PO daily letrozole 2.5 mg PO daily	Subjects 1-10 treated at DL1
DL -1	tucatinib 300 mg PO BID palbociclib 100 mg PO daily letrozole 2.5 mg PO daily	Subjects 11-20 (if palbociclib toxicity increased)
DL -2	tucatinib 250 mg PO BID palbociclib 125 mg PO daily letrozole 2.5 mg PO daily	Subjects 11-20 (if tucatinib toxicity increased)
DL -3	tucatinib 250 mg PO BID palbociclib 100 mg PO daily letrozole 2.5 mg PO daily	Subjects 11-20 (if palbociclib and tucatinib toxicity increased, or unattributable toxicity)
DL -4	tucatinib 250 mg PO BID palbociclib 125 mg PO daily letrozole 2.5 mg PO daily	Subjects 11-20 (if PKs indicate a significant change to the metabolism of tucatinib regardless of SAEs)
DL -5	tucatinib 200 mg PO BID palbociclib 125 mg PO daily letrozole 2.5 mg PO daily	Subjects 11-20 (if PKs indicate a significant change to the metabolism of tucatinib regardless of SAEs)

Safety boundaries	Palbociclib		Tucatinib		Both drugs	
Toxicity rate (upper limit CI)	0.6 (0.812) 0.6 (0.751)	8 out of 10 15 out of 20	0.2 (0.408) 0.2 (0.347)	4 out of 10 7 out of 20	0.5 (0.76) 0.5 (0.694)	8 out of 10 14 out of 20



CURRENT STATUS OF THE STUDY

Study is conducted in 6 academic institutions – members of Academic Breast Cancer Consortium (ABRCC):

- University of Colorado Cancer Center, Aurora, CO
- North Western University, Chicago, IL
- Stony Brook University, Stony Brook, NY
- University of New Mexico Cancer Care Alliance, Albuquerque, NM
- University of Texas Health and Science Center at San Antonio, San Antonio, TX
- University of Arizona Cancer Center, Tucson, AZ

Study is open for enrollment since 11/16/2017 at the University of Colorado Denver. Currently there is 1 patient enrolled and on treatment. Study is managed by contract research organization CRITERIUM, Inc.

Contact information for enrollment in TULiP trial: Dr. Elena Shagisultanova, elena.shagisultanova@ucdenver.edu