A Phase II Randomized Controlled Trial of Palbociclib & Tamoxifen/Fulvestrant in Postmenopausal Women and Men With Hormone-Receptor Positive, HER2-Negative Metastatic Breast Cancer (MBC)

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Background

• Despite new targeted therapies, approx. 40,000 women will die of MBC in the US in 2014
• 75% of MBC is hormone receptor (HR)-positive (ER+ and/or PR+)
• Endocrine therapy (ET) is cornerstone of treatment, but all pts progress & few cured due to development endocrine resistance.
• 35-40% patients have HR+HER2- disease & are not eligible for HER2-directed therapies.
• Renewed interest in combining chemo/experimental therapies with ET to overcome endocrine resistance & expand treatment options
• Recent strategies: addition of mTOR inhibitors and cyclin-dependent kinase 4/6 inhibitors (CDK4/6i), e.g. palbociclib
Mechanism Of Action of Palbociclib & PFS Benefit

• Doubling of PFS noted in PALOMA-1 trial (Palbociclib & letrozole vs. letrozole alone): 20.2 months vs .10.2 months
• Minimal toxicity
Study Hypothesis

- Eligible patients with HR-positive, HER2-negative MBC treated with palbociclib and tamoxifen/fulvestranton have a significant improvement in PFS vs. patients treated with tamoxifen/fulvestranton alone.

- The presence/absence of ER mutations may be a predictive biomarker of response to treatment.
Eligible:
- Postmenopausal women & men
- ECOG 0-2
- ER or PR positive, HER2 negative MBC, progressed on one line endocrine treatment in the metastatic setting

**Randomize**

**Progression**
- Palbociclib + Tamoxifen/fulvestrant
- Tamoxifen/fulvestrant

**Crossover:** Palbociclib + Tamoxifen/fulvestrant (until progression)

**OFF STUDY**

**Tumor tissue biopsy collection** (baseline and at first restaging)

**Blood sampling for research correlates** (baseline, first restaging, progression)
Study Objectives

Primary

• Compare PFS in postmenopausal women and men with ER-positive, HER2-negative MBC treated with tamoxifen /fulvestrant and palbociclib vs. tamoxifen /fulvestrant alone in pts who have progressed on at least one line of endocrine therapy in the metastatic setting.

Secondary

• Compare measures of disease control, including response rate (RR), and clinical benefit rate (CBR) between treatment arms.
• Compare safety and tolerability between treatment arms.
Correlative Objectives

**Exploratory**

- Prospectively follow plasma tumor DNA levels in patients
- Describe alterations in genes and gene products relevant to the cell cycle, drug targets, tumor sensitivity and resistance
- Aim to identify several pathway markers that are predictive of response to CDK4/6 inhibition, considering variables such as ER mutational status, ER- positivity and phosphoproteomics.
Correlates

- **New/fresh biopsies of metastatic site**
  - Baseline/Pre-treatment – for confirmation of ER+HER2- MBC
  - Surgical specimen

- **Study bloods**
  - Pharmacogenomics (optional)
  - ptDNA levels (baseline, after every 2 cycles (i.e. 8 week intervals)
  - PKs (1 and 2 hours post-dose on day 1, pre-dose weeks 4/7/10)

- **Imaging**
  - All patients must receive restaging CT CAP every 2 cycles (i.e. 8 week intervals)
Inclusion Criteria

- Postmenopausal females & men
- Stage IV breast cancer
- ER and/or PR-positive
- Evaluable/measurable disease by RECIST 1.1
- ECOG 0-2
- Progressed on at least one line of prior ET in the metastatic setting
- Use adjuvant TAM/ aromatase inhibitor permitted (stopped >6 months prior to devt MBC)
- Adequate end organ function
- CNS mets allowed if treated ≥ 4 wks from starting study drug & have recovered from toxicities
- Disease free of invasive malignancies ≥ 5 years (except BCC/ SCC skin or CIN)
- Bisphosphonates allowed if started before trial entry
- If baseline biopsy cannot be obtained, pt is still eligible for trial
Exclusion Criteria

• Concurrent CYP2D6 inhibitors (moderate/strong)*
• Inhibitors/inducers of CYP3A4
• Medications that prolong QTc
• Medical/Psych comorbidities affecting compliance or posing increased risk to pt
• Other current experimental therapy

• Uncontrolled intercurrent illness
• Pts developing MBC within 6 months of adjuvant tx
• Pts who have had more than one line of prior treatment for MBC (chemo, hormones, experimental therapy).
Statistical Plan & Study Design

• Non-blinded, randomized phase II study
• 3:1 randomization to palbociclib and tamoxifen/fulvestrant vs. tamoxifen/fulvestrant alone (n=100; 70-80 pts P & T, 20-30 pts T)
• 28 day cycle
  - Tamoxifen 20mg orally daily / Fulvestrant 500mg loading dose, then 250mg I.M monthly
  - Palbociclib 125mg orally days 1-21, then 7 days off
• Patients on tamoxifen/fulvestrant alone arm can cross over to palbociclib at progression
Significance

• The combination of palbociclib and letrozole has already shown to double PFS in patients with HR-positive, HER2-negative MBC who have already progressed on one prior line of ET.

• Therefore, CDK4/6 inhibitors are very promising agents in the treatment of this subgroup of patients given these impressive results and the favorable toxicity profile.

• This trial will evaluate the efficacy of other ET/palbociclib combinations in this setting and aim to identify predictive biomarkers of treatment response.