**A Phase 1/2 Study of Once-Daily Oral VT-464 in Patients with Advanced Androgen Receptor (AR) Positive Triple Negative (TNBC) or Estrogen Receptor (ER) Positive Breast Cancer (BC)**

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**Background**

VT-464 is an oral non-steroidal dual lyase-selective CYP17 Lysace inhibitor and a potent androgen receptor (AR) antagonist (Figure 1). VT-464 is being evaluated without steroid co-administration in multiple Phase 1 and 2 castration-resistant prostate cancer (CRPC) studies.

**Figure 1 – VT-464 Structure and Dual Mechanism of Action**

VT-464 inhibits the growth of multiple breast cancer cell lines in vitro including MDA-MB-231 (estrogen receptor (ER)+/AR low), tamoxifen-resistant MCF-7, and MDA-MB-453 (ER(-) /AR+) in a dose-dependent manner and with greater potency/efficacy than enzalutamide (Ellison et al., 2015 [P3-14-04]). A subset of TNBC and most ER(-) AR+ breast cancers express AR, making them potential targets for VT-464 since it directly inhibits both androgen/estrogen synthesis and AR transcriptional activity.

The current study is an open-label, single arm, Ph 1/2 study of VT-464 in women with AR(+) triple negative (TNBC) or ER(+)HER2-negative unresectable locally advanced or metastatic breast cancer (NCT#02585448).

**Phases 1**

**Study Objectives**

**Primary Objective**

- Describe the dose-limiting adverse events and determination of the maximum tolerated dose of VT-464 in women with unresectable locally advanced or metastatic breast cancer that is ER+ /progesterone receptor negative (PgR(-)) and HER2 normal (TNBC) or post-menopausal women with ER positive and HER2 normal breast cancer (ER(+)/BCA)

**Secondary Objectives**

- Describe the pharmacokinetics of VT-464 in the ITT population
- Estimate efficacy of VT-464 as measured by clinical benefit rate 16 weeks (CBR16) for patients with TNBC and clinical benefit rate at 24 weeks (CBR24) for patients with ER(+)/AR+ breast cancer
- Estimate efficacy of VT-464 as measured by the overall response rate (ORR) based on RECIST 1.1
- Evaluate the safety profile of VT-464

**Phase 2**

**Primary Objective**

- Determine the CBR16 for patients with AR+ receptor (AR+) positive TNBC and CBR24 for patients with ER(+)/BC in their respective evaluable populations

**Secondary Objectives**

- Describe efficacy of VT-464 as measured by PFS
- Estimate efficacy of VT-464 as measured by ORR based on RECIST 1.1
- Evaluate CBR16 for patients in TNBC Cohort with AR 21%
- Estimate CBR24 for patients in ER+ /AR+ Cohort with AR 21%
- Describe the safety profile of VT-464
- Evaluate the pharmacokinetics of VT-464

**Exploratory/ Correlative Objectives**

- To determine the extent of AR expression and signaling in breast tissue and to evaluate the relationship of AR expression with VT-464 effects on circulating tumor biomarkers, circulating hormones and clinical outcomes

**Study Design**

**Main Eligibility Criteria**

- ER(+) ≥ 2% with HER2-negative breast cancer or AR(+) ≥ 1% TNBC
- Evaluable TNBC or ER(+) breast cancer patients for Phase 2 will have AR ≥ 10%
- Postmenopausal or under ovarian suppression (ER+) patients
- Received at least 1 prior line of endocrine therapy (ER+) patients
- ECOG PS ≤ 1
- Unresectable locally advanced or metastatic breast cancer
- Available representative tumor specimen to enable corroborative science

**Study Schema**

- **AR screen**
  - Therapeutic consent
  - Medical history, primary diagnosis, and CYP17
  - Endo panel, cDNA, CTCA, pharmacogenes.
  - ACTH stim test (ph 1 only)
  - Tumor collection (Archie or new)
  - Scans
  - AE/ConMed reporting

- **Screening**
  - Brief physical exam, vital signs, labs, prog test
  - Endo panel, cDNA, CTCA
  - Tumor collection (new)
  - Scan
  - AE/ConMed reporting

- **Treatment**
  - Physical exam, vital signs, labs, ECG
  - Endo panel, cDNA, CTCA
  - Tumor collection (new)

- **EOT**
  - Spot PK (Ph 3)
  - Scans (DB-12 wks)
  - AE/ConMed reporting

**Phase 1**

- 6 patients (either ER(+)HER2-normal or AR(+) TNBC) enrolled per cohort starting at 750 mg qd (the MTD for men with CRPC)
- 2 or more DLTs in the first 28 days of treatment will confirm that the next lower dose be examined in a new cohort
- A DLT is defined as a Grade 3 or greater, drug related (possibly or greater) adverse event within the first 28 days of dosing
- VT-464 given once-nightly with dinner in a continuous dosing schedule
- Six to 12 patients enrolled in Phase 1

**Phase 2**

- Parallel AR(+) TNBC and ER(+)HER2-normal cohorts enrolled using MTD from Phase 1
- VT-464 given once-nightly with dinner in a continuous dosing schedule
- Simon’s two-stage design with pre-determined futility parameters
- ~35 patients enrolled per cohort

**Predictive Biomarker Evaluation Plan**

- Identify predictive biomarkers of response/resistance to VT-464
- Assess if early changes in circulating biomarkers can predict response to VT-464 or impending disease progression in advance of traditional measures such as radiologic measurements and clinical symptoms
- Identify mechanisms of acquired resistance to VT-464 by rebiopsy of tumor tissue (if safe and feasible) and circulating biomarkers at the time of progression in patient who derive significant benefit from therapy
- Provide rationale for future combination studies
- Biomarkers will be evaluated from tumor biopsies, CTCs, cDNA, endocrine panel and genomic DNA

**Site Activation and Accrual**

Five of approximately 30 sites planned for activation have been initiated. The first patient was enrolled August 2015 and 6 patients have been enrolled to date in Phase 1. Phase 2 is expected to be initiated in early 2016.

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