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)

Ayca Gucalp[1], Clifford Hudis[1], Larry Norton[1], Sujata Patil[2], Michael R. Kurman[3], Joel R. Eisner[3], William R. Moore[3], Tiffany A. Traina[1]

[1]Breast Medicine Service, [2]Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY; [3]Innocrin Pharmaceuticals, Inc., Durham, NC.

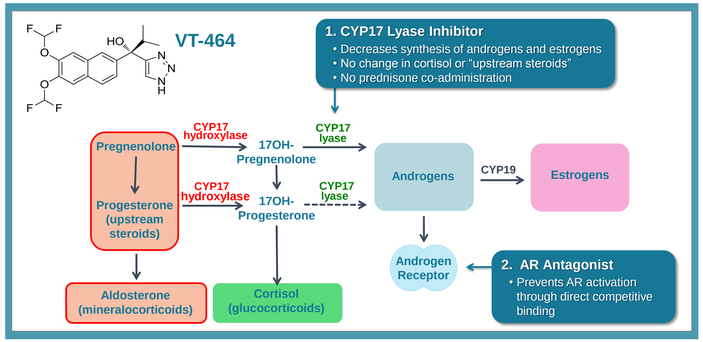
San Antonio Breast Cancer Symposium - December 8-12, 2015

Abstract #OT2-01-03

Background

VT-464 is an oral non-steroidal dual lyase-selective CYP17 Lyase 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 MCF7 (estrogen receptor (ER)(+)/AR low), tamoxifen-resistant MCF7, 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(+) 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 normal unresectable locally advanced or metastatic breast cancer (NCT#02580448).

Study Objectives

Phase 1

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(+) breast cancer)

Phase 1 (cont.)

Secondary Objectives

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

Phase 2

Primary Objective

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

Secondary Objectives

- Estimate efficacy of VT-464 as measured by PFS
- Estimate efficacy of VT-464 as measured by ORR based on RECIST 1.1
- Estimate CBR16 for patients in TNBC Cohort with AR ≥1%
- Estimate CBR24 for patients in ER (+) Cohort with AR ≥1%
- Describe the safety profile of VT-464
- Describe the pharmacokinetics of VT-464

Exploratory/ Correlative Objectives

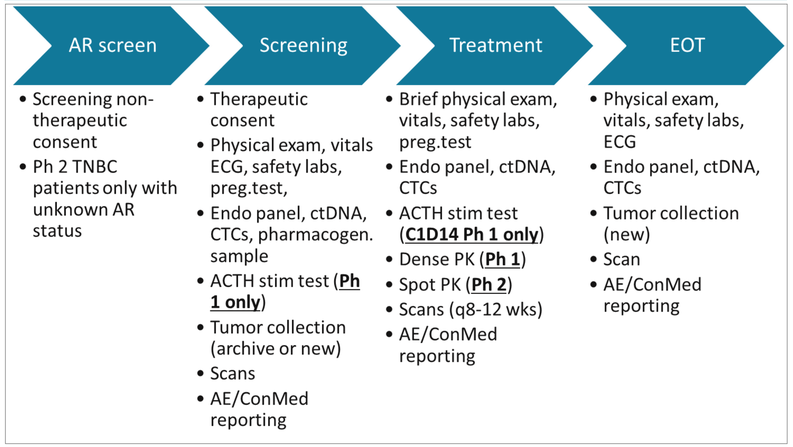
- To determine the extent of AR expression and signaling in breast tissue and to evaluate the relationship of AR expression with VT-464 effects on circulating tumor biomarkers, circulating hormones and clinical outcomes.

Study Design

Main Eligibility Criteria

- ER(+) ≥ 1% with HER2-normal breast cancer or AR(+) ≥ 1% TNBC
  - Evaluable TNBC 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 correlative science

Study Schema



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, ctDNA, 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.