Seviteronel (VT-464) is an oral, non-steroidal, dual lysate-selective CYP17 inhibitor and potent androgen receptor (AR) antagonist (Figure 1). Seviteronel is being evaluated without steroid co-administration in multiple Phase 2 prostate cancer studies. Herein we report initial results from an open-label, single-arm, Ph II study of seviteronel in women with unresectable locally advanced or metastatic AR+ or ER+ or HER2(-) disease (NCT05045449).

**Study Objectives**

**Primary Objective** – Phase 1
- Describe the dose-limiting adverse events and determine the maximum tolerated dose (MTD) of seviteronel in women with unresectable locally advanced or metastatic TNBC or ER+/HER2(-) BC.

**Secondary Objectives** – Phase 1
- Describe the pharmacokinetics of seviteronel in women with BC.
- Estimate clinical benefit rate at 16 weeks (CBR16) for TNBC and clinical benefit rate at 24 weeks (CBR24) for ER+ disease.
- Estimate overall response rate (ORR) and progression-free survival (PFS).
- Describe seviteronel’s safety profile

**Primary Objective** – Phase 2
- Define the CBR16 for AR+ TNBC (evaluable patients have ≥ 10% AR+), and CBR24 for ER+ populations.

**Secondary Objectives** – Phase 2
- Estimate PFS and ORR.
- Estimate CBR16 for TNBC and ER+ patients with ≥ 1%.
- Describe the PK and safety profile.

**Results**

- **ER(-) ≥ 1% with HER2(-) BC, or TNBC**: Ph 1 TNBC patients evaluated for Ph 2 will be AR(-) ≤ 10%.
- **Postmenopausal or pre-menopausal with concurrent ovarian suppression**: Received at least 1 prior line of endocrine therapy (ER(+)) patients.
- **EDGOS ≤ 1**: Unresectable locally advanced or metastatic breast cancer.
- **Available representative tumor specimen to be eligible for Ph 2**.

Seviteronel inhibits the growth of breast cancer cells in vitro including MCF7 (ER+AR+), tamoxifen-resistant MCF7, and MDA-MB-435 (ER+AR-) in a dose-dependent manner and with greater potency/efficacy than enzalutamide (Ellison et al., SABCS 2015). TNBC and most ER+ breast cancers are potential indications since seviteronel inhibits both androgen/estrogen synthesis and AR transcriptional activity.

**Exploratory Correlative Objectives**
- To determine AR expression and signaling in breast tissue and to evaluate the relationship between AR expression and tumor biomarkers, serum hormonetics, and outcomes.

**Serum Estriadiol Concentrations**
- As of 20 May 2016, 6 Phase 1 patients (2 at each dose) were evaluated following Cycle 2 day 1 dose.
- There was a decline in estradiol concentrations in all 6 patients after 1 cycle of dosing (≥ 25% to ≤ 87% median [range]).

**Seviteronel Safety and Tolerability**

**Summary and Conclusions**
- The exposure of seviteronel in women appears to be body mass and area proportional.
- Seviteronel is characterized by a dose-proportional predominantly neuromuscular/CNS AE profile that appeared to be reversible upon dose reduction or discontinuation.
- Oral seviteronel is well tolerated at 450 mg and was selected as the recommended Phase 2 dose for women.
- Preliminary results demonstrate estrogen suppression at all dose levels without concomitant aromatase inhibitor treatment.
- Seviteronel’s dual mechanism of action (reduced steroid production and AR antagonism) may provide a new novel treatment option for AR+TNBC and ER+ breast cancer.

**Current Status**
- Fourteen sites have been initiated as of 20 May 2016. First patient enrolled was August 2015; 30 patients have been enrolled in Phase 1 or 2, including 18 at 450 mg QD.

**Figure 1. Seviteronel Structure and Dual Mechanism of Action**

**Figure 2. Study Schema**

**Figure 3. Seviteronel PK Following Single Oral Dose With Food**

**Figure 4. Seviteronel Exposure vs Body Mass and Surface Area**