Activity of oral VT-464, a selective CYP17 lyase inhibitor in the LNCaP prostate cancer xenograft

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Introduction
With the recent FDA approval of abiraterone acetate1, the inhibition of CYP17 (17a hydroxylase/C17, 20-lyase) is now a validated approach to the treatment of castration-resistant prostate cancer. Inhibition of CYP17-lyase causes a decrease in circulating androgens, severely hampering activation of the androgen receptor signaling pathway that prostate cancer relies on for proliferation. However, inhibition of CYP17-hydroxylase, a second enzymatic activity of CYP17, leads to an increase in upstream steroids that can cause mineralocorticoid excess syndrome as well as a decrease in cortisol production2. This steroid imbalance results in the need to co-administer prednisone with these non-selective agents. VT-464 is a novel, selective CYP17 lyase inhibitor with decreased activity against CYP17 hydroxylase. Dosing has begun in a Phase 1/2 clinical trial.

Objective
The study objectives were to observe the effects of VT-464 in a prostate cancer xenograft model and to compare its activity to abiraterone acetate and surgical castration.

Methods
Six week old male SCID mice from the NCI-Frederick Animal Production Facility were implanted subcutaneously into the rear flank with 3 x 10^6 LNCaP cells.

Methods (cont.)
When tumors reached 100mm^3, mice were randomized (n=7) to receive vehicle (0.5% CMC in saline, 5mL/Kg), or VT-464 at 15, 50, or 100 mg/kg p.o. bid for 28 days. A fresh stock solution of VT-464 was prepared in 0.5% CMC in water on a more than weekly basis and stored at 4°C. The stock solution was diluted with vehicle (0.5% CMC) prior to dosing to maintain a consistent dosing volume (100 µL/20g body weight) at all dose levels. Mice were weighed daily and tumor volume measured 3x/wk as Volume = (pi/6)*l*w*h. Average tumor volumes were analyzed at each time point using the Mann-Whitney U test with p < 0.05 being significant. Terminal blood and tumor collection was performed on day 28, four hours after the last dose was given, for further analysis of steroid and VT-464 levels.

Results
In the first LNCaP xenograft cohort, percent growth inhibition (± S.E.) of 9.6 (± 15.6), 38.5 (± 12.4), and 73.9 (± 13.2) was observed on day 21 of treatment for the VT-464 doses of 15, 50, and 100 mg/kg, respectively. After four weeks of treatment there was a nonsignificant weight loss of approximately 10% in the 100 mg/kg group (Fig 1). All of the mice treated at 100 mg/kg exhibited minor tumor shrinkage at the beginning of the study;

Results (cont.)
and growth reduction was statistically significant from the vehicle control from day 7 to day 28 (Fig 2). Reduction in tumor volumes were similar between VT-464-treated (100 mg/kg) and castrate animals (Fig 3). VT-464 -treated (100 mg/kg) mice had significantly reduced tumor volumes on day 28 compared to control and abiraterone acetate (p<0.05, p<0.01, respectively) (Fig 3.) Plasma and tumor analyses revealed much greater plasma and tumor exposure compared to abiraterone acetate (Fig 4).

Conclusion
VT-464 exhibited dose-dependent growth inhibition with significantly reduced tumor growth compared to abiraterone acetate. The reduction in tumor growth in VT-464-treated animals was similar to that of castrate animals. These preclinical results show promising activity of VT-464 in the treatment of prostate cancer.

References

Figure 1: Safety of VT-464 as indicated by percent body weight loss over 28 days revealed less than 10% reductions in body weight compared to vehicle control.

Figure 2: Efficacy of VT-464 as indicated by average tumor volume ratio over 28 days revealed dose-dependent attenuation of tumor growth compared to vehicle control (☆ significant difference p < 0.05).

Figure 3: In the second cohort, reduction in tumor volume was compared between VT-464, abiraterone acetate and castration over 28 days and revealed significant attenuation in tumor volumes for VT-464 compared to abiraterone acetate.

Figure 4: VT-464 and abiraterone levels in plasma and tumor samples following 28 days of oral treatment at 100 mg/kg b.i.d.