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# Safety, pharmacokinetics, and efficacy of TAK-700 in castration-resistant, metastatic prostate cancer: A phase I/II, open-label study

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Background: TAK-700 is a selective 17,20 lyase inhibitor that, in preclinical studies, substantially reduces adrenal androgen levels in vivo. Methods: This phase I/II, open-label, dose-escalation study assesses the safety and tolerability of oral, twice-daily (BID) TAK- 700 in patients (pts) with metastatic, castration-resistant prostate cancer (MCRPC). Secondary objectives include assessment of TAK-700 efficacy, as shown by prostate-specific antigen (PSA) response, and TAK-700 pharmacokinetics (PK). Here we report on the phase 1 portion of the study. Results: 26 pts received TAK-700 at 5 dose levels: 100 (3 pts), 200 (3), 300 (3), 400 (7) or 600 (5) mg BID; a further 5 pts received TAK-700 400 mg BID plus prednisone 5 mg BID. At data cut-off (Sep 2009), 16 pts remain on study; 10 patients discontinued, including 5 due to adverse events (AEs), 3 due to objective disease progression, and 1 due to PSA progression. Most pts (96%) experienced ≥ 1 treatment-emergent AE (TEAE); 88% were drug- related and 50% were grade ≥ 3; There was no dose-limiting toxicity. The most common TEAE was fatigue (16 pts, including 3 grade ≥ 3 fatigue with 600 mg BID), followed by non-dose-related GI events such as nausea (10 pts, including 1 grade 3), constipation (9), anorexia (9), and vomiting (7). Preliminary PK analysis indicates approximate dose-proportional increases in single- and multiple-dose Cmax and AUC0-8hr over the 100-600 mg BID dose range. Multiple-dose PK are consistent with the single-dose PK. At 4 wks, median testosterone and DHEA-S levels had decreased from 4.9 to 0.6 ng/dL and 53.8 to < 0.1 ug/dL, respectively, in patients treated with 400 mg BID. ACTH stimulation tests showed blunted cortisol response in 2/7 pts at 400 mg BID and 5/5 pts at 600 mg. All patients treated with ≥ 300 mg had a PSA decrease; of 14 pts who received TAK-700 ≥ 300 mg for ≥ 3 cycles and had a 3-month PSA determination, 11 had PSA reductions ≥ 50% and 4 had reductions ≥ 90%. Conclusions: TAK-700 ≥ 300 mg BID appears active and well tolerated in pts with MCRPC. The recommended phase II dose is 400 mg BID. The safety and efficacy of TAK-700 and the necessity for use of concomitant prednisone are being further assessed in the phase II portion of the study.

## Biography

Robert Dreicer, MD, M.S., FACP, is Chairman of the Department of Solid Tumor Oncology at Cleveland Clinic and a Professor of Medicine at the Cleveland Clinic Lerner College of Medicine. Dr. Dreicer is board-certified in internal medicine and medical oncology. His areas of specialization are the management of genitourinary malignancies and the design and conduct of clinical trials in urologic oncology. Dr. Dreicer received his B.S. degree at Colorado State University and his MS degree at the University Of Texas Graduate School Of Biomedical Sciences in Houston, Texas. He received his medical degree from the University of Texas Medical School at Houston. He completed an internal medicine residency at Indiana University in Indianapolis, followed by a medical oncology fellowship at the University of Wisconsin Clinical Cancer Center in Madison, Wisconsin.

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