Early clinical data show galeterone safe, effective against prostate cancer

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Patients with castration-resistant prostate cancer had limited side effects and in many cases a drop in prostate-specific antigen expression with galeterone (TOK-001), a small-molecule oral drug, according to phase I data presented at the AACR Annual Meeting 2012, held here March 31 - April 4.

Castration-resistant prostate cancer (CRPC) is an advanced form of prostate cancer that occurs when the disease progresses after treatment with androgen deprivation therapy. Galeterone works against CRPC by blocking the androgen receptor, reducing levels of the ligand that binds to the receptor and degrading the androgen receptor protein.

"This drug has a novel combined mechanism of action," said co-lead researcher R. Bruce Montgomery, M.D., associate professor of medical oncology at the University of Washington School of Medicine in Seattle, Wash. "Cancer cells are sly and mutate to get around drugs. The fact that this drug hits the prostate cancer cell in three different ways may help prevent resistance. It is a well-tolerated drug that could potentially be more effective than drugs we have now."

In the ARMOR1 study, Montgomery and colleagues assigned 49 patients with CRPC to one of eight dose regimens in single or split oral escalation doses of 650 mg, 975 mg, 1,300 mg, 1,950 mg or 2,600 mg every day for 12 weeks. None of the patients had received chemotherapy for their prostate cancer.

Researchers reported that no patients reached a maximum tolerated dose. Most side effects were minor and included fatigue, nausea and diarrhea. Researchers observed transient, nonserious elevated liver function tests in 15 patients, many of whom were asymptomatic. Eleven of these patients temporarily stopped galeterone treatment, and six returned to treatment with no recurring liver function test elevations. One serious complication occurred involving rhabdomyolysis in the setting of simvastatin therapy and underlying renal insufficiency.

In early efficacy tests, 49 percent of patients had prostate-specific antigen (PSA) reductions of 30 percent or more; 11 of these patients had reductions of 50 percent or more. In addition, CT scans revealed reduction in tumor size for some patients.

"Because the androgen receptor controls PSA expression, improved PSA response shows that the drug is getting to the target," said Montgomery. "For the majority of patients, to reduce their PSAs by 30 percent or more is quite good in a phase I dose-finding trial."

Researchers will investigate long-term safety and an assessment of efficacy in a phase II study that Tokai Pharmaceuticals has planned for the second half of 2012.

More information: ARMOR1: Safety of galeterone (TOK-001) in a phase I clinical trial in chemotherapy naïve patients with castration resistant prostate cancer (CRPC).

Abstract
Introduction: Galeterone is an orally available, semi-synthetic steroid analog for the treatment of castration-resistant prostate cancer (CRPC) that inhibits prostate cancer growth through a triple mechanism-of-action by: a) inhibiting CYP17 lyase activity; b) binding to and inhibiting the androgen receptor; and, c) degrading androgen receptor protein.

ARMOR1, a phase I dose escalation study in men with chemotherapy naive CPRC, evaluated the safety of galeterone. Preliminary efficacy was also assessed by measuring changes in prostate-specific antigen (PSA) levels and tumor response.
Methods: Forty-nine men with metastatic and non-metastatic chemotherapy-naïve CRPC were enrolled in the ARMOR1 study. Patients were enrolled with confirmed adenocarcinoma of the prostate and disease progression during androgen ablation therapy. Patients ranged in age from 48 to 93 years old and had ECOG status of 0 or 1. Patients were randomized to one of eight dose escalation cohorts receiving galeterone capsules in single or split oral doses of 650, 975, 1300, 1950, or 2600mg daily for 12 weeks. After 12 weeks, eligible patients could continue treatment in an extension phase.
Results: Maximum tolerated dose was not reached. The frequency of patients with Grade 1 and Grade 2 adverse events (AEs) reported by body system was 58% and 30% respectively. The most commonly reported AEs by patient were fatigue (36.7%), aspartate aminotransferase (AST) increase (32.7%), alanine aminotransferase (ALT) increase (30.6%), nausea (28.6%), diarrhea (26.5%), and pruritus (24.5%). Grade 2 and 3, transient, non-serious, elevations of liver function tests (LFTs) were observed in 15 patients with the majority being completely asymptomatic. Of these patients, 11 underwent drug interruptions, and 6 of 7 patients were successfully rechallenged and returned to treatment with no recurring Grade 3 or higher LFT elevations. Nine SAEs were reported in the study, with all except one unrelated to galeterone. The single, related, grade 4 case involved rhabdomyolysis that occurred in the setting of simvastatin therapy (40 mg qd) and underlying renal insufficiency. No events of adrenal mineralocorticoid excess (AME) were observed in this study. PSA reductions were seen in a majority of patients; 24 (49%) patients had >30% maximal PSA reductions, including 11 patients (22%) with >50% maximal PSA reductions.
Conclusion: Galeterone was well tolerated, with all cohorts showing an

acceptable safety profile. Galeterone also demonstrated activity in patients with CRPC. Additional long term safety will be further explored in a planned phase II study.

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