Prostate cancer (PC) affects over 200,000 men in the United States each year and is the second leading cause of cancer related death in this population. In the subset of patients with advanced disease, the primary therapy is androgen deprivation but this will be effective for a median of only 24 months. Patients with castration resistant prostate cancer (CRPC) have symptomatic metastases and a poor life expectancy. Standard first line chemotherapy with docetaxel improves both quality of life and survival. Recently, several new hormonal and non-hormonal treatments have been approved in patients previously treated with docetaxel but additional therapeutic options are needed. AEZS-108 is an LHRH-cytotoxic hybrid whose rational design covalently couples the carrier D-Lys6-LHRH (an LHRH agonist) and the cytotoxic drug doxorubicin. LHRH receptors have been demonstrated on the plasma membranes of many cancer cells, including PC cells and their expression persists despite prior LHRH agonist therapy. AEZS-108 exploits the presence of these receptors to target the cytotoxic doxorubicin moiety. Preclinical studies demonstrated efficacy of AEZS-108 in PC mouse models. Our phase I study demonstrated good tolerability and identified the MTD and antitumor activity of AEZS-108 in men with CRPC. We now report the final results from a phase II trial with AEZS-108 in men with metastatic CRPC that have progressed after taxane based chemotherapy.

**Background**

Correlative studies

AEZS-108 Internalization: AEZS-108 contains a doxorubicin moiety that exhibits auto-fluorescence properties. We conducted a feasibility study to capture circulating tumor cells (CTCs) using a novel microfluidic device and test for AEZS-108 internalization. CTCs were immunostained with mouse anti-human PSA (DAKO, 1:100) and mouse anti-human CD45 (DAKO, 1:50), followed by Texas red-conjugated secondary antibody against mouse IgG (DAKO). We conducted a feasibility study to capture circulating tumor cells (CTCs) using a novel microfluidic device and test for AEZS-108 internalization. CTCs were visualized by a fluorescent microscope at an excitation wave length of 488 nm.

**Trial Design**

Patient Population: Eligible patients were men with advanced, histologically confirmed prostatic adenocarcinoma who had been previously treated with androgen deprivation therapy and at least one taxane-based chemotherapy regimen. Adequate organ function and an ECOG performance score < 2 was required. Left ventricular ejection fraction > 50% was required due to the potential requirement of an antiarrhythmic or an anti-coagulant. The null hypothesis for toxicity was AEZS-108; the null hypothesis for efficacy was stable disease. AEZS-108 was used as a salvage therapy in patients with CRPC and a median PSA of 255.8 ng/ml prior to AEZS-108 treatment. Patients received a median of 4 cycles of AEZS-108. Nine patients received >4 cycles of AEZS-108.

**Summary**

- 20 patients had measurable disease with a median of 1 prior chemotherapy regimens and a median PSA of 255.8 ng/ml prior to AEZS-108 treatment. Patients received a median of 4 cycles of AEZS-108. Nine patients received >4 cycles of AEZS-108.

- Maximal PSA response was stable in 20 patients.

- Pain assessment improved on study for 11 patients.

- AEZS-108 demonstrated good tolerability with evidence of anti-tumor activity.

- Internalization of AEZS-108 was consistently visualized in CTCs from subjects’ blood samples 1-3 and 24 hours after administration.

**AEZS-108 met its primary end-point in men with heavily pretreated CRPC. Our results warrant the expansion into larger clinical trials to better define its role in the current landscape of CRPC therapies.**

**References**

