PROSTATE CANCER

New endothelin-A receptor antagonist prolongs survival

Activation of the endothelin-A receptor promotes progression of advanced prostate cancer. ZD4054, a drug candidate that selectively antagonizes this receptor, has been shown to improve the overall survival of men with hormone-resistant metastatic prostate cancer. "The primary end point of [difference in] time to progression was not achieved—but a promising signal for prolonged overall survival compared with placebo was observed for both doses of ZD4054 at first analysis after 40 deaths and at second analysis after 118 deaths," explains lead author Nicholas James of the double-blind placebo-controlled phase II trial.

Atrasentan, another selective endothelin-A receptor antagonist, has a positive impact on PSA-based progression and markers of bone involvement. Failure of this drug to improve overall survival in a phase III trial may be due to the fact that it also inhibits signaling mediated by the endothelin-B receptor, which is thought to promote apoptosis and slow tumor spread. ZD4054 seems to have the advantage of not inhibiting endothelin-B receptor activity.

James and colleagues recruited 312 patients for randomization to either 10 mg or 15 mg of ZD4054, or to placebo, as a daily tablet. Differences in time to progression were consistently insignificant at both analysis points, but differences in median overall survival did reach significance: 17.3 months in the placebo group, 24.5 months in the 10 mg ZD4054 treatment group ($P = 0.008$) and 23.5 months in the 15 mg ZD4054 treatment group ($P = 0.052$).

James and fellow authors consider the results to be clinically and statistically meaningful. "We feel that the results endorse the strategy of targeting the endothelin-A receptor in prostate cancer and support continued investigation of ZD4054."

Kathryn Senior

Original article James, N. D. *et al.* Safety and efficacy of the specific endothelin-A receptor antagonist ZD4054 in patients with hormone-resistant prostate cancer and bone metastases who were pain free or mildly symptomatic: a double-blind, placebo-controlled, randomised, phase 2 trial. *Eur. Urol.* **55**, 1112–1123 (2009).