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Late Breaking

ZD4054, a potent, specific endothelin A receptor antagonist, improves overall survival in pain-free or mildly symptomatic patients with hormone-resistant prostate cancer (HRPC) and bone metastases

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Background: The endothelin axis has been shown to be important in the progression of prostate cancer. ZD4054 is a potent, specific endothelin A receptor antagonist currently in clinical development that has shown activity in hormone-resistant prostate cancer (HRPC).

Patients and Methods: In this double-blind Phase II trial, pain-free or mildly symptomatic HRPC patients with bone metastases were randomized in a 1:1:1 ratio to receive once-daily ZD4054 (15 or 10 mg/day po) or placebo. Progression-free survival (PFS) was the primary endpoint, and overall survival (OS) was a secondary endpoint. The study was sized to detect a hazard ratio of 0.67 in PFS with 80% power at the 20% significance level. PFS was a composite endpoint including clinical progression, requirement for opiate analgesia, worsening of or development of new soft tissue metastases, or death in absence of progression. Data for progression and survival were analysed using a Cox proportional hazards model.

Results: A total of 312 patients were randomized. Baseline characteristics were similar between the groups. The first analysis was carried out after the pre-specified number of progression events (165). Although no significant difference was seen for PFS, there was a significant difference in OS, which was based on only 40 deaths. Further follow-up allowed the collection of additional PFS and OS data. At the second analysis, with data cut-off 28 February 2007, 118 deaths had occurred; the results are shown in the Table. While there continued to be no significant difference in PFS, ZD4054 significantly prolonged OS compared with placebo.

Intent-to-treat population	ZD4054 15 mg	ZD4054 10 mg	Placebo
Number of patients	98	107	107
Number of deaths	34	33	51
Median overall survival (months)	23.5	24.5	17.3
Hazard ratio versus placebo	0.65	0.55	—
80% CI	0.49, 0.86	0.41, 0.73	—
P value	0.052	0.008	—

The most common adverse events (AEs) were those predicted from the pharmacological action of endothelin receptor antagonists; principally headaches, peripheral oedema and nasal congestion, each of which occurred in more than 30% of patients receiving ZD4054. Few AEs were of CTC grade 3 or above.

Conclusion: ZD4054 prolonged OS in HRPC patients with bone metastases. Safety and tolerability appeared to be acceptable for this population.