AstraZeneca	ZD4054 (zibotentan)
Mechanism of Action	Endothelin receptor A (ET_A) antagonist http://iuphar-db.org/DATABASE/ObjectDisplayForward?objectId=219&familyId=21 http://www.ncbi.nlm.nih.gov/gene/1909
Overview	ZD4054 is a potent orally bioavailable ET_A antagonist. ET_A, a G protein-coupled receptor, is one of two known receptors for the three endothelin peptides; ET-1, ET-2 and ET-3. It has widespread distribution, for instance in smooth muscle, cardiomyocytes, keratinocytes and the CNS, and is involved in the regulation of physiological processes such as cellular contraction, proliferation and apoptosis, in addition, ET_A receptors have been implicated in the pathophysiology of a number of diseases including hypertension, myocardial infarction and chronic renal failure. In pre-clinical studies, ZD4054 has an IC_{50} at the ET-A receptor of approximately 5nM, it has no effect at the ET-B receptor nor at a broad panel of other targets. In a range of tumor cell lines including osteoblast, vascular myoepithelial, prostate, breast and ovarian, ZD4054 inhibits pro-oncologic behaviors such as inhibition of apoptosis and proliferation. In murine tumor xenograft models of prostate, ovarian, breast and other cancers, ZD4054 (50mg/kg/day po) inhibited tumor cell proliferation and mortality.
Safety/Tolerability	A comprehensive safety assessment package has been performed on ZD4054 including general toxicity studies of 3 month duration in mouse, 6 month duration in rat and 12 month duration in dog. The respiratory tract, liver, bone marrow and reproductive tissues are indentified target organs for toxicity with no defined NOEL to changes to the respiratory tract. Reproductive toxicity has not been fully evaluated. ZD4054 has been tolerated in healthy volunteers in single doses up to 240 mg and multiple doses of up to 100 mg daily for 14 days. ZD4054 has been tested in multiple clinical trials and in Phase 3 prostate cancer patients with bone metastases at doses of 10 mg and 15 mg for up to 2 years. The most common adverse events were pharmacologically mediated, including peripheral edema, headache and nasal congestion/rhinitis. Analysis of study D4320C00033 (www.clinicaltrials.gov, NCT00617669) has indicated an increased risk and reduced time to onset of pneumonia in the patient group exposed to ZD4054 (10 mg).
Additional Information	ZD4054 has been studied in castrate resistant prostate cancer (CRPC) patients in three Phase 1 studies, two Phase 2 studies and three Phase 3 studies, non-small cell lung cancer patients in one Phase 2 study, patients with advanced solid malignancies in one Phase 1 study and ovarian cancer patients in one Phase 2 study. In Phase 3 CRPC trials, where it has been studied either alone or in combination with docetaxel, dosing has been established for continuous oral administration for up to 2 years duration.
Suitable for and Exclusions	The limited reproductive toxicology data indicate that AZD0530 can induce fetal malformations, therefore, the inclusion of women of child-bearing potential would need to be assessed for any proposal based on the risk benefit and the use of appropriate contraception. No data are available as yet to support use in pediatrics. CNS findings in the dog indicate that patients with a previous history of epilepsy, other CNS adverse events or neurologic symptoms or signs consistent with acute or evolving spinal cord compression or CNS metastases, should be excluded as should patients with NYHA grade II heart failure. ZD4054 is largely renally cleared and the dose in patients with moderate to severe renal impairment would have to be re-evaluated. Dependent on a thorough risk/benefit assessment, proposals for the use of ZD4054 may be supported for chronic indications. Proposals for use in orphan indications would be particularly welcome, however, studies in any field of tumor biology, ophthalmology or dermatology are not of interest.
Clinical Trials	http://clinicaltrials.gov/ct2/results?term=ZD4054
Publications	http://www.ncbi.nlm.nih.gov/pubmed?term=ZD405