

AstraZeneca	Zibotentan (ZD4054)
Mechanism of Action	Selective endothelin type A receptor (ET _A) antagonist http://www.guidetopharmacology.org/GRAC/LigandDisplayForward?ligandId=3539 https://www.ncbi.nlm.nih.gov/gene/1909
Overview	<p>Zibotentan, ZD4054, is a potent and selective antagonist of ET_A (IC₅₀ = 13nM; no effect at the ET_B or broad panel of other targets). In tumour cell lines including osteoblast, vascular myoepithelial, prostate, breast, and ovarian, ZD4054 inhibits pro-oncologic behavior such as inhibition of apoptosis and cellular proliferation. In murine tumor xenograft models of prostate, ovarian, breast, and others, ZD4054 (either 10mg/kg/day, ip or 50mg/kg/day, po) inhibited tumour cell proliferation and mortality. ZD4054 also inhibited blood vessel growth into tumour explants at concentrations of 25 and 50mg/kg/day, po</p> <p>In healthy male volunteers, ZD4054 (10 and 30mg) inhibited an ET_A receptor mediated forearm vasoconstriction response induced by ET-1 infusion while having no effect on ET_B receptors at doses of up to 240mg and no evidence of increased circulating ET-1, which is cleared through binding to ET_B receptors). Although ET_A mechanism-related AEs (i.e. nasal congestion, peripheral oedema, headache) were observed, indicating target engagement, no efficacy was seen in Phase 3 oncology trials at 10mg (~26 x IC₅₀ in plasma).</p>
Safety/Tolerability	<p>The safety package includes general toxicity studies up to 12 months duration in rat and dog. Nasal changes were seen in both. Rhinitis, generally mild, was also seen in humans. Zibotentan is not genotoxic; reproductive toxicology package indicates a risk of fetal toxicity.</p> <p>ZD4054 has been administered orally in healthy volunteers (single doses up to 240mg, multiple doses of up to 100mg daily) for 14 days. It has been tested in multiple clinical trials and in Phase 3 prostate cancer patients with bone metastases at doses of 10mg and 15mg QD for up to 2 years. Most common adverse events were ET_A mechanism related, including peripheral oedema, headache, and nasal congestion/rhinitis. In patients treated with zibotentan in combination with other cancer treatments, severe anaemia has been reported. Analysis of the Phase 3 study in metastatic resistant prostate cancer indicated an increased risk and reduced time to onset of pneumonia in the patient group exposed 10mg QD.</p>
Additional Information	<p>Zibotentan has been studied to phase 3 in castration-resistant prostate cancer, phase 2 in non-small cell lung cancer and advanced ovarian cancer, and phase 1 in advanced solid malignancies. Clinical development of zibotentan in Oncology was terminated due to insufficient efficacy.</p>
Suitable for and Exclusions	<p>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 highly effective contraception. 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. Cardiac failure has been reported in studies with advanced castration-resistant prostate cancer. Assessment of causal relationship to zibotentan is confounded by the high level of co-morbid cardiovascular conditions; recommended that patients with NYHA grade II heart failure are excluded from future clinical trials.</p> <p>ZD4054 is largely renally cleared, so dose in patients with moderate/severe renal impairment would have to be evaluated.</p>

	<p>AstraZeneca is not keen on pursuing ZD4054 for additional preclinical or clinical oncology indication research at this time; nor is there interest in Pulmonary Arterial Hypertension.</p> <p>Given that several endothelin receptor antagonists are already licensed and on the market, research related to conditions for which licensed endothelin receptor antagonists are already used (e.g. pulmonary arterial hypertension) will not be supported. This compound is best suited for novel indications/mechanisms or orphan indications.</p>
Clinical Trials	https://clinicaltrials.gov/ct2/results?cond=&term=zd4054&cntry=&state=&city=&dist
Additional Characteristics: CNS penetrance/ Pediatric Diseases	CNS penetration of zibotentan is low. No data are available as yet to support use of zibotentan in pediatrics. Zibotentan is a metabolised via CYP3A4, however the effects of co-administered CYP3A4 inhibitors are not considered to be of clinical relevance.
Publications	https://www.ncbi.nlm.nih.gov/pubmed/?term=zd4054