AstraZeneca	AZD1775
Mechanism of Action	Wee1 G2 checkpoint serine/threonine protein kinase inhibitor http://www.ncbi.nlm.nih.gov/gene/7465
Overview	AZD1775 is a highly selective, potent, ATP competitive, small molecule inhibitor of Wee1 kinase with an enzyme IC_{50} of 5.18 nM. *In vitro,* AZD1775 inhibits Wee1 activity and induces DNA damage as well as G2 checkpoint escape in cell-based assays with an EC_{50} of about 80 nM. AZD1775 increases cytotoxicity when used in combination with DNA damaging agents, such as gemcitabine, cisplatin, carboplatin and topotecan, in p53-deficient cell lines. *In vivo,* AZD1775 is well tolerated and shows enhancement of anti-tumor efficacy by gemcitabine, carboplatin, cisplatin, 5-fluorouracil (5-FU) and capecitabine in nude rat xenograft tumor models. Similarly, in nude mouse xenograft models, AZD1775 treatment results in significant tumor growth inhibition at tolerated doses and also enhances the anti-tumor growth effect of gemcitabine, carboplatin and radiation therapy.
Safety/Tolerability	AZD1775 is genotoxic, which is considered to be a result of its mechanism of action. No reproductive toxicity studies have been conducted to date. In ongoing Phase I combination studies, the most common dose-limiting adverse events (with chemotherapy) in >10% of patients include: thrombocytopenia, neutropenia, anemia, diarrhea, vomiting, nausea, abdominal pain, constipation. Common serious adverse events (with chemotherapy) include: febrile neutropenia, neutropenia, thrombocytopenia [J. Clin. Oncol. 31, 2013 (suppl; abstr 5518)]. Preclinical studies of up to 1 month duration have been performed.
Additional Information	Phase I studies are investigating target engagement using the phosphorylation status of the pivotal Wee1 substrate, CDC2 (CDK1), in skin as a surrogate for tumor tissue. Current ongoing trials of AZD1775 include monotherapy and combination therapy with certain DNA damaging agents in solid and ovarian tumors.
Suitable for and Exclusions	Preclinical reproductive toxicology data are not available for this compound. The inclusion of women of child-bearing potential using highly effective contraception could be considered based on the risk-benefit and in accordance with territory-specific requirements. We would exclude new proposals in areas of overlap with ongoing trials (see link to clinical trials). Proposals investigating Wee1 target biology and identifying responsive patient populations with compelling pre-clinical data would be entertained.
Clinical Trials	http://clinicaltrials.gov/ct2/results?term=%22MK-1775%22+OR+%22AZD1775%22&Search=Search
Additional Characteristics: CNS Penetrance/Pediatric Diseases	The CNS penetration for AZD1775 is not known. Pediatric disease proposals will be considered dependent on risk/benefit, dosing duration and regimen, and age of the pediatric population.
Publications	http://mct.aacrjournals.org/content/12/8/1442.long; http://clincancerres.aacrjournals.org/content/17/9/2799.long; http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0057523; http://clincancerres.aacrjournals.org/content/17/9/2799.long