

AstraZeneca	AZD2014
Mechanism of Action	<p>Mammalian target of rapamycin (mTOR) serine/threonine kinase (dual mTOR Complex 1 and 2 inhibitor, mTORC1 and mTORC2)</p> <p>http://www.ncbi.nlm.nih.gov/gene/2475</p>
Overview	<p>AZD2014 is a potent (IC₅₀ 2.81 nM), selective (inactive against 220 other kinases) inhibitor of mTOR kinase. It inhibited downstream targets of both mTORC1 (pS6 and p4EBP1) and mTORC2 (pAKT s473) in several <i>in vitro</i> models in a dose- and time-dependent manner. In the MDA-MB-468 cell line, the IC₅₀ for pAKT and pS6 were 78 and 210 nM, respectively. AZD2014 induces dose-dependent tumor growth inhibition in xenograft models at well-tolerated doses. In the MCF-7 ER+ breast cancer model, significant tumor growth inhibition is achieved with continuous or intermittent dosing schedules of AZD2014, and efficacy is enhanced in combination with fulvestrant. Pharmacodynamic knockdown of pAKT, p4EBP1 and pS6 and increased apoptosis in tumor tissue is also seen in preclinical <i>in vivo</i> models.</p>
Safety/Tolerability	<p>AZD2014 has been administered orally to solid tumor cancer patients in single doses up to 100 mg and multiple doses up to 100 mg twice daily (BID). The most common adverse events were fatigue, nausea, mucositis, rash, constipation, vomiting, dyspnea and cough (CTCAE grade 1–2), which improved in severity or resolved completely within 1 day up to 1 week after the drug was stopped or dose reduced, and therefore a relationship with AZD2014 is likely.</p> <p>Preclinical studies of up to 1 month duration have been performed.</p>
Additional Information	<p>At a dose of 50 mg BID, AZD2014 reduced cytoplasmic pS6 (S235/236) immunohistochemistry staining in 8 of 10 evaluable paired tumor biopsies indicating mTORC1 activity. A reduction in cytoplasmic pS6 (S235/236) was observed in 8 out of 8 tumor biopsies obtained after 1 to 5 hours of therapy. In three of these tumors, phosphorylation of S6 was profoundly reduced, falling to below the limit of reliable detection following treatment. Phosphorylation of AKT (S473) was significantly inhibited in platelet-rich plasma, providing evidence for TORC2 inhibition in surrogate tissue.</p> <p>Two patients, one each with pancreatic and breast cancer, have demonstrated partial response to AZD2014 monotherapy by Response Evaluation Criteria in Solid Tumors (RECIST), with four others having stable disease for >100 days.</p>
Suitable for and Exclusions	<p>Preclinical reproductive toxicology data are not available for this compound. The inclusion of women of child-bearing potential using highly effective contraception in trials of modest size and duration could be considered based on the risk-benefit and in accordance with territory-specific requirements.</p>
Clinical Trials	<p>http://clinicaltrials.gov/ct2/results?term=AZD2014&Search=Search</p>
Additional Characteristics: CNS Penetration/Pediatric Diseases	<p>The CNS penetration for AZD2014 is not known.</p> <p>Pediatric disease projects cannot be supported at this time.</p>
Publications	<p>http://www.ncbi.nlm.nih.gov/pubmed/?term=AZD2014</p>