

| AstraZeneca | AZD9291 |
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| Mechanism of Action | Epidermal growth factor receptor (EGFR) tyrosine kinase sensitizing and T790M resistance mutations inhibitor http://www.ncbi.nlm.nih.gov/gene/1956 |
| Overview | <p>AZD9291 is a potent, selective, irreversible inhibitor of both EGFR sensitizing and T790M resistance mutations with less activity towards wild-type EGFR. It inhibits phosphorylation of mutant-EGFR and wild-type EGFR in cells <i>in vitro</i> with IC₅₀ potencies < 100 nM and 0.5–2 μM, respectively. AZD9291 exhibits moderate potency against erbB2: It remains to be determined whether sufficient clinical exposure will be achieved to target erbB2. AZD9291 inhibited proliferation of mutant-EGFR cell lines <i>in vitro</i> with a potency of < 50 nM. AZD9291 is highly selective, only significantly inhibiting ~10 other protein kinases when tested across a kinome panel of ~280 protein kinases at 1 μM.</p> <p>In xenograft studies <i>in vivo</i>, daily oral dosing of AZD9291 causes regression leading to complete and sustained macroscopic response in both sensitizing-mutant EGFR model (PC-9) and T790M model (H1975), at low 5 and 25 mg/kg doses. Similarly, such doses lead to significant regression in lung transgenic tumor models of mutant-EGFR. Tumor growth inhibition is associated with significantly reduced phosphorylation of EGFR and downstream signaling markers (e.g., pERK and pAKT).</p> |
| Safety/Tolerability | <p>AZD9291 has been administered orally in multiple doses every day (QD) to patients with advanced non-small cell lung cancer (NSCLC) who have documented radiological progression while on prior therapy with an EGFR-TKI. No dosing limiting toxicities have been seen up to 160 mg. The most common adverse events (AEs), mostly mild, include rash, diarrhea, pruritus and nausea. Healthy male volunteers have been dosed with single doses of 20 mg AZD9291.</p> <p>Safety studies in preclinical species of up to 3 months duration have been performed.</p> |
| Additional Information | <p>Exposure increased approximately proportional to dose with median t_{max} of 7–8 hours and half-life of about 50 hours. Preliminary PK data suggest no obvious differences in exposure between Asian and non-Asian patients.</p> <p>The multiple daily dose PK profile demonstrates only a small difference between C_{max} and C_{min}, as expected from the t_{max} and half-life.</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. Likewise, male subjects should be willing to use barrier contraception.</p> <p>Patients with evidence of severe or uncontrolled systemic diseases (including uncontrolled hypertension, active bleeding diatheses or active infection), past medical history of interstitial lung disease, drug-induced interstitial lung disease, radiation pneumonitis which required steroid treatment, or any evidence of clinically active interstitial lung disease should probably be excluded given the developmental stage of this compound.</p> <p>Specific Areas of Interest for Proposals: Combination with other anticancer therapy, especially immunotherapy or other novel anticancer agents, in advanced NSCLC; monotherapy and combination studies in EGFRm+ve tumors other than NSCLC. In addition, monotherapy or combination therapy in adjuvant/neoadjuvant setting may be considered.</p> |

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| Clinical Trials | http://clinicaltrials.gov/ct2/results?term=AZD9291&Search=Search |
| Additional Characteristics: CNS Penetrance/Pediatric Diseases | The CNS penetration for AZD9291 is not known. Pediatric disease projects cannot be supported at this time. |
| Publications | http://www.aacr.org/home/public--media/aacr-in-the-news.aspx?d=3182 |