| AstraZeneca | AZD1208 |
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| **Mechanism of Action** | Proviral integration Moloney virus (PIM) serine/threonine kinase family inhibitor (pan-PIM kinase inhibitor)<br>http://www.ncbi.nlm.nih.gov/gene/5292; http://www.ncbi.nlm.nih.gov/gene/11040; http://www.ncbi.nlm.nih.gov/gene/41511 |
| **Overview** | AZD1208 is an ATP competitive inhibitor of PIM-1/2/3 isoforms with $IC_{50}$ values of 0.4/5/1.9 nM, respectively, in enzyme assays and inhibited substrate phosphorylation with $IC_{50}$ values of 10/151/102 nM, respectively, in cells.<br><br>PIM kinases are up-regulated in several types of leukemias and lymphomas. Inhibition of cell proliferation is seen primarily in hematologic tumor cell lines; for example, five of 14 acute myeloid leukemia (AML) cell lines tested showed growth inhibition values ($GI_{50}$) of ≤ 1 µM. Inhibition of phosphorylation of 4EBP1 and p70S6K and suppression of mRNA translation were the most representative effects of PIM inhibition in sensitive AML cell lines.<br><br>*In vivo* studies have demonstrated a clear PK/PD relationship in AML xenografts with strong suppression of pBAD, p4EBP1 and p70S6K for up to 12 hours post-dose. AZD1208 has also demonstrated tumor growth inhibition in other hematological and solid tumor xenograft models and has shown enhancement of anti-tumor activity when combined with various chemotherapeutic and targeted agents. |
| **Safety/Tolerability** | AZD1208 is in Phase I trials to evaluate the safety and tolerability profile and to determine the maximum tolerated dose (MTD). There are two ongoing trials where AZD1208 has been administered orally in AML and solid tumor (of all types) patients.<br><br>Preclinical toxicity studies of up to 1 month duration have been performed. |
| **Additional Information** | AZD1208 inhibits biomarker phosphorylation in *ex vivo* treated primary bone marrow aspirates from AML patients.<br><br>Target engagement has been observed in patients treated with AZD1208 as observed by biomarker inhibition consistent with inhibition of PIM kinase activity. |
| **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.<br><br>Suitable for study in indications, sub-populations and/or endpoints that are manifestly distinct from those previously studied for this compound or mechanism of action. |
| **Clinical Trials** | http://clinicaltrials.gov/ct2/results?term=AZD1208 |
| **Additional Characteristics: CNS Penetrance/Pediatric Diseases** | AZD1208 demonstrates CNS penetration in preclinical radioactivity distribution studies.<br><br>Pediatric disease projects cannot be supported at this time. |
| **Publications** | http://bloodjournal.hematologylibrary.org/content/early/2013/12/20/blood-2013-04-495366.full.pdf;<br>http://www.sciencedirect.com/science/article/pii/S0960894X1200710X |