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## Aurora kinase inhibitor: AS703569



Aurora kinase (AK) functions are associated with centrosome maturation, mitotic spindle organization, chromosome separation and condensation as well as cytokinesis.

Inappropriate expression of aurora kinases can induce centrosome irregularities and chromosomal instability, which cause aneuploidy and malignant cell transformation. Inhibition of AK leads to abnormal mitosis with slippage through the spindle checkpoint, formation of large multilobated nuclei following additional cycles of DNA replication without cytokinesis and eventually cell death.

AS703569 (formerly known as R763) is a novel orally available potent ATP competitive inhibitor of all three Aurora kinase isoforms (A, B and C) and of other kinases involved in growth-factor-mediated signalling of solid and haematological tumours.

Continuous exposure to AS703569 leads to endoreduplication, with cells increasing their DNA content up to 8N. Synchronisation of cancer cells with nocodazole prior to exposure to AS703569 increases both cell cycle arrest in G2/M and endoreduplication. Exposure of solid tumour cell lines to AS703569 also induces rapid apoptosis, as measured by PARP cleavage. Apoptosis may occur before endoreduplication, supporting the view that AS703569 induces cellular death by blocking

not only Aurora kinases but also other signalling pathways that are critical for cancer cell survival. Of potential clinical relevance is the observation that inhibition of Aurora Kinase B is associated with failure of the mitotic spindle checkpoint. The function of this checkpoint is involved in chemo and radiotherapy resistance and its disruption can lead to synergistic effects of a combination of the Aurora Kinase inhibitor with anti-tumour chemo- or radio-therapy.

Testing of AS703569 in several tumor xenograft models *in vivo* has demonstrated inhibition of proliferation and the trigger of apoptosis. As a single agent and in combination with several standard of care anticancer agents AS703569 induces *in vivo* tumour cell death, delays tumour growth and prolongs animal survival.

AS703569 also exhibits potent inhibition of the receptor tyrosine kinase FLT3 making this compound a good candidate for evaluation in patients with hematological malignancies.

AS703569 is orally bioavailable and because of its properties of a potent spectrum selective kinase inhibitor with a dominant *in vitro* and *in vivo* phenotype of Aurora kinases inhibition, it has proceeded into the clinic and is currently being tested in phase I studies as a single agent and in combination.

Further preclinical characteristics

and the initial data of ongoing phase I studies of AS703569 in patients with solid tumors and hematological malignancies will be reported. The objectives of the phase I studies are to determine for each of different dosing regimens tested the MTD and to evaluate safety, PK and pharmacodynamic effects.

*Athos Gianella-Borradori is a full time employee of Merck Serono International.*

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