

P040 Inhibition of cytokinesis by AZD1152, a selective Aurora B kinase inhibitor, reveals a novel mechanism of action for mitotic agents

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Spindle poisons, like the vinca alkaloids and taxanes, activate the spindle checkpoint, ultimately causing cell death. These microtubule-directed agents have long been validated as anticancer drugs with proven clinical efficacy. Interestingly, a new class of targeted therapeutic agents has emerged that abrogates the spindle checkpoint and leads to failure of cytokinesis.

Aurora B kinase is required for activation of the spindle checkpoint, and also for completion of cytokinesis. AZD1152 is a selective inhibitor of Aurora kinase activity, with specificity for Aurora B kinase. Treatment of cell lines with AZD1152 leads to failure of cytokinesis. The resulting tetraploid cells can undergo further rounds of endoreduplication but ultimately lose viability. This phenomenon has been demonstrated in a range of different cancer cell lines. AZD1152 has also been shown to inhibit tumour growth in xenograft models. Biomarker analysis demonstrates that the molecular events observed in cultured cell lines are recapitulated in tumour xenograft tissue and translate into a pronounced antitumour effect.

These observations support inhibition of cytokinesis as a promising novel mechanism of action for the treatment of cancer.