Inhibition of Aurora kinase B is important for biologic activity of the dual inhibitors of BCR-ABL and Aurora kinases R763/AS703569 and PHA-739358 in BCR-ABL transformed cells.

Abstract:
ABL tyrosine kinase inhibitors (TKI) like Imatinib, Dasatinib and Nilotinib are the gold standard in conventional treatment of CML. However, the emergence of resistance remains a major problem. Alternative therapeutic strategies of ABL TKI-resistant CML are urgently needed. We asked whether dual inhibition of BCR-ABL and Aurora kinases A-C could overcome resistance mediated by ABL kinase mutations. We therefore tested the dual ABL and Aurora kinase inhibitors PHA-739358 and R763/AS703569 in Ba/F3- cells ectopically expressing wild type (wt) or TKI-resistant BCR-ABL mutants. We show that both compounds exhibited strong anti-proliferative and pro-apoptotic activity in ABL TKI resistant cell lines including cells expressing the strongly resistant T315I mutation. Cell cycle analysis indicated polyploidisation, a consequence of continued cell cycle progression in the absence of cell division by Aurora kinase inhibition. Experiments using drug resistant variants of Aurora B indicated that PHA-739358 acts on both, BCR-ABL and Aurora Kinase B, whereas Aurora kinase B inhibition might be sufficient for the anti-proliferative activity observed with R763/AS703569. Taken together, our data demonstrate that
dual ABL and Aurora kinase inhibition might be used to overcome ABL TKI resistant CML.