Chapter 20
The Clinical Development of Aurora Kinase Inhibitors in Acute Myeloid Leukemia

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Abstract The Aurora family of serine/threonine kinases is essential for chromosome alignment, segregation, centrosomal maturation, mitotic spindle formation, and cytokinesis during mitosis. Their fundamental role in cell cycle regulation and aberrant expression in a broad range of malignancies prompted the development of small molecules that selectively inhibit their activity. Recent studies have revealed new insights into the cellular effects of Aurora kinase inhibition in the treatment of acute myeloid leukemia (AML). Moreover, early-phase clinical studies on AML have shown that these agents have therapeutic efficacy both alone and in combination with chemotherapy.

Keywords Aurora kinases · Acute myeloid leukemia

20.1 Introduction

The Aurora family of mitotic kinases was discovered while studying mutant alleles in drosophila melanogaster. The mutant allele caused failure of centrosome separation resulting in monopolar spindles reminiscent of the aurora borealis (Glover et al. 1995). In mammalian cells, there are three known members of the Aurora

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family: Aurora A, B, and C. Aurora A and B are expressed in all proliferating cells, whereas the expression of Aurora C is mainly restricted to the testes where it plays a role in spermatogenesis (Kimura Met al. 1999).

Aurora A and B regulate a diverse array of events throughout mitosis. Aurora A is critical for the maintenance of mitotic spindle bipolarity, separation of centrosomes, and accurate chromosome alignment (Crane et al 2004; Liu and Ruderman 2006). The regulation of the progression from G_2 to M by Aurora A has been proposed to occur, in part, through the relocalization of cyclin B1 to the nucleus and activation of cyclin-dependent kinase. Suppression of Aurora A expression leads to G_2/M arrest whereas ectopic expression abrogates the G_2/M checkpoint (Fu et al. 2007).

Aurora B forms the "enzymatic heart" of the chromosomal passenger complex (CPC) (Vader et al. 2006). The CPC includes Aurora-B, survivin, and inner centromere protein. This complex is crucial in the formation of correct microtubule–kinetochore attachments, the establishment of the spindle assembly checkpoint and cytokinesis (Hauf et al. 2003; Ditchfield et al. 2003; Giet and Glover 2001; Goto et al. 2003). In addition, Aurora B phosphorylates histone H3 at Ser^{10} and Ser^{28}, facilitating chromosome condensation and subsequent alignment during mitosis (Monier et al. 2007). Chemical inhibition of Aurora B impairs all CPC functions. Importantly, its depletion results in mitotic exit without cell separation causing a doubling of DNA (Fu et al. 2007).

Aurora C, with its specialized location in spermatocytes, functions similarly to Aurora B (Ducat and Zheng 2004; Sausville 2004). Although its role has not been clearly defined, there are some data to suggest that Aurora C is expressed in leukemic cells and interacts with survivin to prevent apoptosis and induce cell cycle progression (Kobayashi et al. 2006).

20.1.1 Aurora Kinases in Acute Myeloid Leukemia

Aurora kinases are aberrantly expressed in a variety of malignancies including acute myeloid leukemia (AML) and chronic myeloid leukemia (CML), lymphoma, prostate, colon, breast, lung, prostate, head and neck, and thyroid cancer as well as in most forms of leukemia (Bischoff et al. 1998; Sen et al. 1997; Smith et al. 2005; Chieffi et al. 2006; Reiter et al. 2006; Ulisse et al. 2006). A number of mechanisms lead to increased Aurora A expression in malignancies including amplification of the chromosomal region 20q13.2 which comprises the Aurora A kinase gene (Jeng 2004). Other mechanisms leading to Aurora A over expression in malignancy include posttranslational stabilization and transcriptional induction (Farruggio et al. 1999; Crane et al. 2004). In contrast to AURKA, the AURKB gene does not appear to be amplified in cancer. However, Aurora kinase B is highly expressed in many tumor types including prostate as well as head and neck squamous cell carcinoma (Chieffi et al. 2006; Reiter et al. 2006).

Aurora A may function as an oncogene through the induction of genetic instability and enhanced survival signaling. Ectopic over expression of AURKA leads to transformation of rodent fibroblasts (Bischoff et al. 1998; Huang et al. 2008; Zhou et al. 1998). Unsurprisingly, given its role during mitosis, high Aurora A expression is correlated with anueploidy and has also been associated with poor prognosis when present in malignant cells (Huang et al. 2008; Miyoshi et al. 2001; Crosio et al. 2002). Aurora A has been shown to interact with several crucial cell cycle regulators, including p53 (Katayama et al. 2004) and BRCA-1 (Ouchi et al. 2004). By impairing the regulatory function of these proteins, notably at the DNA checkpoint, genetic instability and carcinogenesis are more likely to occur (Huang et al. 2008). Aurora A aberrant expression may also prevent apoptosis in cancer cells by indirectly activating nuclear factor-kappa B (NF-κB) through phosphorylation of its inhibitor IκB, which targets IκB for degradation (Briassouli et al. 2007).

Aurora A and B are over expressed in AML. Aurora A expression by Western blot analysis and immunohistochemistry staining was found to be highly elevated in 65 of 98 (66%) of AML cells from de novo AML patients with no significant difference between age, race, blood count, or French–American–British (FAB) classification. In contrast, stem cells from the normal "control" bone marrow specimens revealed negligible levels of Aurora A protein expression (12 of 12). Fewer patients had elevated Aurora B expression (40 of 98 patients, 40%) (Huang et al. 2008). High Aurora kinase expression in a variety of leukemia types makes it a promising molecular target.

20.1.2 Aurora Kinase Inhibitors in Clinical Development

The awareness that Aurora kinases were aberrantly expressed in malignancies and were involved in tumorigenesis led to the development of a large number of Aurora kinase inhibitors (AKIs) for cancer therapy. Early studies revealed insights into the molecular consequences of Aurora A inhibition in cancer cells. Microinjection of Aurora A antibodies and/or RNAi-mediated knockdown of Aurora A kinase led G_2/M arrest, growth inhibition, and apoptosis (Hirota et al. 2003; Hata et al. 2005; Marumoto et al. 2002). Other consequences of targeted Aurora A inhibition include disruption of multiple mitotic events, culminating in failure of centrosome separation, monopolar spindle formation, and incomplete cytokinesis (Marumoto et al. 2003). On the other hand, RNAi-mediated inhibition of Aurora B expression disrupts chromosomal biorientation, cytokinesis, and the mitotic checkpoint (Goto et al. 2003; Severson et al. 2000). Abrogation of the mitotic checkpoint allows cells to go through multiple cycles of aberrant mitosis without cytokinesis resulting in massive polyploidy leading to cell death by mitotic catastrophe (Nair et al. 2009; Hauf et al. 2003). In the light of these multiple molecular sequelae, AKIs may be selectively more toxic to rapidly dividing cancer cells over nondividing cells.

20.2 Pan-AKIs

20.2.1 ZM447439

ZM44743 is a quinazoline derivative that is an ATP-competitive inhibitor of both Aurora A and B developed by AstraZeneca (Ditchfield et al. 2003). It was one of the first AKIs to be extensively characterized and has been a useful tool to study Aurora kinases in cancer. In preclinical models of AML and acute lymphocytic leukemia (ALL), ZM447439 induced growth inhibition, accumulation of polyploid cells, and apoptosis but had no effect on the clonogenic growth of myeloid stem cells harvested from healthy volunteers (Ikezoe et al. 2007). Consistent with its inhibition of Aurora B, ZM447439 treatment resulted in defects in chromosome condensation and alignment and impairment of the spindle checkpoint, phenotypes indicative of Aurora B inhibition (Ditchfield et al. 2003; Gadea and Ruderman 2005). While the use of ZM447439 has been important to study the preclinical consequences of Aurora inhibition in cancer, it has not been developed clinically.

20.2.2 VX-680/MK-0457

The first AKI to enter clinical evaluation was VX-680/MK-0457, initially developed by Vertex Pharmaceuticals. VX-680 is a pyrimidine derivative that has activity against all three Aurora kinases (inhibition constant values of 0.7, 18, and 4.6 nM for Aurora A, B, and C respectively) (Harrington et al. 2004). Treatment with VX-680 led to cell arrest and apoptosis in leukemia cell lines. As with other pan-AKIs, VX-680 induced a cellular phenotype consistent with Aurora B inhibition, i.e., inhibition of cytokinesis, polyploidy, and reduced phosphorylation of histone H3.

Of potentially important therapeutic implications, VX-680 has significant activity against wild-type and T315I-mutated BCR-ABL (Carter et al. 2005). In turn, it can inhibit the proliferation of cells expressing a wide variety of the clinically important BCR-ABL mutations with IC_{50} values of 100–200 nM. In CML, mutations in BCR-ABL can result in failure of tyrosine kinase inhibitor (TKI) therapy. Of particular importance is the T315I mutation at the base of the ATP-binding pocket of BCR-ABL that accounts for 10–15 % of mutations and is highly resistant to currently available TKI therapy (Giles et al. 2007). Consistent with this preclinical data, three patients with the T315I mutation (two with CML and one with Philadelphia chromosome positive (Ph^+) ALL) had objective responses in a phase I/II study of VX-680/MK-0457 (Giles et al. 2007).

MK-0457 synergizes with the pan-histone deacetylase inhibitor (HDACI) vorinostat in preclinical models of leukemia (Dai et al. 2008; Fiskus et al. 2008). This synergy may be in part mediated through HDACIs disruption of the chaperone function of HSP90, a known client protein of BCR-ABL, and thus may make BCR-ABL more sensitive to MK-0457 inhibition. Both vorinostat and MK-0457 were shown

to induce the expression of the BH3-only pro-apoptotic protein BIM and the lethal effects of the combination were shown to be particularly dependent on this pathway.

Many of the AKIs in clinical development have off-target inhibition of other clinically relevant tyrosine kinases. VX-680 also inhibits FMS like tyrosine kinase (FLT3) that is over expressed or mutated in many AML patients (Harrington et al. 2004; Carter et al. 2005; Schnittger et al. 2002). Several other AKIs including ZM447439 and AS703569 have demonstrated off-target inhibition of FLT3 *in vitro* (Huang et al. 2008; Ikezoe et al. 2007; Sarno et al. 2007; Shiotsu et al. 2007). In addition to off-target effect on FLT3, VX-680 also inhibits Janus kinase 2 (JAK2). The Val617Phe point mutation in the JAK2 gene leads to constitutive tyrosine phosphorylation activity and occurs in the majority of patients with myeloproliferative disorders (MPD) (Baxter et al. 2005). Consistent with this, VX-680 inhibits JAK2 *in vitro* and has normalized platelet counts and induced partial remission in patients with $JAK2^{V617F}$ positive MPD and AML transformed from MPD (Giles et al. 2006a, b, 2007). Despite these promising and intriguing clinical responses, the clinical development of VX-680/MK-0457 was halted due to concerns regarding cardiac toxicity.

20.2.3 PHA739358/Danusertib

PHA739358 is 3-aminopyrazole derivative developed by Nerviano/Pfizer (Fancelli et al. 2006). It is an ATP-competitive inhibitor of all three Aurora kinases (IC_{50} of 0.013, 0.079, and 0.061 for Aurora A, B, and C, respectively). As well as inhibiting the Aurora family of kinases, PHA-739358 inhibited other tumor-related kinases such as fibroblast growth factor receptor 1 (FGFR1), transforming tyrosine kinase protein (TRKA), ABL, and rearranged during transfection (RET) in the low nanomolar range. The parent compound of danusertib, PHA-680632, had demonstrated activity against a wide range of cancer cell lines *in vitro* and *in vivo* at well-tolerated doses (Fancelli et al. 2005).

Danusertib was rationally designed as a more potent Aurora A inhibitor by examining the x-ray co-crystal structure of PHA-680632 in complex with Aurora A. As is the case with other pan-AKIs, cells treated with PHA-739358 underwent endoreduplication and showed reduced phosphorylation of histone H3 (Fancelli et al. 2006). PHA739358 showed significant activity in preclinical models of cancer (Carpinelli and Moll 2008). Like VX-680/MK-0457, PHA-739358 inhibits BCR-ABL including T315I-mutated BCR-ABL and synergistically increased the efficacy of imatinib (Gontarewicz et al. 2008).

Danusertib has been evaluated in a number of early-phase clinical studies using various schedules (Cohen et al. 2009a; Steeghs et al. 2009a). The most common toxicity was neutropenia that was typically of short duration but dose limiting. Non-hematological toxicities reported included nausea, mucositis, and alopecia. Half-life is 30 h and the dosing regimen recommended for phase II study was 330 mg/m^2 as 6-h intravenous infusion was the recommended dose for phase II studies

(Steeghs et al. 2009b). Phase I single-agent data in patients with advanced-stage CML or Ph^+ ALL resistant or intolerant of imatinib or second-generation TKI therapy were encouraging. The cohort of 23 resistant/relapsed patients treated (11 Ph^+ ALL, eight CML blast crisis, four CML-accelerated phase) showed three cytogenetic (one complete, one partial, one minimal) and five hematological responses, and one clinical improvement (reduction in extramedullary disease mass) at the time of reporting (Cortes et al. 2009). Further phase I and II trials evaluating danusertib as single agent or in combination for both solid tumors and hematological malignancies are ongoing (Shiotsu et al. 2007).

20.2.4 R763/AS703569/MSC1992371A

R763 is a pan-AKI developed by Rigel Pharmaceuticals Inc that is orally available (Ahuja et al. 2007). In addition to inhibiting Aurora A and B, it also has activity against FLT3 kinase, vascular endothelial growth factor receptor (VEGFR) kinase, BCR-ABL, and T315I-mutated BCR-ABL. It also has activity against JAK2 kinase but at higher concentrations. Oral administration of R763/AS703569 markedly reduced tumor growth in xenograft models of breast, colon, pancreatic, lung, and ovarian tumors. MV4-11, an AML cell line, which harbors the FLT3 internal tandem duplication mutation, was particularly sensitive to R763 *in vitro* and *in vivo*. Consistent with Aurora kinase inhibition, R763 led to endoreduplication and an increase in the DNA content of the nuclei without subsequent cytokinesis. In addition, the inhibition of other non-Aurora kinases may enhance its antitumor effects. Interesting in a panel of cell lines representing FLT3-ITD AML, there was a trend toward the bypassing of endoreduplication and direct induction of apoptosis.

A phase I study of R763 has been completed in advanced hematologic malignancies evaluating different potential dosing schedules for the drug (Sonet et al. 2008). Dose-limiting toxicities were grade 3–4 mucositis/stomatitis severe neutropenia with infection, sepsis, and diarrhea. There were some responses to monotherapy including two complete responses (CRs) among 54 patients with AML and one among three patients with ALL. Partial responses (PRs) were seen in myelodysplastic syndromes (MDS), MPD, and CML. Four disease-specific expansion cohorts were initiated after the maximum tolerated dose (MTD) had been determined. A total of twenty-six patients were treated in the dose-expansion cohort. While three patients with MPD and two patients with accelerated phase CML had clinical benefit, none of the 20 patients with acute leukemia enrolled in the AML or ALL/CML blast-phase cohorts had clinical benefit. In addition, frequent toxicities were noted necessitating dose reductions and subsequent lack of efficacy at these reduced doses. As a result of these toxicities necessitating dose reductions to therapeutically ineffective doses, the clinical development of R763 was suspended.

20.2.5 ENMD2076

ENMD2076 is an orally available inhibitor of Aurora A and B. It is selectively more active against Aurora A compared to Aurora B (IC_{50} value of 14 nmol/L for Aurora A vs. IC_{50} of 350 nmol/L for Aurora B). It also inhibits kinases involved in angiogenesis (VEGFR and FGFRs) as well as FLT3, Kit, and CSF1R. In preclinical evaluation, ENMD2076 inhibits the growth of AML cell lines and suppresses tumor growth in AML xenograft models (MV4-11 and Hl-60) (Fletcher et al. 2011).

A phase I study of ENMD-2076 in patients with advanced myeloid malignancies (AML and chronic myelomoncytic leukemia) has been reported on (Yee et al. 2009). Several dose-limiting toxicities were reported including typhilits, fatigue, and syncope. However, some responses were seen in heavily pretreated patients. Of 20 evaluable patients, one patient achieved a CR with incomplete hematological recovery, three achieved a morphologic leukemia-free state, and four other patients had reductions in marrow blast count.

20.2.6 KW2249

KW-2449 is a small molecule TKI with known activity against Aurora A, FLT3, FGFR-1, and Abl kinase. Since it has potent FLT-3 as well as Aurora A activity (IC_{50} values of 0.007 and 0.048 μmol/L respectively), targeting AML has been an attractive approach for this agent (Shiotsu et al. 2007). In preclinical studies, KW-2449 was particularly effective at slowing the growth of FLT3-mutated xenograft model (Shiotsu et al. 2009). The sensitivity of FLT3 wild-type leukemia cell lines to KW-2449 was five- to tenfold lower than that in mutant FLT3-expressing leukemia cells. Treatment of FLT3 wild-type human leukemia cells induced a phenotype consistent with Aurora kinase inhibition with reduction of phosphorylated histone H3, G2/M arrest, and apoptosis.

KW2449 was evaluated in 37 patients with leukemia (31 patients had AML, five CML, and one ALL) (Shiotsu et al. 2009). Pharmacodynamic assays confirmed inhibition of FLT3 with reduction of P-FLT3 and P-STAT5. The most frequent severe toxicities were febrile neutropenia, pneumonia, and thrombocytopenia. Clinical responses were observed in eight of 31 patients with AML (26%; FLT3 mutation: five positive and three negative) and one patient with CML. Three of the eight AML patients who responded were FLT3 wild-type indicating that KW-2449 may be having activity independent of FLT3 inhibition.

However, correlative data from this phase I study showed that FLT3 inhibition to less than 20% of baseline was necessary for effective cytotoxic activity of the drug (Pratz et al. 2009). With the BID dosing schedule originally used, this level of FLT3 inhibition as evidenced by inhibition of P-STAT5 and P-FLT3 was not achieved at trough levels of the drug. Although the drug showed activity *in vitro* when cells were exposed at sufficient concentrations and significant FLT-3 inhibition at the 2-h time point *in vivo*, blast reduction was short lived. Given the above and the half-life

of the drug, the trial was discontinued early before the maximal tolerated dose was determined and a modified dosing strategy was planned. Alternative TID and QID dosing schedules are now being evaluated to accommodate for the short half-life and to achieve sufficient target inhibition.

20.2.7 AT9283

AT9283 is a pyrazole–benzimidazole compound that inhibits both Aurora A and B equally (IC_{50} 0nzinM). It is being developed by ASTEX Pharmaceuticals. In addition to inhibiting Aurora A and B, AT9283 was also found to inhibit a number of other kinases including JAK2, FLT3, and ABL (T315I; IC_{50} = 1–30 nM) (Howard et al. 2009). Consistent with its profile as a pan-AKI, AT9283 treatment resulted in endoreduplication and reduction of histone H3 phosphorylation in tumor cells. AT9283 was evaluated as a continuous 72-h infusion in phase I study of 29 patients with refractory leukemia (Foran 2008; Arkenau et al. 2011). Very encouraging single-agent activity in leukemia was observed. One third of patients with refractory AML experienced a significant reduction in bone marrow blasts following treatment with AT9283. Two patients with refractory CML had a hematological response and one had a partial cytogenetic response after four cycles of treatment. Dose-limiting toxicities included elevated transaminases, non-cardiac creatine kinase and lactate dehydrogenase rises, tumor lysis syndrome, myelosuppression, and alopecia. Pharmacodynamic and pharmacokinetic analysis supported increasing the duration of infusion to increase the biological effect of AT9283.

Interestingly, leukemic cells with an Aurora A phenotype may prove even more sensitive to AT9283. In a study using a panel of AML cell lines with or without mutations of c-kit, FLT-3 and RAS two distinct phenotypes emerged. Those driven by the oncogenic mutations listed above showed accumulation of cells in G2/M (4N) arrest followed by apoptosis characteristic of Aurora A inhibition. Those without these mutations developed >4 N DNA content and polyploidy followed by apoptosis consistent with Aurora B inhibition. Authors went on to speculate that their findings indicated that patients with mutations in oncogenic signaling pathways, may prove more susceptible to inhibition by AT9283 due to the presence of an intact mitotic checkpoint and a dominant Aurora A phenotype (Goodall et al. 2008).

20.3 Aurora A-Selective Inhibitors

20.3.1 Alisertib (MLN8237)

Alisertib is a small molecule adenosine triphosphate (ATP)-competitive reversible inhibitor of Aurora A kinase that is being developed for the treatment of advanced malignancies. Alisertib inhibits Aurora A with an inhibition constant (Ki) of

0.43 nM. Unlike many other AKIs undergoing clinical evaluation it is approximately 200-fold more selective for Aurora A than Aurora B (IC_{50} = 1534 nM) (Manfredi et al. 2011). Moreover, alisertib is selective for Aurora A kinase when compared to other kinases (at a minimum 250-fold more selective *in vitro*) and receptors. Like its parent molecule, MLN8054, alisertib has a benzazapine scaffold. The clinical development of MLN8054 was stopped due to excess somnolence that patients experienced. Somnolence is significantly less of a problem with alisertib as it has less affinity for benzodiazapine receptors. As would be expected from its kinase inhibitory profile, alisertib treatment results in the formation of abnormal mitotic spindles, an accumulation of mitotic cells, inductions of p53, p21, p27, and a decrease in the proliferation of a tumor cell lines grown in culture (Manfredi et al. 2011). Alisertib synergizes with docetaxol, another agent that disrupts mitosis in preclinical models of mantle cell lymphoma (Qi et al. 2011). Alisertib is currently being investigated in a large number of clinical studies in solid tumors and hematological malignancies. Several different formulations and dosing schedules have been evaluated in adult and pediatric patients.

The side effects of alisertib have been similar to those observed with other AKIs including myelosuppression, diarrhea, and alopecia. However, the use of a treatment-free period for bone marrow and gastrointestinal tract recovery between each cycle of drug administration allows repeated treatment cycles over periods extending beyond 12–24 months (Kelly et al. 2011a, b). Apart from alopecia, the predominant toxicities are largely reversible.

Objective responses to alisertib treatment have been observed across a broad range of malignancies including AML and lymphomas. In many cases these responses have been sustained more than six months (Dees et al. 2010). In a phase I study of alisertib in 56 patients with advanced hematological malignancies, four patients with lymphoma and one patient with multiple myeloma had PRs to therapy and a further 13 patients had prolonged stable disease (SD) (Kelly et al. 2011a). A phase II study of 48 patients with refractory aggressive non-Hodgkin's lymphoma (NHL) has been reported on. The overall response rate was 32%, but 57% of patients with T-cell lymphoma responded (Friedberg et al. 2010). These promising results have prompted a phase I/II study of alisertib in combination with rituximab and vincristine in B-cell lymphoma in the USA and a phase III registration study comparing alisertib with investigators choice is planned in peripheral T-cell lymphoma.

Alisertib has been investigated in preclinical models of leukemia. It is effective *in vitro* and *in vivo* in preclinical models of CML including T315I-mutated CML (Kelly et al. 2011). In an investigation into the activity and mechanism of action of alisertib in preclinical models of AML, alisertib in combination with cytarabine activated the transcription factor FOXO3a, which in turn led to induction of its targets BIM and P27 (Kelly et al. 2012). Furthermore, alisertib significantly increased the ability of cytarabine to impair tumor growth in xenograft models of AML suggesting that the combination of alisertib and cytarabine may represent an attractive therapeutic strategy in AML.

Based on the promising activity of alisertib in preclinical models of AML an open label phase II study of alisertib was performed in 46 patients with AML and 11 patients with MDS. Most of the patients were significantly pretreated. Consistent with prior clinical experience with alisertib, toxicities included febrile neutropenia, thrombocytopenia, anemia, fatigue, and neutropenia. Some treatment-related somnolence was observed. However, the response to single-agent alisertib in this population was modest with six AML patients (13%) responding and no patients with MDS responding. Only one of these patients had a CR and five patients had a PR (Goldberg et al. 2010).

20.4 Aurora B-Selective Inhibitors

20.4.1 Barasertib (AZD1152)

Barasertib is an Aurora B specific inhibitor developed by AstraZeneca. It is a quinazoline prodrug that is converted to the active metabolite barasertib-HQPA in plasma. In recombinant enzyme assays, it is more than 1000-foldselective for inhibition of Aurora B over Aurora A kinase activity (Ki of 0.36 and 1.7 μM for Aurora B and A, respectively) (Lowenberg et al. 2011). Treatment of colorectal SW620 xenografts induces a phenotype consistent with Aurora B inhibition with reduced histone H3 phosphorylation, accumulation of polyploid cells, and subsequently apoptosis (Wilkinson et al. 2007). Barasertib has also been evaluated in preclinical models of leukemia (Yang et al. 2007). It can potently suppress the proliferation of leukemia cell lines (MOLM13, MV4-11, PALL2, NB4, HL60, and K562) with an IC_{50} ranging from 3 to 40 nM. Similar to the synergy observed following treatment with alisertib and docetaxol, barasertib can enhance the activity of the vincristine, a tubulin depolymerizing agent and the topoisomerase II inhibitor, daunorubicin.

Barasertib was initially investigated in a phase I study in 59 patients with various solid tumors (Boss et al. 2011). It was given as a 2-h intravenous infusion every week. The dose-limiting toxicity observed was neutropenia and while objective responses were not seen, a number of patients had prolonged SD. The drug was otherwise well tolerated.

Two early-phase clinical trials of barasertib in patients with AML have been reported on, one completed in Japan and the other in the USA and Europe (Lowenberg et al. 2011; Tsuboi et al. 2011). Barasertib was administered as a continuous 7-day infusion every 21 days in both studies and a MTD of 1200 mg was defined. Consistent with Aurora kinase inhibition in rapidly proliferating cells the most common toxicities observed were mucositis, stomatitis, and neutropenia. The drug appears to be more active in AML compared with solid tumors. In the AML studies, the overall response rate was 25% in the US/EU study and 19% in the Japanese study. Unlike other Aurora B inhibitors such as AT9283 and AS703569, barasertib and in particular its metabolite, barasertib-HQPA are highly specific for Aurora B over other kinases such as FLT3. Therefore, the efficacy observed in these studies would

be expected to be a consequence of Aurora B inhibition therefore helping validate Aurora B as therapeutic target.

Barasertib has also been investigated in combination with low dose ara-C (LDA-C) in patients over the age of 60 who are considered unfit for intensive chemotherapy (Kantarjian et al. 2010). In this study, the MTD of AZD1152 was 1000 mg when given in combination with LDAC in older patients. Co-treatment with LDAC slightly increased the incidence of adverse events seen with either agent alone including febrile neutropenia, thrombocytopenia, and anemia. However, the overall investigator-reported clinical response rate (CR plus CRi) was 43 %.

20.5 Toxicities of Aurora Kinases Inhibitors

Because of the role that Aurora kinases plays in mitosis in normal cells, inhibition of this family of enzymes is expected to be toxic to proliferating tissues which would include rapidly dividing hematological cells and the cells lining the gastrointestinal tract (Dees et al. 2011). Clinical data from multiple phase I and II studies of Aurora kinases have demonstrated that the predominant toxicities of this class of drugs reflect the mechanism of action in proliferating tissues (bone marrow, gastrointestinal epithelium, and hair follicles). Consistent with this, the most common dose-limiting toxicity observed in phase one studies of AKIs has been grade 3 or 4 neutropenia.

Other reported toxicities of AKIs may reflect off-target effects. The ATP pocket is highly conserved across the more than 500 kinases contained in the human genome (Bantscheff et al. 2007), therefore it is little surprise that many of the agents designed to inhibit the Aurora kinases also influence other tyrosine kinase pathways leading to off-target toxicities.

Common non-hematological toxicities include somnolence, hypertension and liver toxicity. Cardiac toxicity was reported with VX-680/MK-0457 that subsequently halted development of the drug. MK-0457 causes QTc prolongation due to inhibition of the human ether-a-go-go related gene (hERG) channel (Moore et al. 2010), a potassium channel responsible for the "rapid" delayed rectifier current (I_{Kr}). A diverse range of drugs can potentially inhibit this channel and although great effort is taken in the development of a drug to avoid this potential interaction, the predictive value of preclinical testing is in the order of 80 %, thus not infallible (Pollard et al. 2008). QTc prolongation does not appear to be a class effect of Aurora kinases.

Some concern has been raised that Aurora kinases may have an essential role in cardiomyocyte cell cycle control and normal development in response to injury (Cheng and Force 2010; Ahuja et al. 2007), but how significant this is has not been highlighted in clinical trials with small molecule AKIs to date. It is likely that more long-term follow-up will be required to answer this question.

Importantly most of the toxicities observed with AKIs appear to be reversible. Indeed the marrow suppression associated with AZD1152 has been studied in animal models and has been shown to be reversible on withdrawal of the drug (Wilkinson

et al. 2007) Consistent with these findings in animal models, most dosing schedules of AKIs involve administration of the drug for approximately 1 week followed by a 2-week break to allow bone marrow and gastrointestinal epithelial cells to recover. An alternative strategy is to use granulocyte colony stimulating factors (G-CSF) to aid marrow recovery. For example, in a phase I study of danusertib, the MTD without G-CSF was 500 mg/m^2 whereas with factor support the MTD was significantly higher at 750 mg/m^2 (Cohen et al. 2009b)

There are preclinical data to suggest that the chromosomal instability induced by deficiency of Aurora A can lead to enhanced tumorigenesis (Lu et al.2008). A recent study showed that Aurora-A-null mice die in utero whereas Aurora A heterozygosity leads to a significantly increased tumor incidence in mice. This suggests that Aurora A is important in maintaining chromosomal stability and acts as a tumor suppressor. Some concern has also been raised about the potential long-term effect of the AKIs on breast tissue, as polyploidy has been induced in treated normal mammary epithelial cell cultures (Ditchfield et al. 2003). Increased incidence of secondary malignancies have not yet been reported in the clinical studies completed to date but careful long-term follow-up of patients exposed to Aurora inhibitors will be necessary. The possible impact of Aurora C inhibition on spermatogenesis and fertility is also a question that needs to be addressed with longer follow-up data

Conclusion

Our understanding of the biology of Aurora kinases, their role in oncogenesis, and their suitability as anticancer targets has improved considerably over the past 10 years. Despite this, a number of important questions remain to be fully answered. Whether optimal therapeutic efficacy is achieved through the inhibition of Aurora A, Aurora B, or both kinases simultaneously is still unclear and is the subject of continuing research. Ongoing trials may provide new insights regarding whether there are any advantages to selectively targeting individual Aurora isoforms.

There are a large number of kinases in the human genome. Many of the kinase inhibitors in use in the clinic today were originally developed to inhibit a single kinase but their clinical utility has been attributed to the inhibition of other related kinases. It is likely therefore that some of the clinical efficacy observed with the AKIs currently under clinical investigation can be attributed to off-target kinase inhibition. MK-0457, for example, inhibits the activity of Aurora A and B along with BCR-ABL and FLT3. The clinical responses observed with MK-0457 treatment in highly refractory CML patients may be a consequence of off-target inhibition of BCR-ABL. Likewise, KW-2449 is a potent inhibitor of FLT-3 a factor that may account for some of the activity reported with this drug in AML.

It has yet to be determined whether the expression of Aurora A or Aurora B will predict response to treatment with AKIs. Indeed, this has not been clearly shown in clinical studies performed to date. It would appear that AML, a disease frequently

characterized by the rapid proliferation of malignant cells appears to be a disease type associated with objective responses across various AKIs. While high Aurora A or B expression may not necessarily predict response, the expression of the oncogene MYC does appear to predict response to Aurora kinase B inhibitors at least in preclinical models (Hook et al. 2012).

As with many other targeted therapies that are in development the optimal use of AKIs may be in combination with currently available anticancer therapies. Indeed, several promising synergisms between AKIs and chemotherapy and radiotherapy have been demonstrated *in vitro* and *in vivo*. An attractive strategy is, combine Aurora inhibitors with tubulin-disrupting agents that arrest cells in mitosis, a stage in the cell cycle where Aurora kinases play a critical role. However, other potential combinations have been evaluated clinically and in preclinical models such as combinations with DNA-damaging agents and monoclonal antibodies.

Despite some of the limitations outlined above, a great deal of enthusiasm for further evaluation of AKIs in the clinic remains. Innovative preclinical science is providing rationale for the development of effective combination strategies that are now being evaluated in clinical trials in AML. It is hoped that these concerted efforts in Aurora kinase research will translate into novel anticancer strategies that will ultimately improve outcomes for patients with AML.

References

Ahuja P, Sdek P, MacLellan WR (2007) Cardiac myocyte cell cycle control in development, disease, and regeneration. Physiol Rev 87(2):521–544

Arkenau HT et al (2011) A phase I dose escalation study of AT9283, a small molecule inhibitor of aurora kinases, in patients with advanced solid malignancies. Ann Oncol 23(5):1307–1313

Bantscheff M et al (2007) Quantitative chemical proteomics reveals mechanisms of action of clinical ABL kinase inhibitors. Nat Biotechnol 25(9):1035–1044

Baxter EJ et al (2005) Acquired mutation of the tyrosine kinase JAK2 in human myeloproliferative disorders. Lancet 365(9464):1054–1061

Bischoff JR et al (1998) A homologue of Drosophila aurora kinase is oncogenic and amplified in human colorectal cancers. EMBO J17 (11):3052–3065

Boss DS et al (2011) Clinical evaluation of AZD1152, an i.v. inhibitor of Aurora B kinase, in patients with solid malignant tumors. Ann Oncol 22(2):431–437

Briassouli P et al (2007) Aurora-A regulation of nuclear factor-kappaB signaling by phosphorylation of Ikappa Balpha. Cancer Res 67(4):1689–1695

Carpinelli P, Moll J (2008) Aurora kinases and their inhibitors: more than one target and one drug. Adv Exp Med Biol 610:54–73

Carter TA et al (2005) Inhibition of drug-resistant mutants of ABL, KIT, and EGF receptor kinases. Proc Natl Acad Sci U S A 102:11011–11016

Cheng H, Force T (2010) Molecular mechanisms of cardiovascular toxicity of targeted cancer therapeutics. Circ Res 106(1):21–34

Chieffi P et al (2006) Aurora B expression directly correlates with prostate cancer malignancy and influence prostate cell proliferation. Prostate 66(3):326–333

Cohen RB et al (2009a) A phase I dose-escalation study of danusertib (PHA-739358) administered as a 24-hour infusion with and without granulocyte colony-stimulating factor in a 14-day cycle in patients with advanced solid tumors. Clin Cancer Res 15(21):6694–6701

Cohen RB et al (2009b) A phase I dose-escalation study of danusertib (PHA-739358) administered as a 24-hour infusion with and without granulocyte colony-stimulating factor in a 14-day cycle in patients with advanced solid tumors. Clin Cancer Res 15(21):6694–6701

Cortes-F, Dombret JH, Schafhausen P, Brummendorf TH, Boissel N, Latini F, Capolongo L, Laffranchi B, Comis S (2009) Danusertib Hydrochloride (PHA-739358), a multi-kinase aurora inhibitor, elicits clinical benefit in advanced chronic myeloid leukemia and philadelphia chromosome positive acute lymphoblastic leukemia. Blood (ASH Annual Meeting Abstracts) 114:864

Crane R et al (2004) Aurora A, meiosis and mitosis. Biol Cell 96(3):215–229

Crane R, Kloepfer A, Ruderman JV (2004) Requirements for the destruction of human Aurora-A. J Cell Sci 117(Pt 25):5975–5983

Crosio C et al (2002) Mitotic phosphorylation of histone H3: spatio-temporal regulation by mammalian Aurora kinases. Mol Cell Biol 22(3):874–885

Dai Y et al (2008) Vorinostat synergistically potentiates MK-0457 lethality in chronic myelogenous leukemia cells sensitive and resistant to imatinib mesylate. Blood 112(3):793–804

Dees EC, I.J., Burris H, Astsaturov IA, Stinchcombe T, Liu H, Galvin K, Venkatakrishnan K, Fingert HJ, Cohen RB (2010) Phase I study of the investigational drug MLN8237, an Aurora A kinase (AAK) inhibitor, in patients (pts) with solid tumors. J Clin Oncol 28:15s(15):abstr 3010

Dees EC et al (2011) Phase 1 study of MLN8054, a selective inhibitor of Aurora A kinase in patients with advanced solid tumors. Cancer Chemother Pharmacol 67(4):945–954

Ditchfield C et al (2003) Aurora B couples chromosome alignment with anaphase by targeting BubR1, Mad2, and Cenp-E to kinetochores. J Cell Biol 161(2):267–280

Ducat D, Zheng Y (2004) Aurora kinases in spindle assembly and chromosome segregation. Exp Cell Res 301(1):60–67

Fancelli D et al (2005) Potent and selective Aurora inhibitors identified by the expansion of a novel scaffold for protein kinase inhibition. J Med Chem 48(8):3080–3084

Fancelli D et al (2006) 1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazoles: identification of a potent Aurora kinase inhibitor with a favorable antitumor kinase inhibition profile. J Med Chem 49(24):7247–7251

Farruggio DC, Townsley FM, Ruderman JV (1999) Cdc20 associates with the kinase aurora2/Aik. Proc Natl Acad Sci U S A 96(13):7306–7311

Fiskus W et al (2008) Cotreatment with vorinostat enhances activity of MK-0457 (VX-680) against acute and chronic myelogenous leukemia cells. Clin Cancer Res 14(19):6106–6615

Fletcher GC et al (2011) ENMD-2076 is an orally active kinase inhibitor with antiangiogenic and antiproliferative mechanisms of action. Mol Cancer Ther 10(1):126–137

Foran JM (2008) Phase I and pharmacodynamic trial of AT9283, an aurora kinase inhibitor, in patients with refractory leukemia. In: ASCO Annual Meeting

Friedberg J, M.D., Jung J, Persky DO, Lossos IS, Danaee H, Zhou X, Jane E, Leonard J, Bernstein SH (2011) Phase 2 Trial of Alisertib (MLN8237), An Investigational, Potent Inhibitor of Aurora A Kinase (AAK), in Patients (pts) with Aggressive B- and T-Cell Non-Hodgkin Lymphoma (NHL). Blood (Ash Annual Meeting Abstracts) 111(14):4211

Fu J et al (2007) Roles of Aurora kinases in mitosis and tumorigenesis. Mol Cancer Res 5(1):1–10

Gadea BB, Ruderman JV (2005) Aurora kinase inhibitor ZM447439 blocks chromosome-induced spindle assembly, the completion of chromosome condensation, and the establishment of the spindle integrity checkpoint in Xenopus egg extracts. Mol Biol Cell 16(3):1305–1318

Giet R, Glover DM (2001) Drosophila aurora B kinase is required for histone H3 phosphorylation and condensin recruitment during chromosome condensation and to organize the central spindle during cytokinesis. J Cell Biol 152(4):669–682

Giles F et al (2006) MK-0457 is a novel Aurora Kinase and Janus Kinase 2 (JAK2) inhibitor with activity in transformed JAK2-positive myeloproliferative disease (MPD). ASH Annual Meeting Abstracts 108(11):4893

Giles F et al (2006) MK-0457, a novel multikinase inhibitor, has activity in refractory aml, including transformed jak2 positive myeloproliferative disease (mpd), and in philadelphia-positive all. ASH Annual Meeting Abstracts 108(11):1967

Giles FJ et al (2007) MK-0457, a novel kinase inhibitor, is active in patients with chronic myeloid leukemia or acute lymphocytic leukemia with the T315I BCR-ABL mutation. Blood 109(2):500–502

Glover DM et al (1995) Mutations in aurora prevent centrosome separation leading to the formation of monopolar spindles. Cell 81(1):95–105

Goldberg S, Craig GE, Lister J, Kassis J, Pigneux A, Schiller GJ, Jung J, Leonard J, Fingert H, Westervelt P (2010) Phase 2 study of MLN8237, an investigational Aurora A Kinase (AAK) inhibitor in patients with acute myelogenous leukemia (AML) or myelodysplastic syndromes (MDS). In: Annual Meeting of American Society of Hematology

Gontarewicz A et al (2008) *S*imultaneous targeting of Aurora kinases and Bcr-Abl kinase by the small molecule inhibitor PHA-739358 is effective against imatinib-resistant BCR-ABL mutations including T315I. Blood 111(8):4355–4364

Goodall J, Squires MS, Lock V, Ravandi F, Kantarjian HM, Foran J, Thompson NT, Lyons JF (2008) Outcome of Aurora kinase inhibition of acute myeloid leukemia by AT9283 is dependent upon the presence or absence of mutations in type 1 oncogenic kinase signalling pathways. Blood (ASH Annual Meeting Abstracts) 112:1613

Goto H et al (2003) Aurora-B regulates the cleavage furrow-specific vimentin phosphorylation in the cytokinetic process. J Biol Chem 278(10):8526–8530

Harrington EA et al (2004) VX-680, a potent and selective small-molecule inhibitor of the Aurora kinases, suppresses tumor growth in vivo. Nat Med 10(3):262–267

Hata T et al (2005) RNA interference targeting aurora kinase a suppresses tumor growth and enhances the taxane chemosensitivity in human pancreatic cancer cells. Cancer Res 65(7):2899–2905

Hauf S et al (2003) The small molecule Hesperadin reveals a role for Aurora B in correcting kinetochore-microtubule attachment and in maintaining the spindle assembly checkpoint. J Cell Biol 161(2):281–294

Hirota T et al (2003) Aurora-A and an interacting activator, the LIM protein Ajuba, are required for mitotic commitment in human cells. Cell 114(5):585–598

Hook KE et al (2012) An integrated genomic approach to identify predictive biomarkers of response to the aurora kinase inhibitor PF-03814735. Mol Cancer Ther 11(3):710–719

Howard S et al (2009) Fragment-based discovery of the pyrazol-4-yl urea (AT9283), a multitargeted kinase inhibitor with potent aurora kinase activity. J Med Chem 52(2):379–388

Huang XF et al (2008) Aurora kinase inhibitory VX-680 increases BAX/BCL-2 ratio and induces apoptosis in Aurora-A-high acute myeloid leukemia. Blood 111(5):2854–2865

Ikezoe T et al (2007) A novel treatment strategy targeting Aurora kinases in acute myelogenous leukemia. Mol Cancer Ther 6(6):1851–1857

Jeng YM et al (2004) Overexpression and amplification of Aurora-A in hepatocellular carcinoma. Clin Cancer Res 10(6):2065–2071

Kantarjian HM, Sekeres MA, Vincent R et al (2010) Phase I study to assess the safety and tolerability of azd1152 in combination with low dose cytosine arabinoside in patients with acute myeloid leukemia (AML). ASH Annual Meeting Abstracts 116:656

Katayama H et al (2004) Phosphorylation by Aurora kinase A induces MDM2-mediated destabilization and inhibition of p53. Nat Genet 36(1):55–62

Kelly KR et al (2011) The novel Aurora A kinase inhibitor MLN8237 is active in resistant chronic myeloid leukaemia and significantly increases the efficacy of nilotinib. J Cell Mol Med 15(10):2057–2070

Kelly KR et al (2012) Targeting aurora a kinase activity with the investigational agent alisertib increases the efficacy of cytarabine through a FOXO-dependent mechanism. Int J Cancer 131(11):2693–2703

Kelly KR, Goy A, Berdeja JG, Reeder CB, McDonagh KT, Zhou X, Danaee H, Xiao H, Benaim Eand Shea TC (2011) Results from a phase 1 multicenter trial of alisertib (MLN8237)—an investigational Aurora A kinase inhibitor—in patients with advanced hematologic malignancies. ASH Annual Meeting Abstracts 118(118):4110

Kelly KR, Goy A, Berdeja JG, Reeder CB, McDonagh KT, Zhou X, Danaee H, Xiao H, Benaim Eand Shea TC (2011) Results from a phase 1 multicenter trial of alisertib (MLN8237)—an

investigational Aurora A kinase inhibitor—in patients with advanced hematologic malignancies. In: Proc Am Soc Hematol

Kimura M et al (1999) Cell cycle-dependent expression and centrosome localization of a third human aurora/Ipl1-related protein kinase, AIK3. J Biol Chem 274(11):7334–7340

Kobayashi M, Nakamura Satoki, Ono Takaaki, Sugimoto Yuya, Sahara Naohi, Shinjo Kaori, Shigeno Kazuyuki, Ohnishi Kazunori (2006) Analysis of aurora kinase expressions and cell cycle regulation by aurora-c in leukemia cells. Blood (ASH Annual Meeting Abstracts) 108:1366

Liu Q, Ruderman JV (2006) Aurora A, mitotic entry, and spindle bipolarity. Proc Natl Acad Sci U S A 103(15):5811–5816

Lowenberg B et al (2011) Phase 1/2 study to assess the safety, efficacy, and pharmacokinetics of barasertib (AZD1152) in patients with advanced acute myeloid leukemia. Blood 118(23):6030–6036

Lu LY et al (2008) Aurora A is essential for early embryonic development and tumor suppression. J Biol Chem 283(46):31785–3190

Manfredi MG et al (2011) Characterization of Alisertib (MLN8237), an investigational small-molecule inhibitor of Aurora A Kinase using novel in vivo pharmacodynamic assays. Clin Cancer Res 17(24):7614–7624

Marumoto T et al (2002) Roles of Aurora-A kinase in mitotic entry and G2 checkpoint in mammalian cells. Genes Cells 7(11):1173–1182

Marumoto T et al (2003) Aurora-A kinase maintains the fidelity of early and late mitotic events in HeLa cells. J Biol Chem 278(51):51786–51795

Miyoshi Y et al (2001) Association of centrosomal kinase STK15/BTAK mRNA expression with chromosomal instability in human breast cancers. Int J Cancer 92(3):370–3

Monier K, Mouradian S, Sullivan KF (2007) DNA methylation promotes Aurora-B-driven phosphorylation of histone H3 in chromosomal subdomains. J Cell Sci 120(Pt 1):101–114

Moore AS et al (2010) *A*urora kinase inhibitors: novel small molecules with promising activity in acute myeloid and Philadelphia-positive leukemias. Leukemia 24(4):671–678

Nair JS et al (2009) *A*urora B kinase regulates the postmitotic endoreduplication checkpoint via phosphorylation of the retinoblastoma protein at serine 780. Mol Biol Cell 20(8):2218–2228

Ouchi M et al (2004) BRCA1 phosphorylation by Aurora-A in the regulation of G2 to M transition. J Biol Chem 279(19):19643–19648

Pollard CE, Valentin JP, Hammond TG (2008) Strategies to reduce the risk of drug-induced QT interval prolongation: a pharmaceutical company perspective. Br J Pharmacol 154(7):1538–1543

Pratz KW et al (2009).A pharmacodynamic study of the FLT3 inhibitor KW-2449 yields insight into the basis for clinical response. Blood 113(17):3938–3946

Qi W et al (2011) *A*urora inhibitor MLN8237 in combination with docetaxel enhances apoptosis and anti-tumor activity in mantle cell lymphoma. Biochem Pharmacol 81(7):881–890

Reiter R et al (2006) Aurora kinase A messenger RNA overexpression is correlated with tumor progression and shortened survival in head and neck squamous cell carcinoma. Clin Cancer Res 12(17):5136–5141

Sarno S et al (2007) The novel aurora kinase inhibitor as703569 shows potent anti-tumor activity in acute myeloid leukemia (AML). ASH Annual Meeting Abstracts 110(11):915

Sausville EA (2004) Aurora kinases dawn as cancer drug targets. Nat Med, 10(3):234–235

Schnittger S et al (2002) Analysis of FLT3 length mutations in 1003 patients with acute myeloid leukemia: correlation to cytogenetics, FAB subtype, and prognosis in the AMLCG study and usefulness as a marker for the detection of minimal residual disease. Blood 100(1):59–66

Sen S, Zhou H, White RA (1997) A putative serine/threonine kinase encoding gene BTAK on chromosome 20q13 is amplified and overexpressed in human breast cancer cell lines. Oncogene 14(18):2195–2200

Severson AF et al (2000) The aurora-related kinase AIR-2 recruits ZEN-4/CeMKLP1 to the mitotic spindle at metaphase and is required for cytokinesis. Curr Biol 10(19):1162–1171

Shiotsu Y et al (2007) KW-2449, a novel multi-kinase inhibitor against FLT3, Abl, FGFR1 and Aurora, suppresses the growth of aml both in vitro and in vivo. ASH Annual Meeting Abstracts 110(11):1832

Shiotsu Y et al (2009) KW-2449, a novel multikinase inhibitor, suppresses the growth of leukemia cells with FLT3 mutations or T315I-mutated BCR/ABL translocation. Blood 114(8):1607–1617

Shiotsu Y, Kiyoi Hitoshi, Ozeki Kazutaka, Umehara Hiroshi, Shimizu Makiko, Akinaga Shiro, Naoe Tomoki (2007) KW-2449, a novel multi-kinase inhibitor against FLT3, Abl, FGFR1 and Aurora, suppresses the growth of aml both in vitro and in vivo. Blood (ASH Annual Meeting Abstracts) 110:1832

Smith SL et al (2005) Overexpression of aurora B kinase (AURKB) in primary non-small cell lung carcinoma is frequent, generally driven from one allele, and correlates with the level of genetic instability. Br J Cancer 93(6):719–729

Sonet A, Graux C, Maertens J, Hartog C-M (2008) Phase I, dose-escalation study of 2 dosing regimens of AS703569, an inhibitor of aurora and other kinases, administered orally in patients with advanced hematological malignancies. Blood (ASH Annual Meeting Abstracts) 112:2963

Steeghs N et al (2009a) Phase I pharmacokinetic and pharmacodynamic study of the aurora kinase inhibitor danusertib in patients with advanced or metastatic solid tumors. J Clin Oncol 27(30):5094–5101

Steeghs N et al (2009b) Phase I pharmacokinetic and pharmacodynamic study of the aurora kinase inhibitor danusertib in patients with advanced or metastatic solid tumors. J Clin Oncol 27(30):5094–5101

Tsuboi K et al (2011) A Phase I study to assess the safety, pharmacokinetics and efficacy of barasertib (AZD1152), an Aurora B kinase inhibitor, in Japanese patients with advanced acute myeloid leukemia. Leuk Res 35(10):1384–1389

Ulisse S et al (2006) Expression of Aurora kinases in human thyroid carcinoma cell lines and tissues. Int J Cancer 119(2):275–282

Vader G, Medema RH, Lens SM (2006) The chromosomal passenger complex: guiding Aurora-B through mitosis. J Cell Biol 173(6):833–837

Wilkinson RW et al (2007) AZD1152, a selective inhibitor of Aurora B kinase, inhibits human tumor xenograft growth by inducing apoptosis. Clin Cancer Res 13(12):3682–3688

Yang J et al (2007) AZD1152, a novel and selective aurora B kinase inhibitor, induces growth arrest, apoptosis, and sensitization for tubulin depolymerizing agent or topoisomerase II inhibitor in human acute leukemia cells in vitro and in vivo. Blood 110(6):2034–2040

Yee KWL et al (2009) A phase i study of enmd-2076 in patients with relapsed or refractory leukemia. ASH Annual Meeting Abstracts 116:3307

Zhou H et al (1998) Tumour amplified kinase STK15/BTAK induces centrosome amplification, aneuploidy and transformation. Nat Genet 20(2):189–193