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The Potential Role of Aurora Kinase Inhibitors in Haematological Malignancies

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Summary

Aurora kinases play an important role in the control of the cell cycle and have been implicated in tumorigenesis in a number of cancers. Among the haematological malignancies, overexpression of Aurora kinases has been reported in acute myeloid leukaemia, chronic myeloid leukaemia, acute lymphoblastic leukaemia, multiple myeloma, aggressive non-Hodgkin lymphoma and Hodgkin lymphoma. A large number of Aurora kinase inhibitors are currently in different stages of clinical development. In addition to varying in their selectivity for the different Aurora kinases, some also have activity directed at other cellular kinases involved in important molecular pathways in cancer cells. This review summarizes the biology of Aurora kinases and discusses why they may be good therapeutic targets in different haematological cancers. We describe preclinical data that has served as the rationale for investigating Aurora kinase inhibitors in different haematological malignancies, and summarize published results from early phase clinical trials. While the anti-tumour effects of Aurora kinase inhibitors appear promising, we highlight important issues for future clinical research and suggest that the optimal use of these inhibitors is likely to be in combination with cytotoxic agents already in use for the treatment of various haematological cancers.

Keywords

cell cycle; myeloid leukaemia; lymphoma; myeloma

Introduction

Collectively, haematological malignancies account for approximately 10% of newly diagnosed cancers (Jemal, *et al* 2010). The ability to induce efficient killing of cancer cells using combination chemotherapy has significantly improved the survival rates for patients with leukaemia, lymphoma, and multiple myeloma (MM) (Lichtman, 2008). Also, targeted therapies using small molecules, including tyrosine kinase inhibitors (TKI), proteasome inhibitors, and immunomodulatory drugs, have changed the natural history of some diseases, such as chronic myeloid leukaemia (CML) and MM. While representing significant progress, primary or acquired resistance agents, as well as toxicity, remain problematic in many patients, indicating the need for continued investigation of novel agents.

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Of the different cellular processes targeted by small molecule inhibitors, a significant number of novel anti-cancer drugs being developed target protein kinases, particularly those involved in signal transduction and cell cycle control (Noble *et al*, 2004; Zhang *et al*, 2009). Dysregulated protein kinase activity is important in many cancers, including haematological malignancies (Zhang, *et al* 2009). Four groups of protein kinases are generally recognized. First, the receptor tyrosine kinases, which include the epidermal growth factor receptor (EGFR), insulin-like growth factor-1 receptor (IGF1R), vascular endothelial growth factor receptor (VEGFR), fibroblast growth factor receptor (FGFR) 1, FGFR3 and FGFR4, FMS-like tyrosine kinase (FLT3) and c-KIT (Noble *et al*, 2004; Zhang *et al*, 2009). A second group is the non-receptor tyrosine kinases, including c-SRC, ABL, Janus kinase 2 (JAK2), c-YES, and focal adhesion kinase (FAK) (Noble *et al*, 2004; Paul & Mukhopadhyay, 2004; Zhang *et al*, 2009). Third are the lipid kinases, such as phosphatidylinositol 3-kinase (PI3K). A key downstream effector of PI3K is the serine-threonine kinase AKT, which phosphorylates and regulates the activity of a number of targets including other kinases, transcription factors and other regulatory molecules. The PI3K/AKT pathway plays an important role in cell growth and survival, and is activated in various cancers (Hennessy *et al*, 2005). Finally, the serine/threonine kinases, which include proteins such as AKT, ataxia telangiectasia mutated (ATM), mammalian target of rapamycin (mTOR), S6K, b-RAF, and cell cycle control kinases, such as cyclin-dependent kinases (CDK), Aurora kinases, and Polo-like kinases (Zhang *et al*, 2009).

The efficacy of drugs that interfere with cell division has long been recognized in the treatment of the haematological malignancies. The Aurora kinases are intimately involved in the process of mitosis, and, as discussed below, are over-expressed in a number of tumours compared to normal tissues. Therefore, inhibitors of these kinases are now being investigated in a number of cancers. Herein, we review on the function of Aurora kinases and focus on the potential role of Aurora kinase inhibitors in the treatment of the haematological malignancies.

Mitosis and cell division: functional roles of Aurora kinases

Cell proliferation is characterized visually by division of the nucleus (mitosis) and physical splitting of the cell into two daughter cells (cytokinesis); both occurring during the M phase of the cell cycle. After completion of M phase, and in preparation for the next mitosis, a cell replicates its nuclear material (S phase). Before DNA synthesis begins and after it ends, however, two intervals or gap (G) phases intervene where important checkpoints occur (Weinberg 2007). In G1, a checkpoint for DNA integrity blocks a cell's advance into S phase until DNA damage is repaired. Similarly, in G2 a checkpoint occurs to ensure that all DNA replication is complete before the cell advances to M phase. M phase includes four subphases, including prophase, metaphase, anaphase, and telophase, and culminates in cytokinesis.

Aurora kinases are serine/threonine kinases that are essential for cell proliferation, regulating cell cycle transit from G2, formation of the mitotic spindle, centrosome maturation and separation, and cytokinesis (Andrews *et al*, 2003; Hirota *et al*, 2003; Vader *et al*, 2006). There are three human homologues of Aurora kinases, A, B, and C, which have a high degree of sequence homology, particularly in their carboxy-terminal catalytic domains (Bischoff *et al*, 1998; Giet & Prigent, 1999). Aurora kinases A and B are expressed in most normal cells, although their localization and activation during the cell cycle differ (Fig 1). Aurora C, initially thought to be restricted to the testicular tissue where it plays a role in meiosis, is now also known to have overlapping functions with Aurora B kinase in mitosis (Sasai *et al*, 2004; Yan *et al*, 2005), although its role is less well understood and will not be considered further in this review.

Aurora kinase A

The localization and activation of Aurora A is tightly regulated during the cell cycle. Aurora A activity depends on the phosphorylation of a threonine residue (T288) in the activation loop (Littlepage *et al*, 2002; Satinover *et al*, 2004). The level and activity of Aurora A is low in G1. By late S/early G2, Aurora A levels increase and the kinase associates with the duplicated, separating centrosomes, where its function is to recruit multiple proteins, including γ -tubulin, required for centrosome maturation and spindle assembly (Carmena and Earnshaw 2003). The mechanism of recruitment of Aurora A to the centrosome and its activation is incompletely understood, but involves a complex interaction with several proteins and a combination of feedback loops (Fig 2) (Lens *et al*, 2010; Lok *et al*, 2010). Briefly, in late G2, Aurora A autophosphorylates, and also activates polo-like kinase 1 (PLK1), which in turn promotes the binding of Aurora A to centrosomin. The activity of Aurora A is enhanced by several co-factors, including BORA, Ajuba, and TPX2. BORA is specifically required for activation of Aurora A-induced phosphorylation of PLK1 (Macurek *et al*, 2008). Ajuba is located on the centrosomes and promotes Aurora A autophosphorylation (Hirota *et al*, 2003).

After late G2, mitotic entry is triggered by a steep increase in cyclin B-cyclin-dependent kinase (CDK) 1 activity (Lindqvist *et al*, 2009). Aurora A contributes to this event directly, as well as indirectly by activating PLK1 (Watanabe *et al*, 2004). On the centrosome, Aurora A promotes recruitment of cyclin B1 and phosphorylates CDK-activating phosphatase cell division cyclin (CDC) 25B (Dutertre *et al*, 2004), which activates cyclin B-CDK1 activity. Also, Aurora A activates PLK1, which in turn phosphorylates the CDK-inhibitory kinase WEE1, a negative regulator of CDK1, targeting it for degradation. Activated PLK1 also activates the CDK-activating phosphatase CDC25C, which antagonizes WEE1. Therefore, activation of CDC25B and Inhibition and degradation of WEE1 lead to the increase in cyclin B-CDK1 activity. The increase in cyclin B-CDK1 activity phosphorylates BORA, resulting in BORA being recognized for polyubiquitination and degradation (Chan *et al*, 2008). Freed of BORA, Aurora A then interacts with cofactor TPX2, stimulating Aurora A autophosphorylation and protecting against its dephosphorylation by inhibiting protein phosphatase PP1, and thus facilitating the role of the kinase in spindle assembly (Eyers *et al*, 2003; Kufer *et al*, 2002). Recent data suggests that while Aurora-A activity accelerates mitotic entry in normal cells, it is essential for mitotic entry only in DNA-damaged cells (Macurek *et al*, 2008; van Vugt *et al*, 2004).

Throughout mitosis Aurora A localizes mainly near the spindle poles and on the polar microtubules, consistent with its pivotal role in spindle formation (Barr & Gergely 2007). While the mechanisms involved in spindle formation are unclear, it is known that activated Aurora A promotes the formation of a large multi-protein complex that is important for spindle formation by recruiting proteins required for microtubule nucleation, stabilization, bundling, and motor activity (Barr & Gergely 2007, Koffa *et al*, 2006). Aurora A inhibition, therefore, results in mitotic arrest with formation of abnormal spindles. Finally, in late M/early G1, Aurora A is degraded by the anaphase-promoting complex-ubiquitin-proteasome pathway (Honda *et al*, 2000).

In addition to the functions of Aurora A in mitosis, Aurora A also regulates the functions of TP53 (p53) and NF- κ B, which may have important therapeutic implications. Aurora A phosphorylates TP53 at Ser315 leading to its degradation by ubiquitination by MDM2 and proteolysis (Katayama *et al*, 2004). As TP53 is important in activating the pro-apoptotic machinery of the cell, loss of TP53 function can render cells resistant to DNA damaging agents (Ozaki & Nakagawara 2011). Indeed, cells depleted of Aurora A kinase activity appear to be more sensitive to cisplatin-induced apoptosis, and elevated expression of Aurora A kinase abolishes this response (Katayama *et al*, 2004). Finally, Aurora A has been

shown to phosphorylate I B (an antagonist of NF- B), thereby increasing NF- B activity (Sun *et al*, 2007), which is a potent anti-apoptotic effector that contributes to chemotherapy resistance. Inhibition of Aurora A has been shown to downregulate NF- B and enhance the efficacy of cytotoxic drugs (Sun *et al*, 2007).

Aurora kinase B

Aurora B is the catalytic component of the chromosomal passenger complex, which consists of three additional noncatalytic subunits that direct its activity: inner centromere protein (INCENP), survivin and borealin (Ruchaud *et al*, 2007; Vader *et al*, 2008), and is involved in accurate segregation of chromatids during mitosis, histone modification, and cytokinesis (Lens *et al*, 2006). The expression and activity of Aurora B is low in G1 and increases at G2/M transition, with maximal activity reached during mitosis (Bischoff *et al*, 1998; Terada *et al*, 1998). Aurora B is first detected on chromatin in late G2. In prophase, Aurora B localizes along the chromosome arms and inner centromere region, and by metaphase it is found only at the inner centromere region. In anaphase and telophase, Aurora B localizes on the central spindle, cortex and midbody to regulate cytokinesis (Carmena and Earnshaw 2003). The localization of Aurora B in different phases in mitosis correlates with its different functions (Fig 1).

In later G2 and early prophase, Aurora B promotes chromatin modification and facilitates chromosomal condensation by phosphorylating histone H3 at Ser10 and Ser28 (Monier *et al*, 2007) and promoting the dissociation of heterochromatin proteins 1 from chromatin (Fischle *et al*, 2005; Hirota *et al*, 2005). The activation of Aurora B requires additional cofactors, including the components of the chromosome passenger complex (Klein *et al*, 2006). INCENP undergoes autophosphorylation and induces a conformational change in the catalytic pocket of Aurora B, promoting its activity (Sessa *et al*, 2005). Survivin probably plays a related regulatory role, although the mechanism is poorly defined (Andrews 2005). Borealin does not activate Aurora B, but together with INCENP and survivin, targets the complex to the centromere early in mitosis, and to the spindle midzone and cleavage furrow late in mitosis (Gassmann *et al*, 2004).

During prometaphase and metaphase, Aurora B promotes the localization of centromeric proteins, ensuring the appropriate attachment of centromeres with bipolar spindles (Murata-Hori & Wang 2002). In this role, Aurora B is said to play a mitotic spindle checkpoint function (Fig 3). After nuclear envelope breakdown in prometaphase, chromosomes that have duplicated in S phase (sister chromatids) make attachments to a nearby spindle pole via one sister kinetochore, the protein structure on chromosomes where the spindle fibres attach during cell division to pull the chromosomes apart. The free kinetochore then captures a microtubule from the opposite pole resulting in a bipolar attachment that ultimately results in the positioning of the chromosome midway between the spindle poles (Carmena & Earnshaw 2003). Microtubules that attach in a non-bipolar manner to the kinetochore do not generate tension across the centromere, and therefore, the kinetochore remains in close proximity Aurora B located at the inner centromere region (Andrews *et al*, 2004; Liu *et al*, 2009). Close proximity to Aurora B allows it to phosphorylate several kinetochore-associated proteins, known as the KMN network (comprised of KNL1, MIS12, and NDC80), which serves as the main microtubule-binding unit at the kinetochore (Welburn *et al*, 2010). In addition, phosphorylation of KNL1 by Aurora B prevents the binding of a counteracting protein phosphatase PP1 to the kinetochore (Liu *et al*, 2009). Thus, phosphorylation of KMN components and blocking of PP1 binding to the kinetochore significantly reduces kinetochore affinity for microtubules. Attachment of the kinetochore to the microtubules, therefore, is broken, preventing chromatid separation until the appropriate attachments are reassembled (Ditchfield *et al*, 2003). On the other hand, when there is correct bipolar attachment and tension is generated, the kinetochore is physically separated

from Aurora B and PP1 is not inhibited, resulting in dephosphorylation of the KMN network components and stabilization of the microtubule-kinetochore attachment. Once proper chromosome alignment is established and chromatids have separated, Aurora B is translocated to the spindle midzone, where it resides in anaphase until cytokinesis (Carmena & Earnshaw 2003). Aurora B does not appear to be essential for initiation of cytokinesis, but plays a more important role in completion of the process (Burkard *et al*, 2007; Guse *et al*, 2005; Petronczki *et al*, 2007). In this respect, Aurora B is required for localization and stabilization of a tetrameric protein complex, called central spindilin, that is important for contractile ring formation and cleavage furrow ingression (Burkard *et al*, 2009; Petronczki *et al*, 2007; Wolfe *et al*, 2009). Inhibition of Aurora B activity, therefore, leads to incomplete cytokinesis, resulting in unviable polyploid cells (Yokoyama *et al*, 2005).

Role of Aurora kinases in cancer and their potential as therapeutic targets

Aurora kinases A and B have been recently recognized as potential targets for cancer therapy (Gautschi *et al*, 2008; Katayama *et al*, 2003). Over-expression of wild type Aurora A is oncogenic in murine models (Bischoff *et al*, 1998; Zhou *et al*, 1998). Also, the gene encoding for Aurora A, *AURKA*, is located at chromosome position 20q13, a site that is amplified in a number of solid tumour types and is associated with a poor prognosis (Bischoff *et al*, 1998; Bodvarsdottir *et al*, 2007; Klein *et al*, 2004; Nishida *et al*, 2007; Reichardt *et al*, 2003; Sen *et al*, 1997; Sen *et al*, 2002; Tatsuka *et al*, 2005). Unlike *AURKA*, however, amplification of the *AURKB* gene, located on chromosome 17p13.1, has not been reported. Over-expression of both Aurora kinase A and B independently of gene amplification, however, has been reported in a wide range of tumour types, although this may be related to rapid cell division rather than being a cause of the malignant phenotype (Gautschi *et al*, 2008; Keen & Taylor 2009; Mountzios *et al*, 2008). Furthermore, Aurora A and B overexpression has been associated with higher grades of malignancy, higher proliferation rates, and poor prognosis in several tumours (Araki *et al*, 2004; Gritsko *et al*, 2003; Jeng *et al*, 2004; Kurai *et al*, 2005; Miyoshi *et al*, 2001; Smith *et al*, 2005). While *AURKA* gene duplication has not been reported in the haematological malignancies, overexpression occurs in a number of these cancers.

Beyond the direct effect of Aurora kinases A and B on mitosis and cell division, they also participate in other cellular pathways important in cancer. For example, Aurora A is a downstream target of MAPK1/ERK, and constitutive activation of MAPK1 in pancreatic cancer has been reported to result in overexpression of Aurora A (Furukawa *et al*, 2006). Aurora A binds to c-Myc sites on the promoter of telomerase reverse transcriptase and increases its expression and activity, which in turn may confer a survival advantage to cancer cells (Yang *et al*, 2004). Finally, Aurora A upregulates the PI3K/AKT pathway by enhancing phosphorylation of AKT at Ser473 (Dar *et al*, 2008; Yang *et al*, 2006), and possibly GSK-3 (Dar *et al*, 2009), thereby enhancing cell survival and proliferation. The extent to which these effects might be important in specific cancer types, including the haematological malignancies, is uncertain.

Aurora kinases inhibitors in haematological malignancies

A large number of small molecule inhibitors of Aurora kinases have been developed for the treatment of cancer. These small molecules inhibit Aurora kinases by binding to the ATP binding pocket of the kinase, and thus compete with ATP substrate. As the ATP binding pocket is highly homologous across the members protein kinase family (Scapin 2006), many of these inhibitors are not specific for one or other of the Aurora kinases, and also some have additional “off target” effects that may contribute to their clinical efficacy. Differences in molecular structure of Aurora kinase inhibitors that allow them to interact differently with

regions adjacent to the ATP binding site determine to a large extent the kinase specificities of the inhibitors (Pollard & Mortimore 2009). Early inhibitors of the Aurora kinases included Hesperadin (specific for Aurora B) and ZM447439 (inhibitor of Aurora A and B), which did not enter clinical development but are available as research tools (Hauf *et al*, 2003). VX680 (MK0457) is relatively specific inhibitor of Aurora A, as well as of FLT3 and BCR-ABL1, which entered clinical trials but was discontinued after reports of QTc prolongation (Gizatullin *et al*, 2006; Harrington *et al*, 2004; Young *et al*, 2006). The Aurora kinase inhibitors currently in clinical development in the haematological malignancies together with their targets are listed in Table 1 and are discussed below.

Acute Myeloid Leukaemia (AML)

Recent studies have reported aberrantly increased expression of Aurora A and B in human myeloid leukaemia cell lines and fresh leukaemic cells obtained from AML patients. Aurora A and B transcript levels were reported to be significantly higher in freshly isolated leukaemia cells obtained from 44 AML cases compared with peripheral blood mononuclear cells or bone marrow cells obtained from healthy volunteers (Ikezoe *et al*, 2007). Also, in the same study, the dual Aurora A and B inhibitor ZM447439, which has no activity against ABL1 or FLT3 kinase, inhibited the proliferation, induced polyploidy, apoptosis, and inhibited the clonogenic growth of freshly isolated leukaemia cells from AML patients, including those who were refractory to conventional chemotherapy (Ikezoe *et al*, 2007). In another study that examined for Aurora A protein expression by Western blotting, leukaemic blasts from 98 *de novo* AML patients showed markedly increased Aurora A expression compared with negligible expression in bone marrow mononuclear cells obtained from normal donors, with expression considered high in about two thirds of cases as defined by >30% of blasts showing strong cytoplasmic granular immunocytochemical staining (Huang *et al*, 2008). Importantly, VX680, a relatively specific Aurora A inhibitor, induced apoptosis preferentially in leukaemic blasts with high expression of Aurora A compared to blasts with low expression and bone marrow cells from normal donors. VX680-induced apoptosis was associated with destruction of normal bipolar spindles, G2/M cell cycle arrest, reduction of p-AKT, activation of caspases, and a dose-dependent increase in the Bax/Bcl-2 ratio (Huang *et al*, 2008).

A number of Aurora kinase inhibitors have entered early phase clinical trials in patients with AML (Table 2). AZD1152 is a highly selective Aurora B inhibitor, which in *vitro* blocked phosphorylation of histone H3, increased the population of tetraploid cells, and induced apoptosis of human leukaemic cell lines (Yang *et al*, 2007). In a Phase I/II trial, AZD1152 was administered at doses of 50–1600 mg/day for 7 days every 21 days by continuous intravenous (CIV) infusion to 32 patients with advanced AML (Lowenberg *et al*, 2009). The maximum tolerated dose (MTD) was 1200 mg/day, with the most commonly reported grade 3–4 toxicities being febrile neutropenia and stomatitis. Of the 32 patients enrolled in the dose-escalation phase, 1 patient at the 1200 mg dose level achieved a complete response (CR), and 2 patients treated at 400 mg and 800 mg, respectively, achieved CR with incomplete count recovery (CRi). In a Phase II extension of the trial at the MTD, 5 of 32 additional AML patients achieved CR (n=2) or CRi (n=3) with similar toxicity to that observed in the Phase I portion (Lowenberg *et al*, 2009). Based on its observed clinical activity, AZD1152 is being evaluated in combination with low dose cytarabine in newly diagnosed AML patients 60 years and older who are unfit for intensive induction chemotherapy (Kantarjian *et al*, 2010). In a preliminary report, the MTD of AZD1152 was 1000 mg/day (CIV infusion for 7 days) when combined with cytarabine 20 mg subcutaneously twice daily for 10 days, every 28 days, with stomatitis being dose-limiting. Of 21 patients reported, CR was observed in 7 and CRi in 2 patients, for a total response rate

of 43%. A Phase II trial of this combination is currently ongoing to better define the response rate.

MLN8237 is a highly selective inhibitor of Aurora A, which has undergone clinical evaluation in adults with advanced AML or intermediate-2/high-risk myelodysplasia (MDS). In a multicentre Phase II trial, 67 patients of median age 72 (range, 46–85) years, with AML (n=46) or MDS (n=21), received MLN8237 at 50 mg orally twice daily for seven days followed by 14 days rest until progression (Goldberg *et al*, 2010). Patients received a median of 2 (range, 1–16) cycles. One AML patient who did not receive any prior therapy achieved a CR that lasted 1 year, and an additional 5 AML patients achieved partial responses (PR) for an overall response rate of 16%. Treatment-related grade 3–4 adverse events included febrile neutropenia, thrombocytopenia, anaemia, fatigue, neutropenia, and somnolence, with treatment discontinued in 14 patients (25%) because of excessive toxicity.

Some of the Aurora kinase inhibitors also inhibit other kinases, including FLT3. *FLT3* activating internal tandem duplication (ITD) or tyrosine kinase domain (TDK) mutations are found in approximately 20–30% of AML cases and predict a poor prognosis (Kottaridis *et al*, 2001; Yamamoto *et al*, 2001). The additional inhibitory activity against FLT3 may be an important secondary mechanism of anti-leukaemic activity. In preclinical studies, while FLT3 mutational status did not predict drug sensitivity to VX680 in AML blasts with high Aurora A expression, blasts with *FLT3*-ITD mutation that had a lower expression of Aurora A were sensitive to VX680-induced apoptosis (Huang *et al*, 2008). In another study, the inhibition of clonogenic potential of primary AML blasts by AZD1152 was significantly higher in AML samples with *FLT3*-ITD compared with that in *FLT3* wild-type samples (Grundy *et al*, 2010), a finding which has also been confirmed *in vivo* in AML xenografts using AS703569 (McLaughlin *et al*, 2010). These studies suggest that analysis of both Aurora kinase expression and *FLT3*-ITD mutational status may be valuable in identifying patients who may benefit from Aurora kinase inhibitors with concomitant FLT3 kinase inhibitory activity.

As shown in Table 2, four Aurora kinase inhibitors with FLT3 inhibitory activity have entered clinical trials in patients with leukaemia. ENMD-2076 is an oral inhibitor of Aurora A and B, as well as FLT3 and multiple other tyrosine kinases (Fletcher *et al*, 2011). and preliminary results from a Phase I trial in relapsed or refractory AML patients have been reported (Yee *et al*, 2010). In 27 patients, of median age 69 (range, 43–84) years, who received daily doses of ENMD-2076 at 225 mg, 375 mg, 325 mg and 275 mg, dose-limiting toxicity included fatigue, typhilitis, and syncope. The 225 mg dose was best tolerated and was recommended as the Phase II dose for further evaluation. Of 20 evaluable patients, one achieved a CRi and 3 achieved a morphological leukaemia-free state. In the patient achieving a CRi, striking decreases in the stimulation of ERK, AKT, STAT5 and S6 in leukaemic cells were observed (Yee *et al*, 2010). It was not reported, however, if the patient who achieved CRi had *FLT3*ITD⁺ leukaemia.

AS703569 is another inhibitor of Aurora A and B, with additional activity against FLT3 and ABL1 kinases (McLaughlin *et al*, 2010). In preclinical studies *in vitro* and *in vivo*, AML cells with *FLT3*ITD mutations were up to 10-fold more sensitive to AS703569 than those with wild type *FLT3*, and in xenograft models, sustained inhibition of both FLT3 and histone H3 phosphorylation was observed in tumour lysates up to 48 h after the last dose was administered, suggesting that inhibition of both kinases might have been important for anti-leukaemic activity (McLaughlin *et al*, 2010). In a Phase I trial of AS703569 in 45 patients with AML, MDS, CML and myeloproliferative disease, significant reductions in bone marrow and/or peripheral blood blasts were observed in 3 of 33 AML patients who received 5–7 cycles, and a PR was observed in 1 of 5 patients with MDS (Sonet *et al*, 2008).

Frequently observed toxicities included neutropenia, thrombocytopenia, infection, mucositis and diarrhoea, but the MTD is yet to be defined.

Of the Aurora kinase inhibitors with additional kinase inhibitory activity, KW-224 has the most potent activity against FLT3 (Shiotsu *et al*, 2009). In preclinical studies, KW-224 inhibited proliferation and induced apoptosis of AML cell lines that harbored *FLT3* ITD as well as AML cells with wild type *FLT3* (Shiotsu *et al*, 2009). In *FLT3* ITD⁺ AML cell lines, KW-224 also reduced the phosphorylation of FLT3 and STAT5, and in cells with wild type *FLT3*, inhibition of Aurora kinase activity was also demonstrated by reduced phosphorylation of histone H3 and G2/M arrest (Shiotsu *et al*, 2009). In a Phase I trial in patients with leukaemia, that included AML, KW-224 was administered orally at 7 dose levels, escalating from 12.5 mg to 250 mg twice daily (Pratz *et al*, 2009). Only modest clinical activity was observed, with transient reductions in peripheral blood blasts by 50% or more noted in 5 of 11 patients with *FLT3* ITD⁺ AML. However, using this dosing schedule, FLT3 phosphorylation was only transiently inhibited by greater than 80% at the highest dose level, suggesting that the failure to fully inhibit FLT3 in sustained fashion may have been the reason for the minimal success observed (Pratz *et al*, 2009). Therefore, the study was terminated before the MTD was reached, and a new study with a 3–4 times per day dosing strategy, aimed at continually abrogating FLT3 autophosphorylation, is currently ongoing in *FLT3* ITD⁺ AML patients ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00779480) Identifier: NCT00779480).

While Aurora kinase inhibitors have significant therapeutic potential in AML, single agent activity appears to be uniformly modest. It is likely, however, that Aurora kinase inhibitors will find their place in combination therapy, as suggested by the improved response rates to the combination of AZD1152 with low dose cytarabine (Kantarjian *et al*, 2010). In this respect, preclinical studies have also shown synergy of Aurora kinase inhibitors with both daunorubicin (Yang *et al*, 2007) and etoposide (Huang *et al*, 2008), which are commonly used drugs in the frontline treatment of AML. Also, as larger trials of Aurora kinase inhibitors are conducted in the future, it will be important to identify those AML patients who may most benefit from treatment by correlating responses to Aurora kinase inhibitors with Aurora A or B expression in leukaemic blasts, and possibly *FLT3* mutational status, as suggested by results of preclinical studies (Grundy *et al*, 2010; Huang *et al*, 2008; McLaughlin *et al*, 2010).

Acute lymphoblastic leukaemia (ALL) and chronic myeloid leukaemia

Unlike in AML, there is minimal data on the level of expression of Aurora kinases in fresh blasts obtained from patients with ALL or CML, although aberrantly high expression levels have been noted in some cell lines (Ikezoe *et al*, 2007; Yang *et al*, 2007). Also, while direct inhibition of Aurora kinases may be important in ALL (Maris *et al*, 2010), most research has centred on evaluating the potential of inhibitors with additional activity against BCR-ABL1 kinase in Ph⁺ ALL and CML, and in particular, their ability to overcome TKI resistance due to mutations of the ABL1 kinase domain. Point mutations of the ABL1 kinase domain, particularly the T315I mutation, occur in approximately 43% of Ph⁺ leukaemia patients during TKI therapy, with the highest rates of mutations observed in blast crisis CML and Ph⁺ ALL (Quintas-Cardama *et al*, 2007; Soverini *et al*, 2006). Importantly, for many of the Aurora kinases with additional activity against ABL1, activity against mutated ABL1 kinase isoforms (including the T315I mutant) is higher than for the wild-type kinase (Table 1). For example, the Aurora kinase inhibitors, MK0457, AT9283, Danusertib (formerly PHA-739358), XL228, and KW2449, inhibit the T315I ABL1-mutant at lower concentrations than wild type ABL1 (Moore *et al*, 2010), making them of potential benefit for Ph⁺ ALL and CML patients who have failed first and second line TKI therapy.

A number of the Aurora kinase inhibitors are currently undergoing clinical evaluation in patients with Ph+ ALL or CML (Table 3). AT9283 is an Aurora kinase A and B inhibitor with inhibitory activity against ABL1, FLT3, JAK2, FGFR and VEGFR, and has shown preclinical *in vivo* efficacy in murine xenograft models using T315I or E255K mutant BCR-ABL1 transfected BaF3 cells and *in vitro* efficacy against primary CML cells with E255K mutated BCR-ABL1 (Tanaka *et al*, 2008). Consistent with these studies, AT9283 showed clinical activity against CML in a Phase I trial in patients with refractory leukaemia (Foran *et al*, 2008). Using a 72-h CIV infusion at eight different dose levels, two patients with accelerated phase CML refractory to the TKI inhibitors imatinib and dasatinib achieved haematological responses, including a partial cytogenetic response in one patient. Pharmacodynamic studies demonstrated a reduction in phosphorylated histone H3 and of p-STAT5, which is downstream of BCR-ABL1 (as well as FLT3 and JAK2) signalling, suggesting multiple kinase inhibition. A trial utilizing a different schedule is currently ongoing ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study?term=NCT00522990) Identifier: NCT00522990)

Danuserib is an Aurora kinase A, B and C inhibitor with additional activity against ABL1, FLT3, and VEGFR3 (Steehgs *et al*, 2010), which has demonstrated *in vitro* activity against CML cells with wild-type BCR-ABL1 and cells possessing the *ABL1* T315I mutation (Gontarewicz *et al*, 2008). Preliminary results of a Phase I clinical trial in 23 patients with advanced stage CML and Ph+ ALL, refractory or intolerant to TKI therapy (15 of which had the T315I mutation), have recently been reported (Cortes-Franco *et al*, 2009). Danuserib was administered as a 3-h intravenous infusion for 7 days every 2 weeks at five dose levels. To date, the MTD has not been reached. However, 5 patients have achieved a haematological response and three have demonstrated cytogenetic (one complete, one partial, one minimum) responses. Of note, one additional patient with extensively pre-treated ALL with T315I mutation achieved a complete molecular response.

XL228 is a multi-kinase inhibitor with activity against Aurora A, ABL1, IGF1R, SYC and LYN, which is currently being evaluated in patients with refractory leukaemia. In a phase I trial involving 27 CML and Ph+ ALL patients, 10 of whom had the T315I mutation, XL228 was administered as a 1-h intravenous infusion once or twice weekly (Cortes *et al*, 2008a). In patients receiving at least 3.6 mg/kg, objective responses were observed with decreases in white blood cell count and/or > 1 log reduction in the level of *BCR-ABL1* transcripts (Cortes *et al*, 2008a). KW-2449, an Aurora kinase A and B inhibitor with additional activity against ABL1 (including T315I mutant), FLT3 and FGFR1, also shows activity *in vitro* (Shiotsu *et al*, 2009), and clinically against CML (Cortes *et al*, 2008b). Of five imatinib-resistant CML patients included in a Phase I trial, treatment with KW-2449 resulted in disappearance of the T315I clone and an improvement in blast count in one patient with blast crisis CML (Cortes *et al*, 2008b). Finally, in a phase I trial of AS703569 in myeloid malignancies, 1 of 6 CML patients with a T315I mutation achieved a haematological and cytogenetic response (Sonet *et al*, 2008).

While results of early phase clinical trials suggest a potential therapeutic role for Aurora kinase inhibitors in Ph+ ALL and CML, it remains uncertain whether efficacy is simply related to inhibition of BCR-ABL1 signalling or to the combined inhibition of Aurora and BCR-ABL1. Recent data suggests that the contribution of Aurora inhibition is important. Low concentrations of AS703569, a dual inhibitor of Aurora kinase B and ABL1 kinase, induced a phenotype consistent with inhibition of Aurora B and induced apoptosis of *BCR-ABL1* transformed cells while not inhibiting BCR-ABL1 (Seitz *et al*, 2009). Similarly, MK0457 suppressed Aurora kinase activity and induced apoptosis in imatinib-resistant CML cells expressing the T315I and other *BCR-ABL1* mutations but without affecting BCR-ABL1 kinase activity (Donato *et al*, 2010). Finally, Danuserib and MLN8237 have shown synergistic activity with imatinib and nilotinib, respectively, in preclinical studies,

suggesting that the inhibition of both kinases may be important (Gontarewicz *et al*, 2008; Kelly *et al*, 2010; Nawrocki *et al*, 2008), and that combination therapy should be a new avenue of clinical research in Ph+ leukaemias. On the other hand, the potential importance of Aurora kinase inhibition as a mechanism of anti-leukaemia activity, independent of the effect on BCR-ABL1, suggests that Aurora kinase inhibitors may have activity in Ph negative ALL. While patients with Ph negative ALL are included with patients with other haematological malignancies in ongoing trials of Aurora kinase inhibitors (see Tables 2 and 3), the activity of Aurora kinase inhibitors in Ph negative ALL remains to be better defined.

Multiple Myeloma

The Aurora kinases have been validated as potential targets for therapy in multiple myeloma (MM) (Manfredi *et al*, 2007). As MM is characterized by genetic instability with numerous chromosomal abnormalities (Fonseca *et al*, 2004), it was suggested that there must exist disruption of checkpoints that would normally arrest the MM cells at the G₂/M transition or at mitosis to allow potential repair of DNA damage or spindle abnormalities (Manfredi *et al*, 2007). Such deficient checkpoints would render the MM cells susceptible to apoptotic death in mitosis if further disruption of the mitotic pathway were induced, as with inhibition of Aurora kinases (Manfredi *et al*, 2007). Further, the Aurora kinase inhibitor, VX680, induced tetraploidy in 48 h, followed by apoptosis at 72 h in MM cells, which correlated with inhibition of Aurora activity as demonstrated by a reduction of histone H3 phosphorylation (Manfredi *et al*, 2007). Also, ectopic expression of Aurora A by stable transfection of OPM-2 myeloma cells protected against the proapoptotic action of Aurora inhibitors, but not against bortezomib, indicating target specificity (Manfredi *et al*, 2007). Finally, it was recently reported that 24% of previously untreated MM patients expressed Aurora A, and that myeloma cells with detectable Aurora A expression showed significantly higher proliferation rates compared with those without detectable Aurora-A expression (Hose *et al*, 2009).

A number of Aurora kinase inhibitors have been investigated in MM cells (Evans *et al*, 2008a, Evans *et al*, 2008b; Gorgun *et al*, 2010; Hose *et al*, 2009; Negri *et al*, 2009; Santo *et al*, 2011). Some of these inhibitors also have additional off target effects that may contribute to anti-myeloma activity. Of particular interest, ENMD-2076, an inhibitor of Aurora kinase and multiple tyrosine kinases, has been shown to have anti-myeloma activity *in vitro* and *in vivo* and appears to interfere with multiple pathways that are important in MM (Wang *et al*, 2010). ENMD-2076 induces apoptosis of MM cell lines and primary MM cells within 6 h in a dose-dependent manner, with downregulation of MCL1, survivin and XIAP, inhibition of the PI3K/AKT pathway, and induction of G2/M arrest with decreases of cyclins A and B (Wang *et al*, 2010). A potentially important off target effect of ENMD-2076 is inhibition of FGFR3, which is ectopically expressed in approximately 15% of MM cases associated with translocation t(4;14) (Chesi *et al*, 2001; Chesi *et al*, 1997; Otsuki *et al*, 1999). MM cases with t(4;14) have a particularly poor outcome (Chng *et al*, 2008; Moreau *et al*, 2007). The t(4;14) abnormality causes dysregulation of the *FGFR3* by its translocation from chromosome 4p16.3 to chromosome 14q32, adjacent to the immunoglobulin heavy chain locus (*IGH@*) (Chesi *et al*, 1997), resulting in ectopic expression of functional FGFR3 on MM cells that otherwise do not express it (Chesi *et al*, 2001; Chesi *et al*, 1997). The FGF receptors, including FGFR3, are tyrosine kinase receptors and signal primarily through the ERK pathway (Hart *et al*, 2000; Kanai *et al*, 1997). Ectopic expression of FGFR3 on MM cells stimulates myeloma cell proliferation and prevents apoptosis (Plowright *et al*, 2000), and MM cells ectopically expressing FGFR3 are sensitive to the inhibitory and pro-apoptotic effects of specific FGFR inhibitors (Paterson *et al*, 2004), suggesting that FGFR3 may be a good therapeutic target in MM with t(4;14). ENMD-2076 has been shown to inhibit the phosphorylation of FGFR3 in H929 plasmacytoma xenografts in a dose-

dependent manner (Wang *et al*, 2010), and may therefore be a useful drug in this subset of MM.

Aurora kinase inhibitors under clinical investigation in MM are listed in Table 4. Interim results from an ongoing Phase I trial of ENMD-2076 in patients with relapsed or refractory MM indicates that ENMD-2076 has clinical activity in heavily pretreated patients (Farag *et al*, 2010). ENMD-2076 was given orally for 28 days at once daily doses of 150, 225 or 325 mg. In the first 10 patients, activity was observed in 3 of 4 patients treated at the highest dose level of 325 mg/day; one patient achieved a 60% reduction urinary monoclonal (M) protein excretion and a 75% reduction in volume of extramedullary plasmacytomas, and 2 additional patients achieved 21% and 19% reductions in serum M-protein, respectively, after one cycle. Of note, however, none of the patients had t(4;14) MM. Dose-limiting toxicity consisting of grade 3 thrombocytopenia in one patient and posterior reversible encephalopathy syndrome in another, however, has been observed at the 325 mg/day dose. Other toxicities included hypertension, anorexia, nausea, diarrhoea, fatigue, asymptomatic elevation of amylase and lipase, leucopenia, and proteinuria, although none were dose limiting. The trial is currently ongoing, enrolling patients on a reduced dose of 275 mg/day. While the interim results from the Phase I clinical trial indicate that ENMD-2076 has some clinical activity in MM, this appears to occur at a dose where toxicity may be problematic. Further study at the lower dose of 275 mg/day will determine if clinically useful activity will still be observed with this agent when administered singly.

Preliminary results from a Phase I trial of MLN8237 in 29 patients with a variety of haematological malignancies have also been reported (Padmanabhan *et al*, 2010). Of 8 relapsed or refractory MM patients included, one patient was observed to have stabilization at the MTD (90 mg/day for 14 days each 28-day cycle), although no objective responses were observed. Phase II trials of AT9273 and Danusertib are currently ongoing in patients with relapsed or refractory MM, and clinical activity of these agents in MM remains to be determined.

Preclinical studies suggest that the optimal use of Aurora kinase inhibitors in MM may be in combination with other drugs. In this respect, MLN8237 has shown *in vitro* synergistic or additive activity in combination with melphalan, dexamethasone, and bortezomib (Gorgun *et al*, 2010). A Phase I trial of MLN8237 in combination with bortezomib is currently ongoing ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study?term=MLN8237&rank=1) Identifier: NCT01034553). We have also shown *in vitro* and *in vivo* synergy of ENMD-2076 with lenalidomide against MM cell lines and plasmacytoma xenografts (Zhang & Farag 2011). Similarly, AT9283 showed potent *in vitro* anti-myeloma activity in combination with lenalidomide in MM.1S cells cultured with bone marrow stromal cells (Santo *et al*, 2010). Collectively, these results provide rationale for future evaluation of combination therapy in MM. An important issue in future trials in MM, however, is identifying patients who might benefit most from Aurora kinase inhibitors. A recent report indicated that centrosome amplification is common in MM, and that a gene-expression based centrosome index (CI), which correlates with centrosome amplification, correlated with Aurora expression in MM cells (Chng *et al*, 2008). Furthermore, MM cell lines with higher CI were more responsive to Aurora inhibitors. The CI, therefore, may be a promising biomarker and should be prospectively investigated in trials of Aurora kinase inhibitors in MM.

Non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL)

Overexpression of Aurora kinases occurs in NHL and, to a lesser extent, in HL. In NHL, Aurora A and B overexpression has been observed largely in aggressive subtypes. Early studies indicated that Aurora A transcripts are overexpressed in NHL cell lines and Epstein-Barr virus-transformed B cell lines compared with normal B lymphocytes (Hamada *et al*,

2003; Yakushijin *et al*, 2004). Furthermore, in single tumour cell suspensions from patients with different B-cell NHL, Aurora A transcripts were only expressed at high levels in histologically aggressive types, including diffuse large B-cell lymphoma (DLBCL) and Burkitt lymphoma (BL), while cells from patients with follicular lymphoma (FL) and normal B cells did not show overexpression (Hamada *et al*, 2003; Yakushijin *et al*, 2004). Also, DLBCL cases with a high International Prognostic Index (IPI) expressed higher levels than those with lower IPI scores, indicating that Aurora A expression also correlated with disease activity in NHL. Immunohistochemical studies have also indicated that Aurora B overexpression occurs in 48% and 86% of DLBCL and BL cases, respectively, with only 1 of 20 FL cases showing overexpression (Ikezoe *et al*, 2009). The mechanism by which Aurora A and B are upregulated in aggressive NHL is not well understood as gene amplification has not been observed (Hamada *et al*, 2003). However, at least in some cases, upregulation of Aurora kinases may be related to overexpression of *MYC* (den Hollander *et al*, 2010; Yang *et al*, 2010).

Overexpression of Aurora kinases has also been reported in mantle cell lymphoma (MCL). In a study of 26 cases of MCL, the highest levels of *AURKA* transcripts were observed in blastoid variant cases compared with other variants, and were correlated strongly with Ki-67 expression (Camacho *et al*, 2006). In another study, high levels of *AURKA* expression was observed in 88% and *AURKB* in 75% of MCL cases (Qi *et al*, 2011). Furthermore, using the Leukaemia/Lymphoma Molecular Profiling Project database, *AURKA* and *AURKB* expression was studied in 92 MCL patients, and correlated inversely with survival. Patients with *AURKA* and *AURKB* expression in the highest quartiles had significantly reduced overall survival (Qi *et al*, 2011). While systematic evaluation of Aurora kinase expression in other histological subtypes of lymphoma has not been reported, small studies have suggested that overexpression of *AURKA* and *AURKB* may occur in a proportion of patients with HL (Mori *et al*, 2011), and of *AURKA* in some cases of adult T-cell leukaemia/lymphoma (Tomita *et al*, 2010).

The overexpression of Aurora kinases in different lymphoma subtypes has provided rationale for investigating Aurora kinase inhibitors in these diseases. In preclinical studies, the selective Aurora B inhibitor AZD1152 induced growth arrest and apoptosis in BL cell lines in a caspase-dependent and independent manner, and showed synergistic anti-lymphoma activity in association with vincristine (Ikezoe *et al*, 2009). In another study, AZD1152 also showed antiproliferative effects, inhibited the phosphorylation of histone H3, induced polyploidy with cells with >4N DNA content, caspase-dependent apoptosis, and inhibited survivin expression in BL and HL cell lines (Mori *et al*, 2011). AT9283, a pan-Aurora/JAK2 kinase inhibitor also induced apoptosis of B-cell lymphoma cell lines, and while modest *in vivo* anti-lymphoma activity in a mouse xenograft MCL model was observed, significant synergy was observed when AT9283 was combined with docetaxel (Mahadevan *et al*, 2010). Finally, MLN8237, an Aurora kinase inhibitor with relative specificity for Aurora A, also inhibited proliferation and induced apoptosis in aggressive B cell lymphoma cell lines (Huck *et al*, 2008), and showed *in vivo* synergy with docetaxel in a mouse MCL xenograft (Qi *et al*, 2011).

Only a limited number of Aurora kinase inhibitors have been clinically investigated in NHL (Table 5). In a Phase I trial of MLN8237 in patients with advanced haematological malignancies that also included patients with aggressive NHL, anti-tumour activity was observed in 2 of 19 lymphoma patients; one patient with relapsed and refractory DLBCL showed a reduction in tumour volume, and another achieved a PR that has lasted more than 1 year (Padmanabhan *et al*, 2010). Phase II trials in patients with relapsed or refractory aggressive NHL are currently ongoing with MLN8237 ([ClinicalTrials.gov Identifier: NCT00807495](#)) and AZD1152 ([ClinicalTrials.gov Identifier: NCT01354392](#)). It is likely,

however, that the greatest potential for Aurora kinase inhibitors in aggressive NHL will be in combination with other cytotoxic agents, including DNA-damaging and microtubule-damaging agents, already used in the treatment of lymphoma, and potentially with histone deacetylase inhibitors that may modulate *MYC* expression (Kretzner *et al*, 2011).

Conclusion

Aurora kinases are aberrantly expressed in many cancers and have emerged as important therapeutic targets. Overexpression of Aurora kinases A and B is observed in a significant proportion of patients with AML, Ph+ leukaemia, aggressive NHL and HL, and in some cases higher expression is associated with an adverse outcome. Currently a large number of Aurora kinase inhibitors are in various stages of development in the haematological malignancies. However, Aurora target specificity among these inhibitors varies significantly, and many inhibitors exhibit effects against other kinases. Indeed, effects against kinases such as FLT3, BCR-ABL1 mutants, JAK2, and FGFR3 may in some cases contribute to added activity of these agents against the specific malignancies where these targets are important drivers. On the other hand, the additional off target effects might also contribute to increased toxicity. Resolving issues, such as which of the Aurora kinases is the more important target, as well as the relative importance of inhibiting the Aurora kinases versus other kinases in different haematological malignancies, will be important in setting some priority in developing the large number of inhibitors currently available. However, other differences between the inhibitors will also be important, including route of administration and pharmacokinetic profile. While many of the Aurora kinase inhibitors tested in early phase clinical trials have shown anti-tumour activity, future clinical investigation should focus on identifying patient subsets in each of the haematological cancers who might benefit most from treatment. Preclinical data suggests that baseline Aurora kinase expression may predict response to these inhibitors, and this should be further investigated in clinical trials. Similarly, expression of other kinases targeted should be also correlated with response wherever relevant. Finally, it is likely that the optimal use of Aurora kinase inhibitors will be in combination with cytotoxic agents already in use. In this respect, the combination with existing DNA damaging agents should be a priority for future trials. A potentially important limitation of the aurora kinase inhibitors, however, is the possibility of inducing of second cancers. Indeed, sobering data has emerged from studies of Aurora A knockout mice (Lu *et al*, 2008). While the Aurora A null ($A^{-/-}$) genotype was lethal, Aurora A heterozygous ($A^{+/-}$) mice were born healthy with no obvious effects except for a slight decrease in Aurora A levels compared with Aurora A wild-type mice. Importantly, with up to 70 weeks follow-up, Aurora $A^{+/-}$ mice had a three-fold higher incidence of tumours compared with Aurora A wild-type mice (25% vs 8.8%; $P<0.001$) (Lu *et al*, 2008). Approximately half of the tumours were of haematopoietic origin, including lymphoma, leukaemia and myeloma, although a variety of epithelial malignancies were also observed. It is likely that chromosomal instability associated with deficiency of Aurora A led to tumorigenesis. While second cancers have yet not been reported in patients treated with Aurora kinase inhibitors in clinical trials, possibly because most have succumbed to their primary cancer, close vigilance for development of secondary cancers in long-term survivors will be important. The coming decade will determine if the promise of the Aurora kinase inhibitors will be realized in the haematological malignancies.

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Figure 1. Cellular localization of Aurora kinases A and B in mitosis

In G1, the levels of both Aurora A (green squares) and Aurora B (red circles) kinases are markedly reduced, but increase with different localization during M phase. In prophase, Aurora A is located around the centrosomes, whereas Aurora B is nuclear. In metaphase, Aurora A is on the microtubules near the spindle poles, whereas Aurora B is located in the inner centromere. In anaphase, most Aurora A is on the polar microtubules, but some might also be located in the spindle midzone. Aurora B is concentrated in the spindle midzone and at the cell cortex at the site of cleavage-furrow ingression. In cytokinesis, both kinases are concentrated in the midbody. Reprinted by permission from Nature Publishing Group: *Nature Reviews Molecular Cell Biology* 4, 842–854, Carmena & Earnshaw (2003).

Figure 2. Function of Aurora A during late G2 and mitosis

(A) In late G2, Aurora A autophosphorylates and also activates PLK1, which in turn promotes the binding of Aurora A to centrosomin. PLK1 is recruited to the centrosome by cenexin 1. While Aurora A can self-activate, its activity is enhanced by several cofactors, including TPX2 and BORA. Active PLK1 phosphorylates WEE1, a kinase that negatively regulates cyclin B-CDK1 complexes. The cell division cycle 25 (CDC25) phosphatases that antagonize WEE1 are largely inactive in G2. (B) Mitotic entry is triggered by a steep increase in cyclin B-CDK1 activity. On the centrosome, Aurora A and PLK1 promote recruitment and activation of CDC25B, which in turn, activates cyclin B-CDK1. Cyclin B-CDK1 complexes further phosphorylate WEE1 and BORA, which are then recognized by the F-box protein β -transducin repeat containing (β -TrCP) that promotes polyubiquitylation (Ub) and degradation of WEE1 and BORA. Freed of BORA, Aurora kinase A is then able to interact with TPX2, thus facilitating the role of the kinase in spindle assembly (see text). Green phosphates (P) are activating, red phosphates are inhibitory and yellow phosphates prime a protein for degradation. Reprinted by permission from Nature Publishing Group: *Nature Reviews Cancer* 10, 825–841, Lens *et al* (2010).

Figure 3. Aurora B regulation of kinetochore-microtubule interactions

The affinity of the microtubules to the kinetochore is affected by a phosphorylation gradient of Aurora B. (A) In prophase, Aurora B, present at the inner centromere, is in close proximity to the kinetochore due to a lack of tension allowing Aurora B to phosphorylate all components of the KMN network (comprising **KNL1**, **MIS12** and **NDC80** (also known as highly expressed in cancer [**HEC1**]), which serves as the main microtubule-binding unit at the kinetochore; consequently, the kinetochore has low affinity for microtubules. Similarly, non-bipolar attachment of microtubules to the kinetochore does not generate tension across the centromere, and therefore the kinetochore remains in close proximity to Aurora B and the KMN complex is phosphorylated by Aurora B. Also, phosphorylation of **KNL1** by Aurora B prevents the binding of **PP1** (which dephosphorylates KMN substrates) to the kinetochore. Phosphorylation of KMN components and blocking of **PP1** binding to the kinetochore significantly reduce kinetochore affinity for microtubules. Attachment of the kinetochore to the microtubules, therefore, is broken, preventing chromatid separation until the appropriate attachments are reassembled. As the cell progresses through prometaphase (B) and metaphase (C), and when there is correct bipolar attachment of microtubules, tension is generated and the kinetochore is physically separated from Aurora B and **PP1** binding is not inhibited, resulting in dephosphorylation of the KMN components. Further, Aurora B also recruits the kinetochore-associated checkpoint kinase **BURB1** where it is phosphorylated by **PLK1**, which in turn results in reduced Aurora B activity, also promoting

attachment of microtubules to the kinetochore. Reprinted by permission from Nature Publishing Group: *Nature Reviews Cancer* 10, 825–841, Lens *et al* (2010).

Table 1

Target profiles of Aurora kinase inhibitors currently in clinical investigation in the haematological malignancies

Drug	Manufacturer	Target kinase inhibited by drug *											
		Aurora A	Aurora B	FLT3	ABL1	ABL1 (T315I)	KIT	VEGFR	JAK2	FGFR3	SYK	LYN	IGF1R
AZD1152	Astra Zeneca	1369	0.37	-	-	-	-	-	-	-	-	-	-
MLN8237	Millennium	1	1100	-	-	-	-	-	-	-	-	-	-
ENMD-2076	EntreMed	14	290	3	295	81	126	36	120	92	-	-	-
AS703569	Merck Sereno	4	4.8	99% inhibition at 100 nM	92% inhibition at 100 nM	-	-	-	-	-	-	-	-
KW-2449	Kyowa Hakko Kirin Pharma	48	48	6.6	14	4	300	-	150	-	-	-	-
AT9283	Astex Therapeutics	3	3	10	110	4	-	10-30	1.2	10-30	-	-	-
Danuserib	Nerviano	13	70	-	21	4	-	-	-	-	-	-	-
XL228	Exelixis	3.1	0.6	-	5	1.4	-	-	-	3	6.1	5	1.2

* Concentration inhibiting target kinase activity by 50% (IC₅₀) shown (nM) unless otherwise indicated.

Table 2

Aurora kinase inhibitors currently in clinical development in AML

Drug	Clinical trial	Patients included	N	Route	Dose	Main toxicity reported	Responses	Reference
AZD1152	Phase I/II	Advanced AML	64	CIV	50–1600 mg/d $\times$ 7d q 21 days (MTD 1200 mg)	Febrile neutropenia, stomatitis.	Phase I: 1 CR, 2 CRi Phase II: 2 CR, 3 CRi	Lowenberg <i>et al.</i> , (2009)
	Phase I (with low-dose AraC)	AML (60 years)	21	CIV	MTD 1000 mg/d $\times$ 7d (with AraC 20 mg SC bid $\times$ 10 d) q 28d	Stomatitis.	7 CR, 2 CRi	Kantarjian <i>et al.</i> , (2010)
MLN8237	Phase II	Advanced AML/MDS	67	PO	50 mg bid $\times$ 7d q 21 days	Febrile neutropenia, thrombocytopenia, anaemia, fatigue, somnolence	1 CR, 5 PR	Goldberg <i>et al.</i> , (2010)
ENMD-2076	Phase I	Relapsed or refractory AML	20	PO	225–325 mg/d (MTD 225 mg)	Fatigue, typhilitis, syncope	1 CRi, 3 morphological leukaemia-free state	Yee <i>et al.</i> , (2010)
AS703569	Phase I	AML, MDS, CML, MPD	45	PO	3–47 mg/m ² /d $\times$ 6d q 21 days	Neutropenia, thrombocytopenia, mucositis, diarrhoea, infection	3/33 (AML) PR 1/5 (MDS) PR	Sonet <i>et al.</i> , (2008)
KW-2449	Phase II	AML, MDS, ALL, CML	29	PO	12.5–500 mg bid (Trial stopped early; MTD not reached)	Pneumonia, dyspnea, cardiac arrhythmia, cardiac ischaemia.	5/11 <i>FLT3</i> -ITD AML achieved transient reduction in blasts.	Pratz <i>et al.</i> , (2009)
	Phase I/I	Relapsed or refractory AML (AML <i>FLT3</i> ITD in Phase II	NR	PO	NR	NR	NR	NCT00779480*
AT9283	Phase I/II	Refractory AML, MDS, ALL, CML, MF	NR	IV	NR	NR	NR	NCT00522990*

AML, acute myeloid leukaemia; MDS, myelodysplasia; CML, chronic myeloid leukaemia; MPD, myeloproliferative disease; MF, myelofibrosis; ALL, acute lymphoblastic leukaemia; CIV, continuous intravenous infusion; IV intravenous injection; PO, oral; SC, subcutaneous injection; bid, twice daily; MTD, maximum tolerated dose; CR, complete response; CRi, complete response with incomplete count recovery; PR, partial response; NR, not reported; Ara-C, cytarabine; *FLT3*-ITD, *FLT3* internal tandem duplication.

* ClinicalTrials.gov Identifier number (cited where no report is available).

Table 3
Aurora kinase inhibitors currently in clinical development in CML and Ph+ ALL

Drug	Clinical trial	Patients included	N	Route	Dose	Main toxicity reported	Responses	Reference
AT9283	Phase I/II	Refractory AML, MDS, ALL, CML, MF	NR	IV	NR	NR	NR	NCT00522990*
Danuseritin	Phase I	Advanced-stage CML**, Ph+ ALL**	23	IV	90–200 mg/m ² /day × 7d q 2 weeks (MTD not reached)	Diarrhoea, nausea, pyrexia, fainting, headache	5 HR, 1 CCR, 1 PCR, 1 MCR, 1 CMoR	Cortes-Franco <i>et al.</i> (2009)
	Phase II	CML, relapsed after prior RTK inhibitors	NR	IV	NR	NR	NR	NCT00335868*
XL228	Phase I	Refractory CML**, Ph+ ALL	27	IV	0.45–10.8 mg/kg weekly or twice weekly (MTD not reached)	Syncope, hyperglycaemia, nausea, vomiting, fatigue.	3 (2 with T315I) decrease <i>BCR-ABL</i> by > 1 logarithm	Cortes <i>et al.</i> (2008a)
AS703569	Phase I	AML, MDS, CML**, MPD	45	PO	3–47 mg/m ² /d×6d q 21 days	Neutropenia, thrombocytopenia, mucositis, diarrhoea, infection	1/6 CML with T315I cytogenetic response	Sonet <i>et al.</i> (2008)
KW-2449	Phase I	AML, MDS, ALL, CML**	29	PO	12.5–500 mg bid (Trial stopped early; MTD not reached)	Pneumonia, dyspnea, cardiac arrhythmia, cardiac ischaemia.	1/5 CML disappearance of T315I clone.	Pratz <i>et al.</i> (2009)

AML, acute myeloid leukaemia; MDS, myelodysplasia; CML, chronic myeloid leukaemia; MPD, myeloproliferative disease; MF, myelofibrosis; ALL, acute lymphoblastic leukaemia; IV intravenous injection; PO, oral; bid, twice daily; MTD, maximum tolerated dose; HR, haematological remission; CCR, complete cytogenetic response; PCR, partial cytogenetic response; MCR, minor cytogenetic response; CMoR, complete molecular response; NR, not reported.

* [ClinicalTrials.gov](#) Identifier number (cited where no report is available).

** Trials that have reported clinical activity in CML patients with T315I mutations (see text).

Table 4

Aurora kinase inhibitors currently in clinical development in MM

Drug	Clinical trial	Patients included	N	Route	Dose	Main toxicity reported	Responses	Reference
ENMD-2076	Phase I	Relapsed or refractory MM	18	PO	150–325 mg/d (MTD 275 mg)	Thrombocytopenia, PRES, anorexia, hypertension, fatigue, proteinuria, elevated lipase and amylase, diarrhoea.	To date: 2/10 had reduction in M protein; 1/10 had 75% reduction in plasmacytoma	Farag <i>et al.</i> (2010)
MLN8237	Phase I	Haematological malignancies, (including relapsed MM)	29	PO	35–90 mg bid day 1, then once daily×14 d every 28 days (MTD 90 mg)	Neutropenia, thrombocytopenia, asthenia.	1/8 MM had stabilization of M protein.	Padmanabhan <i>et al.</i> (2010)
AT9283	Phase I (with bortezomib)	Relapsed or refractory MM	NR	PO	NR	NR	NR	NCT01034553 *
	Phase II	Relapsed or refractory MM	NR	IV	NR	NR	NR	NCT01145989 *
Danuserib	Phase II	Relapsed or refractory MM with t(4;14).	NR	IV	NR	NR	NR	NCT00872300 *

MM, multiple myeloma; IV intravenous injection; PO, oral; bid, twice daily; MTD, maximum tolerated dose; PRES, posterior reversible encephalopathy syndrome; NR, not reported.

* ClinicalTrials.gov Identifier number (cited where no report is available).

Table 5

Effects of Aurora kinase inhibitors investigated in NHL

Drug	Clinical trial	Patients included	N	Route	Dose	Main toxicity reported	Responses	Reference
MLN8237	Phase I	Haematological malignancies, (including relapsed NHL)	29	PO	35–90 mg bid day 1, then once daily×14 d every 28 days (MTD 90 mg)	Neutropenia, thrombocytopenia, asthenia.	1/19 DLBCL achieved PR.	Padmanabhan <i>et al.</i> , (2010)
	Phase II	Relapsed or refractory aggressive NHL	NR	PO	NR	NR	NR	NCT00807495 *
AZD1152	Phase II	Relapsed or refractory DLBCL or transformed NHL	NR	IV	NR	NR	NR	NCT01354392 *

NHL, non-Hodgkin's lymphoma; DLBCL, diffuse large B-cell lymphoma; IV intravenous injection; PO, oral; bid, twice daily; MTD, maximum tolerated dose; NR, not reported.

* ClinicalTrials.gov Identifier number (cited where no report is available).