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THE ONGOING ROLL-OUT OF AURORA KINASE INHIBITORS IN CANCER TREATMENT

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SUMMARY

The Aurora kinase family comprises three important regulatory proteins of mitosis: Aurora kinases A, B and C. Their dysfunction is associated with abnormal cell division, aneuploidy and possibly tumorigenesis. In addition, overexpression and/or amplification of Aurora kinase A or B has been demonstrated in various cancers. These observations suggested that the Aurora kinases might be attractive therapeutic targets in oncology. Drugs targeting the mitotic spindle such as taxanes and vinca alkaloids have been notably successful in cancer medicine. The Aurora kinase inhibitors represent the latest entrants into this arena. Inhibitors of Aurora kinases have shown promising results in preclinical studies, and are currently under evaluation in numerous clinical trials. Considerable additional work will be required in order to optimize their use in the clinic, including identifying biomarkers for selection of sensitive tumors, refining the administration schedule of these agents and developing useful combinations of Aurora kinase inhibitors with existing cancer therapeutics. This review article will summarize the function of each of the Aurora kinases, with emphasis on their role in tumorigenesis and interactions with other cellular pathways that govern tumor biology. It also discusses those inhibitors that are in the clinic and summarizes the early clinical data.

INTRODUCTION

The Aurora kinases function as critical regulators of mitosis and cytokinesis, with a key role in the development of an intact, functional mitotic spindle (1, 2). Aurora kinases were first discovered in *Drosophila* by Glover et al. who demonstrated formation of monopolar mitotic spindles and abnormal chromosome segregation in the presence of Aurora kinase mutations (3). The Aurora family consists of three highly related serine/threonine kinases known as Aurora kinase A (serine/threonine-protein kinase 6), Aurora kinase B (serine/threonine-protein kinase 12) and Aurora kinase C (serine/threonine-protein kinase 13). Each kinase contains two principal domains: a regulatory domain in the NH_2 terminus and a catalytic domain in the COOH terminus (1). There is a high degree of homology among the catalytic domains of these three kinases; all contain a threonine site that requires phosphorylation for kinase activation (4-7). Despite this homology, each of these kinases has a unique regulatory function during mitosis, and a different location on the mitotic spindle (Fig. 1).

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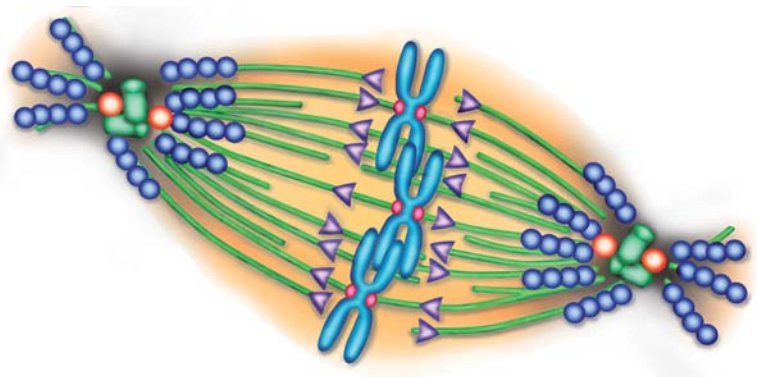
AURORA KINASE A

The gene encoding Aurora kinase A, *AURKA*, maps to chromosome 20q13.2. The role of Aurora kinase A in the regulation of cell cycle events occurring from late S phase through M phase has been well studied (8-10). Activation of Aurora kinase A via phosphorylation of threonine T288 is necessary for mitotic entry, centrosome maturation, bipolar spindle assembly, chromosome alignment, cytokinesis and exit from mitosis (8-12). Aurora kinase A localizes to the pericentriolar area from late G_1 to early S phase and migrates throughout the mitotic spindle as mitosis progresses (Fig. 1) (13). Aurora kinase A activity involves activation of multiple cofactors and regulation by various proteins (2, 14). Table I summarizes some of the main cofactors and regulatory proteins involved in Aurora kinase A function. The best studied cofactor of Aurora kinase A is targeting protein for Xklp2, an important microtubule-associated protein required for bipolar spindle assembly (15). Targeting protein for Xklp2 performs two important tasks: 1) inducing a conformational change in the kinase resulting in its activation; and 2) protecting activated Aurora kinase A from dephosphorylation and inactivation (6, 16).

AURORA KINASE B

Aurora kinase B is critical for accurate chromosomal alignment and segregation, as well as cytokinesis (5). The gene (*AURKB*) has been mapped to chromosome 17q13. Activation occurs via autophospho-



	Gene location	Cell location	Role in mitosis
Aurora A	20q13	Peri-centriole Spindle pole Mitotic spindle	Centrosome function Mitotic spindle assembly Mitotic entry Chromosome alignment cytokinesis
Aurora B	17p13.1	Microtubules near the kinetochores	Chromosome condensation Microtubule-kinetochore attachment Spindle checkpoint protein complex Cytokinesis
Aurora C	19q13.3	Centrosome	Spermatogenesis Chromosomal stability

Figure 1. Location and function of Aurora kinases.

rylation of threonine T232 (17). During the early steps of mitosis, Aurora kinase B regulates chromosome condensation through association with condensin 1 complex (18, 19). Aurora kinase B is a key member of the chromosomal passenger complex (CPC) along with inner centromeric protein, survivin and borealin. The CPC functions to prevent and correct abnormalities in the microtubule–kinetochore attachment prior to anaphase (20). During mitosis, Aurora kinase B and the CPC proteins travel from the centromere to the spindle midzone and finally to the mid-body between the dividing cells (Fig. 1) (21). Localization of Aurora kinase B to the mid-spindle zone is crucial for phosphorylation of several proteins involved in cytokinesis and disassembly of the mitotic spindle (22-25). Many other proteins are involved in the regulation of Aurora kinase B activity throughout mitosis and are summarized in two key reviews (2, 14). Table I also summarizes the main Aurora kinase B cofactors and regulatory proteins.

AURORA KINASE C

Aurora kinase C (encoded by *AURKC*) is the third known kinase in this family and maps to 19q13.43 (26). While it is primarily found in the testis, it is detected in other cell types and overexpressed in some tumor cell lines (27-29). Aurora kinase C is the least-studied Aurora kinase, and thus, limited data are available regarding its regulation and precise functions. Similar to Aurora kinase B, it is thought to interact with inner centromeric protein and survivin (29-31). The role of Aurora kinase C in spermatogenesis and fertility has been studied in mice and humans, with evidence of *AURKC* gene mutations in infertile men (32, 33). To date, the effect of abnormalities of Aurora kinase C expression on tumorigenesis remains controversial.

AURORA KINASES AND TUMORIGENESIS

Aberrations in the function of the Aurora kinases can result in abnormal cell division and aneuploidy due to losses or gains of whole chromosomes (8). Moreover, overexpression of Aurora kinase A has been shown to result in a multipolar spindle, which gives rise to chromosome gains through abnormal cell division (34-36). The resultant genomic instability, aneuploidy and hyperploidy can easily promote tumor development. Aurora kinases A and B have been found to be overexpressed and/or amplified in many different tumor types (Table II). Correlation between overexpression of these kinases and histological grade of the tumor, as well as with poor clinical outcomes, has also been established in various malignancies (37-43).

Table I. *The main cofactors and regulatory proteins of Aurora kinases A and B.*

Protein	Function	Relationship with Aurora kinase A (ref.)
Aurora kinase A		
Polo-like kinase 1 (PLK-1)	Mitotic entry and cell cycle regulation	Following activation by Aurora kinase A, PLK-1 is responsible for promoting entry into G_2 (110)
Pericentriolar material proteins	Centrosome maturation	(Centrosomin, LATS2, TACC, NDEL1) Required for centrosome maturation, recruitment of γ tubulin and initiating formation of the mitotic spindle (111-114)
Serine/threonine-protein kinase PAK 1	Centrosome maturation	Centrosomal protein kinase that directly phosphorylates Aurora kinase A (115)
Targeting protein for Xklp2	Mitotic spindle assembly	A microtubule-associated protein that is required for stability of the mitotic spindle Allows for conformational change of Aurora kinase A to facilitate phosphorylation of threonine T288 and activation of the kinase. In addition, Xklp2 protects from dephosphorylation of activated Aurora kinase A (6, 15, 16, 116)
Ajuba	Mitotic spindle assembly	Activated by Aurora kinase A Works on assembling microtubules from the centrosome to the kinetochore (10)
Ran	Mitotic spindle assembly	Small GTPase that regulates the interaction between Aurora kinase A and targeting protein for Xklp2 (117)
Kinesin-like protein KIF11 (Eg5)	Mitotic spindle assembly	Protein involved in centrosome separation and phosphorylated by Aurora kinase A (118)
Protein phosphatase type 1 (PP1)	Inactivation of Aurora kinase A	Dephosphorylation of threonine T288 during interphase (16)
Aurora kinase B		
Condensin complex subunit 1	Chromosome condensation	Aurora kinase B in association with condensin 1 regulates appropriate chromosome condensation (19)
Inner centromere protein	Chromosomal passenger complex (CPC)	Inner centromere protein binds to Aurora kinase B to enhance the activation of Aurora kinase B via a positive feedback loop (14, 119)
Survivin	Chromosomal passenger complex (CPC)	Survivin augments Aurora kinase B function and assists in localization of Aurora kinase B in the mitotic spindle (controversial) (120, 121)
Borealin	Chromosomal passenger complex (CPC)	Promotes Aurora kinase B activation and localization to the centromere (122)
Tousled-like kinase 1	Activation of Aurora kinase B	Increased Aurora kinase B activation in an inner centromere protein-dependent manner (123)
Serine/threonine-protein kinase Chk1	Activation of Aurora kinase B	Phosphorylates Aurora kinase B and augments its activity at the centromere (124)
Protein phosphatase type 1 and 2 (PP1, PP2)	Inhibition of Aurora kinase B	Inhibition of Aurora kinase B activity by dephosphorylation (125, 126)
End-binding protein (EB1)	Protects Aurora kinase B from inactivation	Shields Aurora kinase B from dephosphorylation by PP2A (126)
Mitotic checkpoint serine/threonine-protein kinase BUB1	Part of the spindle assembly checkpoint proteins	Along with Aurora kinase B regulates normal chromosomal alignment and monitors kinetochore–microtubule attachment prior to anaphase (127, 128)

Some investigators hypothesize that overexpression of Aurora kinase in tumor cells does not influence malignant phenotype per se, but instead is secondary to the nature of cancer itself, in which the process of cell division is globally upregulated. A wide range of assays have been used for evaluation of overexpression or amplification of Aurora kinases (Table II), making comparisons across studies challenging. The clinical significance of these observations remains to be clarified. Additional studies will be needed to determine whether overexpression of Aurora kinase can serve as a biologic predictor of response to specific therapy such as Aurora kinase inhibition.

The relationship between abnormalities in Aurora kinases and tumorigenesis has been widely studied. Wang and colleagues evaluated the relationship between overexpression of Aurora kinase A and tumorigenesis in studies of mammary gland tumor development in Aurora kinase A transgenic mice (44). These mice were

Table II. *Overexpression of Aurora kinases A and B in various cancers.*

Cancer type	Findings	Methods used	Ref.
Aurora kinase A			
Breast	94% amplification	IHC	129
Colon	29-52% amplification	Southern blot, PCR	35, 41, 130
Bladder	50% amplification	Southern blot, IHC, FISH	131
Gastric	50% overexpression	FISH, RT-PCR	132
Pancreas	93% overexpression	IHC, Southern blot, RT-PCR	133
Ovarian	82% overexpression	Western blot, IHC	134
Lung	62% overexpression	IHC, Western blot, RT-PCR	135, 136
Prostate	94% overexpression	RT-PCR, IHC	107
Neuroblastoma	> 90% overexpression	RT-PCR, Western blot	43
Glioblastoma	30% overexpression	PCR	137
Aurora kinase B			
Prostate	94% overexpression	RT-PCR, IHC	42, 107
Lung	93% overexpression	RT-PCR	40, 136
Thyroid	High expression in anaplastic thyroid cancer	IHC, PCR	138
Glioblastoma	32% overexpression	IHC, FISH	139

IHC, immunohistochemistry; RT-PCR, reverse transcription polymerase chain reaction; FISH, fluorescence in situ hybridization.

found to have a high incidence of mammary hyperplasia, as well as mammary tumors (occurring in 40% of mice by 20 months of age). Aurora kinase A overexpression also led to genetic instability characterized by centrosome amplification, premature chromatid segregation and chromosomal abnormalities. Interestingly, among mice carrying a mutation in the *Tp53* gene in addition to Aurora kinase A overexpression, the rate of mammary tumor formation was even higher (70%). Similarly, Bischoff et al. have demonstrated the oncogenic role of Aurora kinase A in vitro and in vivo. Increased cellular growth was documented in Rat1 fibroblasts transfected with a retrovirus expressing overactive mutant *AURKA* (35). In vivo, these transformed cells were found to induce tumor growth when injected into nude mice. These results suggest that Aurora kinase A has intrinsic oncogenic potential. These observations also support the clinical significance of Aurora kinase as a significant regulator of tumor development, thus setting the stage for its exploitation as a target for anticancer therapy.

A number of cellular pathways and oncogenes besides p53 appear to cooperate with Aurora kinase overexpression to induce carcinogenesis, including BRCA1, c-Myc and mTOR (34, 45, 46). The interactions between these proteins and Aurora kinase A are complex. Aurora kinase A is thought to directly inhibit p53 through phosphorylation of serine 215 and p53 has been shown to negatively regulate Aurora kinase A by a direct protein–protein interaction (47-49). The group led by Dar demonstrated the effect of Aurora kinase A overexpression on apoptosis in p53-deficient cell lines (50). Aurora kinase A was found to have an active role in the regulation of apoptosis in p53-deficient cells. Furthermore, Dar and colleagues reported significant apoptosis following treatment of these cells with an Aurora kinase inhibitor. These observations highlight the potential utility of Aurora kinase inhibitors in the treatment of tumors with defective p53 signaling.

Ouchi and colleagues demonstrated phosphorylation of BRCA1 protein by Aurora kinase A to be a necessary step for transition from the G_2 phase to M phase during mitosis. In addition, increased BRCA1 phosphorylation was noted with overexpression of Aurora kinase A, and was decreased when Aurora kinase A was blocked with small interfering RNA (51). The phosphorylation of BRCA1 by Aurora kinase A was halted by treating cells with ionizing radiation, and caused growth arrest at the G_2 phase. Aurora kinase A is also thought to have a role in the regulation of the mTOR pathway, reflected in increased phosphorylation of mTOR and AKT in Aurora kinase A-transformed cells (44, 52). Taga et al. studied the interaction between mTOR/AKT pathways and Aurora kinase A overexpression. Treatment of cells overexpressing Aurora kinase A with the Aurora kinase A inhibitor VX-680 resulted in cell death in the absence of AKT phosphorylation. Rapamycin, an mTOR inhibitor, induced cell death in the presence of Aurora kinase A overexpression and AKT phosphorylation. These results suggest that the malignant phenotype of cells overexpressing Aurora kinase A is likely influenced by the state of activation of the mTOR/AKT pathway. All of these studies point to the central role that Aurora kinases play in multiple cellular pathways. These observations in turn suggest that Aurora kinase inhibition may be effective in a very broad range of tumor types, each driven by different cellular pathways. Finally, Astsaturov and colleagues have used synthetic lethal screening techniques to probe the interactions within the protein network centered on the epidermal growth factor receptor (EGFR), searching for proteins that could modulate the effectiveness of EGFR-targeted therapy. These experiments identified a strong synergy between EGFR antagonists and drugs targeting Aurora kinase A. This interesting and somewhat unexpected observation suggests that dual targeting of the EGFR and Aurora pathways may be a potentially useful therapeutic approach (53).

The role of Aurora kinase B in tumorigenesis has been less well studied. Forced expression of Aurora kinase B in Chinese hamster embryo cells induced chromosome lagging and genetic instability during mitosis (54). Transfection of *H-RAS* mutant cells with Aurora kinase B demonstrated a significant increase in cellular growth, sug-

gesting an interaction between overexpression of Aurora kinase B and oncogenic Ras signaling (45). The interaction between Aurora kinase A/B and the c-Myc oncogene was described by den Hollander et al. who studied Aurora kinase expression in c-Myc-driven B-cell lymphomas in mice and humans (46). An increase was demonstrated in Aurora kinase A and B transcripts and protein levels in these cells. In addition, inhibition of Aurora kinase A/B resulted in transient mitotic arrest of these c-Myc-driven cells. Similar to the larger number of preclinical studies on Aurora kinase A, these and other studies demonstrate an active role for Aurora kinase B in tumor development and support future clinical trials studying inhibition of this target as a therapeutic approach.

AURORA KINASE INHIBITORS

Interfering with mitosis is a well-validated approach to cancer treatment, exemplified by the taxoids and vinca compounds. Despite the utility of mitotic spindle targeting, however, eventual drug resistance is nearly inevitable and neurotoxicity can be dose-limiting and disabling. With the wealth of evidence regarding the relationship between aberrations in Aurora kinase expression and carcinogenesis, it was logical to consider targeting the Aurora kinases as a therapeutic strategy in oncology. A newer approach via Aurora kinase inhibition that could take advantage of the centrality of the mitotic target, perhaps overcome drug resistance and avoid neurotoxicity is extremely attractive. Despite extensive research, the precise mechanism by which Aurora kinase inhibitors induce cell death remains unclear, with ongoing debate regarding the exact point in the cell cycle at which treated cells ultimately die (55). Some studies have shown that treated cells forgo mitosis and remain in a tetraploid state and ultimately die after one or more additional cell cycles, while others have demonstrated cell death occurring during mitosis (56, 57).

Marumoto and colleagues studied Aurora kinase A inhibition in normal human cells using small interfering RNA and anti-Aurora A antibodies during various steps of mitosis. Aurora kinase A inhibition induced centrosome separation defects, formation of monopolar spindles, chromosome misalignment and impaired cytokinesis, all resulting in mitotic arrest (8). These findings were confirmed by other groups reporting a variety of mitotic abnormalities following Aurora kinase A inhibition in tissue culture and in mice (58, 59). Preclinical experiments of Aurora kinase A inhibition in cancer cells revealed encouraging results in various solid tumor cell lines, as well as in hematological malignancies (60-69). Aurora kinase B inhibition results in abnormal kinetochore microtubule attachment, chromosome alignment and cytokinesis (19, 70-72). Following Aurora kinase B inhibition, normal cells lack the activity of the mitotic checkpoint and progress through mitosis despite abnormal chromosomal arrangement (72). Other proteins associated with the mitotic checkpoint fail to function in the absence of Aurora kinase B and the cell undergoes recurrent abnormal mitotic cycles resulting in polyploidy and ultimately apoptosis (71-73). The aforementioned effects of Aurora kinase A/B inhibition in normal cells were noted to be more pronounced when the Aurora kinases were inhibited in cancer cells (73).

Early clinical trials

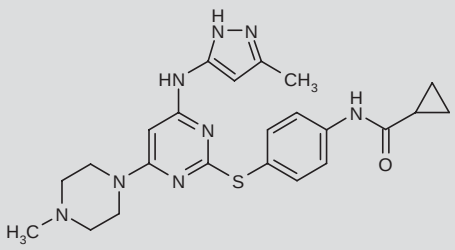
In recent years, several small-molecule Aurora kinase inhibitors have been developed and undergone testing in early-phase clinical trials. Those furthest in development are summarized in Table III. The first small-molecule inhibitors, tozasertib (MK-0457) and ZM-447439, were nonspecific, targeting all three Aurora kinases, as well as targets that included MEK, ABL and FLT-3. More recently, selective inhibitors for Aurora A or B have been developed, including MLN-8054, MLN-8237 and barasertib (AZD-1152). All of these agents have been shown to be relatively well tolerated, with mainly hematological and gastrointestinal adverse events. As would be expected with antimitotic agents, dose-limiting toxicity (DLT) of neutropenia was anticipated and has been documented in most of the clinical trials. Some of these agents have not moved forward in clinical development, but many are continuing in phase II studies in specific malignancies as single agents or in combination with other cancer therapeutics. To date, the question of whether these drugs function in vivo as cytotoxic agents (inducing cell death) or as cytostatic agents (inducing growth inhibition) remains unanswered. It is also not clear from any of the work so far whether inhibition of all Aurora kinases or more selective inhibition of Aurora A or B is the best therapeutic strategy.

Tozasertib (MK-0457/VX-680)

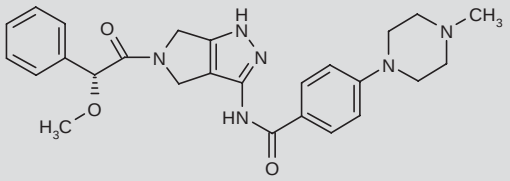
This "pan-Aurora" inhibitor was shown to induce apoptosis and cell death in multiple cancer cell lines, including colorectal and pancreatic cancer, as well as hematological malignancies, both in vitro and in vivo (103). Moreover, tozasertib (Merck & Co.) showed activity in chronic myeloid leukemia (CML) cell lines resistant to imatinib and dasatinib (104). Tozasertib was further tested in preclinical models in combination with other drugs such as taxanes and vorinostat and demonstrated synergism (96, 105). In the first phase I study, tozasertib was given as a 24-h continuous i.v. infusion once every 21 days (74). DLTs were grade 4 neutropenia and grade 3 herpes zoster infection, with the maximal tolerated dose (MTD) defined as 64 mg/m^2/h. Other common side effects included fatigue, nausea, vomiting and diarrhea. One patient with ovarian cancer exhibited prolonged stable disease.

PHA-680632 and danusertib (PHA-739358)

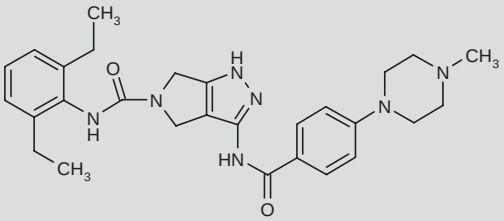
PHA-680632 (Nerviano Medical Sciences) is a potent pan-Aurora inhibitor with additional activity against basic fibroblast growth factor receptor 1 (FGFR-1), and antitumor effects in multiple cancer cell lines in preclinical experiments (75). This particular drug was not taken forward into clinical trials due to the development of a related, more potent, small-molecule inhibitor with better pharmaceutical properties, known as danusertib (PHA-739358) (76). This agent



Tozasertib (MK-0457)



Danusertib (PHA-739358)



PHA-680632

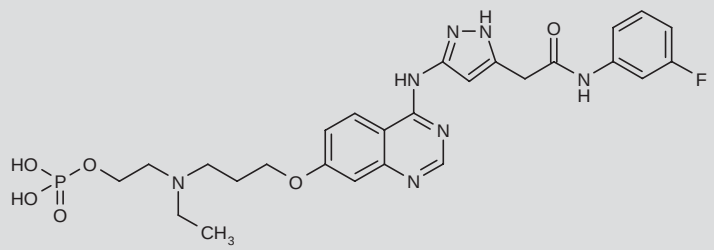
inhibits all members of the Aurora kinase family with maximal inhibition of Aurora kinase B. Danusertib is also not completely Aurora-specific, inhibiting targets such as FGFR-1, ABL and RET with nanomolar potency. Danusertib was active in vivo and in vitro against various tumor types (76). Activity was also observed in CML cell lines, where danusertib caused growth inhibition even in imatinib-resistant cell lines (77).

In one phase I clinical trial, patients were treated with danusertib i.v. on a 3- or 6-h schedule on days 1, 8 and 15 on 28-day cycles (78). The most frequently observed adverse events included fatigue and gastrointestinal complaints, with the documented DLT being neutropenia. Stable disease was seen in 27% of patients, lasting more than 6 months in 10% of patients. The recommended phase II dose was 330 mg/m^2 infused over 6 h. Danusertib was also tested on an alternative schedule in which the drug was given as a 24-h infusion every 14 days with or without filgrastim (79). The DLT was febrile neutropenia, with other adverse events occurring at low rates. The MTD was 500 mg/m^2 without filgrastim and 750 mg/m^2 with filgrastim. Several occurrences of prolonged stable disease were documented across a variety of refractory tumors, as well as a confirmed partial response in a highly refractory case of small cell lung cancer. Phase II studies in hematological malignancies and various solid tumors are ongoing. Early results of a phase II study in 42 patients with advanced metastatic breast cancer and 34 patients with platinum-refractory/resistant ovarian cancer were recently presented (80). The primary endpoint was progression-free survival (PFS) at 4 months; the observed PFS fell short of the predefined goals of the protocol. The best observed responses were stable disease in 11 patients with breast cancer and 10 patients with ovarian cancer. One patient with ovarian cancer exhibited a partial response lasting 17.3 weeks. The toxicity profile was similar to that seen in previous studies. Danusertib was also tested in a phase II study in 33 patients with advanced metastatic colorectal cancer and 35 patients with advanced pancreatic cancer (81). The primary endpoint was PFS at 4 months; only three patients with advanced pancreatic cancer were progression-free at 4 months with stable disease for 6-8.5 months. Finally, Rosen et al. recently presented phase I data on danusertib in combination with bevacizumab in solid tumors and found this regimen to be tolerable (82). Encouraging results were also noted in phase I/II studies in imatinib-resistant CML and Philadelphia-positive acute lymphocytic leukemia (83).

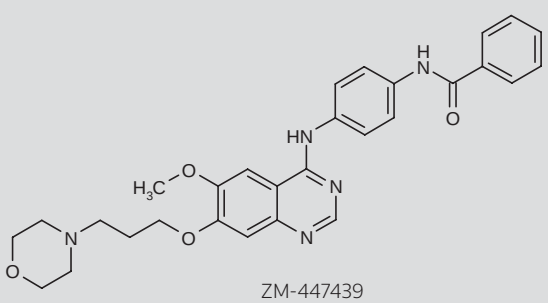
Barasertib (AZD-1152) and ZM-447439

In contrast to the previously discussed agents, barasertib (AZD-1152; AstraZeneca) selectively inhibits Aurora kinase B. Barasertib is a prodrug of AZD-1152-HQPA, which induces in vitro and in vivo chromosomal misalignment, prevents cell division and ultimately causes apoptosis (84). Extensive preclinical research showed activity in a variety of hematological malignancies, as well as in colon and lung cancer cell lines (85, 86). Combinations of barasertib with other chemotherapeutic agents such as irinotecan, vincristine and daunorubicin were found to be synergistic (87, 88). Phase I studies reported the MTD as 300 mg i.v. given as a 2-h infusion every 2 weeks (89). Similar to other Aurora kinase inhibitors, the major DLT was neutropenia, with minimal nonhematological toxicities. Disease stabilization was reported in five patients enrolled in this trial. The drug was also tested as a continuous 7-day infusion on a 21-day cycle in a phase I/II study in patients with advanced AML (90). In the phase I portion of the study, the MTD was found to be 1200 mg, with DLTs consisting of mucositis, stomatitis and febrile neutropenia. In the second phase, 32 patients were treated with 1200 mg of barasertib, with 8 patients (25%) having a clinical response.

AstraZeneca's ZM-447439 is an inhibitor of Aurora kinases A and B. Preclinical models demonstrated the ability of ZM-447439 to induce abnormal mitotic spindle assembly and ultimately apoptosis in multiple models (91-93). Apoptosis induced by this agent was time- and



Barasertib (AZD-1152)



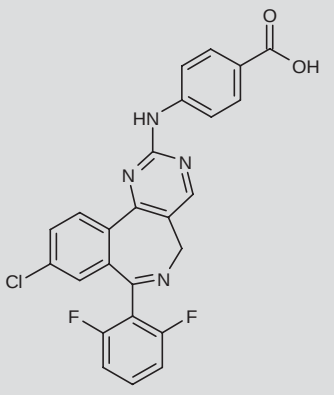
ZM-447439

concentration-dependent and associated with upregulation of p53 (93). Lack of p53 reduced the rate of apoptosis seen following treatment with ZM-447439. Clinical tolerance and efficacy information are not yet available for this agent.

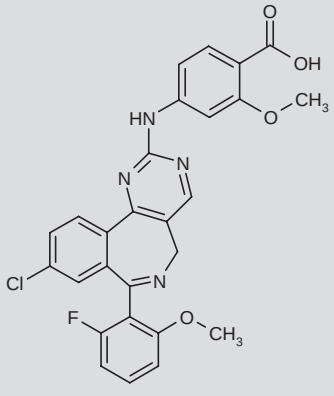
MLN-8054 and MLN-8237

MLN-8054 (Millennium Pharmaceuticals) is a potent ATP-competitive Aurora kinase inhibitor with high affinity for Aurora kinase A at low concentrations and inhibition of Aurora kinase B at higher concentrations. It acts by blocking phosphorylation of the activation site (threonine T288) of *AURKA* (94). MLN-8054 was shown to induce senescence in various tumors both in vivo and in vitro and to cause a high incidence of abnormal mitotic spindle formation, often with unseparated chromosomes (43, 59, 95). The drug also showed promising preclinical activity in B-cell lymphoma cell lines (95, 96). In the phase I study, MLN-8054 had a DLT of reversible grade 3 somnolence, an off-target effect due to its affinity for the γ-aminobutyric acid α1 benzodiazepine receptor. Dose-limiting somnolence occurred before the emergence of on-target toxicities such as neutropenia and further development of this agent was stopped (97).

A second-generation small-molecule Aurora kinase inhibitor developed by Millennium is MLN-8237, which has Aurora kinase A specificity similar to that of MLN-8054, but much lower affinity for the benzodiazepine receptor, with the expectation that it will be less likely to cause somnolence. This orally available agent has been recently evaluated in two phase I trials and moved into phase II studies in various malignancies, alone and in combination with other cytotoxic agents. In the recently completed phase I study, the MTD was 50 mg twice daily for 7 days on a 21-day cycle (98). DLTs were neutropenia, thrombocytopenia and somnolence, all reversible with dose reduction. Other side effects included fatigue and gastrointestinal toxicity. A durable partial response was noted in a patient with platinum- and radiation-refractory ovarian cancer. Patients with various solid tumors have had prolonged stable disease. A second phase I study reported similar DLTs with an objective response in a patient with treatment-resistant pleomorphic liposarcoma (99).



MLN-8054



MLN-8237

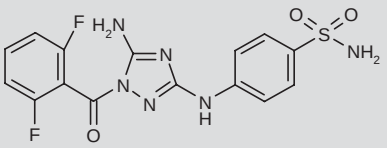
JNJ-7706621

JNJ-7706621 (Johnson & Johnson) is an Aurora kinase inhibitor that exhibits strong inhibition of Aurora kinase A, Aurora kinase B and cyclin-dependent kinases including CDK1, CDK2, CDK4 and CDK6. Treatment with JNJ-7706621 inhibited cell growth and induced apoptosis in various cell lines independent of p53 status (100). Antitumor effects correlating with drug dose were also noted in xenograft models. Combination of this agent with paclitaxel was found to be synergistic in vitro and in vivo (101). There are no reported clinical data for this agent.

PF-03814735

PF-03814735 (Pfizer) is another oral, ATP-competitive, reversible Aurora kinase A and B inhibitor. It blocks cytokinesis, inducing inhibition of cell proliferation and formation of polyploid multinucleated cells (102). In mice, once-daily oral administration of the drug alone or in combination with docetaxel resulted in tumor growth inhibition. Preliminary results from the phase I study conducted with this agent reported a DLT of febrile neutropenia, and other milder adverse events involving the gastrointestinal tract (103). No objective responses were seen. The MTD was defined as 80 mg/m^2/day for 5 days. PF-03814735 will likely proceed to phase II trials.

Much work remains to be done in moving the currently available agents further in clinical development and testing their activity in



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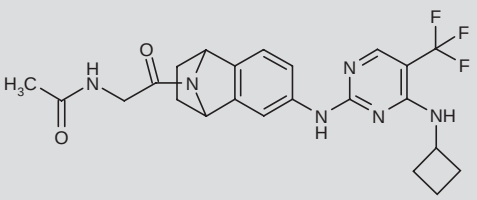
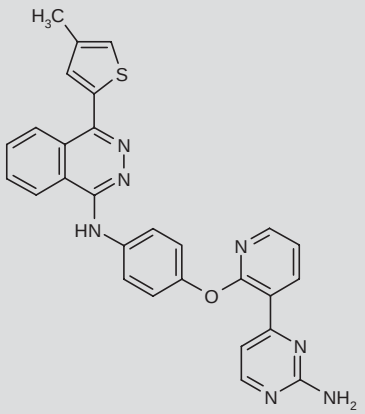


PF-03814735

Table III. *Summary of Aurora kinase inhibitors in development.*

Drug (ref.)	Company	Target	Preclinical data	Dose-limiting toxicities	Best clinical response	Ongoing studies
Tozasertib (VX-680, MK-0457) (74)	Merck & Co.	Aurora A + B + C, FLT-3	Induction of apoptosis and cell death in vitro and in vivo	Neutropenia	Stable disease	Discontinued
Danusertib (PHA-739358) (78-81)	Nerviano Medical Sciences	Aurora A + B + C (mainly B), FGFR-1, ABL, Ret	Activity in vitro and in vivo in various cancers	Neutropenia	Stable disease	Phase II studies in hematological malignancies and prostate cancer
ZM-447439 (91-93)	AstraZeneca	Aurora A + B, MEK, Src, Lck	Induction of apoptosis in multiple cell lines	N/A	N/A	N/A
Barasertib (AZD-1152) (61, 84-86, 89)	AstraZeneca	Aurora B	Activity in hematological and nonhematological malignancies	Neutropenia	Stable disease	Phase I: in solid tumors Phase II: single agent or in combination with chemotherapy in AML
MLN-8054/MLN-8237 (59, 94-96, 98)	Millennium Pharmaceuticals	Aurora A	Senescence and apoptosis in various cell lines	Neutropenia, thrombocytopenia and somnolence	Partial response and stable disease	Phase I: in solid tumors and hematological malignancies Phase II: in ovarian cancer and hematological malignancies
JNJ-7706621 (100, 101)	Johnson & Johnson	Aurora A + B, CDK1, -2, -4, -6	Induction of apoptosis in various cell lines, and synergy with paclitaxel in vivo	N/A	N/A	N/A
PF-03814735 (102, 103)	Pfizer	Aurora A + B	Inhibition of cytokinesis and formation of polyploid multinucleated cells	Neutropenia	None	N/A
AMG-900 (105)	Amgen	Aurora A + B + C	Inhibition of proliferation across multiple cell lines, including multi-drug-resistant cell lines	N/A	N/A	Ongoing phase I studies in solid tumors
SNS-314 (140, 141)	Sunesis Pharmaceuticals	Aurora A + B + C	Inhibition of cell growth in various cell lines, and xenograft models	Neutropenia	None	N/A
BI-811283 (142)	Boehringer Ingelheim	Aurora B	Inhibition of cell growth in various cell lines and xenograft models	Neutropenia	Stable disease	Phase II: combination with cytarabine in AML
GSK-1070916 (143, 144)	GlaxoSmithKline	Aurora B + C	Inhibition of cell growth in cell lines and xenograft models	N/A	N/A	N/A
AT-9283 (145-148)	Astex Therapeutics	Aurora A + B, BCR-ABL T3151, JAK2	Inhibition of cell growth in various cell lines and xenograft models, including imatinib-resistant BCR-ABL(+) cells, and JAK2-dependent cell lines	Neutropenia	Partial response and stable disease	Phase II study
CYC-116 (149)	Cyclacel	Aurora A + B, VEGFR-2	Preclinical studies show inhibition of cytokinesis resulting in polyploidy and apoptosis			Ongoing phase I study
CCT-129202 (150)	Cancer Research UK	Aurora A + B + C	Induction of abnormal mitotic spindles in various cell lines and xenograft models	N/A	N/A	N/A

N/A, not available.



AMG-900

various clinical settings alone or in combination with other agents. Additional Aurora kinase inhibitors are also entering the clinical trial arena, some of which are summarized in Table III. Reports of cells with resistance to Aurora kinase inhibition have emerged in the literature. Thus, Sloane et al. recently published preclinical observations on cell lines harboring a T217D *AURKA* mutation that are resistant to Aurora kinase inhibition with MLN-8054 or MLN-8237 (104). AMG-900, a new Aurora kinase inhibitor currently in phase I testing, is a small-molecule, oral pan-Aurora inhibitor that was shown to inhibit proliferation in multiple cell lines, including those with multidrug and Aurora kinase inhibitor resistance (105).

SUMMARY OF INITIAL CLINICAL EXPERIENCE WITH AURORA KINASE INHIBITORS

Response rates to the Aurora kinase inhibitors that have entered the clinic have been very modest so far, and frankly somewhat disappointing given the preclinical data showing potent antitumor activity on a par with many approved cytotoxic agents. A few partial responses have been observed in diverse cancer types. The most common beneficial response has been prolonged stable disease. Most patients with refractory solid tumors have probably not derived much clinical benefit. Perhaps not surprisingly, response rates have been somewhat more promising in hematological malignancies such as lymphomas. Prolonged stable disease is unlikely to suffice for regulatory approval of a class of drug with properties that are essentially those of a cytotoxic agent unless prolonged disease control results in meaningful increments in survival.

Low response rates must first raise the question of whether the doses and schedules have been properly selected and optimized. The modal DLT of neutropenia predicted in preclinical animal toxicology and observed in most of the clinical trials with Aurora kinase inhibitors provides some indirect pharmacodynamic evidence of target inhibition. Even with cytokine support, further and meaningful dose intensification is probably not practical, especially with the oral agents. Some but not all of the studies have included surrogate tissue (e.g., skin) and tumor biopsies at various time intervals after dosing, demonstrating the expected effects on the mitotic spindles and mitosis. These effects have been dose-dependent, again suggesting that target engagement is not the main problem. A variety of schedules have been examined, modeled after the clinical development of cytotoxic agents such as paclitaxel, without any clear advantages to date for any one schedule. Evaluated schedules have included continuous infusions, as well as one example of very prolonged (21-day) administration (MLN-8237). Given the diversity of schedules assessed already, one must wonder if further variations on the theme will achieve the desired breakthroughs in tumor response rates.

What have the biomarkers told us so far? Based upon preclinical work, most of the clinical studies have evaluated the level of phosphorylation of serine 10 of histone H3 (pHH3) in skin biopsies and/or tumor biopsies as evidence of mitotic arrest and therefore a functional biomarker of target effect (17, 106). Aurora kinase A inhibition results in accumulation of cells in mitosis and an increase in pHH3. Conversely, Aurora kinase B inhibition is predicted to result in a decrease in pHH3 (histone H3 is a known downstream target of Aurora kinase B). While confirming target engagement, changes in pHH3 have not been shown to correlate with treatment outcomes. Recently, some experts have presented a more detailed and refined evaluation of the effects of Aurora kinase A inhibition in tumor samples of patients treated with an Aurora kinase A inhibitor, including loss of mitotic cell spindle bipolarity and evidence of misaligned chromosomes (Chakravarty, A., personal communication). Others have evaluated the rate of autophosphorylation of residue T288 of *AURKA* as a marker for inhibition of the protein itself (94). Collectively, these experiments have confirmed the mechanism of action of Aurora kinase inhibition in human tumors but have not provided insights into the modest evidence of antitumor activity in the clinic.

A spectrum of Aurora kinase inhibitors has been evaluated to date, including highly selective inhibitors of Aurora A or B, inhibitors of both Aurora A and B, and drugs with additional kinase-inhibitory activities. There is ongoing uncertainty as to the best type of agent to use —one that inhibits both Aurora kinase A and B or a more selective approach. Some hypothesize that Aurora kinase B inhibition might selectively promote more aneuploidy and thereby even promote tumor growth, while Aurora kinase A inhibition is more likely to induce mitotic arrest (17). In theory, inhibition of the Aurora kinases should result in cell death due to abnormal cell division and increased genetic instability. However, as noted above, little is known about the exact mechanism by which these agents induce cell death. There has to be concern that the genomic changes that might occur in normal tissue as the result of Aurora kinase inhibition, especially with prolonged exposures, could ultimately result in new tumor development. Additional experience with these agents and careful patient monitoring will be required to ascertain the consequences of their long-term use.

What are the opportunities for development of combinations with Aurora kinase inhibitors? Single agent development is reasonable and feasible if a patient population could be identified that will exhibit a high response rate. This is clearly going to be a challenge based on what has been observed in the clinic thus far. Preclinical studies have reported synergy of the combination of Aurora kinase inhibitors with cytotoxic chemotherapy, particularly other antimitotic agents such as taxanes (60, 64, 87, 107, 108). However, the DLT of neutropenia seen in most of the phase I studies reported to date may

significantly constrain the ability to combine Aurora kinase inhibitors with the cytotoxic armamentarium at adequate doses. The intriguing interactions between Aurora kinases and other cancer-relevant signaling pathways provide an alternative pathway forward for investigations of combinations of Aurora kinase inhibitors with agents inhibiting these pathways (i.e., EGFR inhibitors). Directed rather than empirical development of combinations, ideally targeted to tumors that depend on both targeted pathways, would probably enhance the chances of success for this approach (53).

The fact that some objective responses have occurred in the clinic is intriguing. Alas, at this time we do not have any information regarding the molecular characteristics of the tumors (biomarkers or signatures of response) in those few patients who did respond. Attempts in the past at identifying biological markers for activity of other mitotic agents such as taxanes have been largely futile (108, 109). For this new family of drugs, an obvious place to look is the association between overexpression or amplification of Aurora kinases in tumors and the response to Aurora kinase inhibitors. However, the assays available for detection of overexpression/amplification of Aurora kinase are far from ready for clinical use. Identifying validated biomarkers that could predict for response to these agents and allow efficacy trials in those patient populations most likely to respond will be keys to the further clinical development of these agents.

In conclusion, the Aurora kinases are new targets for cancer therapy that remain very worthy of investigation. The early round of clinical trials has established proof of mechanism and revealed some early signs of beneficial antitumor activity. Toxicities have been predictable and manageable, and importantly, have not included the type of neurotoxicity seen with taxoids and vinca alkaloids. An improved understanding of the transition from mitotic arrest to actual cell death, identification of validated biomarkers of response and methods for patient selection will determine the fate of these agents in phase II and beyond.

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