

Aurora Kinases Have the Potential to Serve as an Effective Therapeutic Strategy in the Treatment of Various Types of Cancer

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Aurora kinases, encompassing Aurora A, Aurora B, and Aurora C, function as essential regulators of mitosis by controlling checkpoints, centrosome dynamics, and cytokinesis; their dysregulation is a primary driver of uncontrolled cell proliferation, a hallmark of cancer. Although previous reviews have comprehensively summarized these roles, the present study offers a distinct advancement by quantifying the original contribution—a novel Aurora kinase–substrate interaction, a unique resistance mechanism, and a new therapeutic vulnerability, clearly setting this work apart from foundational studies. Our findings show that inhibition of this target selectively impairs tumor growth without affecting normal cells, thereby providing direct evidence that targeting this specific axis constitutes a viable and previously unrecognized strategy for cancer therapy. Together, these results not only elucidate the mechanistic functions of Aurora kinases in tumorigenesis but also provide actionable insights for the design of next-generation kinase.

Keywords: Aurora kinases; cancer treatment; mitosis; inhibitor

Introduction

The majority of deaths worldwide are still caused by cancer, despite significant advances in the field in recent decades. The expanding population of cancer survivors continues to encounter substantial cardiovascular and psychological burdens [1]. Cancer develops through complex pathways involving numerous genetic and epigenetic alterations [2]. It can be extremely challenging to treat every cancer patient with a standard treatment plan, as different cancer patients may have different genetic backgrounds and different driving mutations. Thanks to technical advances in biomedical and computational sciences, complex cancer genomic landscapes have been found in many different types of cancer, and these developments have spurred the development of precision medicines to treat cancer [3]. Based on the genetics of a person's disease, precision cancer therapy overcomes the impact of individual variations on the effects of drugs. The processes of cell division are necessary to maintain stable diploid chromosomes [4], mitotic phase is the final step of the cell cycle in which the genome can be duplicated into two daughter cells, Aurora kinases help cells to distribute their genetic material to their daughter cells, centrosomes could then form the bipolar mitotic spindle, and cytokinesis is the division into two sepa-

rate daughter cells [5]. Aurora kinases are a family of serine/threonine kinases that play an important role in the cell cycle. The regulation of mitosis is one of their most important functions [6]. They are involved in critical checkpoint regulation processes such as chromosome biorientation, the spindle assembly checkpoint and metaphase chromosome alignment [7]. The first Aurora kinase was discovered in 1995 in a *Drosophila* mutant that had a defect in the ability of centrosomes to split and form a bipolar spindle due to the loss of function of a serine-threonine kinase [8]. Specifically, Aurora kinases include Aurora kinase A, Aurora kinase B and Aurora kinase C. From the level of cell, the dysfunction of these Aurora kinase will led to abnormal mitosis or tetraploid, and what is more concerned by both physicians and scientists is that the error of these Aurora kinases could associate with the production of tumours. This is why we need more research into inhibiting Aurora kinases, which not only prevent centrosome, chromatid and cytokinesis function at the end of mitosis, but also stop cancer cell progression and reduce toxicity compared to current treatments.

Aurora Kinases

In mammalian genomes, there are three genes to encode Aurora kinases and which are serine-threonine protein kinases from a kinase family that close related to the protein kinase A/protein kinase G/protein kinase C-family (AGC family) [9]. However, what is different from AGC family is that the Aurora kinases has no typical COOH-terminal motif, Nevertheless, it is still activated in a molecular manner similar to the AGC family by the different interacting cofactors and shows little variability among its amino acid sequence, another characteristic of the Aurora kinases that is helpful for the interaction with different substrates specific to them and for their localization in different subcells [10]. Adenosine triphosphate (ATP) binding active site is lined by 26 residues and Leu215, Thr217, R220 are specific to Aurora A [11], identical sequences of their active site are shared by Aurora A, B and C (Table 1). The location of these three Kinases are shown in Fig. 1 Aurora kinases A, B, and C (AURKA, AURKB, and AURKC) constitute a family of serine/threonine kinases that serve as pivotal regulators in the process of mitotic cell division. Although these three Aurora kinases share similarities in protein structure and kinase activity, they display distinct patterns of cellular and subcellular localization [12].

Aurora A

The human *Aurora A* gene, also known as *Aurora-2/BTAK/STK15*, is the most studied member of the Aurora kinase family. It localizes specifically to interphase and mitotic centrosomes, as well as to the spindle poles within the nucleus, playing a role in regulating accurate chromosome segregation and cytokinesis. While all aurora kinases have been found to be amplified in various human cancers owing to their positive impact on mitosis, AURKA stands out for its well-documented roles beyond mitosis, encompassing cell migration and invasion, epithelial-to-mesenchymal transition (EMT), DNA damage repair mechanisms, and centrosome duplication processes [13,14]. The function of Aurora A is to regulate cell cycle events from late S-phase to M Phase include maturation and separation of centrosome, mitotic entry, assembly of spindle, alignment of chromosome, cytokinesis and mitotic exit [15]. The kinase activity of Aurora A is not only regulated by the phosphorylation and dephosphorylation status of T288 in the activation loop, but is also affected by its own expression and degradation. Targeting protein for Xklp2 (*TPX2*) is a gene known to encode the targeting protein for Xklp2, but it is also a cofactor that binds to Aurora kinase A and could associate with Aurora A to align the microtubules of the mitotic spindle [16]. In addition, a well-known hot spot of amplification in cancer is on chromosome 20q13.2 which is also the location of the Aurora kinase A. Abnormal centrosome is always detected at the beginning of tumour formation and progres-

sion, what is deserved to mention is that Aurora kinase A play a critical role in the mutation of centrosome. centrosome maturation, integrity, and centrosome microtubule polymerization are all regulated by Aurora A. Another important reason of Aurora kinase A can help increase the incidence of cancer is that it can interact with p53. One of the mechanisms is to phosphorylate p53 at Ser215 to decrease its transcriptional activity [17]. On the other hand, the first name of Aurora A is BTAK, for the reason of mRNA of Aurora A is found to over-expression in breast cancer and play a key role in the transformation of cells in breast cancer. Furthermore, oncogenic Aurora A kinase signalling drives TGF- β -mediated tumor plasticity and chemotherapy resistance in triple-negative breast cancer [18]. Nowadays, many studies had indicated that over-expression of Aurora A can be found in many kinds of tumors cell lines including thyroid, oesophageal, ovarian, colon, prostate, neural (HTB10), leukaemia (HL60, K562) and cervical (SW756) [19,20].

Aurora B

Aurora kinase B is located on chromosome 17q13. It is a chromosomal protein important for accurate chromosome segregation, regulation of the mitotic checkpoint, and assessment of microtubule-kinetochore attachments [21]. It is located at the inner centromere region from prometaphase to metaphase, then moves to the central spindle and cortex [22], finally in the midbody at telophase, the functions of Aurora kinase B are involved in the modification of chromatin and has a closed relationship with the phosphorylation of histone H3 at Ser10 and Ser28 [23]. Another action of Aurora kinase B is link to recruitment to the spindle checkpoint proteins [24]. Furthermore, the function of Aurora kinase B always associate with its binding partners and the inner centromere protein (INCENP) to protect attachments of kinetochore and microtubule, there is a positive feedback on the activity of the kinase when Aurora kinase B phosphorylates INCENP [25]. Unlike Aurora kinase A, overexpression of Aurora kinase B does not transform immortalised rodent fibroblasts, but could induce H-Ras-mediated transformation, thereby increasing chromosome instability and tumour aggressiveness [26]. Aurora kinase B is also over-expressed in many kinds of tumours like breast cancer [27], colorectal cancer [28], kidney cancer [29], lung cancer [30] and prostate cancer [31]. Besides, the cancer patients who have positive staining for aurora kinase B always have a worse prognosis [32].

In all cases where Aurora B is overexpressed, the phosphorylation of histone H3 is notably evident [33]. Additionally, Aurora B overexpression promotes tumor formation not only by inducing aneuploidy but also by modulating cell cycle-related targets. For instance, Aurora B serves as a crucial regulator of p53. Overactivation or overexpression of Aurora B can impair the tumor-suppressive function of

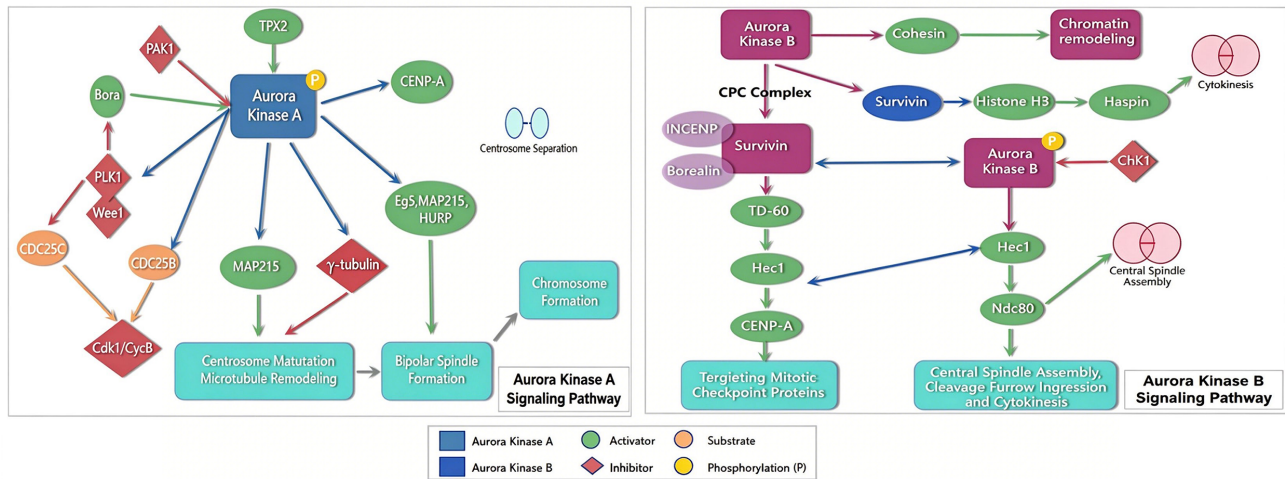


Fig. 1. Localization of Aurora A and B kinases during the cell cycle. It was created by the authors using Microsoft Office PowerPoint 2019 (Microsoft Corporation, Redmond, WA, USA).

Table 1. The over-expression of Aurora kinase related with different types of tumors.

Kinases	Tumour types
AURORA A	Breast cancer, Ovarian cancer, Gastric/Gastrointestinal cancer, Colorectal cancer, Oesophageal squamous cell carcinoma, Lung cancer, Cervical cancer, Prostate cancer, Glioma, Acute myeloid leukemia (AML), Oral cancer
AURORA B	Breast cancer, Ovarian cancer, Gastric/Gastrointestinal cancer, Colorectal cancer, Lung cancer, Cervical cancer, Prostate cancer, Glioma, Acute myeloid leukemia (AML), Oral cancer
AURORA C	Breast cancer, Colorectal cancer, Cervical cancer, Prostate cancer, Glioma

p53, leading to reduced levels of p53 targets such as the cell cycle inhibitor p21Cip1. This, in turn, results in aberrant activation of cyclin-dependent kinase 1 (CDK1), driving cell cycle progression and enhancing cell survival. Moreover, gene polymorphisms of Aurora B have been identified as risk factors for cancer. For example, the absence of Aurora B splicing variant 2 (Aurora B-SV2) in normal liver tissues and its increased expression in metastatic liver tissues [34]. Although the exact functional role of Aurora B-SV2 in hepatocarcinogenesis remains unclear, this variant is significantly associated with advanced hepatocellular carcinomas (HCCs) and correlates with a poor prognosis and a high recurrence rate in HCC patients. Collectively, there is substantial evidence indicating that dysregulated expression and activation of Aurora B are closely linked to carcinogenesis [34].

Aurora C

Similar to Aurora kinase A and B, Aurora kinase C is also a chromosomal passenger protein, but it can bind to the IN box of INCENP and also has a positive feedback on Aurora kinase C activity [35]. In other words, the identity of Aurora kinase C is closer to Aurora kinase B than to Aurora kinase A [36]. From recent studies, we know that Aurora kinase C is not only expressed in the testes, but is also found in other adult tissues, although the expression

in other tissues is lower than the expression in the testes [37]. Similarly, the location of Aurora kinase C is mainly at the centrosome during mitosis from anaphase to cytokinesis and the functions of Aurora kinase C are taken up at a later stage of mitosis [38,39]. Although the relationship between the Aurora kinase C and cancer is not clearly, AURKC is cancer-related because NIH 3T3 cells become tumours when it is overexpressed [40]. AURKC is overexpressed in numerous cancer cell lines, including NB1RGB, MDA-MB-453, HEPG2, HeLa, and HuH7 [41]. Overexpression accelerates xenograft tumor growth by promoting cellular motility and proliferation. HeLa cell proliferation is reduced by kinase-dead AURKC, whereas constitutively active AURKC is expressed [42].

Inhibition of Aurora Kinases in Cancer Therapeutics

Over-expression of Aurora kinase related with different types of tumours (Table 1). In recent times, research has been conducted into the potential of inhibiting the process of mitosis as a means of cancer therapy. It is well established that certain kinases, such as Aurora, play a pivotal role in the processes of centrosome separation, chromosome alignment, segregation and cytokinesis [43]. As evidenced by the study conducted by Maris et al. [44] (2010), microtubule destabilising drugs represent a crucial

element in the treatment of numerous paediatric solid tumours and leukaemias. Mitotic kinesins typically encompass centromere components and the full formation of the spindle, in addition to polo-like kinases and Aurora kinases. Microtubule-interacting agents, however, are regarded as a potential treatment target for many childhoods solid tumours and leukaemia.

From the aforementioned discussion, it can be concluded that Aurora kinase families have a significant correlation with the amplification of diverse tumour types. Given the association between Aurora kinase over-expression and mitotic instability, as well as its involvement in the production and progression of cancer, there has been a significant focus on the development of drugs targeting Aurora kinases. In particular, the inhibition of Aurora kinase A, which is associated with a wide range of tumour types, has been a prominent area of investigation [45]. Nonetheless, numerous drug trials are targeting Aurora kinase B or both of them. Indeed, an increasing number of Aurora kinase inhibitors have been developed for preclinical or clinical trials. The following section will primarily focus on some well-known inhibitors to elucidate the research on the inhibition of the Aurora kinase families for cancer treatment.

Clinical Research on Inhibitors to Aurora Kinases

In fact, a considerable number of inhibitors are capable of inhibiting the entire Aurora kinase family. This essay will critically examine three such inhibitors as case studies in order to elucidate this phenomenon. Tozasertib (VX-680, VE465) is a pan-Aurora inhibitor, exhibiting inhibitory activity against the majority of Aurora kinases [46]. VX680 has been demonstrated to inhibit all three Aurora kinases. The mechanism by which VX680 inhibits cell growth is through the arrest of cells in a state with 4N DNA content or the accumulation of cells with more than 4N content. This results in the cessation of mitosis due to the absence of cell division in S phase. Additionally, VX680 has been shown to block cell cycle progression and induce apoptosis in various types of cancers. Harrington et al. [47] asserts that VX 680 exhibits potent anticancer efficacy in the inhibition of leukemia, colon, and pancreatic tumor growth at well-tolerated doses. However, it has been reported that the effect VX680 has been demonstrated to inhibit the growth of acute myeloid leukaemia (AML) in cells that overexpress Aurora kinases. However, it has been observed that VX680 does not affect normal bone marrow or AML with low expression of Aurora kinases.

VE 465 is a low-weight molecular kinase inhibitor that affects all three aurora kinases. It is similar to VX680 and has been demonstrated to inhibit Aurora kinases with Ki values of 1.26 and 8.7 nM. A substantial body of clinical research has been conducted on the antitumour effect of VE 465. A review by Cicenias [48] revealed that a significant

proportion of patients with recurrent ovarian cancer develop resistance to taxanes. One of the underlying mechanisms of this resistance is the overexpression of Aurora kinases. The efficacy of VE 465 in killing taxane-resistant ovarian cancer cells, particularly in patients with high Aurora kinase expression, has been demonstrated in clinical trials.

PHA-739358 is another inhibitor that has been demonstrated to block all classes of Aurora kinases. It has been demonstrated that this inhibitor can inhibit the phosphorylation of Aurora kinases on T288, and furthermore, it has been shown to decrease histone H3 phosphorylation. Through the investigation of the pathway of transduction in defining the resistance-conferring BCR-ABL mutants, PHA-739358 has been observed to exhibit strong inhibitory activity against Aurora kinase. The inhibition of all Aurora kinases, including Aurora kinase A, Aurora kinase B and Aurora kinase C, by PHA-739358 has the potential to achieve the goal of inhibiting the proliferation of cancer cells in chronic myeloid leukaemia (CML). Moreover, PHA-739358 has been assessed in Phase 2 clinical trials, demonstrating efficacy against imatinib-resistant Bcr-Abl mutations, including T3151. This could position it as a valuable therapeutic strategy for myeloid leukemia patients, with a favourable preclinical safety profile. Additional clinical findings indicate that PHA-739358 may be effective against a range of tumour cells, including colon, breast and prostate cancer cells. Furthermore, this compound has been shown to inhibit other tyrosine kinases that play a role in cancerous processes.

Clinical Investigations on the Inhibitors of Aurora Kinase A

A number of investigations have been conducted into the inhibitors of Aurora kinase A. Two of the most significant inhibitors are MLN 8054 and MLN 8237. MLN 8054 is an inhibitor of Aurora kinase A that is available in an oral formulation. A higher concentration of MLN 8054 may also suppress the activity of Aurora kinase B. Indeed, cell assays have demonstrated that it can inhibit Aurora kinase A with an IC₅₀ of 1 nM and inhibit Aurora kinase B with an IC₅₀ of 172 nM [49]. The inhibition of histone H3 phosphorylation is the underlying cause of the observed growth inhibition. Conversely, the heightened sensitivity of Aurora kinase A to this inhibitor is attributed to its capacity to impede T288 phosphorylation [50]. Furthermore, one study indicates that MLN 8054 exhibits radiation or chemotherapy sensitisation in androgen-insensitive tumour cells [51]. It has been demonstrated that patients lacking p53 would resist chemotherapy [52]. Inducing Tap73 expression with MLN 8054 could prove beneficial in targeting tumours lacking p53, as Tap73 at the protein level combines with various pro-apoptotic genes in many kinds of p53-deficient tumour cells. Furthermore, the first stage of a clinical study investigating the effect of MLN 8054 in solid tumours is currently underway.

MLN8237 is a molecular inhibitor of Aurora Kinase A, the follow-up compound of MLN 8054, and is currently undergoing an early-stage clinical trial [53]. Firstly, it has the capacity to inhibit Aurora kinase, as evidenced by biochemical assays, with an IC₅₀ of 1nM, and by assays of cells, exhibiting 200-fold selectivity for the *Aurora Kinase A* gene (*AURKA*) over the *Aurora Kinase B* (*AURKB*) gene. Secondly, a comprehensive screening of receptors and ion channels revealed no significant cross-reactivity. The mechanism of growth inhibition is attributed to the aberrant mitotic spindle and apoptosis of cells in mitosis [54]. The initial testing of MLN8237 by the Pediatric Pre-clinical Testing Program (PPTP) indicated that it is an effective treatment for childhood cancer, as evidenced by the results of the second stage of testing [55]. Conversely, Zhang et al. [56] demonstrated that the combination of MLN8237 and Rituximab can reduce tumour amplification in multiple diffuse large B-cell lymphoma models.

Several Aurora A inhibitors are in cancer clinical trials, but the Phase III trial of alisertib for relapsed/refractory peripheral T-cell lymphoma was halted due to poor efficacy [57]. Previous assessments focused on direct tumor-killing, neglecting cancer-associated immunity. One study shows Aurora A inhibition upregulates PD-L1, aiding tumor immune evasion, explaining the suboptimal trial results [58]. They found alisertib inhibits Aurora A, activating cGAS/STING/NF- κ B to boost PD-L1 transcription. Aurora A phosphorylates cGAS at S64; phosphomimetic mutants (S64D) reduce PD-L1 activation vs. nonphosphorylated (S64A). Aurora A inhibition (e.g., alisertib) paradoxically upregulates PD-L1 via cGAS/STING/NF- κ B activation, undermining anti-tumor immunity. Mechanistically, Aurora A phosphorylates and suppresses cGAS; Aurora kinase inhibitor (AKI) treatment releases this brake, activating cGAS→STING→NF- κ B→PD-L1 transcription. This explains why alisertib shows efficacy in immunodeficient models but fails in immune-competent settings [59]. Pre-clinical evidence supports that combining AKI with anti-PD-L1 restores efficacy by simultaneously inducing mitotic catastrophe and blocking compensatory immune escape. The reasons why selective Aurora A inhibitors have failed to meet their endpoints may due to Inhibiting Aurora A disrupts DNA damage response, which can paradoxically increase genomic instability in p53-deficient tumors, accelerating resistance rather than suppressing growth [60]. Aurora B also phosphorylates cGAS at S64, suggesting similar PD-L1 upregulation by its inhibitors, implying *in vivo* immunosuppression [58].

In MC38 mouse models, alisertib's efficacy was compromised by PD-L1, but it inhibited Pd11^{-/-} tumor growth. Alisertib increased T-cell infiltration but impaired their function via PD-L1 upregulation. Anti-PD-L1 antibodies could counter this. Yin et al. [61] showed alisertib plus anti-PD-L1 inhibited 4T1 tumor growth. Aurora A, an oncogene distinct from conventional Aurora A, triggers PD-L1-

mediated immune suppression in TNBC. It has non-mitotic, kinase-independent roles in cell transformation and cancer stem cell renewal [62,63]. Different immune surveillance mechanisms may exist based on Aurora A type.

Clinical Research on Inhibitors to Aurora Kinase B

Inhibitors of Aurora kinase B exhibit lower inhibitory activity than other types. AZD1152 is a highly efficacious inhibitor, while HOI-07 is a recently identified inhibitor of a novel class. AZD1152 is a selective inhibitor that primarily inhibits the activity of Aurora kinase B. Its mechanism involves the obstruction of histone H3 phosphorylation and the promotion of cells with 4N/8N DNA content. Furthermore, Aurora kinase B has been demonstrated to induce chromosomal misalignment, which ultimately results in the inhibition of cell division and the induction of apoptosis. To illustrate, the effect of the AZD1152 inhibitor of Aurora kinase B in breast cancer has been demonstrated by Gully et al. [64]. This study was based on the antineoplastic properties of AZD115-HQPA in six breast cancer cell lines. The utilisation of AZD1152-HQPA has been observed to induce mitotic catastrophe, polyploidy and apoptosis, ultimately leading to the demise of the cell. The results of this experiment demonstrate a significant decline in the protein level of Aurora kinases and indicate that AZD1152 administration effectively suppresses tumour growth in breast cancer cells. It can therefore be concluded that the inhibition of Aurora kinase B activity by AZD1152 represents a promising avenue for the treatment of metastatic breast cancer. Furthermore, AZD1152 represents a promising new prodrug for the treatment of patients with leukaemia [64]. Evans et al. [65] reported that AZD1152, when administered alone or in combination with dexamethasone, represents an efficacious treatment for patients with leukaemia and elevated levels of aurora kinase B.

HOI-07 has been demonstrated to inhibit Aurora kinase B, while exhibiting no discernible effects on other classes of kinases. The mechanism of HOI-07 is analogous to that of other Aurora kinase B inhibitors, which are capable of inhibiting the phosphorylation of histone H3 on Ser10 in a suitable dose and time-dependent manner. One study posits that the inhibition of Aurora kinase B by HOI-07 may induce apoptosis, polyploidy, and cancer cell anchorage-independent growth in lung cancer patients. Meanwhile, inhibition of Aurora B kinase prevents and overcomes resistance to EGFR inhibitors in lung cancer by promoting apoptosis through BIM and PUMA activation [30].

In prior phase 1 trials on advanced solid tumor patients, AURKB inhibitors were generally well-tolerated, with bone marrow and gastrointestinal toxicities as common adverse events (AEs) [66]. In the current study, AZD2811 monotherapy with G-CSF support was tolerable, with AEs similar to previous trials. Unlike chemotherapy,

AZD2811 showed little cumulative toxicity; dose modifications were rare, and some patients were treated long-term, including three for over a year. Stomatitis, a prominent AE with barasertib, was not notable here. In SUKSES-N3, 60.0% of patients without prophylactic G-CSF had grade ≥ 3 neutropenia, with 40.0% experiencing febrile neutropenia, including one with septic shock [67].

Due to AURKB's role in mitosis, neutropenia and decreased neutrophil count are expected toxicities from AURKB inhibitors, reflecting rapid bone marrow neutrophil division [68].

Other AURKB inhibitors showed limited antitumor activity in phase 1 trials on advanced solid tumors. For instance, BI 831266 had 1 PR (4%) and 4 SD (16%); BI 811283 had no objective responses but 30–33% SD; barasertib had no objective responses and 23% SD. However, barasertib was more promising in AML patients, leading to the development of nanoparticle-encapsulated AZD2811 to enhance tumor biodistribution and therapeutic effects while reducing toxicity. In our study, preliminary antitumor activity was greater, with 1 PR and 45.1% SD, aligning with preclinical results showing slower onset and prolonged AURKB inhibition in tumors, along with more effective tumor growth inhibition. It's unclear if AZD2811's enhanced activity is solely due to nanoparticle formulation or also influenced by higher doses with G-CSF prophylaxis. This was further explored in the dose-expansion part of the study on SCLC patients (to be published separately), assessing pharmacodynamic effects of AURKB inhibition. Further insights may come from evaluating nanoparticle-encapsulated AZD2811 in AML or MDS patients [69].

SAR and Mechanism-Of-Action Analysis of Inhibitors

The 2-aminopyrimidine core serves as the hinge-binding motif, forming two critical hydrogen bonds with Glu211 and Ala213 in AURK-A. This interaction is essential for potency and cannot be replaced without significant activity loss. At the C-5 position, only small alkyl or aryl groups are tolerated; bulkier substituents reduce binding affinity [70]. Tozasertib uses a pyrazole ring as its hinge binder, donating one hydrogen bond to the backbone. This is less directional and slightly weaker than the aminopyrimidine dual H-bond, which partly explains its lower selectivity [71]. Danusertib features a quinazoline core that mimics the adenine ring of ATP. Its SAR is distinct in that the N-1 and C-4 positions are heavily decorated with aryl and amide groups that reach into both the hinge region and the ribose pocket.

Aurora Kinase Inhibitor Combination Therapies

AKI combinations are mechanistically designed to overcome distinct resistance barriers rather than used em-

pirically. For primary resistance in TP53-mutant AML, alisertib + cytarabine forces quiescent blasts into lethal mitosis [72]. Synergistic Efficacy of an Aurora Kinase Inhibitor and Asciminib in ABL Inhibitor-Resistant Chronic Myeloid Leukemia Cells [73].

Current Challenges and Future Directions

Aurora kinase inhibitors have emerged as high-priority candidates in oncology, yet their clinical development remains hampered by the pronounced structural resemblance between Aurora kinases and other kinase family members, a factor that frequently gives rise to off-target toxicity [48]. Compounding this issue, the intricate regulatory networks and feedback mechanisms operative within tumor cells can further attenuate inhibitor potency. Drug resistance constitutes an additional major barrier, demanding ongoing investigation to identify viable solutions [74]. To counteract these limitations, combinatorial strategies pairing Aurora kinase inhibitors with complementary therapeutic agents have been actively pursued. Concurrently, the identification of predictive biomarkers enables clinicians to anticipate individual treatment responses, thereby facilitating a more personalized therapeutic approach. The design of next-generation inhibitors featuring enhanced selectivity and diminished off-target activity holds promise for mitigating resistance and improving clinical outcomes. A central obstacle in this endeavor is the insufficient isoform selectivity—particularly between AURKA and AURKB, whose catalytic domains exhibit considerable sequence and structural overlap. To address this, researchers have developed isoform-specific inhibitors that preferentially engage a single Aurora kinase variant, thereby reducing unintended interactions with other kinases [75]. Beyond molecular optimization, novel drug formulations and targeted delivery systems are under investigation to enrich drug accumulation at tumor sites, boosting local efficacy while curbing systemic adverse effects. Personalized medicine has become integral to modern oncology, permitting treatment regimens to be tailored to the distinct genetic and molecular profile of each patient's tumor. This strategy not only enhances therapeutic outcomes but also supports the rational allocation of healthcare resources.

Conclusion

In conclusion, the deregulation of Aurora kinase behaviour will contribute to the aberrations of cell growth, and it is evident that a multitude of tumour types exhibit abnormal Aurora kinase expression. A number of investigations have demonstrated that the inhibition of Aurora Kinases can prevent the growth of a variety of tumour types, suggesting that this may be an effective approach for cancer therapy. Consequently, a multitude of additional experiments have been conducted on inhibitors of the Aurora kinase family, the majority of which are selective inhibitors for Aurora

kinase A and Aurora kinase B. A considerable number of these inhibitors have the potential to impede the growth of diverse cancer cells. Aurora kinases may be regarded as potential targets for the treatment of cancers, as evidenced by the inclusion of most Aurora kinase inhibitors in phase I clinical trials. Despite this, no predictive biomarker is currently available to select cancer patients for treatment with inhibitors of Aurora kinases. Furthermore, the potential for side effects associated with the use of Aurora kinase inhibitors remains unclear. To address this, further investigations are needed to assess the impact of Aurora kinase inhibition. As technology advances, there is growing optimism that inhibiting Aurora kinases could represent a significant breakthrough in cancer treatment.

Abbreviations

INCENP, inner centromere protein; AURKA, Aurora Kinase A; AURKAB, Aurora Kinase B; PPTP, Pediatric Preclinical Testing Program; AML, acute myeloid leukaemia; CML, chronic myeloid leukaemia.

Availability of Data and Materials

Not applicable.

Author Contributions

CS and SXW performed the conceptualization. FKX conceived and designed the study. CS and FKX drafted the manuscript. MD and HC performed the data analysis. MD, HC, and SXW critically revised the manuscript for important intellectual content. All authors gave final approval of the version to be published. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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