

Review

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Aurora kinase B in non-small cell lung cancer: molecular mechanisms, therapeutic resistance, and targeted therapies

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Abstract: Non-small cell lung cancer (NSCLC) remains the leading cause of cancer-related mortality worldwide, and therapeutic resistance continues to be a major barrier to achieving durable clinical benefit. Increasing evidence has identified Aurora kinase B (AURKB), a key catalytic component of the chromosomal passenger complex (CPC), as an essential regulator of mitosis, chromosome segregation, and chromosomal instability (CIN) in NSCLC. Elevated AURKB expression or excessive AURKB signaling is closely associated with increased tumor proliferation, epithelial-mesenchymal transition (EMT), metastatic progression, and poor clinical outcomes. Mechanistically, AURKB interacts with multiple oncogenic signaling networks, including MYC, PI3K/AKT, MAPK, KRAS, and p53-related pathways, thereby promoting mitotic adaptation, survival under therapeutic stress, and tumor evolutionary plasticity. Accumulating evidence suggests that AURKB contributes to resistance to chemotherapy and epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) in NSCLC, partly by suppressing apoptosis, inducing mitotic slippage, and enhancing CIN-driven tumor heterogeneity. In this review, we comprehensively summarize the molecular structure, biological functions, and regulatory mechanisms of AURKB in NSCLC. We further discuss its oncogenic roles in tumor progression, EMT, metastasis, and therapeutic resistance, with particular emphasis on EGFR-TKI resistance and KRAS-driven lung cancer. We also discuss current challenges in the clinical translation of AURKB inhibitors and future biomarker-guided therapeutic strategies. Collectively, current evidence indicates that AURKB is a biologically and clinically relevant therapeutic target with promising translational potential in NSCLC.

Key words: Aurora kinase B (AURKB); Non-small cell lung cancer; Chromosomal instability; therapeutic resistance; Epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) resistance; Precision oncology; Aurora kinase inhibitor

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1 Introduction

Lung cancer remains the leading cause of cancer-related death worldwide and continues to pose a major global public health burden, despite substantial advances in cancer diagnosis and treatment (Siegel et al., 2025). Among its histological subtypes, non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancer cases and is characterized by pronounced molecular heterogeneity, dynamic evolutionary patterns, and variable responses to therapy (Herbst et al., 2018). Molecularly targeted therapies against oncogenic drivers, including epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), and Kirsten rat sarcoma viral oncogene homolog (KRAS), together with immune checkpoint inhibitors (ICIs), have significantly improved survival outcomes in selected patient populations (Reck et al., 2016; Mok et al., 2017; Camidge et al., 2019; Skoulidis and Heymach, 2019). Therefore, identifying novel molecular vulnerabilities involved in tumor progression, mitotic adaptation, and therapeutic resistance is crucial for improving precision-based therapeutic strategies for NSCLC.

Chromosomal instability (CIN), characterized by persistent chromosome mis-segregation, aneuploidy, and structural chromosomal alterations, is now recognized as a major driver of tumor heterogeneity, metastatic dissemination, immune evasion, and drug resistance (Sansregret and Swanton, 2017; Bakhoum and Cantley, 2018; Vasudevan et al., 2020; Quinton et al., 2021). Importantly, CIN not only increases genomic diversity but also facilitates the emergence of resistant tumor subclones and adaptive cellular states during targeted therapy (Sansregret and Swanton, 2017; Bakhoum and Cantley, 2018). Aberrant activation of mitotic regulators frequently results in defective spindle assembly checkpoint (SAC) signaling, chromosome segregation errors, cytokinesis failure, and uncontrolled tumor proliferation (Dominguez-Brauer et al., 2015). Among these regulators, the mammalian Aurora kinase family comprises AURKA, AURKB, and AURKC, which differ in tissue distribution and physiological function. AURKA and AURKB are broadly expressed in proliferating somatic cells, whereas AURKC is predominantly expressed in meiotically active germ cells; ectopic expression of active AURKC can nevertheless show oncogenic potential in somatic cells (Khan et al., 2011; Quartuccio and Schindler, 2015). A high CIN burden has been closely linked to intratumoral heterogeneity, metastatic evolution, and poor responses to targeted therapy and immunotherapy in NSCLC.

AURKB is a highly conserved serine/threonine kinase and a catalytic core component of the chromosomal passenger complex (CPC), which also includes inner centromere protein (INCENP), Survivin, and Borealin (Carmena and Earnshaw, 2003; Lens and Medema, 2019b). During mitosis, AURKB coordinates several essential processes, including chromosome condensation, correction of kinetochore-microtubule attachments, spindle checkpoint regulation, chromosome segregation, and cytokinesis, thereby ensuring faithful chromosomal inheritance and genomic stability (Carmena and Earnshaw, 2003; Tang et al., 2017; Lens and Medema, 2019b). These genome-protective functions require precise spatiotemporal control of AURKB activity. By contrast, AURKB overexpression or excessive/imbalanced activation can perturb chromosome-segregation fidelity and promote chromosome-number instability or aneuploidy in experimental models (Ricke et al., 2011; González-Loyola et al., 2015). Elevated AURKB expression is closely associated with increased tumor proliferation, epithelial-mesenchymal transition (EMT), metastatic progression, CIN, and poor clinical outcomes (Den Hollander et al., 2010; Bielski et al., 2018). Importantly, such clinical associations do not by themselves establish that elevated AURKB expression is the primary cause of CIN. Thus, the physiological role of AURKB in maintaining mitotic fidelity should be distinguished from the consequences of excessive AURKB signaling in cancer cells.

Mechanistically, AURKB is involved in multiple oncogenic signaling networks that collectively promote tumor progression and therapeutic adaptation in NSCLC. Emerging evidence suggests that AURKB functionally interacts with several key oncogenic pathways, including MYC, PI3K/AKT, MAPK, KRAS, and p53-related signaling, thereby supporting tumor cell survival and stress adaptation in NSCLC (de Bruin et al., 2014; Goldenson and Crispino, 2015; Hata et al., 2016; Marine et al., 2020). In addition, reduced AURKB activity can promote cytokinesis failure and

polyploidization, whereas excessive or imbalanced AURKB signaling can promote chromosome-segregation errors and aneuploidy, with both perturbations potentially contributing to tumor evolution and treatment adaptation (Ricke et al., 2011; González-Loyola et al., 2015; Sansregret and Swanton, 2017; Bakhoun and Cantley, 2018; Vasudevan et al., 2020; Quinton et al., 2021). Recent studies have further highlighted the critical role of AURKB in epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) resistance (Sharma et al., 2010). AURKB inhibition has been shown to restore apoptotic signaling and overcome resistance to EGFR-targeted therapies, partly by enhancing BIM- and PUMA-mediated mitochondrial apoptosis (Sharma et al., 2010). Moreover, AURKB has been implicated in chemotherapy resistance, the adaptive survival of drug-tolerant persister cells, and stress-induced tumor evolution in NSCLC (Vasudevan et al., 2020; Quinton et al., 2021).

Given its central role in mitotic regulation, CIN, and treatment resistance, AURKB has emerged as an attractive target for anticancer drug development. Over the past decade, multiple Aurora kinase inhibitors, including pan-Aurora kinase inhibitors and selective AURKB inhibitors, have shown promising antitumor activity in preclinical and early clinical studies (Bavetsias and Linardopoulos, 2015; Yan et al., 2016; Borisa and Bhatt, 2017). More recently, rational combination strategies integrating Aurora kinase inhibition with EGFR-targeted therapy, chemotherapy, immune checkpoint blockade, and DNA damage response (DDR)-targeted therapy have further expanded the translational potential of AURKB-directed treatment in NSCLC (Bavetsias and Linardopoulos, 2015; Yan et al., 2016; Quinton et al., 2021). However, several major challenges continue to limit the clinical translation of Aurora kinase inhibitors, including hematologic toxicity, insufficient target selectivity, adaptive resistance mechanisms, and the lack of robust predictive biomarkers (Bavetsias and Linardopoulos, 2015; Yan et al., 2016; Borisa and Bhatt, 2017).

In this review, we comprehensively summarize the molecular structure, biological functions, and regulatory mechanisms of AURKB in NSCLC. We discuss its oncogenic roles in CIN, tumor progression, EMT, metastasis, and therapeutic resistance, with particular emphasis on EGFR-TKI resistance and KRAS-driven lung cancer. In addition, we review recent advances in Aurora kinase-targeted therapies, including pan-Aurora kinase inhibitors, selective AURKB inhibitors, and emerging combination strategies involving targeted therapy, immunotherapy, and DDR-directed agents. Finally, we discuss the current limitations and future translational perspectives of AURKB-targeted therapies in the context of biomarker-guided and precision-based treatment strategies for NSCLC. Taken together, current evidence suggests that AURKB may represent not only a key mitotic regulator but also a therapeutically exploitable vulnerability in biologically aggressive NSCLC.

2 Structure and biological functions of AURKB

2.1 Structure, activation, and mitotic dynamics of AURKB

AURKB is an evolutionarily conserved serine/threonine kinase of the Aurora kinase family. Conservation is particularly strong within the catalytic kinase domain, whereas non-catalytic terminal regions are more divergent across Aurora family members and phylogenetic homologs (Carmena and Earnshaw, 2003; Carmena et al., 2012; Willems et al., 2018). The CPC comprises four core proteins: AURKB, inner centromere protein (INCENP), Survivin, and Borealin. These components act cooperatively to regulate chromosome alignment, chromosome segregation, and mitotic progression during cell division. Within the CPC, INCENP functions as a scaffold protein essential for AURKB activation and spatial localization, whereas Survivin and Borealin contribute to centromere targeting, CPC stabilization, and spindle assembly checkpoint (SAC) regulation (Jeyapragash et al., 2007; Ruchaud et al., 2007).

Structurally, AURKB contains an N-terminal regulatory region, a highly conserved catalytic kinase domain, and a short C-terminal domain (Yasui et al., 2004). Its activation is tightly controlled in a spatiotemporal manner throughout mitosis and depends mainly on autophosphorylation at

threonine 232 (Thr232) within the activation loop of the kinase domain. Binding of the INCENP IN-box domain induces conformational rearrangement of AURKB and promotes full kinase activation by stabilizing Thr232 phosphorylation (Yasui et al., 2004; Abdul Azeez et al., 2019). Once activated, AURKB phosphorylates multiple mitotic substrates involved in chromosome condensation, correction of kinetochore-microtubule attachments, SAC signaling, and cytokinesis (Carmena and Earnshaw, 2003; Lampson and Grishchuk, 2017b).

The subcellular localization of AURKB changes dynamically during mitotic progression and is critical for its biological functions. During prometaphase and metaphase, the CPC predominantly localizes to inner centromeres and kinetochores, where AURKB monitors kinetochore tension and regulates chromosome alignment, correction of erroneous kinetochore-microtubule attachments, and SAC signaling (Carmena et al., 2012; Lampson and Grishchuk, 2017b). During anaphase and telophase, the CPC subsequently relocates to the spindle midzone and midbody, where it coordinates cleavage furrow ingression, cytokinesis, and abscission (Lampson and Cheeseman, 2011). This highly coordinated spatial redistribution ensures accurate chromosome segregation and faithful completion of cell division.

In NSCLC, elevated AURKB expression has been associated with aggressive clinicopathological features, increased proliferative activity, poor prognosis, and resistance to anticancer therapies (Tanaka et al., 2021b). Collectively, these findings support AURKB as an important regulator of both mitotic integrity and tumor evolutionary adaptation in NSCLC.

2.2 Biological functions of AURKB in mitotic regulation and CIN

AURKB plays essential roles throughout mitosis and is critical for accurate chromosome segregation and successful completion of cell division (Carmena and Earnshaw, 2003). One of its primary functions is to regulate chromosome condensation through phosphorylation of histone H3 at serine 10 (H3S10ph), a hallmark event required for chromatin remodeling during mitotic entry (Hirota et al., 2005). In addition, AURKB is a key regulator of kinetochore-microtubule attachment fidelity. By destabilizing erroneous attachments, AURKB promotes chromosome biorientation before sister chromatid separation (Carmena et al., 2012; Krenn and Musacchio, 2015). Failure of these corrective mechanisms often leads to lagging chromosomes, micronucleus formation, and aneuploidy.

The SAC is a critical surveillance mechanism that prevents premature anaphase onset until proper kinetochore-microtubule attachment and chromosome bi-orientation have been achieved (Musacchio and Salmon, 2007a). AURKB functions as a central regulator of kinetochore tension sensing and SAC signaling by phosphorylating multiple kinetochore- and checkpoint-associated substrates (Musacchio and Salmon, 2007a; Lampson and Grishchuk, 2017b). Inhibition or depletion of AURKB impairs error correction, SAC signaling, and cytokinesis, promoting chromosome mis-segregation and polyploidization (Musacchio and Salmon, 2007b; Lampson and Grishchuk, 2017a; Lens and Medema, 2019a). Conversely, excessive or imbalanced AURKB signaling can perturb kinetochore-microtubule attachment dynamics and promote chromosome misalignment, lagging chromosomes, and aneuploidy (Ricke et al., 2011; González-Loyola et al., 2015). SAC signaling may remain active under these conditions, because checkpoint activation does not necessarily guarantee error-free segregation and some erroneous attachments, including merotelic attachments, can escape SAC detection (Ricke et al., 2011).

Beyond chromosome segregation, AURKB plays an important role in cytokinesis (Lampson and Cheeseman, 2011). During late mitosis, AURKB relocates to the central spindle and midbody, where it regulates cleavage furrow formation and abscission through phosphorylation of multiple cytokinesis-associated proteins (Lampson and Cheeseman, 2011; Lens and Medema, 2019b). Deficiency or inhibition of AURKB frequently induces cytokinesis failure, multinucleation, tetraploidization, and polyploid cell formation, all of which are commonly observed in highly aggressive cancers (Lens and Medema, 2019b). Increasing evidence suggests that polyploid tumor cells generated through mitotic adaptation may further contribute to tumor plasticity, stress tolerance, and therapeutic resistance (Quinton et al., 2021).

Emerging evidence has identified CIN as a central link between AURKB dysregulation, tumor evolution, and therapeutic adaptation (Sansregret and Swanton, 2017; Bakhoun and Cantley, 2018; Vasudevan et al., 2020; Quinton et al., 2021). CIN refers to persistent whole-chromosome or structural chromosomal alterations during cell division and is increasingly recognized as a major driver of intratumoral heterogeneity, metastatic dissemination, immune evasion, and treatment resistance (Sansregret and Swanton, 2017; Bakhoun and Cantley, 2018). The biological consequences of altered AURKB activity are context dependent. Reduced AURKB activity primarily impairs error correction, SAC signaling, and cytokinesis, whereas excessive or imbalanced AURKB signaling can perturb chromosome-segregation dynamics (Ricke et al., 2011; González-Loyola et al., 2015). Importantly, CIN-driven tumor evolution has recently emerged as a key mechanism underlying adaptive resistance to targeted therapy and immunotherapy in NSCLC (Sansregret and Swanton, 2017; Vasudevan et al., 2020; Quinton et al., 2021).

Recent studies further suggest that AURKB-mediated mitotic adaptation may facilitate the survival of drug-tolerant persister cells under therapeutic stress (Hata et al., 2016; Marine et al., 2020). Increased AURKB signaling can promote mitotic slippage and apoptosis evasion, thereby enabling tumor cells to survive despite extensive chromosomal abnormalities and anticancer treatment (Tanaka et al., 2021a). In EGFR-mutant NSCLC, AURKB inhibition has been shown to restore apoptotic sensitivity and overcome resistance to EGFR-TKIs through activation of BIM- and PUMA-dependent mitochondrial apoptosis pathways (Tanaka et al., 2021b). In addition, AURKB can cooperate with oncogenic signaling pathways, including MYC, KRAS, PI3K/AKT, and MAPK signaling, to enhance tumor proliferation, adaptive survival, and therapeutic resistance (Den Hollander et al., 2010; Goldenson and Crispino, 2015; Skoulidis and Heymach, 2019).

Beyond its canonical mitotic functions, accumulating evidence suggests that dysregulated AURKB may contribute to CIN-associated tumor evolution and treatment adaptation in NSCLC. Although AURKB inhibition can induce mitotic catastrophe and suppress tumor growth, excessive CIN caused by prolonged mitotic disruption may, under certain conditions, paradoxically facilitate tumor adaptation and clonal evolution. Therefore, the therapeutic window and biological consequences of sustained AURKB inhibition require further investigation in NSCLC. Notably, recent evidence suggests that the biological consequences of CIN are highly context dependent. Moderate levels of CIN may enhance tumor adaptability and clonal evolution, whereas excessive CIN may exceed the tolerable threshold for tumor survival and ultimately trigger mitotic catastrophe or immunogenic cell death. This dual role of CIN may partially explain the heterogeneous therapeutic responses observed following AURKB inhibition.

2.3 Clinical and translational significance of AURKB in NSCLC

Increasing evidence supports the clinical relevance of AURKB in NSCLC. Multiple transcriptomic analyses based on TCGA and GEO datasets have shown that AURKB expression is significantly upregulated in both lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (Watkins et al., 2020) compared with normal lung tissues (Hayama et al., 2007; Bertran-Alamillo et al., 2019). Elevated AURKB expression is associated with aggressive clinicopathological features, including advanced TNM stage, high proliferative activity, and poor overall survival (Xia et al., 2015; Gao et al., 2021).

Immunohistochemical studies further indicate that increased AURKB expression positively correlates with the Ki-67 proliferation index and histone H3 phosphorylation, reflecting enhanced mitotic activity in aggressive NSCLC subtypes (Bakhoun and Cantley, 2018). Because AURKB expression increases toward G2/M and mitosis (Kimura et al., 2004), high tumor expression may partly reflect a larger proliferative or mitotic fraction. Moreover, AURKB abundance does not necessarily correspond directly to kinase activity (Britigan et al., 2022). In addition, emerging evidence suggests that CIN-high and KRAS-mutant NSCLC tumors may show increased dependence on mitotic stress-related pathways, highlighting the potential value of AURKB as both a prognostic biomarker and a candidate therapeutic target (Manchado et al., 2016; Bakhoun and Cantley, 2018; Bielski et al., 2018; Quinton et al., 2021).

Notably, recent pan-cancer analyses and single-cell transcriptomic studies further suggest that tumors with elevated mitotic stress and CIN signatures may be more sensitive to mitotic kinase inhibition (Sansregret and Swanton, 2017; Bielski et al., 2018; Quinton et al., 2021). These findings provide a biological rationale for patient stratification based on CIN-associated biomarkers, proliferative signatures, or KRAS-driven mitotic dependency in future AURKB-targeted therapeutic strategies. The biological functions and oncogenic roles of AURKB in NSCLC are summarized in Fig. 1.

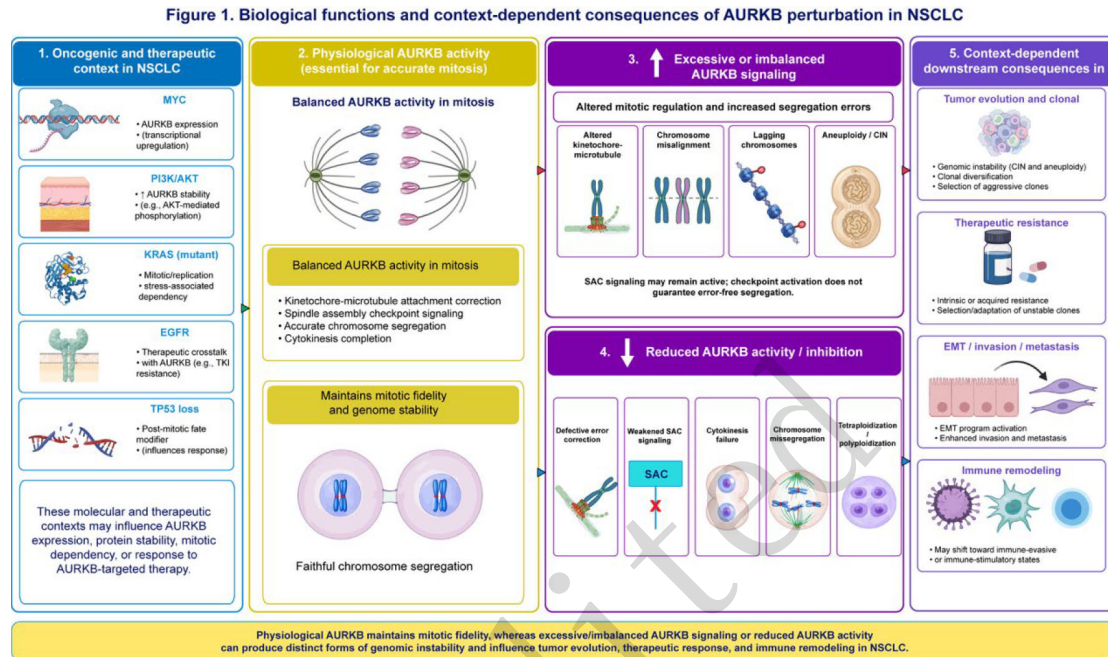


Fig. 1 Biological functions and context-dependent consequences of AURKB perturbation in NSCLC. AURKB, a core catalytic component of the chromosomal passenger complex (CPC), regulates kinetochores-microtubule attachment correction, spindle assembly checkpoint signaling, chromosome segregation, cytokinesis, and histone H3 Ser10 phosphorylation. Physiologically regulated AURKB activity maintains mitotic fidelity, whereas excessive or imbalanced AURKB signaling can promote chromosome misalignment, lagging chromosomes, and aneuploidy/CIN. In contrast, reduced AURKB activity or inhibition can impair error correction, checkpoint signaling, and cytokinesis, resulting in chromosome mis-segregation, multinucleation, and polyploidization. These distinct perturbations may influence tumor evolution, therapeutic response, and immune remodeling in a context-dependent manner.

3 Molecular mechanisms of AURKB in NSCLC

3.1 MYC-AURKB signaling axis

MYC is one of the most frequently dysregulated oncogenic transcription factors in human malignancies and plays a central role in NSCLC proliferation, metabolic reprogramming, tumor plasticity, and therapeutic resistance (Dang, 2012; Dhanasekaran et al., 2022). Recent studies have identified AURKB as an important downstream effector of MYC-driven mitotic programs. MYC can transcriptionally activate AURKB expression by directly binding to E-box motifs within the AURKB promoter region, thereby enhancing mitotic progression, chromosome segregation, and proliferative capacity (Den Hollander et al., 2010). In highly proliferative NSCLC subtypes, aberrant MYC activation is closely associated with increased mitotic stress, CIN, and poor clinical outcomes (Dang, 2012; Sansregret and Swanton, 2017; Quinton et al., 2021).

Importantly, MYC-driven tumors frequently exhibit excessive replication stress, centrosome amplification, and aberrant mitotic progression, which may increase their dependence on mitotic checkpoint regulators such as AURKB for survival. Under sustained oncogenic stress, AURKB inhibition may preferentially induce catastrophic chromosome segregation defects and apoptotic

collapse in MYC-high NSCLC cells, supporting the concept of synthetic lethality between MYC activation and mitotic checkpoint disruption.

MYC-induced replication stress and accelerated cell-cycle progression increase tumor cell dependence on mitotic checkpoint regulators, including AURKB, to preserve mitotic fidelity (Kotsantis et al., 2018). This dependency may create a therapeutic vulnerability in MYC-high tumors, whereas excessive or imbalanced AURKB signaling can itself perturb chromosome segregation (Ricke et al., 2011; González-Loyola et al., 2015). A reciprocal MYC-AURKB feed-forward circuit has been demonstrated in T-cell leukemia but remains to be established in NSCLC (Jiang et al., 2020).

In NSCLC models, pharmacological or genetic inhibition of AURKB induces mitotic catastrophe, polyploidization, and apoptosis in MYC-dependent tumor cells (Yang et al., 2010; Otto and Sicinski, 2017). In addition, MYC-mediated upregulation of AURKB has been implicated in resistance to chemotherapy and targeted therapies through maintenance of proliferative signaling and suppression of apoptosis (Topatana et al., 2020). Collectively, these findings suggest that the MYC-AURKB signaling axis acts as a critical mediator of mitotic adaptation and therapeutic resistance in aggressive NSCLC and may represent a promising therapeutic vulnerability for biomarker-guided treatment strategies.

3.2 Crosstalk between AURKB and PI3K/AKT-MAPK signaling

The PI3K/AKT and MAPK pathways are major oncogenic signaling cascades involved in NSCLC progression. They regulate tumor proliferation, survival, metabolism, invasion, and therapeutic responsiveness (Molina et al., 2008; Ryan and Corcoran, 2018). However, the mechanistic hierarchy between AURKB signaling and PI3K/AKT-MAPK activation remains poorly defined, and current evidence is derived mostly from preclinical experimental systems.

Emerging evidence suggests functional crosstalk between AURKB and the PI3K/AKT pathway during tumor progression. In EGFR-mutant NSCLC models, AURKB inhibition reduces AKT phosphorylation, although AKT has not been established as a direct substrate of AURKB (Tanaka et al., 2021a). Conversely, AKT can directly phosphorylate AURKB at Thr73 and increase its protein stability (Xu et al., 2021).

The MAPK signaling cascade also plays an important role in AURKB-mediated tumor progression. Constitutive activation of KRAS-RAF-MEK-ERK signaling promotes mitotic dysregulation, replication stress, and increased dependence on mitotic checkpoint regulators during rapid tumor growth (Samatar and Poulikakos, 2014; Ryan and Corcoran, 2018). MAPK pathway activation has been associated with increased AURKB expression and CIN-related signaling in NSCLC (Samatar and Poulikakos, 2014).

Importantly, both PI3K/AKT and MAPK pathways are closely linked to EMT, a key biological process underlying tumor invasion and metastasis (Dongre and Weinberg, 2019). Increasing evidence suggests that AURKB overexpression is associated with tumor invasion and metastasis by regulating EMT-associated pathways (Borah and Reddy, 2021).

3.3 p53/FBXW7/MDM2 regulatory network

The p53 signaling pathway serves as a major safeguard against genomic instability and oncogenic stress (Levine, 2020). Functional inactivation of TP53 is among the most common molecular alterations in NSCLC and contributes to defective cell-cycle checkpoints, apoptosis evasion, genomic instability, and therapeutic resistance (Donehower et al., 2019). Increasing evidence indicates that AURKB closely interacts with p53-associated regulatory networks and may promote tumor progression by disrupting mitotic surveillance mechanisms.

AURKB negatively regulates p53 activity through multiple mechanisms. Aberrant activation of AURKB can suppress p53 transcriptional activity and reduce the expression of pro-apoptotic mediators, thereby allowing tumor cells to survive despite extensive mitotic abnormalities (Gully et al., 2012b). Conversely, pharmacological inhibition of AURKB induces mitotic defects, DNA damage accumulation, and activation of p53-dependent apoptotic signaling (Wilkinson et al., 2007).

Loss of p53 function may instead permit continued survival or cell-cycle progression following mitotic and cytokinetic defects induced by AURKB inhibition (Vora et al., 2025).

FBXW7, a tumor-suppressive E3 ubiquitin ligase, is another important regulator of mitotic homeostasis and genomic stability (Yeh et al., 2018). FBXW7 promotes ubiquitin-mediated degradation of multiple oncogenic substrates, including MYC, Cyclin E, and Aurora kinases (Davis et al., 2014; Yeh et al., 2018). Deficiency or downregulation of FBXW7 results in AURKB accumulation and contributes to uncontrolled cell-cycle progression, CIN, and tumor aggressiveness (Wang et al., 2012). Dysregulation of the FBXW7-AURKB axis may therefore facilitate tumor evolution under therapeutic pressure.

MDM2, a major negative regulator of p53 signaling, is frequently overexpressed in NSCLC and contributes to suppression of p53-dependent checkpoint responses (Wade et al., 2013). Mechanistically, AURKB directly phosphorylates p53 at Ser183, Thr211, and Ser215, thereby facilitating MDM2-mediated polyubiquitination and proteasomal degradation of p53 (Gully et al., 2012a). This AURKB-p53-MDM2 cascade provides a direct molecular link between AURKB signaling and p53 suppression (Gully et al., 2012a; Luna-Maldonado et al., 2021). Increasing evidence further indicates that dysregulation of the MDM2-p53 axis contributes to resistance to chemotherapy and targeted therapies by impairing apoptosis induction (Senturk and Manfredi, 2012). Collectively, interactions among AURKB, p53, FBXW7, and MDM2 form an integrated regulatory network that governs mitotic fidelity, apoptosis escape, and therapeutic adaptation in NSCLC.

3.4 AURKB-mediated EMT, metastasis, and metabolic adaptation

Metastatic dissemination remains the primary cause of cancer-related mortality in patients with NSCLC (Steeg, 2016). Increasing evidence indicates that AURKB contributes to metastatic progression by regulating EMT, tumor invasion, migration, and adaptive cellular plasticity (Dongre and Weinberg, 2019; Pastushenko and Blanpain, 2019). EMT is characterized by loss of epithelial polarity and acquisition of mesenchymal traits, enabling tumor cells to acquire enhanced motility and invasive capacity (Dongre and Weinberg, 2019).

AURKB overexpression has been associated with reduced E-cadherin expression and increased levels of mesenchymal markers, such as N-cadherin and vimentin, thereby promoting invasive and metastatic phenotypes (Thiery and Lim, 2013; Borah and Reddy, 2021). Conversely, AURKB inhibition has been shown to suppress migratory and invasive behaviors in NSCLC cells and to modulate EMT-associated molecular markers, including partial restoration of epithelial characteristics and attenuation of mesenchymal features (Al-Khafaji et al., 2017). Mechanistically, AURKB-mediated EMT appears to involve multiple downstream pathways, including PI3K/AKT, MAPK, and NF- κ B signaling (Tang et al., 2017; Borah and Reddy, 2021).

Recent studies have further highlighted potential interactions between AURKB signaling and metabolic reprogramming during NSCLC progression. Phosphoserine aminotransferase 1 (PSAT1), a key enzyme involved in serine biosynthesis, has emerged as an important regulator of tumor proliferation, metabolic adaptation, and EMT (Possemato et al., 2011). Recent evidence suggests that PSAT1-mediated metabolic reprogramming may interact with AURKB-associated mitotic adaptation pathways under metabolic stress conditions (Yang et al., 2015). In addition, AURKB-driven CIN may accelerate metastatic evolution by increasing intratumoral heterogeneity and promoting the selection of aggressive tumor subclones (Sansregret and Swanton, 2017; Bakhoun and Cantley, 2018; Vasudevan et al., 2020; Quinton et al., 2021).

4 AURKB and therapeutic resistance in NSCLC

Therapeutic resistance remains a major barrier to durable clinical benefit in patients with NSCLC (Cooper et al., 2022; Passaro et al., 2022). Although substantial advances in chemotherapy, molecularly targeted therapy, and immune checkpoint blockade have significantly improved

survival outcomes in selected patient populations, most patients eventually experience disease progression due to intrinsic or acquired resistance (Holohan et al., 2013; Herbst et al., 2018; Passaro et al., 2022). Increasing evidence suggests that dysregulation of mitotic regulators, particularly AURKB, plays a critical role in therapeutic adaptation by modulating apoptosis, CIN, mitotic plasticity, and pro-survival signaling pathways (Martinez-Martí and Felip, 2011; Vasudevan et al., 2020; Quinton et al., 2021). In NSCLC, elevated AURKB expression has been closely associated with resistance to chemotherapy and EGFR-targeted therapy, highlighting AURKB as a potential therapeutic vulnerability in treatment-resistant tumors (Sharma et al., 2010; Martinez-Martí and Felip, 2011).

4.1 AURKB and chemotherapy resistance

Platinum-based chemotherapy and microtubule-targeting agents remain important therapeutic options for advanced NSCLC, particularly for patients without actionable driver mutations (Hanna et al., 2020). However, resistance to cytotoxic agents such as cisplatin and paclitaxel frequently limits long-term treatment efficacy and contributes to tumor recurrence and poor prognosis (Galluzzi et al., 2012; O'Grady et al., 2014). Recent studies indicate that AURKB contributes substantially to chemotherapy resistance by regulating mitotic progression, apoptosis escape, and adaptive genomic instability.

Paclitaxel exerts its antitumor effects mainly by stabilizing microtubules and inducing prolonged mitotic arrest (Weaver, 2014). Because AURKB is a central regulator of spindle checkpoint signaling and chromosome segregation, elevated AURKB activity may influence tumor responses to paclitaxel-induced mitotic stress (Lens and Medema, 2019b). Mitotic slippage during prolonged mitotic arrest can permit the survival of polyploid tumor cells, thereby reducing paclitaxel sensitivity and enabling the emergence of drug-tolerant cellular states (Brito and Rieder, 2006). Several preclinical studies have shown that pharmacological inhibition of AURKB enhances paclitaxel-induced apoptosis and suppresses tumor proliferation, supporting the rationale for combining mitotic kinase inhibition with microtubule-targeting agents (Walsby et al., 2008).

Cisplatin induces DNA damage mainly through the formation of DNA adducts and activation of apoptotic signaling pathways (Galluzzi et al., 2014). However, tumor cells can acquire resistance through enhanced DNA repair capacity, suppression of apoptosis, activation of survival signaling, and adaptive cell-cycle reprogramming (Galluzzi et al., 2012; Amable, 2016). Emerging evidence suggests that AURKB overexpression may contribute to cisplatin resistance by impairing DNA damage-induced apoptotic responses and promoting tolerance to mitotic and genomic stress in NSCLC cells (Yu et al., 2018; Liu et al., 2023).

Importantly, chemotherapy-induced CIN may further select for tumor subclones with enhanced mitotic tolerance and adaptive survival capacity (Sansregret and Swanton, 2017; Bakhoun and Cantley, 2018; Vasudevan et al., 2020; Quinton et al., 2021). Because AURKB functions as a key regulator of mitotic fidelity and chromosome segregation, the contribution of AURKB signaling to tumor evolution under chemotherapeutic pressure is likely to be context dependent (Vasudevan et al., 2020; Quinton et al., 2021). Collectively, these findings provide a strong biological rationale for integrating AURKB inhibitors into combination chemotherapy strategies for NSCLC.

4.2 AURKB and EGFR-TKI resistance

The introduction of EGFR-TKIs has profoundly transformed the treatment landscape of EGFR-mutant NSCLC (Mok et al., 2017; Passaro et al., 2022). Third-generation EGFR-TKIs, such as osimertinib, have become standard first-line therapies because of their potent activity against both sensitizing EGFR mutations and the EGFR T790M resistance mutation (Ramalingam et al., 2020). Nevertheless, acquired resistance to EGFR-targeted therapy remains inevitable in most patients and continues to represent a major clinical challenge (Leonetti et al., 2019).

Recent studies have identified AURKB as an important mediator of resistance to EGFR-targeted therapy (Sharma et al., 2010). Notably, Tanaka et al. demonstrated that AURKB activation directly contributes to resistance to anti-EGFR therapy by suppressing apoptotic signaling pathways

in lung cancer cells (Sharma et al., 2010). Mechanistically, AURKB inhibition significantly enhanced the antitumor efficacy of EGFR inhibitors and restored apoptotic responses in resistant NSCLC models (Sharma et al., 2010).

Osimertinib-resistant NSCLC cells frequently maintain persistent survival signaling despite an effective EGFR blockade (Wu and Shih, 2018; Leonetti et al., 2019). AURKB-mediated suppression of apoptosis may therefore enable tumor cells to survive EGFR-targeted therapeutic stress and facilitate the emergence of resistant tumor clones (Ben-David and Amon, 2020). Beyond apoptosis suppression, increasing evidence suggests that AURKB may contribute to the establishment and maintenance of drug-tolerant persister (DTP) states during EGFR-targeted therapy. Increased AURKB signaling may contribute to the survival of a subset of tumor cells during sustained EGFR inhibition, although a direct role in CIN tolerance remains to be established. In addition, excessive or imbalanced AURKB signaling may promote chromosome-segregation errors, mitotic adaptation, and cellular plasticity, thereby increasing intratumoral heterogeneity and accelerating the acquisition of resistance-associated molecular alterations (Sansregret and Swanton, 2017; Bakhoun and Cantley, 2018; Vasudevan et al., 2020; Quinton et al., 2021).

Recent evidence suggests that co-targeting EGFR and mitotic kinases may represent a promising strategy for overcoming adaptive resistance (Shah et al., 2019). Combined inhibition of EGFR and AURKB has been shown to synergistically enhance apoptosis induction and suppress tumor proliferation in resistant NSCLC models (Sharma et al., 2010; Passaro et al., 2021). Moreover, CIN-driven evolutionary adaptation may represent a previously underappreciated mechanism contributing to osimertinib resistance, further supporting the therapeutic rationale for targeting mitotic regulators in EGFR-mutant NSCLC (Vasudevan et al., 2020; Quinton et al., 2021). Given the growing clinical significance of osimertinib resistance, further investigation into the mechanistic interplay between AURKB signaling and EGFR-targeted therapy is warranted.

4.3 Potential mechanisms underlying AURKB-associated resistance

The molecular mechanisms underlying AURKB-associated therapeutic resistance are highly complex and involve multiple interconnected signaling pathways and adaptive cellular processes (Camidge et al., 2014). One major mechanism is the activation of bypass survival pathways that sustain tumor cell viability despite therapeutic inhibition (Hoxhaj and Manning, 2020). Reactivation of PI3K/AKT signaling is frequently observed in resistant NSCLC and may cooperate with AURKB-mediated mitotic adaptation to suppress apoptosis and maintain proliferative signaling under therapeutic stress (Fruman et al., 2017; Vats et al., 2025).

Mitotic adaptation represents another critical mechanism contributing to resistance development. Tumor cells exposed to prolonged mitotic stress may undergo mitotic slippage, evade apoptosis, and survive as polyploid or aneuploid cells (Vitale et al., 2011). These surviving cells can subsequently acquire additional genomic alterations that promote therapeutic resistance, aggressive tumor behavior, and metastatic progression (Vitale et al., 2011). AURKB-dependent mitotic control may influence cellular responses to mitotic stress during treatment (Dominguez-Brauer et al., 2015).

Emerging evidence also highlights the role of CIN in adaptive resistance. Persistent CIN may accelerate clonal evolution and intratumoral heterogeneity, thereby facilitating the selection of resistant tumor subpopulations (Sansregret and Swanton, 2017; Bakhoun and Cantley, 2018; Vasudevan et al., 2020; Quinton et al., 2021). Increased CIN has been associated with poor prognosis and reduced responsiveness to chemotherapy, targeted therapy, and immunotherapy in NSCLC (Sansregret and Swanton, 2017; Vasudevan et al., 2020; Quinton et al., 2021). Furthermore, recent studies suggest that CIN-driven micronucleus formation and inflammatory signaling may contribute to immune evasion and tumor adaptation under therapeutic pressure (Bakhoun and Cantley, 2018).

Another potentially important mechanism involves the survival of DTP cells. DTP cells can transiently survive targeted therapy through reversible adaptive programs and subsequently acquire stable resistance-associated alterations (Marine et al., 2020). Mitotic stress response pathways and CIN-associated signaling have increasingly been implicated in the maintenance of persister cell

states (Hangauer et al., 2017; Marine et al., 2020). Whether AURKB directly contributes to the survival and evolutionary fitness of DTP populations during therapy remains to be established.

Recent studies indicate that CIN can affect tumor immunity in both immunostimulatory and immunosuppressive directions, depending on its magnitude, duration, and cellular context (Bakhoun and Cantley, 2018; Wang et al., 2021; Beernaert and Parkes, 2023b). Chromosome mis-segregation and micronucleus formation can expose DNA to the cytosol and activate cGAS-STING-dependent innate immune signaling (Bakhoun and Cantley, 2018; Ignatiadis et al., 2021b; Beernaert and Parkes, 2023b).

However, persistent CIN can also favor tumor-promoting inflammatory signaling and immune-evasive states through chronic cytosolic-DNA signaling (Bakhoun and Cantley, 2018; Ignatiadis et al., 2021b; Beernaert and Parkes, 2023b). Thus, the immune consequences of CIN are context dependent rather than uniformly stimulatory or suppressive.

Polyploidy and ongoing CIN should also be distinguished. Newly generated hyperploid cells may be more immunogenic in some settings (Senovilla et al., 2012), whereas chronically adapted polyploid or CIN-high tumor populations can persist and acquire immune-evasive phenotypes (Was et al., 2022; Li et al., 2023). Accordingly, whether AURKB inhibition can improve responses to immune checkpoint blockade in NSCLC remains to be established.

Collectively, current evidence indicates that AURKB contributes to therapeutic resistance through coordinated regulation of apoptosis suppression, bypass of survival signaling, mitotic adaptation, CIN, and tumor evolutionary plasticity. These findings provide a strong mechanistic rationale for developing combination therapeutic strategies incorporating AURKB inhibition in resistant NSCLC. However, although multiple resistance-associated mechanisms have been linked to AURKB dysregulation, it remains unclear which adaptive processes predominate clinically during treatment evolution in patients with NSCLC.

5 AURKB-targeted therapeutic strategies in NSCLC

Despite encouraging preclinical activity, most Aurora kinase inhibitors have shown relatively modest efficacy in solid tumors during clinical evaluation. This discrepancy highlights the biological complexity of mitotic dependency and suggests that biomarker-unselected patient populations may dilute potential therapeutic benefits. Given the central role of AURKB in mitotic regulation, CIN, tumor evolutionary adaptation, and therapeutic resistance, pharmacological inhibition of AURKB has emerged as a promising therapeutic strategy in NSCLC and other solid malignancies (Borisa and Bhatt, 2017; Gupta et al., 2024; Teli et al., 2025). Over the past two decades, extensive efforts have been devoted to the development of Aurora kinase inhibitors (AURKis), including both pan-Aurora kinase inhibitors and selective AURKB-targeted agents (Borisa and Bhatt, 2017; Gupta et al., 2024; Teli et al., 2025). Although the clinical efficacy of AURKis as monotherapy in solid tumors has generally been limited by hematologic toxicity and adaptive resistance, increasing evidence suggests that rational combination strategies may substantially enhance therapeutic efficacy in NSCLC (Lens et al., 2010; Bavetsias and Linardopoulos, 2015; Teli et al., 2025). In particular, co-targeting AURKB with EGFR signaling, chemotherapy-induced mitotic stress, DDR pathways, or immune-associated mechanisms has emerged as an important direction for translational investigation (Lens et al., 2010; Bavetsias and Linardopoulos, 2015; Turajlic and Swanton, 2016; Teli et al., 2025).

5.1 Pan-AURKis

Pan-AURKis simultaneously target multiple Aurora kinase family members, predominantly AURKA and AURKB, thereby inducing mitotic arrest, chromosome mis-segregation, cytokinesis failure, and mitotic catastrophe in tumor cells (Carpinelli et al., 2007; Lens et al., 2010). Several pan-Aurora inhibitors have shown preclinical antitumor activity in NSCLC models, particularly in tumors characterized by high proliferative activity, CIN, and therapeutic resistance (Carpinelli et al.,

2007; Lens et al., 2010; Bavetsias and Linardopoulos, 2015; Teli et al., 2025). Representative pan-AURKis are summarized in Table 1.

5.1.1 Danusertib (PHA-739358)

Danusertib (PHA-739358) is a pan-Aurora kinase inhibitor that targets AURKA, AURKB, and AURKC, with additional inhibitory activity against several oncogenic tyrosine kinases, including BCR-ABL, RET, TrkA, and FGFR1 (Carpinelli et al., 2007; Gontarewicz et al., 2008). Preclinical studies have shown that danusertib disrupts mitotic progression, leading to G2/M arrest, polyploidization, and apoptosis in cancer cells (Carpinelli et al., 2007).

5.1.2 AMG900

AMG900 is an orally bioavailable pan-Aurora kinase inhibitor with potent inhibitory activity against AURKA, AURKB, and AURKC (Payton et al., 2010). Preclinical studies have demonstrated that AMG900 induces mitotic arrest, polyploidization, and apoptotic cell death across multiple solid tumor models (Payton et al., 2010). Importantly, AMG900 has shown activity in taxane-resistant tumor cells, indicating its potential utility in overcoming resistance to microtubule-targeting agents (Payton et al., 2010; Falchook et al., 2015). Emerging evidence further suggests that AMG900 may suppress CIN-associated adaptive survival pathways and enhance the cytotoxic effects of conventional chemotherapy (Falchook et al., 2015; Teli et al., 2025). These findings support further investigation of AMG900-based combination strategies in resistant NSCLC.

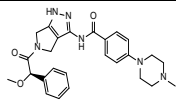
5.1.3 VX-680 (Tozasertib)

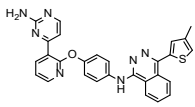
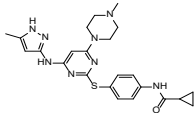
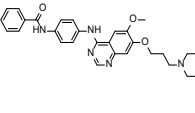
VX-680, also known as tozasertib, was among the earliest Aurora kinase inhibitors evaluated in clinical oncology and provided critical proof-of-concept evidence supporting mitotic kinase inhibition as an anticancer strategy (Harrington et al., 2004; Keen and Taylor, 2004). VX-680 inhibits Aurora kinases and several other kinases, including FLT3 and ABL (Harrington et al., 2004). In NSCLC models, VX-680 induces mitotic catastrophe, cytokinesis failure, and apoptotic cell death, particularly in p53-deficient tumor cells with defective postmitotic checkpoint control (Gizatullin et al., 2006). Nevertheless, concerns regarding cardiotoxicity and QT interval prolongation substantially limited its subsequent clinical development (Traynor et al., 2011). Despite these limitations, VX-680 established an important mechanistic foundation for the development of more selective and better-tolerated AURKis.

5.1.4 ZM447439

ZM447439 is a selective ATP-competitive Aurora kinase inhibitor that has been widely used in mechanistic studies of AURKB biology (Ditchfield et al., 2003; Girdler et al., 2006). Pharmacological inhibition of AURKB by ZM447439 disrupts chromosome alignment, spindle assembly checkpoint signaling and cytokinesis, ultimately leading to polyploidization and apoptosis (Ditchfield et al., 2003; Girdler et al., 2006). Preclinical studies have shown that ZM447439 disrupts mitotic progression and may enhance apoptotic responses following chemotherapeutic stress (Scharow et al., 2015). Although its clinical application has been limited by suboptimal pharmacokinetic properties, ZM447439 remains an important experimental tool for investigating mitotic dysregulation and CIN-associated therapeutic vulnerabilities.

Table 1 Representative pan-AURKis targeting AURKB in NSCLC

Inhibitor	Molecular formula	Primary targets	Mechanism of action	References
Danusertib (PHA-739358)		AURKA/B/C, BCR-ABL, RET	Block chromosome correction, interfere with cell division, and induce apoptosis and autophagy	Carpinelli et al., 2007; Gontarewicz et al., 2008;

Inhibitor	Molecular formula	Primary targets	Mechanism of action	References
AMG900		AURKA/B/C	The AURKA/B autophosphorylation and downstream histone H3 phosphorylation were inhibited to block cell division	Steeghs et al., 2009 Payton et al., 2010; Falchook et al., 2015; Teli et al., 2025
VX-680 (Tozasertib)		AURKA/B/C, FLT3, ABL	Targeting AURKA and AURKB, combined with Haspin inhibitors showed synergistic anticancer effects	Harrington et al., 2004; Keen and Taylor, 2004; Gizatullin et al., 2006; Traynor et al., 2011
ZM447439		Predominantly AURKB	By competing for ATP sites, reduced substrate phosphorylation leads to abnormal cell division and apoptosis	Ditchfield et al., 2003; Girdler et al., 2006; Scharow et al., 2015

AURKA/B/C: Aurora kinase A/B/C; BCR-ABL: breakpoint cluster region-Abelson fusion protein; FLT3: Fms-like tyrosine kinase 3; RET: rearranged during transfection; TrkA: tropomyosin receptor kinase A; FGFR1: fibroblast growth factor receptor 1; ATP: adenosine triphosphate.

5.2 Selective AURKB inhibitors

Compared with pan-Aurora kinase inhibitors, selective AURKB inhibitors may offer improved therapeutic specificity and reduce off-target inhibition of AURKA-associated pathways (Bavetsias and Linardopoulos, 2015). Selective inhibition of AURKB is particularly attractive in NSCLC because AURKB appears to be the principal Aurora kinase involved in chromosome segregation, cytokinesis, and CIN-associated tumor adaptation (Carmena and Earnshaw, 2003; Bavetsias and Linardopoulos, 2015). Several selective AURKB inhibitors have shown encouraging preclinical and early translational activity. Representative selective AURKB inhibitors are summarized in Table 2.

5.2.1 Barasertib (AZD1152)

Barasertib, also known as AZD1152, is one of the best-characterized selective AURKB inhibitors and has shown potent antitumor activity in both hematological malignancies and solid tumors (Mortlock et al., 2007; Wilkinson et al., 2007). After intracellular conversion to its active metabolite AZD1152-HQPA, Barasertib selectively suppresses AURKB kinase activity, resulting in defective chromosome segregation, multinucleation, polyploidization, and apoptosis (Mortlock et al., 2007; Wilkinson et al., 2007). In preclinical solid tumor models, Barasertib inhibits tumor proliferation and enhances sensitivity to chemotherapeutic agents, supporting its potential utility in combination treatment strategies (Azzariti et al., 2011). Moreover, AURKB inhibition by Barasertib appears to preferentially affect highly proliferative, CIN-high tumor cells, supporting the concept of mitotic stress-directed precision therapy (Teli et al., 2025).

5.2.2 AZD2811

AZD2811, the active moiety of Barasertib, was subsequently developed as a nanoparticle formulation to optimize pharmacokinetic properties and reduce systemic toxicity (Ashton et al., 2016). Sustained release of nanoparticle-encapsulated AZD2811 enables prolonged AURKB inhibition and extended systemic exposure while reducing peak drug concentrations associated with hematologic toxicity (Ashton et al., 2016; Opzoomer et al., 2021). Preclinical studies have shown that AZD2811 induces sustained mitotic abnormalities, polyploidy, apoptosis, and significant tumor

growth inhibition in xenograft models (Floc'h et al., 2017; Opzoomer et al., 2021). Compared with earlier Aurora kinase inhibitors, AZD2811 exhibits improved tolerability and a more favorable therapeutic window (Floc'h et al., 2017). These findings suggest that nanoparticle-based delivery systems may substantially improve the translational feasibility of AURKB-targeted therapies in solid tumors.

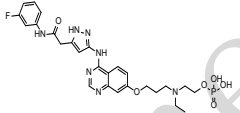
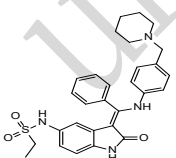
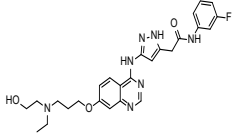
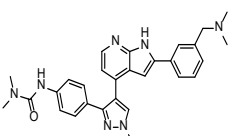
5.2.3 GSK1070916

GSK1070916 is a potent and highly selective inhibitor of AURKB and AURKC, characterized by prolonged target residence time (Hardwicke et al., 2009). Pharmacological inhibition of AURKB by GSK1070916 induces cytokinesis failure, polyploidization, and apoptosis across multiple cancer models (Yang et al., 2007; Hardwicke et al., 2009). Importantly, GSK1070916 has shown activity in tumor cells resistant to taxanes and other antimitotic therapies, suggesting potential therapeutic value in chemotherapy-resistant NSCLC (Falchook et al., 2015). Although clinical data in lung cancer remain limited, its potent suppression of mitotic adaptation and polyploid cell survival pathways makes GSK1070916 an attractive candidate for future translational studies.

5.2.4 Hesperadin

Hesperadin is an early-generation AURKB-selective inhibitor that promotes mitotic defects and apoptosis by interfering with AURKB-dependent substrate phosphorylation, including phosphorylation of histone H3. As an indolinone derivative, Hesperadin acts as a potent ATP-competitive inhibitor. Cell-free assays have reported an IC₅₀ of 250 nmol/L, whereas autoradiographic detection suggests substantially greater potency, with an IC₅₀ of about 3 nmol/L (Lens and Medema, 2019b). In A549 cells, Hesperadin induces apoptosis through the intrinsic mitochondrial pathway, characterized by downregulation of Bcl-2 and Bcl-xL and upregulation of pro-apoptotic factors, including Bax, Bid, tBid, caspase-9, caspase-3, and PARP (Walsby et al., 2008).

Table 2 Representative selective AURKB inhibitors targeting AURKB in NSCLC

Inhibitor	Molecular formula	Primary target	Mechanism of action	References
Barasertib (AZD1152)		AURKB	AURKB was inhibited to affect cell division and apoptosis	Mortlock et al., 2007; Wilkinson et al., 2007; Azzariti et al., 2011; Löwenberg et al., 2011; Teli et al., 2025
Hesperadin		AURKB	Interference with AURKB phosphorylation of substrates induces mitotic abnormalities and apoptosis	Walsby et al., 2008; Lens and Medema, 2019b
AZD2811		AURKB	Induction of polyploidy and apoptosis	Harrington et al., 2004; Keen and Taylor, 2004; Gizatullin et al., 2006; Traynor et al., 2011
GSK1070916		AURKB	Binding to the kinase ATP binding site blocks the kinase activity of Aurora B	Yang et al., 2007; Hardwicke et al., 2009; Falchook et al., 2015

AURKB: Aurora kinase B; AURKC: Aurora kinase C; ATP: adenosine triphosphate; IC₅₀: half-maximal inhibitory concentration; PAR: poly(ADP-ribose) polymerase; Bcl-2: B-cell lymphoma 2; Bcl-xL: B-cell lymphoma-extra large; Bax: Bcl-2-associated X protein; Bid: BH3-interacting domain death agonist; tBid: truncated Bid.

Overall, selective AURKB inhibitors may offer several theoretical advantages over pan-Aurora kinase inhibitors by reducing off-target effects while preserving antitumor activity associated with mitotic disruption (Bavetsias and Linardopoulos, 2015). However, major challenges remain, including hematologic toxicity, insufficient tumor selectivity, compensatory activation of survival pathways, and adaptive resistance driven by CIN-associated tumor evolution (Teli et al., 2025). Future development of AURKB-targeted therapies will likely require biomarker-guided patient selection and rational combination strategies integrating EGFR inhibition, chemotherapy, DDR-targeted therapy, or immunotherapy to maximize therapeutic efficacy in NSCLC. Current therapeutic strategies targeting AURKB in NSCLC are summarized in Fig. 2.

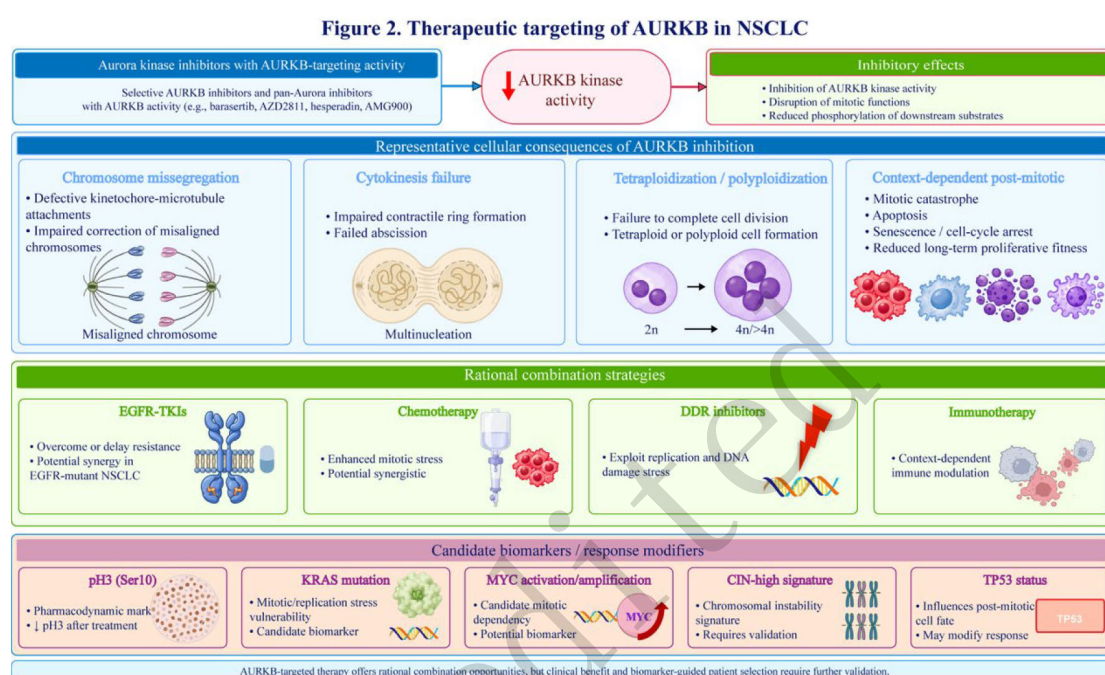


Fig. 2 Therapeutic targeting of AURKB in NSCLC. Pharmacological inhibition of AURKB kinase activity disrupts chromosome segregation and cytokinesis and can lead to chromosome mis-segregation, multinucleation, tetraploidization/polyploidization, and context-dependent post-mitotic cell fates. Rational combination strategies include EGFR-TKIs, chemotherapy, DDR inhibitors, and immunotherapy, although the latter requires further preclinical and clinical validation. Candidate biomarkers or response modifiers include pH3, KRAS mutation, MYC activation/amplification, CIN-associated signatures, and TP53 status.

6 Clinical challenges and translational barriers

Despite encouraging preclinical activity, the clinical efficacy of AURKis in solid tumors, including NSCLC, has generally remained modest. Several early-phase clinical trials have reported limited objective response rates and relatively short durations of disease control, particularly in biomarker-unselected patient populations. One major obstacle is the narrow therapeutic window associated with Aurora kinase inhibition, as dose-limiting hematologic toxicities, including neutropenia and thrombocytopenia, frequently restrict treatment intensity and long-term administration.

Emerging evidence suggests that not all highly proliferative tumors exhibit sustained dependence on AURKB signaling, and the degree of mitotic vulnerability may vary substantially according to the CIN burden, TP53 status, replication stress, and co-occurring oncogenic alterations. This biological heterogeneity may partly explain the inconsistent clinical responses observed across different tumor subtypes and treatment settings.

Another important challenge is the adaptive plasticity of tumor cells following mitotic stress. Transient mitotic suppression may be insufficient to eradicate highly adaptable tumor populations capable of undergoing mitotic slippage, polyploidization, or non-genetic drug-tolerant reprogramming. In certain contexts, intermediate levels of CIN may even promote clonal diversification and therapeutic adaptation rather than catastrophic cell death. Collectively, these observations highlight the substantial translational gap between preclinical mitotic vulnerability and durable clinical benefit in NSCLC. They also underscore the need for biomarker-guided therapeutic strategies and more precise approaches to exploiting mitotic vulnerabilities in NSCLC.

7 Challenges and future perspectives

Despite growing evidence supporting AURKB as a therapeutically actionable mitotic regulator in NSCLC, several major obstacles continue to hinder the successful clinical translation of AURKB-targeted therapies. Current AURKis have shown encouraging antitumor activity in preclinical studies and early-phase clinical trials but their efficacy in solid tumors remains limited, and treatment-associated toxicities frequently restrict dose intensity and long-term administration (Chhouri et al., 2023; Gupta et al., 2024). In addition, the substantial molecular heterogeneity of NSCLC, together with the dynamic evolution of resistance-associated signaling networks, further complicates therapeutic optimization and patient selection (Galluzzi et al., 2012; Passaro et al., 2022). Consequently, future progress in this field will likely depend on improving target selectivity, refining biomarker-guided therapeutic strategies, and developing rational combination regimens capable of overcoming adaptive resistance.

Several important unresolved questions remain regarding AURKB-targeted therapy in NSCLC. First, it is unclear whether AURKB represents a true oncogenic dependency or reflects mainly highly proliferative tumor states. Second, the threshold at which CIN shifts from a tumor-promoting process to a tumor-suppressive stressor remains poorly defined. Third, whether prolonged AURKB inhibition may paradoxically accelerate adaptive tumor evolution under therapeutic pressure requires further investigation. Another major challenge is the identification of robust biomarkers capable of accurately predicting mitotic vulnerability in clinical settings. Although phosphorylated histone H3 expression, MYC amplification, KRAS/TP53 co-mutation, and CIN-associated signatures have shown potential translational relevance, their predictive value remains insufficiently validated in prospective clinical studies. Future translational efforts will therefore require the integration of biomarker-guided patient selection, dynamic pharmacodynamic monitoring, and rational combination strategies targeting both mitotic adaptation and tumor evolutionary plasticity.

7.1 Toxicity and selectivity challenges

One of the main limitations of currently available AURKis is insufficient target selectivity (Bavetsias and Linardopoulos, 2015; Gupta et al., 2024). Many first-generation AURKis simultaneously inhibit AURKA, AURKB, and multiple off-target kinases, thereby increasing systemic toxicity and narrowing the therapeutic window (Bavetsias and Linardopoulos, 2015; Borisa and Bhatt, 2017). Because Aurora kinases are essential for normal mitotic progression, their inhibition inevitably affects rapidly proliferating normal tissues, particularly hematopoietic progenitor cells (Hosoya and Ozasa, 2024). Consequently, hematologic toxicities, including neutropenia, thrombocytopenia, and anemia, remain the most reported dose-limiting adverse events in clinical studies of AURKis (Löwenberg et al., 2011). Gastrointestinal toxicity, mucositis, and fatigue have also been observed in patients receiving prolonged treatment (Chhouri et al., 2023).

Another important challenge is achieving an appropriate balance between sufficient mitotic suppression and preservation of normal tissue homeostasis (Duan and Maki, 2024). Excessive inhibition of AURKB activity may induce severe mitotic defects and cytotoxicity in normal proliferating cells, whereas incomplete inhibition may be insufficient to suppress tumor growth effectively (Teli et al., 2025). Moreover, prolonged exposure to AURKis may paradoxically

facilitate mitotic slippage and the survival of polyploid tumor cells, potentially contributing to adaptive resistance and tumor recurrence (Vitale et al., 2011). These findings suggest that optimized treatment schedules, intermittent dosing strategies, and pharmacodynamic monitoring may be necessary to maximize antitumor efficacy while minimizing systemic toxicity.

Recent advances in nanoparticle-based drug delivery systems and tumor-targeted formulations may partly overcome these limitations (Ashton et al., 2016). For example, the nanoparticle formulation AZD2811 has shown improved pharmacokinetic properties and reduced systemic exposure-related toxicity compared with conventional barasertib formulations (Chhouri et al., 2023). In addition, the development of highly selective AURKB inhibitors may reduce off-target inhibition of AURKA-associated pathways while preserving antitumor activity mediated by mitotic disruption (Gupta et al., 2024). Nevertheless, further translational and clinical studies are required to determine whether improved selectivity can meaningfully enhance therapeutic tolerability and clinical efficacy in NSCLC. Another unresolved issue is whether prolonged AURKB inhibition may paradoxically facilitate tumor adaptation in certain biological contexts. Although excessive CIN can induce mitotic catastrophe and tumor cell death, intermediate levels of CIN may instead enhance clonal diversity and adaptive fitness. This context-dependent effect may partly explain the heterogeneous therapeutic responses observed following Aurora kinase inhibition. The paradoxical role of CIN in tumor evolution and therapeutic response is summarized in Fig. 3.

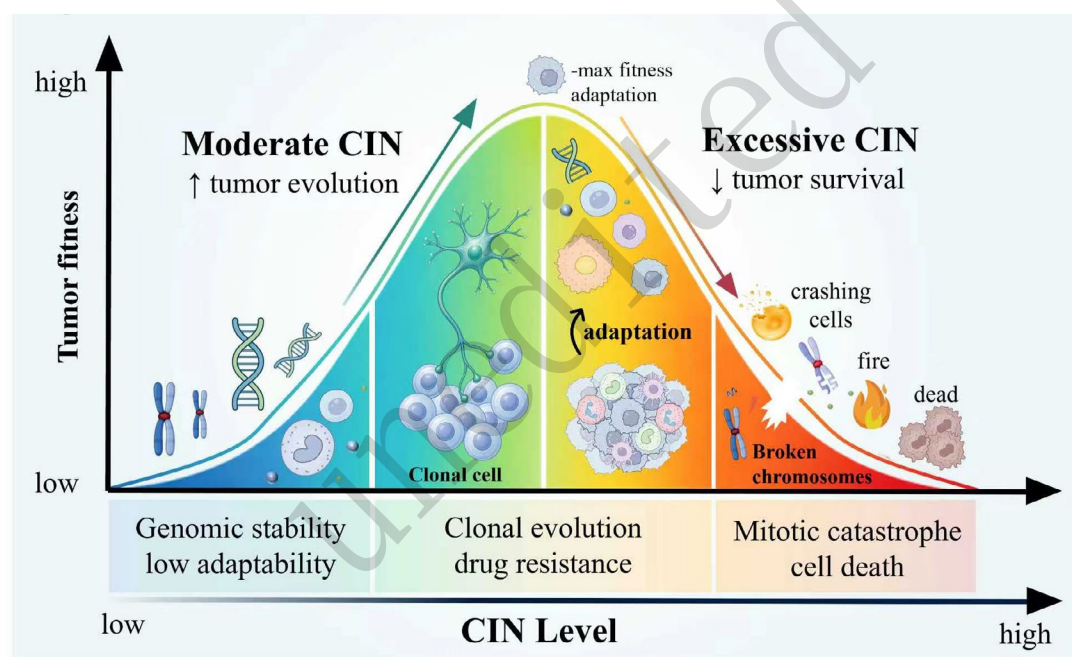


Fig. 3 The paradoxical role of CIN in NSCLC evolution and therapy response. Moderate levels of CIN may promote clonal diversity, tumor adaptability, and therapeutic resistance by facilitating genomic evolution and the selection of resistant subclones. In contrast, excessive CIN induced by severe mitotic disruption or AURKB inhibition may exceed the tolerable threshold for tumor cell survival, thereby triggering mitotic catastrophe, apoptosis, or immunogenic cell death. This context-dependent dual role of CIN may partially explain the heterogeneous therapeutic responses observed following AURKB-targeted treatment in NSCLC.

7.2 Biomarker-guided therapy

The identification of predictive biomarkers represents a critical step toward the precision-based application of AURKB-targeted therapies in NSCLC. Given the substantial biological heterogeneity of NSCLC, not all tumors are equally dependent on mitotic checkpoint signaling or chromosomal maintenance pathways (Skoulidis and Heymach, 2019; Drosten and Barbacid, 2020). Biomarker-guided patient stratification may therefore help identify molecular subgroups that are most likely to benefit from AURKB inhibition.

Phosphorylated histone H3 (pH3), a downstream substrate directly regulated by AURKB, has emerged as a potential pharmacodynamic biomarker reflecting mitotic activity and target engagement (Crosio et al., 2002). Elevated pH3 expression has been associated with increased proliferative capacity and aggressive clinicopathological behavior in several malignancies, including NSCLC (Hayama et al., 2007). In clinical studies evaluating AURKis, suppression of pH3 levels has frequently been used as an indicator of effective AURKB inhibition (Wilkinson et al., 2007; Bavetsias and Linardopoulos, 2015). Therefore, dynamic monitoring of pH3 may provide a useful approach for assessing target inhibition, evaluating treatment response, and optimizing therapeutic dosing in future clinical trials.

AURKB overexpression itself may also serve as a clinically relevant biomarker (Teli et al., 2025). Elevated AURKB expression has been associated with poor prognosis, increased CIN, increased proliferative activity, and resistance to chemotherapy and EGFR-targeted therapy in NSCLC (Hoxhaj and Manning, 2020; Ramalingam et al., 2020). Tumors with high AURKB expression may exhibit increased dependence on mitotic checkpoint regulation and chromosomal maintenance mechanisms, thereby rendering them more susceptible to mitotic kinase inhibition (Yang et al., 2010; Dhanasekaran et al., 2022).

In addition, KRAS-mutant NSCLC may represent a particularly promising molecular subtype for AURKB-targeted therapy (Awad et al., 2021). KRAS-driven tumors frequently display increased mitotic stress, replication stress, and CIN, all of which may increase dependence on AURKB-mediated mitotic control (Ben-David and Amon, 2020). Importantly, co-occurring TP53 or STK11 alterations, which are commonly observed in KRAS-mutant NSCLC, may further exacerbate genomic instability and increase vulnerability to mitotic checkpoint disruption (Pastushenko and Blanpain, 2019). These observations support the rationale for integrating AURKB-targeted therapies into biomarker-guided precision oncology strategies for molecularly defined NSCLC subgroups. In our view, the future clinical value of AURKB-targeted therapy may depend less on absolute AURKB expression alone and more on the broader mitotic stress landscape of individual tumors, including CIN burden, replication stress, and checkpoint dysfunction. Potential biomarker-guided therapeutic strategies targeting AURKB in NSCLC are summarized in Table 3.

Table 3 Potential biomarker-guided therapeutic strategies targeting AURKB in NSCLC

Biomarker	Biological significance	Potential therapeutic implication	References
pH3	Mitotic activity	Pharmacodynamic biomarker	Crosio et al., 2002; Hayama et al., 2007; Wilkinson et al., 2007
KRAS mutation	Replication stress	Increased mitotic dependency	Den Hollander et al., 2010; Goldenson and Crispino, 2015; Skoulidis and Heymach, 2019
TP53 loss	CIN tolerance	Sensitivity to mitotic disruption	Pastushenko and Blanpain, 2019; Rosenthal et al., 2019
MYC amplification	Mitotic stress	Synthetic lethality	Den Hollander et al., 2010; Dang, 2012; Goldenson and Crispino, 2015; Rosenthal et al., 2019; Dhanasekaran et al., 2022

Biomarker	Biological significance	Potential therapeutic implication	References
CIN-high signature	Genome instability	Candidate population for AURKB inhibition	Du et al., 2021; Teli, et al., 2025

pH3: phosphorylated histone H3; KRAS: Kirsten rat sarcoma viral oncogene homolog; TP53: tumor protein p53; MYC: MYC proto-oncogene; CIN: chromosomal instability; AURKB: Aurora kinase B; NSCLC: non-small cell lung cancer.

7.3 Future combination strategies

Given the multifactorial nature of therapeutic resistance in NSCLC, combination therapeutic strategies are likely to represent the most effective direction for the future development of AURKB-targeted therapies (Turajlic and Swanton, 2016). Accumulating evidence indicates that AURKB inhibition may synergize with multiple treatment modalities by enhancing apoptosis, suppressing adaptive survival signaling, and disrupting CIN-driven tumor evolution (Passaro et al., 2021).

The combination of AURKB inhibitors with EGFR-TKIs represents one of the most promising translational strategies, particularly for EGFR-mutant NSCLC with acquired resistance (Hoxhaj and Manning, 2020). Concurrent inhibition of EGFR signaling and mitotic adaptation may restore apoptotic sensitivity and suppress the emergence of resistant tumor clones (Turajlic and Swanton, 2016; Tanaka et al., 2021b). Preclinical studies have shown that AURKB inhibition enhances BIM- and PUMA-mediated mitochondrial apoptosis and potentiates the antitumor activity of EGFR inhibitors in resistant NSCLC models (Hoxhaj and Manning, 2020). These findings strongly support further clinical evaluation of dual EGFR/AURKB-targeting strategies.

Combination with platinum-based chemotherapy or microtubule-targeting agents has also been explored as a potential approach to enhance therapeutic efficacy (Leonetti et al., 2019). Cytotoxic agents such as cisplatin induce DNA damage, whereas taxanes disrupt microtubule dynamics and impose mitotic stress. Concurrent AURKB inhibition may further impair mitotic adaptation, cytokinesis, and post-mitotic survival pathways (Boss et al., 2009). Consequently, combined targeting of mitotic progression and DDRs may produce synergistic antitumor effects in highly proliferative NSCLC subsets, although treatment responses are likely to be context- and schedule-dependent.

Recent studies have additionally highlighted important interactions between CIN and tumor immunity (Steeg, 2016; Tripathi et al., 2016). CIN can influence inflammatory signaling, immune surveillance, and responsiveness to immune checkpoint blockades (Tripathi et al., 2016). Because AURKB is a central regulator of mitotic fidelity and CIN, its inhibition may alter tumor immune signaling through context-dependent effects on genomic instability. Whether this improves responsiveness to immune checkpoint blockades in NSCLC requires direct preclinical and clinical validation (Hiam-Galvez et al., 2021; Beernaert and Parkes, 2023a).

Targeting DDR pathways may provide another rational combination strategy (Yap et al., 2020). Tumors characterized by persistent CIN and mitotic dysfunction often become increasingly dependent on compensatory DNA repair pathways for survival (Pilié et al., 2019). Therefore, simultaneous inhibition of AURKB and DDR-associated signaling pathways, including ATR, CHK1, or PARP, may induce synthetic lethality and selectively eliminate genomically unstable tumor cells (O'Connor, 2015; Yap et al., 2020). This strategy may be particularly relevant for NSCLC subtypes characterized by high CIN, TP53 deficiency, or replication stress-associated phenotypes.

Overall, the future clinical development of AURKB-targeted therapies will likely require the integration of biomarker-guided patient selection, rational combination strategies, and precision oncology-based molecular stratification. Continued advances in translational research, tumor profiling technologies, and targeted drug delivery systems may ultimately improve the therapeutic efficacy and clinical applicability of AURKB inhibition in NSCLC.

8 Clinical translation and emerging precision oncology strategies

Despite substantial progress in elucidating the biological functions of AURKB in NSCLC, translating these findings into durable clinical benefit remains challenging. One major limitation is that most available evidence is derived from preclinical models or early-phase clinical studies, and prospective biomarker-driven trials in NSCLC remain scarce. In recent years, however, advances in molecular profiling, single-cell sequencing, and spatial transcriptomics have provided new opportunities to refine patient stratification and identify mitosis-dependent tumor subpopulations that may preferentially respond to AURKB inhibition (Jamal-Hanjani et al., 2015).

An important emerging concept is that AURKB dependency appears to be more closely associated with genomic instability states than with a single oncogenic driver alteration alone (Bielski et al., 2018). NSCLC tumors characterized by high CIN, elevated replication stress, TP53 deficiency, or MYC amplification may exhibit increased reliance on mitotic checkpoint signaling for survival (Watkins et al., 2020). This observation may partly explain why AURKB inhibition creates selective vulnerability in highly proliferative and genomically unstable tumors. Accordingly, future therapeutic strategies will likely require integration of mitotic stress biomarkers, CIN signatures, and transcriptional profiling to identify biologically defined subgroups most likely to benefit from AURKB-targeted therapy (Rosenthal et al., 2019).

Recent multi-omics studies have also suggested that AURKB participates in broader regulatory programs involving metabolic adaptation, immune remodeling, and epigenetic reprogramming (Dominguez-Brauer et al., 2015). Aberrant mitotic signaling may reshape the tumor microenvironment through induction of inflammatory cytokines, micronucleus formation, and activation of cyclic GMP-AMP synthase-stimulator of interferon genes (cGAS-STING) signaling pathways (Bakhoun et al., 2018). Persistent CIN can promote both antitumor immune activation and immune evasion, depending on the magnitude and temporal dynamics of genomic instability (Bakhoun and Cantley, 2018). These findings raise the possibility that modulation of mitotic stress through AURKB inhibition may influence immunotherapy responsiveness in NSCLC.

Another promising direction involves integrating AURKB inhibition into adaptive precision oncology frameworks. With the increasing use of longitudinal circulating tumor DNA (ctDNA) monitoring and dynamic molecular surveillance, emerging resistant subclones might become detectable before radiographic progression becomes clinically evident (Ignatiadis et al., 2021a). Early identification of mitotic stress-associated resistance patterns could facilitate timely incorporation of AURKB-targeted therapy into combination regimens, thereby delaying clonal evolution and therapeutic escape (Abbosh et al., 2023). Such adaptive treatment strategies may be particularly relevant in EGFR-mutant or KRAS-driven NSCLC, where intratumoral heterogeneity frequently limits the long-term efficacy of targeted therapies (Passaro et al., 2021). In the future, integration of longitudinal ctDNA monitoring, single-cell sequencing, and spatial transcriptomic profiling may enable dynamic identification of mitotic stress-associated resistant subclones during treatment evolution and support adaptive therapeutic intervention before overt clinical progression occurs.

Novel approaches, including proteolysis-targeting chimeras (PROTACs), antibody-drug conjugates, and tumor-selective nanoparticle delivery systems, may further enhance tumor specificity while minimizing systemic toxicity (Sun et al., 2019). In parallel, rational scheduling strategies designed to exploit transient mitotic vulnerability rather than continuous kinase suppression may improve tolerability and reduce hematologic adverse effects (Otto and Sicinski, 2017).

Nevertheless, several important limitations remain. Most current evidence regarding AURKB-targeted therapy in NSCLC is derived from preclinical studies, and prospective biomarker-driven clinical trials remain limited. In addition, the context-dependent effects of CIN and mitotic stress may complicate therapeutic optimization across different molecular subtypes of NSCLC.

Collectively, current evidence supports AURKB as more than a conventional mitotic kinase. Rather, it appears to function as a central regulator linking CIN, oncogenic signaling, therapeutic

adaptation, and tumor evolution in NSCLC. Continued integration of biomarker-guided patient selection, molecular stratification, and mechanism-based combination therapies will likely determine the future clinical value of AURKB-targeted strategies in precision thoracic oncology. Despite substantial progress in understanding AURKB biology, whether mitotic vulnerability can ultimately be translated into durable clinical benefit remains an open question in NSCLC. Future advances will require not only improved inhibitors but also a deeper understanding of context-specific mitotic dependency, CIN thresholds, and tumor evolutionary dynamics.

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Compliance with ethics guidelines

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This article does not contain any studies with human or animal subjects performed by any of the authors.

Declaration on the use of generative AI tools

During the preparation of this work, the authors used ChatGPT in order to improve language only. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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