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Review Article

Role of Protein Kinases in Cancer and Drug Resistance: Molecular Mechanisms, Therapeutic Targeting and Emerging Strategies

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ABSTRACT

Protein kinases are central regulators of cellular communication and control processes including proliferation, differentiation, metabolism, survival, migration, DNA-damage responses and immune function. Their abnormal activation or expression contributes to the development and progression of many cancers through mutations, gene amplification, chromosomal rearrangements, altered expression and disruption of regulatory networks. Because cancer cells may become highly dependent on aberrant kinase signalling, protein kinases have become important targets for precision cancer therapy. The clinical development of kinase inhibitors has produced substantial benefits in several malignancies, particularly those driven by actionable molecular alterations. However, the initial effectiveness of these therapies is frequently followed by disease progression as tumor cells adapt to treatment. Drug resistance may result from secondary mutations in the target kinase, activation of bypass pathways, downstream signalling reactivation, tumor heterogeneity, phenotypic and epigenetic adaptation, altered drug transport, metabolic reprogramming and protective interactions with the tumor microenvironment. This review examines the structural and biological characteristics of protein kinases and their contribution to cancer development and progression. It further discusses major mechanisms responsible for resistance to kinase-targeted therapy and evaluates current approaches for overcoming resistance, including next-generation inhibitors, rational combination therapy, allosteric and covalent inhibition, biomarker-guided treatment, liquid biopsy, adaptive treatment, tumor-agnostic therapy and targeted protein degradation. Emerging applications of computational drug discovery and multi-omics approaches are also considered. A clearer understanding of kinase signalling and tumor evolution may support more durable treatment strategies and help move precision oncology toward earlier prediction and prevention of therapeutic resistance.

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INTRODUCTION

Cancer is not a single disease but a broad group of disorders in which normal mechanisms controlling cellular growth, survival, differentiation and tissue organization become progressively disturbed. Although genetic alterations are central to malignant transformation, cancer behavior also depends heavily on signalling networks, cellular adaptation, metabolism and interactions with the surrounding microenvironment. Protein kinases are particularly important within these networks because they translate extracellular and intracellular signals into functional changes through phosphorylation of target proteins. By regulating proliferation, apoptosis, metabolism, DNA repair, migration and immune responses, kinases help maintain normal cellular homeostasis. When their activity becomes persistently altered, however, these same signalling systems can support malignant transformation and tumor progression (Roskoski, 2025; Taylor & Kornev, 2011). This biological importance has made protein kinases major targets for anticancer drug development. The success of imatinib against BCR::ABL1-positive chronic myeloid leukemia provided a landmark demonstration that targeting a disease-driving kinase could produce profound clinical benefit (Druker *et al.,* 2001). Since then, kinase inhibitors have expanded into numerous cancer types, although resistance remains a major obstacle to durable treatment (Dell'Aversana *et al.,* 2024; Yang *et al.,* 2022).

1.1 Rationale for Targeting Protein Kinases in Cancer

Protein kinase inhibitors can be classified according to their binding interactions and the conformational state of the target kinase. Type I inhibitors bind within the ATP-binding pocket of the active kinase conformation, typically characterized by a DFG-in motif, and compete with ATP for binding. Type II inhibitors occupy the ATP-binding pocket and extend into an adjacent hydrophobic pocket exposed in the inactive, usually DFG-out, conformation. In contrast, type III inhibitors bind to allosteric sites adjacent to the ATP-binding pocket, whereas type IV inhibitors bind to allosteric sites distant from both the ATP-binding and substrate-binding sites. Type VI inhibitors form covalent bonds with their target kinases. These different binding modes can provide opportunities to improve target selectivity by exploiting structural features beyond the conserved ATP-binding pocket. However, classification terminology varies across the literature, and not all classification systems use every category uniformly (Roskoski, 2016; Attwood *et al.,* 2021).

1.2 Aim and Scope of the Review

This review examines the role of protein kinases in cancer development, progression, therapeutic targeting and drug resistance. It first considers the structural organization and classification of protein kinases and explains how their normal signalling functions become disrupted during malignant transformation. Particular attention is given to kinase-dependent regulation of proliferation, survival, metabolism, angiogenesis, migration, metastasis and tumor–microenvironment interactions. The review then explores major mechanisms through which cancer cells evade kinase inhibition, including secondary target mutations, pathway bypass, downstream signalling reactivation, clonal selection, phenotypic plasticity, altered drug exposure and microenvironmental protection (Dell'Aversana *et al.,* 2024; Yang *et al.,* 2022; Poei *et al.,* 2024). Current therapeutic approaches for managing resistance are subsequently discussed, including next-generation inhibitors, combination therapy, allosteric inhibition, molecular monitoring, liquid biopsy and rational drug sequencing. Finally, emerging strategies such as tumor-agnostic kinase inhibition, targeted protein degradation, artificial intelligence-assisted drug discovery and multi-omics approaches are considered. The overall aim is to connect the biological complexity of kinase signalling with the practical challenge of achieving durable responses in patients receiving targeted cancer therapy.

2. PROTEIN KINASES: STRUCTURE, CLASSIFICATION AND BIOLOGICAL FUNCTIONS

2.1 Review and Structural Organization of Protein Kinases

The three-dimensional structure of a protein kinase influences its stability, molecular interactions and catalytic activity. Most eukaryotic protein kinases possess a conserved catalytic domain consisting of a smaller N-

terminal lobe and a larger C-terminal lobe, separated by an ATP-binding cleft. The N-terminal lobe contains a glycine-rich loop that helps position ATP, while the C-terminal lobe contributes to substrate recognition and catalysis. The hinge region forms important hydrogen-bond interactions with ATP and many kinase inhibitors, making it a major site for inhibitor binding. Other structural elements, including the activation loop and the conserved Asp-Phe-Gly (DFG) motif, regulate kinase activity by controlling conformational changes between active and inactive states (Attwood *et al.,* 2021; Roskoski, 2016).

The gatekeeper residue, located near the ATP-binding pocket, regulates access to an adjacent hydrophobic pocket and can influence inhibitor binding and selectivity. Mutations at this position may reduce drug sensitivity by altering inhibitor–kinase interactions or changing the kinase's affinity for ATP. For example, the EGFR T790M gatekeeper mutation increases ATP affinity and contributes to resistance to first-generation EGFR inhibitors. Similarly, the ALK L1196M gatekeeper mutation can interfere with inhibitor binding and confer resistance to ALK inhibitors, including crizotinib. These examples demonstrate how a single amino acid substitution can compromise targeted therapy and influence the selection of subsequent inhibitors (Ko *et al.,* 2017; Roskoski, 2016).

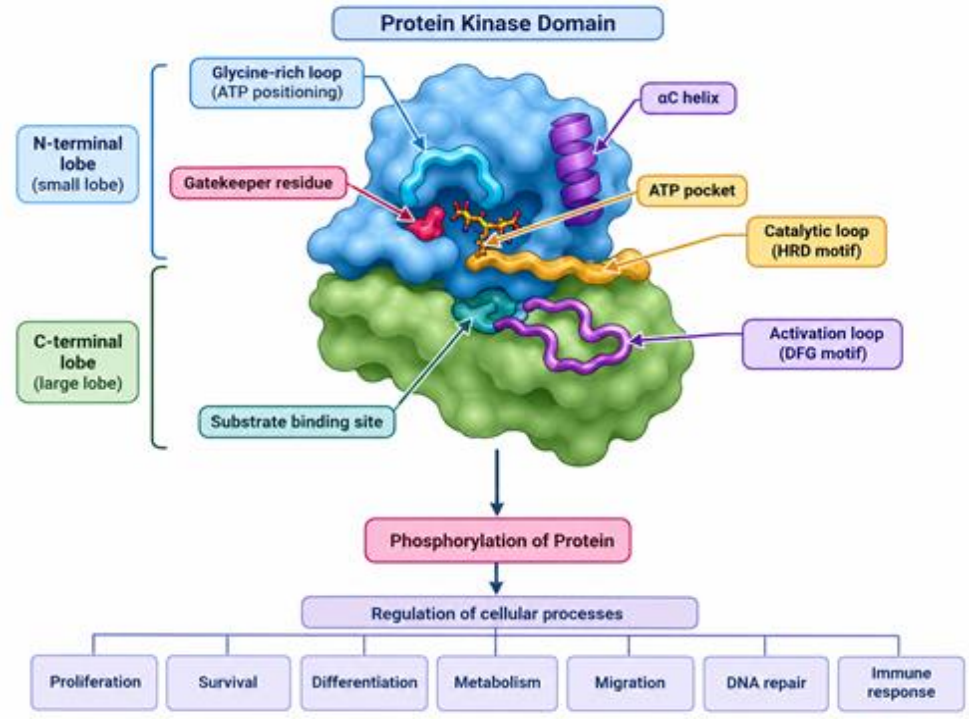


Figure 1: Structural Organization of a Typical Protein Kinase

Figure 1 illustrates the conserved structural organization of a typical protein kinase catalytic domain, comprising the smaller N-terminal lobe and larger C-terminal lobe, which form the ATP-binding cleft. Key structural features include the glycine-rich loop, αC helix, HRD catalytic motif, activation loop containing the DFG motif, gatekeeper residue and substrate-binding site. These elements contribute to ATP positioning, substrate recognition, catalytic activity and the regulation of kinase conformational states. Structural changes involving these regions can influence inhibitor binding and contribute to resistance to targeted therapies. Created by the authors based on published literature (Attwood *et al.,* 2021; Taylor & Kornev, 2011).

2.2 Classification of Protein Kinases

Protein kinases can be classified according to their evolutionary relationships, structural features, cellular location and the amino-acid

residues they phosphorylate. The major functional groups include serine/threonine kinases, tyrosine kinases and dual-specificity kinases, although the human kinome contains many additional families with specialized functions (Taylor & Kornev, 2011). Receptor tyrosine kinases, such as EGFR, HER2, MET, VEGFR, FGFR, RET and ALK, are located at the cell surface and transmit extracellular signals into the cell. Non-receptor tyrosine kinases, including ABL and SRC-family members, operate primarily within intracellular signalling networks. Serine/threonine kinases include important cancer-associated enzymes such as RAF, AKT, mTOR and cyclin-dependent kinases (Attwood *et al.,* 2021; Khorasani *et al.,* 2024). The human kinome contains hundreds of protein kinases, yet only a fraction has been extensively studied or successfully targeted therapeutically (Taylor & Kornev, 2011). This leaves a large group of comparatively understudied kinases that may represent future opportunities for cancer research and drug development (Kullmann *et al.,* 2026). Understanding kinase classification therefore remains important for linking molecular function with therapeutic vulnerability.

Table 1: Classification of Protein Kinases

Table 1 presents the major classes of protein kinases according to their structural and functional characteristics, representative members, principal cellular functions, and relevance to cancer development and targeted therapy.

Kinase Class	Representative Members	Major Cellular Functions	Clinical Significance
Receptor Tyrosine Kinases (RTKs)	EGFR, HER2, VEGFR, FGFR, RET, MET, ALK	Growth-factor signaling, proliferation, differentiation, survival, and angiogenesis	Frequently mutated, amplified, rearranged, or overexpressed in cancer and represent major targets of targeted therapy (Attwood *et al.,* 2021; Roskoski, 2025)
Non-Receptor Tyrosine Kinases	ABL, SRC, JAK, FAK	Cell growth, survival, migration, adhesion, and immune signaling	Important therapeutic targets in hematological malignancies and solid tumors (Attwood *et al.,* 2021; Roskoski, 2025)
Serine/Threonine Kinases	RAF, AKT, mTOR, CDKs, PIM	Cell-cycle regulation, proliferation, apoptosis, metabolism, and cellular stress responses	Major regulators of tumor development and progression and important therapeutic targets (Attwood *et al.,* 2021; Khorasani *et al.,* 2024; Rout *et al.,* 2024; Asciolla *et al.,* 2025)
Dual-Specificity Kinases	MEK1/2, DYRK, CLK	MAPK signaling, cell-cycle regulation, transcription, and cellular differentiation	Important therapeutic targets, particularly MEK1/2 in MAPK-driven cancers (Attwood *et al.,* 2021; Grogan & Shapiro, 2024; Roskoski, 2025)

Compiled from Asciolla et al. (2025), Attwood et al. (2021), Grogan and Shapiro (2024), Khorasani et al. (2024), Roskoski (2025), and Rout et al. (2024).

2.3 Biological Functions of Protein Kinases

Protein kinases participate in almost every major aspect of cellular regulation. Through reversible phosphorylation, they control cell-cycle progression, proliferation, differentiation, apoptosis, metabolism, DNA-damage responses, cytoskeletal organization, migration and immune-cell activity (Attwood *et al.,* 2021; Taylor & Kornev, 2011). Their effects are rarely isolated; instead, kinases function within interconnected signalling cascades in which activation of one enzyme influences several downstream proteins. For example, growth-factor receptors can activate intracellular kinase

pathways that ultimately alter transcription and cellular behaviour. Protein phosphatases and feedback mechanisms subsequently help reduce or terminate these signals. This balance allows normal cells to respond appropriately to changing environmental conditions. The importance of phosphorylation becomes especially clear when kinase activity is disrupted. Persistent or inappropriate activation can maintain growth and survival programs even when the normal extracellular stimulus is absent. Conversely, excessive kinase inhibition can interfere with essential physiological functions in healthy tissues. This duality explains why kinases are both attractive therapeutic targets and potential sources of treatment-related toxicity. Their biological importance also means that cancer-associated alterations can have effects far beyond the original signalling pathway (Khorasani *et al.,* 2024; Taylor & Kornev, 2011).

2.4 Regulation of Kinase Activity

Normal kinase activity is tightly controlled through several mechanisms, including ligand binding, phosphorylation and dephosphorylation, conformational changes, protein–protein interactions, subcellular localization, autoinhibitory domains and feedback loops. These mechanisms ensure that signalling occurs with the appropriate intensity and duration. Structural studies show that many kinases alternate between active and inactive conformations, with movements of the activation loop and other conserved regions influencing catalytic activity (Reveguk & Simonson, 2024). Cancer can disrupt this carefully balanced regulation through activating mutations, gene amplification, overexpression, chromosomal rearrangements, or abnormal upstream stimulation (Roskoski, 2025). Some mutations stabilize the active state of a kinase, while fusion events may remove regulatory domains that normally restrain activity. Amplification can increase the amount of kinase available for signalling, whereas excessive ligand production can maintain receptor activation. These changes may convert an enzyme that normally responds briefly to an external signal into a persistent driver of malignant behaviour. Understanding how kinase activity is regulated is therefore essential for identifying the molecular abnormalities that create therapeutic vulnerabilities and for designing inhibitors capable of selectively interfering with cancer-associated signalling (Attwood *et al.,* 2021; Reveguk & Simonson, 2024).

2.5 Kinase-Dependent Signalling Networks

Protein kinases operate as interconnected networks rather than isolated molecular switches. Major cancer-associated signalling systems include the RAS–RAF–MEK–ERK pathway, PI3K–AKT–mTOR pathway, JAK–STAT pathway and several receptor tyrosine kinase networks (Dell'Aversana et al., 2024; Khorasani et al., 2024). These pathways communicate with one another and collectively regulate growth, survival, metabolism, differentiation, migration and immune responses. This interconnectedness is biologically useful because it allows cells to adapt to changing conditions, but it also creates a major problem for targeted therapy. Blocking one pathway can stimulate compensatory signalling through another. For example, suppression of one growth-factor receptor may increase dependence on a different receptor or reactivate downstream signalling through alternative mechanisms (Dell'Aversana *et al.,* 2024; Yang *et al.,* 2022). The PI3K–AKT–mTOR pathway is particularly important because it integrates signals controlling cell growth, survival, metabolism and treatment response (Khorasani *et al.,* 2024). Such network redundancy means that the clinical effect of a kinase inhibitor depends not only on whether its intended target is inhibited, but also on what happens elsewhere in the signalling network. This concept provides an important biological foundation for understanding drug resistance and designing rational combination therapies.

3. DYSREGULATION OF PROTEIN KINASES IN CANCER

3.1 Genetic Mechanisms of Kinase Dysregulation

Kinase dysregulation in cancer can result from activating point mutations, gene amplification, chromosomal rearrangements, abnormal transcription, or changes in upstream regulatory signals. These alterations may produce a kinase that is permanently active, excessively expressed, or placed under the control of an abnormal regulatory environment (Roskoski, 2025). Some mutations occur within the kinase domain and directly alter its catalytic activity or conformational stability, whereas other

alterations affect extracellular ligand binding, receptor dimerization, intracellular regulatory regions, or protein degradation. Chromosomal rearrangements can be especially powerful because they may generate fusion proteins with constitutive kinase activity. BCR::ABL1 is a classic example, while ALK, ROS1, RET and NTRK fusions have subsequently become important therapeutic targets in solid tumors (Adashek *et al.,* 2025; Liu *et al.,* 2025; Roskoski, 2025). Importantly, the biological effect of a kinase alteration depends on its cellular context. The same pathway can have different consequences in different tissues because signalling networks and lineage-specific transcriptional programs vary between cell types. Consequently, identifying an alteration is only the beginning; understanding whether it functions as a genuine oncogenic driver is critical for selecting effective targeted treatment.

3.2 Receptor Tyrosine Kinases as Oncogenic Drivers

Receptor tyrosine kinases are among the most extensively studied kinase families in cancer. They normally respond to extracellular growth factors and transmit signals across the cell membrane through receptor dimerization, autophosphorylation and recruitment of downstream signalling proteins. When altered, however, these receptors can become persistently active and drive malignant growth (Roskoski, 2025). EGFR, HER2, MET, FGFR, ALK, RET and VEGFR-associated signalling are examples of receptor kinase systems with important roles in cancer. Their abnormal activation can stimulate MAPK, PI3K–AKT–mTOR, JAK–STAT and other pathways, producing coordinated effects on proliferation, survival, migration, angiogenesis and metabolism (Khorasani *et al.,* 2024; Roskoski, 2025). The therapeutic success of receptor kinase inhibitors demonstrates the value of identifying molecular dependencies within tumors. At the same time, receptor signalling is highly adaptable. Cancer cells can increase the activity of another receptor, alter ligand availability, or activate downstream signalling to maintain growth despite treatment. This ability to rewire receptor networks is one reason why resistance frequently emerges after an initially successful response to targeted therapy (Dell'Aversana *et al.,* 2024; Yang *et al.,* 2022).

3.3 Intracellular and Serine/Threonine Kinases in Cancer

Cancer is not driven exclusively by receptor tyrosine kinases. Numerous intracellular and serine/threonine kinases contribute directly to malignant behaviour. The RAF–MEK–ERK pathway, for example, is a major regulator of proliferation and is frequently activated by oncogenic alterations involving RAS or BRAF (Hanrahan *et al.,* 2024). Similarly, AKT and mTOR coordinate growth, survival, protein synthesis and metabolism, while cyclin-dependent kinases control progression through the cell cycle (Khorasani *et al.,* 2024). PIM kinases have also attracted interest because they influence survival, proliferation, metabolism and other processes associated with tumor development (Rout *et al.,* 2024). These examples demonstrate that kinases can drive cancer at different levels of cellular regulation. Some act as upstream signal receptors, whereas others function deeper within signalling cascades or directly regulate the cell-cycle machinery. This diversity has expanded the therapeutic landscape but has also complicated treatment. Inhibiting a downstream kinase may be bypassed by upstream or parallel signalling, while inhibiting a central signalling node may cause greater toxicity in normal tissues. Effective targeting therefore requires careful understanding of pathway architecture and tumor-specific dependencies.

3.4 Consequences of Aberrant Kinase Activation

Persistent kinase activation can influence several cancer hallmarks simultaneously. A single oncogenic kinase may stimulate proliferation, suppress apoptosis, promote angiogenesis, alter metabolism and enhance migration or invasion through different downstream pathways (Hanrahan *et al.,* 2024; Khorasani *et al.,* 2024; Roskoski, 2025). This explains why kinase alterations can have such profound effects on tumor behaviour. For example, activation of PI3K–AKT–mTOR signalling can support cell growth and survival while simultaneously altering glucose metabolism, lipid metabolism, autophagy and responses to cellular stress (Khorasani *et al.,* 2024). Similarly, MAPK signalling can stimulate transcriptional programs that favour cell-cycle progression and proliferation (Hanrahan *et al.,* 2024). Because

these pathways interact extensively, their effects may reinforce one another. Cancer cells can therefore develop a signalling state in which several processes required for malignant growth are coordinated by a relatively small number of regulatory nodes. This creates opportunities for targeted therapy but also creates evolutionary pressure. When a dominant kinase is inhibited, surviving cells are strongly selected for alternative signalling mechanisms that preserve these essential functions. Thus, the same network architecture that makes kinases effective cancer targets can also facilitate the emergence of resistance.

4. ROLE OF PROTEIN KINASES IN CANCER PROGRESSION

4.1 Proliferation and Cell-Cycle Progression

Uncontrolled proliferation is one of the defining characteristics of cancer and protein kinases are central to the signalling processes that regulate cell division. Growth-factor receptors can activate MAPK and PI3K–AKT pathways, which ultimately influence transcriptional programs supporting cell growth and cell-cycle progression (Khorasani *et al.,* 2024; Roskoski, 2025). Cyclin-dependent kinases provide another important layer of regulation by coordinating transitions between cell-cycle phases. CDK4 and CDK6, for example, promote progression through the G1 phase by phosphorylating retinoblastoma protein, thereby facilitating release of E2F transcription factors and entry into S phase. When these pathways become abnormally activated, cells can continue dividing despite signals that would normally impose growth arrest (Asciolla *et al.,* 2025). Kinase-dependent regulation also contributes to the response to DNA damage and other cellular stresses. Cancer cells may exploit these systems to tolerate genomic instability while continuing to proliferate. Consequently, kinase inhibition can interrupt several aspects of tumor biology simultaneously. However, tumors may restore cell-cycle progression through alternative cyclins, kinases, or downstream pathways, which helps explain why resistance to kinase-directed therapy can develop even when the original target remains pharmacologically inhibited.

4.2 Survival and Resistance to Cell Death

The PI3K–AKT–mTOR signalling pathway plays a central role in regulating cell survival, metabolism, protein synthesis and resistance to apoptosis (Khorasani *et al.,* 2024). AKT promotes cell survival by phosphorylating and inactivating the pro-apoptotic protein BAD (Datta *et al.,* 1997) and by phosphorylating FOXO transcription factors, promoting their exclusion from the nucleus and reducing the expression of genes involved in apoptosis (Brunet et al., 1999). mTOR supports the biosynthetic activity required for continued growth. Other kinase pathways can similarly influence pro-survival transcriptional programmes and cellular stress responses. This persistent signalling allows cancer cells to tolerate hypoxia, nutrient limitation, DNA damage and therapeutic pressure. From a treatment perspective, this creates an important problem: a drug that successfully stops proliferation may not necessarily eliminate every malignant cell. Surviving populations can remain in a reversible dormant or drug-tolerant state and later resume growth (Dell'Aversana *et al.,* 2024; Yang *et al.,* 2022). The relationship between survival signalling and resistance is particularly relevant when different pathways compensate for one another. For example, inhibition of one kinase may increase dependence on PI3K–AKT or another pro-survival pathway. Understanding these relationships is therefore important for developing combination therapies that target both proliferative and survival dependencies.

4.3 Angiogenesis and Tumor Vascularization

As tumors enlarge, their demand for oxygen and nutrients increases, creating pressure for new blood-vessel formation. Protein kinases are central to this process because receptor signalling in endothelial cells controls proliferation, migration, survival and vascular permeability. VEGF receptor signalling is particularly important in tumor angiogenesis, while other receptor tyrosine kinases can contribute by regulating endothelial and stromal responses (Roskoski, 2025). Cancer cells themselves can also produce growth factors that stimulate kinase-dependent signalling in surrounding vascular cells. The resulting vascular network is often structurally abnormal, with irregular blood flow and permeability. These characteristics influence not only tumor growth but also drug delivery and the tumor microenvironment. Poor vascular function can create hypoxic regions that promote

additional signalling adaptations and may reduce exposure to some therapies. At the same time, angiogenic signalling can support metastatic dissemination by facilitating access to the circulation. Kinase inhibitors targeting angiogenic pathways have therefore been explored extensively in oncology. Their effectiveness, however, can be limited by alternative pro-angiogenic pathways and adaptive changes within the tumor environment, illustrating again how biological redundancy can reduce the durability of single-pathway inhibition.

4.4 Migration, Invasion and Metastasis

Metastasis requires cancer cells to detach from the primary tumor, invade surrounding tissues, enter and survive within the circulation and establish growth at distant sites. Protein kinases participate in many of these steps by regulating cytoskeletal organization, cell adhesion, extracellular-matrix interactions, motility and responses to environmental signals (Roskoski, 2025). Kinases within receptor tyrosine kinase and SRC-associated networks can influence cellular structures and transcriptional programs that facilitate migration and invasion. MAPK and PI3K–AKT signalling can also promote phenotypic changes associated with increased motility and survival (Khorasani *et al.,* 2024). Importantly, metastatic cells encounter very different environmental conditions from those present in the primary tumor. They must adapt to changes in oxygen availability, nutrient supply, extracellular matrix and interactions with immune and stromal cells. Kinase signalling helps coordinate these adaptations. This plasticity contributes to the difficulty of treating metastatic disease because the signalling dependencies of metastatic lesions may differ from those of the original tumor. Consequently, a therapy that is effective against the primary tumor may have a different effect on resistant or newly adapted metastatic populations.

4.5 Metabolic Reprogramming

Cancer cells frequently reprogramme their metabolism to meet the increased energy and biosynthetic demands of uncontrolled proliferation. Protein kinase signalling networks contribute to this adaptation by regulating glucose utilization, lipid synthesis, amino acid metabolism and cellular energy balance. The PI3K–AKT–mTOR pathway promotes glucose uptake and anabolic processes, including protein and lipid synthesis, thereby supporting cancer cell growth and survival (Khorasani *et al.,* 2024; Xu *et al.,* 2023). These metabolic changes are heterogeneous across cancer types and may allow malignant cells to adapt to differences in nutrient availability, oxygen supply and other environmental conditions (Xu *et al.,* 2023).

AMP-activated protein kinase (AMPK) is an important cellular energy sensor that responds to declining energy availability, including increases in the AMP-to-ATP and ADP-to-ATP ratios. Once activated, AMPK helps restore energy homeostasis by promoting ATP-producing catabolic processes while suppressing energy-consuming anabolic activities. It can also inhibit mechanistic target of rapamycin complex 1 (mTORC1), thereby limiting protein synthesis and other energy-intensive processes when cellular energy is insufficient (Steinberg & Hardie, 2023). Through these functions, AMPK links cellular energy status to the regulation of metabolism, growth and survival.

The relationship between AMPK and cancer is complex and context-dependent. AMPK can suppress tumor development by restraining anabolic growth and supporting metabolic homeostasis; however, established cancer cells may also use AMPK-mediated stress responses to survive nutrient deprivation and other adverse conditions. Consequently, AMPK activity does not have a uniformly tumor-suppressive or tumor-promoting effect in every cancer setting (Steinberg & Hardie, 2023; Vara-Ciruelos *et al.,* 2020). The interaction between AMPK and growth-promoting pathways such as PI3K–AKT–mTOR therefore illustrates how kinase signalling coordinates metabolic adaptation in cancer. Understanding these context-dependent relationships may help identify metabolic vulnerabilities and inform the development of therapeutic strategies that target both growth signalling and cancer-cell energy adaptation.

4.6 Tumor Microenvironment and Immune Regulation

The tumor microenvironment contains cancer cells alongside fibroblasts, endothelial cells, immune cells, extracellular matrix and soluble signalling molecules. Protein kinases help coordinate communication among these

populations and can influence inflammation, angiogenesis, immune-cell function and stromal support (Roskoski, 2025). Kinase signalling may also modify the ability of malignant cells to interact with immune surveillance mechanisms. This is important because treatment response is determined not only by what happens inside cancer cells but also by the surrounding biological environment. Stromal cells can provide growth factors or survival signals that partially compensate for inhibition of an oncogenic kinase, allowing cancer cells to persist despite effective drug exposure (Dell'Aversana *et al.,* 2024). Immune and inflammatory signalling can similarly influence tumor behaviour and therapeutic response. These interactions help explain why laboratory models based solely on isolated cancer cells may not fully predict clinical resistance. Understanding the tumor microenvironment therefore provides an important complement to studying cancer-cell-intrinsic kinase signalling and may support combination strategies that target both malignant cells and the external signals that help them survive.

5. PROTEIN KINASES AND CANCER DRUG RESISTANCE

5.1 Primary and Acquired Resistance

Resistance to kinase inhibitors can be broadly divided into primary resistance and acquired resistance. Primary resistance refers to the failure of a tumor to respond adequately from the beginning of treatment, whereas acquired resistance develops after an initial period of therapeutic benefit (Dell'Aversana *et al.,* 2024; Yang *et al.,* 2022). The distinction is clinically useful, although the underlying biology can overlap. A tumor may contain resistant clones before treatment begins, while treatment itself creates selective pressure that allows those populations to expand. Other tumors may initially depend strongly on the targeted kinase but later adapt through genetic or non-genetic mechanisms. Resistance is therefore best understood as a dynamic process rather than a single event. Recent reviews emphasize that kinase inhibitor resistance can involve target mutations, gene amplification, bypass signalling, downstream pathway activation, altered drug transport and changes in tumor-cell state (Dell'Aversana *et al.,* 2024; Poei *et al.,* 2024; Yang *et al.,* 2022). The specific mechanism varies according to the cancer, target, inhibitor and treatment history. Recognizing this diversity is important because simply switching from one drug to another without understanding the mechanism of resistance may provide little benefit.

5.2 Secondary Mutations in the Drug Target

One of the best-characterized mechanisms of acquired resistance is the emergence of secondary mutations within the kinase being targeted. These mutations can alter the structure of the drug-binding region, reduce inhibitor affinity, or favour kinase conformations that are less susceptible to inhibition (Attwood *et al.,* 2021; Yang *et al.,* 2022). Epidermal growth factor receptor (EGFR)-mutant non-small-cell lung cancer provides a well-characterized example of mutation-mediated resistance. The T790M gatekeeper mutation increases EGFR's affinity for ATP, helping the kinase retain activity in the presence of earlier-generation EGFR inhibitors (Wang *et al.,* 2016; Shaikh *et al.,* 2022). Third-generation inhibitors such as osimertinib were developed to inhibit T790M-containing EGFR; however, subsequent mutations can compromise their effectiveness. In particular, the C797S mutation replaces cysteine with serine at residue 797, disrupting the covalent interaction required for effective binding of osimertinib and contributing to acquired resistance (Wang *et al.,* 2016; Shaikh *et al.,* 2022). The effects of combined T790M and C797S mutations can also depend on whether they occur on the same or different EGFR alleles, influencing sensitivity to potential combination strategies (Wang et al., 2017). Similar evolutionary patterns occur in ALK-positive cancers, where secondary mutations can alter sensitivity to successive generations of ALK inhibitors (Poei *et al.,* 2024). These examples demonstrate that resistance can emerge through changes in the target itself, creating a continuing need for molecular monitoring and the development of inhibitors that retain activity against resistant variants.

5.3 Bypass Signalling and Downstream Reactivation

Cancer cells can resist kinase inhibition without acquiring a new mutation in the original drug target. One mechanism is bypass signalling, in which an alternative receptor or signalling

pathway compensates for the inhibited kinase and restores signals required for tumour growth and survival. For example, activation or amplification of alternative receptor tyrosine kinases can reactivate the PI3K–AKT or MAPK pathways despite inhibition of the original driver (Dell'Aversana *et al.,* 2024; Yang *et al.,* 2022). Resistance can also arise through downstream pathway reactivation, whereby signalling is restored at a point beyond the inhibited kinase. The MAPK pathway illustrates this mechanism because changes in downstream components or feedback regulation can restore extracellular signal-regulated kinase (ERK) activity despite inhibition of upstream signalling components (Hanrahan *et al.,* 2024). These mechanisms have important implications for treatment. If resistance is driven by an alternative receptor or downstream reactivation, switching to another inhibitor of the original target may be insufficient because the compensatory pathway remains active. Rational combination strategies may therefore be needed to inhibit both the original driver and the pathway responsible for resistance. However, simultaneous inhibition of multiple signalling pathways can increase toxicity, making the identification of appropriate molecular biomarkers and the careful evaluation of treatment combinations essential (Dell'Aversana *et al.,* 2024; Khorasani *et al.,* 2024).

5.4 Phenotypic and Epigenetic Adaptation

Not all resistant cancer cells acquire new mutations. Some can survive treatment by entering a reversible state characterized by altered gene expression, metabolism, differentiation, or signalling dependence (Dell'Aversana *et al.,* 2024; Yang *et al.,* 2022). This form of adaptation is particularly challenging because the resistant phenotype may not be obvious from DNA sequencing alone. A cell can temporarily reduce its dependence on the inhibited kinase, activate alternative survival programs, or enter a slower-growing state that makes it less vulnerable to treatment. Over time, these drug-tolerant populations may acquire stable genetic alterations and become permanently resistant. Changes in cellular identity can produce an even more dramatic effect. In some cancers, treatment can select for histological or phenotypic transformation, creating a tumor population with substantially different biological characteristics and therapeutic vulnerabilities (Yang *et al.,* 2022). This emphasizes the importance of considering cancer as an evolving cellular ecosystem rather than a static collection of mutations. Therapeutic strategies that address only genetic alterations may therefore miss important reversible states that contribute to treatment failure.

5.5 Tumor Heterogeneity and Clonal Evolution

Tumors rarely consist of genetically identical cells. Instead, they contain multiple subclones that differ in their mutations, signalling activity, metabolic behavior and response to treatment. When a kinase inhibitor is administered, sensitive populations may shrink while resistant populations survive and expand. Treatment therefore acts as an evolutionary selection pressure (Dell'Aversana *et al.,* 2024; Poei *et al.,* 2024). Resistance can arise from a pre-existing clone or from new adaptations that develop during therapy. Different metastatic sites may also evolve independently, meaning that resistance mechanisms can vary between lesions in the same patient. This spatial and temporal heterogeneity complicates treatment because a drug chosen on the basis of the original tumor biopsy may no longer match the dominant biology at disease progression. Longitudinal sampling and liquid biopsy can help reveal some of these changes, particularly when resistant genetic alterations are detectable in circulating tumor DNA. However, molecular monitoring cannot capture every form of resistance, especially purely phenotypic or microenvironmental adaptations. A complete understanding of tumor evolution therefore requires integration of genomic information with cellular, clinical and environmental data.

5.6 Altered Drug Exposure and Pharmacological Resistance

A kinase inhibitor must reach its target at a sufficient intracellular concentration and remain there long enough to produce effective inhibition. Changes that reduce intracellular drug exposure can therefore contribute to resistance. One important mechanism involves ATP-binding cassette (ABC) transporters, particularly ABCB1 (P-glycoprotein) and ABCG2 (breast cancer resistance protein), which use ATP hydrolysis to transport various compounds across cellular

membranes. Increased expres sion or activity of these transporters can enhance the efflux of anticancer agents, reduce intracellular drug accumulation and weaken treatment efficacy. The extent of this effect depends on the substrate specificity of the transporter and the pharmacological properties of the inhibitor; therefore, not all kinase inhibitors are equally susceptible to transporter-mediated resistance (Robey *et al.,* 2018).

Altered drug transport can operate alongside other resistance mechanisms, including secondary mutations in the drug target, activation of bypass signalling pathways, tumour heterogeneity, epigenetic adaptation and microenvironment-mediated protection. These mechanisms may coexist within the same tumour, contributing to multidrug resistance and limiting the effectiveness of targeted therapies (Ge *et al.,* 2025; Robey *et al.,* 2018). Understanding the contribution of drug efflux and other resistance processes may help inform the design of inhibitors with improved pharmacological properties and the development of combination strategies to overcome resistance.

5.7 Metabolic and Microenvironmental Resistance

Cancer cells can survive kinase inhibition by changing their metabolism or by receiving protective signals from surrounding cells. Metabolic plasticity allows cells to alter glucose utilization, mitochondrial activity, lipid metabolism, or amino-acid dependence when their primary growth pathway is suppressed (Khorasani *et al.,* 2024). At the same time, fibroblasts, immune cells, endothelial cells and other stromal populations can release growth factors and cytokines that activate alternative survival pathways (Dell'Aversana *et al.,* 2024). These mechanisms are important because they may occur without a detectable resistance mutation in the cancer cell itself. A drug can therefore inhibit its intended kinase effectively while the tumor remains viable because another source of survival signalling has taken over. This helps explain why resistance sometimes appears inconsistent between patients with apparently similar driver alterations. The surrounding tissue context may be different, producing different selective pressures and adaptive responses. Future resistance management will therefore require greater attention to the tumor microenvironment and metabolic state, rather than focusing exclusively on mutations within the original kinase target

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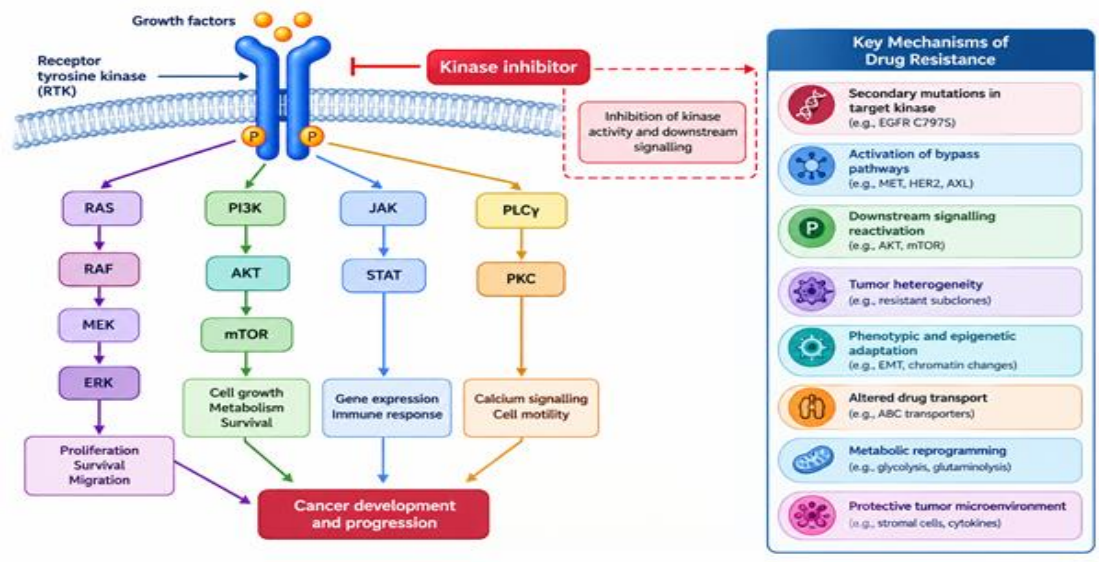


Figure 2 illustrates major protein kinase signalling pathways involved in cancer development and progression, including the RAS–RAF–MEK–ERK, PI3K–AKT–mTOR, JAK–STAT, and PLCγ–PKC pathways. It also summarises eight major mechanisms of resistance to kinase inhibitors: secondary mutations in the target kinase, activation of bypass pathways, downstream signalling reactivation, tumour heterogeneity, phenotypic and epigenetic adaptation, altered drug transport, metabolic reprogramming, and

microenvironment-mediated protection. These mechanisms enable cancer cells to sustain survival and proliferation despite targeted therapy. (Attwood et al. 2021; Dell'Aversana et al. 2024; Poei et al. 2024; Yang et al. 2022).

6. STRATEGIES FOR OVERCOMING KINASE INHIBITOR RESISTANCE

6.1 Next-Generation Kinase Inhibitors

The development of next-generation kinase inhibitors has been one of the most direct responses to acquired resistance. When a secondary mutation reduces the effectiveness of an existing drug, structural and biochemical studies can be used to design a new compound that retains binding to the altered kinase (Attwood *et al.,* 2021; Poei *et al.,* 2024; Yang *et al.,* 2022). This strategy has been particularly successful in EGFR- and ALK-driven cancers, where successive generations of inhibitors have been developed to address emerging resistance mutations and improve activity against disease in the central nervous system (Poei *et al.,* 2024). The approach is more sophisticated than simply increasing drug potency. An inhibitor may need to recognize a different kinase conformation, avoid steric interference created by a mutation, or exploit a previously underused binding pocket. The development of allosteric inhibitors has further expanded these possibilities by allowing drugs to interact with regions outside the highly conserved ATP-binding site (Attwood *et al.,* 2021). Nevertheless, every new inhibitor creates another evolutionary challenge for the tumor. Resistant populations may eventually emerge against the newer drug as well. Next-generation drug development must therefore anticipate likely resistance mechanisms rather than simply reacting to the previous generation.

6.2 Rational Combination Therapy

Combining therapies that block complementary survival pathways can reduce the ability of cancer cells to bypass a single inhibited kinase. One strategy is vertical inhibition, in which different components of the same signalling cascade are targeted simultaneously. Another is horizontal inhibition, in which parallel pathways that can compensate for one another are blocked together (Dell'Aversana *et al.,* 2024; Khorasani *et al.,* 2024). For example, simultaneous suppression of MAPK signalling at different levels may reduce pathway reactivation, while combining inhibition of a receptor kinase with blockade of PI3K–AKT signalling may limit downstream escape. Combination therapy can also involve kinase inhibitors with chemotherapy, endocrine therapy, immunotherapy, or other targeted agents, depending on the biological context. However, combining drugs is not automatically beneficial. Kinases are involved in normal physiological functions and simultaneous inhibition of multiple pathways can increase toxicity. The challenge is therefore to identify combinations that exploit a vulnerability specific to cancer cells. Biomarker-guided selection and careful pharmacological studies are essential to distinguish biologically rational combinations from combinations that simply increase adverse effects without providing meaningful therapeutic benefit.

6.3 Allosteric and Covalent Inhibition

Allosteric inhibitors bind to regulatory sites distinct from the ATP-binding pocket, modulating kinase activity through changes in protein conformation. Such compounds can achieve greater selectivity and may retain activity against some mutations that interfere with ATP-competitive drugs (Attwood *et al.,* 2021; Baldi *et al.,* 2025). Covalent inhibitors provide another strategy by forming a stable chemical bond with a suitable residue on the target protein. For example, osimertinib (AZD9291), an irreversible epidermal growth factor receptor (EGFR) inhibitor, forms a covalent bond with cysteine 797 (Cys797) in the EGFR ATP-binding site and retains activity against the T790M resistance mutation (Cross *et al.,* 2014). This irreversible binding can prolong target engagement and support sustained inhibition. Both approaches expand the structural possibilities available to medicinal chemists and illustrate how understanding kinase structure can inform cancer treatment. However, resistance can still arise through mutations that alter an allosteric pocket, changes affecting the covalent-binding residue, or alterations in kinase conformation. These strategies should therefore be viewed as valuable additions to the therapeutic toolbox rather than permanent solutions to resistance.

6.4 Biomarker-Guided Treatment

Molecular biomarkers are increasingly important for selecting kinase inhibitors and understanding why treatment succeeds or fails. Genomic

sequencing can identify activating mutations, gene fusions, amplifications and secondary resistance alterations, while transcriptomic and proteomic approaches can provide information about pathway activity and cellular state (Dell'Aversana *et al.,* 2024; Yang *et al.,* 2022). A biomarker-guided approach is particularly valuable because the presence of an actionable mutation does not always mean that the tumor will remain dependent on that pathway throughout treatment. Tumor biology can change under therapeutic pressure. Consequently, molecular testing at diagnosis and, where feasible, reassessment at progression can provide a more accurate picture of the current disease state. The increasing use of liquid biopsy makes repeated assessment more practical because circulating tumor DNA can sometimes reveal emerging resistance alterations without requiring an invasive tissue biopsy. Nevertheless, biomarkers must be interpreted carefully. A negative blood test does not necessarily exclude resistance, particularly when resistance is driven by epigenetic, phenotypic, or microenvironmental mechanisms. The most useful strategy is therefore likely to combine genomic biomarkers with clinical, pathological and functional information.

6.5 Liquid Biopsy and Circulating Tumor DNA

Liquid biopsy has become an increasingly useful approach for monitoring tumor evolution during targeted therapy. Circulating tumor DNA released by cancer cells can contain genetic information reflecting the tumor's current molecular state. Serial analysis may therefore identify emerging resistance-associated mutations before they become obvious through conventional clinical assessment (Dell'Aversana *et al.,* 2024; Yang *et al.,* 2022). This is particularly attractive in cancers where repeated tissue biopsies are difficult or risky. Liquid biopsy may also reveal heterogeneity because DNA from multiple tumor sites can contribute to the circulating pool. However, ctDNA has limitations. Some tumors release very little DNA into the circulation, while resistance mechanisms based on histological transformation, altered transcription, metabolism, or the tumor microenvironment may not be detectable through DNA sequencing alone. The most useful role of liquid biopsy is therefore not to replace tissue analysis completely but to complement it. When combined with imaging, clinical assessment and other molecular measurements, serial liquid biopsy could support earlier recognition of resistance and allow treatment to be adapted before resistant disease becomes widespread.

6.6 Rational Drug Sequencing

The emergence of resistance has made treatment sequencing increasingly important. When a tumor progresses on one kinase inhibitor, the next treatment should ideally be selected according to the mechanism responsible for resistance rather than simply switching to another drug at random (Poei *et al.,* 2024; Yang *et al.,* 2022). For example, the specific secondary mutation present in an ALK- or EGFR-driven tumor can influence which subsequent inhibitor is most likely to retain activity. Structural information can further help predict whether a resistance alteration will interfere with the binding of a particular drug. Rational sequencing may also exploit situations in which resistance to one inhibitor creates renewed sensitivity to another. This evolutionary perspective changes the way targeted therapy is viewed. Instead of treating each drug as an independent intervention, clinicians can consider the sequence of treatments as a series of selective pressures acting on a changing tumor population. Such an approach requires regular monitoring and a good understanding of the molecular consequences of previous therapy. It may ultimately allow treatment to be planned around predictable evolutionary trajectories rather than waiting for resistance to become clinically advanced.

6.7 Targeted Protein Degradation

Targeted protein degradation offers a fundamentally different approach to controlling kinase-driven cancer. Instead of simply occupying a kinase and blocking its catalytic activity, degraders can recruit the target protein to the ubiquitin–proteasome system and promote its destruction. PROTACs use bifunctional molecules to bring a target protein and an E3 ubiquitin ligase into proximity, while molecular glues can stabilize interactions between a target and an E3 ligase without requiring a conventional bifunctional structure (Hinterndorfer *et al.,* 2025). This distinction may be therapeutically important because degradation can remove both

catalytic and non-catalytic functions of a protein. It may also provide opportunities to target proteins that are difficult to inhibit effectively through conventional occupancy-based drugs. The field is advancing rapidly, with increasingly sophisticated degrader designs entering preclinical and clinical development (Hinterndorfer *et al.,* 2025). However, targeted degradation is not automatically resistant to resistance. Changes in target expression, mutations that interfere with degrader binding, alterations in E3-ligase availability and other mechanisms may reduce efficacy. Nevertheless, the strategy represents an important expansion of the therapeutic possibilities for kinase-driven cancers.

7. CLINICAL APPLICATIONS OF KINASE-TARGETED THERAPY

7.1 BCR::ABL-Directed Therapy

The development of BCR::ABL-directed therapy represents one of the clearest demonstrations of precision oncology. The BCR::ABL1 fusion protein results from a chromosomal rearrangement that produces constitutive tyrosine kinase activity. Imatinib was designed to inhibit this abnormal kinase and transformed the treatment of chronic myeloid leukemia by producing high rates of durable responses (Druker *et al.,* 2001). Its success demonstrated that identifying a specific molecular driver and designing a drug against that driver could be more effective than relying exclusively on nonspecific cytotoxic therapy. Subsequent generations of BCR::ABL inhibitors have been developed to address resistance and improve treatment options for patients whose disease becomes less sensitive to earlier drugs. The experience with CML also provided an important conceptual framework for targeted therapy in solid tumors. However, it showed that even a highly effective molecular therapy does not eliminate the possibility of resistance. Mutations in BCR::ABL1, changes in drug dependence and other biological mechanisms can allow residual malignant cells to survive. Thus, the history of BCR::ABL therapy illustrates both the power and the limitations of kinase-directed treatment.

7.2 EGFR-Targeted Therapy

EGFR-targeted therapy has become an important component of treatment for selected patients with EGFR-mutant non-small-cell lung cancer. Activating EGFR alterations can make tumor cells strongly dependent on receptor signalling, creating a therapeutic vulnerability. EGFR inhibitors can suppress downstream MAPK and PI3K–AKT pathways and produce substantial clinical responses in appropriately selected patients (Dell'Aversana *et al.,* 2024; Yang *et al.,* 2022). However, resistance frequently develops as tumors evolve under treatment pressure. Secondary mutations, bypass signalling, downstream pathway reactivation and phenotypic transformation have all been described (Yang *et al.,* 2022). The development of successive generations of EGFR inhibitors reflects attempts to anticipate and overcome these mechanisms. More recent strategies also emphasize central nervous system activity because brain metastases are an important clinical problem in lung cancer. EGFR-targeted therapy therefore illustrates the broader evolution of precision oncology: treatment begins with identification of a molecular driver, but long-term management requires continuous attention to the changing biology of the tumor. Molecular monitoring and rational sequencing have consequently become increasingly important components of EGFR-directed treatment.

7.3 ALK-Directed Therapy

ALK rearrangements create oncogenic fusion proteins that can drive a subset of lung cancers and other malignancies. The development of ALK inhibitors has produced substantial therapeutic benefit, but resistance has repeatedly emerged as different inhibitors impose new selective pressures on tumor cells (Poei *et al.,* 2024). Secondary mutations within the ALK kinase domain can alter inhibitor binding, while bypass pathways and changes in drug distribution can also contribute to treatment failure. The clinical development of successive ALK inhibitors demonstrates how structural understanding can guide therapeutic evolution. Later-generation drugs have been designed to inhibit resistance-associated mutations and improve penetration into the central nervous system, where metastatic disease can be difficult to control. Importantly, different resistance mutations may produce different sensitivity patterns, meaning that treatment selection after progression requires molecular information whenever possible. ALK-directed therapy

therefore provides a useful example of how targeted cancer treatment has moved from a simple "target and inhibit" model toward an adaptive approach based on tumor evolution, resistance mechanisms and drug-specific structural properties.

7.4 BRAF–MEK-Directed Therapy

BRAF is an important component of the MAPK signalling pathway and activating BRAF alterations can drive tumor growth across several cancer types. The BRAF V600E alteration is particularly well characterized and has become a target for selective inhibition. However, BRAF inhibition alone can lead to reactivation of MAPK signalling and the development of resistance. Combining BRAF and MEK inhibitors provides more comprehensive pathway suppression and has improved therapeutic outcomes in several BRAF-driven cancers (Hanrahan *et al.,* 2024). The importance of BRAF inhibition has expanded further through tumor-agnostic treatment approaches in selected BRAF V600E-mutant solid tumors (Roskoski, 2025). Nevertheless, resistance remains common, with tumors capable of restoring MAPK activity through multiple mechanisms. These include alterations affecting RAF signalling, upstream pathway activation and changes in downstream signalling. The BRAF experience therefore reinforces an important principle of kinase therapy: targeting a single point within a signalling cascade may be insufficient when the cancer can restore pathway activity elsewhere. Combination therapy and continued molecular investigation remain important for improving the durability of responses.

7.5 Tumor-Agnostic Kinase Inhibition

Tumor-agnostic therapy represents a major shift in how cancer treatment can be organized. Instead of defining treatment solely according to the organ in which a tumor originated, this approach uses a specific molecular alteration as the primary basis for selecting therapy. Several kinase alterations, including NTRK fusions, RET alterations and BRAF V600E mutations, have helped demonstrate the feasibility of this model (Roskoski, 2025). The concept is particularly attractive because the same oncogenic mechanism can occur across anatomically different cancers. A patient may therefore become eligible for a targeted therapy because of the molecular feature of the tumor rather than its tissue of origin. However, tumor-agnostic treatment does not eliminate biological context. The surrounding signalling network, coexisting genomic alterations, tumor lineage and microenvironment can influence therapeutic response (Roskoski, 2025). Resistance can also emerge despite successful initial targeting. Tumor-agnostic kinase therapy should therefore be understood as an expansion of precision oncology rather than a replacement for comprehensive cancer characterization.

Table 2: Selected Cancer-Associated Protein Kinases and Representative FDA-Approved Targeted Inhibitors

Table 2 presents selected cancer-associated protein kinases, major molecular alterations, associated malignancies, and representative FDA-approved targeted inhibitors.

Protein Kinase	Major Genetic/Molecular Alteration	Associated Cancer(s)	Representative FDA-Approved Inhibitors
BCR::ABL1	Gene fusion	Chronic myeloid leukemia	Imatinib, dasatinib, nilotinib, bosutinib, ponatinib, asciminib (Druker *et al.,* 2001; Roskoski, 2025; Roskoski, 2026)
EGFR	Activating mutations, including exon 20 insertions	Non-small-cell lung cancer (NSCLC)	Gefitinib, erlotinib, afatinib, dacomitinib, osimertinib; sunvozertinib (for EGFR exon 20 insertion–mutated NSCLC following platinum-based

Protein Kinase	Major Genetic/Molecular Alteration	Associated Cancer(s)	Representative FDA-Approved Inhibitors
			chemotherapy) (Roskoski, 2025; Roskoski, 2026)
ALK	Gene fusion	NSCLC	Crizotinib, ceritinib, alectinib, brigatinib, lorlatinib (Poei *et al.,* 2024; Roskoski, 2026).
ROS1	Gene fusion	ROS1-positive NSCLC	Crizotinib, entrectinib, repotrectinib, taletrectinib (Roskoski, 2025; Roskoski, 2026)
RET	Gene fusion or activating mutation	Thyroid cancer, NSCLC	Selpercatinib, pralsetinib (Adashek *et al.,* 2025; Roskoski, 2025; Roskoski, 2026)
BRAF	V600E mutation	Melanoma, colorectal cancer, thyroid cancer	Vemurafenib, dabrafenib, encorafenib (Hanrahan *et al.,* 2024; Roskoski, 2025; Roskoski, 2026)
MEK1/2	MAPK pathway activation	Melanoma and other MAPK-driven cancers; KRAS-mutated recurrent low-grade serous ovarian cancer (avutometinib plus defactinib); NF1-associated symptomatic plexiform neurofibromas (mirdametinib; non-malignant tumours)	Trametinib, cobimetinib, binimetinib, avutometinib (in combination with defactinib), mirdametinib (Grogan & Shapiro, 2024; Roskoski, 2025, 2026; Abbas et al., 2025).
HER2 (ERBB2)	Amplification or activating mutation	Breast cancer, gastric cancer, and HER2-mutated non-squamous NSCLC	Lapatinib, neratinib, tucatinib; zongertinib (for HER2 tyrosine kinase domain–mutated non-squamous NSCLC) (Roskoski, 2025; Roskoski, 2026)
MET	Exon 14 skipping alteration	NSCLC	Capmatinib, tepotinib (Roskoski, 2025; Roskoski, 2026)
NTRK	Gene fusion	Tumor-agnostic solid tumors	Larotrectinib, entrectinib (Adashek *et al.,* 2025; Roskoski, 2025; Roskoski, 2026)
CDK4/6	Amplification/overexpression and pathway dysregulation	Breast cancer	Palbociclib, ribociclib, abemaciclib (Asciolla *et al.,* 2025; Roskoski, 2026)

Protein Kinase	Major Genetic/Molecular Alteration	Associated Cancer(s)	Representative FDA-Approved Inhibitors
VEGFR	Pathway activation/overexpression	Renal cell carcinoma, hepatocellular carcinoma	Sunitinib, sorafenib, axitinib, pazopanib (Roskoski, 2025; Roskoski, 2026)

Source: Compiled from Abbas et al. (2025), Adashek et al. (2025), Grogan and Shapiro (2024), Hanrahan et al. (2024), Poei et al. (2024), Roskoski (2025, 2026), Asciolla et al. (2025), and relevant U.S. Food and Drug Administration approval notices.
Note: The inhibitors listed are representative examples and do not constitute an exhaustive list of FDA-approved therapies. Regulatory approvals and clinical indications may vary by jurisdiction and may change over time.

7.6 Current Limitations of Kinase-Targeted Therapy

Despite major advances, kinase-targeted therapy has several important limitations. Resistance remains the most obvious challenge, but toxicity, incomplete target selectivity, pharmacokinetic variability, tumor heterogeneity and access to molecular diagnostics also influence clinical outcomes (Dell'Aversana *et al*., 2024; Yang *et al.,* 2022). Because kinases perform essential functions in normal tissues, inhibiting them can produce adverse effects when drug activity extends beyond the tumor. Another challenge is that the presence of a molecular alteration does not always mean that the cancer remains dependent on it. Tumors can evolve, activate alternative pathways, or change cellular identity during treatment. Cost and access are additional concerns, particularly in healthcare systems where molecular testing and expensive targeted medicines are not readily available. Recent reviews of kinase inhibitors emphasize that technological progress has not automatically translated into equal clinical benefit across all cancer types or populations (Adashek *et al.,* 2025). Future advances must therefore address not only drug potency but also patient selection, treatment durability, toxicity, affordability and equitable access.

8. EMERGING STRATEGIES AND FUTURE DIRECTIONS

8.1 Artificial Intelligence in Kinase Drug Discovery

Artificial intelligence and machine learning are increasingly being applied to drug discovery, including the identification and optimization of kinase inhibitors. Computational models can help predict molecular properties, estimate drug–target interactions, prioritize compounds for experimental testing, and analyse large chemical libraries. Advances in protein structure prediction have also expanded the structural information available for studying kinase conformations and potential drug-binding sites. For example, AlphaFold uses deep learning to predict protein structures from amino acid sequences, providing useful structural models when experimental structures are unavailable (Jumper *et al.,* 2021). However, predicted structures may not fully represent the conformational flexibility of kinases or the structural changes associated with ligand binding. Therefore, AI-based predictions should be interpreted alongside experimental evidence and, where appropriate, molecular modelling and validation to support reliable kinase inhibitor discovery.

8.2 Multi-Omics and Functional Profiling

Genomic sequencing has transformed cancer classification, but DNA alterations alone cannot fully describe the functional state of a tumor. Transcriptomics can reveal gene-expression programs, proteomics can measure protein abundance and phosphoproteomics can provide direct information about kinase activity and signalling states. Recent work demonstrates that kinase abundance and activity can vary considerably between tumors and even among different cancer subtypes (Piersma *et al.,* 2024). Integrating these layers of information could therefore provide a more complete picture of why a tumor responds to one kinase inhibitor but not another. Functional profiling may also identify signalling pathways that remain active despite genomic evidence suggesting that they should be

suppressed. This is particularly relevant to resistance, where non-genetic adaptations can occur without obvious DNA changes. Multi-omics approaches may consequently help distinguish the original driver from the pathways that a tumor has become dependent on after treatment. Although cost, data complexity, standardization and clinical interpretation remain challenges, integrating multiple molecular layers offers an important route toward more precise and dynamic cancer treatment.

8.3 Predicting Resistance Before It Develops

Most current approaches to resistance management are reactive: treatment is changed after disease progression becomes evident. A more ambitious goal is to predict resistance before resistant disease becomes clinically dominant. Achieving this will require longitudinal monitoring of tumor evolution, identification of pre-existing resistant clones and modeling of likely evolutionary pathways (Dell'Aversana *et al.,* 2024; Yang *et al.,* 2022). Liquid biopsy may provide repeated molecular measurements, while tissue analysis and functional assays can reveal phenotypic changes that circulating DNA cannot capture. Computational methods could then integrate these data to estimate which resistant populations are most likely to expand under a particular treatment. Such information might allow clinicians to select combinations or treatment sequences designed to prevent the emergence of those populations. The concept is challenging because tumors evolve unpredictably and different patients can follow different trajectories. Nevertheless, the increasing availability of high-resolution molecular data makes predictive resistance management increasingly realistic. Moving from reaction to anticipation could represent one of the most important future developments in kinase-targeted oncology.

8.4 Targeted Degradation and Beyond Inhibition

Traditional kinase inhibitors generally work by occupying a binding site and preventing catalytic activity. Targeted protein degradation takes a different approach by physically removing the target protein from the cell (Hinterndorfer *et al.,* 2025). PROTACs and molecular glues can redirect the ubiquitin–proteasome system toward selected proteins, potentially eliminating both catalytic and scaffolding functions. This may be especially valuable when simple inhibition leaves important non-catalytic functions intact or when resistance mutations reduce inhibitor binding. The rapid expansion of degrader technologies has also produced new molecular designs beyond conventional PROTACs and molecular glues (Hinterndorfer *et al.,* 2025). Nevertheless, degradation depends on several factors, including target accessibility, suitable E3 ligase expression, formation of productive molecular complexes and appropriate pharmacokinetic properties. Resistance to degraders is also possible. Even so, targeted degradation represents a broader conceptual shift in drug discovery: rather than asking whether a protein can be inhibited, researchers can ask whether its cellular abundance or interactions can be deliberately altered. This expanded perspective may create therapeutic opportunities against previously difficult cancer targets.

8.5 Combination with Immunotherapy

Kinase signalling is closely connected to immune regulation, making combinations between kinase inhibitors and immunotherapy an area of considerable interest. Kinases can influence cytokine signalling, immune-cell activation, antigen presentation, inflammatory responses and the behavior of stromal cells. In principle, suppressing oncogenic signalling while simultaneously enhancing antitumor immunity could attack cancer through complementary mechanisms. However, the relationship is not straightforward. Some kinase inhibitors may alter immune-cell function in beneficial ways, whereas others may produce immunological effects that reduce the effectiveness or tolerability of combination treatment. The tumor microenvironment further complicates the picture because immune suppression, hypoxia, abnormal vasculature and stromal signalling can influence both kinase dependence and immune response (Roskoski, 2025). Rational combinations therefore require a strong understanding of the biological context rather than simply combining two active drugs. Biomarkers that identify tumors likely to benefit from the interaction will be important. Continued research may ultimately establish kinase inhibitors as components of broader treatment strategies rather than isolated targeted agents.

8.6 Precision Oncology in Low- and Middle-Income Countries

The scientific progress surrounding kinase inhibitors raises an important practical question: who can benefit from these advances? Precision oncology often depends on molecular testing, specialized laboratories, expensive medicines and long-term monitoring. These requirements can be difficult to meet in low- and middle-income countries, where diagnostic infrastructure and access to targeted therapies may be limited (Adashek *et al.,* 2025). As a result, the global availability of kinase-targeted therapy does not necessarily translate into equal access to its benefits. Addressing this gap will require investment in molecular diagnostic capacity, training, regional research infrastructure, affordable testing and sustainable access to essential medicines. Local clinical research is also important because the frequency of particular cancer-associated alterations and treatment responses may vary among populations. Future progress in kinase-targeted oncology should therefore be measured not only by the number of new inhibitors developed but also by how effectively those therapies reach patients who need them. Greater international collaboration could help reduce the gap between advances in cancer biology and their practical availability worldwide.

9. CONCLUSION

Protein kinases occupy a central position in the biological systems that control cancer-cell growth, survival, metabolism, angiogenesis, migration, metastasis and interactions with the tumor microenvironment. Their abnormal activation through mutations, amplification, fusion events, overexpression and altered signalling has created important therapeutic vulnerabilities and led to the development of a growing number of clinically useful kinase inhibitors (Adashek *et al.,* 2025; Roskoski, 2025). The success of BCR::ABL, EGFR, ALK, BRAF and other kinase-directed therapies demonstrates the value of matching treatment to the molecular characteristics of individual tumors (Druker et al., 2001; Hanrahan *et al.,* 2024; Poei *et al.,* 2024; Yang et al., 2022). However, these successes have also exposed a fundamental weakness of targeted therapy: cancer cells are remarkably adaptable. Resistance can arise through secondary target mutations, bypass signalling, pathway reactivation, clonal evolution, phenotypic plasticity, metabolic adaptation, altered drug exposure and microenvironmental protection (Dell'Aversana *et al.,* 2024; Poei *et al.,* 2024; Yang *et al.,* 2022). Overcoming these challenges will require a shift from single-target thinking toward integrated strategies combining structural drug design, molecular profiling, rational combinations, longitudinal monitoring and evolutionary understanding. Next-generation inhibitors, tumor-agnostic therapies, liquid biopsy, targeted protein degradation and AI-assisted drug discovery offer promising opportunities (Adashek *et al.,* 2025; Hinterndorfer *et al.,* 2025; Roskoski, 2025). Ultimately, the most durable progress is likely to come from anticipating how tumors adapt rather than waiting until resistance is fully established.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest, financial or otherwise, related to this review.

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