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Signaling Pathway-Specific Anticancer Agents: Current Status and Future Prospects

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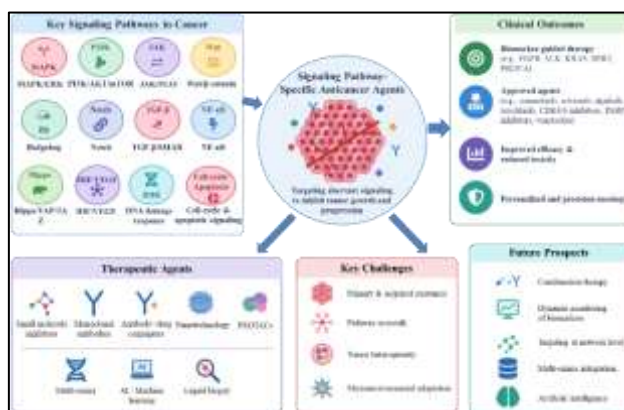
Keywords

Signaling pathways; Targeted therapy; Anticancer agents; Molecular biomarkers; Therapeutic resistance.

ABSTRACT

Introduction: The management of cancer has evolved from conventional cytotoxic chemotherapy to molecularly targeted strategies that exploit aberrant oncogenic signaling. This review summarizes the current status of anticancer agents targeting specific signaling pathways in terms of molecular targets, biomarkers, clinical applications, mechanisms of resistance, and emerging therapeutic approaches. **Methods:** A structured literature search was performed on PubMed/MEDLINE, Scopus, Web of Science, Embase and Google Scholar. Studies published between 2015 and 2026 were preferred, but earlier seminal studies were included when necessary. We included peer-reviewed research, clinical trials, systematic and narrative reviews and regulatory or clinical reports on targeted agents. Studies were screened by title, abstract and full text and data were thematically synthesized based on pathway, target, cancer type, biomarker, clinical status and resistance mechanism. **Results:** Therapeutic pathways involved MAPK, PI3K/AKT/mTOR, JAK/STAT, Wnt/ β -catenin, Hedgehog, Notch, TGF- β /SMAD, NF- κ B, Hippo/YAP/TAZ, HIF/VEGF, DNA damage response, cell-cycle and apoptotic signaling. Established agents such as osimertinib, sotorasib, alpelisib, ruxolitinib, CDK4/6 inhibitors, PARP inhibitors and venetoclax demonstrate the value of biomarker-guided therapy. But primary and acquired resistance, pathway crosstalk, tumor heterogeneity and microenvironmental adaptation remain major limitations. Combination therapy, liquid biopsy, nanotechnology, antibody–drug conjugates, PROTACs, multi-omics and artificial intelligence are promising strategies. **Conclusion:** Signaling pathway-specific therapy has become a cornerstone for the evolution of precision oncology to guide informed treatment. Future progress in durable personalized cancer treatment will depend on the dynamic monitoring of biomarkers, combination strategies, targeting at the network level, and the integration of multi-omics and AI.

Graphical Abstract



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1. INTRODUCTION:

Cancer still represents a major health issue worldwide killing millions of people every year and impacting profoundly the society and economy. The burden of cancer incidence and mortality is projected to rise in the coming decades in the world, primarily as a result of the ageing of the population and exposures to the environment and lifestyles, according to recent estimates by the World Health Organization (WHO) and Global Cancer Observatory. Although the use of new tests and supportive care has improved survival, most cancer deaths continue to be caused by therapeutic resistance and metastasis, so further improved and sustained therapy is needed. One of the features of contemporary cancer is the molecular heterogeneity of the disease [1]. Tumors are not homogeneous or straightforward. They are multi-dimensional dynamic ecosystems that are fuelled by many genetic and epigenetic and microenvironmental changes. Such molecular changes may occur even within a single tumor and occur in different metastasis of the same patient and also between different types of cancer. This diversity can complicate the creation of 'one size fits all' treatments, and often leads to uneven responses to treatments and drug resistance [2].

A key feature of cancer pathogenesis and progression is dysregulation of intracellular signaling pathways. These pathways involve MAPK/ERK, PI3K/AKT/mTOR, JAK/STAT, Wnt/ β -catenin, Hedgehog, Notch, TGF- β /SMAD, NF- κ B and DNA damage response networks that regulate essential cellular functions including proliferation, survival, metabolism, migration and immune evasion. Mutations, amplifications, deletions, or epigenetic modifications within these signaling networks can be oncogenic and drive malignant transformation, tumor growth, and resistance to therapy [3].

For most cancers, the traditional standard of care was conventional cytotoxic chemotherapy that broadly targeted rapidly dividing cells. Agents were effective in some settings, but often very toxic to normal tissues due to lack of selectivity, limiting their therapeutic index. The last 20 years have seen

a revolution in the therapeutic landscape with the introduction of molecularly targeted therapy. Such therapies may be more effective and have less off-target toxicity if they are targeted to tumor-specific molecular vulnerabilities, such as a mutated kinase, abnormal growth factor receptor, or defective DNA repair mechanism [4].

This revolution is being driven by signaling pathway-specific anticancer agents that are rationally designed to modulate or inhibit the activity of dysregulated oncogenic signaling pathways. Conceptually, these agents are predicated on the realization that aberrant signaling is not merely a consequence of cancer, but a fundamental driver of the malignant phenotype. Targeting these pathways holds promise for selective killing of tumor cells, less collateral damage to normal tissues and the potential to overcome or delay resistance mechanisms associated with conventional therapies [5].

Advances in genomics, proteomics, and biomarker discovery have further enabled the identification of those patient subsets most likely to respond to specific targeted agents, giving further support to pathway-directed intervention. Molecular profiling is now an overall goal in cancer care, with precision oncology the objective of matching the right therapy to the right patient at the right time [6].

In this review, we attempt to provide an overview of the mechanistic and clinical aspects of the current landscape of signaling pathway-specific anticancer agents. We will review molecular basis of important oncogenic pathways, highlight approved and emerging agents and discuss their clinical applications and limitations. Special emphasis will be given to mechanisms of primary and acquired resistance, the role of biomarkers in patient selection and the impact of pathway crosstalk on therapeutic outcomes. Finally, we critically evaluate emerging therapeutic modalities and outline future directions for the field, with the aim to inform next-generation strategies for precision cancer therapy.

Methodology

Several scientific databases, including PubMed, Scopus, Web of Science, Embase, and Google Scholar, were used to conduct a comprehensive search of the literature. Publications from 2015 to 2026 were included in the search (with previous key research included as appropriate to give historical background or essential insights). "Signaling pathway," "targeted therapy," "anticancer agents," "clinical trials," "biomarkers," "precision oncology," and particular pathways or agent names were among the search phrases that were chosen and combined with Boolean operators [7].

To maximize scientific rigor and relevance of the review, the inclusion criteria were: peer-reviewed original research; Phase I–III clinical trials; systematic and narrative reviews; regulatory or clinical reports concerning approved targeted agents; and studies pertaining to signaling pathways in cancer. Non peer-reviewed sources, preclinical-only studies (except for mechanistically pivotal), duplicates and case reports and editorials were excluded. All articles were selected based on the aim/title and abstract and then, full text of the articles was checked for eligibility. Key pathways, molecular targets, drugs, classes of drugs, cancer types, biomarkers, clinical status and mechanisms of resistance were all included in the extracted data. Each agent was categorized by signaling pathway, molecular target, cancer type, biomarker, and stage of clinical development to guide thematic synthesis and structured discussion [8, 9].

Molecular Signaling Pathways for Therapeutic Targets in Cancer

Disruption and maladaptation of molecular signaling pathways is an essential component of cancer biology and forms the basis for the hallmarks that define tumor behavior and therapeutic response. These intricate networks control not only normal cellular functions but when dysregulated, drive malignant transformation, support tumor growth and promote resistance to therapy. Recent advances in molecular oncology have shown that these pathways represent new opportunities for precision medicine and improved patient outcomes [10].

Hallmarks of cancer and signaling dysregulation

Aberrant signaling underpins the continued proliferation, evasion of apoptosis, sustained angiogenesis, invasion and metastatic capacity that characterizes cancer. For instance, at the large scale, genomic studies of The Cancer Genome Atlas (TCGA) have shown that more than 90% of solid tumors have alterations in at least one major signaling pathway. For example, TP53 mutations are found in >50% of all cancers, while activating mutations in KRAS and BRAF are identified in 30–45% of lung and colorectal tumors and in nearly 50% of melanomas, respectively. These mutations, amplifications or epigenetic modifications abrogate normal cell cycle control, differentiation and death creating a permissive environment for unrestrained growth and progression. Importantly, dysregulated signaling does not occur in isolation but rather within the framework of tumor microenvironmental factors, and contributes to heterogeneity within and between tumors [11].

Signaling via Receptor and Intracellular

Oncogenic signaling is often initiated at the cell surface, where receptor tyrosine kinases (RTKs)

including EGFR, HER2 and MET play key roles in sensing extracellular cues and transducing signals into the cell. For instance, EGFR mutations are found in 10–15% of Western and up to 50% of Asian NSCLC patients, and HER2 amplification is found in approximately 20% of breast cancers. Other receptors, like G protein-coupled receptors (GPCRs), also contribute to the activation of intracellular networks. Activation of these receptors leads to cascade activation such as MAPK/ERK, PI3K/AKT/mTOR and JAK/STAT pathways. These networks control transcription, translation, metabolism, survival and the immune response. The PI3K/AKT/mTOR pathway is altered in >40% of breast cancers and in many other solid tumors. Convergence and divergence of these signaling axes enable the cancer cells to adapt to environmental stresses and therapeutic interventions [12].

Feedback regulation and pathway crosstalk

Targeting signaling pathways is challenging in many ways, one of which is the crosstalk and feedback regulation between pathways. Cancer signaling pathways are intricately linked networks rather than simple linear pathways. Drug resistance and low effective inhibition is often driven by therapeutic resistance due to parallel activation of other pathways (e.g., PI3K/AKT) upon therapeutic inhibition of one pathway (e.g., MAPK). Another layer of complexity is added by inhibition of mTORC1, which relieves negative feedback and induces the activation of the upstream PI3K/AKT signaling. Systems biology and computational modeling have shown that multiple pathways or nodes need to be targeted simultaneously to achieve effective and successful cancer treatment. This is a clinical situation. BRAF and MEK inhibitors in BRAF mutant melanoma are examples of combination regimens that have better response rates and delay resistance compared to monotherapy [13].

Molecular Biomarkers and Individualized Medicine

Precision oncology is founded on the discovery and utilization of molecular markers. These may be point mutations (EGFR, BRAF), gene fusions (ALK, ROS1) or gene amplification (HER2, MET) that indicate whether this is a targetable mutation or not. For example, BRAF V600E mutation is a biomarker for melanoma patients that show response rate >60% when treated with BRAF/MEK inhibitors. Likewise, ALK fusions in NSCLC are also associated with exquisite responses to ALK inhibitors [14]. New sequencing technology like next generation sequencing (NGS) can provide detailed molecular characterization and guide the application of pathway-specific agents and adaptive treatment approaches. As a summary, understanding of

molecular complexity and the interdependencies of the networks involved in signaling in cancer is essential for the rational design and clinical application of targeted therapies. Biomarkers can be used in clinical decision making which has ushered the precision medicine era, but the challenge of pathway redundancy and resistance still exist (Figure 1) [15].

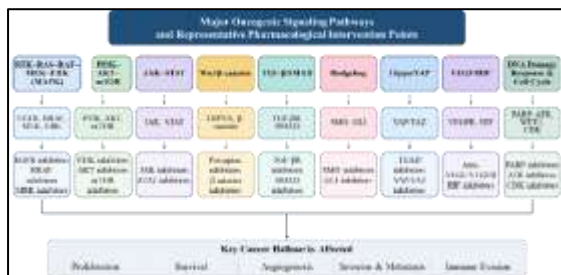


Figure 1. Major oncogenic signaling pathways and their pharmacological intervention sites.

Major Signaling Pathways for Anticancer Drugs

The development and clinical use of drugs that specifically inhibit dysregulated molecular signaling pathways have changed the therapeutic panorama of oncology. These agents take advantage of the vulnerabilities of cancer cells induced by genetic and epigenetic changes in key intracellular pathways. This selectivity leads to enhanced therapeutic efficacy and reduced toxicity compared to non-selective cytotoxic chemotherapies. In this section, we present a detailed and integrated discussion of the major oncogenic pathways, biological roles in cancer, representative targeted agents, clinical applications, resistance mechanisms and the latest advances in next-generation therapeutics [16].

EGFR/RAS/RAF/MEK/ERK (MAPK) cascade

A key axis that regulates cell survival, differentiation, and proliferation is the MAPK pathway. Growth factors often activate it by attaching to receptor tyrosine kinases (RTKs), including EGFR, which activates RAS and initiates a series of events involving RAF, MEK, and ERK kinases. Many cancers, including melanoma, colorectal cancer (CRC), and non-small cell lung cancer (NSCLC), often exhibit dysregulation of this cascade. Among the most prevalent gene alterations in cancer are those in this pathway: About 50% of East Asian individuals with NSCLC and 10–15% of Caucasian patients had EGFR mutations, KRAS mutations occur in around 30–45% of CRC and around 25% of lung adenocarcinomas, and BRAF V600E mutations occur in around 50% of melanomas and 10% of CRC. These mutations cause constitutive pathway activation, leading to oncogenesis, tumor progression and resistance to apoptosis [17].

Several targeted agents have been developed to inhibit specific nodes of MAPK pathway. EGFR inhibitors such as erlotinib and gefitinib and later generation EGFR inhibitors such as osimertinib have transformed the treatment paradigm in EGFR-mutant NSCLC. Osimertinib had a median progression-free survival of 18.9 months, whereas conventional EGFR TKI has a median of 10.2 months. Although KRAS had long been thought to be "undruggable," sotorasib and adagrasib are first-in-class drugs that specifically target the G12C mutant version, which can be targeted in NSCLC with objective response rates of around 37%. The mainstay of therapy for BRAF-mutant melanoma is BRAF inhibitors (vemurafenib and dabrafenib), either by themselves or in conjunction with MEK inhibitors (trametinib and cobimetinib), which have improved response rates, durability, and overall survival [18].

However, the clinical use of MAPK pathway inhibitors is limited by the development of resistance mediated by on-target mutations such as EGFR T790M, bypass pathway activation by MET or HER2 amplification and pathway reactivation via feedback loops. Emerging strategies in response to this include the development of fourth generation EGFR inhibitors, additional KRAS allele-specific compounds, and rational combination regimens targeting multiple nodes or parallel pathways simultaneously [19].

PI3K/AKT/mTOR Signaling Pathway

The PI3K/AKT/mTOR pathway is an important regulator of cell metabolism, growth and survival. PI3K activation generates PIP3, which recruits and activates AKT, leading to downstream phosphorylation events that drive proliferation and prevent apoptosis. mTOR reads these signals and controls cell growth and metabolic adaptation. Deregulation of this pathway is frequent in cancer. PIK3CA mutations, for example, can be found in 30 to 40% of breast cancers, but also in other tumors such as endometrial, ovarian and colorectal cancers. Loss of PTEN (a tumor suppressor and negative regulator of PI3K) is found in up to 50% of glioblastomas and 20–40% of endometrial cancers. AKT activation is seen in a broad range of tumor types [20].

Medications that target this pathway include copanlisib and idelalisib, which target the delta isoform of PI3K in lymphomas, and PI3K inhibitors like alpelisib, which is authorized for PIK3CA-mutated, hormone receptor-positive/HER2-negative breast cancer. Clinical studies for breast, prostate, and other malignancies are now in their final stages for AKT inhibitors such as capivasertib and ipatasertib. Renal cell carcinoma, breast cancer, and pancreatic

neuroendocrine tumors may all be treated with the mTOR inhibitors everolimus and temsirolimus. Crucially, fulvestrant with alpelisib increased the median progression-free survival in breast cancer from 5.7 months to 11.0 months. Because of feedback activation of upstream RTKs, metabolic adaptability, and compensation by other PI3K isoforms, resistance to PI3K/AKT/mTOR inhibitors is prevalent. As a result, more selective or dual inhibitors have emerged [21].

JAK/STAT Signaling Pathway

The JAK/STAT pathway is important for transmitting signals from cytokine and growth factor receptors to the nucleus, regulating proliferation, differentiation, and immune responses. Dysregulated activation, particularly through JAK2 V617F mutations, is a signature of myeloproliferative neoplasms (MPNs) and some leukemias. Ruxolitinib and fedratinib are oral JAK1/2 inhibitors approved for the treatment of myelofibrosis and polycythemia vera. Ruxolitinib improves symptoms and reduces spleen size in approximately half of treated patients. But resistance can occur through additional pathway mutations and clonal evolution, and next generation inhibitors and combination approaches are being investigated [22].

Wnt/ β -catenin Pathway

The Wnt/ β -catenin pathway plays a critical role in embryonic development, tissue regeneration and stem cell maintenance. Importantly, mutations in APC and CTNNB1 (β -catenin) cause constitutive activation of the pathway, especially in colorectal cancer, where APC loss is observed in >80% of cases. Targeting the pathway is difficult because it is complex and involved in normal tissue homeostasis. Porcupine inhibitors like WNT974, which inhibit Wnt ligand secretion, are in early phase trials in solid tumors, while β -catenin antagonists remain mostly in the preclinical arena [23].

Hedgehog and Notch Signaling Pathways

Both Hedgehog and Notch pathways are involved in cell fate, differentiation and stem cell dynamics. In basal cell carcinoma, mutations in SMO, which is a member of the Hedgehog pathway, activate the pathway. Dysregulation of Notch has been implicated in T-cell acute lymphoblastic leukemia and some solid tumors. Vismodegib and sonidegib are SMO inhibitors that have been approved for advanced basal cell carcinoma and γ -secretase inhibitors are being experimentally tested to block Notch activation in T-cell malignancies. Unfortunately, the resistance to SMO inhibitors can develop through secondary SMO mutations or pathway bypass and the search for tolerable Notch inhibitors continues [24].

TGF- β /SMAD and NF- κ B Pathways

TGF- β signaling is a major driver of epithelial-mesenchymal transition (EMT), invasion and immune evasion. NF- κ B is a master regulator of inflammation and cell survival and is often constitutively active in a wide variety of cancers. TGF- β receptor inhibitors such as galunisertib are in trials in glioma, pancreatic and liver cancer and IKK inhibitors targeting NF- κ B are in preclinical development. The dual tumor-suppressive and tumor-promoting roles of these pathways make targeted intervention complex, requiring better patient selection and combination strategies [25].

Hippo/YAP/TAZ and HIF/VEGF Pathways

YAP/TAZ hyperactivation increases stemness and survival in a number of solid tumors, whereas the Hippo/YAP/TAZ pathway regulates organ growth, regeneration, and cell proliferation. The response to hypoxia and the angiogenesis process depend heavily on the HIF/VEGF axis. To encourage neovascularization, HIF-1 α and HIF-2 α control VEGF expression. TEAD inhibitors that target YAP/TAZ transcription are in preclinical research, whereas belzutifan and HIF-2 α inhibitors are authorized for renal cell carcinoma linked with von Hippel-Lindau (VHL). VEGF inhibitors including bevacizumab and ramucirumab are widely used in colorectal, lung and renal cancers. Bevacizumab provides an OS benefit of about four months in metastatic CRC when given in combination with chemotherapy. However, resistance frequently develops via adaptive angiogenesis and upregulation of alternative pro-angiogenic signals [26].

Cell cycle and DNA damage response signaling

Cancer cells show a high dependence on defective DNA damage response (DDR) pathways and dysregulated cell cycle checkpoints due to their genomic instability and replicative stress. Olaparib, niraparib, and rucaparib are PARP inhibitors approved for BRCA-mutated ovarian, breast, pancreatic, and prostate cancers. They exploit the concept of synthetic lethality in tumors with deficient homologous recombination [27]. ATR and ATM inhibitors are being tested in early clinical trials for tumors with DDR deficiencies. WEE1 inhibitors like adavosertib inhibit the G2/M checkpoint and are in clinical trials for ovarian and other cancers. The CDK4/6 inhibitors (palbociclib, ribociclib, abemaciclib) have changed the treatment landscape for hormone receptor-positive/HER2-negative breast cancer, with a doubling of the median progression-free survival to approximately 24 months when adding CDK4/6 inhibitors, versus 14 months with endocrine therapy alone. Resistance to these agents can occur by restoration of homologous recombination, drug efflux, and mutation of the drug-binding sites [28].

Apoptotic Signaling

Overexpression of anti-apoptotic members, such as BCL-2 and MCL-1, may result in resistance to cell death in hematologic malignancies and some solid tumors. The BCL-2 family of proteins regulates the mitochondrial mechanism of apoptosis. Venetoclax is a first-in-class BCL-2 inhibitor that can be used to treat acute myeloid leukemia and chronic lymphocytic leukemia. Combination therapy with venetoclax has been shown to achieve complete remission rates as high as 66% in acute myeloid leukemia patients who are unfit for intensive chemotherapy. MCL-1 inhibitors and BH3 mimetics are in clinical development to bypass resistance due to upregulation of other anti-apoptotic proteins or clonal evolution [29, 30].

Clinical status, biomarkers and therapeutic applications

A new era of precision oncology, where treatment is increasingly customized to the genetic and molecular landscape of individual malignancies, has been ushered in by the translation of molecularly targeted medicines from lab to bedside. The European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) have approved signaling pathway-specific anti-cancer drugs, demonstrating their high effectiveness and safety in certain patient groups. Osimertinib, a third-generation EGFR tyrosine kinase inhibitor approved for EGFR-mutant non-small cell lung cancer (NSCLC); sotorasib, the first KRAS G12C inhibitor approved for KRAS-mutant NSCLC; alpelisib, a PI3K α inhibitor for PIK3CA-mutated, hormone receptor-positive breast cancer; and venetoclax, a BCL-2 inhibitor that is currently the standard of care for acute myeloid leukemia (AML) and chronic lymphocytic leukemia (CLL) [31].

The clinical pipeline continues to expand with next-generation inhibitors and novel combination regimens targeting multiple nodes of the same pathway or overcoming resistance. For example, next generation KRAS inhibitors are targeting other common KRAS mutations (e.g., G12D and G12V) and combination strategies (e.g., dual EGFR and

MET inhibition or BRAF/MEK inhibition) are used to prevent adaptive resistance and improve outcomes in melanoma, NSCLC and colorectal cancer. In addition several agents are being tested for pathway aberrations in breast, renal and hematologic malignancies with an increasing focus on rational biomarker-based therapy selection [32].

This paradigm focuses on molecular biomarkers to aid in the selection of initial treatment and subsequent management. Mutations in EGFR, BRAF, and KRAS are routinely evaluated in NSCLC and melanoma to guide the use of pathway-specific inhibitors. Likewise, PIK3CA mutations and PTEN loss are important for stratifying patients for PI3K pathway therapy in breast and endometrial cancers, and CDK4/6 amplification may be predictive of sensitivity to cell cycle inhibitors. In hematologic malignancies, BCL-2 expression is utilized to select patients for venetoclax therapy. The growing application of companion diagnostics – including liquid biopsy approaches (such as circulating tumor DNA [ctDNA] analysis and next generation sequencing [NGS] panels) – enables real-time, minimally invasive molecular profiling, better detection of resistance mutations and the opportunity to modify treatment strategies [33].

Table 1 summarizes representative signaling pathway-specific anticancer agents, their major molecular targets, associated biomarkers, clinical indications and current regulatory status. For example, osimertinib is approved for NSCLC and targets EGFR mutations in the MAPK pathway, whereas vemurafenib is used for BRAF-mutant melanoma. Two drugs, alpelisib and everolimus, target the PI3K/AKT/mTOR axis and have approvals in breast and renal cancers, respectively, based on the presence of actionable PIK3CA mutations. Ruxolitinib (JAK/STAT pathway example) has been approved for the treatment of myeloproliferative neoplasms with the JAK2 V617F mutation. Venetoclax (BCL-2-directed agent) targets the apoptosis pathway, where the treatment is guided by the BCL-2 expression in CLL and AML [34].

Table 1. Representative signaling pathway-specific anticancer agents, targets, biomarkers, indications, and clinical status.

Pathway	Target	Agent	Biomarker	Indication	Status	Ref.
MAPK	EGFR	Osimertinib	EGFR mutation	EGFR-mutated non-small cell lung cancer (advanced/metastatic NSCLC)	Approved	[35]
	KRAS (G12C)	Sotorasib	KRAS mutation	KRAS G12C-mutant NSCLC (previously treated cases)	Approved/Trials	[36]
	BRAF (V600E)	Vemurafenib	BRAF mutation	BRAF V600E-mutant metastatic or unresectable melanoma	Approved	[37]
PI3K/AKT/mTOR	PI3K	Alpelisib	PIK3CA mutation	PIK3CA-mutated, hormone receptor-positive advanced breast cancer	Approved	[38]

Pathway	Target	Agent	Biomarker	Indication	Status	Ref.
	mTOR	Everolimus	Pathway activation	Advanced hormone receptor-positive breast cancer and renal cell carcinoma	Approved	[39]
JAK/STAT	JAK2	Ruxolitinib	JAK2 V617F	Myeloproliferative neoplasms (polycythemia vera, myelofibrosis)	Approved	[40]
Apoptosis	BCL-2	Venetoclax	BCL-2 expression	Chronic lymphocytic leukemia (including relapsed/refractory cases)	Approved	[41]
	BCL-2	Venetoclax	BCL-2 expression	Acute myeloid leukemia (newly diagnosed/elderly or unfit patients)	Approved	[42]

Mechanisms of resistance to therapy and pathway crosstalk

The remarkable progress in signaling pathway-specific anticancer agents has been universally tempered by therapeutic resistance. Early responses to targeted treatments may be dramatic, but resistance often develops, leading to disease progression and limiting long-term efficacy. Resistance mechanisms are complex reflecting the complexity and adaptability of cancer biology. Understanding these phenomena will not only inform the development of new therapeutic approaches but also guide the rational design of combination treatments and patient selection in precision oncology [43].

Primary and Acquired Resistance

Resistance to targeted therapy is generally categorized into primary (intrinsic) resistance and acquired (secondary) resistance. Primary resistance occurs prior to therapy exposure and is often ascribed to pre-existing genetic, epigenetic or microenvironmental factors that render tumor cells inherently insensitive to the drug. For example, a patient with a KRAS mutation in a non-small cell lung cancer (NSCLC) tumor will not respond to EGFR inhibitors as the downstream pathway remains constantly active even when EGFR is blocked. Acquired resistance, in contrast, occurs following an initial period of clinical benefit as tumor cells adapt under the selective pressure of therapy. This adaptation may be facilitated by further genetic changes, activation of compensatory pathways or phenotypic changes in the tumor cell population [44].

On-target Mutations & Amplification

One well-known mechanism of acquired resistance is via secondary (on-target) mutations in the molecular target of the drug that diminish drug binding or efficacy. In EGFR-mutant NSCLC, for example, the EGFR T790M 'gatekeeper' mutation is found in approximately 50–60% of patients progressing on first- or second-generation EGFR tyrosine kinase inhibitors (TKIs). This mutation affects the kinase domain making the drug less effective and re-establishing downstream signaling.

This has been partially overcome by the introduction of 3rd generation inhibitors (e.g. osimertinib), however, new resistance mutations (e.g. EGFR C797S) are still emerging. Also, in chronic myeloid leukemia (CML) treated with BCR-ABL inhibitors, T315I mutation causes widespread resistance to several TKIs. The other resistance mechanism is gene amplification of the target gene. For instance, the MET gene can be inhibited by an EGFR mutation, but this is counterbalanced by additional copies of the MET gene [45].

Signaling Bypass

Bypass signaling is the increased expression of different pathways or receptors that can support survival and proliferation in the presence of targeted therapy. One example of this is the amplification or upregulation of MET or HER2 in EGFR inhibitor resistant NSCLC where the tumour cells become addicted to the other receptor, which is not targeted by the inhibitors. This bypass signaling can be mediated by the upregulation of insulinlike growth factor1 receptor (IGF-1R), AXL or other receptor tyrosine kinases. The mechanisms illustrate the redundancy and plasticity of oncogenic signaling networks and the argument for combination or multi-targeted therapeutic strategies [46].

Downstream Pathway Re-activation

However, oncogenic signaling and resistance can be reactivated from nodes down-stream by activation of effectors, even if the upstream nodes have been successfully inhibited. After some initial response to BRAF inhibitors, NRAS mutations, MEK mutations or upregulation of the COT1 kinase may reactivate the MAPK pathway in BRAF-mutant melanoma. This leads to re-activation of ERK phosphorylation and survival of the tumour cells. In the PI3K/AKT/mTOR pathway, inhibition of mTORC1 may overcome negative feedback on PI3K pathway activation, leading to paradoxical activation of AKT. Such re-activation demonstrates the need for multi-target therapy to obtain sustained results as has been observed with dual BRAF and MEK inhibitors [47].

Tumor Heterogeneity and Plasticity

A significant challenge for durable responses

obtained with targeted therapy is that tumors tend to be heterogeneous, meaning that there are genetically or phenotypically distinct subpopulations within the same tumor. Mutations are continuous and selection pressures favor resistant clones, leading to clonal evolution. Cancer cells can adopt different states of the disease, such as the epithelial to mesenchymal transition (EMT), depending on the therapeutic treatment or microenvironmental changes, this is called phenotypic plasticity. These processes lead to primary and acquired resistance and make it difficult for biomarker-based treatment approaches since one biopsy may only reflect a small fraction of the mechanisms of resistance in a tumor [48].

Cancer Stem Cell

Cancer stem cells (CSCs) are a subset of tumor cells, which has the capacity to self-renew and to differentiate and resist therapy. CSCs are frequently associated with the expression of drug efflux pumps and anti-apoptotic proteins, which make them resistant to conventional and targeted drugs. Once the tumor is shrunk, the remaining CSCs can re-invade the tumor and cause a relapse and metastasis. Their intrinsic resistance emphasizes the importance of therapies aimed at targeting CSC populations, possibly in combination with conventional therapies [49].

Tumor Microenvironment Mediated Resistance

The tumor microenvironment (TME) is critical for the modulation of therapeutic response. Non-malignant stromal cells including fibroblasts, immune cells, and endothelial cells produce growth factors, cytokines, and components of the extracellular matrix that protect tumor cells from therapy-induced stress. Hypoxic conditions inside TME can induce expression of survival pathways (eg. HIF-1 α /VEGF) and promote immunosuppressive milieu that blunts the efficacy of targeted and immune therapies. Crosstalk between tumor and stromal cells drives resistance, highlighting the need for strategies to break these protective interactions [50].

Cross-Talk Between Pathways

Finally, resistance is invariably mediated through crosstalk between signaling pathways. The main oncogenic signaling routes, including MAPK, PI3K/AKT/mTOR, JAK/STAT, Wnt and NF- κ B, are tightly interconnected and have wide-ranging feedback and compensatory networks. Inhibition of one pathway often results in activation of another, such as PI3K/AKT activation when the MAPK pathway is inhibited. This network resilience calls for multi-pathway inhibition or adaptive therapy strategies and is being tackled by rational drug combinations and the incorporation of systems biology approaches into drug development [51].

Approaches to Enhance the Efficacy of Signaling-Targeted Therapy

Considerable progress has been made in the design of anticancer agents directed against specific signaling pathways. Therapeutic resistance, pathway crosstalk and tumor heterogeneity, however, present challenges to the durability and breadth of responses observed in patients. To overcome these barriers, several novel strategies have been designed to improve the efficacy and extend the clinical benefit of targeted treatments (Table 2) [52].

Combination Pathway Blockade

One of the main strategies is combination pathway inhibition and can be divided into vertical and horizontal inhibition. Vertical inhibition is targeted at inhibiting multiple nodes within the same signaling cascade to prevent pathway reactivation and resistance. An excellent example is the combination of BRAF and MEK inhibitors in BRAF V600E-mutant melanoma. Vemurafenib and dabrafenib, two BRAF inhibitors, have strong initial response rates; nevertheless, resistance often develops by reactivation of downstream MEK-ERK signaling. By blocking this feedback, the addition of MEK inhibitors (such as trametinib) improves overall survival, progression-free survival, and the development of cutaneous toxicities linked to paradoxical MAPK activation. On the other hand, in order to stop compensatory activation, horizontal inhibition targets parallel signaling pathways. For instance, concurrent targeting of the MAPK and PI3K/AKT/mTOR pathways (with MEK and PI3K inhibitors) may overcome resistance shown when each route is blocked separately. This approach is being actively investigated in clinical trials for a range of solid tumors and hematologic malignancies [53].

Immunotherapy + Targeted Therapy

Combining immunotherapy and targeted treatment is another potential strategy. Kinase inhibitors may improve the effectiveness of immune checkpoint inhibition and alter the tumor microenvironment and immunogenicity of cancer cells. When VEGF inhibitors and PD-1/PD-L1 inhibitors are combined, response rates and survival rates for renal cell carcinoma are better than with conventional treatments. Additionally, preclinical and clinical studies suggest that MAPK pathway inhibitors may enhance T-cell infiltration and tumor antigen presentation, which justifies their combination with PD-1 inhibitors in melanoma and NSCLC. However, some combinations may exacerbate immune-related adverse effects, necessitating careful timing and toxicity considerations [54].

Targeted Therapy with Chemotherapy or Radiotherapy

The combination of targeted agents with chemotherapy or radiotherapy takes advantage of both direct cytotoxicity and pathway inhibition to produce synergistic effects. For instance, improved response rates and delayed resistance have been observed by combining EGFR inhibitors with platinum-based chemotherapy in NSCLC or by adding BCL-2 inhibitors to hypomethylating agents in AML. In some instances, radiosensitizers are used as targeted agents to boost the effectiveness of radiotherapy through inhibition of DNA repair or induction of apoptosis [55].

Synthetic Lethality

Synthetic lethality targets the weakness brought about by certain genetic changes in cancer cells. The most clinically advanced example is the use of PARP inhibitors in cancers with defects in homologous recombination repair, such as BRCA1/2-mutated breast and ovarian cancers. Inhibition of PARP leads to accumulation of DNA damage and selective killing of tumor cells compared with normal cells. Synthetic lethality is a very hot topic and people are working very hard to identify new gene-drug pairs and to extend the use of synthetic lethality through combination strategies [56].

Sequential and Adaptive Treatment

As tumor cell populations dynamically evolve under therapeutic pressure, sequential and adaptive treatment strategies are being developed. Sensitive

diagnostics such as liquid biopsies for circulating tumor DNA can be used to track molecular responses, allowing clinicians to modify therapy in real time, switching agents or combinations as resistance develops. The adaptive approach is designed to avoid clonal selection and extend response duration [57].

Targeted Delivery Based on Nanotechnology

Advances in nanotechnology have facilitated the creation of targeted delivery systems for anticancer agents. Nanoparticles, liposomes, and other delivery vehicles may boost the accumulation of drug in the tumor, improve the stability of the drug, and reduce the off-target toxicity. Delivery using nanotechnology looks particularly promising for drugs with a narrow therapeutic window or for the co-delivery of multiple agents [58].

Antibody–Drug Conjugates and Multispecific Therapies

Modern approaches that combine the potency of cytotoxic drugs or several targeting moieties with the specificity of monoclonal antibodies include antibody–drug conjugates (ADCs) and multispecific therapies. With little systemic exposure, ADCs like trastuzumab emtansine (T-DM1) for HER2-positive breast cancer are designed to deliver very powerful medications straight to tumor cells that express a particular antigen. Multispecific antibodies or bi-specific T-cell engagers (BiTEs) can target more than one antigen at the same time or link tumor and immune cells to boost anti-tumor responses [59].

Table 2. Major mechanisms of resistance and emerging strategies to overcome resistance.

Target/Pathway	Resistance Mechanism	Molecular Basis	Therapeutic Consequence	Overcoming Strategy	Ref.
EGFR	T790M gatekeeper mutation	Steric hindrance in ATP-binding pocket	Loss of response to first/second generation EGFR-TKIs	Osimertinib; third-generation EGFR inhibitors	[60]
	C797S mutation	Prevents covalent binding of irreversible inhibitors	Resistance to osimertinib	Allosteric EGFR inhibitors; combination therapy	[61]
	MET amplification	Activation of bypass signaling	EGFR-TKI resistance	EGFR + MET inhibitor combinations	[62]
	MAPK pathway reactivation	MEK/ERK feedback activation	Drug resistance and tumor regrowth	Combined BRAF + MEK inhibition	
BRAF	NRAS mutation	Upstream pathway reactivation	Reduced response to BRAF inhibitors	MEK inhibitors; ERK pathway blockade	[63]
PI3K/AKT/mTOR	PTEN loss	Constitutive PI3K pathway activation	Therapeutic resistance	PI3K/mTOR dual inhibition	[64]
	AKT activation	Downstream signaling persistence	Reduced drug efficacy	AKT inhibitors; combination therapy	
JAK/STAT	JAK2 secondary mutations	Altered kinase domain binding	Loss of ruxolitinib sensitivity	Next-generation JAK inhibitors	[65]
	STAT3 hyperactivation	Persistent transcriptional signaling	Cytokine-independent survival	STAT3 inhibitors; combination immunotherapy	
Apoptosis (BCL-2)	MCL-1 upregulation	Alternative anti-apoptotic survival pathway	Venetoclax resistance	MCL-1 inhibitors; combination BCL-2 blockade	[66]
	BAX/BAK downregulation	Impaired apoptotic execution	Reduced apoptosis induction	BH3 mimetics combination therapy	
RTK	Ligand overexpression	Autocrine/paracrine	Drug resistance across TKIs	Ligand-neutralizing	[67]

Target/Pathway	Resistance Mechanism	Molecular Basis	Therapeutic Consequence	Overcoming Strategy	Ref.
(general)		signaling activation		antibodies	
MAPK/RTK cross-talk	EGFR-HER2 dimerization	Compensatory receptor signaling	Resistance to single-target therapy	Dual HER inhibition (EGFR/HER2)	[68]

Translational Issues and Future Directions

The future of signaling pathway targeted therapy of cancer is moving away from single target inhibition and toward network level intervention. Tumor cells are seldom dependent on a single oncogenic driver, but rather utilize a network of connected signaling pathways which compensate for therapy-induced inhibition. Therefore, next generation strategies are aimed at simultaneous targeting of multiple signaling nodes and feedback loops, using systems biology and network pharmacology approaches for designing more effective and durable interventions.

Precision oncology is leading the way in personalized and adaptive therapy [52]. The integration of multi-omics technologies such as genomic, transcriptomic, proteomic and metabolomic data can provide a better understanding of tumor heterogeneity and evolution. This in turn allows for dynamic adaptation of therapy as tumors evolve under selective pressure. Circulating tumor DNA (ctDNA) analysis and other liquid biopsy approaches have the potential to enable minimally invasive real-time monitoring of emergent resistance mutations, clonal evolution, and disease progression, facilitating timely therapeutic modifications [69].

Artificial Intelligence (AI) and machine learning will transform the way patient stratification and therapeutic decision making are made. Algorithms based on AI can quickly process multi-omics data, clinical and imaging parameters to accurately forecast patient responses, combination of treatments and new therapeutic targets. This is one crucial capability to overcome the formidable challenge of intratumoral heterogeneity, which leads to variable sensitivity and resistance of individual cells within the tumor of a single patient. Combining therapies and adapting them in real time with AI and molecular monitoring will be critical to outpacing the evolution of tumor cells and achieve long-lasting remissions [70].

Next generation combination therapies aim to prevent or overcome resistance and often include novel agents such as PROTACs, molecular glues or RNA-based therapeutics, in addition to conventional targeted drugs. But the therapeutic index, the balance between efficacy and toxicity, is critical to optimize. At the same time, it is equally important to make these advanced therapies accessible and affordable as high costs may prevent their broad

acceptance [71].

Lastly, the translation of preclinical findings into clinical practice remains a major bottleneck. Filling the void will need more predictive preclinical models, faster regulatory paths and joint efforts among academia, industry and regulatory agencies. The end game is to deliver on the promise of precision oncology and bring personalized, network-informed cancer therapy to all patients (Figure 2) [72].

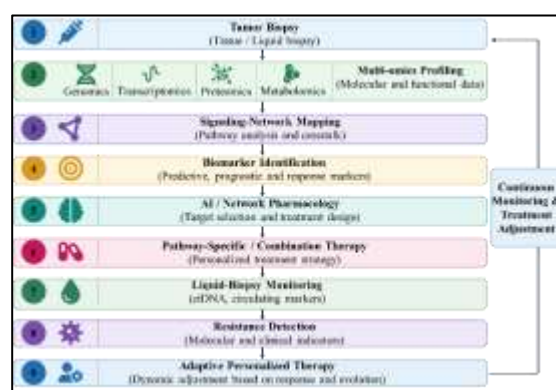


Figure 2. Future framework for precision cancer therapy based on signaling-network profiling, biomarker selection, targeted treatment, and dynamic monitoring.

CONCLUSION:

Signaling pathway specific anticancer agents have transformed cancer therapy by enabling selective interference with the molecular abnormalities that drive tumor growth, survival, angiogenesis, metastasis, and treatment resistance. The evidence reviewed highlights clinically important advances across MAPK, PI3K/AKT/mTOR, JAK/STAT, apoptosis, DNA damage response, angiogenic and other oncogenic pathways, with biomarkers to inform patient selection. However, obstacles to durable responses such as primary and acquired resistance, pathway crosstalk, tumor heterogeneity, cancer stem cells, and tumor microenvironmental adaptation still exist. Progress will depend on combination and adaptive treatment strategies, real-time monitoring by liquid biopsy, multi-omics-guided precision medicine, and network-level therapeutic approaches. Emerging technologies such as PROTACs, multispecific therapeutics, nanotechnology, RNA-based strategies, and artificial intelligence have the potential to further widen the therapeutic landscape and facilitate personalized and durable cancer care.

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