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Targeted Therapeutics for Cancer Treatment: A Review of Kinase Inhibitors, Angiogenesis Inhibitors, and Other Molecularly targeted Agents

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Abstract

Targeted therapeutics have transformed modern oncology by offering precision, efficacy, and improved tolerability compared to conventional cytotoxic chemotherapy. This review synthesizes current advances in molecularly targeted cancer treatments, with a focus on kinase inhibitors, angiogenesis inhibitors, and other emerging classes of precision medicines. Kinase inhibitors remain central to targeted therapy, exploiting dysregulated signaling pathways such as Epidermal Growth Factor Receptor (EGFR), Human Epidermal Growth Factor Receptor 2 (HER2), B-Rapidly Accelerated Fibrosarcoma (BRAF), Anaplastic Lymphoma Kinase (ALK), and Phosphatidylinositol 3-Kinase/AKT (PI3K/AKT) to halt tumor progression across diverse malignancies. Parallel progress in anti-angiogenic strategies has reshaped therapeutic approaches for solid tumors by disrupting Vascular Endothelial Growth Factor (VEGF)-mediated vascular growth and tumor nutrient supply. Beyond these established categories, newer targeted agents such as Poly (ADP-ribose) Polymerase (PARP) inhibitors, proteasome inhibitors, epigenetic modulators, and antibody drug conjugates are expanding the therapeutic landscape by exploiting tumor-specific vulnerabilities and introducing innovative mechanisms of action. Despite significant clinical benefits, challenges such as acquired resistance, tumor heterogeneity, limited biomarker accuracy, and therapy-related toxicity continue to constrain treatment outcomes. Addressing these barriers requires a deeper understanding of adaptive signaling networks, rational drug combinations, and integrative precision-medicine approaches. Emerging tools such as liquid biopsies, multi-omic profiling, and AI-driven decision systems hold promise for refining patient selection, predicting therapeutic responses, and guiding personalized interventions. This review provides a comprehensive and well-focused evaluation of established and evolving targeted therapies, highlighting their mechanisms, clinical applications, limitations, and future directions. By integrating current evidence and emerging innovations, it aims to offer a clear understanding of how molecularly targeted agents are reshaping the aspect of cancer treatment and to inspire continued research in this rapidly advancing field.

Keywords: *Kinase Inhibitors, Cancer, Therapy, Angiogenesis Inhibitors, Drug Resistance, and Precision Oncology.*

1. Introduction

Recently, cancer therapy has shifted dramatically from non-specific cytotoxic chemotherapy toward precision medicine that targets molecular aberrations within tumors. Molecularly targeted agents disrupt oncogenic proteins or signaling pathways that are central to malignant cell survival and growth, rather than indiscriminately damaging all proliferating cells. This strategy yields more effective cancer control with fewer off-target effects, especially when paired with genomic profiling to stratify patients based on actionable biomarkers [1, 2]. Advances in next-generation sequencing, liquid biopsy, and companion diagnostics now enable oncologists to individualize therapy, driving both regulatory approval and clinical adoption of precision agents [1, 3].

Among targeted therapies, kinase inhibitors remain foundational, owing to the central role of dysregulated phosphorylation signaling in tumorigenesis. Protein kinases, both receptor tyrosine kinases (RTKs) and serine/threonine kinases, are frequently mutated, overexpressed, or constitutively active in cancer. Modern small molecules have evolved to include ATP-competitive inhibitors, allosteric compounds, and even covalent binders, enhancing specificity and potency [1, 4]. Clinically, these agents have revolutionized treatment for malignancies such as EGFR-mutated lung cancer, BCR-ABL-positive leukemia, and HER2-amplified

breast cancer [1]. Nevertheless, resistance is a persistent challenge: tumors escape through secondary kinase mutations, bypass pathway activation, or compensatory signaling, demanding next-generation inhibitors and smarter combination strategies [2, 4].

Targeting tumor angiogenesis through inhibition of the VEGF/VEGFR axis is another cornerstone of modern oncology. Agents such as monoclonal antibodies, ligand traps, and VEGFR-specific small molecules can deprive tumors of vascular support, impairing growth [5, 6]. For example, highly selective VEGFR2 inhibitors have shown favorable biochemical profiles and antitumor activity in solid malignancies [5]. However, the clinical benefits of anti-angiogenic therapy are often undermined by adaptive resistance: tumors may invoke alternative pro-angiogenic pathways, co-opt existing vessels, or exploit hypoxic microenvironments to survive [6, 7]. In addition, vascular toxicities such as hypertension are common and may limit therapy, especially when combined with other targeted agents [8, 9].

Beyond kinase blockade and angiogenesis inhibition, a growing suite of other molecularly targeted therapies is reshaping the oncology space. PARP inhibitors, for example, exploit synthetic lethality by targeting DNA-repair-deficient tumors, particularly those harboring BRCA mutations [3, 10]. Epigenetic modulators such as histone deacetylase (HDAC) or DNA methyltransferase (DNMT) inhibitors reprogram aberrant gene expression in cancer cells [1, 2]. Proteasome inhibitors disturb cellular protein homeostasis, while antibody drug conjugates (ADCs) deliver potent cytotoxins specifically to cancer cells, sparing normal tissues [4, 10].

These therapies increasingly integrate with cutting-edge technologies like multi-omics, liquid biopsy, and artificial intelligence to more precisely guide treatment decisions [2, 3].

The scope and purpose of this review are to offer a highly focused, clinically relevant synthesis of the rapidly evolving field of molecularly targeted cancer therapeutics. Specifically, three major therapeutic classes, including kinase inhibitors, angiogenesis inhibitors, and other targeted modalities such as PARP inhibitors, epigenetic agents, proteasome inhibitors, and ADCs, were examined, and their mechanisms of action, clinical applications, and approved uses are also discussed. We critically analyze major resistance mechanisms, including genetic mutations, signaling bypass, microenvironmental adaptation, and toxicity-related limitations, drawing on recent trials and preclinical insights. In addition, we identify strategies to overcome these barriers through next-generation compounds, rational combinations, sequencing approaches, and biomarker-guided patient selection. We also highlight emerging innovations such as circulating tumor DNA monitoring, integrative multi-omic tumor profiling, and AI-driven predictive models that hold promise for adaptive therapy. Finally, we address translational and practical challenges such as regulatory issues, cost, and access disparities across health systems and propose actionable recommendations for clinicians, researchers, and policy makers. By integrating mechanistic, clinical, and translational perspectives, this review aims to inform evidence-based decision-making and chart future directions toward more effective and equitable deployment of targeted therapies in oncology.

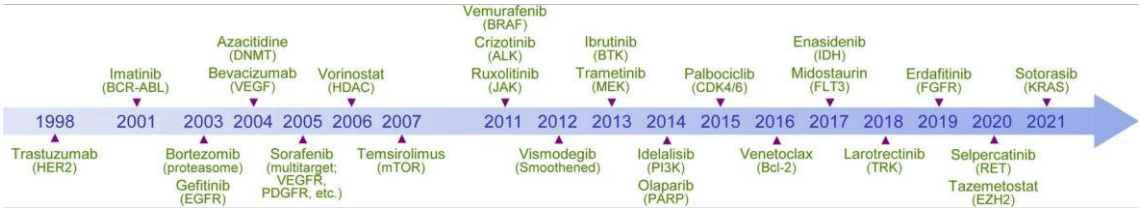

Figure 1. Timeline for the approval of selected molecular targeted therapeutic agents. The figure illustrates the years to which each of the therapeutic agents was approved ranging from 1998 to 2021.
***Source:** [11]*

Molecular Foundations of Targeted Therapy

A deep understanding of the molecular architecture of cancer is fundamental to the development and effective use of targeted therapies. The two major types of molecular targeted therapy are monoclonal antibodies (mAbs) and small molecule kinase inhibitors (SMKIs) [11, 12]. Unlike conventional cytotoxic treatments, molecularly targeted agents are designed to interfere with specific genetic or biochemical abnormalities that drive malignant transformation and progression. These therapeutic strategies rely on identifying disrupted signaling pathways, characterizing actionable genomic alterations, and integrating biomarker-guided diagnostics to match patients with the most appropriate treatments.

Oncogenic Signaling Pathways: MAPK, PI3K/AKT, JAK/STAT

Oncogenic signaling pathways play critical roles in cancer initiation, maintenance, and drug resistance (**Figure 2**). The MAPK pathway, composed of RAS–RAF–MEK–ERK, is one of the most frequently altered cascades in solid tumors. Activating mutations such as KRAS G12C and BRAF V600E promote unchecked cellular proliferation and survival [13, 14]. Therapeutic inhibitors targeting BRAF and MEK have shown efficacy in melanoma, lung cancer, and colorectal cancer; however, adaptive resistance via ERK reactivation or pathway bypass remains a clinical challenge [15].

The PI3K/AKT/mTOR pathway controls cell metabolism, growth, and survival. Aberrations such as PIK3CA mutations, AKT activation, and PTEN loss drive oncogenesis and influence therapeutic sensitivity [16].

PI3K inhibitors, AKT inhibitors, and mTOR inhibitors have demonstrated meaningful therapeutic activity, though metabolic adverse effects and compensatory signaling often necessitate combination approaches [17].

The JAK/STAT signaling pathway regulates transcriptional responses to cytokines and growth factors. Constitutive JAK2 or STAT3 activation contributes to hematologic malignancies and several solid tumors [18]. JAK inhibitors such as ruxolitinib have transformed the management of myeloproliferative neoplasms, but their immunomodulatory actions and emerging resistance require ongoing refinement.

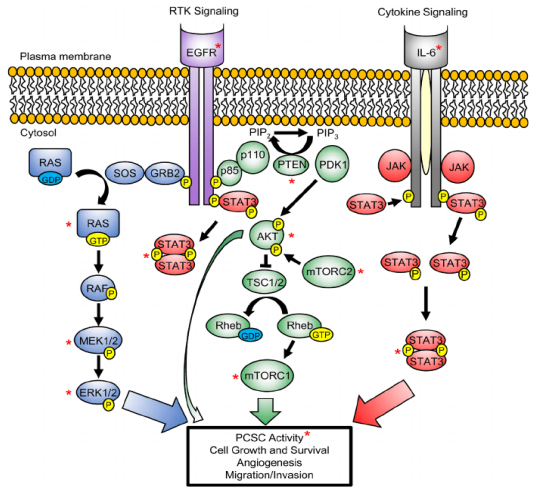

Figure 2. PI3K/AKT, RAS/MAPK and STAT3 signaling pathways. Growth factor-driven receptor tyrosine kinase (RTK) (e.g., EGFR) or cytokine (e.g., IL-6) signaling activates the PI3K/AKT (green), RAS/MAPK (blue), and STAT3 (red) signaling pathways, which promote PCSC self-renewal activity and the various hallmarks of PCa development. These signaling pathways act directly or through cross-talk activation to mediate prostate tumorigenesis; the red asterisk (*) indicates important proteins within these signaling pathways that have been linked to PCSC activity.

***Source:** [19]*

Actionable Mutations and Biomarkers

Actionable mutations are genomic alterations for which clinically beneficial targeted therapies exist. Classic actionable drivers include EGFR exon 19 deletions and L858R, ALK fusions, ROS1 fusions, BRAF V600E, and BRCA1/2 loss-of-function mutations, each of which guides the choice of specific kinase inhibitors, fusion-targeted therapies, or PARP inhibitors [20]. The clinical utility of an actionable biomarker depends on its analytical validity, ability to predict therapeutic response, and proven benefit in clinical settings. Beyond single-gene markers, composite biomarkers such as tumor mutational burden (TMB) and microsatellite instability (MSI-H) help identify patients likely to respond to immune checkpoint inhibitors [21]. Dynamic biomarkers, particularly circulating tumor DNA (ctDNA), support real-time monitoring of treatment response, detection of emerging resistance mutations (e.g., EGFR T790M or C797S), and early relapse surveillance. These biomarker categories collectively inform drug selection, dosing decisions, and adaptive therapy frameworks. Table 1 summarizes selected genetic biomarkers and their corresponding targeted therapies in solid tumor malignancies.

Table 1: Selected genetic biomarkers and targeted therapies in solid tumor malignancies

Biomarkers	FDA-approved indications	FDA-approved therapies	Drug class
ALK	NSCLC	Alectinib, crizotinib, ceritinib, brigatinib, lorlatinib	ALK inhibitors
BRAF	Melanoma, colorectal, thyroid (anaplastic) cancers	Dabrafenib (trametinib), encorafenib (binimetinib), vemurafenib (cobimetinib)	BRAF (with or without MEK) inhibitors
BRCA1/BRCA2	Breast, ovarian, pancreatic, prostate cancers	Olaparib, talazoparib, niraparib, rucaparib	PARP inhibitors
ER/PR	Breast cancer	Aromatase inhibitors: anastrozole, letrozole, exemestane; SERM: tamoxifen; SERD: fulvestrant; CDK4/6 inhibitors: palbociclib, ribociclib, abemaciclib	Aromatase inhibitors, SERM, SERD, CDK4/6 inhibitors
EGFR	NSCLC	Osimertinib, erlotinib (with or without ramucirumab), gefitinib, afatinib, dacomitinib	EGFR inhibitors, VEGF inhibitor (ramucirumab)
FGFR, FGFR2	Bladder cancer	Erdafitinib, pemigatinib	FGFR inhibitors
HER2	Breast, colorectal, gastric, esophageal, gastroesophageal junction cancers	Trastuzumab, pertuzumab, lapatinib, ado-trastuzumab emtansine, fam-trastuzumab deruxtecan, neratinib, tucatinib	HER2 inhibitors
HRD	Ovarian, fallopian tube, peritoneal cancers	Olaparib	PARP inhibitor
HRR	Prostate cancer	Olaparib	PARP inhibitor
KIT	GIST	Imatinib	KIT inhibitors
KRAS (wild-type)	Colorectal cancer	Cetuximab, panitumumab	EGFR inhibitors
MET exon 14 skipping	NSCLC	Capmatinib	MET inhibitor
NTRK	Tumor agnostic	Larotrectinib, entrectinib	NTRK inhibitors
PIK3CA	Breast cancer	Alpelisib	PI3K inhibitor
PDGFRA exon 18	GIST	Avapritinib	PDGFRA inhibitors
RET	NSCLC, thyroid cancer	Selpercatinib, pralsetinib	RET inhibitors
ROS1	NSCLC	Crizotinib	ROS1 inhibitors

Adapted from [22]

Companion Diagnostics and Patient Stratification

Companion diagnostics (CDx) are essential tools that enable the precise identification of patients who are candidates for specific targeted therapies. The U.S. Food and Drug Administration (FDA) requires the use of an approved companion diagnostic (CDx) test to guide treatment with targeted oncology therapies, including EGFR-, ALK-, BRAF/MEK-, and selected PARP inhibitors [23]. CDx platforms include immunohistochemistry, PCR-based assays, fluorescence in situ hybridization (FISH), and increasingly next-generation sequencing (NGS) panels capable of identifying multiple actionable alterations simultaneously. NGS-based testing has become a cornerstone of modern oncology because it detects a broad range of mutations, copy-number changes, and gene fusions from both tissue and liquid biopsies [24]. Effective patient stratification requires integration of molecular profile, tumor histology, and clinical characteristics to optimize therapy selection. **Figure 3** illustrates this process, showing patient group identification, companion diagnostic testing, and stratification into subgroups for targeted therapy.

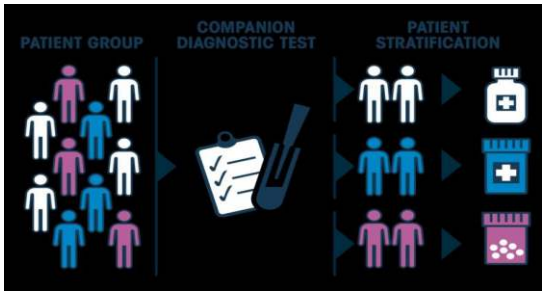

Figure 3. Simple illustration of companion diagnostics and patient stratification. The figure illustrates personalised oncology through three steps: patient groups are identified, companion diagnostic tests detect specific biomarkers, and patients are stratified into subgroups for targeted therapy selection.
***Source:** [25]*

Kinase Inhibitors

Dysregulated kinase activity is a hallmark of many cancers and underpins uncontrolled proliferation, survival, and metastatic behavior. Protein kinases—enzymes that transfer phosphate groups to substrate proteins—are frequently hyperactivated in cancer through mutation, overexpression, or aberrant signaling, making them prime therapeutic targets [2]. The development of small-molecule kinase inhibitors has thus revolutionized oncology by offering highly selective drugs that block these pathogenic signaling processes. The clinical impact of kinase inhibition has been profound: therapeutic agents targeting receptor tyrosine kinases (RTKs) or downstream serine/threonine kinases have changed the prognosis for many malignancies, with ongoing development of next-generation compounds to enhance efficacy and overcome resistance. **Table 2**, provides some of the FDA approved kinase inhibitors from 2018 to 2023.

Table 2. Some FDA-Approved kinase inhibitors

Compound Name	First Approved	Target	Type
Quizartinib	2023	FLT3 inhibitors	Type II
Capivasertib	2023	AKT-1, AKT-2, AKT-3	Type I
Pirtobrutinib	2023	BTK C481S inhibitor	Type II
Repotrectinib	2023	ALK, ROS1, TRKA, TRKC	Type II
Fruquintinib	2023	VEGFR1, VEGFR2, VEGFR3	Type I/II
Futibatinib	2022	FGFRs	Type V
Tepotinib	2021	c-Met	Type I
Amivantamab	2021	EGFR, c-Met	
Tucatinib	2020	HER2	Type I/II
Margetuximab	2020	HER2	Monoclonal antibody
Alpelisib	2019	PI3Kα	Type I/II
Gilteritinib	2018	AXL, FLT3	Type I

Adapted from [1]

Major Classes of Kinase Inhibitors

i. Tyrosine Kinase Inhibitors (TKIs)

This class includes inhibitors targeting RTKs such as EGFR, HER2, ALK, and VEGFR. For example, EGFR inhibitors like gefitinib, erlotinib, and, more recently, osimertinib have been central in the management of EGFR-mutant non-small cell lung cancer (NSCLC) [26]. HER2-targeted TKIs and monoclonal antibodies similarly play critical roles in HER2-amplified breast cancer. ALK inhibitors (e.g., alectinib, crizotinib) treat ALK-rearranged malignancies, while VEGFR-targeting TKIs (such as sunitinib or cabozantinib) exert both anti-proliferative and anti-angiogenic effects in vascularized solid tumors [27].

ii. Serine/Threonine Kinase Inhibitors

These inhibitors act downstream of or parallel to RTKs. BRAF/MEK inhibitors (dabrafenib, vemurafenib, trametinib) are used in BRAF V600E mutant melanoma and, increasingly, in NSCLC [26].

CDK inhibitors are typically identified by high-throughput, fragment-based screening and virtual methods to facilitate the development of novel anticancer medicines with potent therapeutic properties [28]. CDK inhibitors, particularly CDK4/6 inhibitors (e.g., palbociclib, abemaciclib), disrupt cell-cycle progression in hormone receptor–positive breast cancer and other tumors [28]. mTOR inhibitors, both allosteric (rapalogs like everolimus, temsirolimus) and newer macrocyclic compounds, suppress nutrient-sensing and growth-related signaling via mTOR complexes [29].

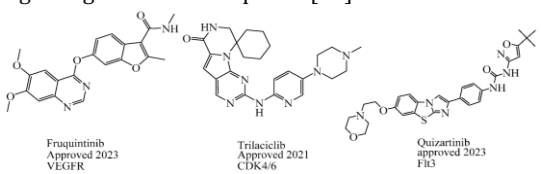

Figure 4. The molecular compositions of various newly authorized anticancer drugs that specifically act on kinase families such as VEGFR, CDKs, and Flt3.
***Source:** [28]*

Mechanisms of Action

Kinase inhibitors achieve their therapeutic effects through distinct biochemical strategies, primarily classified into three mechanisms: ATP-competitive, allosteric, and irreversible (covalent) inhibition. These modes differ in binding sites, kinetics, and long-term pharmacological behavior, each offering unique advantages and challenges in drug design and clinical use.

i. ATP-Competitive Inhibitors

ATP-competitive inhibitors bind directly to the ATP-binding pocket of kinases, competing with ATP and blocking the phosphorylation of substrates. These inhibitors are further subclassified based on how they interact with the activation loop (DFG motif) of the kinase: Type I inhibitors bind to the active conformation (DFG-in), while Type II inhibitors prefer the inactive DFG-out conformation [30]. Because many kinases share a conserved ATP-binding site, achieving selectivity is a major challenge; dual inhibitors that target ATP-binding pockets of both kinases and non-kinase ATP-dependent proteins have been explored to enhance therapeutic efficacy and minimize off-target effects [30].

ii. Allosteric Inhibitors

Allosteric inhibitors bind to regulatory sites outside the ATP-binding pocket such as the pleckstrin homology (PH) domain in AKT, that modulate the enzyme's conformation and reduce catalytic activity without directly competing with ATP. For example, in AKT, allosteric inhibitors lock the kinase into a conformation that impairs membrane localization and activation, unlike ATP-competitive inhibitors that stabilize a conformation favorable for membrane binding. Structural comparisons show that competitive and allosteric inhibitors share chemical scaffolds more often than expected, suggesting a continuum rather than discrete categories. Moreover, allosteric inhibitors exploit less-conserved binding sites, which can confer higher subtype specificity and reduce toxicity [31].

iii.Irreversible (Covalent) Inhibitors

Irreversible inhibitors form a covalent bond with a nucleophilic residue, often a cysteine near or in the ATP-binding site, leading to permanent inactivation of the kinase. This covalent mechanism enhances potency, prolongs target engagement, and can overcome high intracellular ATP concentrations. Clinically approved examples include osimertinib and mobocertinib, which target mutant EGFR by forming a covalent bond with a cysteine in the active site [32]. However, covalent inhibitors also carry risks: their irreversible nature can lead to off-target toxicity, and development of resistance can still occur via mutation of the targeted residue or alternative signaling pathways [1].

Understanding these three distinct mechanisms is critical for optimizing kinase inhibitor design. The choice among ATP competitive, allosteric, or covalent inhibition depends on multiple factors including target biology, required selectivity, resistance profile, and therapeutic index.

Rational drug design increasingly aims to combine these mechanisms (e.g., covalent allosteric inhibitors) to harness the benefits of each while minimizing drawbacks.

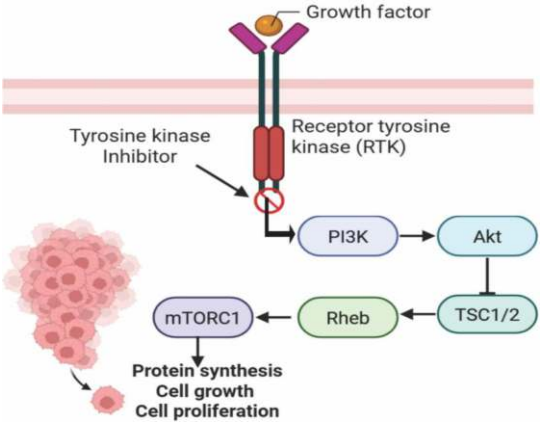

Figure 5. General mechanism of action of tyrosine kinase inhibitors (TKIs). Small molecule inhibitors inhibit the ligand-mediated phosphorylation of RTKs, thereby preventing the activation of downstream protumorigenic signaling pathways. This inhibition leads to downregulation of transcription of genes that are involved in cell proliferation, survival, angiogenesis, and migration and invasion.
***Source:** [2]*

Clinical Impact

Kinase inhibitors have dramatically transformed the management of several cancers. In NSCLC, EGFR-targeted TKIs provide robust responses in patients with sensitizing EGFR mutations, while ALK inhibitors have reshaped the prognosis for ALK-rearranged disease. In melanoma, BRAF V600E inhibition (with dabrafenib or vemurafenib) plus MEK inhibition (e.g., trametinib) has become standard, substantially extending survival. Breast cancer therapy has also been revolutionized by CDK4/6 inhibitors, which delay progression in hormone receptor–positive disease [28]. In hematologic malignancies, although beyond the core of this section, BCR-ABL inhibitors remain foundational in chronic myeloid leukemia, and newer TKIs and combination approaches continue to evolve [2].

Resistance Mechanisms

Despite the remarkable clinical success of kinase inhibitors, the development of drug resistance remains a significant challenge that limits long-term efficacy (See Figure 6). Resistance can arise through a variety of mechanisms, reflecting the genetic and phenotypic plasticity of tumor cells. One of the most common forms is the emergence of secondary or on-target mutations within the kinase domain that reduce inhibitor binding. Classic examples include the T790M mutation in EGFR, which confers resistance to first-generation EGFR inhibitors, and the T315I mutation in BCR-ABL, which diminishes the efficacy of early-generation tyrosine kinase inhibitors [2, 33]. These mutations often alter the ATP-binding pocket or adjacent residues, thereby decreasing drug affinity while maintaining kinase activity. Resistance also frequently occurs through pathway reactivation or bypass signaling. Tumor cells can compensate for inhibited kinases by upregulating parallel or downstream signaling pathways.

For instance, reactivation of MEK/ERK signaling or activation of the PI3K/AKT pathway can circumvent BRAF inhibition in melanoma, allowing cells to continue proliferating despite targeted therapy [34]. Similarly, amplification of alternative receptor tyrosine kinases, such as MET or HER3, has been documented as a bypass mechanism in lung and breast cancers.

In addition to genetic alterations, phenotype switching and cellular plasticity contribute to resistance. Tumor cells can undergo epithelial-to-mesenchymal transition, adopt stem-like states, or shift lineage identity, reducing dependence on the targeted kinase. This non-genetic adaptation enables survival under selective pressure and is particularly relevant in melanoma and lung cancer [34]. Finally, pharmacokinetic and microenvironmental factors can modulate drug efficacy. Increased drug efflux, sequestration within tumor niches, stromal interactions, and altered angiogenesis can collectively reduce intracellular drug concentrations, thereby promoting survival despite inhibitor exposure [33]. Understanding these multifaceted resistance mechanisms has guided the development of next-generation inhibitors, combination therapies, and sequential treatment strategies aimed at prolonging therapeutic response and overcoming adaptive tumor escape.

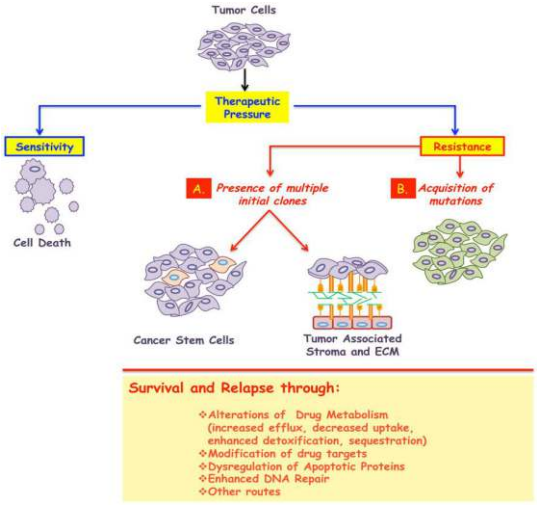

Figure 6. Resistance Mechanisms in Tumor Cells. This diagram illustrates the mechanisms of cancer therapy resistance, including primary and acquired resistance, clonal selection, genetic/epigenetic changes, biochemical adaptations, and their role in minimal residual disease and relapse.
***Source:** [35]*

Angiogenesis Inhibitors

Tumor angiogenesis is a fundamental process by which growing neoplasms acquire a blood supply; it is largely orchestrated by the vascular endothelial growth factor family (VEGF-A, VEGF-B, VEGF-C, VEGF-D) signaling through VEGF receptors (principally VEGFR-2) on endothelial cells to drive proliferation, migration, and new vessel sprouting [36] (see Figure 7). The tumor vasculature is structurally and functionally abnormal, tortuous, leaky, and heterogeneous, producing regions of hypoxia that further upregulate pro-angiogenic signals and select for aggressive phenotypes; these features also reduce effective drug delivery and impair immune cell infiltration [36, 37]. The concept of transient "vascular normalization" after VEGF blockade, proposed to improve perfusion and drug delivery for a limited window, has provided a mechanistic rationale for combining anti-angiogenic agents with chemotherapy or immunotherapy [36].

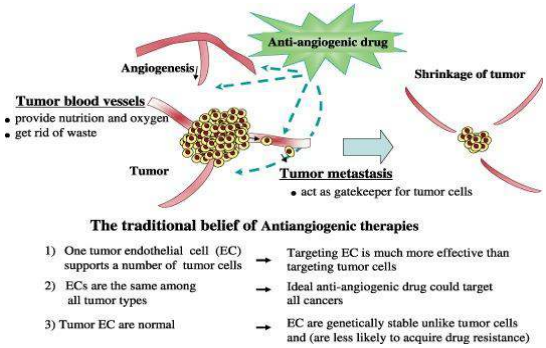

Figure 7. Generally accepted concept of tumor angiogenesis and anti-angiogenic therapy. This diagram illustrates the process of tumor angiogenesis, where new blood vessels form to supply nutrients and oxygen to the growing tumor, and highlights points where anti-angiogenic therapies can inhibit vessel formation to restrict tumor growth.
***Source:** [38]*

Therapeutic Classes

Anti-angiogenic therapies that target the VEGF/VEGFR axis fall into three main classes. First, monoclonal antibodies such as bevacizumab bind VEGF-A and prevent ligand-receptor interaction [39]. Second, VEGFR-targeting small-molecule tyrosine kinase inhibitors (TKIs) (for example, sunitinib, axitinib, cabozantinib) inhibit the receptor kinase activity and frequently have multi-kinase activity [37]. Third, ligand traps (e.g., aflibercept, also called ziv-aflibercept) are recombinant decoy receptors that sequester multiple VEGF family members [40]. Each class has distinct pharmacology: antibodies/ligand traps neutralize extracellular ligands, while TKIs inhibit intracellular kinase signaling and may target additional pro-angiogenic receptors.

Table 3. Angiogenesis inhibitors approved by FDA

Drug	Target molecule	Approved disease
Bevacizumab	Anti-VEGF monoclonal antibody	mCRC, NSCLC, mRCC, ovarian cancer, malignantglioma, advanced cervical cancer, fallopian tubecancer, primary peritoneal cancer
Ramucirumab	Anti-VEGFR2 monoclonal antibody	Advanced gastric or gastroesophageal junctionadenocarcinoma, NSCLC, advanced colorectal cancer
Ziv-aflibercept	Soluble decoy of VEGFR	Metastatic colorectal cancer
Sunitinib	TKI: VEGFR, PDGFR, FLT3, KIT	RCC, Gastrointestinal stromal tumor, pancreaticneuroendocrine tumorSorafenibTKI:
Sorafenib	TKI: VEGFR, PDGFR, FLT3, KIT, Raf	RCC, unresectable hepatocellular carcinoma,metastatic or recurrent thyroid carcinomia
Axitinib	TKI: VEGFR, PDGFR, KIT	Advanced RCC
Pazopanib	Multiple targeted receptor TKI	RCC, Advanced soft tissue sarcoma
Vandetanib	TKI: VEGFR, EGFR, RET	Unresectable or metastatic medullary thyroid cancer

Adapted from [41]

Mechanisms of Action

Mechanistically, these agents reduce endothelial proliferation and new vessel formation, alter vascular permeability, and can transiently normalize abnormal tumor vasculature. Bevacizumab and aflibercept function by ligand neutralization/ sequestration, thereby preventing VEGF-VEGFR engagement and downstream signaling [39, 40]. VEGFR TKIs inhibit ATP binding in the receptor kinase domain and often suppress parallel angiogenic RTKs (e.g., PDGFR, MET), producing both anti-proliferative and anti-angiogenic effects [37]. These changes can lower interstitial pressure, modulate immune cell trafficking, and synergize with cytotoxics and immune checkpoint inhibitors when scheduling aligns with the vascular normalization window [36, 37].

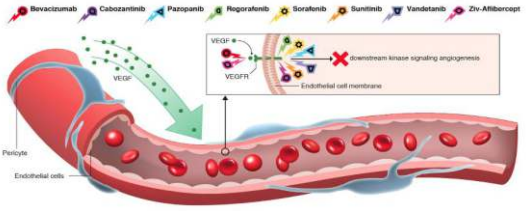

Figure 8. Mechanisms of some angiogenic inhibitors. This figure illustrates the mechanisms of action of various angiogenesis inhibitors, highlighting how they disrupt VEGF/VEGFR signaling to inhibit tumor blood vessel formation.
Source: *https://angio.org/learn/treatments/angiogenesis-inhibitors-for-cancer/*

Clinical Use

Anti-angiogenic agents are integrated into standard care for multiple tumor types. In metastatic colorectal cancer, adding bevacizumab to combination chemotherapy significantly improved survival in the pivotal AVF2107g trial [39]. (Hurwitz et al., 2004)Aflibercept showed survival benefit when added to FOLFIRI in second-line mCRC [40]. (Van Cutsem et al., 2012). In renal cell carcinoma (RCC), VEGFR TKIs such as sunitinib improved progression-free survival versus interferon alfa and became standard frontline therapy [42]. More recently, TKIs are commonly used in combination with immune checkpoint inhibitors. In non-small cell lung cancer and other solid tumors, anti-angiogenic TKIs or antibodies have niche and combination roles, while in glioblastoma, bevacizumab reduces edema and provides symptomatic benefit, though overall survival benefit remains limited [36, 40, 42].

Resistance Mechanisms

Multiple, often overlapping mechanisms underlie both intrinsic and acquired resistance to VEGF-targeted therapies (See figure 9). Tumors can upregulate alternative pro-angiogenic factors (FGFs, angiopoietins, PlGF, PDGF) that bypass VEGF blockade [36]. Vessel co-option, where tumor cells hijack pre-existing host vessels rather than inducing angiogenesis, has been shown clinically to mediate resistance (e.g., colorectal cancer liver metastases refractory to bevacizumab) and is increasingly recognized across tumor types [43]. Tumors may also develop vasculogenic mimicry (tumor cells forming vessel-like channels), recruit pro-angiogenic stromal cells or endothelial progenitors, and the resulting hypoxia following aggressive VEGF blockade can select for more invasive, metastatic phenotypes and immunosuppressive microenvironments [36, 43]. These insights motivate combination approaches (for example, dual angiogenesis pathway blockade, or angiogenesis inhibitors plus immunotherapy) and suggest that predictive biomarkers distinguishing angiogenesis-dependent tumors from co-option-dominant lesions will be critical for patient selection [37].

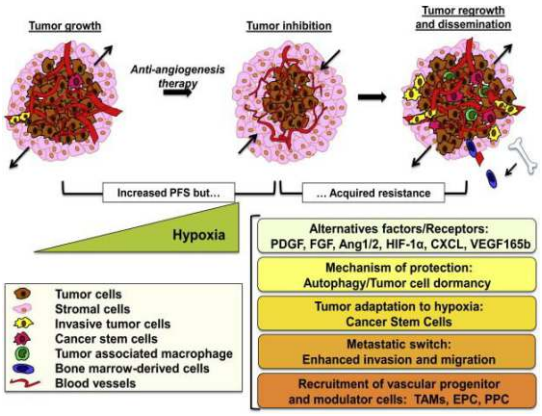

Figure 9. Resistance mechanisms. The figure illustrates the key resistance mechanisms by which tumor cells evade VEGF blockade and other anti-angiogenic therapies, including activation of alternative pro-angiogenic pathways, recruitment of stromal support, and adaptive cellular responses.
Source: *[44]*

Other Key Molecularly Targeted Agents

There are some other molecular targeted agents that are involved in the fight against cancer cells, and some of them are discussed below;

i. PARP Inhibitors (DNA-Repair Targeting)

PARP inhibitors (PARPis) exploit defects in homologous-recombination repair (HRR) to induce synthetic lethality in tumor cells. By inhibiting PARP activity and trapping PARP on DNA, these agents convert single-strand breaks into cytotoxic double-strand breaks that HRR-deficient cells (e.g., BRCA1/2-mutant) cannot repair, leading to cell death [445, 46]. Clinically, olaparib, niraparib, rucaparib, and talazoparib are approved for ovarian, breast, pancreatic, and prostate cancers with HRR deficiency or specific indications demonstrated in pivotal trials [47]. Key challenges include primary and acquired resistance mechanisms, including restoration of HRR via BRCA reversion mutations, upregulation of replication-fork protection, decreased PARP trapping, and drug efflux, prompting development of rational combinations (with immunotherapy, ATR/CHK1 inhibitors, anti-angiogenics) and better predictive biomarkers [45, 46]. Recent meta-analyses confirm PARPi maintenance significantly prolongs progression-free survival in ovarian cancer, particularly in BRCA-mutant or HRD-positive cohorts [46].

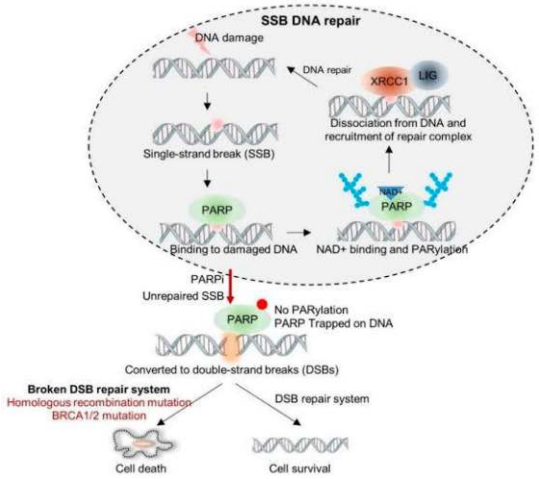

Figure 10. Mechanism of action of PARP inhibitors. PARPs recognize damaged DNA sites and recruit DNA-repairing machineries through PARylation.
***Source:** [48]*

i. Epigenetic Modulators (HDAC and DNMT Inhibitors)

Epigenetic drugs target dysregulated chromatin modifiers to reactivate silenced tumor-suppressor programs or alter tumor immune phenotypes. DNMT inhibitors (azacitidine, decitabine) incorporate into DNA and trap DNMTs, reducing methylation and re-expressing silenced genes; HDAC inhibitors (vorinostat, romidepsin, and newer isoform-selective agents) increase histone acetylation, alter transcriptional programs, and influence non-histone substrates [49]. In hematologic malignancies and certain solid tumors, epigenetic therapies show single-agent efficacy and can sensitize tumors to immunotherapy via viral-mimicry and enhanced antigen presentation [49]. Toxicities (myelosuppression, fatigue, GI effects) and limited monotherapy durability have driven combination strategies (epigenetic + immune checkpoint inhibitors or targeted agents) and the development of next-generation selective inhibitors.

ii. Proteasome Inhibitors (Protein-Degradation Control)

Proteasome inhibitors (PIs) block the 26S proteasome, disrupting ubiquitin-mediated protein degradation, causing proteotoxic stress and apoptosis. Bortezomib, carfilzomib, and ixazomib are established in multiple myeloma and some lymphomas, where malignant plasma cells are particularly dependent on proteasomal function [50]. Clinical benefit includes high response rates and improved survival in combination regimens; limitations include peripheral neuropathy (bortezomib), cardiovascular toxicity (carfilzomib), and acquired resistance mechanisms such as proteasome subunit mutations, induction of compensatory autophagy, and alterations in protein homeostasis pathways leading to research into next-generation PIs and combination approaches to circumvent resistance [51].

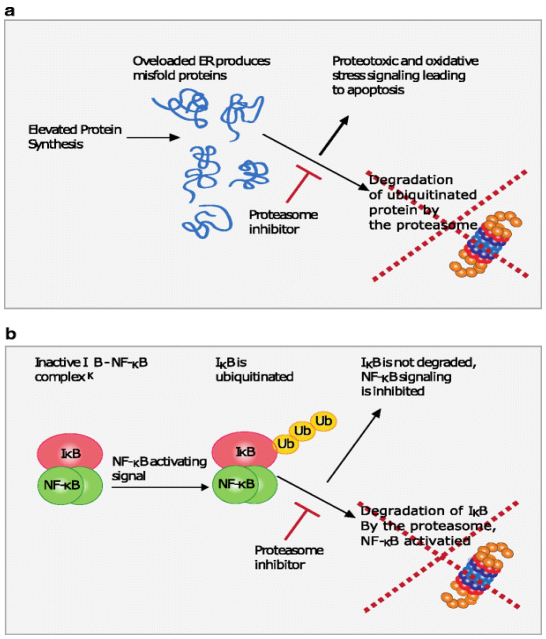

Figure 11. Mechanisms of how proteasome inhibition inhibits cancer cell survival. The up (a) is needed for detoxification when cancer cells produce misfolded proteins as a result of increased protein synthesis. When proteasome suppression occurs, misfolded proteins build up and cause oxidative and proteotoxic stress. b. NFκB pro-survival signaling is abrogated when proteasome inhibition occurs.
***Source:** [52]*

i. Hormone Receptor–Targeted Therapies (ER/PR, AR Inhibitors)

Steroid-hormone receptor targeting remains a cornerstone in breast and prostate cancers. In ER-positive breast cancer, endocrine therapies (aromatase inhibitors, selective estrogen receptor modulators/downregulators) combined with CDK4/6 inhibitors have substantially improved progression-free and overall survival in advanced disease; ongoing work refines sequencing and management after CDK4/6 resistance [53]. In prostate cancer, potent androgen-receptor pathway inhibitors (enzalutamide, apalutamide, abiraterone) have extended survival in castrate-sensitive and castrate-resistant settings; resistance evolves via AR amplification, splice variants (eg, AR-V7), intratumoral steroidogenesis, and lineage plasticity, motivating combinations (PARPi, AKT inhibitors) and novel AR degraders.

ii. Antibody–Drug Conjugates (ADCs) — Targeted Cytotoxic Delivery

ADCs couple a monoclonal antibody specific for a tumor antigen to a potent cytotoxic payload via a chemical linker, enabling targeted delivery and intracellular release of toxin upon internalization. Clinical successes. Trastuzumab emtansine (T-DM1) and trastuzumab deruxtecan (T-DXd/DS-8201) have transformed HER2-positive breast cancer, with T-DXd showing superior PFS/ORR vs T-DM1 in randomized trials and notable intracranial activity [54]. ADC design evolution (stable linkers, higher drug-to-antibody ratios, novel payload classes) broadens indications (e.g., HER2-low, nectin-4, TROP2) but brings unique toxicities such as interstitial lung disease (with some payloads) and hematologic

effects; antigen selection, bystander effects, and payload optimization remain active translational areas [54].

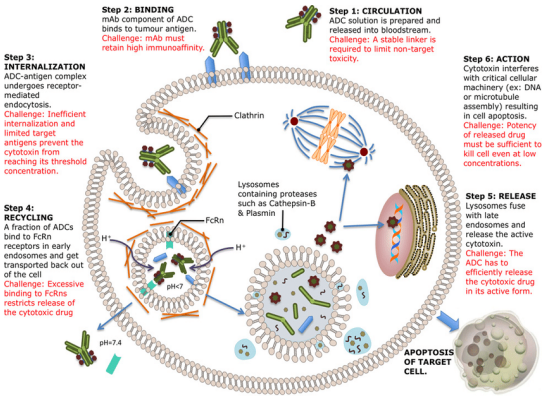

Figure 12. Mechanisms of action of ADCs. This figure depicts the key mechanisms by which antibody drug conjugates (ADCs) selectively deliver cytotoxic agents to tumor cells, enhancing therapeutic efficacy while minimizing systemic toxicity.
***Source:** [55]*

Current Challenges

Despite the transformative impact of molecularly targeted therapies, several challenges remain that hinder their long-term effectiveness and broad implementation. Tumor heterogeneity, both spatial and temporal, remains a primary barrier. Clonal diversity within a tumor and across metastatic sites allows subpopulations lacking the targeted mutation to survive and repopulate, and sampling bias during biopsies or liquid biopsies may misrepresent this diversity [56, 57]. Drug resistance further limits durability. Resistance mechanisms include on-target secondary mutations, activation of bypass signaling, phenotypic plasticity (e.g., epithelial-to-mesenchymal transition), and microenvironmental protection [58]. Tackling resistance increasingly demands adaptive combination strategies, sequential therapy, and next-generation inhibitors capable of overcoming such resistance. Off-target and cumulative toxicities also restrict treatment options. Many kinase and targeted agents cause adverse effects affecting cardiovascular, dermatologic, gastrointestinal, and other systems; chronic use often exacerbates toxicity and reduces tolerability, especially in older or comorbid patients [59]. Optimizing selectivity, dosing, and patient monitoring is critical.

Also, economic and regulatory barriers create access inequities. Precision therapy depends on costly diagnostics, drugs, and monitoring, placing a substantial burden on healthcare systems. Reimbursement models struggle to address value for both drug and companion diagnostics, and regulatory inconsistencies limit global adoption [60]. Addressing these challenges requires integrated solutions: better molecular profiling (e.g., multi-region biopsies, serial ctDNA), smarter trial designs, safer drug design, and updated policies to align cost, regulation, and patient benefit.

Future Perspectives

Future advances in targeted cancer therapy will rely on strategies capable of overcoming pathway redundancy, resistance evolution, and the need for deeper personalization. Next-generation multi-target inhibitors are being developed to simultaneously block multiple oncogenic nodes within interconnected signaling pathways, thereby delaying resistance and improving durability of response [47]. These rationally designed agents embody controlled polypharmacology, enabling broader pathway suppression without proportionally increasing toxicity.

Expanding the landscape of synthetic lethality and combination therapy represents another major direction. Beyond the well-established PARP–BRCA paradigm, large-scale CRISPR screening and functional genomic mapping continue to reveal new synthetic-lethal interactions suitable for therapeutic exploitation. Combining targeted therapies with immunotherapies or metabolic inhibitors also offers a means to shut down bypass pathways and reduce adaptive resistance. The integration of AI-driven precision oncology is accelerating innovation by enabling predictive modeling of drug sensitivity, resistance evolution, and optimal treatment sequencing. Machine-learning tools that integrate genomic, transcriptomic, radiologic, and clinical data have demonstrated improved accuracy in treatment response prediction and biomarker discovery [61, 62, 63, 63]. Conclusively, real-time tumor monitoring using liquid biopsy is transforming clinical surveillance. Circulating tumor DNA and other blood-based biomarkers allow early detection of resistance mutations, facilitate rapid therapy adjustment, and provide a less invasive alternative to serial tissue biopsies [62, 65, 66, 67, 68, 69, 70, 71]. Collectively, these innovations point toward a future of adaptive, anticipatory, and highly individualized targeted cancer therapy.

Conclusion

Molecularly targeted therapies have transformed modern oncology by shifting treatment paradigms from broad cytotoxic approaches to precision-driven interventions tailored to the molecular profile of each tumor. Advances in kinase inhibition, angiogenesis modulation, DNA repair targeting, epigenetic regulation, and antibody drug conjugate technology continue to expand therapeutic options across diverse malignancies. Yet, the field remains challenged by tumor heterogeneity, adaptive resistance, and gaps in equitable access. Emerging innovations, including multi-target inhibitor design, synthetic lethality-based combinations, AI-enabled precision oncology, and real-time molecular surveillance through liquid biopsy, promise to refine therapeutic accuracy and durability. As these next-generation strategies evolve, integrating mechanistic insight with clinical translation will be essential to achieving more effective, personalized, and sustainable cancer care for patients worldwide.

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Conflict of Interest

The authors declared that there are no conflicts of interest.

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