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Review Article

Targeted Drug Therapy in Cancer: Mechanisms, Advances, and Challenges

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ABSTRACT

Cancer includes many diseases in which genetic and epigenetic changes disturb the normal controls of cell growth, survival, DNA repair, and communication with surrounding tissues. Conventional chemotherapy remains an important part of cancer treatment, but it can also damage healthy cells that divide quickly, often causing side effects. Targeted drug therapy takes a more selective approach by acting on particular molecular changes that help a tumour grow or survive. Biomarker testing can identify patients who may benefit from certain treatments, as shown in cancers with specific, actionable genetic alterations. However, this approach still faces several difficulties, including differences between cancer cells within the same tumour, drug resistance, treatment-related adverse effects, and unequal access to diagnostic testing. This review describes the biological basis of targeted cancer therapy, its main mechanisms, important clinical developments, and the challenges that influence treatment outcomes. It also considers emerging approaches such as antibody–drug conjugates, targeted protein degradation, carefully selected drug combinations, and biomarker-guided treatment.

INTRODUCTION

Cancer begins when cells accumulate changes that help them grow, survive stress, and interact differently with the tissues around them. These changes can activate oncogenes, disable tumour-suppressor genes, interfere with DNA repair, or alter immune and stromal responses. As a result, cancers are biologically diverse: even tumours that start in the same organ may have different molecular drivers and respond differently to treatment. [1,2,11]

Targeted therapy is designed to block a particular molecular target or biological process that a tumour relies on for growth or survival. Common approaches include small-molecule drugs that inhibit abnormal kinases, monoclonal antibodies that act on cell-surface receptors, medicines that interfere with DNA-repair

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pathways, and treatments that change immune-regulatory signals. These treatments are most useful when the target is present and plays an important role in the tumour's biology. [1,2,15,17]

Precision oncology uses information about a tumour's molecular features to help guide treatment, rather than basing decisions only on where the cancer began. This approach has improved outcomes in selected settings, including BCR::ABL1-positive chronic myeloid leukaemia and some EGFR-mutated non-small-cell lung cancers. Still, finding a molecular alteration does not guarantee that a treatment will work. Clinicians must also consider the strength of the evidence, the patient's general health, the behaviour of the tumour, and the possibility that resistance may develop. [6,9,10,14,16]

This review discusses how targeted anticancer medicines work, highlights important developments in clinical practice, and considers issues related to resistance and safety. It also looks at future directions that may be relevant to pharmaceutical research and patient care. [1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18]

2. REVIEW APPROACH

This narrative review is based on selected studies indexed in PubMed, papers published in major oncology journals, clinical-trial reports, regulatory information, and relevant review articles. Particular attention was given to influential mechanistic studies and literature available up to October 2026. The aim is to provide a clear overview of the topic rather than a systematic review; accordingly, no formal risk-of-bias assessment or meta-analysis was performed. [1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18]

3. BIOLOGICAL BASIS AND MAJOR TARGET CLASSES

3.1 Oncogenic Signalling Pathways

Cancer cells often depend on abnormal signals passing through receptor tyrosine kinases and related networks, such as the RAS–RAF–MEK–ERK, PI3K–AKT–mTOR, JAK–STAT, and cell-cycle pathways. Mutations, extra copies of genes, excess receptor expression, or persistent signalling can keep these pathways active and support tumour growth. Medicines that block them can be effective when the tumour relies heavily on the affected signal. However, other pathways may compensate, which can limit how long the treatment remains effective. [1,2,14,15]

3.2 Hormone-Receptor Signalling

In cancers that respond to hormones, tumour growth may be driven by oestrogen, androgen, or related receptor signals. Endocrine treatments can lower hormone production, block receptor activity, or encourage receptor breakdown. Aromatase inhibitors and selective oestrogen-receptor degraders are used in hormone-receptor-positive breast cancer, while drugs that block androgen signalling are important in prostate cancer. Resistance may develop if receptors change, signalling pathways become active again, or tumour cells become less dependent on hormones. [14,15,18]

3.3 DNA Damage Response And Synthetic Lethality

Some cancer cells become unusually reliant on one DNA-repair pathway because another repair route is already defective. Synthetic lethality takes advantage of this weakness by blocking the remaining pathway. PARP inhibitors are a well-established example, particularly for selected cancers with BRCA1/2 alterations or other defects in homologous recombination. The benefit depends on the tumour's biology and careful patient selection. Resistance can still emerge if DNA repair is restored or the cancer adapts in other ways. [4]

3.4 Tumour Angiogenesis And Microenvironment

A solid tumour needs a blood supply to keep growing. Vascular endothelial growth factor (VEGF) signalling helps new blood vessels form, so it has become an important treatment target. Anti-VEGF antibodies and VEGF-receptor inhibitors can reduce new-vessel formation or change the tumour's blood supply. Their benefit differs by cancer type and treatment setting, and patients need monitoring for adverse effects associated with these medicines. [1,15,18]

3.5 Immune-Regulatory Targets

Immune checkpoint inhibitors target regulatory proteins such as PD-1, PD-L1, and CTLA-4. These proteins normally help keep immune responses under control. Blocking them can release some of the brakes on T cells, allowing them to attack cancer cells more

effectively; some patients experience long-lasting responses. However, not everyone benefits, and immune-related adverse effects can affect different organs. [5,12]

4. MECHANISMS OF ACTION OF TARGETED ANTICANCER THERAPIES

Targeted anticancer medicines work in several ways. Some slow the growth and division of tumour cells, while others cause cell death. Certain drugs act directly on cancer cells; others affect the environment surrounding the tumour or help the immune system recognise and attack it. [1,3,5,15]

Table 1: Major Classes of Targeted Anticancer Therapy

Therapeutic class / example	Main mechanism	Key limitation
Small-molecule kinase inhibitors Osimertinib; imatinib	Block abnormal kinase signals that help the tumour grow.	Mutations in the target, alternative signalling routes, and acquired resistance (15,16).
Monoclonal antibodies Trastuzumab; cetuximab	Attach to selected cell-surface targets, block signals, and/or recruit immune responses.	Target levels vary; tumour penetration may be limited and escape mechanisms can develop (14).
Antibody–drug conjugates (ADCs) Trastuzumab deruxtecan	Carry a cytotoxic drug to cells expressing the target antigen.	Antigen loss, payload resistance, and effects on healthy tissues .
PARP inhibitors Olaparib	Exploit DNA-repair weaknesses, particularly in selected tumours with homologous-recombination defects.	Benefit depends on tumour biology; resistance can develop .
Anti-angiogenic agents Bevacizumab	Block VEGF-related signals involved in the formation of new blood vessels.	Alternative vascular pathways and treatment-related adverse effects.
Endocrine therapies Aromatase inhibitors; SERDs	Lower hormone production or block/ degrade hormone receptors.	Receptor changes and reactivation of growth pathways.
Immune checkpoint inhibitors Pembrolizumab; nivolumab	Block inhibitory immune checkpoints to restore antitumour T-cell activity.	Responses vary and immune-related adverse effects may occur .
Targeted protein degraders PROTACs; molecular glues	Direct a target protein to the cell's machinery for degradation .	Selectivity, drug exposure, tissue delivery, and clinical validation remain challenges .

4.1 Inhibition Of Driver Oncogenes

Small-molecule inhibitors can block an altered protein when the medicine binds to a suitable site and the tumour still depends on that protein. Imatinib was a major milestone because it inhibits BCR::ABL1 in chronic myeloid leukaemia and showed the value of treating cancer according to a defined molecular driver. Similar approaches now target several other cancer-related kinases. Over time, however, changes in the target or activation of alternative signalling routes may reduce the drug's effect. [6,14,15,16]

4.2 Receptor Blockade And Antibody-Based Targeting

Monoclonal antibodies attach to specific regions of cell-surface receptors or to soluble molecules involved in cancer growth. Trastuzumab, for example, targets HER2 and may interrupt signalling, reduce receptor activity, and recruit immune mechanisms. Cetuximab blocks EGFR in certain clinical settings. Some antibodies also carry cytotoxic drugs to cells that express a particular antigen. Their effectiveness depends on the amount and distribution of the target, how easily the tumour can be reached, and the characteristics of the disease. [12,13,14]

4.3 Targeted Degradation Of Proteins

Proteolysis-targeting chimeras (PROTACs) are designed to bring a target protein close to an E3 ubiquitin ligase. This can mark the protein for destruction by the proteasome. Traditional inhibitors usually block a protein's activity by binding to it, whereas targeted degraders aim to remove the protein itself. These medicines are still being investigated, with important

questions remaining about selectivity, movement through the body, and tolerability. [7]

4.4 Tumour-Agnostic Targeting

Tumour-agnostic treatments are chosen because a cancer has a particular validated biomarker, even when the cancer arises in a different organ. Examples include treatments for selected tumours with NTRK gene fusions, mismatch-repair deficiency, or high microsatellite instability. These treatments show how a shared molecular feature can guide therapy across different cancer types. Reliable testing and careful interpretation of the evidence are essential. [10]

5. CLINICAL ADVANCES AND EMERGING STRATEGIES

5.1 Biomarker-Guided Precision Oncology

Molecular profiling can reveal mutations, gene amplifications, gene fusions, and defects in DNA repair that may be useful for treatment decisions. Testing can involve tumour tissue, immunohistochemistry, fluorescence in situ hybridisation, next-generation sequencing, or circulating tumour DNA (ctDNA). Tissue testing remains important for diagnosis and examining tumour structure, while liquid biopsy may provide additional information when there is not enough tissue or repeat sampling is difficult. Each method has limitations, so a negative result does not always rule out a relevant alteration. [2,9,10,14,16]

Predictive biomarkers help estimate whether a treatment is likely to benefit a patient. Prognostic biomarkers, in contrast, provide information about the likely course of the disease regardless of treatment. Biomarkers used in clinical decisions include PD-L1 expression, tumour mutational burden, mismatch-repair deficiency, receptor expression, and specific genetic alterations. Results should be interpreted using validated clinical criteria, taking account of the cancer type, the test's performance, and the evidence for the proposed treatment. [9,10,12,13]

5.2 Combination Therapy And Treatment Sequencing

Combining targeted medicines can block more than one pathway and may delay resistance; BRAF and MEK inhibitors are one established example. Depending on the evidence, targeted drugs may also be used with chemotherapy, endocrine therapy, radiotherapy, or immunotherapy. Combinations can improve disease control, but they may also add side effects, make treatment more complicated, and increase costs. Treatment choice and sequence should therefore reflect clinical evidence and the needs of the individual patient. [3,8,14,15]

5.3 Antibody–Drug Conjugates And Bispecific Approaches

Antibody–drug conjugates (ADCs) combine an antibody with a powerful cytotoxic drug payload. The antibody helps direct the payload towards cells carrying a selected antigen. How well an ADC works, and how safe it is, depends on factors such as antigen distribution, linker stability, payload characteristics, and exposure of healthy tissues. Interstitial lung disease or pneumonitis is an important risk with some ADCs and needs prompt assessment if suspected. Bispecific antibodies provide another option by bringing two targets —or an immune cell and a tumour cell—together in one therapeutic interaction. [13]

5.4 Immunotherapy And Rational Combinations

Checkpoint inhibitors have changed treatment for several cancers, but they do not produce long-lasting benefit for every patient when used alone. Resistance may occur when tumour cells display few recognisable antigens, fail to present antigens properly, prevent T cells from entering the tumour, encourage suppressive immune cells, or activate other inhibitory pathways. Researchers are testing combinations intended to address these problems, but the added toxicity and real clinical benefit need careful evaluation. [5,8,12]

5.5 Artificial Intelligence And Functional Precision Oncology

Machine-learning methods can examine genomic, transcriptomic, proteomic, imaging, and clinical information to look for patterns linked to drug response or resistance. Organoids, patient-derived models, and other functional tests may add useful information when the meaning of a genetic finding is unclear. Although these approaches are promising, they need reproducible

methods, independent validation, and evidence that they improve treatment decisions or patient outcomes before they can be relied on in routine care. [1,2,7,9]

6. MAJOR CHALLENGES AND MECHANISMS OF RESISTANCE

6.1 Intratumour Heterogeneity And Clonal Evolution

A tumour is not made up of identical cells. Different groups of cells may carry different genetic or epigenetic changes. Treatment can kill the cells that are sensitive to a drug while resistant groups survive and multiply. Different areas of one tumour may also behave differently, so a biopsy from one site may not reflect all metastatic sites. As the cancer changes over time, repeat molecular testing may sometimes help explain treatment failure and guide the next decision. [2,3,8]

6.2 Primary And Acquired Resistance

Primary resistance means that a tumour does not respond well to a treatment from the beginning. Acquired resistance develops after the treatment has initially worked or controlled the disease for a period. Possible causes include new mutations in the drug target, increased activity of alternative receptors, reactivation of downstream signalling, changes in drug transport or metabolism, and adaptation of the tumour microenvironment. Understanding these changes may help researchers develop newer inhibitors and more effective combinations. [3,8,15,16]

6.3 Pharmacokinetics, Delivery, And Target Accessibility

A medicine may match a tumour's molecular profile and still fail if enough drug does not reach all affected sites. Limited blood flow, high pressure within the tumour, stromal barriers, poor penetration across the blood–brain barrier, metabolism, protein binding, and active drug efflux can all reduce drug exposure. For patients with cancer involving the brain, the ability of a medicine to reach the central nervous system may therefore be an important part of treatment selection. [14,15,16]

6.4 Toxicity And Therapeutic Window

A targeted mechanism does not mean that a medicine is free from adverse effects. The protein being targeted may also have a useful role in healthy tissues, and a drug may affect related proteins as well. For example, EGFR inhibitors can cause skin and gastrointestinal effects, some kinase inhibitors can affect the cardiovascular system, and checkpoint inhibitors can trigger immune-related reactions. Baseline assessment, clear patient education, and appropriate monitoring are important parts of treatment. [12,13,14,15,16,18]

6.5 Biomarker Limitations And Access

Molecular tests differ in their sensitivity, the genes they cover, the time needed to produce results, and their ability to detect structural changes or rare mutations. A variant with uncertain significance should not be treated as a therapeutic target unless there is adequate supporting evidence. Access to testing may also depend on whether tissue is available, whether costs are reimbursed, access to specialist interpretation, and the resources of the healthcare system. These barriers can prevent some eligible patients from receiving biomarker-guided treatment. [9,10,18]

6.6 Evidence Gaps In Clinical Translation

Laboratory models do not always reproduce the way human tumours evolve, interact with the immune system, or receive a drug. Studies of rare molecular subgroups may use single-arm designs, but questions can remain about comparisons with other treatments, the best treatment sequence and duration, and long-term safety. Surrogate endpoints also need to be interpreted carefully. Promising laboratory results should ultimately be tested in well-designed clinical studies. [3,8,9]

7. FUTURE DIRECTIONS

Future progress will depend on linking molecular diagnosis with ongoing monitoring and changes in treatment when needed. Broader profiling may uncover rare alterations that can be treated, while better interpretation of test results can help distinguish meaningful findings from incidental variants. Tracking circulating tumour DNA over time may help identify resistance earlier, provided the tests are validated and the results can guide a clear clinical decision. [2,8,9,10]

Newer approaches—including antibody–drug conjugates, bispecific antibodies, radioligand treatments, cell-based therapies, RNA-based medicines, and targeted protein degraders—may expand treatment options beyond conventional enzyme inhibition. Better laboratory models that preserve tumour diversity and immune interactions will also be important. At the same time, clinical evidence must be transparent, access to testing should be fair, and costs should be assessed so that scientific progress can translate into meaningful benefits for patients. [7,13,18]

In practice, precision oncology usually involves several linked steps: [1] confirm the cancer type and stage; [2] choose biomarker tests that have been validated for that cancer; [3] interpret the results alongside the patient's clinical history and the strength of the evidence; [4] select a treatment supported by the biomarker and approved for the relevant setting; and [5] plan how adverse effects and treatment response will be monitored. A multidisciplinary team can be helpful when the case is complex. [9,10,14,16]

CONCLUSION

Targeted drug therapy has changed cancer care by turning knowledge of tumour biology into treatments aimed at specific growth signals, hormone pathways, DNA-repair weaknesses, blood-vessel formation, tumour antigens, and immune checkpoints. Important advances include biomarker-selected kinase inhibitors, synthetic-lethality approaches, antibody–drug conjugates, and checkpoint immunotherapy. Even so, treatment outcomes remain affected by resistance, differences between tumour cells, adverse effects, limitations in diagnostic testing, cost, and unequal access. Further progress will depend on dependable biomarkers, well-chosen treatment combinations, stronger clinical evidence, and making precision oncology available to more patients. [1,2,3,4,5,6,7,8,9,10,12,13,14,15,16,17,18]

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