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Decoding Drug Resistance in Cancer: Mechanisms, Clinical Challenges, and Emerging Therapeutic Strategies

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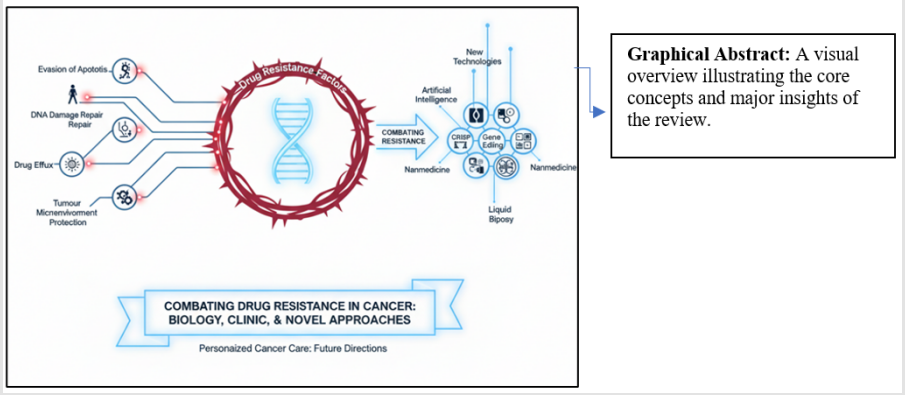
ABSTRACT

Cancer is a deadly disease and always remains one of the most significant challenges in the field of medicine. This is mainly because it is unique from other diseases, and tumour cells can easily become resistant to almost all current therapies available. Resistance can be developed over time, which persistently compromises the clinical outcomes, resulting in relapse, metastasis, and less survival of the patient. For many years, scientists have identified key molecular and cellular processes that contribute to the development of resistance. These factors include the modifications in drug efflux transporters, evasion of apoptosis, DNA damage repair mechanisms, metabolic reprogramming, and the protective effects of the tumour microenvironment. Resistance is also different, depending on the type of treatment, which includes chemotherapy, targeted therapy, immunotherapy, or hormonal therapy. Each type has its own drawbacks. Our perspective is that the therapeutic failure has been further altered by the identification of cancer stem cells and tumour heterogeneity as key factors. New technologies, such as the integration of artificial intelligence, CRISPR-based gene editing, nanomedicine, and liquid biopsy, are providing new opportunities to anticipate, track, and counter resistance. This review summarises current knowledge on drug resistance in cancer, its biological basis, clinical consequences, and novel approaches to enhance the effectiveness of treatment, as well as defining future directions that could characterise the field of personalised approaches to cancer care (Graphical Abstract).



Graphical Abstract.

Keywords: Drug Resistance; Chemoresistance; Targeted Therapy Resistance; Multidrug Resistance; Tumour Heterogeneity; Phenotypic Plasticity; Liquid Biopsy; AI in Cancer; Immunotherapy Resistance

Abbrevations: ctDNA: Circulating Tumor DNA; DTP: Drug-Tolerant Persister; EPR: Enhanced Permeability And Retention; ERCC1: Excision Repair Cross-Complementation Group 1; ESR1: Estrogen Receptor 1; EZH2: Enhancer Of Zeste Homolog 2; HGF: Hepatocyte Growth Factor, HIF-1α: Hypoxia-Inducible Factor 1-Alpha; Hsp90: Heat Shock Protein 90; IMC: Imaging Mass Cytometry, lncRNA: Long Non-Coding RNA; MCL-1: Myeloid Cell Leukemia 1; MGMT: O-6-Methylguanine-Dna Methyltransferase; MLH1: MutL Homolog 1; MRD: Minimal Residual Disease; MRP1: Multidrug Resistance-Associated Protein 1; OXPHOS: Oxidative Phosphorylation; PDCD4: Programmed Cell Death 4; PIK3CA: Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha; PROC: Platinum-Resistant Ovarian Cancer; scRNA-seq: Single-Cell Rna Sequencing; TIM-3: T-Cell Immunoglobulin And Mucin-Domain Containing-3.

Introduction

In recent years, the landscape of cancer therapy has undergone a paradigm shift, moving from traditional chemotherapeutic regimens toward highly specific molecularly targeted drugs and immunotherapies. These innovations have significantly improved patient outcomes, yet the clinical benefit is often transient due to the inevitable development of drug resistance. Resistance not only compromises treatment efficacy but also promotes tumor recurrence and metastasis, making it a central obstacle in cancer management. A deeper understanding of the biological basis and adaptive mechanisms of resistance is therefore vital to designing next-generation therapeutic strategies [1]. Drug resistance is not a new concept The first discoveries that initially effective medications quickly lost their effectiveness as tumors evolved were made during the 1940s and 1950s, when chemotherapeutic treatment of hematological malignancies was being used [2]. In recent years, it has become increasingly apparent that resistance to treatment is a significant problem affecting all areas of oncology, particularly with traditional cytotoxic treatments [3]. To a great extent, this issue has been substantially addressed by the introduction of specific therapies, which have provided both researchers and clinicians with a greater number of more effective and creative treatment options.

One notable example is the introduction of imatinib in chronic myeloid leukemia (CML) and the deployment of epidermal growth factor receptor (EGFR) inhibitors in non-small cell lung cancer (NSCLC)Nevertheless, the co-existence of secondary mutations in the EGFR gene and BCR-ABL kinase domain has demonstrated that drug resistance is not localized to the surface, it is, in fact, a hallmark of cancer biology, which is changing, and thus, cancer management is becoming more intricate [4]. The effect of immunotherapy, particularly that of immune checkpoint inhibitors, was so remarkable that it marked a significant milestone in the field of research and treatment, ushering it into a completely new era. Despite the elevation of resistance that came with this progression, for example, the exhaustion of T-cells, immunosuppression of tumors induced by them, and impermeability of antigen presentation, the demand for research using advanced biological techniques to unravel the intricate cause of cancer resistance mechanisms has not diminished [5]. The nature of drug resistance is multifactorial, highlighting its complexity as one key factor. The resistance can be caused by acquired mechanisms, which are characterized by adaptive phenomena triggered by drug exposure leading to resistance, or by intrinsic mechanisms in which tumour cells are inherently resistant to drugs [6].

However, it is almost impossible for resistance to have only one cause. the most common way is the synergistic rewiring of the signalling network, epigenetic modifications, gene mutations, and influences of the tumour microenvironment, which eventually lead to resistance [7]. Human diversity in cancer, to a large extent, is both compositionally intertumoral (differences between patients) and intratumoral (differences within one tumour mass), etc. Such diversity in tumour cells is one of the main reasons why treatment becomes more complex, as it allows those sub clonal populations that coexist within one tumour to not only survive the selective pressure but also to multiply after therapy [8]. Resistance leads to big health problems. It is directly responsible for a poor prognosis, lowers the effectiveness of frontline regimens, and makes it obligatory to resort to more toxic or experimental therapies. For instance, the resistance to androgen receptor signalling inhibitors in prostate cancer is almost always the auxiliary cause of the castration-resistant condition. Meanwhile, Platinum resistance in ovarian cancer (PROC) occurs when the cancer stops responding to platinum-based chemotherapy, leading to recurrence within 6 months of treatment, which is referred to as the main reason for mortalities [9]. In addition, resistance to BRAF inhibitors in melanoma is likely to develop a few months following treatment due to compensatory activation of either the MAPK or PI3K-AKT pathways.

These clinical situations, being the underlying causes, thus indicate the need for the implementation of a comprehensive platform to better understand the resistance mechanisms and facilitate the development of countermeasures [10]. This article broadly discusses cancer drug resistance, starting from the differences between acquired and intrinsic resistance types. Firstly, we discuss cellular and molecular factors relevant to this purpose, including DNA repair, cancer stem cells, apoptotic evasion, efflux pumps, epigenetic regulation, and the

role of the tumour microenvironment. In this context, resistance is dramatically illustrated for various types of therapy, demonstrating how cancer cells develop resistance to chemotherapeutics, targeted drugs, hormonal agents, and immunotherapeutic. We also consider the clinical aspects of resistance by examining the evolution of cancer and the failure of treatment, as well as evaluating new treatments aimed at addressing the problem, such as combination therapies, nanomedicine, and precision oncology [11]. Moreover, we discuss advanced and futuristic concepts that may serve as catalysts for the drug-resistance struggle to transition into a new era, including CRISPR technologies, liquid biopsy-based monitoring, and artificial intelligence-driven drug design. This review outlines the drug resistance landscape in cancer by adeptly intertwining mechanistic insights with translational advancements, making it a valuable resource for scientists, clinicians, and students committed to solving one of the most intractable issues in oncology today

Types of Drug Resistance in Cancer

Drug resistance in cancer can be categorized into two main types: intrinsic resistance and acquired resistance. These two types are distinct yet interconnected, and they have a significant impact on the effectiveness of treatments [12]. Their categories are not just the timing, mechanism, or clinical manifestation in which treatment fails, but also understanding these categories is vital. Acquired resistance appears after the initial response to treatment and reflects the adaptive evolution of cancer cells under selective pressure. on the other hand, intrinsic resistance indicates a tumour that is naturally insensitive/resistant to therapy from the start [13].

Intrinsic Resistance

Intrinsic resistance refers to the situation in which tumour cells are ineffective against a therapeutic agent from the very beginning of treatment. Here, even if patients receive sufficient drug exposure, they show little to no clinical benefit. The tumor's genetic and epigenetic composition, which includes features that inherently protect cells from drug-induced cytotoxicity, is the most prevalent association with this mechanism [14]. Patients with KRAS gene mutations suffering from non-small cell lung cancer (NSCLC) are a typical example. Since KRAS-driven signalling offers a bypass survival pathway that avoids EGFR blockade, patients with KRAS mutations are thus non-responders to EGFR tyrosine kinase inhibitors (TKIs), like gefitinib or erlotinib, which, on the other hand, are characterized by high efficacy in patients with activating EGFR mutations [15]. Correspondingly, as a result of triple-negative breast cancers (TNBC) not having HER2 amplification and estrogen and progesterone receptors, individuals with TNBC are the ones who are most likely to be resistant to hormone therapies such as tamoxifen or aromatase inhibitors intrinsically [16]. As one of the most aggressive brain tumour, glioblastoma multiforme (GBM) is a prime example of inherent resistance. Moreover, the primary reason for GBM's inherent resistance to these drugs is that the level of the DNA repair enzyme O-6-methylguanine-DNA methyltransferase (MGMT), which efficiently reverses the DNA-damaging effect of alkylating agents such as temozolomide, is very high [17].

Generally, patients with unmethylated MGMT promoters and actively expressed MGMT are not good candidates for temozolomide treatment. Whereas those with promoter methylation resulting in suppressed MGMT expression tend to have the most favorable treatment outcomes. Apart from genetics, both phenotypic and microenvironmental factors contribute to intrinsic resistance. For example, the poor vascularization, desmoplastic stroma, and hypoxic microenvironment of pancreatic ductal adenocarcinoma (PDAC) not only limit drug delivery but also serve as a refuge for the resistant tumour cells, hence they make PDAC very resistant to both chemotherapy and targeted therapy [18]. The situation may also be comparable with that of stem-like cancer cells (CSCs) at the baseline, which are capable of rendering tumors less sensitive naturally. CSCs are non-dividing. they possess extremely efficient DNA repair mechanisms and are resistant to apoptosis as shown in Figure 1, allowing them to survive treatments that primarily target proliferating cells [19]. Hence, intrinsic resistance remains a significant barrier to the benefits of frontline therapies for certain patient cohorts. This thus points to a greater extent to the necessity of predictive biomarkers for detecting therapy-resistant tumors prior to treatment, as well as the therapeutic strategies guided by them as alternatives [20].

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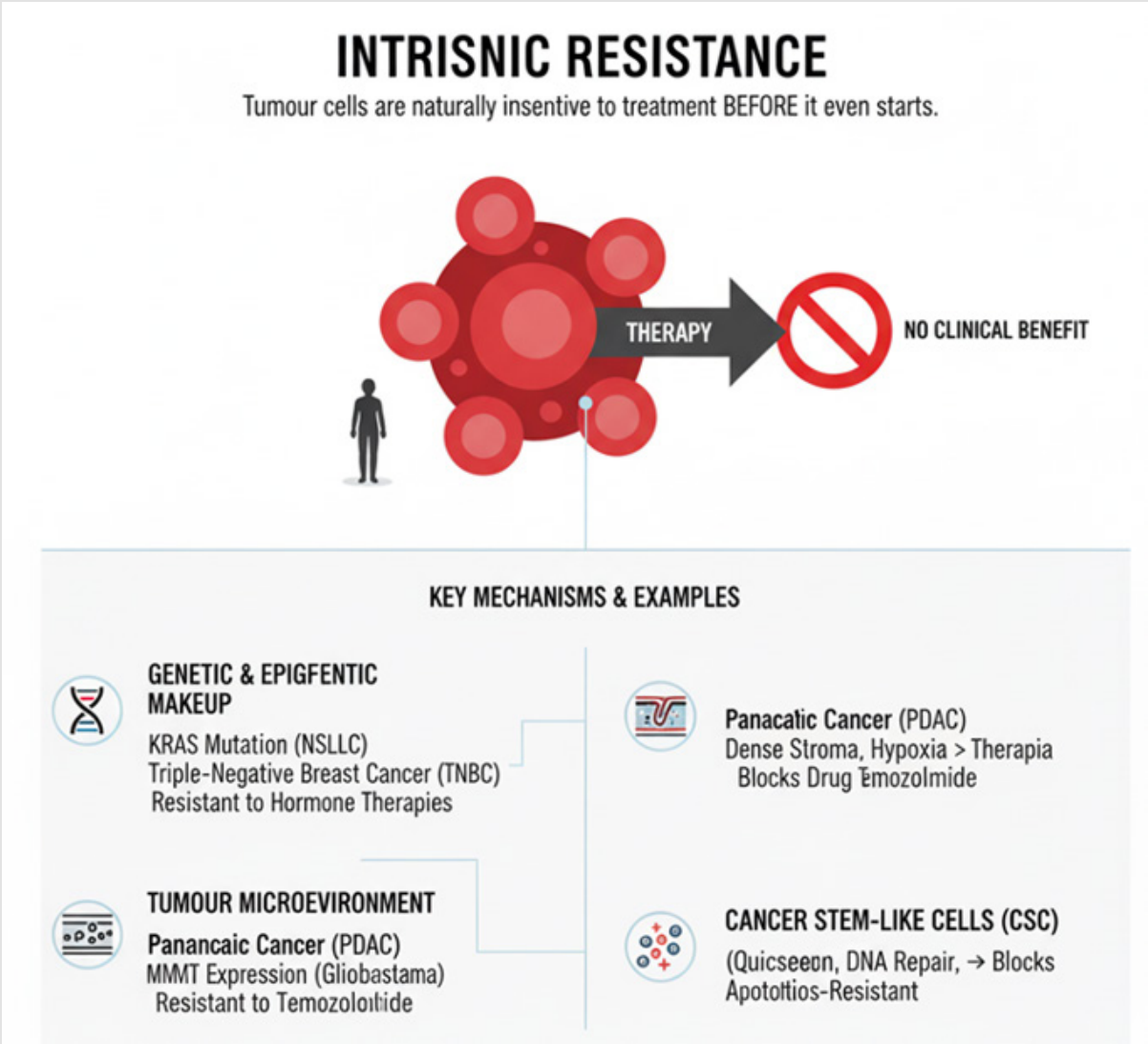


Figure 1.

Acquired Resistance

In contrast to intrinsic resistance, acquired resistance is defined as the development of resistance after a certain period of time, when the drug or therapy has been effective. A good reaction to the therapy is then headed off by the appearance of resistance, and the tumour will continue to grow. The adaptability of cancer cells to treatment is illustrated by the metabolic rewiring, epigenetic changes, genetic mutations, and reactivation of signalling pathways they undergo under therapeutic pressure [21]. Acquired resistance represents one of the most extensively researched cases in the application of imatinib in chronic myeloid leukemia (CML). Imatinib, a selective inhibitor of the BCR-ABL tyrosine kinase, caused long-lasting reductions in most patients and thus radically changed the treatment of CML [22]. However, secondary mutations in the BCR-ABL kinase domain, with the T315I gatekeeper mutation being the most prominent example, prevent drug binding and are the cause of eventual relapse in most patients. Subsequent-generation TKIs, for example, dasatinib, nilotinib, and ponatinib, were actually conceptualized to address the problem of resistance mutations, and their clinical development followed this line [23]. Besides, those patients having NSCLC with EGFR mutation are initially sensitive to first-generation EGFR inhibitors, like erlotinib or gefitinib, but, most frequently, relapse is due to the EGFR T790M mutation that leads to resistance by facilitating ATP binding at the kinase domain, and therefore, the vast majority of cases return after 9–12 months [24].

Therefore, osimertinib, as a third-generation inhibitor, has come to efficiently target the T790 M mutation. However, osimertinib resistance can be caused by MET amplification, the C797S mutation, or histological transformation to small-cell lung cancer. The situation is the same with melanoma patients who are treated with BRAF inhibitors (vemurafenib or dabrafenib), and acquired resistance follows them [25]. Despite the amazing initial responses of tumors with BRAF V600E mutations, almost all patients relapse, and the resistance usually develops within 6–8 months. Reactivation of the MAPK pathway by the NRAS mutations, MEK amplification or alternative splicing of BRAF itself is the underlying cause of resistance. The combination of BRAF and MEK inhibitors, although it delays resistance, allows for the development of resistance which is not completely stopped. Moreover, immunotherapies are not safe from acquired resistance [26]. Examples of the latter could be those patients who were given the immune checkpoint inhibitors (anti-PD-1 or anti-CTLA-4) treatment, thereby achieving long-lasting responses, but resistance has come along due to T cell exclusion from the tumour microenvironment, upregulation of alternative immune checkpoints, or loss of antigen presentation machinery (e.g., B2M mutations) [27].

In a similar manner, receptor mutations, receptor amplification, or bypass pathway activation that are adaptable and compatible with tumour expansion without hormonal signalling are frequent events during the use of anti-estrogen or anti-androgen drugs in hormone-dependent cancers, such as breast or prostate cancer, through which the cancer becomes resistant [28] Additionally, it is crucial to note that these resistances may be triggered by non-genetic changes, including metabolic plasticity, phenotypic switching, and epigenetic reprogramming, in conjunction with genetic mutations. The cancer cells undergo a transformation from the epithelial state to the mesenchymal state (EMT), a process associated with resistance to chemotherapy and targeted therapies, which renders cells drug-tolerant and more invasive. Furthermore, these non-genetic changes are reversible, meaning that the resistant cells can quickly change their phenotypes and therefore evade therapy in unexpected locations, which is the main reason for their being one of the most difficult issues [29].

Interplay Between Intrinsic and Acquired Resistance

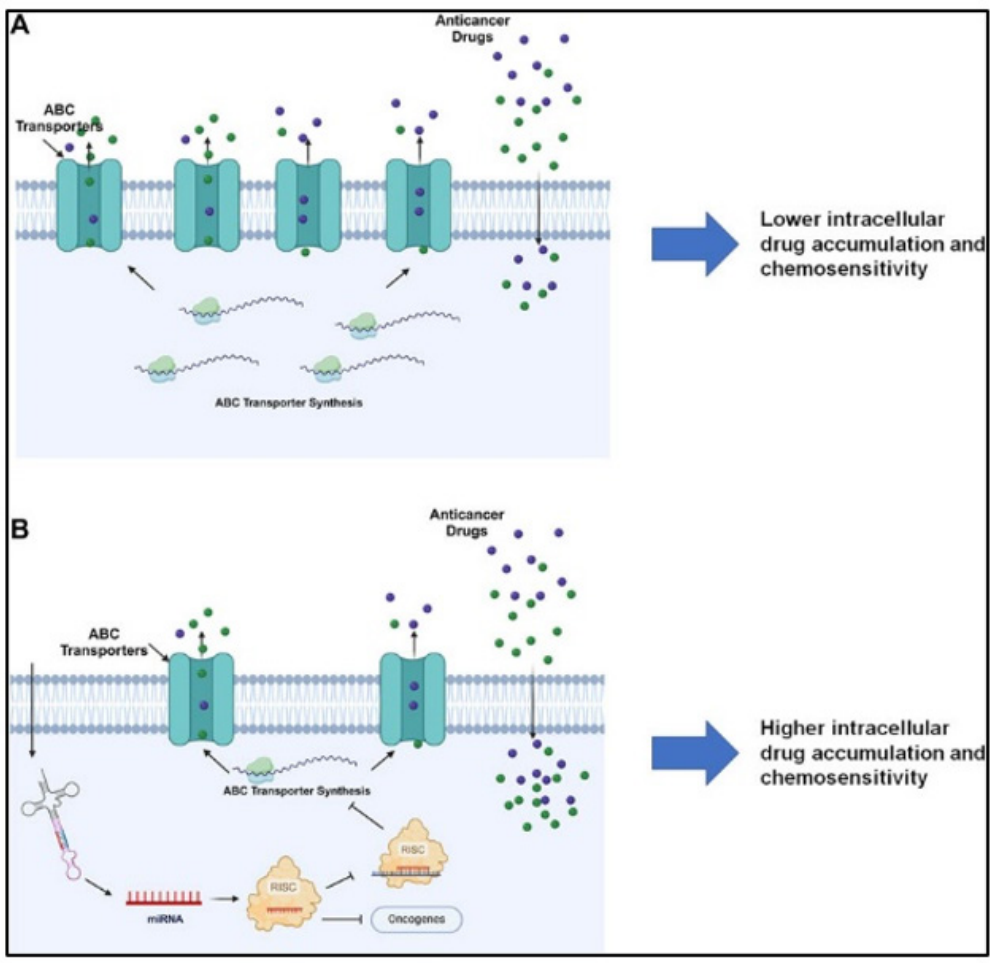
Even though they are different in concept, intrinsic and acquired resistance are frequently found together and have a cross that influences practical scenarios. A tumour may be loaded with such resistance mechanisms that empower certain cells to have some survival advantages. Those cells can then be further developed by the treatment, resulting in additional resistance traits [30]. For example, the function of MGMT can contribute to intrinsic resistance to temozolomide in glioblastoma. The tumour may then become a mismatch repair-deficient tumour, leading to hypermutation and increasing resistance to therapy after treatment. Mutations that cause alterations in the downstream signalling pathways eventually become those that display the full resistance phenotype of breast cancer, while the variability in HER2 expression that exists prior to treatment may be the origin of intrinsic resistance to trastuzumab. Thus, the separation between intrinsic and acquired resistance is not a classic one, but rather a consequence of the cancer biology properties that are dynamic and adaptive. Those therapies that can effectively overcome both ingrained and developed resistance, as well as prevent the latter, need to have this understanding of the interaction [31].

Mechanisms of Drug Resistance in Cancer

The drug resistance of cancer is complicated by various mechanisms, which not only allow the tumour cells to survive but also make it quite difficult for the treatment to have its cytostatic or cytotoxic effect on cancer cells. These mechanisms can be phenotypic (changes in the cell state or influences of the microenvironment), epigenetic (methylation and histone modification), or genetic (mutations, amplifications, and deletions). Significantly, resistance is typically the result of the combined operation of several acclimatisation strategies rather than a single one. To reverse the sensitivity or to eliminate the resistance completely, we need to understand these mechanisms [32].

Drug Efflux Transporters and Altered Drug Accumulation

ATP-binding cassette (ABC) transporters are mediators that facilitate the efflux of drugs from the cell, leading to increased resistance, which is one of the first and most well-identified forms of resistance. Through active pumping, these membrane proteins remove cancer cells that are susceptible to various chemotherapeutic agents. Hence, they lower intracellular drug concentrations below the cytotoxicity thresholds, as shown in Figure 2. P-glycoprotein (P-gp, encoded by the MDR1/ABCB1 gene) is the most prominent of the proteins that lead to multidrug resistance (MDR), characterised by resistance to structurally diverse drugs such as vincristine, doxorubicin, and paclitaxel [33]. P-gp overexpression has been raised as one of the reasons for the negative outcome of the disease and low treatment response in leukaemia, breast cancer, colon cancer, and various solid tumour types, which is the place where P-gp has been found, too. We cannot overstate the significance of the roles that different transporters, for example, MRP1 (ABCC1) and BCRP (ABCG2), play in mesothelioma and several other types of cancer. Even though the function of BCRP in topoisomerase inhibitors, such as mitoxantrone, and targeted therapies, like tyrosine kinase inhibitors (TKIs) is very strong, MRP1, however, is always there supporting the anthracyclines and the vinca alkaloids in their struggle against cancer [34]. It is noteworthy that the presence of BCRP has also been associated with resistance to imatinib in CML and to gefitinib in NSCLC.



Note: Note that miRNAs introduced into the cells may inhibit the expression of some oncogenes to exert anticancer effects, explained by Yimei Wang et al. [36].

Figure 2: By escaping miRNA-mediated PTGR, efflux ABC transporters are overexpressed in cells to pump out substrate drugs, exhibiting lower drug exposure and chemosensitivity. Restoration of PTGR of efflux transporters, e.g., through the introduction of bioengineered miRNA molecules, reduces ABC transporter expression, enhances intracellular drug exposure, and increases cell sensitivity to the drugs.

If the aim was to overcome efflux-mediated resistance by employing inhibitors of ABC transporters, clinical translation has been largely hampered by factors such as transporter redundancy, off-target toxicity, and the physiological roles of these proteins in normal tissues. Despite that, new techniques, namely nanoparticle drug delivery and drug changes that allow bypassing of efflux transporters, are already revealing surprising success in preclinical studies [35,36].

Changes in Drug Targets

Besides, direct changes in the target of a drug may lead to resistance to the medication. Through mutations, gene amplifications, or alternative splicing events, the drug binding can be lowered, the target activity increased, or even the compensatory pathways upregulated. Non-small cell lung cancer (NSCLC) with an EGFR T790M mutation is one such example, as it preserves kinase activity while blocking the binding of first-generation TKIs. Furthermore, BCR-ABL mutations, particularly the emergence of the T315I mutation, render imatinib ineffective against CML. The changes in BRAF that are splice variants and do not contain the RAS-binding domain are the primary source of melanoma resistance to vemurafenib, as they promote dimerization and continuous MAPK pathway activation, despite the presence of the drug [37]. Additionally, target amplification is another method. To illustrate, the amplification of the HER2 gene in breast cancer can overcome the inhibitory effect of trastuzumab, whereas MET amplification provides a bypass signalling pathway for EGFR-inhibited lung cancers. Additionally, the alternative splicing of genes can also alter

the targets of drugs. The resistance in castration-resistant prostate cancer (CRPC) is due to the splice variants of the androgen receptor (AR), such as AR-V7, which remains active despite lacking the ligand-binding domain that anti-androgens like enzalutamide target. The discovered facts indicate a dependence on the new generation of inhibitors, which are capable of overcoming resistance mutations, as well as the use of combined tactics to prevent pathway reactivation.

Evasion of Apoptosis and Cell Death Pathways

Escaping the process of programmed cell death (apoptosis) is among the most notable features of cancer cells, which becomes even more evident when these cells are subjected to therapeutic stress. Most anticancer drugs initiate apoptosis. resistance is, thus, often associated with changes in the apoptotic regulators. The overproduction of anti-apoptotic members of the BCL-2 family (BCL-2, BCL-XL, and MCL-1), which keeps cancer cells alive by inhibiting the activity of pro-apoptotic proteins such as BAX and BAK, is the main cause of this phenomenon, whereby BCL-2 overexpression is the source of chemotherapy resistance that can be found in hematological malignancies [38]. The clinical outcome of using venetoclax, a selective BCL-2 inhibitor approved for the treatment of chronic lymphocytic leukemia (CLL), as a therapeutic strategy targeting apoptotic evasion, is a clear indication of the massive therapeutic potential. Conversely, the loss or inactivity of pro-apoptotic proteins also leads to resistance. The downregulation of BAX or the loss of PUMA and NOXA interrupts apoptosis in response to DNA damage [39]. Additionally, p53 mutations, which are detected in more than 50% of cancers, inhibit apoptosis triggered by DNA damage, leading to widespread drug resistance. Besides activating other survival pathways, cancer cells can also become resistant to apoptosis through the activation of the autophagy mechanism.

Autophagy can be a stress-relieving process, as it recycles cellular components and provides metabolic substrates, thereby enabling cancer cells to resist chemotherapy or targeted therapies. For instance, therapy-induced autophagy increases survival in melanoma and pancreatic cells, and its suppression can restore the sensitivity of these cells [40].

Enhanced DNA Damage Repair

One of the mechanisms behind the action of radiotherapy and several chemotherapeutic drugs is the induction of DNA damage. Tumour cells, in order to reduce the cytotoxic effects of these therapies, often become resistant through the upregulation of DNA repair pathways. For example, elevated nucleotide excision repair (NER), which removes platinum-DNA adducts, is the primary cause of resistance to platinum-based drugs such as cisplatin. Overexpression of ERCC1, a key protein involved in NER, is a hallmark of poor response to cisplatin in ovarian and lung cancers [41]. Tumors become more vulnerable to PARP inhibitors when there are defects in homologous recombination (HR) repair, e.g. those induced by BRCA1 or BRCA2 mutations. However, resistance emerges when secondary mutations occur, restoring BRCA function and HR proficiency. Moreover, loss of 53BP1, a protein that normally antagonizes HR, can also lead to restoration of DNA repair capability in BRCA-deficient cells and thereby confer resistance to PARP inhibitors. However, resistance occurs when secondary mutations restore BRCA function and HR competence [42] Similarly, in BRCA-deficient cells, loss of 53BP1, a protein that normally opposes HR, can restore DNA repair ability and thus resistance to PARP inhibitors. Mismatch repair (MMR) is another major pathway.

Besides elevating mutational load and resistance to alkylating agents, MMR deficiency now also generates neoantigens, which paradoxically render tumors more sensitive to immune checkpoint blockade. So, DNA repair capacity is a double-edged sword in terms of therapeutic response [43].

Tumour Microenvironment (TME) and Stromal Interactions

The tumour microenvironment is one of the major factors that significantly impact drug resistance. Fibroblasts, immune cells, the extracellular matrix, and vasculature of the TME cooperate to form a protective niche that shields tumour cells from treatment. Growth factors such as hepatocyte growth factor (HGF), which is secreted by cancer-associated fibroblasts (CAFs), not only activate bypass signalling pathways like MET but also lead to resistance to EGFR inhibitors. As it has been discovered in pancreatic cancer, CAFs also produce extracellular matrix components, which thicken tissue and make drug absorption more difficult [44]. Solid tumors often suffer from hypoxia, and thus, resistance is amplified by the stabilization of hypoxia-inducible factor 1α (HIF-1α), which causes the expression of genes related to multidrug resistance and alters cellular metabolism to favour glycolysis. Since radiotherapy relies on oxygen to produce free radicals that damage DNA, hypoxia also lowers its effect. Immune cells that are present in the TME also contribute to resistance. Tumour-associated macrophages (TAMs), by secreting cytokines like TGF-β and IL-10, which suppress immune surveillance and increase tumour cell survival, can facilitate chemoresistance. Besides this, regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), as shown in Figure 3 constitute an immunosuppressive milieu which lessens the effect of immunotherapy [45].

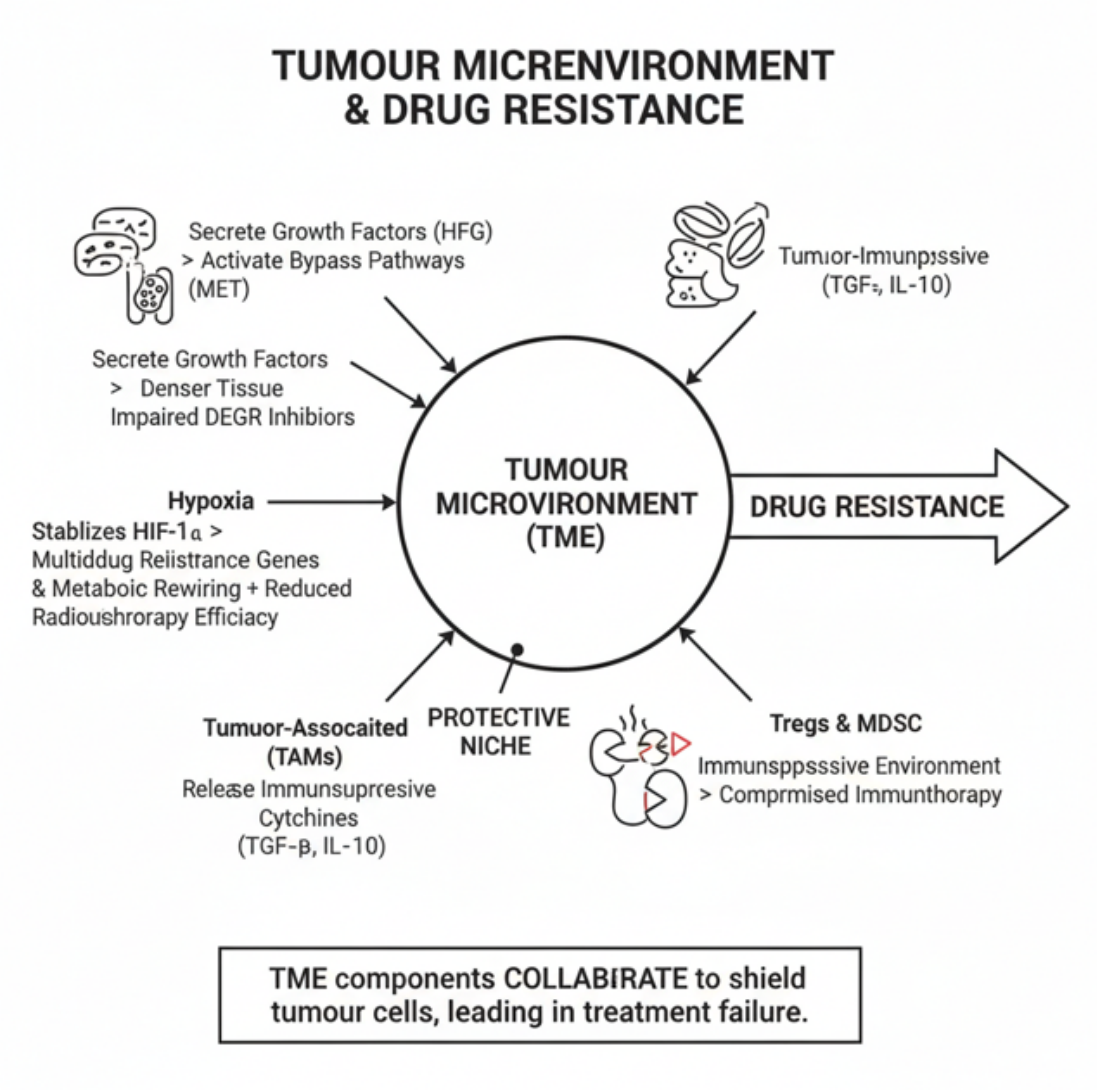


Figure 3.

CSCs, or Cancer Stem Cells

Because of their ability to self-renew and be pluripotent, CSCs are a type of cancer cell that is frequently referred to as the main cause of tumour recurrence and treatment resistance. Besides their dormancy, more effective DNA repair, high expression of efflux transporters, and resistance to apoptosis, CSCs are treatment-escaping agents that are killed along with the majority of tumour cells. Chemotherapy-resistant, CD44 high/CD24 low phenotype CSCs have a role in breast cancer relapse [46]. Similarly, glioblastoma radio-resistant and temozolomide-resistant CSCs are the ones that have CD133 expression. The CSCs of colorectal and pancreatic cancers remain resistant because of the activation of signalling pathways such as WNT, NOTCH, and Hedgehog. The problem of targeting them remains significant. however, there are only a few drugs that can kill CSCs without affecting normal stem cells. Still, new methods, such as immunotherapy targeting the CSC antigen, differentiation therapy, and the use of CSC-specific inhibitors, are currently under research [47].

Epigenetic Modifications

Epigenetic changes, including DNA methylation, histone modification, and non-coding RNA regulation, are the primary mechanisms that lead to alterations in gene expression. however, the underlying base DNA sequence remains unchanged. The promoter methylation of tumour suppressor genes may gradually turn off the drug-induced apoptotic pathways that are vital for the therapy. For example, MMR deficiency resulting from the silencing of the MLH1 gene by methyla-

tion is the primary reason for resistance to alkylating agents. Side by side, histone modifications have the potential not only to alter gene expression but also to open or close chromatin, thereby providing the basis for changes in therapeutic responses [48]. Besides, non-coding RNAs are the major contributors to the gene regulation machinery. For example, miR-21, by silencing tumour suppressors such as PTEN and PDCD4, supports tumour growth and the evolution of resistance to chemotherapy and targeted therapies. The oncogenic pathways may develop due to the downregulation of tumour-suppressive miRNAs that repress them. In addition to the issue of drug resistance, long non-coding RNAs also regulate the processes of drug efflux, apoptosis, and EMT. One of the key features that qualifies epigenetic changes as potential therapeutic targets is their reversibility.

The first generation of epigenetic drugs, such as DNA methyltransferase inhibitors (azacitidine, decitabine) and histone deacetylase inhibitors (vorinostat, panobinostat), have been highly effective in their cancer and haematological indications, while their efficacy in solid tumors still being evaluated [49].

Therapy-Specific Mechanisms

In addition, the resistance mechanisms are different for each treatment option. The major contributors to resistance situations are drug efflux caused by chemotherapy, increased DNA repair, evasion of apoptosis, and metabolic reprogramming. For example, both the suppression of NER activity and alteration of glutathione metabolism have been linked to cisplatin resistance in ovarian cancer [50]. Targeted therapy has the typical resistance mechanisms include secondary mutations, activation of bypass pathways, and phenotypic switching. The two instances are the reactivation of MAPK in BRAF-inhibited melanoma and the overexpression of MET in EGFR-inhibited lung cancer [51]. Hormonal therapy: Breast cancer ESR1 mutations cause the estrogen receptor to be turned on ligand-independently, thus causing aromatase inhibitor resistance. At the very same moment that androgen deprivation is happening, AR splice variants in prostate cancer are still sending out signals [52]. Resistance to immunotherapy is marked by the following mechanisms: the presence of immune-suppressive cells, T cell exclusion from tumours, the upregulation of inhibitory checkpoints (TIM-3, LAG-3), and the absence of antigen presentation (e.g., B2M mutations). As a result, each therapeutic class selects for various resistance mechanisms thus, counterstrategies must be appropriately adapted [53].

Clinical Implications of Drug Resistance

The primary cause of treatment failure in oncology, drug resistance, has a direct impact on clinical judgment, patient outcomes, trial design, and the allocation of healthcare resources. It is not just a lab curiosity. Resistance can have a wide range of clinical effects, including reduced long-term disease control, earlier and more frequent relapses, accelerated metastatic disease progression, decreased quality of life, and increased morbidity from the disease and subsequent treatment lines. Resistance affects the regulatory evaluation of new agents, complicates drug development, and imposes a significant financial strain on both health systems and individual patients [54]. To translate mechanistic insights into better patient care, it is crucial to comprehend these clinical implications, including how resistance manifests, how it is identified and tracked, and how it should inform therapy sequencing and selection. Resistance typically manifests at the bedside in two ways: primary (or innate) non-response, where a patient never benefits significantly from an agent, and secondary (or acquired) progression, which follows an initial response [55]. Clinically, these differences help guide immediate management: acquired resistance raises concerns about the mechanism (on-target mutation, bypass signaling, phenotypic switch, microenvironmental protection), whether the original therapy can be changed (dose escalation, switch to a next-generation inhibitor), combined with other agents, or abandoned in favor of an alternative modality, while primary non-responders need alternative first-line strategies [56].

In contrast to heterogeneous, non-genetic resistance (EMT, epigenetic reprogramming, or stromal protection), which is more difficult to reverse and frequently signals a worse prognosis, the emergence of on-target resistance mutations in targeted therapy (EGFR T790M, BCR-ABL T315I) has historically been linked to predictable next steps—use of specific next-generation inhibitors. One of the main clinical challenges is detecting and tracking resistance. Only when there has been a discernible increase in tumor burden can traditional radiographic criteria (RECIST) detect progression, by which point resistant clones may have already seeded distant sites. As a result, molecular monitoring has become a vital supplement. Targeted salvage treatments can be informed by the identification of actionable resistance mechanisms (secondary mutations, amplifications, and gene fusions) through tumour genotyping at baseline and at progression using next-generation sequencing (NGS) of tissue biopsies. Since it allows for minimally invasive, real-time evaluation of tumour evolution and can identify new resistance clones weeks to months before radiographic progression, serial liquid biopsy —the analysis of circulating tumour DNA (ctDNA) — has gained significance. The potential of ctDNA to guide early treatment modification, detect minimal residual disease (MRD) following curative-intent therapy, and stratify patients for trials of novel or combinational approaches is what makes it clinically useful.

However, practical issues like reimbursement, assay standardization, and sensitivity in low-tumour-burden settings continue to be obstacles to widespread adoption. Clinical solutions to the inevitable occurrence of resistance include treatment sequencing and combination strategies. Clinicians are increasingly using upfront combinations (e.g., BRAF and MEK inhibitors in BRAF-mutant melanoma) instead of monotherapy to suppress multiple nodes within a signalling network and delay the growth of resistant clones. When the resistance mechanism is known, sequential use of targeted medications (first-, second, and third-generation inhibitors) is an example of a precision

approach. however, sequential monotherapy runs the risk of selecting for multidrug-resistant clones and may only offer temporary relief. A common clinical challenge is striking a balance between optimizing immediate tumour control and maintaining options for the future. Some adaptive treatment paradigms based on evolutionary principles have been piloted and show promise, but they need to be validated in larger, controlled trials. Examples of these include intermittent dosing and lower-intensity therapy, which aim to maintain a population of drug-sensitive cells to suppress the growth of resistant clones. The core of clinical decision-making in the age of resistance is biomarkers. Prognostic biomarkers, which show the overall course of the disease, and predictive biomarkers, which show the likelihood of benefit from a particular therapy, direct patient counselling, trial enrollment, and treatment selection [57].

EGFR/ALK/BRAF mutations in lung and melanoma, ER/PR/HER2 status in breast cancer, and BRCA status in ovarian and breast cancer are a few examples. It's crucial that biomarkers are dynamic because relying solely on archival tissue may be deceptive, as a tumor's actionable landscape may change during treatment. For patients receiving targeted treatments, the idea of "re-biopsy at progression" has become commonplace in many facilities. ctDNA is a useful substitute in situations where tissue biopsy is unsafe or uninformative. Although not yet common, multimodal biomarker approaches—which combine genomics, transcriptomics, proteomics, and functional assays (such as organoids and ex vivo drug sensitivity testing)—promise a more comprehensive picture of resistance. Designing clinical trials and making regulatory decisions are also impacted by resistance [58]. The molecular heterogeneity of resistance mechanisms must be taken into consideration in trials, which frequently use biomarker-driven cohorts (umbrella and basket trials). Overall survival (OS) remains the gold standard, although endpoints like progression-free survival (PFS) are helpful for identifying early signs of benefit. In contemporary oncology, the interaction of subsequent therapies and crossover makes OS interpretation more challenging. In response, regulatory bodies permit expedited approvals based on surrogate endpoints in populations chosen by biomarkers, which are then followed by confirmatory trials.

According to trialists, studies can become more clinically relevant and move more quickly from the bench to the bedside by incorporating resistance monitoring (tissue and ctDNA) early on and implementing adaptive protocols that allow switching therapy based on new mechanisms. Resistance has both financial and psychological costs, in addition to the costs associated with therapy selection. Multiple lines of therapy are necessary for recurrent or refractory disease, and the cumulative toxicities that result from these treatments lower the quality of life. Patients and their families face long-term uncertainty, more frequent hospital stays, and higher out-of-pocket expenses. Health systems have to deal with costly targeted agents, repeated molecular testing, and extended supportive care. For patients who are unlikely to benefit from more aggressive therapy, these realities underscore the need for health-economic analyses and supportive care pathways that incorporate palliative measures early. Finally, there are significant logistical and ethical issues raised by the clinical implications of resistance. With recover therapies that have little proof of benefit, how aggressive should clinicians be in their pursuit of marginal gains? When should the emphasis change from controlling the disease to managing symptoms and improving quality of life? In multidisciplinary tumour boards, clinicians have to make these choices while combining molecular data, clinical context, patient values, and anticipated trajectories [59].

Equality issues are also brought up by the growth of precision medicine and frequent molecular testing, as access to novel agents, clinical trials, and high-quality molecular diagnostics is unequally distributed both internationally and domestically. If improvements in overcoming resistance are to benefit large patient populations, it is both morally and practically necessary to address these disparities. In conclusion, drug resistance has a profound impact on nearly every aspect of clinical oncology, encompassing trial design, resource allocation, patient monitoring, and the sequencing of therapies. Strong, standardized diagnostic tests (such as ctDNA), evidence-based combination and sequential therapy approaches, and a focus on patient-centered outcomes are necessary for implementing mechanistic insights into standard practice [60]. Clinicians will need to strike a balance between aggressive disease control, preservation of future options, and quality of life as the field shifts toward more adaptive, evolution-informed treatment paradigms and routine molecular surveillance. These decisions are best made in multidisciplinary frameworks and with real-time molecular data in mind.

Strategies to Overcome Drug Resistance

One of the biggest problems in contemporary oncology is overcoming drug resistance in cancer. No single approach is always successful because resistance arises from a variety of mechanisms, including genetic, epigenetic, metabolic, and microenvironmental. Rather, to both stop resistance from developing and to re-sensitize resistant tumour, an integrative strategy combining targeted therapy, immunotherapy, nanotechnology, epigenetic modification, and precision medicine is required. This section describes the main therapeutic approaches being used, emphasizing their benefits, drawbacks, and clinical justification.

Combination Therapy Approaches

Combination therapy is the most popular method of overcoming resistance. It works by attacking cancer cells using multiple mechanisms simultaneously, which reduces the likelihood that resistant clones will survive, as shown in Figure 4. Combinations in clinical oncology may include immunotherapy plus targeted therapy, chemotherapy plus targeted therapy, chemotherapy plus chemotherapy, or targeted therapy plus targeted therapy. NSCLC, or non-small cell lung cancer, is a notable example. Single-agent EGFR tyrosine kinase inhib-

itors (TKIs) often yield dramatic but transient effects, and resistance typically develops due to MET amplification or EGFR T790M mutations [61]. Resistance may be delayed by combining EGFR inhibitors with MET or MEK inhibitors. Comparably, by inhibiting bypass MAPK signalling, the combination of BRAF inhibitors (vemurafenib, dabrafenib) and MEK inhibitors (trametinib, cobimetinib) in melanoma considerably increases progression-free and overall survival when compared to BRAF inhibitor monotherapy. Although chemotherapy combinations are older, they remain useful. To prevent tumour cells from developing cross-resistance, multi-agent regimens such as FOLFOX/FOLFIRI for colorectal cancer or CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) for lymphomas rely on agents with distinct mechanisms of action.

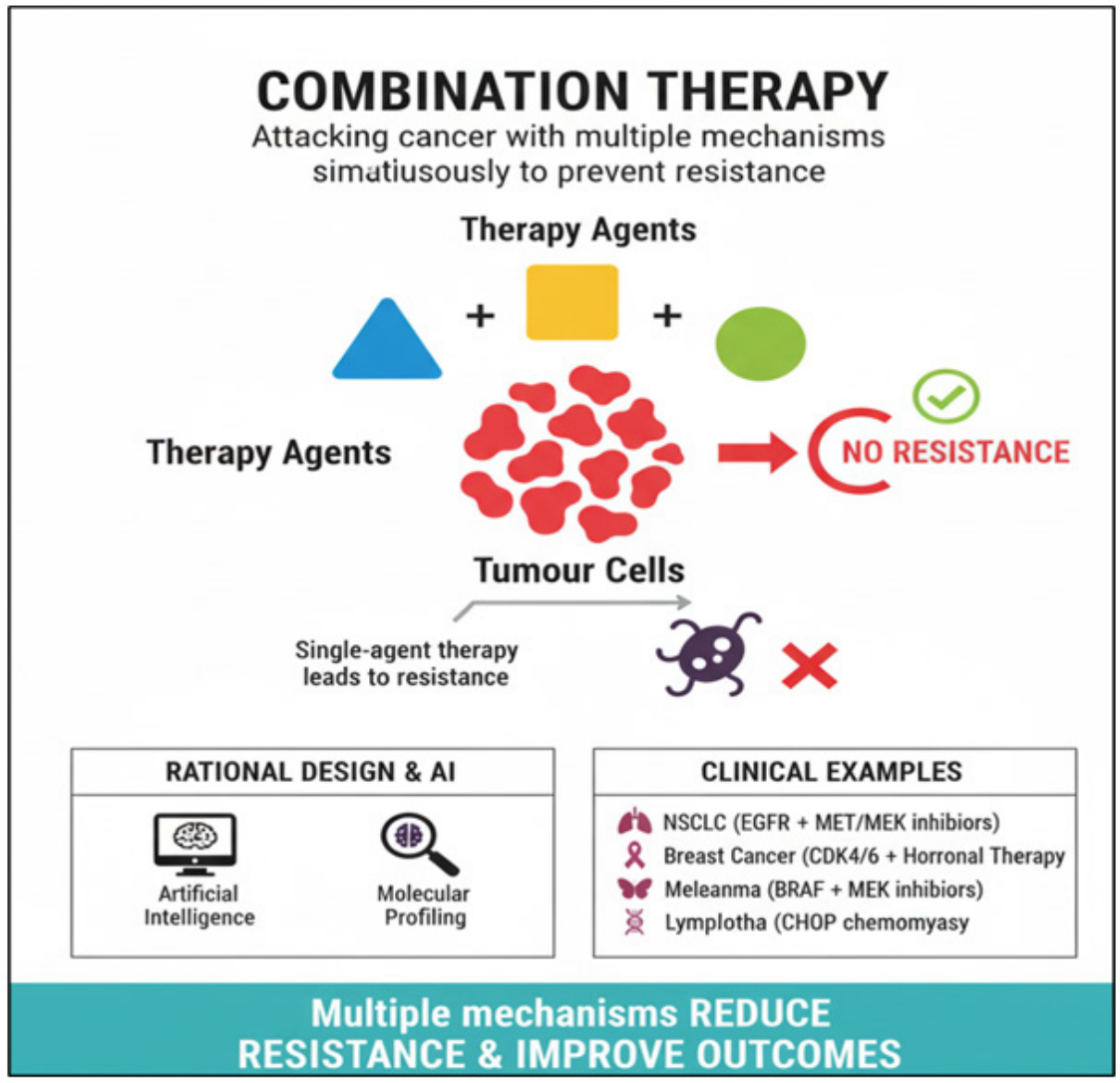


Figure 4.

Combining CDK4/6 inhibitors with hormonal therapies improves disease control in breast cancer by addressing both cell-cycle progression and proliferative signalling [62]. Combination therapy presents difficulties despite its achievements. Tolerability is limited by overlapping toxicities, and not all combinations work well together. some can even be antagonistic. Therefore, choosing successful pairings requires rational design that is informed by preclinical modelling and molecular profiling. Artificial intelligence and computational modelling are being used increasingly to predict the most effective drug combinations.

Nanotechnology-Based Drug Delivery

By modifying drug pharmacokinetics, enhancing tumour penetration, and circumventing efflux mechanisms, nanomedicine offers a novel strategy for combating drug resistance. Chemotherapeutics can be encapsulated in nanoparticles to prevent degradation and enable targeted delivery to tumors through the enhanced permeability and retention (EPR) effect. For instance, doxorubicin (Doxil) liposomal formulations minimize cardiotoxicity without sacrificing effectiveness. Additionally, drug efflux pumps such as P-glycoprotein (P-gp), a primary contributor to multidrug resistance (MDR), can be circumvented by nanoparticles. Nanoparticle formulations enable greater intracellular drug accumulation, even in resistant cancer cells, by modifying the distribution and uptake of the drug [63]. Drug delivery to the resistant tumour while preserving healthy tissue is ensured by targeted nanocarriers functionalized with ligands (antibodies, peptides, and aptamers) that can bind selectively to overexpressed receptors on cancer cells. Nanoparticles that target HER2 in breast cancer or folate receptors in ovarian cancer are two examples. Furthermore, nanocarriers enable the co-delivery of several agents. For example, chemotherapy and siRNA can be delivered together, with siRNA silencing genes linked to resistance (such as MDR1 or BCL-2), while chemotherapy induces cytotoxicity [64].

Although preclinical and early clinical research on nanomedicine has shown promise, issues with reproducibility, long-term toxicity, and the scalability of nanoparticle manufacturing have slowed large-scale clinical translation. Nonetheless, it is anticipated that continued advancements in smart nanocarrier stimuli-responsive systems activated by pH, temperature, or enzymatic activity will expand the clinical applicability of nanotechnology in overcoming resistance.

Epigenetic Therapy

Drug resistance is largely caused by epigenetic changes, which modify gene expression without changing the DNA sequence. These changes include DNA methylation, histone modifications, and the regulation of non-coding RNA. The epigenetic reprogramming of resistant cancer cells frequently silences pro-apoptotic genes or activates survival pathways. Crucially, epigenetic modifications are reversible, which makes them appealing therapeutic targets in contrast to genetic mutations. The FDA has approved DNA methyltransferase inhibitors (DNMTs), such as decitabine and azacytidine, for the treatment of acute myeloid leukemia and myelodysplastic syndromes [65]. These substances can increase sensitivity to chemotherapy or targeted therapy by demethylating the promoter regions of tumour suppressor genes. Likewise, oncogenic transcription programs are disrupted and silenced genes are reactivated by histone deacetylase inhibitors (HDACis), such as vorinostat and romidepsin. Immunotherapy and epigenetic medications also work in concert. For instance, HDACs increase the expression of MHC molecules and tumour-associated antigens, which helps T-cells recognise resistant tumour cells. As a result, studies are now being conducted to test epigenetic agents in combination with immune checkpoint inhibitors (anti-PD-1, anti-CTLA-4 in refractory cancers. Another level of epigenetic control is represented by non-coding RNAs, especially microRNAs (miRNAs) [66].

Chemotherapy resistance has been linked to the dysregulation of miRNAs, including miR-21 and miR-34. Though clinical translation is still in its infancy, preclinical promise has been demonstrated in resensitizing resistant tumors by restoring tumour-suppressive miRNAs or blocking oncogenic miRNAs through synthetic oligonucleotides. Since these substances alter global gene expression and may have off-target effects, the non-specificity of epigenetic therapy is a drawback. Ongoing research into selective epigenetic modulators, however, promises to improve safety and specificity, making epigenetic reprogramming a vital component of resistance treatment.

Immunotherapy-Based Strategies

The treatment of cancer has been transformed by immunotherapy, especially with immune checkpoint inhibitors (ICIs) that target CTLA-4, PD-1, and PD-L1 [67]. Nonetheless, both primary and acquired immunotherapy resistance are still prevalent. To overcome this resistance, immunotherapy must be combined with other treatment modalities, and the tumour immune microenvironment must be modulated. Insufficient T-cell infiltration, loss of antigen presentation, or upregulation of alternative immune checkpoints are common causes of resistance to ICIs. These mechanisms can be resisted by combining ICIs with traditional treatments. For instance, by releasing neoantigens, chemotherapy or radiation therapy can boost tumour immunogenicity and improve the effectiveness of ICIs. In a similar vein, targeted treatments like BRAF/MEK inhibitors can change the tumour microenvironment to make it more vulnerable to immune attack. Another way to get past resistance is through adoptive cell therapies, such as tumour-infiltrating lymphocyte (TIL) therapy and chimeric antigen receptor (CAR) T-cells, particularly in haematological malignancies. However, solid tumors present obstacles, such as immunosuppressive microenvironments and inadequate infiltration. To circumvent these restrictions, novel CAR designs are being developed, such as those that target multiple antigens or incorporate "armoured" constructs that release cytokines.

In an effort to improve immune recognition of tumors that are resistant to treatment, oncolytic viruses and cancer vaccines are also being reexamined. The value of combining various immunotherapeutic platforms is demonstrated by the oncolytic virus T-VEC, which has shown synergy with ICIs in melanoma [68]. Immunotoxic side effects, such as cytokine storms and autoimmune reactions, continue to be a problem and may restrict widespread use. However, immunotherapy-based approaches remain among the most promising avenues for combating resistance.

Precision Medicine and Biomarker-Guided Therapy

Precision oncology, where treatment is customised to the distinct molecular makeup of each patient's tumour, is the best way to over-

come resistance. To find actionable vulnerabilities, thorough profiling utilizing proteomics, metabolomics, transcriptomics, and genomics is necessary. Precision medicine has already revolutionised cancer care in practice. For example, patients with EGFR, ALK, ROS1, or RET mutations are paired with corresponding inhibitors in NSCLC, which significantly improves results when compared to chemotherapy [69]. Importantly, repeat molecular profiling enables dynamic therapy adaptation when resistance develops, such as in patients with EGFR T790M, allowing for a switch to osimertinib. Precision oncology has become possible, in large part, thanks to liquid biopsy (ctDNA analysis). It enables real-time, non-invasive tracking of resistance evolution, which helps clinicians modify treatment before a clinical relapse occurs. Including AI-powered prediction algorithms enhances the ability to anticipate resistance and develop customised treatment plans. The development of synthetic lethality strategies, such as PARP inhibitors in BRCA-mutated cancers, is another aspect of precision oncology. These tactics can specifically target and destroy resistant tumour cells while preserving healthy tissue by exploiting specific genetic flaws. There is potential for wider clinical use if the synthetic lethality framework is extended beyond BRCA and PARP.

Despite the unparalleled potential of precision medicine, obstacles include tumour heterogeneity, clonal evolution during treatment, the scarcity of targeted medications for numerous alterations, and unequal access to molecular diagnostics. Transforming precision oncology into standard care worldwide will depend on overcoming these challenges

Future Perspectives in Overcoming Resistance

Integrative oncology, a paradigm where therapy selection is guided by ongoing molecular monitoring, evolutionary modelling, and logical combination strategies, holds the key to the future of resistance management. Adaptive trial designs represent a significant paradigm shift, in which patients are dynamically reassigned to new arms in response to emerging resistance mechanisms. Furthermore, cutting-edge technologies like single-cell sequencing, CRISPR-based gene editing, and AI-driven network modelling will expand our knowledge of resistance and reveal new vulnerabilities. Drug resistance may eventually be transformed from an unavoidable obstacle to a controllable, predictable, and potentially preventable phenomenon by combining these approaches with well-established clinical tools.

Recent Advances in Understanding Resistance Mechanisms

In the field of oncology today, significant advancements in high-throughput genomics, multimodal imaging modalities, molecular biology, and advanced computational modelling have transformed our understanding of cancer drug resistance. With this paradigm shift, resistance is no longer viewed as a single, unchangeable entity, but rather as a complex, time-varying evolutionary process influenced by the intricate interactions between adaptive cellular plasticity, intratumoral heterogeneity, and the tumour microenvironment (TME) [70]. By combining these state-of-the-art technologies, researchers and clinicians can anticipate resistance signatures, precisely outline their mechanistic foundations, and create customised treatment plans. This section describes the significant new developments that are changing the clinical and epistemic approaches to resistance research. These developments use artificial intelligence (AI)-powered analytics and integrative multi-omics datasets to predict and reduce treatment recalcitrance. These advancements also demonstrate that resistance is a systemic adaptation that involves immune evasion, metabolic changes, and epigenetic remodeling, rather than just a cellular response.

These factors all contribute to the persistence of minimal residual disease and eventual relapse. New research also highlights how cell-free nucleic acids and extracellular vesicles facilitate the spread of resistance signals to distant metastatic sites, further complicating the resistance network.

Tumour Heterogeneity and Clonal Evolution

The understanding that tumors are complex ecosystems with genetically and phenotypically varied subclones, rather than homogeneous cellular aggregates, represents a fundamental discovery in the aetiology of resistance. Intratumoral heterogeneity creates a reservoir for selective pressures, manifesting as subpopulations with distinct metabolic dependencies, transcriptomic profiles, mutational landscapes, and drug susceptibilities. Non-genetic plasticity and dedifferentiation processes, akin to "reverse evolution," amplify the Darwinian outgrowth of pre-existing minor subclones that withstand therapeutic onslaughts, a process that often leads to the development of resistance. In breast cancer, for example, single-cell sequencing analyses have revealed uncommon pre-therapy subpopulations with PIK3CA or ESR1 mutations that multiply under the selective influence of endocrine or PI3K inhibitors, ultimately leading to overt resistance [71]. The same is true for EGFR-mutant non-small cell lung cancer (NSCLC), where sub clonal T790M variants predominate after exposure to EGFR tyrosine kinase inhibitors (TKIs) but persist at allelic fractions below detection thresholds prior to treatment. These insights have recently been extended to other cancers, including colorectal cancer, where APC and KRAS mutations in subclones confer resistance to anti-EGFR therapies, and prostate cancer, where androgen receptor variants drive castration resistance through clonal expansion [72].

Furthermore, clonal hierarchies develop under chemotherapy in haematological malignancies, such as acute myeloid leukaemia, with founder clones producing resistant offspring through repeated mutations in genes like FLT3 or IDH1/2 [73]. Clonal evolution includes metabolic rewiring, microenvironmental niche selection, and epigenetic reprogramming in addition to genomic changes. Mathematical models, such as those that combine game theory and stochastic branching processes, emphasise that resistance is an inevitable consequence of evolutionary dynamics and support interventions that

reduce clonal diversity, rather than focusing on a single dominant clone. Using whole-genome sequencing to track sub clonal dynamics in various cancers, recent studies have demonstrated that heterogeneity is primarily driven by subclones rather than polyclonal origins, underscoring the role of genomic instability in relapse and treatment resistance. Through immune surveillance, nutrient scarcity, and hypoxia, the tumour microenvironment creates selective pressures that support the survival of adaptive clones, further influencing this evolution. Myeloid-derived suppressor cells and cancer-associated fibroblasts, for example, have the ability to release substances that encourage clonal diversification, increasing resistance to immunotherapies. By disrupting diverse protein networks, heat shock protein 90 (Hsp90) inhibitors have also demonstrated potential in eliminating tumour-initiating cells and possibly avoiding the evolution of resistance [74].

To prevent the dominance of resistant lineages, adaptive dosing strategies could be informed by the early detection of branching events, highlighting the necessity of longitudinal monitoring to capture the temporal aspects of clonal shifts.

Cancer Stem Cells and Phenotypic Plasticity

Due to their capacity for self-renewal, differentiation, and resistance to genotoxic insults, cancer stem cells (CSCs) have emerged as key players in the development of therapeutic resistance. CSCs are described by modern single-cell transcriptomics as fluid states that alternate between stem-like and differentiated phenotypes in response to external stimuli and therapeutic perturbations, rather than as strict hierarchies. Melanoma cells that undergo reversible switching to a quiescent, invasive mesenchymal phenotype during BRAF inhibition and revert upon drug cessation exemplify how this phenotypic plasticity confers transient drug-tolerant persister (DTP) states without requiring irreversible genetic alterations [75]. EMT gives breast cancer stemness, preventing apoptotic cascades and promoting resistance to taxanes and anthracyclines. Similar dynamics have been revealed by recent studies in bladder cancer, where CSCs express markers such as CD44 and ALDH1A1, enabling resistance to cisplatin through improved efflux pumps and DNA repair. By upregulating pathways like Wnt and Notch, CSCs help prostate cancer become androgen independent, whereas in colorectal cancer, they cause resistance to oxaliplatin through metabolic changes. When CSC plasticity is strategically targeted, new countermeasures are introduced, such as differentiation-inducing agents that force CSCs into vulnerable differentiated states and inhibitors of canonical stemness pathways (e.g., WNT/β-catenin, NOTCH, and Hedgehog).

To overcome CSC-mediated resistance, delivery systems based on nanomaterials have surfaced [76] These systems encapsulate therapeutics to take advantage of CSC-specific weaknesses, such as pH-sensitive nanoparticles that release medications in acidic tumour niches. The necessity for combinatorial regimens to eliminate heterogeneous CSC pools is further highlighted by the discovery of dual CSC states, proliferative and quiescent, during tumorigenesis. These dynamics are mapped with fine-grained resolution by single-cell RNA sequencing (scRNA-seq), which makes precise CSC ablation possible. It has been demonstrated that hypoxia increases CSC plasticity, changing gene expression toward stem-like characteristics and resulting in therapy resistance. Glioblastoma CSCs in perivascular niches use increased angiogenesis signalling to withstand temozolomide. To eliminate the underlying cause of tumour regrowth and metastasis, these discoveries open the door to treatments that interfere with CSC-microenvironment interactions, such as preventing exosome-mediated transfer of stemness factors [77].

Liquid Biopsy and Real-Time Resistance Monitoring

Liquid biopsy, which involves analysing circulating tumour DNA (ctDNA) and extracellular vesicles from biofluids, represents a revolutionary development in oncology by providing non-invasive, long-term monitoring of tumour phylogenetics and resistance development. Serial ctDNA profiling in EGFR-mutant NSCLC accelerates the administration of osimertinib by detecting T790M months before imaging-detected progression. While ctDNA kinetics predict minimal residual disease (MRD) and guide adjuvant escalation in hormone receptor-positive breast cancer, ESR1 mutations signal the futility of aromatase inhibitors. Current applications include tracking BRAF V600E mutations during targeted therapy for colorectal cancer and monitoring FGFR changes in bladder cancer [78]. Additionally, liquid biopsies identify MRD in early-stage cancers, which helps with adjuvant immunotherapy decision-making. Advanced technologies, such as digital droplet PCR and ultra-sensitive next-generation sequencing (NGS), can identify variant allele frequencies as low as 0.01%. AI-enhanced bioinformatics can also be used to deconvolute complex ctDNA signatures and predict adaptive resistance. Although there are still issues with assay harmonisation, variant interpretation during clonal hematopoiesis, and sensitivity in oligometastatic situations, liquid biopsy is becoming increasingly clinically accepted and has the potential to change resistance paradigms.

By detecting the post-translational changes that cause resistance, recent mass spectrometry-based proteomics in liquid biopsies improves precision monitoring and further enriches the detection of tumour-derived analytes. Future developments will integrate wearable technology for real-time biofluid sampling, enabling ongoing surveillance of resistance biomarkers, such as miRNA profiles or methylated circulating tumour DNA (ctDNA) [79]. Liquid biopsies reduce the need for invasive procedures in pediatric cancers, capturing systemic heterogeneity in multi-site metastases that is not visible in single-site tissue biopsies. This allows treatment regimens to be dynamically adjusted to counter emerging resistance.

Metabolic Plasticity in Resistance

Resistance is based on metabolic reprogramming, in which cancerous cells dynamically adjust their anabolic and bioenergetic cir-

cuits to evade treatments that aim to stop their growth. In melanoma, where BRAF inhibitor-resistant clones rely on mitochondrial respiration for redox homeostasis, resistance to PI3K/AKT/mTOR antagonists frequently involves increased oxidative phosphorylation (OXPHOS) [80] Preclinical effectiveness in recalcitrant models has been demonstrated for the simultaneous inhibition of OXPHOS, glycolysis, or glutaminolysis, which work in concert to destroy these adaptations. Whereas fatty acid oxidation promotes endocrine resistance in breast cancer, mitochondrial metabolic reprogramming in colorectal cancer increases resistance to anti-angiogenic agents. Metabolic reprogramming, the basis of resistance, occurs when cancerous cells dynamically modify their anabolic and bioenergetic circuits to avoid therapies intended to halt their growth. Resistance to PI3K/AKT/mTOR antagonists often involves increased oxidative phosphorylation (OXPHOS) in melanoma, where clones resistant to BRAF inhibitors depend on mitochondrial respiration for redox homeostasis [81]. The simultaneous inhibition of OXPHOS, glycolysis, or glutaminolysis has been shown to be preclinically effective in recalcitrant models, as these adaptations are destroyed by their combined action. In colorectal cancer, mitochondrial metabolic reprogramming increases resistance to anti-angiogenic agents, whereas fatty acid oxidation in breast cancer promotes endocrine resistance [82].

Epigenomic and Transcriptomic Plasticity

Adaptive resistance is actively pushed by epigenetic and transcriptomic changes, going beyond simple aftereffects. The unique chromatin architectures of persister cells—characterised by altered accessibility and histone acetylation/methylation patterns—are revealed by single-cell multi-omics, which facilitates transcriptional reprogramming under stress. This results in reversible DTP states that can be reversed during a break in therapy, suggesting that cyclic dosing is necessary to capitalise on plasticity. While histone alterations in prostate cancer drive lineage plasticity toward neuroendocrine states resistant to hormone therapy, epigenetic mediators such as EZH2 control phenotypic changes in glioblastoma. This environment is controlled by non-coding RNAs. lncRNA dysregulation triggers bypass pathways, while miR-21 upregulation promotes platinum resistance. Epigenetic modifiers that target histone deacetylases or DNA methyltransferases are among the therapeutic frontiers. sensitivity is restored by CRISPR-based disruption of resistance loci. Resistance is influenced by evolving epitranscriptomics RNA modifications, which broaden the arsenal of epigenetic weapons [83]. According to recent research, m6A RNA methylation controls EMT in breast cancer and increases resistance to HER2 inhibitors.

Traditional targeted therapies for lung cancer are challenged by epigenetic heritability, which permits a single genotype to produce multiple resistant phenotypes. By upregulating antigen presentation, the combination of epigenetic medications and immunotherapies reverses immune-cold tumor's, demonstrating the interaction between epigenomics and immune resistance.

Spatial and Temporal Mapping of Resistance

Imaging mass cytometry (IMC) and spatial transcriptomics provide insight into the geospatial heterogeneity of resistance by identifying niches influenced by stromal crosstalk, nutrient gradients, and hypoxia. In breast cancer, marginal clones use immune-matrix interactions to adapt, while resistant foci colocalise with hypoxic, CAF-enriched stroma in pancreatic ductal adenocarcinoma [84]. While spatial mapping in colorectal cancer identifies prognostic architectures, three-dimensional spatial technologies capture the evolution of metastases. By charting evolutionary trajectories through serial and liquid biopsies, temporal profiling allows for proactive interventions. Niche-targeted treatments are informed by multi-modal spatial omics, which decode TME-cellular dialogues. By combining spatial transcriptomics and proteomics, recent platforms have revealed how immune cells assemble around resistant clones to prevent T-cell infiltration.

Artificial Intelligence and Predictive Modelling

Predictive modelling and artificial intelligence have quickly become effective strategies in oncology, especially when it comes to tackling one of the most difficult problems in therapy, resistance. AI and machine learning can now predict resistance, reconstruct clonal phylogenies, suggest logical treatment sequences, and inform adaptive therapy strategies by combining various multi-omics datasets, including single-cell profiles, transcriptomics, proteomics, epigenomics, metabolomics, and genomics. Large databases of patient-derived data are processed by these computational frameworks, enabling the early detection of resistance mechanisms that would otherwise remain undetected until a clinical relapse occurs. Deep learning techniques are being applied to complex data types on several platforms that are currently undergoing development or clinical trials. By utilising sophisticated image analysis from CT, MRI, or PET scans, for instance, radiomics enables convolutional neural networks to detect subtle imaging phenotypes associated with molecular changes, thereby predicting treatment failure ahead of time compared to traditional radiological criteria. Another quickly developing field, circulating tumour DNA analysis, uses AI to analyse ctDNA's methylation patterns, fragmentomics, and mutational signatures. It frequently presents with resistance or recurrence months before it becomes clinically or radiologically visible.

In a similar vein, single-cell RNA sequencing, in conjunction with clustering and trajectory inference algorithms, allows for the identification of uncommon resistant subclones at baseline, mapping transcriptional reprogramming and lineage evolution under therapeutic pressure, and predicting which clones are likely to dominate as the disease progresses [85]. Beyond predicting relapse, AI can actively mitigate resistance by spotting weaknesses in resistant phenotypes. By using multi-omics fusion models, AI combines microenvironmental signals and molecular changes to identify compensatory circuits and bypass pathways that support tumors that are resistant. For ex-

ample, in KRAS-mutant cancers, where inhibition of the canonical RAF–MEK–ERK cascade frequently fails, predictive modelling has found that parallel signalling pathways, such as PI3K/Akt, Ral-GDS, or receptor tyrosine kinase-driven feedback loops, are activated. This suggests that PI3K or SHP2 inhibitors are a reasonable combination therapy. Additionally, resistant cell populations frequently develop new dependencies, such as stress reactions, epigenetic reprogramming, or altered metabolic states. Whether it's metabolic inhibitors, epigenetic medications, or repurposed agents that exploit synthetic lethal interactions, AI models can identify these adaptive changes and inform therapeutic targeting.

Optimising treatment sequencing and dosage plans is another important use. In adaptive therapy trials, predictive models are being used to model the evolutionary dynamics of tumour subclones under varying drug exposures. This helps clinicians modify schedules or doses to prevent resistance while preserving efficacy. The current situation illustrates how rapidly these tools are being adopted in clinical settings. In colorectal and breast cancers, ongoing trials that integrate AI algorithms with ctDNA monitoring have demonstrated that algorithmic thresholds for molecular relapse can guide early therapeutic interventions, redefining progression-free survival metrics. It is now possible to tailor immunotherapy regimens by developing deep learning frameworks that incorporate multimodal data, such as radiomics, omics, and clinical metadata, to predict not only resistance but also immune evasion in patients undergoing checkpoint blockade [86]. Additionally, generative algorithms are creating new small molecules to target vulnerabilities found computationally in resistant clones, demonstrating how AI is starting to directly impact drug discovery. These developments demonstrate that AI and predictive modelling are increasingly influencing oncology decision-making in real time and are no longer just theoretical or experimental concepts. Together, they signify a paradigm shift away from reactive treatment modifications made after resistance appears and toward proactive, precision-guided, and predictive interventions intended to postpone or even eliminate resistance completely.

Integration of Multi-Omics for Resistance Management

With its comprehensive framework for analysing the intricate interactions between genetic, epigenetic, transcriptional, proteomic, metabolic, and microenvironmental factors, multi-omics integration has emerged as a key component in the modern understanding and treatment of therapy resistance. Resistance is now understood as a dynamic and complex adaptive continuum influenced by tumour heterogeneity, cellular plasticity, metabolic versatility, and orchestration by the tumour microenvironment (TME), rather than the result of a single molecular change [87]. Researchers are creating a comprehensive resistance map by combining various omics layers, which reveal coexisting mechanisms, interdependent vulnerabilities, and cooperative adaptive strategies that enable tumour persistence in the face of therapeutic pressure. The basis for detecting driver mutations and transcriptional reprogramming underlying acquired resistance remains genomic and transcriptomic profiling. The addition of epigenomics, however, has shed light on non-genetic processes that support phenotypic plasticity and reversible drug-tolerant states, including DNA methylation, histone modifications, and chromatin remodelling. Proteomics, in particular, bridges the gap between genomic changes and phenotypic behavior by measuring protein abundance, post-translational modifications, and signalling fluxes.

Combining it with metabolomics reveals more about how resistant cells adapt their redox balance, energy use, and nutrient acquisition mechanisms to withstand selective pressure. One significant advancement in this field is the emergence of spatial multi-omics, which maps molecular events in relation to their microenvironmental and histological context. Spatial transcriptomics and proteomics have mapped out metastatic ecosystems in breast cancer and other solid tumours, shedding light on how vascular heterogeneity, immune cell positioning, and stromal niches influence treatment resistance. These technologies speed the conversion of multi-omics insights into clinically useful strategies by elucidating the role that stromal orchestration and tumour–immune interactions play in drug evasion while maintaining spatial architecture. With the integration of ctDNA, exosomes, and the circulating proteome or metabolome, liquid biopsy-based multi-omics offers a minimally invasive, longitudinal perspective that enables real-time tracking of resistance emergence throughout the disease course. Cutting-edge modalities that complement multi-omics integration are increasingly influencing the current landscape. Metabolomics identifies adaptive metabolic dependencies, while liquid biopsy offers dynamic surveillance of evolving clones [88].

Artificial intelligence unifies multi-layered datasets into clinically interpretable models, and single-cell RNA sequencing (scRNA-seq) reveals resistant subpopulations and lineage trajectories. To integrate heterogeneous data modalities and provide personalised treatment recommendations, accurate resistance trajectory prediction, and effective patient stratification, deep learning frameworks have become essential. Together, these strategies are making it easier to map resistance spatiotemporally, which tracks resistance dynamically over the course of treatment cycles and disease progression rather than just at a fixed point in time. A proactive paradigm in resistance management is indicated by this move from descriptive to predictive and integrative frameworks. Multi-omics integration enables the early detection of adaptive changes, stratifies patients for optimal treatments, and identifies combinatorial strategies that prevent resistance before it becomes clinically evident, as opposed to responding to resistance that is already clinically evident. In this changing environment, resistance is increasingly seen as a predictable, modelable continuum that can be intercepted by combining computational modelling, multi-omics technologies, and translational innovation. This opens the door for precision oncology, which predicts and overcomes resistance.

Future Directions and Emerging Therapies

The field of oncology is changing from post hoc mitigation to anticipatory and preventive strategies due to the quick advancement of knowledge about resistance mechanisms. Systems biology, precision oncology, the evolution of immunotherapy, synthetic biology, and computational prognostics are combining to shape the future therapeutic landscape, with the goal of reversing the onset of resistance before it becomes clinically established [89]. This paradigm shift focuses on tailored, adaptive interventions that combine biological knowledge with technological advancements, potentially preventing and delaying the development of resistance. At the same time, microenvironment-targeted treatments are breaking down the stromal and immune barriers that support resistant phenotypes, and the combination of multi-omics and artificial intelligence is revolutionising the way physicians forecast resistance trajectories. The significance of guaranteeing the fair, secure, and long-term application of these discoveries in practical settings is further underscored by preventive measures and ethical considerations. In contrast to the traditional maximum tolerated dose paradigm, which accelerates the dominance of resistant clones and applies constant selective pressure, adaptive therapy represents a significant shift. With its origins in evolutionary ecology, adaptive therapy dynamically adjusts dosage based on tumour burden measurements by preserving a population of drug-sensitive cells to competitively suppress resistant ones.

In breast and prostate cancer, preclinical research has demonstrated that these tactics postpone resistance and increase survival, and early-stage trials are currently investigating real-time monitoring tools like imaging and liquid biopsy to direct dose titration [90]. Adaptive therapy aims to control rather than eliminate disease by embracing evolutionary cycling, which maintains sensitive and resistant populations in dynamic equilibrium. This gives ovarian and lung cancers new hope for managing resistance. Targeting the molecular drivers of resistance, gene editing tools—specifically, CRISPR-Cas9 and its derivatives—are transforming the ability to directly overcome resistance. The loss of tumour suppressors can be restored, and resistance-promoting changes, such as efflux transporter upregulation, DNA repair gene mutations, or secondary mutations in oncogenic kinases, can be specifically eliminated [91]. It has been demonstrated in preclinical models that CRISPR-based disruption of resistance mutations in EGFR-mutant non-small cell lung cancer restores sensitivity to tyrosine kinase inhibitors. Additionally, genome-wide CRISPR screens enable the systematic identification of novel vulnerabilities specific to resistant clones. Advances in delivery technologies, such as base editors, adenoviral vectors, and nanoparticles, are helping to overcome translational barriers and advance the potential of gene-editing therapies toward clinical use in hematologic malignancies and solid tumours [92].

Another promising tactic to exploit the distinct genetic dependencies of resistant cancer cells is the use of synthetic lethality. Genome-wide CRISPR and RNAi screens are mapping synthetic lethal networks across various tumour contexts, going beyond the now-established PARP-BRCA paradigm. For instance, KRAS-mutant cancers exhibit selectively targetable weaknesses in metabolic and RNA-processing pathways, whereas ATM-deficient tumors exhibit synthetic lethal effects from ATR inhibition. These interactions are being systematised by advances in computational genomics, which make it possible to create customised treatments based on each patient's unique resistance profile and expand synthetic lethality strategies to new targets, such as RNA quality control complexes. Immunotherapy, which employs techniques to overcome adaptive immune evasion, remains a potent weapon against cancer that is resistant. To counteract the immunosuppressive rewiring that occurs after checkpoint inhibitor resistance, multi-checkpoint blockade targeting PD-1, CTLA-4, LAG-3, and TIM-3 is being investigated in melanoma and non-small cell lung cancer [93]. Neoantigen vaccines, which are customised to the tumour mutanomes of individual patients, are showing promise in producing new immune responses against resistant clones of pancreatic and colorectal cancers.

Solid tumor's, such as gliomas and sarcomas, pose challenges that are being addressed by engineered immune cell therapies, including CAR-T, CAR-NK, and TCR-T cells [94]. With encouraging results in head and neck cancers, oncolytic virotherapy is regaining traction by directly lysing tumour cells and boosting immunity in conjunction with checkpoint inhibitors. In all of these methods, artificial intelligence is being used more and more to tailor immunotherapy regimens and maximise combination strategies. One important area of resistance management is the combination of artificial intelligence and multi-omics. AI-enabled systems can predict resistance trajectories by integrating genomic, transcriptomic, proteomic, and metabolomic data. This enables therapies to be modified dynamically rather than based on static baseline profiles. Meanwhile, deep learning frameworks are decoding the spatial features of the tumour microenvironment to predict drug responses with increasing accuracy in cancers such as breast and lung. Pilot studies have already shown that multi-omics-AI symbiosis can optimise treatment regimens in real time. With the help of these technologies, precision oncology workflows are becoming possible, in which treatment is continuously modified to fit changing tumour characteristics.

Since resistance is frequently maintained by non-autonomous factors, tactics that specifically target the tumour microenvironment are equally crucial. Hypoxia-activated prodrugs are being tested in gliomas to take advantage of oxygen gradients, and cancer-associated fibroblast inhibitors are being tested to break down stromal barriers in pancreatic cancer. In breast tumours, metabolic modulators that alter nutrient ecologies are showing promise, and spatial multi-omics analytics are aiding in the identification of resistance niches in the microenvironment that can be specifically targeted, thereby disrupting immune evasion pathways and the epithelial-mesenchymal transition. Emerging preventive strategies seek to completely avoid

resistance. Proactive multi-pathway blockade techniques, adaptive low-dose cycling to lessen selection pressure, early interventions triggered by liquid biopsies, and the upfront application of combination therapies directed by molecular profiling are a few examples. Although chemoprevention using natural compounds is being studied in high-risk populations to reduce the likelihood of resistance developing, nanoparticle-mediated drug delivery and cancer stem cell suppression are also being explored to enhance sensitivity [95].

Ultimately, there are significant practical and ethical considerations that resistance management will need to address in the future. It remains challenging to provide everyone with equal access to cutting-edge omics technologies, AI-powered platforms, and innovative treatments, particularly in regions with limited resources. The sustainability of healthcare must be weighed against the cost-effectiveness of ongoing monitoring and intricate combination regimens, and the understanding that cancer adapts is a fundamental biological characteristic, which must temper expectations of curing resistance. However, new approaches, such as advanced immunotherapies and CRISPR-based interventions, also raise concerns about safety, including long-term risks and off-target effects. To address these problems, an interdisciplinary discussion that combines science, medicine, ethics, and policy is necessary. This will ensure that innovations are applied responsibly and fairly, minimising inequalities and optimising benefits for patients worldwide. Resistance persists as the Gordian knot of oncology, but biological-technological convergences transform it into a manageable dialectic. Future possibilities include real-time monitoring, multi-omics interpretation, combinatorial reasoning, immunotherapy, and evolution-based architectures, which promote cooperative ecosystems to document or eliminate cancer [96].

Discussion and Conclusion

One of the most significant obstacles in oncology is still drug resistance, which compromises the long-term effectiveness of almost all currently available therapeutic approaches. This review emphasises that resistance is a dynamic, adaptive continuum influenced by cellular plasticity, tumour heterogeneity, and the intricate coordination of the tumour microenvironment, rather than being a static event. The complexity of resistance, which encompasses metabolic reprogramming, epigenetic remodelling, genetic mutations, and immune evasion, necessitates a similarly complex response that integrates cutting-edge technologies with mechanistic knowledge. The inevitable emergence of resistance in advanced cancers underscores the critical need for transformative strategies that can anticipate, intercept, and ideally prevent its development, even in the face of significant advancements in targeted therapy, immunotherapy, and precision oncology. Moving from a reactive to a proactive paradigm will be crucial for effective resistance management in the future. By applying evolutionary principles and real-time monitoring through liquid biopsy and imaging, adaptive therapy offers a framework for containing resistant clones rather than completely eliminating them, potentially extending disease control without increasing selective pressure.

While safety and delivery issues need to be resolved before clinical adoption, gene-editing platforms like CRISPR and novel base-editing systems show promise in directly eradicating mutations that confer resistance or restoring tumour suppressor pathways. Through systematic CRISPR and computational screens, synthetic lethality strategies—already proven effective in BRCA-mutant cancers using PARP inhibitors—are being applied to broader contexts of resistance, providing opportunities to exploit unique vulnerabilities specific to resistant clones. Additionally, immunotherapy is beginning a new stage of improvement. Oncolytic virotherapy, neoantigen vaccines, multi-checkpoint blockade, and engineered cellular therapies are being investigated as integrative strategies to prevent immune evasion in addition to being tested as salvage options. Especially compelling is the combination of immunotherapy and multi-omics-guided stratification, which enables the logical creation of patient-specific regimens that can be adjusted in real time. These potentials are further enhanced by artificial intelligence, which combines radiomics, multi-omics, and clinical metadata to forecast resistance trajectories, optimise combination tactics, and even create new therapeutic agents. Methods that disrupt the tumour microenvironment's protective niches will be equally important.

Potential strategies to make resistant ecosystems more amenable to treatment include reprogramming hypoxia, targeting cancer-associated fibroblasts, and upsetting metabolic symbioses. Low-dose adaptive cycling, upfront multi-pathway blockade, nanotechnology-enabled delivery, and chemoprevention in high-risk cohorts are examples of preventive strategies that emphasise the move away from crisis management and toward resistance prophylaxis [97]. However, these developments also raise urgent practical and ethical concerns. It remains challenging to provide everyone with equal access to molecular diagnostics, AI-powered platforms, and next-generation treatments, particularly in resource-constrained environments. Furthermore, the possible advantages of complex combinatorial regimens and continuous monitoring must be carefully balanced against their cost-effectiveness and long-term safety. Realistic expectations must be balanced with the promise of curative results, acknowledging that resistance is a reflection of the inherent evolutionary nature of cancer. In conclusion, the combination of systems biology, advanced technologies, and translational innovation is making drug resistance in cancer, which was previously thought to be an insurmountable barrier, a manageable problem.

A new era of precision oncology is promised by the combination of adaptive therapy, gene editing, synthetic lethality, immunotherapy refinement, and multi-omics-guided AI, where resistance is a predictable and controllable phenomenon rather than an inevitable endpoint. In addition to scientific advances, future development will rely on global equity in implementation, collaborative infrastructures, and ethical foresight. Oncology may get closer to turning resistance from an insurmountable obstacle into a manageable aspect of long-term cancer treatment by adopting these ideas.

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Conflicts of Interest

The authors declare no conflicts of interest.

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