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Review

Modern Strategies in Cancer Therapy: From Chemotherapy to Precision Oncology

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Abstract

Cancer remains one of the leading causes of morbidity and mortality worldwide, necessitating continuous advances in therapeutic strategies to improve treatment efficacy and patient outcomes. Over recent decades, cancer management has evolved from conventional cytotoxic approaches toward more sophisticated, individualized interventions that target specific molecular alterations and harness the immune system. This review provides a comprehensive overview of the paradigm shift in cancer treatment, tracing the evolution from conventional chemotherapy to modern precision oncology and immunotherapy. We examine traditional diagnostic staging and highlight the integration of liquid biopsies and advanced biosensor technologies for real-time, non-invasive clinical monitoring. The review explores the mechanistic pillars of cell cycle-specific and non-specific chemotherapeutic agents, alongside the complex multidrug resistance pathways and metabolic rewiring that drive chemoresistance. We also evaluate the growing efficacy of targeted treatments, including small-molecule kinase inhibitors and antibody-drug conjugates, and detail the transformative clinical impact of immune checkpoint inhibitors, CAR-T cell therapies, and therapeutic vaccines. Emphasizing personalized medicine, we discuss the critical role of pharmacogenomics, biomarker-guided therapies, and the integration of artificial intelligence and quantitative systems pharmacology in optimizing dosing. Finally, we address future directions, including CRISPR-engineered cellular therapies and the modulation of the hypoxic tumor microenvironment using natural phytochemicals.

Keywords: cancer therapy; precision oncology; immunotherapy; chemoresistance; biosensors; tumor microenvironment; artificial intelligence; pharmacogenomics

1. Introduction

1.1. The Hallmarks of Cancer and Therapeutic Targets

Cancer is a heterogeneous genetic disease basically defined by uncontrolled cell division and proliferation follow-on from a serious physiological imbalance between mitotic events and cell loss by differentiation or programmed death. The regulation of this physiological process is performed

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through a coordinated system of cellular signaling pathways, where each unique sub-pathway is designed to control specific functions, known as the hallmarks: self-sufficiency in growth signals, resistance to growth inhibition, insensitivity to anti-growth signals, evasion of programmed cell death, unlimited replicative potential, sustained angiogenesis, and metastasis [1].

These features can be detected at the molecular level through the abnormal activity of signaling pathways. Some examples of these targets are the Ras-Raf-MAPK pathway, which has an important role in mediating the effects of growth factors on cell proliferation and stress response, and the PI3K-Akt-mTOR pathway, which regulates the cellular metabolic activities and autophagy via GPCRs or RTKs. These hallmarks are characterized by high frequency genetic alterations in some specific malignancies such as cholangiocarcinoma (CCA); AXIN1 (40%), TP53 (35%), ARID1A (25%), SMAD4 (25%) and KRAS (20%) [2].

Metabolic reprogramming, specifically the Warburg effect is described by (increased glycolytic metabolism resulting in elevated intracellular ATP within cell), is known as a near-universal hallmark that enables cell survival under cytotoxic conditions. Moreover, cancer cells activity the GSH-GST detoxification system and energy-dependent efflux pumps, for example P-glycoprotein (ABCB1) and MRP1 (ABCC1), to establish Multidrug Resistance (MDR) [3]. Current target identification also emphases on metabolic plasticity and mechanisms of immune evasion inside the Tumor Microenvironment (TME), requiring indicators like the TMEPRE computational method to score T-cell infiltration and response to protected checkpoints [4].

1.2. Evolution of Cancer Treatment

A structured system of study in oncology was first established by the passage of the National Cancer Act of 1971 (“War on Cancer”). During the 1970s and 1980s, treatment advances have been made possible by the use of microscopy and molecular cloning, resulting in the discovery of chromosomal changes, including the BCR-ABL translocation in chronic myeloid leukemia and ERBB2 (HER2) in breast cancer [5].

The conclusion of the Human Genome Project in 2003 served as a model shift, allowing the identification of tumor-specific somatic alterations [5]. This was followed by the start of Next-Generation Sequencing (NGS) in 2005, which allowed for the characterization of cancer genomes at single-nucleotide resolution [1]. The methodology of clinical trials has followed a similar path and has moved from anatomical based recruitment to genotype based recruitment. The IMPACT trial that began in 2007 demonstrated that using matching treatment protocols to molecular testing resulted in a significant increase in response rate (27 percent for matched versus 5 percent for mismatched participants) (Song et al., 2023). This led to basket type studies such as NCI-MATCH (2015), TAPUR (2016) and DRUP (2016) where patients are assigned to drugs based on specific genotypic characteristics, regardless of their tumor type [6].

The development of modern medicine is characterized by highly efficacious drug antibodies called ADCs, such as Sacituzumab govitecan, used in the delivery of SN-38 (about 1000 times stronger than irinotecan). Another example of an advanced treatment is the CAR T-cell therapy, where T-cells can be programmed to target the CD19 antigen [7]. The current cutting edge involves the merging of Artificial Intelligence (AI) and deep learning exemplified by the work of AlphaFold in protein structure prediction and PocketMiner in determining cryptic pockets of previously un-druggable targets to predict how tumor cells respond to drug interactions [1].

We conducted a literature search using PubMed, Scopus, and Google Scholar on 20 May 2026 to identify publications relevant to the evolution of cancer treatment from conventional chemotherapy to precision oncology. The search focused primarily on literature published over the preceding 10 years, while five older publications were retained when necessary to provide important historical background or foundational evidence. The search strategy covered conventional chemotherapy, targeted therapies, immunotherapy, drug resistance, the tumor microenvironment, liquid biopsies, biosensing technologies, artificial intelligence, machine learning, and pharmacogenomics.

The following search query was used:

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(Neoplasms OR Cancer) AND (Precision Oncology OR Targeted Therapy OR Immunotherapy OR CAR-T) AND (Drug Resistance OR Chemoresistance OR Tumor Microenvironment) AND (Biosensing Techniques OR Liquid Biopsy OR Machine Learning OR Artificial Intelligence OR Pharmacogenomics).

Publications were considered eligible when they addressed one or more of the principal themes of this review, including conventional and emerging cancer therapies, molecular mechanisms of treatment resistance, biomarker-guided treatment, cancer diagnostics and monitoring, pharmacogenomics, and computational approaches to personalized oncology. We considered relevant original research articles, clinical studies, and review articles. We retained older publications when they provided essential historical or conceptual information.

Publications were excluded when they were not sufficiently relevant to the review objectives or did not provide meaningful information on the therapeutic, diagnostic, molecular, or technological themes under consideration.

The selection process involved assessing the relevance of retrieved publications to the scope of the review and identifying studies that contributed to the discussion of the major themes. [Specify whether titles and abstracts and/or full-text articles were screened, whether selection was performed independently by multiple authors, and how disagreements were resolved, if applicable.]

We organized information from the selected publications by the major topics addressed in the review. These included cancer diagnosis and staging, conventional chemotherapy, mechanisms of chemoresistance, targeted therapies, cancer immunotherapy, personalized medicine, pharmacogenomics, biomarker-guided treatment, artificial intelligence, and emerging therapeutic strategies. We compiled a summary matrix in Appendix A (Table A1) presenting relevant study characteristics, including population or experimental model, sample size where available, study design, geographical setting, outcomes, principal findings, and references.

The findings were synthesized narratively to provide an integrated overview of developments in cancer treatment, highlight advances in precision oncology, and discuss current challenges and future directions. Given the review's broad scope and the diversity of the included evidence, the synthesis was descriptive and thematic rather than a quantitative meta-analysis.

2. Principles of Cancer Diagnosis and Staging

The diagnosis and staging of cancer have high importance in clinical oncology; they facilitate the prediction of patient prognosis and therapeutic selection. Historically, oncological staging has relied heavily on the anatomical extent of the disease, but the clinical paradigm is rapidly shifting toward a more comprehensive, molecularly driven approach [8,9]. In Cancer therapy, understanding the transition from traditional surgical approach to highly sensitive biosensing technologies is absolutely required because it directly impacts the development and application of precision medicines in this field [10,11]. Figure 1 demonstrates the general TNM staging system.

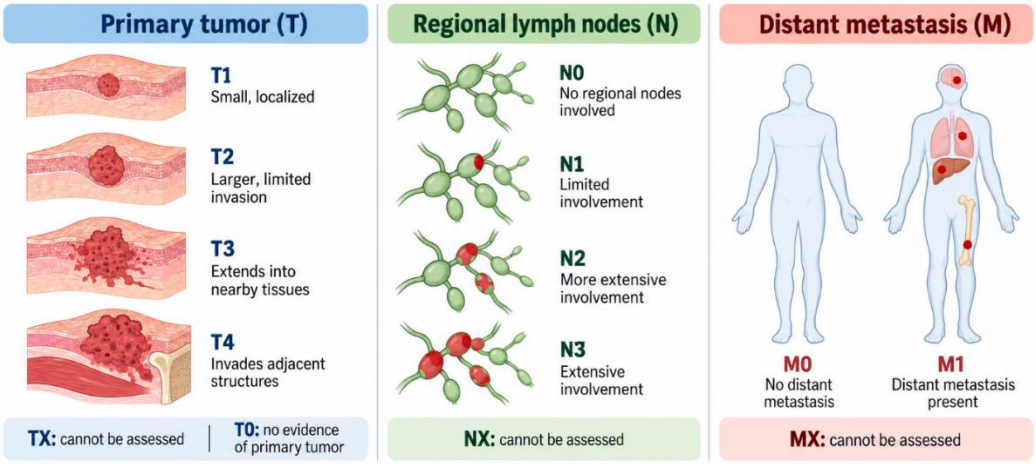

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Figure 1. TNM staging system.

2.1. Traditional Staging Methods

The beginning of traditional cancer staging is the Tumor, Node, Metastasis (TNM) classification system, was developed by organizations such as the International Union against Cancer (UICC) and the American Joint Committee on Cancer (AJCC). The TNM system evaluates the size of how much the primary tumor has invaded the nearby tissues (T), if the cancer spread into the lymph node (N), and the presence of the tumor cell in different parts of the body (M). for example, the 8th edition of the lung cancer TNM staging system refined the 'M' descriptor by introducing the M1b category to designate patients with a single extrathoracic metastasis (oligometastatic disease), distinguishing them from the M1c category characterized by multiple metastatic lesions. there are more grading systems, for example the Dukes and Jass classifications for colorectal carcinoma, they classified tumors based on bowel wall and its morphological features [8,9].

Even with constant improvements on the traditional staging methods there was still a noticeable limitation in clinical practice. for example, wherein patients classified within the exact same TNM stage can experience vastly different clinical outcomes, survival rates, and responses to chemotherapy. This variability highlights a pressing clinical need to incorporate non-anatomic factors—such as molecular markers, tumor grade, and vascular invasion—into staging algorithms to more accurately classify patient risk categories [9].

Moreover, standard tissue biopsies that are used to assess these stages are limited, as they only provide a snapshot of a very heterogeneous tumor at a given timepoint, and involve many hazards for the patient and are often hard to access [12].

2.2. Liquid Biopsies and Advanced Biosensors in Clinical Monitoring

Liquid biopsies have evolved as a novel alternative for clinical monitoring to address the constraints of conventional tissue biopsies. Liquid biopsies analyze the tumor-derived materials shed into biological fluids such as blood, saliva and urine, and capture the whole geographic and temporal heterogeneity of a patient's cancer [13]. This approach looks for several key circulating biomarkers, primarily circulating tumor DNA (ctDNA), circulating tumor cells (CTCs), extracellular vesicles (exosomes), and microRNAs (miRNAs) [14].

The clinical utility of ctDNA is particularly profound in the detection of minimal residual disease (MRD) and the ongoing assessment of adjuvant therapy efficacy [14,15]. The ctDNA monitoring enables the early detection of molecular relapse, giving a significant lead time of several months before clinical or radiological progression becomes seen on standard CT or other scans [15]. For example, dynamic ctDNA analysis in patients with esophageal adenocarcinoma is highly prognostic; patients whose ctDNA status converts from positive pre-surgery to negative post-surgery demonstrate highly disease-free survival, whereas continued ctDNA positivity strongly predicts the relapse [16]. in case of lymphomas, there are some advanced new techniques, such as Cancer Personalized Profiling by Deep Sequencing (CAPP-seq) and Phased Variant Enrichment and Detection Sequencing (PhasED-seq), allow for more sensitive ctDNA monitoring, achieving a very low analytical detection threshold [17]. Moreover, CTC molecular profiling provide real-time information to the metastatic cascade, cellular plasticity, and acquired resistance mechanisms, which are critical for deciding on therapy decisions [18].

To use these circulating biomarkers into actionable clinical tools requires using of advanced biosensor technologies [10]. Pharmaceutical and bioengineering research has some advancements in the development of highly sensitive systems capable of detecting very low concentrations of biomarkers in undiluted biofluids of the body [11].

Below are some examples of new technological innovations, which are also summarized in Figure 2:

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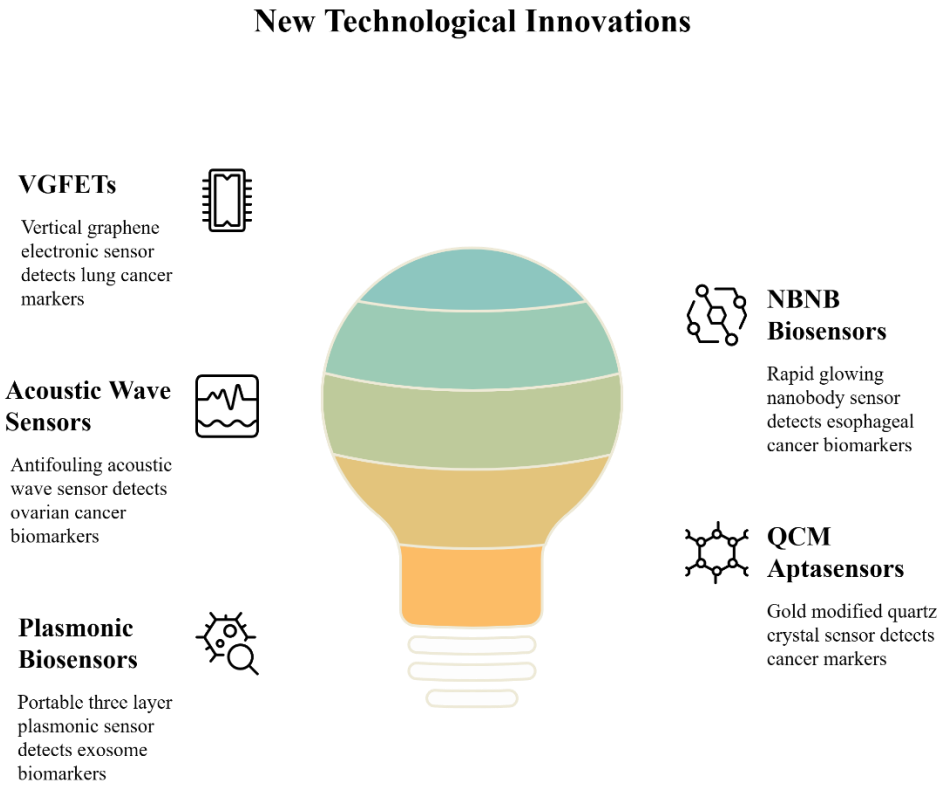

Figure 2. New technological innovations.

1. Vertical Graphene Field-Effect Transistors (VGFETs)

Combined with Mesoporous Silica Nanospheres (MSNs) to enhance the local electric field, these immunosensors achieve sub-femtomolar detection limits for lung cancer tumor markers, including Carcinoembryonic Antigen (CEA), Cyfra21-1, and Neuron-Specific Enolase (NSE) [11].

2. NanoBiT-Nanobody (NBNB) Biosensors

The NBNB biosensor is a novel platform that combines split nano-luciferase fragments for target-specific nanobodies. Based on the proximity-induced complementation idea, the fragments re-assemble an active enzyme upon binding to a biomarker and provide a measurable bioluminescent signal. The major advantage of this method is the ability to do quick, wash-free, sub-picomolar detection directly in complicated biofluids, such as serum. This technique is very useful in early cancer screening [19].

3. Acoustic Wave Sensors:

The development of a very sensitive acoustic biosensor for early detection of ovarian cancer by the identification of the biomarker Lysophosphatidic Acid (LPA). To overcome the problem of measuring such a small molecule in complicated fluids like human serum, the researchers employed a gelsolin-actin protein probe that loses mass upon binding with LPA, a change easily detected by the sensor's Thickness Shear Mode (TSM-D) technology [20].

4. Quartz Crystal Microbalance (QCM) Aptasensors:

Quartz Crystal Microbalance aptasensor used for selective detection of Carcinoembryonic Antigen (CEA), an important biomarker for cancer diagnosis. Scientists electrochemically attached a thiol-terminated nanofilm to a gold surface and then strengthened this attachment using gold nanoparticles that could bind two specific DNA aptamers to build the platform. The study reveals that this technology is capable of detecting CEA at very low detection limits of 102 and 108 pg/mL with higher binding affinity than previous methods. The authors successfully tested the sensor in

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spiked human serum, proving its practical utility as a cost-effective, quick, and accurate alternative to current clinical immunoassays [21].

5. Plasmonic Biosensors:

New three-layer plasmonic sensor for the portable and ultra-sensitive detection of exosomes, a critical biological marker for early cancer diagnosis. The researchers sandwiched a silica spacer between a gold mirror and a gold nanohole array to form an optical cavity that causes mode hybridization, which greatly narrows the resonance signal and enhances the electromagnetic field. This structural modification allows the gadget to reach an impressive low limit of detection of 600 particles per microliter without the need for complicated signal amplification tags. Also, the sensor can differentiate between healthy and tumor produced exosomes using specialized aptamers and it works reliably in difficult conditions such as fake serum. Finally, the paper proposes a low-cost production method – nanosphere self-assembly – to translate complex surface plasmon resonance technology from the laboratory to the clinic [22].

3. Conventional Chemotherapy

3.1. Cell Cycle–Specific Agents

Cell cycle–specific therapeutic agents are formulated to selectively target cancer cells during definite phases of active cellular division. Among these, antimetabolites, such as cytarabine (Ara-C) and gemcitabine, target cells at the S-phase of cell cycle by incorporating into DNA or inhibiting replication enzymes. In vitro studies of acute megakaryoblastic leukemia have demonstrated that Ara-C exerts its antileukemic effect by inducing S-phase damage. Nevertheless, resistant cells manage to escape this type of treatment by pausing their growth in the G1 phase, thereby bypassing the S-phase where most of the DNA fragmentation normally occurs, this helps them survive despite the drug's effect [23]. The therapeutic efficacy of S-phase targeting can be improved; for instance, the addition of the ATR kinase inhibitor berzosertib to gemcitabine was found to significantly prolong progression-free survival in platinum-resistant high-grade ovarian cancer mainly by preventing DNA damage repair during replication [24]

Taxanes (e.g., paclitaxel and docetaxel) belong to a chemical class of microtubule stabilizers which bind to the -tubulin subunit, inhibiting microtubule depolymerization and leading to an irreversible G2/M phase mitotic arrest [25,26]. Advanced formulations, such as albumin-bound paclitaxel, have been shown to enhance drug penetration in glioblastoma (GBM) models and to uniquely interfere with the nuclear transport of nucleotide excision repair (NER) proteins like ERCC1 and XPC. Taxanes are the backbone of clinical breast cancer therapy, and combination regimens of taxanes with carboplatin have been associated with high pathological complete response (pCR) rates in patients with stage II-III triple-negative breast cancer (TNBC) [27]. However, comprehensive genomic analysis of pre-treatment and post-treatment biopsies indicates that tumor cells may fully evade phase-specific chemotherapeutic pressure by suppressing proliferative activity, including downregulation of markers such as Ki67. By doing so, they can transition into a reversible dormant or senescence-like state enabling them to withstand genotoxic stress and persist despite treatment [28].

3.2. Cell Cycle–Nonspecific Agents

These agents inflict massive macromolecular damage independent of the cell cycle phase. Alkylating agents, such as cyclophosphamide and temozolomide (TMZ), create highly reactive intermediates that covalently bind to DNA bases. Though alkylating chemotherapy using high doses has been tested in BRCA-altered TNBC for increased induction of double-stranded DNA breaks, it has not been applied clinically due to sever side effects. [29]. In addition, TMZ efficacy can be boosted further by combination therapy with HDAC inhibitors like PCI-24781. The mechanism of action for the increased efficacy is mostly through the inhibition of the DNA repair processes that are based on

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homologous recombination pathways. [30]. Another alkylating agent, dacarbazine, also demonstrates immunomodulatory activity. Besides having cytotoxic activity, it has also been found to overcome resistance to checkpoint inhibitors by inducing the expression of MHC class I and NKG2D ligands in melanoma cells [31]

The cytotoxic activity of platinum complexes, like cisplatin, carboplatin, oxaliplatin, and lobaplatin, occurs through the induction of crosslinking of DNA at purine nucleotide bases. Cisplatin (CDDP) activity is highly influenced by the interaction pathway of the HDAC/RXR/HtrA1 signaling axis [32]. The process of oxaliplatin internalization is regulated by the OCTN1 protein of the organic cation transporter family. In addition, oxaliplatin has a significant relationship between its metabolic impact and the metabolism of polyamines [33]. The incorporation of carboplatin into sequential treatment, which consists of taxane-anthracycline chemotherapy, significantly enhances the EFS in TNBC [34]. Lobaplatin combined with taxanes represents an effective and anthracycline-free regimen that shows very high percentages of complete response [35]. Conversely, newly discovered platinum(IV) derivatives such as cisPt(PhB)2 affect lipids metabolism and exploit the mechanism known as the Warburg effect; therefore, they are able to overcome the intrinsic resistance of cancer cells to cisplatin [36]. In advanced disease settings, cisplatin-gemcitabine doublet regimens are commonly employed as a strategy for maintenance chemotherapy. Aiming to sustain disease control following initial therapeutic response [37].

Anthracyclines such as doxorubicin and daunorubicin exert cytotoxicity by inhibiting topoisomerase II, leading to DNA double-strand breaks. The expression levels of APE1 and NPM1 have independently emerged as prognostic indicators of cellular tolerance to both anthracycline- and platinum-induced DNA damage [38]. It is worth noting that the anthracycline aclarubicin kills cancer cells just by damaging the chromatin and histones, but not via DNA double-stranded breaks, demonstrating meaningful efficacy in relapsed AML without the cardiotoxic profile characteristic of conventional doxorubicin therapy [39]. In addition, structurally altered oxazolinoanthracyclines, namely O-DOX and O-DAU, can trigger apoptosis and autophagy through activation of neutral sphingomyelinase and mitochondrial membrane permeabilization [39].

To provide a comprehensive overview of how these classical pillars of chemotherapy disrupt neoplastic replication, the distinct intersection of phase-specific and phase-nonspecific agents across the cellular lifecycle is presented diagrammatically in Figure 3.

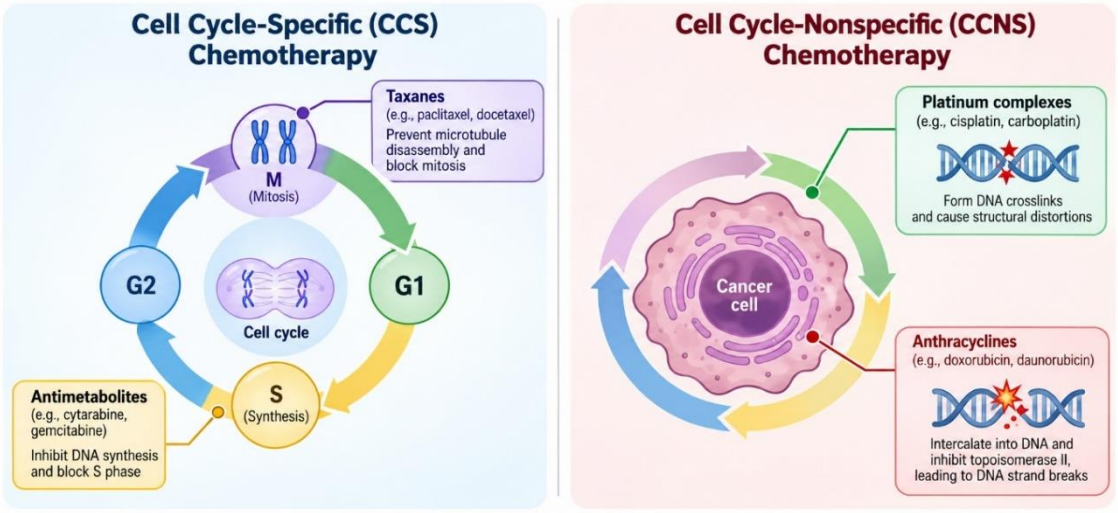

Figure 3. Comparative Schematics of Phase-Specific and Phase-Nonspecific Chemotherapeutic Dynamics. The left panel highlights cell cycle-specific agents targeting active division windows: antimetabolites (e.g., cytarabine, gemcitabine) interrupting DNA replication during the S-phase, and taxanes (e.g., paclitaxel, docetaxel) stabilizing microtubules to trigger mitotic arrest in the M-phase. The right panel depicts phase-nonspecific macromolecular damage executed indiscriminately throughout the cellular lifespan by DNA-

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crosslinking platinum complexes (e.g., cisplatin, oxaliplatin) and topoisomerase II-poisoning anthracyclines (e.g., doxorubicin).

3.3. Adverse Effects of Chemotherapy

Chemotherapy toxicity is strongly associated with the classes of agents causing the toxicity. The worst dose-limiting effect caused by conventional anthracyclines is cardiotoxicity. This is because anthracycline-induced cardiotoxicity results from the secondary alcohols formed by the reduction reaction mediated by AKR1C3 and CBR1 in the metabolism of anthracyclines; studies in silico and in vitro show that inhibition of both enzymes by ASP9521 is potent in protecting cardiomyocytes from the damage [40].

Non-hematological toxicities in observational studies have been well-classified, where anthracyclines mostly cause asthenia, vomiting, and mucositis, while taxanes commonly produce peripheral sensory neuropathies, hypersensitivity reactions, and arthromyalgias [41]. Myelosuppression, including leukopenia, neutropenia, and anemia, is common The use of regimens with high levels of alkylators (cyclophosphamide) increases the incidence of grades 3-4 infection events and febrile neutropenia, according to clinical studies [29]. In studies conducted in clinics, it was found that regimes of CbD (carboplatin with docetaxel, but no anthracyclines) chemotherapy had lower grades of 3-4 neutropenia than CbP->AC chemotherapy regimes [42]. Similarly, replacing anthracyclines with lobaplatin results in changes in the toxicity profile, characterized by lower grades of 3-4 neutropenia, as well as higher anemia [35]. Regarding the use of maintenance therapy, it is evident that doublet platinum therapy causes increased rates of hematological toxicity in contrast to monotherapy [37]. The addition of atezolizumab to cytotoxic backbones introduces immune-mediated toxicities such as rash and hypothyroidism, without appearing to compound the underlying chemotherapy toxicity profile [43].

3.4. Mechanisms of Chemoresistance

ABC Transporters: Beyond efflux, resistance is further sustained through enhanced DNA repair and apoptosis evasion overexpression of ATP-binding cassette (ABC) transporter proteins, especially the P-glycoprotein (P-gp/ABCB1) type, helps transport anthracyclines and taxane drugs actively from the cells through the efflux pathway [44–47]. From whole exome sequencing, it is apparent that the progression of docetaxel resistance follows a stepwise process, which is through the amplification of ABCB1 [45]. FOXM1, acting as a transcription factor, is responsible for the upregulation of these transporters, leading to the enrichment of the cancer stem cells population [26]. The expression of P-glycoprotein can be inhibited transcriptionally through C/EBP-beta LIP. This is accomplished pharmacologically by co-administration of chloroquine and bortezomib which inhibits the breakdown of C/EBP-beta LIP and boosts nitric oxide production, thereby suppressing the activity of P-gly [46]. Nanotechnology bypasses efflux completely because solid lipid nanoparticles loaded with stearoyl gemcitabine use clathrin-mediated endocytosis for drug delivery via lysosomes in addition, silica-based nanoparticles carrying both PTX and let-7a molecules inhibit MDR pathways via silencing of mTOR/STAT3/EZH2 genes [48]. Additionally, Cytochrome P450 enzymes within the tumor mass (CYP3A4/ CYP2C8) efficiently metabolize the taxanes within the tumor mass itself, but this process may be inhibited by antiretroviral protease inhibitors such as ritonavir [47].

Cisplatin resistance is also driven by adaptive enhancements in DNA repair capacity, most notably through the expansion of mutational signatures linked to nucleotide excision repair (NER) pathway upregulation [49]. The MKP-1 phosphatase blocks the breakdown of PARP-1 through JNK1/2 dephosphorylation but remains capable of repairing DNA; therefore, cisplatin-resistant [50]. It has been reported that SIRT7 interacts epigenetically with EZH2 to regulate RND3 resistance to platinum [51]. The phenomenon of resistance occurs due to apoptosis evasion as well, where the oncoprotein LEDGF/p75 causes taxane resistance by surviving without caspase-3 activation [52]. TRIB2 up-regulation and CEBPA down-regulation confer cancer stem-like properties, making them

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resistant to cisplatin-induced cell death [53]. On the other hand, tumorigenesis and platinum resistance are determined by the expression level of MYPT1 within the Hippo signaling pathway [54].

Cancer Cells with Drug Resistance Reprogram metabolism and ER Stress: Ovarian cancer cells resistant to platinum decrease the levels of GSH and depend on TXNRD1 as a survival mechanism under oxidative stress conditions. [55]. TMZ resistance in GBM cells is caused by SH3GLB1-dependent autophagy, leading to mitochondrial OXPHOS rewiring. The inhibition of the gene ATG4C involved in the autophagy process leads to resistance breakdown in gliomas [56]. Multidrug-resistant gastric cancer cells are characterized by high ER stress levels; the antibiotic tunicamycin selectively targets this condition by inhibiting N-glycosylation, increasing the ER stress to lethal levels to cause apoptosis [57]. Rather than relying on a solitary pathway, persistent tumor clones dynamically orchestrate a multi-tiered molecular network to survive genotoxic insults, mapping across efflux, repair, and energetic adaptations (Figure 4).

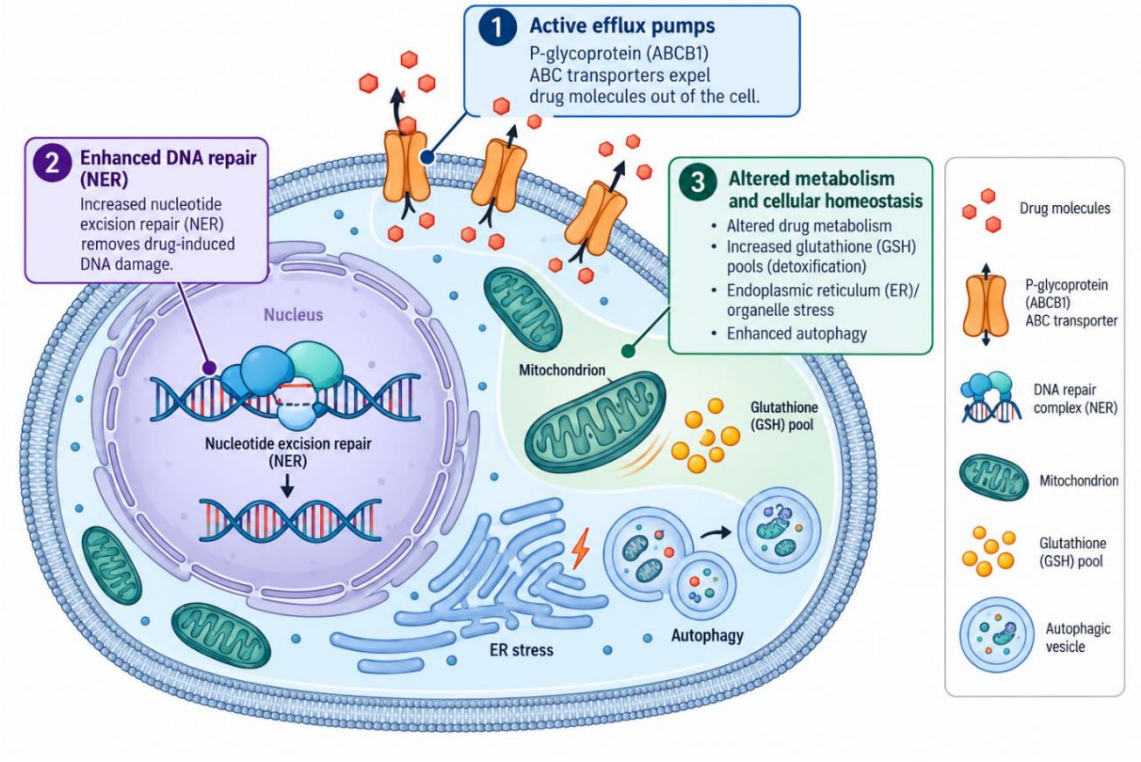

Figure 4. The Intracellular Landscape of Tumor-Mediated Chemoresistance Pathways. Visual summary of the localized molecular adaptations driving therapeutic evasion across three distinct cellular zones: Zone 1 highlights active drug extrusion via upregulated ABC transporter superfamilies (P-gp/ABCB1); Zone 2 depicts enhanced nuclear DNA repair machinery, notably Nucleotide Excision Repair (NER) adaptations against platinum complexes; Zone 3 displays cytoplasmic metabolic rewiring characterized by altered glutathione (GSH) pools, mitochondrial alterations under duress, and activated ER/organelle stress autophagic fluxes.

Predictive Biomarkers and Advanced Models: Genomic and transcriptomic profiling has identified several pre-treatment biomarkers of resistance. Elevated PRSS1 expression, for instance, reliably predicts poor outcomes and platinum resistance [58]. NCOR2 and PDXK are predictive genes for detection of resistance to platinum/taxanes combination therapy [59]. Chromosomal Instability (CIN) Signatures have been discovered using Retrospective Whole Genome Sequencing that successfully predicted resistance among taxane, anthracycline, and platinum families by identifying cancers that exploit the use of cGAS-STING pathway to cope with chemotherapeutic drugs that generate micronuclei [60]. Organoids grown in 3D culture systems prove to be far more advanced than the 2D models in researching evolutionary pathways, since organoids are able to mimic actual

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real-life architecture and acquire mutations to EGFR, HER2, and KRAS from paclitaxel and etoposide treatment [61].

4. Targeted Therapies

4.1. Small-Molecule Kinase Inhibitors

Inhibitors are small molecules that can cross the cell membrane to disrupt the signal transduction pathway. PLK1 Inhibitors (for example, BI2536 and BI6727) lead to G2/M arrest, hence causing disruption in cell division. Dehydrodiisoeugenol (DHIE), which is a natural substance, acts as a PLK1 inhibitor and disrupts the PLK1-p53 pathway in such a way that the mutant form of p53 is down-regulated in TNBC cells and up-regulated in the case of Luminal breast cancer [25]. On the other hand, pterostilbene inhibits both Tdp1 (Tyrosyl-DNA phosphodiesterase 1) and topoisomerase I; thus, overcoming CPT resistance [62].

Kinase inhibitors become resistant due to the phenomenon of bypass signaling. Cells which are resistant to EGFR/HER2 kinase inhibitors, for example, lapatinib, are known to acquire resistance through EMT and escape apoptosis. Subsequently, FGFR1 and NRP1 get activated due to EMT. Bypass signaling gets epigenetically blocked by inhibition of BRD4/BET, resulting in decreased NRP1 and increased cellular sensitivity [63]. On another front, hepatocellular carcinoma is known to develop resistance against multi-kinase inhibitors such as sorafenib by increasing GRP78 expression, ensuring VEGFR/FGFR signaling persists. Polyphyllin I works against GRP78 binding and thus blocks bypass signaling [64].

In relation to synthetic lethality, the inhibitors are used as a way of targeting certain gene mutations. An example of this can be seen from PARG inhibitors, which include compounds like PDD00017273, where cell death occurs through NAD+ depletion and replicative stress; however, this is only achieved in cancers with mutations in DNA polymerase beta (Pol-β), thus overcoming the inherent problem with PARP inhibitors [65]. Furthermore, bortezomib in conjunction with the ALDH inhibitor disulfiram and copper causes cell death in leukemia types that are mutated in PSMB5 (Q62P); this allows cells to bypass the resistance to Ara-C and bortezomib [23].

4.2. Monoclonal Antibodies

Monoclonal antibodies act by engaging extra-cellular receptors to prevent ligand binding or to cause immune-mediated cytotoxicity. Trastuzumab and pertuzumab represent the two major drugs for treating HER2-overexpressing cancer cells. However, spatial single-cell multi-omics demonstrates marked spatial heterogeneity of HER2 expression within tumors and its ability to affect CD80/CD86 and PD1-PDL1 interaction, thus explaining resistance to HER2-targeted antibodies in some patients Immunophenotyping studies conducted on several patient groups have confirmed that understanding the interaction between these cells and their environment is crucial for predicting treatment outcomes for HER2-targeted treatments [66].

Immune checkpoint inhibitors, such as the monoclonal PD-L1 inhibitor, atezolizumab, interfere with immunosuppressive receptors by blocking their signals. As an example, the administration of atezolizumab along with nab-paclitaxel and anthracyclines is associated with high pCR in patients with triple-negative breast cancer. [43]. In conditions of primary checkpoint inhibitor resistance, intermittent dacarbazine exposure has been shown to overcome this barrier by driving CD8+ T-cell infiltration and NK cell activation, achieved through upregulation of MHC class I and NKG2D ligands on the tumor surface. [31].

4.3. Antibody–Drug Conjugates

ADCs serve as pharmacological Trojan horses, which consist of three major components: highly specific monoclonal antibody, chemical linker, cleavable or non-cleavable, and cytotoxic payload [67]. A case in point is HER3-DXd, which entails attachment of a HER3-directed antibody to a

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topoisomerase I inhibitor drug through a cleavable linker. One key limitation in the effectiveness of an ADC involves the low basal level of receptors. However, treatment of NSCLC cells with EGFR-kinase inhibitors, such as osimertinib, leads to induction of HER3 receptor levels at the plasma membrane of the target tumor. [67]. The increased availability of receptors greatly increases the ability of the ADC HER3-DXd to internalize into the cells and localize within the lysosomes. Subsequently, through cleavage of the linker, the drug gains the ability to penetrate through the cell membrane and diffuse inside the target cells. Lastly, the cytotoxicity elicited by the agent results in killing of tumor cells in the targeted tumor mass and even neighboring tumors that lack the receptor [67]. Once cleaved inside the lysosome, the membrane-permeable DXd payload destroys the targeted cell and subsequently diffuses to eradicate adjacent, receptor-negative tumor cells, an essential 'bystander effect' that effectively overcomes local tumor heterogeneity (Figure 5).

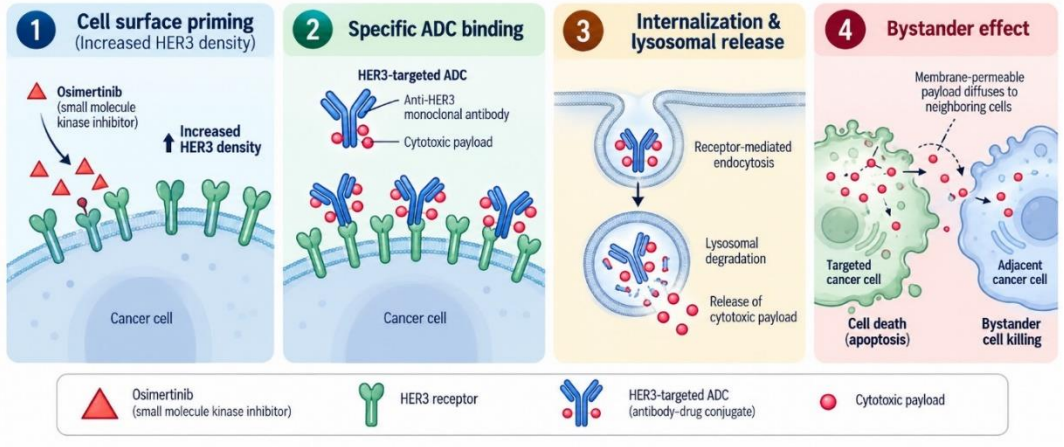

Figure 5. Mechanism of Receptor-Mediated Internalization and the Cytotoxic Bystander Effect of Antibody-Drug Conjugates (ADCs). The sequential pharmacological cascade highlights Step 1: Upfront small-molecule kinase inhibition (osimertinib) to induce cell-surface HER3 receptor density; Step 2: High-affinity binding of the tripartite antibody-drug conjugate (blue mAb to red payload); Step 3: Receptor-mediated endocytic internalization, lysosomal trafficking, and subsequent enzymatic cleavage via proteases to liberate the free cytotoxic payload; Step 4: Outward free-diffusion of the membrane-permeable payload into the microenvironment, successfully executing bystander killing of neighboring antigen-negative tumor niches [67].

4.4. The Role of TME in Immune Evasion

TME is a hard-to-pass barrier to the success of modern immunotherapies because it fosters conditions of immune exclusion, exhaustion, and suppression. A primary driver of this immunosuppression is the heavy infiltration of specific myeloid populations, most notably Tumor-Associated Macrophages (TAMs) and Myeloid-Derived Suppressor Cells (MDSCs) [68]. Quite recently, single-cell RNA sequencing and spatial transcriptomic analyses demonstrated a high heterogeneity of TAMs across primary Colorectal Cancer (CRC) and its metastatic features, revealing two distinctly polarized subtypes: SEPP1+ TAMs and SPP1+ TAMs. While SEPP1+ TAMs are heavily surrounded adjacent normal tissues and perform standard immune-related functions, SPP1+ TAMs on the other hand are heavily enriched in the primary tumor and liver metastases, where they are closely linked to several complications such as tumor angiogenesis, immune evasion, and eventually, a poorer prognosis for the patient [69].

It was also shown that the TME exerts selective metabolic pressures that further differentiate SPP1+ TAMs into distinct, tissue-specific functional subsets. Single-cell transcriptomic profiling indicates that an ATP5F1E+ SPP1+ TAM subpopulation, which highly relies on glycolysis, is mainly enriched in primary lesions and lymph node metastases. On the other hand, an MT-CO1+ SPP1+ TAM subset, which relies on oxidative phosphorylation, dominates the microenvironment of colorectal liver metastases. Spatial transcriptomic maps validate this adaptive divergence, showing

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that glycolytic ATP5F1E+ TAMs reside in the hypoxic cores of tumors, whereas MT-CO1+ TAMs localize to the oxygen-rich invasive margins. Functionally, these SPP1+ TAMs directly drive the exhaustion and spatial exclusion of critical CD8+ cytotoxic T-cells. Modulating the TME to overcome these barriers is a major therapeutic goal. Using regorafenib (a multi-kinase inhibitor) with an anti-PD-1 reduced the infiltration of SPP1+ TAMs significantly, reversing local immunosuppression and putting a stop to tumor growth and metastasis indefinitely in preclinical models [69].

4.5. Immune Checkpoint Inhibitors

Immune Checkpoint Inhibitors (ICIs), mainly targeting the PD-1 and CTLA-4 pathways, have updated the therapeutic view by releasing the brakes on adaptive anti-tumor immunity. While anti-PD-1 monotherapy is a standard first-line therapy, combined checkpoint blockade using both nivolumab (an anti-PD-1) and ipilimumab (an anti-CTLA-4) shows a remarkable clinical efficacy, particularly across diverse and notoriously rare malignancies. As it is shown in the MoST-CIRCUIT phase 2 basket trial, patients with advanced mismatch repair (MMR) deficiencies or microsatellite instability-high (MSI-H) non-CRC achieved an impressive objective response rate (ORR) of 63% and a 6-month progression-free survival (PFS) of 71% [70]. This dual blockade has demonstrated its usefulness even in ultrarare diseases evaluated in the large-scale DART/SWOG S1609 basket trials. Nivolumab plus ipilimumab in heavily pre-treated desmoid tumors achieved an ORR of 18.8% with a durable clinical benefit rate of 62.5% [71]. Rare gynecologic CRC and high-grade Pancreatic Neuroendocrine Neoplasms (PNEN) showed relevant activity with tolerable toxicity [72,73].

Leaving the metastatic setting aside, ICIs are also reshaping neoadjuvant standards. The MATISSE trial investigated neoadjuvant nivolumab alone or combined with ipilimumab in patients with resectable stage I-IVa Cutaneous Squamous Cell Carcinoma (CSCC). The combination regimen achieved major pathological response rates up to 83% of patients. Crucially, this robust downstaging allowed a subset of patients to skip standard, often highly disfiguring, surgical resections entirely. Organ preservation was durable with no surgical delays in patients with complete response and statistically significant improvement in health-related quality of life and decreased surgery was achieved [74]. FRACTION-RCC (an adaptive platform trial) showed the advantages of dual ICIs as a salvage strategy, achieving disease control rates of 58.7% in advanced renal cell carcinoma patients who had already progressed on prior immunotherapies [75].

4.6. CAR-T Cell Therapy

Chimeric Antigen Receptor (CAR) T-cell therapy succeeded exceptionally in hematologic malignancies. However, its application in solid tumors has been hindered severely by the lack of unique target antigens, poor persistence, the immunosuppressive TME, and dangerous on-target/off-tumor toxicities [68,76]. Early generation clinical trials highlighted these limitations. As an example, testing first-generation CAR-T cells targeting the CEACAM5 antigen in metastatic gastrointestinal malignancies resulted in poor systemic CAR-T persistence and caused acute, preconditioning-dependent respiratory toxicity due to low-level CEACAM5 expression on normal lung epithelium. Similarly, CAR-T cells targeting TAG-72 in CRC proved to be actually safe but showed very limited clinical efficacy and persistence [77,78].

However, next generation CAR engineering and non-traditional immune cell investigation are overcoming solid tumor barriers. Phase I trial of GCC19CART (a novel CAR-T targeting guanylate cyclase-C) showed an encouraging 40% ORR in heavily pre-treated metastatic CRC patients with well-tolerated, target-specific toxicities [79]. In order to address the immunosuppressive TME, researchers have engineered Prostate-Specific Membrane Antigen (PSMA) directed CAR-T cells to co-express a dominant-negative TGF-β receptor (TGFβRDN). This modification protects the CAR-T cells from TGF-β mediated suppression, leading to massive in vivo clonal expansion and improved functional persistence in patients with metastatic castration-resistant prostate cancer [80].

At the same time, the field is advancing toward universal “off-the-shelf” allogeneic therapies to resolve the high costs and logistical failures of autologous CAR-T production. Utilizing

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hematopoietic stem and progenitor cells from umbilical cord blood, researchers have successfully manufactured highly pure, allogeneic CAR-engineered invariant natural killer T (CAR-NKT) cells. When engineered to target mesothelin and express IL-15 (Allo15MCAR-NKT), these cells demonstrated superior tumor-homing capacities and robust, sustained tumor suppression in murine triple-negative breast cancer xenograft models. Importantly, because NKT cells do not express highly polymorphic endogenous T-cell receptors, this allogeneic platform exerted potent antitumor cytotoxicity without inducing Graft-versus-Host Disease (GvHD), presenting a scalable, safe, and highly effective therapeutic avenue for solid tumors [68].

4.7. Therapeutic Vaccines

Cancer vaccines are designed usually to actively prime the patient's immune system to recognize and eradicate tumor-associated antigens. They stimulate durable cellular and humoral immunity, resulting in a highly synergistic complement to ICIs. Dendritic Cell (DC) vaccines, which utilize the most potent professional antigen-presenting cells, are the head of this strategy. In an expansion cohort of phase II including patients with resected pancreatic ductal adenocarcinoma, adjuvant DC-based immunotherapy led to potent vaccine-specific T-cell responses. This particular immune activation was correlated with a very promising 2-year recurrence-free survival rate of 64% and an overall survival rate of 83%, demonstrating their ability to delay or prevent disease relapse even in a notoriously aggressive cancer [81].

Rationally designed combination therapies can greatly enhance the efficacy of vaccines. Combining DC vaccines targeting tumor blood vessel antigens with immediate co-administration of dasatinib (a tyrosine kinase inhibitor) was found to be really useful in patients with checkpoint-refractory advanced melanoma. Immediate administration of dasatinib resulted in vastly superior systemic immune response rates (66.7% vs. 28.6%) and striking objective clinical responses (66.7% vs. 0%) in comparison to a delayed administration approach. This combination altered the T-cell inventory, hurling epitope spreading and reversing established therapeutic resistance [82].

Apart from cell-based platforms, highly innovative bio-friendly nanoparticle vaccines are showing preclinical and clinical success. A lambda phage-based vaccine targeting the oncofetal protein aspartate β-hydroxylase (ASPH) showed a huge antigen-specific CD8+ and CD4+ T-cell responses. The mentioned vaccine in combination with a PD-1 checkpoint inhibitor was able to suppress primary tumor growth and eliminate distant pulmonary metastases in models of hepatocellular carcinoma and triple-negative breast cancer by inducing the formation of Tertiary Lymphoid Structures (TLSs) [83]. A Viral-Based Immunotherapy Regimen (VBIR) using an adenoviral vector (AdC68) combined with plasmid DNA was also tested and evaluated in a first-in-human phase I trial for prostate cancer. The above regimen with ICIs was well-tolerated, and consistently broke immune tolerance to induce targeted T-cell immunity, with 50% PSA declines and durable tumor control in biochemically recurrent patients [84].

5. Personalized Medicine in Oncology

5.1. Pharmacogenomics

Pharmacogenomics integrates the study of genetic mutations and exome evolution to predict the individual patient's response to specific oncological therapies accurately. For precision immunotherapy, the detection of MMR deficiency, MSI-H, and overall tumor mutational burden (TMB) are very reliable pharmacogenomic predictors of clinical benefit. MMR deficiency, resulting from structural mutations in proteins such as MLH1, PMS2, MSH2, or MSH6, causes profound genomic instability. This generates significant amounts of neoantigens, which in turn lead to heavy infiltration of cytotoxic T-cells in the tumor and make these tumors highly susceptible to immune checkpoint inhibitors. In particular, the MoST-CIRCUIT clinical trial employed these genomic markers to direct therapy, showing that MMR deficient/MSI-H advanced non-colorectal cancers have

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very high objective response rates (63%) to combination nivolumab and ipilimumab, regardless of their specific underlying anatomical tumor origin [70].

Pharmacogenomic analysis is also critical in predicting intrinsic or acquired resistance to immunotherapy. Stepwise exome evolution analysis suggests that non-responders to PD-1 blockades often harbor distinct somatic structural mutations in particular molecular pathways. Genetic aberrations in interferon-gamma signaling (*JAK2*, *IFNGR1*), antigen presentation (*B2M*) and other important oncogenic drivers (*CTNNB1*, *PTEN*) promote immune evasion actively and directly influence resistance to T-cell-mediated cytotoxicity [70].

In addition to structural mutations, full pharmacogenomic profiling should evaluate the dynamic modulation of gene expression by exogenous factors, including dietary and herbal supplements. For example, traditional medicinal plants can strongly alter the mRNA expression of key pharmacokinetic targets, e.g., the cytochrome P450 enzyme CYP1A1 and the efflux transporter P-gp. In vitro studies have demonstrated that extracts from plants such as *Paronychia argentea* and *Ruta graveolens* induce CYP1A1 expression in breast and colon cancer cell lines, whereas extracts from other plants, e.g., *Teucrium polium*, have inhibitory effects on P-gp. Since CYP enzymes are responsible for the metabolism of xenobiotics and P-gp actively protects cells by expelling toxic molecules, these transcriptomic changes represent a major risk for pharmacokinetic herb-drug interactions. Therefore, such gene expression variables need to be incorporated for precision dosing regimens to avoid unexpected toxicity or therapeutic failure in oncology patients using complementary medicine [85].

Moreover, pharmacogenomic principles are broadly applicable to the pharmacokinetic behavior of engineered living drugs such as CAR-T cells. Researchers can precisely map where viral vectors have integrated into the patient's genome through comprehensive integration site profiling by sequencing. In trials of PSMA-directed CAR-T therapies for prostate cancer, massive and sudden in vivo clonal expansion of the therapeutic T-cells was directly associated with specific lentiviral integration events into the *NELL2* and *GLCCI1* gene loci. Additionally, these genomic integration sites can be followed in conjunction with vector copy numbers for accurate monitoring of the safety, clonality and persistence of the cell product in the peripheral blood, alleviating the concerns of insertional mutagenesis and unregulated proliferation [68,80].

5.2. Biomarker-Guided Therapy

The success of personalized oncology is strongly reliant on the identification and validation of predictive biomarkers to select those patients most likely to benefit from a particular therapy. In the TME, the spatial distribution and density of specific immune cells are highly prognostic markers. Clinical testing proved that the presence of TLSs combined with a high count of infiltrating CD8+ cytotoxic T-cells are important factors that can be used to predict accurate and clean objective clinical responses and prolonged progression-free survival in patients receiving therapeutic vaccines and ICIs [83,86]. Also, overly enriched immunosuppressive signatures, like high density of SPP1+ TAMs, can act as a negative predictive biomarker indicating exhausted CD8+ T-cell state, high chance of liver metastasis in CRC and the need for specific precision medicine [69].

Usually, Targeted adoptive cell therapies rely mainly on the molecular validation of target antigen expression to achieve their targeting ability. Pre-treatment biopsy screening in phase I trials of IMA203 (a T-cell receptor (TCR) therapy targeting the melanoma-associated antigen PRAME) confirmed that patients had the necessary HLA-A*02:01 haplotype and shown satisfactory baseline PRAME mRNA expression. Retrospective analysis revealed that the higher baseline PRAME expression the higher its connection to greater tumor regression and improved progression-free survival. Baseline antigen expression aside, CAR-T or TCR T-cell engraftment degree in peripheral blood and infiltration density into the solid tumor (measured as vector copies/μg of genomic DNA) is an important, potent and dynamic biomarker that impacts the magnitude of clinical response directly [86].

Liquid biopsies and profiling of peripheral blood also allow for minimally invasive, real-time monitoring of biomarkers. For example, the analysis of TCR convergence in the blood, which is the

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phenomenon when different nucleotide sequences encode for the same functional TCR amino acid sequence, accurately identifies patients with a focused, antigen-specific adaptive immune response. In trials that combined both dendritic cell vaccines with precision medicine, measurable peripheral TCR convergence was directly proportional with patients achieving high objective clinical response rates, confirming its value as an early systemic biomarker of therapeutic efficacy [82].

5.3. Bioinformatics and Machine Learning in Treatment Design

The rapid evolution of precision oncology is heavily supported by the integration of bioinformatics and machine learning (ML) models, which automate the interpretation of massive, multidimensional biological datasets. It is an important aspect to ensure the quality and functional potency of manufactured CAR T-cells in cellular immunotherapy, before patient administration. The main determinant of CAR-T efficacy is the quality of the Immunological Synapse (IS) (which can be defined as the highly organized structural interface formed between the CAR-T cell and the tumor cell). Evaluating the traditional IS parameters like F-actin accumulation and the polarization of lytic granules has been a low-throughput, labor-intensive, and subjective manual process [87,88].

To overcome such limitations, advanced Artificial Neural Networks (ANN) were developed to automate the quantification of CAR-T IS quality from in vitro planar lipid bilayer imaging. Exploiting state-of-the-art multi-scale cell instance segmentation, these ML algorithms can accurately detect even single CAR-T cells, separate irregular overlapping cellular boundaries from complex background noise, and generate precise predictive masks and contours. The said ML practice can swiftly quantify the total fluorescence intensities of crucial IS biomarkers, including F-actin, perforin, tumor antigen clustering, and phosphorylated Zeta (pZeta) signaling molecules. After using this ML practice with actual clinical data, the ML-quantified IS parameters reported highly significant statistical differences between patient samples, directly correlating high IS quality scores with patients who achieved positive clinical responses (responders) rather than those who failed treatment (non-responders) [87].

Beyond the traditional image analysis, machine learning algorithms such as Random Forests (RFs) are routinely employed in bioinformatics to work on and process vast clinical datasets and rank the predictive power of various biomarkers. In computational systems analyzing advanced hepatocellular carcinoma, RF models processed simulated patient outcomes and successfully isolated and identified six top-tier predictive variables out of hundreds of parameters. The used RF models confirmed that baseline T-cell density, regulatory T-cell (Treg) density, the T-cell-to-Treg ratio, and the total number of tumor-specific T-cell clones are the most important predictive biomarkers for deciding whether a patient will respond to combined PD-1 and CTLA-4 immune checkpoint blockade [89].

5.4. Integrating PK/PD Modeling for Dose Optimization

When developing a complex immunotherapy treatment plan, standard trial-and-error approaches to early-phase clinical testing are usually hugely expensive and time-consuming. In order to avoid these limitations, integrating Quantitative Systems Pharmacology (QSP) modeling (a mathematical framework that bridges the pharmacokinetic (PK) profiles of drugs with their dynamic pharmacodynamic (PD) interactions across biological pathways) is the practice under trial now. By using and exploiting detailed PK compartmental models that represent the tumor, the draining lymph nodes, central blood circulation, and peripheral tissues, QSP platforms allow clinicians to conduct hi-fi virtual clinical trials [89].

A real-life application of this approach was the development of the first QSP model for advanced Hepatocellular Carcinoma (aHCC) to optimize ICIs dosing. The model begins by defining physiologically realistic parameters based on human data. Using Latin Hypercube Sampling (LHS), the clinicians generated a virtual cohort of 5,000 unique virtual patients, recording rather important interpatient diversity in highly critical variables like tumor mutational burden and baseline immune cell densities. Rejection sampling was used then to filter this pool into a “plausible” (or accepted)

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population that strictly aligned with the physiological T-cell ranges and tumor diameters documented in the real-world CheckMate 040 clinical trial [89].

Once these processes are done, this virtual patient cohort was subjected to multiple simulated treatment plans evaluating nivolumab monotherapy and various nivolumab/ipilimumab combination dosing regimens. The QSP model accurately simulated and predicted the temporal changes in target lesions and immune cell dynamics, ultimately predicting ORRs that perfectly matched the actual CheckMate 040 trial outcomes. By running these rapid computational simulations, oncologists can virtually evaluate thousands of different PK/PD interactions, identifying the optimal drug dosages and synergistic scheduling combinations that maximize the critical CD8+ T-cell to Treg ratio within the tumor, thereby accelerating the safe transition of novel regimens into human patients and skipping the so-dangerous trail-and-error practices [89].

6. Future Directions in Cancer Treatment

6.1. Next-Generation Cellular Immunotherapy and Gene Editing

6.1.1. Overcoming the Immunosuppressive Tumor Microenvironment

The immunosuppressive tumor microenvironment (TME) is a major obstacle for cellular therapies. To keep these therapies working effectively, we need advanced bioengineering techniques[90,91]. Recently engineered structures have led to the development of an implantable iCAR-M system within a three-dimensional structure printed using GelMA, it acts as a biologically active reservoir to deliver IL13Rα2-directed CAR-M along with SIRPα-overexpressing extracellular vesicles, thereby negating CD47-based immune escape and anoikis [92]. CircCAR-NK has been designed by using circRNA engineering to avoid the loss of antigens from stromal cells. The circCAR-NK system remains efficient in killing cancer cells despite antigen shedding caused by the cancer-associated fibroblasts. In addition, by creating CAR-NK cells targeted against CEACAM5 via the deletion of the glucocorticoid receptor, there is no immunosuppression caused by steroids, and consequently, the body can still use its innate capability for tumor rejection[93].

6.1.2. CRISPR and Synthetic Biology Applications

The implementation of CRISPR-based technology with synthetic biological approaches can improve therapeutic safety, efficacy, and efficiency in cellular engineering[94]. Simultaneous genome editing by applying non-viral delivery systems accelerated the rapid development of allogeneic CAR-T and CAR-NK cell-based immunotherapy through silencing of innate immune checkpoints and receptors to minimize host immune responses[95]. To prevent off-target toxic effects, synthetic biological approaches have employed combinatorial genetic circuits such as AND, OR, and IF-THEN gates for combinatorial antigen detection before cellular activation[90]. Furthermore, spatial-temporal precision can be achieved through the application of ultrasound-responsive genetic switches, whereby ultrasound induces HSP-mediated CAR induction, and suicide switches, for example, iCas9, enable rapid cell elimination in response to toxic effects[90,96]. Conventional CAR constructs are restricted due to they only enable targeting of surface-expressed proteins, while the TCR-engineered immunotherapy allows for targeting of intracellular proteins using genetic modification strategies,this approach efficient for targeting and maintains an efficient approach for attacking solid malignancies that are deeply invasive [95].

6.2. Natural Phytochemicals and Hypoxic Stress Modulation

6.2.1. Overcoming Chemoresistance via Phytochemical Signaling Pathways

The employment of bioactive compounds derived from nature helps us successfully target the MDR phenotype, which is mainly due to the expression of membrane transport proteins, and enhances the activity of signaling pathways that inhibit apoptosis [97]. In particular, unique multi-

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target mechanisms mediated through melatonin thoroughly neutralize complex chemoresistance across a broad spectrum of non-responsive neoplastic diseases [98]. Co-administered inside next-generation nanocarrier systems, melatonin Acts as a site-specific therapeutic enhancer, Facilitating intractable anti-apoptotic cascades thoroughly suppressed and chemotherapeutic impact is significantly enhanced [98]. As a result, therapeutic susceptibility is fundamentally restored via these phytochemicals, which lead to disabling established MDR pathways and establish phytochemical signaling modulation as an essential clinical strategy [98].

6.2.2. Targeting Hypoxic Stress and Cellular Plasticity in the TME

Across the oncological landscape, sustained oxygen deprivation continuously reorganizes phenotypic flexibility, and aggressively promotes malignant stem-like properties, and upregulates compensatory gene expression profiles for chemotherapeutic escape [99]. To determine the adaptive survival response, we should use hepatocyte nuclear factor 4 alpha (HNF4A)because it has been used as a marker that can be used as a tool for identifying the genes responsible for their gene expression under long-term oxygen deficiency[99,100]. So inhibiting these specific oxygen-deprivation responses will lead to reduced TME-mediated survival mechanisms and a site-specific molecular intervention to overcome Therapeutic escape through non-responsive tumor models [101]. Figure 6 summarizes these natural hypoxic stress modulation pathways.

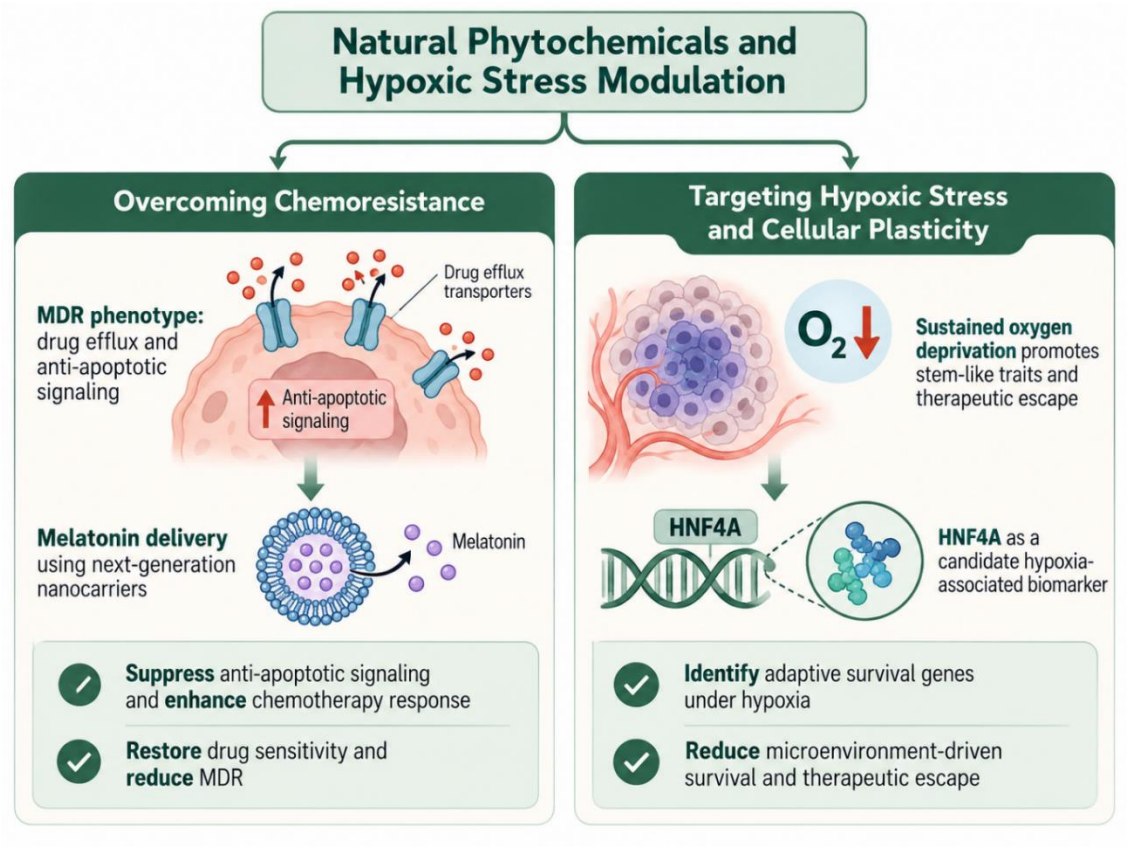

Figure 6. Therapeutic Pathways of Natural Phytochemicals in Modulating Chemoresistance and TME Hypoxia. This flowchart outlines the dual role of phytochemicals in modern oncology: MDR via melatonin-loaded nanocarrier systems and targeting TME hypoxia using the HNF4A biomarker to disable adaptive survival pathways and restore therapeutic susceptibility.

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6.3. Artificial Intelligence and Multi-Omics Integration

6.3.1. AI-Driven Target Prediction and Drug Repurposing

AI technology and systems biology are demonstrating the field of therapeutic target discovery and the science of cancer structural biology [102]. The application of deep learning offers the potential to model protein structures and interactions and to identify neoantigens. In addition, deep learning allows for highly predictive models of peptide-MHC interactions [102]. This predictive computational capability enhances drug repurposing by linking SL discovery to in silico drug screening. For instance, AI models have also found context-dependent SL of common compounds; metformin, an activator of AMPK, can be used to exert metabolic stress on only those cancer cells that lack LKB1 or contain mutated mitochondrial DNA[102].

6.3.2. Biomarker Discovery Through Multi-Omics

Achieving the promise of precision medicine is becoming more dependent upon developing a system of oncology that regularly responds to new information, with therapy being modified according to real-time feedback at the molecular level [102]. The framework of this approach applies high-throughput omics-based profiling, which involves genomics, transcriptomics, proteomics, metabolomics, and epigenomics, to address the heterogeneity burden of tumor cells [102,103]. Also, the routine monitoring of somatic mutations and other advanced analytic domains, for instance, multidimensional fragment omics and methylation of ctDNA, enables deep understanding of subclonal structure, epigenomic remodeling, and changes within the tumor microenvironment [102] However, the huge amount of data collected by using these techniques requires highly advanced data interpretation skills. When these huge amounts of data obtained through these omics techniques are then input into artificial intelligence and machine learning algorithms, they help clinicians to predict resistance patterns and detect drug tolerance before the disease advances clinically or radiologically [102,103].

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Abbreviations

The following abbreviations are used in this manuscript:

Abbreviation	Definition
ABC	ATP-binding cassette
ADCs	Antibody-drug conjugates

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AdC68	Adenoviral vector
aHCC	Advanced Hepatocellular Carcinoma
AI	Artificial Intelligence
AJCC	American Joint Committee on Cancer
ANN	Artificial Neural Networks
Ara-C	Cytarabine
ASPH	Aspartate β-hydroxylase
CAPP-seq	Cancer Personalized Profiling by Deep Sequencing
CAR	Chimeric Antigen Receptor
CAR-NKT	CAR-engineered invariant natural killer T
CbD	Carboplatin with docetaxel
CbP->AC	Carboplatin-Paclitaxel followed by Adriamycin-Cyclophosphamide
CCA	Cholangiocarcinoma
CDDP	Cisplatin
CEA	Carcinoembryonic Antigen
CIN	Chromosomal Instability
CRC	Colorectal Cancer
CSCC	Cutaneous Squamous Cell Carcinoma
CTCs	Circulating tumor cells
ctDNA	Circulating tumor DNA
DC	Dendritic Cell
DHIE	Dehydrodiisoeugenol
EFS	Event-Free Survival
EMT	Epithelial-Mesenchymal Transition
GBM	Glioblastoma
GenAI	Generative AI
GSH	Glutathione
GvHD	Graft-versus-Host Disease
HNF4A	Hepatocyte nuclear factor 4 alpha
ICIs	Immune checkpoint inhibitors
IS	Immunological Synapse
LHS	Latin Hypercube Sampling
LPA	Lysophosphatidic acid
MDR	Multidrug resistance
MDSCs	Myeloid-Derived Suppressor Cells
miRNAs	MicroRNAs
ML	Machine learning
MMR	Mismatch repair
MRD	Minimal residual disease
MSI-H	Microsatellite instability-high
MSNs	Mesoporous silica nanospheres
NBNB	NanoBiT-Nanobody
NER	Nucleotide excision repair
NGS	Next-Generation Sequencing
NSE	Neuron-Specific Enolase
ORR	Objective response rate
OXPHOS	Oxidative phosphorylation
pCR	Pathological complete response
PD	Pharmacodynamic
PFS	Progression-free survival
P-gp	P-glycoprotein
PhasED-seq	Phased Variant Enrichment and Detection Sequencing
PK	Pharmacokinetic
PNEN	Pancreatic Neuroendocrine Neoplasms
Pol-β	DNA polymerase beta
PSMA	Prostate-Specific Membrane Antigen
pZeta	Phosphorylated Zeta
QCM	Quartz Crystal Microbalance
QSP	Quantitative Systems Pharmacology

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RFs	Random Forests
SL	Synthetic Lethality
TAMs	Tumor-Associated Macrophages
TCR	T-cell receptor
Tdp1	Tyrosyl-DNA phosphodiesterase 1
TGFβRDN	Dominant-negative TGF-β receptor
TLSs	Tertiary Lymphoid Structures
TMB	Tumor mutational burden
TME	Tumor Microenvironment
TMZ	Temozolomide
TNBC	Triple-negative breast cancer
TNM	Tumor, Node, Metastasis
Treg	Regulatory T-cell
TSM-D	Thickness shear mode
UICC	International Union against Cancer
VBIR	Viral-Based Immunotherapy Regimen
VGFETs	Vertical Graphene Field-Effect Transistors

Appendix A

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Table A1. Summary of the main included studies.

No.	Population	Sample size	Methods/Study design	Location	Outcomes	Main Findings	Reference
1	General cancer population	N/A (Review)	Review of foundations and frontiers in precision oncology	India	Analysis of signaling pathway deregulation and the role of Multi-Omics and AI.	Precision oncology identifies specific molecular alterations for tailored treatment; integration with AI and multi-omics is essential for a holistic cure.	[1]
2	Patients with advanced or metastatic Cholangiocarcinoma (CCA)	N/A (Review)	Clinical trial and genetic landscape review	Italy and Spain	Comparison of traditional chemotherapy (cisplatin/gemcitabine) versus target-oriented drugs.	Actionable targets like FGFR2 fusions and IDH1 mutations allow for more effective precision treatments compared to standard palliative chemotherapy	[2]
3	Patients with various cancers (focused on chemo-resistant types)	N/A (Review)	Systematic literature review	Jordan	Identification of natural products targeting MDR biomarkers (P-gp, MRP, BCRP, etc.)	Natural products provide a cost-effective way to overcome multidrug resistance by targeting multiple molecular mechanisms simultaneously.	[3]
4	General cancer population	N/A (Editorial)	Research topic editorial/Metadata study	Luxembourg, Italy, South Korea	Overview of innovative precision immuno-oncology markers and stratified response prediction.	While personalized therapies offer benefit, trials like NCI-MATCH show only 18% of patients with actionable mutations derive significant clinical benefit	[4]
5	Cancer patients undergoing genomic profiling	N/A (Editorial	Overview of current applications of genomics in clinical translation	USA	Review of the trajectory from microscopy-based studies to single-nucleotide resolution sequencing.	Advances in sequencing technology (NGS) have enabled clinicians to intelligently exploit genomic vulnerabilities using target-specific small molecule inhibitors	[5]
6	Patients with advanced/metastatic cancer across diverse tumor types	Multiple trials (e.g., IMPACT N=3487; NCI-MATCH N=1199)	Comparative review of selected clinical trials (IMPACT, SHIVA, NCI-MATCH, TAPUR, DRUP)	USA	Evaluation of matched targeted therapy (MTT) vs. non-matched therapy outcomes.	Matched targeted therapy is consistently associated with superior response rates, progression-free survival, and overall survival across independent cohorts.	[6]

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7	General cancer population	N/A (Editorial)	Policy and research review	USA	Summary of FDA breakthrough designations, ADCs, and CAR T-cell therapies.	The focus has shifted from histology-based treatment to mutation-specific treatment, with ADCs and immunotherapies transforming the clinical landscape	[7]
8	Patients with M1b NSCLC (single extrathoracic metastasis)	Not specified	Retrospective clinical cohort study	USA	Overall survival by metastasis pattern	Validated the clinical relevance of the 8th edition M1b descriptors, illustrating survival differences (e.g., single liver metastasis vs. others) crucial for oligometastatic treatment decisions.	[8]
9	Colorectal carcinoma patients	N/A (Review)	Critical Appraisal / Review	Italy	TNM staging refinement, prognosis	Although the TNM classification remains essential, integrating non-anatomic, morphologic, and molecular factors is required to more accurately stratify patient risk and plan treatments.	[9]
10	Biosensor technologies for healthcare	N/A (Review)	Literature Review	China	Machine learning applications in biosensing	Integrating AI algorithms (e.g., SVM, PCA, CNN) with biosensors revolutionizes diagnostics by improving accuracy and data analysis, though seamless system integration remains challenging.	[10]
11	Lung cancer patients and ordinary controls	8 clinical serum samples	Experimental / Biosensor development	China	Detection limits of CEA, Cyfra21-1, NSE	The vertical graphene field effect transistor (VGFET) combined with C60 and mesoporous silica achieved sub-femtomolar detection limits for multiple lung cancer markers with high accuracy.	[11]
12	Non-small cell lung cancer (NSCLC) patients	N/A (Review)	Literature Review	France	Treatment selection, acquired resistance	Liquid biopsies exhibit great potential across all stages of NSCLC for screening, monitoring responses to immunotherapy/targeted therapies, and tracking acquired resistance.	[12]
13	Patients with oral precancerous and cancerous lesions	N/A (Review)	Literature Review	Italy	Identification of circulating miRNAs and proteins	Saliva and blood liquid biopsies offer a promising, non-invasive method for early oral cancer diagnosis via reliable profiling of circulating miRNAs and proteins.	[13]
14	Patients with solid tumors	N/A (Review)	Literature Review	Australia	Prognostic value (RFS, OS, MRD detection)	ctDNA provides robust prognostic value across multiple solid tumors for minimal	[14]

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						residual disease detection and predicting recurrence, facilitating precision medicine.	
15	Stage III colorectal cancer patients	160 patients	Prospective observational cohort study	Spain & Denmark	Recurrence-free survival, early relapse detection	Serial ctDNA monitoring accurately assesses adjuvant chemotherapy efficacy, enables early detection of relapse, and allows clinicians to distinguish fast- versus slow-growing tumors.	[15]
16	Esophageal adenocarcinoma (EAC) patients	20 patients	Prospective observational cohort study	UK & USA	Disease-free survival (DFS), ctDNA status	Dynamic ctDNA monitoring is highly prognostic; patients who convert from pre-surgery ctDNA-positive to post-surgery ctDNA-negative show good prognoses, whereas post-surgery positivity predicts relapse.	[16]
17	Lymphoma patients (e.g., DLBCL, MCL, BL)	N/A (Review)	Literature Review	China	Mutation tracking, diagnostic accuracy, MRD	Modern ctDNA sequencing (CAPP-seq, PhasED-seq) provides high-sensitivity molecular profiling, aiding in lymphoma classification, predicting progression-free survival, and adapting therapy.	[17]
18	Patients with solid metastatic cancers	N/A (Review)	Literature Review	USA	CTC enumeration, metastasis biology	CTC analysis enables real-time insights into cancer metastasis, EMT plasticity, and therapeutic resistance (e.g., AR-V7 in prostate cancer), guiding clinical decision-making.	[18]
19	Esophageal cancer (EC) patients, healthy controls	96 EC patients, 99 controls	Experimental / Biosensor assay	China	Serum FGL1 levels, diagnostic ROC (AUC)	A novel mix-and-read NBNB biosensor successfully detected ultra-low levels of FGL1 (11.38 pM). FGL1 was found to be significantly elevated in early EC patients compared to controls.	[19]
20	Lysophosphatidic acid (LPA) in PBS & human serum	N/A (In vitro sensor developme nt)	Experimental / Thickness shear mode acoustic sensor (TSM-D)	Canada & Slovakia	Limit of detection for LPA	TSM-D sensors with antifouling surface chemistry successfully detected the early-stage ovarian cancer 55biomarker LPA even in complex media like human serum.	[20]
21	Human serum samples spiked with CEA	N/A (Method validation)	Experimental / QCM Aptasensor development	Turkey	Detection limit and analytical recovery of CEA	The QCM aptasensor detected CEA with a limit of detection of 102 pg/mL (antiCEA1)	[21]

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						and >95.4% recovery in real human serum, demonstrating practical applicability.	
22	Exosomes (HepG2 and L02) / Artificial serum	N/A (In vitro sensor developme nt)	Experimental / Biosensor development	China	Exosome detection, bulk sensitivity	The designed three-layer CIMH (cavity induced mode hybridization) sensor optimized surface plasmon resonance performance, demonstrating high sensitivity for exosome detection.	[22]
23	Acute Megakaryoblastic Leukemia (AMKL) cell lines	Not specified (in vitro study)	Colony formation, flow cytometry, proteasome assays	Phoenix, AZ, USA	Cell viability, apoptosis, clonogenic survival, CT-like proteasome activity, and drug resistance markers	Disulfiram (DSF) combined with copper overcomes resistance to Bortezomib (BTZ) and Ara-C in AMKL cells	[23]
24	Platinum-resistant high-grade serous ovarian cancer patients	70 randomized patients	Phase 2, open-label, randomized trial	11 cancer centers, USA	Progression-free survival (PFS), overall survival (OS), objective response rate, clinical benefit rate, duration of response, and adverse events	The addition of berzosertib to gemcitabine improved progression-free survival (HR 0.57) compared to gemcitabine alone	[24]
25	Human hepatoma cell lines	Not specified (in vitro study)	IHC, molecular docking, Western blot	Guangdong, China	Cell cycle progression, cell viability, and expression of PLK1 and p53	Dehydrodiisoeugenol modulates PLK1-p53 pathways, affecting cell cycle and proliferation markers in hepatoma	[25]
26	Prostate, NPC, and ovarian cancer cell lines	In vitro/in vivo	RT-PCR, ChIP-PCR, clonogenic assays	Changsha, China	Cell survival/viability (IC50), relative colony formation ability, apoptosis-associated molecule expression (XIAP, Survivin), and tumor size	FOXM1 overexpression promotes taxane resistance and expansion of cancer stem cells (CSCs) via regulation of UHRF1	[26]
27	Stage II-III TNBC patients	273 patients	Retrospective study	Harbin, China	Pathological complete response (pCR), residual cancer burden (RCB), event-free survival (EFS), and overall survival (OS)	Patients achieving pCR and RCB 0-1 experienced significantly prolonged survival. Treatment groups showed differential baseline responses	[27]

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28	Locally advanced breast cancer patients (LUM and TN)	317 patients	WES, RNAseq on pre- and post-treatment biopsies	Amsterdam, Netherlands	Neoadjuvant Response Index (NRI), pathological complete response (pCR), residual breast cancer burden (RCB), recurrence-free survival (RFS), and cell viability (IC50)	Proliferation rate (e.g., CCND1), immune response, and ECM jointly predict therapy response and potential resistance mechanisms	[28]
29	Stage II-III BRCA-altered TNBC patients	122 patients	Randomized, open-label, multicenter trial	13 hospitals, Netherlands	Neoadjuvant Response Index (NRI), pathological complete response (pCR), recurrence-free survival (RFS), overall survival (OS), and adverse events (AEs)	High-dose alkylating chemotherapy didn't improve pCR over conventional therapy but showed a potential RFS benefit in stage III patients, albeit with higher toxicity	[29]
30	Glioblastoma (GBM) mouse models and cells	In vitro and mouse cohorts	In silico, MRI, and photon data analysis	Omaha, NE, USA	Connectivity score, cell viability, apoptosis, tumor volume/growth, and overall survival	Differential gene expression and Connectivity Map analysis identified novel combinations targeting specific GBM molecular signatures	[30]
31	Melanoma patients with primary resistance to checkpoint inhibitors	38 patients	Clinical study	Erlangen, Regensburg, Würzburg, Munich, Germany	Overall response rate (ORR), progression-free survival (PFS), overall survival (OS), and physical/role-functioning Quality of Life (QoL)	Re-exposure to therapy with dacarbazine yielded specific clinical responses and significantly improved physical and role-functioning QoL	[31]
32	Non-small-cell lung carcinoma (NSCLC) cells	Not specified (in vitro study)	Real-time cell analysis, ChIP, RNA sequencing	Shenyang, China (and NY, USA)	IC50 values, reversal of resistance, and cell viability metrics	Elucidated the mechanism by which the HDAC/RXR/HtrA1 pathway mediates cisplatin (CDDP) resistance	[32]
33	Colon cancer cells (HCT116)	In vitro	ICP-MS (metallomics) and HILIC-HR-MS (metabolomics)	Vienna, Austria	Drug accumulation (platinum levels), cell viability, metabolic perturbation (changes in low molar mass fraction), cell number, and protein amount	Acquired oxaliplatin resistance correlates with altered drug accumulation, alongside massive changes in energy, fatty acid, and polyamine metabolism	[33]

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34	TNBC patients (stage I-III)	720 patients	Phase III randomized clinical trial	Single tertiary center, India	Event-free survival (EFS), overall survival (OS), pathologic complete response (pCR), toxicity, and residual cancer burden	Adding carboplatin improved pCR significantly (54.5% vs 40.3%), and increased OS and EFS specifically in premenopausal patients	[34]
35	Stage I-III TNBC patients	103 patients	Phase II randomized controlled trial	Chongqing, China	Pathological complete response (pCR), event-free survival (EFS), overall survival (OS), and grade 3/4 treatment-related toxicity (leukopenia, neutropenia, anemia, thrombocytopenia)	Taxane + lobaplatin achieved a significantly higher pCR (41.2%) than taxane + anthracycline (21.2%), with differing hematologic toxicities but similar OS/EFS	[35]
36	Broad panel of cancer cells and mice models	Multiple cell lines and mice	ICP-MS, Live-cell microscopy, allografts	Vienna, Austria	Drug accumulation (platinum levels), mode of action of PhB, IC50, cell migration, cell viability, and metabolic perturbation	cisPt(PhB)2 exhibits high nano-molar activity across cell lines, including platinum-resistant variants, deeply tied to lipid/energy metabolism alterations	[36]
37	Metastatic/recurrent breast cancer patients	40 patients	Retrospective analysis	Asia (inferred)	Progression-free survival (PFS) and overall survival (OS)	No significant differences in PFS or OS were found between doublet vs. single maintenance chemotherapy, though doublet had more hematologic toxicity	[37]
38	Triple-negative breast cancer (TNBC) patients and cell lines	111 patients	Retrospective cohort and in vitro study	Udine, Italy	Event-free survival (EFI), overall survival (OS) compared below/above 5 years, disease recurrence, and platinum compound IC50 values	APE1 and NPM1 protect TNBC cells from platinum cytotoxicity, and low NPM1 levels are associated with worse EFI prognosis in anthracycline-naïve patients	[38]
39	HepG2, SKOV-3 cell lines	In vitro	Sphingomyelinase assay, JC-1 assay, RNS detection	Poland	Cell viability, migration (wound width), oxidative/nitrosative stress generation, mitochondrial membrane potential,	Oxazolinoanthracyclines trigger apoptosis and autophagy via neutral sphingomyelinase and mitochondrial pathways, with O-DAU generating high RNS	[39]

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					intracellular calcium levels, and apoptosis/autophagy markers		
40	Lung carcinoma (A549) and cardiomyocytes	In vitro	Cell viability, in silico molecular modeling	Cracow, Poland	Cell viability and IC50 values for DNR	The AKR1C3 inhibitor ASP9521 inhibits CBR1 and has the potential to sensitize cancer cells to anthracycline therapy	[40]
41	Women with localized breast cancer	122 patients	Observational structured interview/survey	Marrakech, Morocco	Short-term side effects including asthenia, vomiting, mucositis, allergies, neuropathy, arthromyalgia, hospitalizations, and premature cessation of chemotherapy	Anthracyclines were linked to more asthenia, vomiting, and mucositis, while taxanes caused more allergies, neuropathy, and arthromyalgia	[41]
42	Stage I-III TNBC patients	100 patients	Phase II randomized trial (NeoSTOP)	Kansas, USA	Pathological complete response (pCR), residual cancer burden (RCB), event-free survival (EFS), overall survival (OS), and treatment-related toxicity (leukopenia, neutropenia, anemia)	Carboplatin plus docetaxel achieved similar pCR (54%) to anthracycline-containing regimens but with a significantly more favorable toxicity profile and lower cost	[42]
43	Early-stage TNBC patients	333 patients	Phase 3, randomized, double-blind trial	13 countries (75 centres)	Pathological complete response (pCR), event-free survival (EFS), disease-free survival (DFS), and overall survival (OS)	Combining atezolizumab with sequential chemotherapy significantly increased pCR rates (58%) vs. placebo plus chemotherapy (41%)	[43]
44	Tumor resistance models	Literature review	Review	Inner Mongolia, China / Texas, USA	Tumor volume, cell viability (cytotoxicity), tumor resistance/sensitivity, and cellular uptake	Nanoparticles bypass efflux pumps and leverage lysosomal pathways, showing benefits like stearoyl gemcitabine-incorporated lipid nanoparticles	[44]
45	Breast cancer cell lines (MCF-7, MDA-MB-231)	In vitro	Whole exome sequencing, CNA analysis	Copenhagen, Denmark	Cell viability (absorbance), cell cycle distribution (G1,	Exome evolution during docetaxel resistance is step-wise; key alterations like	[45]

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					S, G2/M, SubG1), genomic single point mutations, insertions/deletions, copy number alterations (CNAs), and gene expression	ABCB1 amplification and structural gene mutations accumulate progressively	
46	Murine tumor cells and draining lymph nodes	In vitro and in vivo models	qRT-PCR, ChIP, Griess method, immunofluorescence	Turin, Italy	Dose-dependent cell viability, IC50, lysosome/proteasome activity, nitrite/NO production levels, and Pgp expression/activity	Modulating C/EBP-beta and NO levels alters Pgp expression and mitigates multidrug resistance in the tumor microenvironment	[46]
47	Breast, prostate, lung, endometrial, ovarian tumors	Literature review	Review article	Amsterdam & Utrecht, Netherlands	Expression levels of CYP3A4, CYP3A5, and CYP2C8 (protein and mRNA), and clinical benefit/tumor response	Intratumoral CYP enzyme expression limits taxane efficacy; concomitant treatment with protease inhibitors (e.g., ritonavir) can reverse this	[47]
48	Glioblastoma stem cells and various cancer models	Not specified (in vitro/in vivo models)	Experimental in vitro and animal models	Zhengzhou, China	Target cell uptake, cell apoptotic rate, relative protein levels (Mcl-1, Bax, Bcl-xl), tumor volume, and mouse health status	Active targeting co-delivery of siRNA and antineoplastic drugs via magnetic nanoparticles induces synergistic programmed cell death	[48]
49	Muscle-invasive bladder cancer (MIBC)	101 patients	Whole exome sequencing of pre/post-treatment tumors	USA (DFCI, MSKCC, FCCC)	Mutational signatures, clonal evolution, and overall survival (prop survival)	Cisplatin treatment induces specific mutational signatures; analyzing clonal evolution uncovers heterogenous resistance mechanisms	[49]
50	Ovarian cancer cell lines (CAOV3) and MEFs	In vitro	siRNA knockdown, Immunoprecipitation, Immunoblotting	USA (NIH supported)	Cell viability/proliferation, apoptosis (Annexin V/PI), PARP-1 and PAR protein levels, and JNK phosphorylation/activation	MKP-1 suppresses PARP-1 degradation via JNK signaling pathways, thereby contributing directly to cisplatin resistance	[50]
51	Bladder cancer/urothelial carcinoma	126 patients	Co-IP, Kaplan-Meier, Cox regression	Beijing, China	Overall survival (OS), disease-free survival	SIRT7 physically interacts with EZH2; its high expression correlates with platinum	[51]

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					(DFS), and SIRT7 / RND3 expression levels	resistance and significantly worse patient prognosis	
52	Prostate cancer cell lines	In vitro	Cell survival assays, clonogenic assays	Loma Linda, CA, USA	Cellular survival/cell death and expression of LEDGF/p75	LEDGF/p75 promotes multi-taxane resistance; depleting it re-sensitizes cells to taxanes, though cells remain sensitive to TRAIL	[52]
53	Small cell lung cancer (SCLC) cells and patients	10 mice, 2 patients	In vivo resistance generation, microarray, IHC	USA	Cell viability (IC50), tumor volume, TRIB2 and CEBPA protein expression levels, and cisplatin resistance	Upregulation of TRIB2 and degradation of CEBPA promote cisplatin resistance and confer cancer stem-cell-like properties in SCLC	[53]
54	Platinum-sensitive and resistant ovarian cancer patients/cells	22 patients	IHC, Western blot, FACS, RNA expression	Sevilla, Spain	MYPT1 expression, Hippo target gene expression (BIRC5, CTGF, FGF1, GLI2), overall survival, and cancer stem cell (CSC) markers	Resistance to platinum is driven by MYPT1 downregulation and miR-30b upregulation, correlating with poorer survival probability	[54]
55	High-Grade Serous Ovarian Cancer (HGSOC) cells and patients	N/A (in vitro/datasets)	In vitro metabolomics, qPCR, survival dataset analysis	Naples & Florence, Italy	Glutathione (GSH) levels, changes in metabolite levels, changes in gene expression levels, overall survival (OS), response to platinum-based therapy, and post-progression survival	Resistant cells lower GSH levels and activate alternative antioxidant pathways (like TXNRD1); high TXNRD1 correlates with worse survival	[55]
56	Glioma patients and cell lines	975 patients (datasets)	Prognostic analysis, qPCR, flow cytometry, xenografts	Changsha, China	Gene expression levels via qPCR, overall survival, cell growth, and in vivo tumorigenesis (tumor volume)	High ATG4C expression predicts poor prognosis; its knockdown inhibits glioblastoma cell growth and tumorigenesis in vivo	[56]
57	Gastric cancer cells (SGC7901)	In vitro	Cytotoxicity, PCR array, Immunofluorescence	Xi'an, China	Cell viability, combination index (CI) values for synergism/antagonism, ER stress/UPR response, and	Multidrug-resistant (MDR) cells are more sensitive to Tunicamycin due to basal ER stress; blocking autophagy further enhances Tunicamycin's toxicity	[57]

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					upregulated/downregulated gene expression		
58	Epithelial Ovarian Cancer (EOC) patients and cell lines	20 pairs of EOC tissues	Tissue microarray, IHC, in vitro assays	Shanghai, China	COPS5 expression level via IHC, cell viability (IC50), number of clones in colony formation, cell cycle phase percentages, cell migration, tumor weight/volume, PFS, and OS	COPS5 is overexpressed in platinum-resistant lines, enhancing proliferation and migration, conferring resistance to platinum therapies	[58]
59	Ovarian cancer patients	1816 dataset samples, 81 tissues	ROC plotter database mining, RT-PCR validation	Budapest, Hungary	Relapse-free survival (RFS) at 6 months, pathological complete response (PCR), and gene expression levels	Identified genes like TFE3, NCOR2, PDXK, and MARVELD1 as significant biomarker candidates for combined platinum and taxane resistance	[59]
60	Ovarian, breast, prostate, and sarcoma patients	840 patients	Retrospectively emulated randomized-control trials (WGS, cell-free DNA)	Madrid, Spain & Cambridge, UK	Time to treatment failure (TTF), hazard ratios (HR), progression-free survival (PFS), cell line dose response (AUC), and chromosomal instability (CIN) signature activity	Chromosomal instability (CIN) signatures can accurately predict resistance to platinum, taxanes, and anthracyclines from a single genomic test	[60]
61	Lung cancer models	In vitro/in vivo models	Drug sensitivity tests, mutation profiling	China	Drug sensitivity/resistance evolution, 3D spatial structure simulation, morpho-functional advantages, and de novo mutations (EGFR/HER2)	Organoids better simulate 3D spatial structures and detect de novo resistance mutations (e.g., EGFR, HER2) compared to adherent models post-chemotherapy	[61]
62	Colorectal cancer cell lines and nude mice	In vitro and in vivo models	CCK-8 assay, LC-MS/MS, xenografts with HE staining	Nanjing & Jiangsu, China	Cell inhibition/survival rates, IC50 values, tumor volume, tumor weight, and Top1/Tdp1 expression	Pterostilbene is highly distributed to the nucleus/mitochondria, inhibiting Top1 and showing stronger anti-colon cancer efficacy than resveratrol	[62]
63	Breast cancer models and TCGA datasets	1105 TCGA tumors; mice	Bioinformatics, in vivo metastasis assays	West Lafayette, IN, USA	Tumor cell growth, invasion of resistant cells, tumor cell migration, gene expression changes (NRP1,	Elevated FGFR1 links to poor prognosis; targeting NRP1 epigenetically may prevent bypass signaling in FGFR1-amplified tumors	[63]

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					FGFR1), and acquired resistance		
64	Hepatoma cells	In vitro / mouse models	CCK-8, flow cytometry, immunofluorescence, docking	Shenzhen, China	Cell viability (OD at 450nm), expression of GRP78, E-cadherin, Vimentin, ABCG2, and markers of cell invasion and metastasis	Polyphyllin I (PPI) targets GRP78 to overcome sorafenib resistance and reduce invasion and metastasis in hepatocellular carcinoma	[64]
65	Ovarian cancer cells	In vitro	Exome sequencing, bioinformatics, cell viability, IF	Nottingham, UK	DNA repair markers, cell survival/viability, platinum sensitisation, and mutation impact	Resistant cells have variants in Polβ-interacting proteins; knocking down Polβ effectively re-sensitizes these cells to cisplatin	[65]
66	Cancer patients	Clinical datasets	Statistical correlation of clinical data	Shenzhen, China	Pathological complete response (pCR), Residual Cancer Burden (RCB) scores, and Miller-Payne grading system scores	Analyzed the most prominent immunophenotypes at the patient level to determine their association with dynamic treatment responses and outcomes	[66]
67	NSCLC cell lines and PDX models	Multiple PDX models	In vitro flow cytometry, in vivo PDX	Boston, MA, USA	Cellular uptake/internalization of HER3-DXd, tumor regression/growth delay, tumor volume, viability of PDX fragments, and HER3 membrane expression	EGFR inhibition upregulates HER3 membrane expression, enhancing the internalization and efficacy of the HER3-DXd antibody-drug conjugate	[67]
68	Mice bearing human triple-negative breast cancer (TNBC) xenografts	Exact *n* not provided (multiple mouse cohorts utilized)	In vivo orthotopic and metastasis murine TNBC xenograft models	UCLA and Cedars-Sinai Medical Center, CA, USA	Tumor load, survival, tissue biodistribution, immune cell activation/exhaustion	Allo15MCAR-NKT cells demonstrated superior tumor suppression, prolonged survival, and targeted tumor homing compared to conventional CAR-T cells without inducing GvHD.	[68]
69	Human CRC patients and MC38 murine CRC models	420 human samples (998,204 cells) & 200	scRNA-seq, spatial transcriptomics, multiplex IHC, and in vivo murine subcutaneous/liver metastasis models	Peking University People's Hospital, Beijing, China	TAM subpopulation mapping, tumor growth/metastasis, immune infiltration	SPP1+TAMs drive CD8+ T-cell exhaustion/exclusion. Regorafenib combined with anti-PD-1 reversed this, reducing SPP1+TAMs and suppressing tumor growth/metastasis.	[69]

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		validation tissues					
70	Patients with advanced dMMR/MSI-H non-colorectal cancers	52 patients	Phase 2 nonrandomized clinical basket trial (MoST-CIRCUIT) of nivolumab + ipilimumab	Multiple centers, Australia	Objective response rate (ORR), PFS, overall survival, safety/irAEs	Dual blockade achieved an ORR of 63% and a 6-month PFS of 71%, demonstrating significant activity in dMMR/MSI-H non-CRC malignancies.	[70]
71	Patients with desmoid tumors	16 evaluable patients	Prospective, open-label, multicenter phase II basket trial (ipilimumab + nivolumab)	1,016 US sites (SWOG network), USA	ORR, PFS, OS, clinical benefit rate (CBR), toxicity	First prospective study of this combo in desmoid tumors yielded an ORR of 18.8% and a CBR of 62.5% with durable responses and manageable toxicities.	[71]
72	Patients with gynecologic clear cell carcinomas (ovary, endometrium, cervix)	32 evaluable patients	Phase II basket trial (DART SWOG S1609) of nivolumab plus ipilimumab	23 US National Clinical Trial Network institutions, USA	ORR, safety/toxicities	Detailed the safety and potential efficacy of combined immunotherapy in rare gynecologic clear cell tumors, mapping toxicities and prior therapy impacts.	[72]
73	Patients with pancreatic neuroendocrine neoplasms (PNEN)	19 patients	Phase II basket two-stage trial of ipilimumab and nivolumab	12 US National Clinical Trials Network institutions, USA	ORR, PFS, OS, CBR, toxicity assessment	Evaluated the clinical activity of dual checkpoint blockade in refractory PNENs (efficacy specifics truncated in text, but trial endpoints successfully evaluated).	[73]
74	Patients with stage I–IVa resectable cutaneous squamous cell carcinoma (CSCC)	50 patients (40 underwent surgery, 10 declined surgery)	Randomized phase 2 trial (MATISSE) comparing nivolumab alone vs nivolumab + ipilimumab before standard of care (surgery RT)	Netherlands Cancer Institute, Amsterdam, Netherlands	Pathological response rate (MPR, PPR), disease-specific survival (DSS), HRQoL, toxicity	High pathological response rates were observed (80% for combo vs 55% for monotherapy), allowing durable organ preservation for patients opting out of surgery, without surgical delays.	[74]
75	Patients with advanced renal cell carcinoma (aRCC) previously treated with IO therapies	46 patients	FRACTION-RCC adaptive platform trial (Track 2), phase II, assessing nivolumab + ipilimumab	Multicenter (USA, Israel, Italy, Canada, France)	ORR, duration of response, PFS, OS, disease control rate	Demonstrated an ORR of 17.4% and a disease control rate of 58.7%, showing ongoing clinical benefits with manageable safety in heavily pre-treated patients.	[75]

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76	Women with c-Met expressing metastatic breast cancer	6 patients	Phase 0/1 clinical trial (intratumoral injection of mRNA c-Met-CAR T cells) and NSG mouse models	University of Pennsylvania, Philadelphia, PA, USA	Safety, pharmacokinetics, tumor c-Met expression, necrosis	c-Met was expressed in ~50% of tumors. Intratumoral CAR-T injection was well-tolerated, inducing tumor necrosis and localized loss of c-Met expression at the injection site.	[76]
77	Patients with metastatic colorectal cancer	16 treated patients	Phase I clinical trials (C-9701 and C-9702) assessing intravenous or intra-hepatic artery CAR-T infusions	Cell Genesys, UCSF, and Stanford University, USA	Safety, tumor trafficking (CC49- DNA copies), anti-tumor activity	As one of the first human CAR-T trials for solid tumors, it demonstrated safety but showed limited clinical efficacy and CAR-T cell persistence.	[77]
78	Patients with metastatic gastrointestinal malignancies (CEACAM5+)	14 treated patients	Phase I clinical trial assessing pre-conditioning chemotherapy, MFEz CAR T cells, and systemic IL-2	The Christie NHS Foundation Trust, Manchester, UK	Tumor response, MFEz T cell persistence, toxicity	Clinical efficacy was limited (mostly stable or progressive disease) due to poor CAR T cell persistence and transient respiratory toxicities dependent on pre-conditioning.	[78]
79	Patients with metastatic colorectal cancer (mCRC) expressing GCC	15 treated patients	Phase 1 nonrandomized clinical trial of GCC19CART cells following fludarabine/cyclophosphamide lymphodepletion	First Hospital of Jilin University, Changchun, China	Safety, objective response, overall survival	GCC19CART achieved an ORR of 40% in heavily pretreated mCRC patients. The therapy was well tolerated, with on-target diarrhea being the primary toxic effect.	[79]
80	Patients with metastatic castration-resistant prostate cancer (mCRPC) and NSG mouse models	13 patients treated in phase I; various mouse cohorts	Phase 1 trial and preclinical xenograft models evaluating PSMA-directed CAR-T cells resisting TGF-	University of Pennsylvania, Philadelphia, PA, USA	Safety (DLTs, CRS), CAR T-cell expansion, PSA decline, clonal expansion integration	Evaluated feasibility/safety; induced massive clonal expansion of CAR-T cells due to integration in NELL2/GLCCI1 genes.	[80]
81	Patients with resected pancreatic ductal adenocarcinoma (PDAC) post standard-of-care	38 patients (10 safety, 28 expansion cohort)	Phase I/II single-center, open-label trial of adjuvant dendritic cell (DC) therapy	Erasmus MC Cancer Institute, Rotterdam, Netherlands	2-year recurrence-free survival (RFS), overall survival (OS), immune responses	DC therapy was able to induce robust vaccine-specific immune responses, yielding a promising 2-year RFS rate of 64% and an OS rate of 83%.	[81]
82	HLA-A2+ patients with advanced-stage	16 accrued patients (13 evaluable)	Randomized pilot phase II clinical trial comparing immediate (week 1) vs	University of Pittsburgh/UPCI, PA, USA	T cell response (IFN-ELISpot), objective clinical	Immediate dasatinib yielded vastly superior immune response rates (66.7% vs 28.6%) and ORR (66.7% vs 0%) compared to delayed	[82]

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	melanoma (mostly PD-1 refractory)		delayed (week 5) dasatinib combined with dendritic cell vaccines		response (ORR), tumor/blood profiling	administration, correlating with TCR convergence.	
83	Female immunocompetent BALB/c mice	*n*=6 to 10 per group	Subcutaneous HCC and orthotopic TNBC murine models treated with ASPH-based lambda phage vaccine and PD-1 blockade	Rhode Island Hospital and Brown University, RI, USA	Tumor volume/weight, survival rate, pulmonary metastases, TIL infiltration	The combined vaccine and PD-1 blockade significantly suppressed primary tumor growth and distant metastases, driving adaptive immune responses and CD4+/CD8+ T cell expansion.	[83]
84	Patients with mCRPC and biochemical recurrence (BCR) prostate cancer	91 patients (35 BCR, 56 mCRPC)	Phase 1 dose escalation and expansion study of a VBIR (AdC68 + pDNA) combined with immune checkpoint inhibitors	Multiple centers (MSKCC, Fred Hutchinson, Duke, etc.), USA	Safety, PSA decline (PSA-50), antigen-specific T-cell response, radiographic PFS	The regimen was generally safe, stimulated antigen-specific immunity in most patients, and led to a 50% PSA decline in 25.7% of BCR patients without androgen deprivation therapy.	[84]
85	Human breast cancer (MCF7) and colon adenocarcinoma (Caco2) cell lines	In vitro model evaluating 10 different medicinal plant extracts	In vitro experimental study utilizing MTT cell proliferation assays and relative Real-Time PCR (RT-PCR)	Amman, Jordan	Cytotoxicity (cell survival percentage) and relative mRNA expression levels of CYP1A1 and P-glycoprotein (P-gp)	Only *Catha edulis* showed anti-proliferative effects on MCF7; numerous plant extracts significantly induced CYP1A1 expression while exerting varying, concentration-dependent induction or inhibition on P-gp, suggesting a high potential for herb-drug interactions.	[85]
86	HLA-A*02+ patients with PRAME+ recurrent/refractory solid tumors (e.g., melanoma, synovial sarcoma)	40 treated patients	Phase 1a dose-escalation and phase 1b dose-expansion open-label, multicenter trial of IMA203 T cells	Multiple centers (Immatics, MD Anderson, etc.), Germany and USA	Safety/tolerability (DLTs, CRS), ORR, progression-free survival (PFS), duration of response	IMA203 T cells were safe (MTD not reached) and showed promising anti-tumor activity (unconfirmed/confirmed ORR of 52.5%) with rapid engraftment and long-term persistence.	[86]
87	Primary kappa-CAR-modified T cells derived from NHL/CLL patients	Samples from clinical trial patients	In vitro imaging of CAR immunological synapse (IS) using planar lipid bilayers, combined with Artificial	Rutgers University, Newark, NJ, USA	IS quality (F-actin, perforin, pZeta intensity), model prediction accuracy	Successfully developed an ML-based method to quantify CAR T cell IS images. IS quality (e.g., F-actin, perforin) correlated significantly with patient clinical responses (responders vs non-responders).	[87]

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			Neural Network (ANN) modeling				
88	Geriatric Population	N/A (Review)	*Literature review*	Jordan	Pharmacokinetic/Pharmacodynamic (PopPK/PD) and Bayesian models to optimize precision dosing in geriatric patients with age-related organ decline and polypharmacy	Machine learning models (e.g., Random Forest, ANNs, XGBoost) consistently outperform traditional PopPK models in predicting drug exposure in elderly patients	[88]
89	Virtual patients (modeled after aHCC patients in CheckMate 040)	5,000 proposed; 1,365 generated virtual patients	Quantitative systems pharmacology (QSP) modeling and random forest machine learning for virtual clinical trials	Johns Hopkins University, Baltimore, MD, USA	Model-predicted ORR, tumor size percent change, predictive biomarker identification	The first QSP model for HCC with ICIs successfully predicted outcomes matching the CheckMate 040 trial, identifying T cell density and T cell:Treg ratios as key predictive biomarkers.	[89]
90	Solid malignancy patients	Not reported	Literature review	China	CAR-T efficacy, safety, tumor infiltration	Reviews AI, CRISPR, and synthetic biology approaches to overcome solid tumor barriers like heterogeneity.	[90]
91	Cancer patients	Not reported	Literature review	Ecuador	Immune response, combination therapy efficacy	Explores next-generation combinations (e.g., CAR-T with oncolytic viruses) to reprogram tumor immunity.	[91]
92	BALB/c mice (4T1 mammary carcinoma model)	25 mice	Experimental study (In vivo/In vitro)	China	Tumor recurrence, macrophage polarization	Implantable hydrogels delivering CAR-macrophages prevent tumor recurrence by remodeling the immunosuppressive niche.	[92]
93	Mice (C57BL/6J, NSG), human primary NK cells, NSCLC patients	421 patient datasets, multiple mouse cohorts	Experimental study (In vivo/In vitro)	United Kingdom	Immune evasion, tumor growth, survival	Cortisol-resistant CAR-NK cells demonstrate improved efficacy in overcoming steroid-induced immune evasion.	[93]
94	Cancer patients	Not reported	Literature review	USA	Gene editing precision, CAR-T cell functionality	CRISPR-Cas9 targeted editing and combination therapies significantly improve CAR-T outcomes and limit toxicities	[94]
95	Cancer patients	Not reported	Literature review	China / UK	TCR pairing, immunosuppression resistance	Details genetic engineering strategies for T cells to overcome tumor microenvironment suppression and avoid antigen loss.	[95]

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96	Cancer patients	Not reported	Literature review	Poland	Checkpoint inhibition, oncolytic virus efficacy	Highlights combined biological therapies improving outcomes.	[96]
97	N/A (In vitro, in vivo, and clinical studies reviewed)	N/A (Literature review)	Literature review	Amman, Jordan	Mechanisms of cancer drug resistance (e.g., drug efflux, evasion of apoptosis) and the role of natural products in overcoming them	Natural products possess multiple mechanisms to inhibit targets causing chemotherapy resistance. Efflux pumps like P-glycoprotein and breast cancer resistance protein (BCRP) are highly sensitive targets for many natural phytochemicals.	[97]
98	N/A (Epidemiological, experimental, and clinical studies reviewed)	N/A (Literature review)	Literature Review	Amman, Jordan	Melatonin's biosynthesis, bioavailability, prophylactic properties, and mechanisms targeting cancer hallmarks	Melatonin demonstrates varied anti-cancer activities, including apoptosis induction, proliferation inhibition, and metastasis reduction. It functions as an effective adjuvant that decreases drug resistance and mitigates the toxicity of conventional therapies.	[98]
99	PANC-1 human pancreatic cancer cell line	7,000 cells (MTT assay); 50,000 cells (wound healing)	In vitro experimental study using RT-PCR arrays, MTT proliferation assay, and wound-healing assay	Amman and Zarqa, Jordan	Gene expression changes linked to chronic hypoxia, cell migration behavior, and doxorubicin chemoresistance	Prolonged hypoxic exposure (20 and 40 episodes) induces distinct gene alterations and sanctions doxorubicin resistance. Genes *HIF1AN*, *HMOX-1*, and *PKM* were significantly up-regulated and may serve as promising hypoxia biomarkers.	[99]
100	MCF-7 human breast cancer cell lines	MCF-7 human breast cancer cell lines	In vitro experimental study using RT-PCR arrays, transwell migration assays, and Western blotting	Amman, Jordan & Rochester, Minnesota, USA	Genetic expression alterations and cellular migration capabilities following short-term vs. chronic/acute long-term hypoxia	*HNF4A* expression significantly increased by 32.71-fold and 14.95-fold after 12 continuous and 60 intermittent hypoxic episodes, respectively. Cell migration capacity increased, establishing *HNF4A* as a highly viable biomarker for chronic tumor hypoxia.	[100]
101	N/A (In vitro, in vivo, and clinical studies reviewed)	N/A (Literature review)	Literature Review	Amman, Jordan & Abu Dhabi, UAE	Tumor microenvironment (TME) targets of resveratrol and the pharmacological mechanisms manipulating these cellular components	Resveratrol efficiently coordinates and disrupts TME components by suppressing reactive oxygen species (ROS), tumor-associated macrophages, VEGF, fibrosis, and Interleukin-6 (IL-6). It is a promising prophylactic and anti-cancer treatment.	[101]

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102	Cancer patients	Not reported	Literature review	Italy	Synthetic lethality, precision oncology	Proposes AI-driven integration of multi-omics and drug repurposing to tackle tumor heterogeneity.	[102]
103	Cancer patients	Not reported	Literature review	Ethiopia	Biomarker detection, targeted therapy specificity	Emphasizes personalized medicine using biomarkers for precise treatment	[103]

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References

1. Kumar, M. Targeting Cancer Cell Signaling Using Precision Oncology Towards a Holistic Approach to Cancer Therapeutics 2023.
2. Capuozzo, M.; Santorsola, M.; Landi, L.; Granata, V.; Perri, F.; Celotto, V.; Gualillo, O.; Nasti, G.; Ottaiano, A. Evolution of Treatment in Advanced Cholangiocarcinoma: Old and New towards Precision Oncology. *Int. J. Mol. Sci.* **2022**, *23*, 15124, doi:10.3390/ijms232315124.
3. Talib, W.H.; Alsayed, A.R.; Barakat, M.; Abu-Taha, M.I.; Mahmod, A.I. Targeting Drug Chemo-Resistance in Cancer Using Natural Products. *Biomedicines* **2021**, *9*, 1353, doi:10.3390/biomedicines9101353.
4. Cerella, C.; Lorant, A.; Aquilano, K.; Diederich, M. Editorial: Next-Generation Cancer Therapies Based on a (R)Evolution of the Biomarker Landscape. *Front. Pharmacol.* **2022**, *13*, 861424, doi:10.3389/fphar.2022.861424.
5. Carpten, J.C.; Mardis, E.R. The Era of Precision Oncogenomics. *Mol. Case Stud.* **2018**, *4*, a002915, doi:10.1101/mcs.a002915.
6. Song, I.-W.; Vo, H.H.; Chen, Y.-S.; Baysal, M.A.; Kahle, M.; Johnson, A.; Tsimberidou, A.M. Precision Oncology: Evolving Clinical Trials across Tumor Types. *Cancers* **2023**, *15*, 1967, doi:10.3390/cancers15071967.
7. Bode, A.M.; Dong, Z. Recent Advances in Precision Oncology Research. *Npj Precis. Oncol.* **2018**, *2*, 11, s41698-018-0055–0, doi:10.1038/s41698-018-0055-0.
8. Park, H.; Dahlberg, S.E.; Lydon, C.A.; Araki, T.; Hatabu, H.; Rabin, M.S.; Johnson, B.E.; Nishino, M. M1b Disease in the 8th Edition of TNM Staging of Lung Cancer: Pattern of Single Extrathoracic Metastasis and Clinical Outcome. *The Oncologist* **2019**, *24*, e749–e754, doi:10.1634/theoncologist.2018-0596.
9. Puppa, G.; Sonzogni, A.; Colombari, R.; Pelosi, G. TNM Staging System of Colorectal Carcinoma: A Critical Appraisal of Challenging Issues. *Arch. Pathol. Lab. Med.* **2010**, *134*, 837–852, doi:10.5858/134.6.837.
10. Jin, X.; Liu, C.; Xu, T.; Su, L.; Zhang, X. Artificial Intelligence Biosensors: Challenges and Prospects. *Biosens. Bioelectron.* **2020**, *165*, 112412, doi:10.1016/j.bios.2020.112412.
11. Liu, R.; Song, H.; Wu, H.; Yang, Z.; Fang, S.; Zhu, J.; Ba, L. Sub-Femtomolar Vertical Graphene Field Effect Immunosensor for Detection of Lung Tumor Markers. *Talanta* **2024**, *278*, 126498, doi:10.1016/j.talanta.2024.126498.
12. Guibert, N.; Pradines, A.; Favre, G.; Mazieres, J. Current and Future Applications of Liquid Biopsy in Nonsmall Cell Lung Cancer from Early to Advanced Stages. *Eur. Respir. Rev.* **2020**, *29*, doi:10.1183/16000617.0052-2019.
13. Gattuso, G.; Crimi, S.; Lavoro, A.; Rizzo, R.; Musumarra, G.; Gallo, S.; Facciponte, F.; Paratore, S.; Russo, A.; Bordonaro, R.; et al. Liquid Biopsy and Circulating Biomarkers for the Diagnosis of Precancerous and Cancerous Oral Lesions. *Non-Coding RNA* **2022**, *8*, 60, doi:10.3390/ncrna8040060.
14. Hitchen, N.; Shahnam, A.; Tie, J. Circulating Tumor DNA: A Pan-Cancer Biomarker in Solid Tumors with Prognostic and Predictive Value. *Annu. Rev. Med.* **2025**, *76*, 207–223, doi:10.1146/annurev-med-100223-090016.
15. Henriksen, T.V.; Tarazona, N.; Frydendahl, A.; Reinert, T.; Gimeno-Valiente, F.; Carbonell-Asins, J.A.; Sharma, S.; Renner, D.; Hafez, D.; Roda, D.; et al. Circulating Tumor DNA in Stage III Colorectal Cancer, beyond Minimal Residual Disease Detection, toward Assessment of Adjuvant Therapy Efficacy and Clinical Behavior of Recurrences. *Clin. Cancer Res. Off. J. Am. Assoc. Cancer Res.* **2022**, *28*, 507–517, doi:10.1158/1078-0432.CCR-21-2404.
16. Ococks, E.; Sharma, S.; Ng, A.W.T.; Aleshin, A.; Fitzgerald, R.C.; Smyth, E. Serial Circulating Tumor DNA Detection Using a Personalized, Tumor-Informed Assay in Esophageal Adenocarcinoma Patients Following Resection. *Gastroenterology* **2021**, *161*, 1705-1708.e2, doi:10.1053/j.gastro.2021.07.011.
17. Fu, L.; Zhou, X.; Zhang, X.; Li, X.; Zhang, F.; Gu, H.; Wang, X. Circulating Tumor DNA in Lymphoma: Technologies and Applications. *J. Hematol. Oncol.J Hematol Oncol* **2025**, *18*, 29, doi:10.1186/s13045-025-01673-7.

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18. Dai, C.S.; Mishra, A.; Edd, J.; Toner, M.; Maheswaran, S.; Haber, D.A. Circulating Tumor Cells: Blood-Based Detection, Molecular Biology, and Clinical Applications. *Cancer Cell* **2025**, *43*, 1399–1422, doi:10.1016/j.ccell.2025.07.008.
19. Li, L.; Lan, Z.; Qiao, H.; Meng, X.; Shi, Z.; Zhang, W.; Wang, Y.; Sun, Z.; Cui, Q.; Wang, L.; et al. Design of NanoBiT-Nanobody-Based FGL1 Biosensors for Early Assisted Diagnosis of Esophageal Cancer. *Biomaterials* **2025**, *320*, 123286, doi:10.1016/j.biomaterials.2025.123286.
20. Davoudian, K.; Spagnolo, S.; Chan, E.; Hianik, T.; Thompson, M. Acoustic Wave Sensor Detection of an Ovarian Cancer Biomarker with Antifouling Surface Chemistry. *Sensors* **2024**, *24*, 7884, doi:10.3390/s24247884.
21. Erkal-Aytemur, A.; Mülazımoğlu, İ.E.; Üstündağ, Z.; Caglayan, M.O. A Novel Aptasensor Platform for the Detection of Carcinoembryonic Antigen Using Quartz Crystal Microbalance. *Talanta* **2024**, *277*, 126376, doi:10.1016/j.talanta.2024.126376.
22. Luo, X.; Yan, S.; Chen, G.; Wang, Y.; Zhang, X.; Lan, J.; Chen, J.; Yao, X. A Cavity Induced Mode Hybridization Plasmonic Sensor for Portable Detection of Exosomes. *Biosens. Bioelectron.* **2024**, *261*, 116492, doi:10.1016/j.bios.2024.116492.
23. Bista, R.; Lee, D.W.; Pepper, O.B.; Azorsa, D.O.; Arceci, R.J.; Aleem, E. Disulfiram Overcomes Bortezomib and Cytarabine Resistance in Down-Syndrome-Associated Acute Myeloid Leukemia Cells. *J. Exp. Clin. Cancer Res.* **2017**, *36*, 22, doi:10.1186/s13046-017-0493-5.
24. Konstantinopoulos, P.A.; Cheng, S.-C.; Wahner Hendrickson, A.E.; Penson, R.T.; Schumer, S.T.; Doyle, L.A.; Lee, E.K.; Kohn, E.C.; Duska, L.R.; Crispens, M.A.; et al. Berzosertib plus Gemcitabine versus Gemcitabine Alone in Platinum-Resistant High-Grade Serous Ovarian Cancer: A Multicentre, Open-Label, Randomised, Phase 2 Trial. *Lancet Oncol.* **2020**, *21*, 957–968, doi:10.1016/S1470-2045(20)30180-7.
25. Li, L.; Zheng, Y.; Yang, Y.; Shi, S.; Liu, S.; Huang, K.; Qiu, L.; Zhang, R.; Huang, W.; Leng, Y. Dehydrodiisoeugenol Targets the PLK1-P53 Axis to Inhibit Breast Cancer Cell Cycle. *Front. Pharmacol.* **2025**, *16*, 1545498, doi:10.3389/fphar.2025.1545498.
26. Yuan, B.; Liu, Y.; Yu, X.; Yin, L.; Peng, Y.; Gao, Y.; Zhu, Q.; Cao, T.; Yang, Y.; Fan, X.; et al. FOXM1 Contributes to Taxane Resistance by Regulating UHRF1-Controlled Cancer Cell Stemness. *Cell Death Dis.* **2018**, *9*, 562, doi:10.1038/s41419-018-0631-9.
27. Wang, H.; Zhang, N.; Sun, Q.; Zhao, Z.; Pang, H.; Huang, X.; Zhang, R.; Kang, W.; Shan, M. Comparison of the Efficacy of Taxanes with Carboplatin and Anthracyclines with Taxanes in Neoadjuvant Chemotherapy for Stage II–III Triple Negative Breast Cancer: A Retrospective Analysis. *J. Cancer Res. Clin. Oncol.* **2024**, *150*, 291, doi:10.1007/s00432-024-05738-x.
28. Hoogstraat, M.; Lips, E.H.; Mayayo-Peralta, I.; Mulder, L.; Kristel, P.; Van Der Heijden, I.; Annunziato, S.; Van Seijen, M.; Nederlof, P.M.; Sonke, G.S.; et al. Comprehensive Characterization of Pre- and Post-Treatment Samples of Breast Cancer Reveal Potential Mechanisms of Chemotherapy Resistance. *Npj Breast Cancer* **2022**, *8*, 60, doi:10.1038/s41523-022-00428-8.
29. Vliek, S.; Hilbers, F.S.; Van Werkhoven, E.; Mandjes, I.; Kessels, R.; Kleiterp, S.; Lips, E.H.; Mulder, L.; Kayembe, M.T.; Loo, C.E.; et al. High-Dose Alkylating Chemotherapy in BRCA-Altered Triple-Negative Breast Cancer: The Randomized Phase III NeoTN Trial. *Npj Breast Cancer* **2023**, *9*, 75, doi:10.1038/s41523-023-00580-9.
30. Vengoji, R.; Atri, P.; Macha, M.A.; Seshacharyulu, P.; Perumal, N.; Mallya, K.; Liu, Y.; Smith, L.M.; Rachagani, S.; Mahapatra, S.; et al. Differential Gene Expression-Based Connectivity Mapping Identified Novel Drug Candidate and Improved Temozolomide Efficacy for Glioblastoma. *J. Exp. Clin. Cancer Res.* **2021**, *40*, 335, doi:10.1186/s13046-021-02135-x.
31. Haferkamp, S.; Schilling, B.; Berking, C.; Drexler, K.; Gesierich, A.; Tomsitz, D.; Erdmann, M.; Jakob, L.; Geissler, E.K.; Zeman, F.; et al. Breaking Primary Checkpoint Inhibitor Resistance with Intermittent Alkylating Chemotherapy in Patients with Metastatic Melanoma: Results of a Multicentre Phase II Trial.
32. Wang, W.; Zhao, M.; Cui, L.; Ren, Y.; Zhang, J.; Chen, J.; Jia, L.; Zhang, J.; Yang, J.; Chen, G.; et al. Characterization of a Novel HDAC/RXR/HtrA1 Signaling Axis as a Novel Target to Overcome Cisplatin Resistance in Human Non-Small Cell Lung Cancer. *Mol. Cancer* **2020**, *19*, 134, doi:10.1186/s12943-020-01256-9.

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33. Galvez, L.; Rusz, M.; Schwaiger-Haber, M.; El Abiead, Y.; Hermann, G.; Jungwirth, U.; Berger, W.; Keppler, B.K.; Jakupec, M.A.; Koellensperger, G. Preclinical Studies on Metal Based Anticancer Drugs as Enabled by Integrated Metallomics and Metabolomics. *Metallomics* **2019**, *11*, 1716–1728, doi:10.1039/c9mt00141g.
34. Gupta, S.; Nair, N.; Hawaldar, R.W.; Joshi, S.; Gulia, S.; Shet, T.; Sarin, R.; Parmar, V.; Desai, S.; Ghosh, J.; et al. Addition of Carboplatin to Sequential Taxane-Anthracycline Neoadjuvant Chemotherapy in Triple-Negative Breast Cancer: A Phase III Randomized Controlled Trial. *J. Clin. Oncol.* **2026**, *44*, 9–19, doi:10.1200/JCO-25-01023.
35. Wang, C.; Yuan, L.; Wu, X.; Wang, Y.; Tian, H.; Zhang, G.; Wan, A.; Xiong, S.; Wang, C.; Zhou, Y.; et al. Taxane Combined with Lobaplatin or Anthracycline for Neoadjuvant Chemotherapy of Triple-Negative Breast Cancer: A Randomized, Controlled, Phase II Study. *BMC Med.* **2024**, *22*, 252, doi:10.1186/s12916-024-03474-0.
36. Mendrina, T.; Poetsch, I.; Schueffl, H.; Baier, D.; Pirker, C.; Ries, A.; Keppler, B.K.; Kowol, C.R.; Gibson, D.; Grusch, M.; et al. Influence of the Fatty Acid Metabolism on the Mode of Action of a Cisplatin(IV) Complex with Phenylbutyrate as Axial Ligands. *Pharmaceutics* **2023**, *15*, 677, doi:10.3390/pharmaceutics15020677.
37. Joung, E.K.; Yang, J.H.; Oh, S.; Park, S.J.; Lee, J. Maintenance Chemotherapy after 6 Cycles of Platinum-Doublet Regimen in Anthracycline-and Taxane-Pretreated Metastatic Breast Cancer. *Korean J. Intern. Med.* **2021**, *36*, 182–193, doi:10.3904/kjim.2019.129.
38. Malfatti, M.C.; Gerratana, L.; Dalla, E.; Isola, M.; Damante, G.; Di Loreto, C.; Puglisi, F.; Tell, G. APE1 and NPM1 Protect Cancer Cells from Platinum Compounds Cytotoxicity and Their Expression Pattern Has a Prognostic Value in TNBC. *J. Exp. Clin. Cancer Res.* **2019**, *38*, 309, doi:10.1186/s13046-019-1294-9.
39. Rogalska, A.; Gajek, A.; Łukawska, M.; Oszczapowicz, I.; Marczak, A. Novel Oxazolinoanthracyclines as Tumor Cell Growth Inhibitors—Contribution of Autophagy and Apoptosis in Solid Tumor Cells Death. *PLOS ONE* **2018**, *13*, e0201296, doi:10.1371/journal.pone.0201296.
40. Jamrozik, M.; Piska, K.; Bucki, A.; Koczurkiewicz-Adamczyk, P.; Sapa, M.; Władyka, B.; Pękala, E.; Kołaczkowski, M. In Silico and In Vitro Assessment of Carbonyl Reductase 1 Inhibition Using ASP9521—A Potent Aldo-Keto Reductase 1C3 Inhibitor with the Potential to Support Anticancer Therapy Using Anthracycline Antibiotics. *Molecules* **2023**, *28*, 3767, doi:10.3390/molecules28093767.
41. Choulli, F.; Tafenzi, H.A.; Hattimy, F.E.; Choulli, M.K.; Belbaraka, R. Chemotherapy-Related Adverse Effects with Anthracycline and Taxane-Containing Regimens in Patients with Localized Breast Cancer: A Descriptive Study: Mohammed VI University Hospital, Medical Oncology Department, Marrakech, Morocco. *BMC Cancer* **2024**, *24*, 17, doi:10.1186/s12885-023-11616-5.
42. Sharma, P.; Kimler, B.F.; O'Dea, A.; Nye, L.; Wang, Y.Y.; Yoder, R.; Staley, J.M.; Prochaska, L.; Wagner, J.; Amin, A.L.; et al. Randomized Phase II Trial of Anthracycline-Free and Anthracycline-Containing Neoadjuvant Carboplatin Chemotherapy Regimens in Stage I–III Triple-Negative Breast Cancer (NeoSTOP). *Clin. Cancer Res.* **2021**, *27*, 975–982, doi:10.1158/1078-0432.CCR-20-3646.
43. Mittendorf, E.A.; Zhang, H.; Barrios, C.H.; Saji, S.; Jung, K.H.; Hegg, R.; Koehler, A.; Sohn, J.; Iwata, H.; Telli, M.L.; et al. Neoadjuvant Atezolizumab in Combination with Sequential Nab-Paclitaxel and Anthracycline-Based Chemotherapy versus Placebo and Chemotherapy in Patients with Early-Stage Triple-Negative Breast Cancer (IMpassion031): A Randomised, Double-Blind, Phase 3 Trial. *The Lancet* **2020**, *396*, 1090–1100, doi:10.1016/S0140-6736(20)31953-X.
44. Chen, Z.; Zheng, Y.; Shi, Y.; Cui, Z. Overcoming Tumor Cell Chemoresistance Using Nanoparticles: Lysosomes Are Beneficial for (Stearoyl) Gemcitabine-Incorporated Solid Lipid Nanoparticles. *Int. J. Nanomedicine* **2018**, *Volume 13*, 319–336, doi:10.2147/IJN.S149196.
45. Hansen, S.N.; Ehlers, N.S.; Zhu, S.; Thomsen, M.B.H.; Nielsen, R.L.; Liu, D.; Wang, G.; Hou, Y.; Zhang, X.; Xu, X.; et al. The Stepwise Evolution of the Exome during Acquisition of Docetaxel Resistance in Breast Cancer Cells. *BMC Genomics* **2016**, *17*, 442, doi:10.1186/s12864-016-2749-4.
46. Salaroglio, I.C.; Gazzano, E.; Abdullrahman, A.; Mungo, E.; Castella, B.; Abd-elrahman, G.E.F.A.; Massaia, M.; Donadelli, M.; Rubinstein, M.; Riganti, C.; et al. Increasing Intratumor C/EBP-β LIP and Nitric Oxide Levels Overcome Resistance to Doxorubicin in Triple Negative Breast Cancer. *J. Exp. Clin. Cancer Res.* **2018**, *37*, 286, doi:10.1186/s13046-018-0967-0.

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Preprints.org | NOT PEER-REVIEWED | Posted: 12 November 2026 https://doi.org/10.20944/preprints202611.1294.v1

47. Van Eijk, M.; Boosman, R.J.; Schinkel, A.H.; Huitema, A.D.R.; Beijnen, J.H. Cytochrome P450 3A4, 3A5, and 2C8 Expression in Breast, Prostate, Lung, Endometrial, and Ovarian Tumors: Relevance for Resistance to Taxanes. *Cancer Chemother. Pharmacol.* **2019**, *84*, 487–499, doi:10.1007/s00280-019-03905-3.
48. Wang, X.; Xiong, T.; Cui, M.; Li, N.; Li, Q.; Zhu, L.; Duan, S.; Wang, Y.; Guo, Y. A Novel Targeted Co-Delivery Nanosystem for Enhanced Ovarian Cancer Treatment via Multidrug Resistance Reversion and mTOR-Mediated Signaling Pathway. *J. Nanobiotechnology* **2021**, *19*, 444, doi:10.1186/s12951-021-01139-1.
49. Liu, D.; Abbosh, P.; Keliher, D.; Reardon, B.; Miao, D.; Mouw, K.; Weiner-Taylor, A.; Wankowicz, S.; Han, G.; Teo, M.Y.; et al. Mutational Patterns in Chemotherapy Resistant Muscle-Invasive Bladder Cancer. *Nat. Commun.* **2017**, *8*, 2193, doi:10.1038/s41467-017-02320-7.
50. Wang, J.; Kho, D.H.; Zhou, J.-Y.; Davis, R.J.; Wu, G.S. MKP-1 Suppresses PARP-1 Degradation to Mediate Cisplatin Resistance. *Oncogene* **2017**, *36*, 5939–5947, doi:10.1038/onc.2017.197.
51. Cao, Y.; Wang, S.; Ma, J.; Long, M.; Ma, X.; Yang, X.; Ji, Y.; Tang, X.; Liu, J.; Lin, C.; et al. Mechanistic Insights into SIRT7 and EZH2 Regulation of Cisplatin Resistance in Bladder Cancer Cells. *Cell Death Dis.* **2024**, *15*, 931, doi:10.1038/s41419-024-07321-1.
52. Ríos-Colón, L.; Cajigas-Du Ross, C.K.; Basu, A.; Elix, C.; Alicea-Polanco, I.; Sanchez, T.W.; Radhakrishnan, V.; Chen, C.-S.; Casiano, C.A. Targeting the Stress Oncoprotein LEDGF/P75 to Sensitize Chemoresistant Prostate Cancer Cells to Taxanes. *Oncotarget* **2017**, *8*, 24915–24931, doi:10.18632/oncotarget.15323.
53. Liang, Y.; Yu, D.; Perez-Soler, R.; Klostergaard, J.; Zou, Y. TRIB2 Contributes to Cisplatin Resistance in Small Cell Lung Cancer. *Oncotarget* **2017**, *8*, 109596–109608, doi:10.18632/oncotarget.22741.
54. Muñoz-Galván, S.; Felipe-Abrio, B.; Verdugo-Sivianes, E.M.; Perez, M.; Jiménez-García, M.P.; Suarez-Martinez, E.; Estevez-Garcia, P.; Carnero, A. Downregulation of MYPT1 Increases Tumor Resistance in Ovarian Cancer by Targeting the Hippo Pathway and Increasing the Stemness. *Mol. Cancer* **2020**, *19*, 7, doi:10.1186/s12943-020-1130-z.
55. Criscuolo, D.; Avolio, R.; Parri, M.; Romano, S.; Chiarugi, P.; Matassa, D.S.; Esposito, F. Decreased Levels of GSH Are Associated with Platinum Resistance in High-Grade Serous Ovarian Cancer. *Antioxidants* **2022**, *11*, 1544, doi:10.3390/antiox11081544.
56. Wen, Z.; Zeng, W.; Chen, Y.; Li, H.; Wang, J.; Cheng, Q.; Yu, J.; Zhou, H.; Liu, Z.; Xiao, J.; et al. Knockdown ATG4C Inhibits Gliomas Progression and Promotes Temozolomide Chemosensitivity by Suppressing Autophagic Flux. *J. Exp. Clin. Cancer Res.* **2019**, *38*, 298, doi:10.1186/s13046-019-1287-8.
57. Wu, J.; Chen, S.; Liu, H.; Zhang, Z.; Ni, Z.; Chen, J.; Yang, Z.; Nie, Y.; Fan, D. Tunicamycin Specifically Aggravates ER Stress and Overcomes Chemoresistance in Multidrug-Resistant Gastric Cancer Cells by Inhibiting N-Glycosylation. *J. Exp. Clin. Cancer Res.* **2018**, *37*, 272, doi:10.1186/s13046-018-0935-8.
58. Zhang, H.; Yan, T.; Zhong, A.; Guo, L.; Lu, R. COPS5 Conferred the Platinum Resistance in Epithelial Ovarian Cancer. *Curr. Issues Mol. Biol.* **2022**, *44*, 3948–3958, doi:10.3390/cimb44090271.
59. Fekete, J.T.; Ősz, Á.; Pete, I.; Nagy, G.R.; Vereczkey, I.; Győrffy, B. Predictive Biomarkers of Platinum and Taxane Resistance Using the Transcriptomic Data of 1816 Ovarian Cancer Patients. *Gynecol. Oncol.* **2020**, *156*, 654–661, doi:10.1016/j.ygyno.2020.01.006.
60. Thompson, J.S.; Madrid, L.; Hernando, B.; Sauer, C.M.; Vias, M.; Escobar-Rey, M.; Leung, W.-K.; Garcia-Lopez, D.; Huckstep, J.; Sekowska, M.; et al. Predicting Resistance to Chemotherapy Using Chromosomal Instability Signatures. *Nat. Genet.* **2025**, *57*, 1708–1717, doi:10.1038/s41588-025-02233-y.
61. Yun, W.; Li, Y.; Ge, Y.; Zhang, X.; Liu, H.; Chen, W.; Xiao, L. Tumor Organoids May Be More Suitable for Clinical Personalized Chemotherapeutic Drug Screening in Lung Adenocarcinoma. *Front. Cell Dev. Biol.* **2025**, *13*, 1639922, doi:10.3389/fcell.2025.1639922.
62. Zhang, Y.; Li, Y.; Sun, C.; Chen, X.; Han, L.; Wang, T.; Liu, J.; Chen, X.; Zhao, D. Effect of Pterostilbene, a Natural Derivative of Resveratrol, in the Treatment of Colorectal Cancer through Top1/Tdp1-Mediated DNA Repair Pathway. *Cancers* **2021**, *13*, 4002, doi:10.3390/cancers13164002.
63. Abdullah, A.; Akhand, S.S.; Paez, J.S.P.; Brown, W.; Pan, L.; Libring, S.; Badamy, M.; Dykuizen, E.; Solorio, L.; Andy Tao, W.; et al. Epigenetic Targeting of Neuropilin-1 Prevents Bypass Signaling in Drug-Resistant Breast Cancer. *Oncogene* **2021**, *40*, 322–333, doi:10.1038/s41388-020-01530-6.

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Preprints.org | NOT PEER-REVIEWED | Posted: 12 November 2026 https://doi.org/10.20944/preprints202611.1294.v1

64. Du, H.; Wu, H.; Kang, Q.; Liao, M.; Qin, M.; Chen, N.; Huang, H.; Huang, D.; Wang, P.; Tong, G. Polyphyllin I Attenuates the Invasion and Metastasis via Downregulating GRP78 in Drug-Resistant Hepatocellular Carcinoma Cells. *Aging* **2023**, *15*, 12251–12263, doi:10.18632/aging.205176.
65. Ali, R.; Alblihy, A.; Miligy, I.M.; Alabdullah, M.L.; Alsaleem, M.; Toss, M.S.; Algethami, M.; Abdel-Fatah, T.; Moseley, P.; Chan, S.; et al. Molecular Disruption of DNA Polymerase β for Platinum Sensitisation and Synthetic Lethality in Epithelial Ovarian Cancers. *Oncogene* **2021**, *40*, 2496–2508, doi:10.1038/s41388-021-01710-y.
66. Jin, H.; Yang, Y.; Yan, C.; Liu, M.; He, X.; Yuan, D.; Zhang, W.; Mu, Y.; Wu, C.; Liu, X.; et al. The Landscape of Dynamic Tumor Immunophenotyping on Neoadjuvant Chemotherapy Combined with Trastuzumab for the Treatment of HER2-Positive Breast Cancer. *Mol. Cancer* **2025**, *24*, 287, doi:10.1186/s12943-025-02483-8.
67. Haikala, H.M.; Lopez, T.; Köhler, J.; Eser, P.O.; Xu, M.; Zeng, Q.; Teceno, T.J.; Ngo, K.; Zhao, Y.; Ivanova, E.V.; et al. EGFR Inhibition Enhances the Cellular Uptake and Antitumor-Activity of the HER3 Antibody–Drug Conjugate HER3–DXd. *Cancer Res.* **2022**, *82*, 130–141, doi:10.1158/0008-5472.CAN-21-2426.
68. Li, Y.-R.; Shen, X.; Zhu, Y.; Li, Z.; Hon, R.; Tian, Y.; Huang, J.; Zhao, A.S.; Ma, N.Y.; Zhang, C.; et al. Targeting Triple-Negative Breast Cancer Using Cord-Blood CD34+ HSPC-Derived Mesothelin-Specific CAR-NKT Cells with Potent Antitumor Activity. *J. Hematol. Oncol.J Hematol Oncol* **2025**, *18*, 86, doi:10.1186/s13045-025-01736-9.
69. Lin, Y.; Chen, Z.; Zhao, S.; Zhao, L.; Yang, C.; Zhu, M.; Ye, Y.; Wang, S.; Shen, Z. Targeting *SPP1*+ TAMs Associated with Liver Metastasis Reverses Immunosuppression and Synergizes with Immunotherapy in Colorectal Cancer. *J. Immunother. Cancer* **2026**, *14*, e014128, doi:10.1136/jitc-2025-014128.
70. Carlino, M.S.; Gao, B.; Michael, M.; Marshall, H.; Gunjur, A.; Chan, H.; Zielinski, R.; So, J.; Harris, S.J.; Kee, D.; et al. Nivolumab and Ipilimumab in Advanced Mismatch Repair–Deficient/Microsatellite Instability–High Noncolorectal Cancers: A Nonrandomized Clinical Trial. *JAMA Oncol.* **2026**, *12*, 39, doi:10.1001/jamaoncol.2025.4721.
71. Chae, Y.K.; Othus, M.; Patel, S.; Powers, B.; Hsueh, C.-T.; Govindarajan, R.; Bucur, S.; Kim, H.S.; Chung, L.I.-Y.; McLeod, C.; et al. Phase II Basket Trial of Dual Anti-CTLA-4 and Anti-PD-1 Blockade in Rare Tumors (DART) SWOG S1609: The Desmoid Tumors. *J. Immunother. Cancer* **2024**, *12*, e009128, doi:10.1136/jitc-2024-009128.
72. Chae, Y.K.; Othus, M.; Patel, S.P.; Backes, F.J.; O'Malley, D.M.; Cristea, M.; Naing, A.; Kurnit, K.; Eskander, R.N.; T Goodrich, S.; et al. DART/SWOG/NCI Phase II Anti-CTLA-4/PD-1 Trial: Clear Cell Carcinomas of Ovary, Endometrium, Cervix. *J. Immunother. Cancer* **2026**, *14*, e012805, doi:10.1136/jitc-2025-012805.
73. Patel, S.P.; Fisher, J.; Chae, Y.K.; Soto, L.S.; Kasi, A.; Konda, B.; Walshauser, M.; Parra, E.; Zhang, J.; Duault, C.; et al. Phase II Basket Trial of Dual Anti-CTLA-4 and Anti-PD-1 Blockade in Rare Tumors (DART) SWOG S1609: Pancreatic Neuroendocrine Neoplasm (PNEN) Cohort. *J. Immunother. Cancer* **2025**, *13*, e011760, doi:10.1136/jitc-2025-011760.
74. Breukers, S.E.; Traets, J.J.H.; Van Dijk, S.W.; Ostos, M.M.; Fraterman, I.; Crommelin, R.D.; Van Der Hulst, H.; Qiao, X.; Boere, T.; Van De Poll-Franse, L.V.; et al. Neoadjuvant Ipilimumab and Nivolumab in Resectable Cutaneous Squamous Cell Carcinoma: A Randomized Phase 2 Trial. *Nat. Med.* **2025**, *31*, 4055–4064, doi:10.1038/s41591-025-03943-w.
75. Choueiri, T.K.; Kluger, H.; George, S.; Tykodi, S.S.; Kuzel, T.M.; Perets, R.; Nair, S.; Procopio, G.; Carducci, M.A.; Castonguay, V.; et al. FRACTION-RCC: Nivolumab plus Ipilimumab for Advanced Renal Cell Carcinoma after Progression on Immuno-Oncology Therapy. *J. Immunother. Cancer* **2022**, *10*, e005780, doi:10.1136/jitc-2022-005780.
76. Tchou, J.; Zhao, Y.; Levine, B.L.; Zhang, P.J.; Davis, M.M.; Melenhorst, J.J.; Kulikovskaya, I.; Brennan, A.L.; Liu, X.; Lacey, S.F.; et al. Safety and Efficacy of Intratumoral Injections of Chimeric Antigen Receptor (CAR) T Cells in Metastatic Breast Cancer. *Cancer Immunol. Res.* **2017**, *5*, 1152–1161, doi:10.1158/2326-6066.CIR-17-0189.
77. Hege, K.M.; Bergsland, E.K.; Fisher, G.A.; Nemunaitis, J.J.; Warren, R.S.; McArthur, J.G.; Lin, A.A.; Schlom, J.; June, C.H.; Sherwin, S.A. Safety, Tumor Trafficking and Immunogenicity of Chimeric Antigen Receptor

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Preprints.org | NOT PEER-REVIEWED | Posted: 12 November 2026 https://doi.org/10.20944/preprints202611.1294.v1

(CAR)-T Cells Specific for TAG-72 in Colorectal Cancer. *J. Immunother. Cancer* **2017**, *5*, 22, doi:10.1186/s40425-017-0222-9.

78. Thistlethwaite, F.C.; Gilham, D.E.; Guest, R.D.; Rothwell, D.G.; Pillai, M.; Burt, D.J.; Byatte, A.J.; Kirillova, N.; Valle, J.W.; Sharma, S.K.; et al. The Clinical Efficacy of First-Generation Carcinoembryonic Antigen (CEACAM5)-Specific CAR T Cells Is Limited by Poor Persistence and Transient Pre-Conditioning-Dependent Respiratory Toxicity. *Cancer Immunol. Immunother.* **2017**, *66*, 1425–1436, doi:10.1007/s00262-017-2034-7.
79. Chen, N.; Pu, C.; Zhao, L.; Li, W.; Wang, C.; Zhu, R.; Liang, T.; Niu, C.; Huang, X.; Tang, H.; et al. Chimeric Antigen Receptor T Cells Targeting CD19 and GCC in Metastatic Colorectal Cancer: A Nonrandomized Clinical Trial. *JAMA Oncol.* **2024**, *10*, 1532, doi:10.1001/jamaoncol.2024.3891.
80. Narayan, V.; Barber-Rotenberg, J.S.; Jung, I.-Y.; Lacey, S.F.; Rech, A.J.; Davis, M.M.; Hwang, W.-T.; Lal, P.; Carpenter, E.L.; Maude, S.L.; et al. PSMA-Targeting TGFβ-Insensitive Armored CAR T Cells in Metastatic Castration-Resistant Prostate Cancer: A Phase 1 Trial. *Nat. Med.* **2022**, *28*, 724–734, doi:10.1038/s41591-022-01726-1.
81. Van 'T Land, F.R.; Willemsen, M.; Bezemer, K.; Van Der Burg, S.H.; Van Den Bosch, T.P.P.; Doukas, M.; Fellah, A.; Kolijn, P.M.; Langerak, A.W.; Moskie, M.; et al. Dendritic Cell–Based Immunotherapy in Patients With Resected Pancreatic Cancer. *J. Clin. Oncol.* **2024**, *42*, 3083–3093, doi:10.1200/JCO.23.02585.
82. Storkus, W.J.; Maurer, D.; Lin, Y.; Ding, F.; Bose, A.; Lowe, D.; Rose, A.; DeMark, M.; Karapetyan, L.; Taylor, J.L.; et al. Dendritic Cell Vaccines Targeting Tumor Blood Vessel Antigens in Combination with Dasatinib Induce Therapeutic Immune Responses in Patients with Checkpoint-Refractory Advanced Melanoma. *J. Immunother. Cancer* **2021**, *9*, e003675, doi:10.1136/jitc-2021-003675.
83. Bai, X.; Zhou, Y.; Yokota, Y.; Matsumoto, Y.; Zhai, B.; Maarouf, N.; Hayashi, H.; Carlson, R.; Zhang, S.; Sousa, A.; et al. Adaptive Antitumor Immune Response Stimulated by Bio-Nanoparticle Based Vaccine and Checkpoint Blockade. *J. Exp. Clin. Cancer Res.* **2022**, *41*, 132, doi:10.1186/s13046-022-02307-3.
84. Autio, K.A.; Higano, C.S.; Nordquist, L.; Appleman, L.J.; Zhang, T.; Zhu, X.-H.; Babiker, H.; Vogelzang, N.J.; Prasad, S.M.; Schweizer, M.T.; et al. First-in-Human, Phase 1 Study of PF-06753512, a Vaccine-Based Immunotherapy Regimen (VBIR), in Non-Metastatic Hormone-Sensitive Biochemical Recurrence and Metastatic Castration-Resistant Prostate Cancer (mCRPC). *J. Immunother. Cancer* **2023**, *11*, e005702, doi:10.1136/jitc-2022-005702.
85. Zihlif, M.; Tanina, N.; Batah, A.; Tawaha, K.; Qudsi, S.; Hasoun, L.; Alsayed, A. The Medicinal Plants Effects on the Gene Expression of Cytochrome P450 and P-Glycoprotein in Cultured Colon and Breast Cancer Cell Line. *Pharm. Pract.* **2024**, *22*, 1–7, doi:10.18549/PharmPract.2024.2.2931.
86. Wermke, M.; Araujo, D.M.; Chatterjee, M.; Tsimberidou, A.M.; Holderried, T.A.W.; Jazaeri, A.A.; Reshef, R.; Bokemeyer, C.; Alsdorf, W.; Wetzko, K.; et al. Autologous T Cell Therapy for PRAME+ Advanced Solid Tumors in HLA-A*02+ Patients: A Phase 1 Trial. *Nat. Med.* **2025**, *31*, 2365–2374, doi:10.1038/s41591-025-03650-6.
87. Naghizadeh, A.; Tsao, W.; Hyun Cho, J.; Xu, H.; Mohamed, M.; Li, D.; Xiong, W.; Metaxas, D.; Ramos, C.A.; Liu, D. In Vitro Machine Learning-Based CAR T Immunological Synapse Quality Measurements Correlate with Patient Clinical Outcomes. *PLOS Comput. Biol.* **2022**, *18*, e1009883, doi:10.1371/journal.pcbi.1009883.
88. Alsayed, A.R.; Al-Darraji, M.; Al-Qaiseiah, M.; Samara, A.; Al-Bayati, M. Machine Learning in Personalized Medication Regimen Design for the Geriatric Population: Integrating Pharmacokinetic and Pharmacodynamic Modeling with Clinical Decision-Making. *Technologies* **2026**, *14*, 241.
89. Sové, R.J.; Verma, B.K.; Wang, H.; Ho, W.J.; Yarchoan, M.; Popel, A.S. Virtual Clinical Trials of Anti-PD-1 and Anti-CTLA-4 Immunotherapy in Advanced Hepatocellular Carcinoma Using a Quantitative Systems Pharmacology Model. *J. Immunother. Cancer* **2022**, *10*, e005414, doi:10.1136/jitc-2022-005414.
90. Chen, Y.; Ren, R.; Yan, L.; Zhou, Y.; Sun, R.; Song, H.; Yan, H.; Li, Y. From Bench to Bedside: Emerging Paradigms in CAR-T Cell Therapy for Solid Malignancies. *Adv. Sci.* **2025**, *12*, e05822, doi:10.1002/advs.202505822.
91. Kyriakidis, N.C.; Echeverría, C.E.; Bautista, J.; Rivera-Orellana, S.; Ramos-Medina, M.J.; Salazar-Santoliva, C.; Izquierdo-Condoy, J.S.; Ortiz-Prado, E.; Guerrero, S.; López-Cortés, A. Reprogramming Cancer

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Preprints.org | NOT PEER-REVIEWED | Posted: 12 November 2026 https://doi.org/10.20944/preprints202611.1294.v1

Immunity with Next-Generation Combination Therapies. *Front. Cell Dev. Biol.* **2025**, *13*, 1652047, doi:10.3389/fcell.2025.1652047.

92. Nie, D.; Shen, Y.; Xu, Y.; Hu, X.; Qiu, J.; Hu, X.; Meng, Q.-F.; She, P.; Rao, L.; Huang, Q. 3D-Printed Implantable CAR-Macrophages for Post-Surgery Cancer Immunotherapy. *J. Nanobiotechnology* **2026**, doi:10.1186/s12951-026-04360-y.
93. Chakraborty, S.; Pramanik, J.; Alviter-Raymundo, G.; Ward, C.J.; Shaji, S.K.; Yamashita-Kanemaru, Y.; Ali, F.A.Z.; Banik, D.; Zhang, Z.; Veiga-Villauriz, C.; et al. Cortisol-Resistant CAR-NK Cells Overcome Steroid-Induced Immunosuppression in Lung Cancer. *Signal Transduct. Target. Ther.* **2026**, *11*, 128, doi:10.1038/s41392-026-02638-z.
94. Youssef, E.; Fletcher, B.; Palmer, D. Enhancing Precision in Cancer Treatment: The Role of Gene Therapy and Immune Modulation in Oncology. *Front. Med.* **2025**, *11*, 1527600, doi:10.3389/fmed.2024.1527600.
95. Wei, F.; Cheng, X.-X.; Xue, J.Z.; Xue, S.-A. Emerging Strategies in TCR-Engineered T Cells. *Front. Immunol.* **2022**, *13*, 850358, doi:10.3389/fimmu.2022.850358.
96. Papież, M.A.; Krzyściak, W. Biological Therapies in the Treatment of Cancer—Update and New Directions. *Int. J. Mol. Sci.* **2021**, *22*, 11694, doi:10.3390/ijms222111694.
97. Talib, W.H.; Alsayed, A.R.; Barakat, M.; Abu-Taha, M.I.; Mahmod, A.I. Targeting Drug Chemo-Resistance in Cancer Using Natural Products. *Biomedicines* **2021**, *9*, 1353, doi:10.3390/biomedicines9101353.
98. Talib, W.H.; Alsayed, A.R.; Abuawad, A.; Daoud, S.; Mahmod, A.I. Melatonin in Cancer Treatment: Current Knowledge and Future Opportunities. *Molecules* **2021**, *26*, 2506, doi:10.3390/molecules26092506.
99. Zihlif, M.; Khader, H.A.; Younis, L.; Sharab, A.; Tahboub, F.; Hasoun, L.; Hajaj, H.; Alawneh, Z.; Alsayed, A.R. The Gene Expression Alterations in Chronic Hypoxic PANC-1 Pancreatic Cancer Cell Line. *Pharm. Pract.* **2026**, *23*, 1–8, doi:10.18549/PharmPract.2025.4.3238.
100. Zihlif, M.; Zakaraya, Z.; Hamdan, F.; Sharab, A.; Tahboub, F.; Qudsi, S.; Abuarab, S.F.; Daghash, R.; R Alsayed, A. Hepatocyte Nuclear Factor 4, Alpha (HNF4A): A Potential Biomarker for Chronic Hypoxia in MCF7 Breast Cancer Cell Lines. *Pharm. Pract.* **2025**, *23*, 1–8, doi:10.18549/PharmPract.2025.3.3227.
101. Talib, W.H.; Alsayed, A.R.; Farhan, F.; Al Kury, L.T. Resveratrol and Tumor Microenvironment: Mechanistic Basis and Therapeutic Targets. *Molecules* **2020**, *25*, 4282, doi:10.3390/molecules25184282.
102. Di Mauro, A.; Berretta, M.; Santorsola, M.; Ferrara, G.; Picone, C.; Savarese, G.; Ottaiano, A. Towards Post-Genomic Oncology: Embracing Cancer Complexity via Artificial Intelligence, Multi-Targeted Therapeutics, Drug Repurposing, and Innovative Study Designs. *Int. J. Mol. Sci.* **2025**, *26*, 7723, doi:10.3390/ijms26167723.
103. Molla, G.; Bitew, M. The Future of Cancer Diagnosis and Treatment: Unlocking the Power of Biomarkers and Personalized Molecular-Targeted Therapies. *J. Mol. Pathol.* **2025**, *6*, 20, doi:10.3390/jmp6030020.

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