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Cancer treatment: A review of methods, drug combinations, availability, and ethical considerations

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Abstract

Cancer remains a major clinical challenge that requires adaptive strategies. This review synthesizes principal therapeutic modalities, with emphasis on drug resistance, how drugs are ordered, and dealing with side effects while keeping the patient in mind. Evidence from pivotal trials and real-world practice demonstrates that resistance affects the treatments selected. Side effects and patient situations are considered to find the right balance between the treatment's effectiveness and the patient's quality of life. This review also examines the sequencing of chemotherapy with immune checkpoint blockade, as well as new approaches such as messenger RNA vaccines and proteolysis-targeting chimeras. Cross-cutting issues—including treatment standards, ethical considerations, and economic barriers—are discussed to help shape future cancer care delivery.

Keywords: Cancer treatment; Therapeutic resistance; Treatment sequencing; Immunotherapy; Targeted therapy; Patient-reported outcomes; Global health equity

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1. Introduction

Cancer treatment has evolved substantially over the past century, with each change improving on what came before. In the early 20th century, surgery, exemplified by Halsted's radical mastectomy, established the principles of tumor resection, controlling the edges and determining disease stage. Subsequently, advances in radiation sources and treatment planning transformed radiotherapy, enabling organ preservation and improved locoregional control. Additionally, novel chemotherapeutic agents, such as alkylating agents and antimetabolites, are used before and after surgery, helping people with many types of cancer live longer.[1-4]

Over the past two decades, therapeutic approaches have changed with the introduction of novel targeted therapies, such as tyrosine kinase inhibitors, anti-human epidermal growth factor receptor 2 (HER2) antibodies, antibody-drug conjugates (ADCs), and

poly(ADP-ribose) polymerase (PARP) inhibitors, as well as immunotherapies, such as programmed death-1/ligand-1 (PD-1/PD-L1) and cytotoxic T-lymphocyte antigen-4 (CTLA-4) checkpoint inhibitors, and chimeric antigen receptor T-cell (CAR-T) therapy. These advances have contributed to improved survival outcomes.[5-18] Alongside this, radiotherapy has advanced with technologies such as intensity-modulated radiation therapy (IMRT), volumetric-modulated arc therapy (VMAT), image-guided radiation therapy (IGRT), stereotactic body radiation therapy (SBRT), stereotactic radiosurgery (SRS), and proton therapy. These improvements allow for higher radiation doses to tumors while also lowering radiation exposure to organs.[19-23]

These past successes show how each method helped improve survival and quality of life. However, significant challenges persist, including therapeutic resistance, optimal treatment sequencing, and patient-centered care.

1.1. Global epidemiology and geography

Global cancer statistics from the Global Cancer Observatory (GLOBOCAN) 2020 reported over 19 million new cases of all cancer types annually and about 10 million deaths.[24,25] Historical data demonstrate that each modality incrementally improved survival rates and quality of life. Challenges persist, including acquired resistance, optimal treatment sequencing, and individual patient factors. Epidemiologic trends vary by region. Lung cancer mortality in men has declined in high-income countries, showing the impact of tobacco rules, screenings, and better treatments. Although breast cancer incidence has risen, mortality has declined due to early detection and new drugs. Colorectal cancer mortality has decreased in older adults, yet early-onset incidence (age < 50) has increased. Prostate cancer survival has improved due to intensified androgen-deprivation strategies, with new hormone drugs.[24-35]

These disparities underscore the need for global strategies that broaden access to diagnostic tools, key medicines, and radiotherapy, while also tackling financial burdens and unfairness in health systems.

1.2. Persistent gaps

Despite therapeutic advances, certain malignancies—including pancreatic adenocarcinoma and glioblastoma—remain associated with poor survival. Current treatments are limited by immunosuppressive tumor microenvironments, inadequate drug delivery, and early metastatic dissemination.[27,36]

Common challenges exist across tumor types. Resistance—both primary and acquired—limits the durability of targeted and immune therapies. Spatial and temporal tumor heterogeneity complicates biomarker interpretation and treatment planning, necessitating serial tumor profiling and adaptive treatment strategies. The high cost of novel therapeutics and diagnostics creates financial barriers for patients, thereby limiting equitable access to care.[37]

These challenges require comprehensive strategies that ought to integrate mechanistic understanding with practical solutions, including circulating tumor DNA (ctDNA)-based monitoring, rational treatment sequencing, and healthcare system reforms to reduce costs and increase accessibility (Figure 1).

1.3. Ethical/Patient-reported outcomes context

Patient-reported outcomes (PROs) are essential for rigorous research and ethical practice. Systematic monitoring of symptoms—including nausea, mucositis, diarrhea, fatigue, and neuropathy—improves treatment tolerability, maintains treatment intensity, and decreases unplanned hospitalizations.[38-41] Validated PRO instruments (PRO-common terminology criteria for adverse events [CTCAE], European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 [EORTC QLQ-C30]) enable a shift from reactive to proactive care, personalizing treatment to align with patient experiences and lifestyles.

Equity is a fundamental consideration. Access to effective treatments is not equally distributed, particularly between richer and poorer nations. Potential strategies to address this difference include the use of biosimilars, price standardization, and shared availability of biomarker tests.[42,43] An ethical, patient-centered approach requires ensuring that novel cancer treatments are both accessible and affordable for all.

1.4. Purpose of the review

This review organizes common cancer treatments and successful combinations. For each treatment, we cover the basic science, clinical applications, and relevant cellular and systemic processes. The focus is on human side effects, including patient experiences and key drug interactions, with cases illustrating real-world advantages and disadvantages.

We also discuss cross-cutting issues such as primary and acquired resistance, quality of life, disparities in access across countries, and the integration of technologies such as messenger RNA (mRNA) vaccines and proteolysis-targeting chimeras (PROTACs).

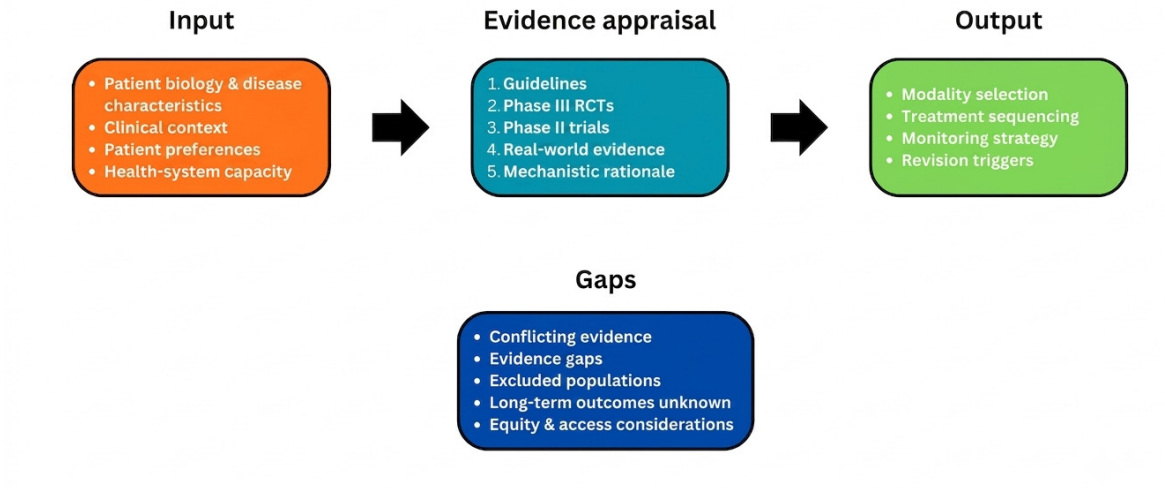

Figure 1. Evidence-to-decision framework. Image created by the authors with Microsoft PowerPoint.
Abbreviation: RCT: Randomized controlled trial.

To improve the review's utility, three tables are included: Table 1 presents comparative efficacy outcomes (overall survival [OS], progression-free survival [PFS], objective response rate [ORR]); Table 2 summarizes clinically significant drug–drug interactions (DDIs); and Table 3 maps resistance mechanisms to corresponding therapeutic solutions.

By combining mechanistic knowledge with pragmatic clinical considerations, this review aims to inform both everyday practice and future research directions in precision oncology.

2. Methods

2.1. Methodological clarification

This is a narrative (state-of-the-art) review designed to provide interpretative synthesis rather than exhaustive systematic enumeration. We prioritized practice-changing evidence and guideline-supported strategies over comprehensive study capture. Selection was relevance-weighted and interpretative, not protocol-driven or quantitative.

2.2. Design and aim

This manuscript is a narrative review intended to provide an interpretative synthesis of clinically relevant evidence across modalities (sequencing, resistance, toxicity/PROs, and implementation). It is not a systematic review; therefore, Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow accounting and formal risk-of-bias scoring were not performed.

2.3. Sources and period

We conducted literature searches in PubMed/MEDLINE, Embase, and the Cochrane Library spanning January 2015 to September 2025. We included English-language publications. We also consulted the National Comprehensive Cancer Network (NCCN), the European Society for Medical Oncology (ESMO), and the American Society of Clinical Oncology (ASCO) guidelines, as well as systematic reviews/meta-analyses and phase II-III trials. The final database search was run in September 2025.

2.4. Search strategy (representative)

Representative concepts included (adapted per database): ("cancer" OR "malignancy") AND ("treatment sequencing" OR "therapy sequence") AND ("resistance" OR "progression") AND ("toxicity" OR "patient-reported outcomes" OR "PRO-CTCAE") AND ("trial" OR "guideline" OR "real-world").

Representative examples of prioritized practice-changing studies included the following. For non-small cell lung cancer (NSCLC): KEYNOTE-189/-407 (chemotherapy plus immune checkpoint inhibitor [ICI])[1,2] and IMpower150 (ICI plus anti-vascular endothelial growth factor [VEGF] plus chemotherapy).[3] For melanoma and renal cell carcinoma (RCC): CheckMate-067/-214 (dual checkpoint blockade).[4,44] For *EGFR*-mutated NSCLC: FLAURA and ADAURA (osimertinib).[9-11] For HER2-positive breast cancer: CLEOPATRA, EMILIA, and DESTINY-Breast03 (trastuzumab- and ADC-based treatments).[5,6,12-14] For cell therapies: ZUMA-1, JULIET,

Table 1. Cross-modality comparison (two-tier efficacy: OS/PFS/ORR)

Modality	Core principle	Typical clinical roles	Efficacy signal (qualitative)	Frequent patient-relevant toxicities (including PROs)	Key clinically relevant DDIs/cautions	Cost/Access (typical)	Strengths	Limitations
Surgery	Macroscopic tumor removal aiming for R0; provides definitive pathology/staging and tissue for biomarkers	Curative intent (early/localized); selected locally advanced; cytoreduction in selected settings	OS: potentially maximal (curative) in localized disease; PFS/ORR: not applicable in systemic response terms	Pain, fatigue, infection, bleeding, thromboembolism; organ-specific functional impairment; late sequelae (e.g., lymphedema)	Anti-VEGF agents require peri-operative washout (wound complications); peri-procedural anticoagulants/ antiplatelets	Medium-high (infrastructure-/ volume-dependent)	Curative potential; definitive staging; enables biomarker-guided adjuvant strategies	Not feasible/ insufficient alone in disseminated disease; morbidity/ functional loss; outcomes depend on center volume
Radiotherapy (RT)	Local tumor control via ionizing radiation with OAR protection; modern conformal/ adaptive techniques	Definitive, neoadjuvant/ adjuvant, palliation; oligometastatic SBRT/SRS	Local control/PFS: high in selected sites; OS: benefit in select contexts (e.g., combined-modality curative settings)	Dermatitis, mucositis, fatigue; site-specific toxicities; late fibrosis/ strictures; pneumonitis (thoracic RT)	Thoracic RT + ICI increases pneumonitis risk; pelvic RT + anti-VEGF increases fistula/ necrosis; concurrent radiosensitizing CT increases toxicity	Medium-high; advanced modalities (protons) limited	Organ preservation; precise local control; synergy with systemic therapy in curative settings	OAR constraints; late toxicity; variable radioresistance by histology
Chemotherapy (CT)	Systemic cytotoxic therapy targeting proliferating cells (DNA damage, mitotic disruption)	Neoadjuvant/ adjuvant; metastatic disease control; backbone for combinations	ORR/PFS: moderate-substantial (tumordependent); OS: variable, context-dependent	Nausea/vomiting, diarrhea/mucositis, alopecia, fatigue; myelosuppression/ FN; neuropathy (taxanes/platinums); cardiotoxicity (anthracyclines)	5-FU/capecitabine ↔ warfarin increases INR; aprepitant (CYP3A4 inhibitor) up taxane exposure; cisplatin + aminoglycosides up nephro/ototoxicity	Generally high availability worldwide	Broad applicability; strong evidence base; synergizes with ICI/TT	Non-specific toxicity; MDR; cumulative dose-limits
Targeted therapy (TT)	Inhibition of oncogenic driver pathways in biomarker-defined subsets (TKI/mAb/ ADC/PARP/anti-VEGF)	First-line in driver-positive cancers; maintenance; later-line sequencing; adjuvant in select settings	ORR/PFS: often high in predictive subsets; OS: improved in select molecular contexts	Rash/diarrhea (EGFR), HTN/proteinuria (anti-VEGF), hepatotoxicity; cardiotoxicity (HER2); ILD risk (notably with some ADCs)	CYP3A4 inhibitors/ inducers affect many TKIs; acid suppression reduces absorption of pHdependent TKIs; QT prolongation risk (drug-specific)	High; requires access to validated biomarker testing	Depth of response in selected patients; oral options; precision sequencing possible	Resistance nearly universal; access/ testing costs; heterogeneity limits durability

(*Cont'd...*)

Table 1. (*Continued*)

Modality	Core principle	Typical clinical roles	Efficacy signal (qualitative)	Frequent patientrelevant toxicities (including PROs)	Key clinically relevant DDIs/cautions	Cost/Access (typical)	Strengths	Limitations
Immune checkpoint inhibitor (ICI)	Re-activates antitumor T-cell responses via PD-1/PD-L1 and/or CTLA-4 blockade	Durable control in responsive phenotypes; combinations with CT/anti-VEGF/ RT in defined indications	ORR: moderate-high in responsive subsets; OS: "tail" (durable benefit) in subset	irAEs: dermatitis, colitis, hepatitis, endocrinopathies, pneumonitis; can affect QoL disproportionately	Baseline systemic steroids may reduce efficacy (context-dependent); immunosuppressants for irAEs (anti-TNF, mycophenolate) guided by severity; thoracic RT increases pneumonitis risk	High; access varies widely by region	Durable remissions in a subset; paradigm-shifting in multiple tumors	Low response in "cold" tumors; severe irAEs; biomarker imperfection
CAR-T therapy	Autologous engineered T cells targeting tumor antigens (hematologic malignancies)	Relapsed/ Refractory B-cell malignancies; multiple myeloma (platform-specific)	CR/DoR: high CR rates in selected settings; OS: meaningful in subsets	CRS, ICANS, prolonged cytopenias, infections; QoL impact from hospitalization	Immunosuppression may impair expansion/ persistence; infection prophylaxis and supportive pathways critical	Very high; limited specialized centers	High activity in refractory hematologic cancers	Cost/logistics; toxicity; limited efficacy in solid tumors
Hormone therapy (HT)	Suppresses or modulates ER/AR signaling; often combined with targeted agents (e.g., CDK4/6)	ER+ breast cancer; prostate cancer across disease states	PFS: improved with combinations; OS: improved in defined combination strategies; ORR: low-moderate	Hot flashes, fatigue, sexual dysfunction; bone loss/fractures; metabolic syndrome (ADT)	Tamoxifen ↔ warfarin; CYP interactions for some antiandrogens; bone-health co-management (bisphosphonates/ denosumab)	High availability overall	Generally tolerable; oral; long-term disease control	Endocrine resistance; chronic metabolic/bone risks
Genetic/ vaccine/ cell-genetic platforms	Gene delivery/ silencing/editing; individualized neoantigen vaccination; engineered immune cells (early-phase)	Predominantly investigational; niche indications	Clinical efficacy: early signals; survival benefit not established broadly	Vector immunogenicity; off-target effects; inflammatory toxicity; delivery-related risks	Concomitant immunosuppression may blunt vaccine/ immune activity; interactions depend on platform	Limited; high complexity/cost	Novel mechanisms; personalization potential	Delivery barriers; limited phase III validation; scalability concerns

Notes: OS/PFS/ORR entries are qualitative, representative summaries intended for cross-modality orientation only and should not be interpreted as quantitative cross-trial comparisons. Magnitude and direction of benefit vary substantially by tumor type, stage, biomarker context, line of therapy, and regimen. Readers are referred to tumor-specific guidelines and pivotal trial publications for precise estimates of efficacy in defined clinical contexts.
Abbreviations: 5-FU: Fluorouracil; ADC: Antibody–drug conjugate; ADT: Androgen deprivation therapy; AR: Androgen receptor; CAR-T: Chimeric antigen receptor T-cell; CDK4/6: Cyclin-dependent kinase 4/6; CR: Complete response; CRS: Cytokine release syndrome; CTLA-4: Cytotoxic T-lymphocyte antigen-4; CYP3A4: Cytochrome P450 family 3 subfamily A member 4; DDI: Drug–drug interaction; DoR: Duration of response; EGFR: Epidermal growth factor receptor; ER: Estrogen receptor; FN: Febrile neutropenia; HER2: Human epidermal growth factor receptor 2; HTN: Hypertension; ICANS: Immune effector cell-associated neurotoxicity syndrome; ILD: Interstitial lung disease; INR: International normalized ratio; irAE: Immune-related adverse event; mAB: Monoclonal antibody; MDR: Multidrug resistance; OAR: Organ at risk; ORR: Objective response rate; OS: Overall survival; PARP: Poly(ADP-ribose) polymerase; PD-1: Programmed death-1; PD-L1: Programmed death ligand-1; PFS: Progression-free survival; PRO: Patient-reported outcome; QoL: Quality of life; SBRT: Stereotactic body radiation therapy; SRS: Stereotactic radiosurgery; TKI: Tyrosine kinase inhibitor; TNF: Tumor necrosis factor; VEGF: Vascular endothelial growth factor.

Table 2. Clinically significant DDIs (selected)

Drug/Class	Interacting drug(s)	Mechanism/Rationale	Potential clinical consequence	Mitigation (practical)	Evidence basis (typical)
5-FU/Capecitabine	Warfarin	Variable effects on anticoagulation (multifactorial; reported interaction)	Increase INR, bleeding risk	Close INR monitoring; consider alternative anticoagulation when feasible; dose adjustment	Post-marketing reports + clinical pharmacology experience; drug labels
Aprepitant/Fosaprepitant (NK1RA)	Taxanes (CYP3A4 substrates), other CYP3A4 substrates	CYP3A4 inhibition	Increase exposure/toxicity risk (e.g., myelosuppression, neuropathy)	Monitor closely; consider regimen-specific adjustments per institutional protocols	PK rationale + labeling; guideline-informed supportive care pathways
Cisplatin	Aminoglycosides (and other nephro/ototoxic agents)	Additive nephrotoxicity/ ototoxicity	AKI; hearing loss	Avoid if possible; hydration; renal/audiology monitoring	Clinical pharmacology + supportive care guidance
Trastuzumab/Pertuzumab	Anthracyclines (concurrent/ close sequencing)	Additive cardiomyocyte injury risk	Increase cardiomyopathy/ HF risk	Avoid concurrent use when possible; spacing; serial LVEF monitoring	Trial practice patterns + guidelines + labeling
TKIs (multiple; drug-specific)	Strong CYP3A4 inhibitors/ inducers	Altered metabolism	Over-exposure (toxicity) or under-exposure (loss of efficacy)	Medication reconciliation; avoid strong modulators; adjust per label	PK studies + labeling; guideline practice
pH-dependent oral agents (subset of TKIs)	PPIs/H2 blockers/antacids	Reduced solubility/absorption	↓ exposure → reduced efficacy risk	Avoid PPIs if possible; separate dosing; follow agent-specific instructions	PK studies + labeling
Tamoxifen	Strong CYP2D6 inhibitors; warfarin	Reduced active metabolite formation (CYP2D6); anti-coagulation interaction	Reduced endocrine efficacy; bleeding risk	Avoid strong CYP2D6 inhibitors; INR monitoring if warfarin required	PK + observational data; guidelines
Abiraterone	CYP substrate drugs; glucocorticoid co-therapy	Enzyme interactions; mineralocorticoid excess physiology	HTN, hypokalemia; interaction-related toxicity	Monitor BP/K^+; review concomitant meds; adhere to co-steroid protocols	Labeling + guideline-based management
ICI (PD-1/PD-L1/CTLA-4)	Baseline systemic steroids (context-dependent)	Immunosuppression may attenuate antitumor immunity	Potentially reduced response in some contexts	Use steroids only when clinically indicated; lowest effective dose; document indication	Retrospective clinical data; expert guidance (not a classic PK DDI)
Anti-VEGF agents (e.g., bevacizumab)	Major surgery; pelvic RT (context)	Impaired wound healing; vascular effects	Wound complications; fistula/ necrosis risk (esp. pelvic settings)	Pre/post washout; multidisciplinary timing decisions	Trial/observational safety data + practice guidelines

Notes: This table lists selected, clinically common, and/or high-impact interactions and is not exhaustive. Actual risk depends on agent, dose, comorbidities, and treatment setting.
Abbreviations: 5-FU: Fluorouracil; AKI: Acute kidney injury; BP: Blood pressure; CTLA-4: Cytotoxic T-lymphocyte antigen-4; CYP3A4: Cytochrome P450 family 3 subfamily A member 4; DDI: Drug–drug interaction; HF: Heart failure; HTN: Hypertension; ICI: Immune checkpoint inhibitor; INR: International normalized ratio; LVEF: Left ventricular ejection fraction; NK1RA: Neurokinin-1 receptor antagonist; PD-1: Programmed death-1; PD-L1: Programmed death ligand-1; PK: Pharmacokinetics; PPI: Proton pump inhibitor; RT: Radiotherapy; TKI: Tyrosine kinase inhibitor; VEGF: Vascular endothelial growth factor.

Table 3. Resistance mutation/mechanism and solution

Disease/Target context	Common resistance mechanisms (examples)	Clinical approach/Matched strategy (representative)
EGFR-mutant NSCLC (post-osimertinib)	On-target *EGFR* mutations (e.g., C797S); bypass activation (*MET* amplification, HER2); phenotypic shift (e.g., SCLC transformation); EMT/heterogeneity	Re-biopsy and/or ctDNA to define mechanism; consider MET-directed combinations where validated/available; switch class (e.g., ADCs) when appropriate; if SCLC transformation suspected/confirmed, treat per SCLC paradigms
ALK-rearranged NSCLC	*ALK* domain mutations (e.g., G1202R); compound mutations; bypass signaling	Next-generation *ALK* TKI sequencing guided by mutation profile; consider clinical trials of combination suppression of bypass pathways
BRAF V600 melanoma	MAPK reactivation; PI3K/AKT pathway activation; microenvironmental immune escape	Combined BRAF+MEK inhibition; integration/sequence with ICI per clinical scenario and risk profile
ER+ breast cancer	*ESR1* mutations; CDK pathway escape (e.g., RB pathway alterations); PI3K pathway activation	Switch endocrine backbone (e.g., SERD where indicated/available); rational targeted additions (e.g., PI3K-directed therapy in *PIK3CA*-mutant disease); reassess CDK4/6 benefit case-by-case
HER2$^+$ breast cancer	HER2 heterogeneity; antigen downmodulation; pathway rewiring	Sequential HER2-directed strategy with class switching (mAbs → ADCs); consider bispecifics/next-gen ADCs in trials where relevant
ICI-treated tumors (various)	Impaired antigen presentation (e.g., *B2M* loss); alternative checkpoints (LAG-3/TIGIT/TIM-3); immune-excluded TME (TGF-β, myeloid suppression)	Consider dual-checkpoint strategies where approved; trial enrollment for TME-modulating agents (e.g., anti-TGF-β, innate immune agonists); integrate local therapies (RT) selectively to modify immunogenicity (risk-adapted)

Notes*:* Listed strategies are representative examples intended to illustrate mechanism-guided decision logic and are not exhaustive. Clinical application requires interpretation within tumor type-specific guidelines, regional drug availability, institutional protocols, and individual patient factors. Emerging resistance mechanisms and novel therapeutic approaches continue to evolve; readers are encouraged to consult current literature and multidisciplinary tumor boards for complex cases.
Abbreviations: ADC: Antibody–drug conjugate; BRAF: B-Raf proto-oncogene, serine/threonine kinase; CDK: Cyclin-dependent kinase; ctDNA: Circulating tumor DNA; EMT: Epithelial–mesenchymal transition; ER: Estrogen receptor; HER2: Human epidermal growth factor receptor 2; ICI: Immune checkpoint inhibitor; LAG-3: Lymphocyte activation gene-3; MAPK: Mitogen-activated protein kinase; MEK: Mitogen-activated protein kinase kinase; mAB: Monoclonal antibody; MET: MET proto-oncogene, receptor tyrosine kinase; NSCLC: Non-small cell lung cancer; PI3K: Phosphoinositide 3-kinase; RB: Retinoblastoma protein; RT: Radiotherapy; SCLC: Small cell lung cancer; SERD: Selective estrogen receptor degrader; TGF-β: Transforming growth factor-beta; TIGIT: T-cell immunoreceptor with Ig and ITIM domains; TIM-3: T-cell immunoglobulin and mucin-domain containing-3; TKI: Tyrosine kinase inhibitor; TME: Tumor microenvironment.

KarMMa, and TRANSCEND (CAR-T platforms).[15-18] For pembrolizumab monotherapy in PD-L1-high NSCLC: KEYNOTE-024.[45]

We also consulted supportive-care guidelines and toxicity-focused reviews to capture adverse events, clinically relevant DDIs, and PROs.

2.5. Study selection and scope

This manuscript is a narrative (state-of-the-art) synthesis that prioritizes interpretative integration over exhaustive study enumeration. Given the narrative scope, we did not aim to capture all eligible records exhaustively, nor did we perform a PRISMA-style study flow accounting. Instead, we used a relevance-weighted selection focused on practice-changing trials, major guidelines, and high-yield evidence addressing sequencing, resistance, toxicity, and implementation. We prioritized studies with clear clinical applicability to treatment sequencing, resistance, toxicity/PROs, and implementation. We preferentially included international guidelines, meta-analyses, and phase III randomized trials; early-phase studies were included when they introduced a clinically influential mechanism or a near-term practice-relevant platform. We excluded non-English publications, preclinical-only studies without translational relevance, single-patient case reports, and studies not focused on therapeutic decision-making.

Screening and relevance-weighted prioritization were performed by two authors, with disagreements resolved by consensus discussion and clinical adjudication when needed.

2.6. Strategy and prioritization

We prioritized evidence hierarchically: international clinical guidelines (NCCN, ESMO, ASCO) and meta-analyses took precedence, followed by phase III randomized trials, then phase II trials and large observational cohorts. Selection emphasized studies that established current standards of care or demonstrated practice-changing efficacy.

We consulted supportive-care guidelines to reduce toxicity-related hospitalizations and avoidable healthcare utilization.[39-41] The Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) system aided in setting dose limits and organ-at-risk dose constraints for radiotherapy that are evidence-based.[22] Special reviews of ICI toxicity were included to ensure coverage of immune-related adverse events (irAEs) and their management.[38]

2.7. Extraction and synthesis

For each modality, we synthesized evidence focusing on: (i) clinical positioning and sequencing logic, (ii) strength and limitations of the evidence base (guidelines, randomized trials, and real-world data), (iii) resistance patterns and actionable implications, (iv) toxicity burden including PROs, (v) clinically relevant DDIs and implementation constraints, and (vi) key uncertainties and research priorities. Mechanistic detail was included only when it informed sequencing, resistance mitigation, or clinically meaningful toxicity. When evidence was discordant, we prioritized the most recent high-quality studies and major guidelines to maintain an up-to-date synthesis (Table 4).

2.8. Limitations

This narrative review does not provide pooled quantitative estimates. Study heterogeneity limits direct cross-trial comparisons. Emerging modalities are supported primarily by early-phase data requiring validation in larger trials.

3. Results

To enable cross-modality comparison, each modality is summarized using a consistent structure emphasizing clinical role and sequencing, evidence strength, toxicity/PROs, DDIs, and implementation constraints, followed by key controversies and unresolved questions. Mechanistic detail is included only when it directly informs sequencing decisions, resistance mitigation, or toxicity management (Table 1).

3.1. Surgery

3.1.1. Definition and principle

Surgery represents a fundamental treatment modality in oncology. The process involves resecting macroscopic tumor burden and achieving negative surgical margins (R0 resection). Surgical resection provides definitive staging through histopathologic examination of resected specimens, with lymph node dissection to assess metastatic involvement.

Surgery is a cornerstone modality for localized disease, aiming for complete resection (R0) when feasible and providing definitive histopathology, staging, and tissue for biomarker testing. In contemporary oncology, surgery is increasingly integrated with neoadjuvant and adjuvant systemic approaches to improve margin status and reduce recurrence risk in biologically aggressive tumors.

For early-stage disease and selected locally advanced tumors, surgery may be sufficient for curative intent. Nevertheless, surgery is now often used with other treatments. Neoadjuvant treatments are given before surgery to achieve tumor downstaging and facilitate resection, and possibly activate antitumor immunity. Adjuvant systemic treatments are given after surgery to eradicate micrometastatic disease.[5-7] This reflects the dual role of surgery: it can be the main treatment in the early stages and part of a broader treatment plan in more advanced stages.

3.1.2. Typical workflow

The typical workflow proceeds through five non-prescriptive stages. First, staging and selection involve computed tomography (CT)/magnetic resonance imaging (MRI)/positron emission tomography (PET)-CT assessments of technical resectability and physiologic reserves, as well as multidisciplinary tumor board review. Second, neoadjuvant therapy is administered when indicated to achieve tumor shrinkage and downstaging, increasing R0 rates—for example, chemoradiation for rectal cancer or systemic therapy for borderline-resectable disease. Third, the operation itself adheres to oncologic resection principles with attention to anatomic planes and nodal templates. Fourth, pathology and molecular profiling provide definitive diagnosis with next-generation sequencing (NGS)/in situ hybridization (ISH)/immunohistochemistry (IHC) as indicated. Fifth, adjuvant therapy is tailored to risk and biomarkers.[5-11]

3.1.3. Mechanisms

The primary mechanisms include macro- and microscopic tumor removal, reduced risk of dissemination, and provision of tissue for biomarkers enabling downstream targeted and immune strategies.

Table 4. Cross-modality trade-offs matrix

Modality	Evidence maturity	Durability potential	Toxicity & PRO burden	DDI & coordination complexity	Access & infrastructure needs
Surgery	H	M	M	L	M
Radiotherapy	H	M	M	L	M
Chemotherapy	H	M	H	M	M
Targeted therapy	M	M	M	H	M
Hormonal therapy	H	M	L	L	L
Immunotherapy (ICI)	M	H	M	L	M
Cellular therapies	L	H	H	H	H
Emerging platforms	L	Variable	Variable	M/H	H

Note: Variable reflects evolving or inconsistent evidence.
Abbreviations: DDI: Drug–drug interaction; H: High; ICI: Immune checkpoint inhibitor; L: Low; M: Moderate; PRO: Patient-reported outcome.

3.1.4. Toxicities

Toxicities include pain, fatigue, organ-specific dysfunction, bleeding, infections, and thromboembolic events, as well as late sequelae such as strictures and lymphedema. Postoperative cognitive dysfunction has been reported in older adults.[5-8]

3.1.5. Drug–drug interactions

Periprocedural anticoagulants and antiplatelets require careful management. Anti-VEGF agents (bevacizumab) require pre- and postoperative washout to mitigate wound complications[23] (Table 2).

3.1.6. Strengths and limitations

Surgery offers the potential for cure, precise staging, and tissue for biomarker analysis. Its limitations include inapplicability in disseminated disease and operative morbidity with functional loss.

3.1.7. Validated combinations and sequences

Adjuvant folinic acid, fluorouracil, and oxaliplatin (FOLFOX) in stage III colorectal cancer and adjuvant osimertinib after resection of *EGFR*-mutant NSCLC (ADAURA) represent validated combination strategies.[9-11,46,47]

3.1.8. Evidence strength and implementation gap

Evidence is strongest for surgery in early-stage solid tumors and in guideline-defined multimodality pathways. Outcomes are highly volume-dependent and influenced by access to high-quality pathology, imaging, and biomarker testing.

3.1.9. Critical considerations

While surgery remains curative for early-stage disease, R0 resection rates vary substantially across tumor types (>90% in early colon cancer versus < 60% in pancreatic cancer) and depend heavily on surgical expertise and institutional volume. Real-world evidence suggests that pathologic complete response rates after neoadjuvant chemoradiation in rectal cancer (15–30%) correlate strongly with long-term survival, yet optimal patient selection for organ preservation versus radical resection remains debated. The integration of neoadjuvant immunotherapy in resectable NSCLC has shown promising pathologic response rates in CheckMate-816, but whether this translates into a survival benefit compared with adjuvant approaches requires longer follow-up.

3.2. Radiotherapy

3.2.1. Definition and principle

Radiotherapy is a medical procedure where ionizing radiation is precisely aimed at a tumor to eliminate cancer cells while maintaining organ-at-risk doses within established tolerance limits. Modern radiotherapy leverages conformal planning and image guidance to maximize tumor dose while respecting organ-at-risk constraints. Fractionation and technique selection—for example, IMRT/VMAT, SBRT/SRS, and protons in selected settings 3 are primarily driven by tumor site, proximity to critical structures, and intent (definitive, adjuvant, or palliative).

Radiotherapy can be crucial at different stages of cancer treatment. Radiotherapy may be delivered as definitive therapy, as neoadjuvant treatment to facilitate resection, as adjuvant therapy to eradicate residual microscopic disease, or for palliation of symptoms. In cases where cancer has spread to a limited number of sites, SBRT can achieve durable local control, potentially increasing survival rates without cancer progression.[19-23]

3.2.2. Typical workflow

The workflow begins with simulation and planning using CT (with adjunct MRI/PET) for target delineation. Contouring defines gross tumor volume/clinical target volume/planning target volume and the organ at risk according to established atlases. Technique and fractionation selection encompasses 3D-conformal radiotherapy, IMRT/VMAT, IGRT, SBRT, brachytherapy, and proton therapy, with a choice between conventional and hypofractionated schedules. Verification and adaptation involve image guidance and adaptive replanning as anatomy evolves. Supportive care throughout includes skin and oral care, nutrition, and prophylaxis for dermatitis and mucositis.[19-22]

3.2.3. Mechanisms

Radiotherapy induces DNA single- and double-strand breaks and mitotic catastrophe. Radiosensitization occurs with DNA-damaging chemotherapy. Immunogenic cell death with damage-associated molecular pattern (DAMP) release may produce potential abscopal effects.[19-21]

3.2.4. Toxicities

Acute toxicities include radiodermatitis, mucositis, esophagitis/proctitis, fatigue, and nausea. Late toxicities encompass fibrosis, strictures, pneumonitis, cardiac exposure (left breast/chest wall), and second malignancies.[19-22]

3.2.5. Drug–drug interactions

Platinum, fluorouracil (5-FU), and taxanes increase radiosensitization and toxicity. Anti-VEGF agents increase the risk of necrosis and fistulas during pelvic radiotherapy. Lung radiotherapy combined with ICI elevates pneumonitis risk[20-24] (Table 2).

3.2.6. Strengths and limitations

Radiotherapy offers organ preservation, precise dosimetry, and high local control. Its limitations include organ-at-risk dose constraints, late toxicities, and radioresistance in some histologies.

3.2.7. Validated combinations and sequences

Validated approaches include chemoradiation in head-and-neck and rectal cancers, SBRT for oligometastases, and radiotherapy as priming for ICI (investigational).[19-24]

3.2.8. Unresolved questions

The optimal integration of radiotherapy with ICIs remains controversial. While preclinical data support radiation-induced immunogenic cell death and potential abscopal effects, clinical trials show mixed results. Concurrent chemoradiation plus durvalumab in stage III NSCLC (PACIFIC trial) demonstrated clear benefit, yet similar strategies in other tumor types have been complicated by increased pneumonitis rates (up to 30% grades 3–4 in some series). The timing question—concurrent versus sequential immunotherapy—and the role of radiation dose and fractionation in modulating immune response require prospective evaluation. Additionally, proton therapy's theoretical advantage in reducing integral dose to normal tissues has not consistently translated to superior clinical outcomes compared to modern photon techniques in randomized trials, raising cost-effectiveness concerns.

3.3. Chemotherapy

3.3.1. Definition and principle

Chemotherapy is a treatment that uses drugs to kill cancer cells all over the body. It targets the rapid growth of these cells by damaging their DNA and disrupting their division, inducing DNA cross-links and adducts, and causing replicative stress.

Currently, chemotherapy has two important roles in treating cancer. First, it eradicates micrometastatic disease, especially at the time of surgery, thereby reducing recurrence risk and improving survival. Second, chemotherapy provides disease control in metastatic settings. It may be administered as monotherapy or combined with targeted agents and immunotherapy to enhance therapeutic efficacy. For example, chemotherapy may enhance ICI efficacy by releasing cancer markers that activate dendritic cells. It can also help targeted therapies by blocking cell signals more completely. Regimen selection is determined by tumor histology, disease stage, and comorbidities to optimize dose intensity while minimizing toxicity. Evidence demonstrates that chemotherapy remains integral to contemporary oncology, providing both direct cytotoxicity and synergistic enhancement of immunotherapy and targeted therapy efficacy.[27,36]

3.3.2. Typical workflow

Regimen selection is followed by antiemetic prophylaxis, which is typically selected using guideline-based emetogenic and neutropenia risk stratification (e.g., ASCO), adapted to comorbidities and local protocols.[39-41] Primary granulocyte colony-stimulating factor (G-CSF) prophylaxis is commonly considered in higher-risk settings and is individualized based on patient-level risk factors.[39-41] Pharmacogenetic testing (e.g., *DPYD*) may be used to reduce fluoropyrimidine toxicity through risk-adapted dosing.[41] Monitoring and dose modification proceed according to toxicity and organ function throughout treatment.

3.3.3. Mechanisms

Alkylators and platinum compounds produce inter- and intra-strand cross-links. Antimetabolites inhibit nucleotide synthesis. Antimicrotubule agents cause mitotic arrest. Topoisomerase inhibitors interfere with DNA replication.[48-50]

3.3.4. Toxicities

Toxicities include myelosuppression (neutropenia, anemia, thrombocytopenia), nausea and vomiting, diarrhea and mucositis, alopecia, peripheral neuropathy (platinum and taxanes), cardiotoxicity (anthracyclines), nephro- and ototoxicity (cisplatin), and late myelodysplastic syndrome/acute myeloid leukemia (MDS/AML).[39-41,48-50]

3.3.5. Drug–drug interactions

Aprepitant (a CYP3A4 inhibitor) elevates taxane exposure. 5-FU interacts with warfarin, increasing the international normalized ratio (INR). Cisplatin combined with aminoglycosides increases nephro- and ototoxicity. Proton pump inhibitors (PPIs) alter the absorption of selected agents[39-41] (Table 2).

3.3.6. Strengths and limitations

Chemotherapy offers universality, cost-effectiveness, and synergy with ICI and targeted therapy. Its limitations include non-specific toxicity and multidrug resistance.[37,48]

3.3.7. Validated combinations and sequences

In NSCLC, platinum–pemetrexed plus pembrolizumab (KEYNOTE-189)[1] and platinum–paclitaxel plus pembrolizumab (KEYNOTE-407)[2] are established standards. In metastatic colorectal cancer, FOLFOX or Folinic acid, fluorouracil, and irinotecan (FOLFIRI) plus bevacizumab or cetuximab (RAS wild-type with sidedness considered) are standard.[26] In pancreatic ductal adenocarcinoma, folinic acid, fluorouracil, and oxaliplatin (FOLFIRINOX) is superior to gemcitabine for OS.[27,36]

3.3.8. Evidence strength and key controversy

Chemotherapy has one of the most robust cross-tumor evidence bases (multiple phase III trials) and remains a frequent backbone for combinations. Optimal duration, intensity, and de-escalation strategies remain tumor- and patient-specific, with quality-of-life trade-offs.

3.3.9. Evidence gaps

Dose-dense chemotherapy regimens have demonstrated survival benefit in adjuvant breast cancer (CALGB 9741), but extrapolation to other solid tumors lacks robust validation. In ovarian cancer, dose-dense weekly paclitaxel showed benefit in Japanese populations (JGOG 3016) but not in Western cohorts (ICON8), highlighting potential pharmacogenomic or practice-pattern differences. Patient selection for intensive versus standard dosing remains empiric, and predictive biomarkers beyond performance status are lacking. Furthermore, the optimal duration of palliative chemotherapy is poorly defined—continuing until progression versus planned breaks (as in OPTIMOX strategies for colorectal cancer) shows no consistent survival difference but may impact quality of life differently across patients.

3.4. Targeted therapy

3.4.1. Definition and principle

Targeted therapy works by blocking the specific pathways that cancer cells use to grow. These pathways must represent critical dependencies for tumor proliferation, and validated inhibitors must be available for that specific cancer to use targeted therapy. Targeted therapy is indicated when a validated predictive biomarker identifies a tumor dependency and when an agent has demonstrated clinically meaningful benefit in that biomarker-defined population. Its clinical value is maximized when biomarker testing, access to drugs, and resistance-monitoring pathways are available.

Targeted therapy aims to maximize efficacy while minimizing off-target toxicity by targeting the signals that are the main drivers of cancer growth. The principal challenge is acquired resistance, which can occur through secondary mutations, the reactivation of pathways, or clonal evolution. At progression, repeat tissue and/or liquid biopsy, together with ctDNA monitoring, is often considered to characterize resistance mechanisms and inform subsequent treatment selection.[51-53]

3.4.2. Typical workflow

Diagnostics begin with NGS/IHC/ISH for epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), ROS1, B-Raf proto-oncogene, serine/threonine kinase (BRAF)/mitogen-activated protein kinase kinase (MEK), mesenchymal-epithelial transition factor (MET), rearranged during transfection (RET), and neurotrophic tyrosine receptor kinase (NTRK); HER2; breast cancer protein (BRCA)/PARP; and microsatellite instability-high (MSI-H)/tumor mutational burden (TMB) for ICI eligibility. Agent selection follows, choosing the appropriate tyrosine kinase inhibitor (TKI), monoclonal antibody (mAb), ADC, or PARP inhibitor and line of therapy. Monitoring encompasses efficacy and toxicity assessment, cardiac surveillance with HER2 therapies, and

interstitial lung disease (ILD) vigilance with trastuzumab deruxtecan (T-DXd). Re-profiling at progression uses tissue or ctDNA to define resistance and guide the switch in mechanism—for example, from EGFR inhibition to adding a MET inhibitor or using an ADC.

3.4.3. Mechanisms

The major classes include TKIs (EGFR/ALK/ROS1/BRAF/MEK/MET/RET/NTRK), mAbs, ADCs (HER2/EGFR), PARP inhibitors, and anti-VEGF/VEGF receptor agents.[51-55] This iterative re-profiling is necessary to transition from one generation of TKIs to the next, switch to an ADC, or consider new approaches such as PROTACs.

3.4.4. Toxicities

Toxicities include rash and diarrhea (EGFR TKIs), hypertension and proteinuria (anti-VEGF), ILD (rare but material with T-DXd and some TKIs), cardiotoxicity (HER2 agents), and hepatotoxicity.[12-14]

3.4.5. Drug–drug interactions

CYP3A4 inhibitors and inducers affect many TKIs. Acid-reducing agents reduce pH-dependent TKI absorption. QT prolongation risks are drug-specific.[39-41] Given the narrow therapeutic index and high prevalence of TKI metabolism via CYP3A4, systematic medication reconciliation is important to minimize clinically significant interactions and avoid under- or over-exposure (Table 2).

3.4.6. Strengths and limitations

Targeted therapy offers high selectivity and depth of response in predictive subsets. Its limitations include near-universal resistance and the cost of and access to testing and drugs.

3.4.7. Validated combinations and sequences

In HER2-positive breast cancer, the validated sequence is trastuzumab plus pertuzumab plus docetaxel (CLEOPATRA) → trastuzumab emtansine (T-DM1; EMILIA) → T-DXd (DESTINY-Breast03).[5,6,12-14] In NSCLC, osimertinib is standard first-line (FLAURA) and adjuvant (ADAURA).[9-11] The IMpower150 regimen—atezolizumab plus bevacizumab plus chemotherapy—is validated in systemic NSCLC.[3]

3.4.8. Resistance patterns

Acquired resistance to targeted therapy is nearly universal and mechanistically diverse. In *EGFR*-mutant NSCLC, osimertinib resistance emerges through on-target mechanisms (C797S mutation in 15–20% of cases) or bypass pathways (*MET* amplification in 15%, *HER2* amplification in 5%, *BRAF* mutations, histologic transformation to small cell). Serial liquid biopsy can identify these mechanisms and guide subsequent therapy—for example, combining osimertinib with MET inhibitors in *MET*-amplified resistance. In *ALK*-rearranged NSCLC, sequential ALK TKI therapy (crizotinib → alectinib/brigatinib → lorlatinib) can achieve multi-year disease control by overcoming different resistance mutations. However, in *RAS*-mutant cancers, pathway inhibition shows limited single-agent activity, and rational combinations remain investigational. The challenge of polyclonal resistance—where multiple mechanisms coexist in different tumor subclones—limits the efficacy of sequential monotherapy strategies.

3.5. Immunotherapy: Checkpoint inhibitors and cellular therapies

3.5.1. Definition and principle

Immunotherapy encompasses systemic treatments that enhance or redirect antitumor immunity to achieve durable tumor control in selected patients. The two major clinical platforms are ICIs and cellular therapies (most prominently CAR-T). ICIs targeting PD-1/PD-L1 and/or CTLA-4 can produce long-term survival benefit in a subset of patients, often reflected by a plateau ("tail") in survival curves. CAR-T therapy involves *ex vivo* engineering of autologous T cells to recognize tumor-associated antigens and has demonstrated high activity in several hematologic malignancies; translation to solid tumors remains limited by antigen heterogeneity, trafficking barriers, and immunosuppressive tumor microenvironments.[2,4,15-18,52,53,56] Biomarkers such as PD-L1 expression, MSI-H status, and TMB provide imperfect enrichment and should be interpreted within tumor-specific and indication-specific frameworks.[52,53,56]

3.5.2. Typical workflow

For ICIs, the workflow involves biomarker-based stratification where validated (e.g., PD-L1, MSI-H, TMB in selected contexts), followed by baseline assessment for autoimmune conditions or clinically relevant immunosuppression, and then proactive monitoring for irAEs using predefined evaluation and management pathways, including corticosteroids and escalation to additional immunosuppression for refractory cases. For CAR-T, the process proceeds from leukapheresis through manufacturing, genetic modification and expansion, lymphodepleting chemotherapy, infusion, and then monitoring and management of cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), and prolonged cytopenias.[15-18,44,45,56]

3.5.3. Mechanisms

Immune checkpoint inhibitors restore antitumor T-cell activity by reversing immune exhaustion and re-engaging cytotoxic responses through blockade of the PD-1/PD-L1 and CTLA-4 pathways. CAR-T cells mediate antigen-dependent cytotoxicity, undergo *ex vivo* expansion, and persist after infusion. Radiotherapy may act as an immune-priming modality via immunogenic cell death and microenvironmental modulation, although optimal integration remains context-dependent.[19-21,44,45,56]

3.5.4. Toxicities

Immune checkpoint inhibitor toxicities—irAEs—affect the skin, endocrine organs, liver, gastrointestinal tract, and lungs (notably pneumonitis), with variable onset and potential chronicity.[38,44,45,56] CAR-T toxicities include CRS, ICANS, infections, and prolonged cytopenias, often requiring hospitalization and intensive supportive care.[15-18,44,45,56]

3.5.5. Drug–drug interactions

Baseline systemic corticosteroids and other immunosuppressants may attenuate ICI activity in some contexts. Treatment of irAEs may require corticosteroids and, for refractory cases, agents such as antitumor necrosis factor (TNF) or mycophenolate. Thoracic radiotherapy combined with ICIs may increase pneumonitis risk; risk mitigation requires careful sequencing and monitoring (Table 2).[20-24,38]

3.5.6. Strengths and limitations

Immunotherapy offers durable remissions in a subset of patients and long OS tails. Its limitations include low response fractions in "cold" tumors, severe irAEs, CRS, ICANS, and high cost and center requirements.

3.5.7. Validated combinations and sequences

Phase III evidence supports chemo-immunotherapy as a standard first-line approach in metastatic NSCLC (KEYNOTE-189/-407).[1,2] Dual checkpoint blockade is validated in advanced melanoma (CheckMate-067)[4] and RCC (CheckMate-214).[44] In early-stage triple-negative breast cancer (TNBC), neoadjuvant pembrolizumab plus chemotherapy improves outcomes (KEYNOTE-522).[57,58] CAR-T products (axi-cel, tisa-cel, liso-cel, and ide-cel in myeloma) achieve high response rates in selected relapsed/refractory hematologic malignancies.[15-18] Across settings, sequencing is typically guided by the evidence base, tumor biology, toxicity constraints, and feasibility; in several chemo-ICI regimens, chemotherapy may also contribute biologically via immunogenic cell death and microenvironment modulation, potentially enhancing ICI activity.[1,2]

3.6. Hormone therapy

3.6.1. Definition and principle

Hormone therapy targets steroid hormone-dependent signaling to suppress proliferation and survival of endocrine-driven tumors. Its clinical value lies in enabling prolonged disease control with comparatively favorable tolerability, while delaying or overcoming endocrine resistance through rational combinations.[28-35] In estrogen receptor (ER)-positive breast cancer, endocrine backbones include aromatase inhibitors and ER-directed agents (selective estrogen receptor modulators [SERMs]/selective estrogen receptor degraders [SERDs]), with major advances achieved by combining endocrine therapy with targeted partners such as cyclic-dependent kinase (CDK)4/6 inhibitors, which prolong disease control in metastatic settings and support modern sequencing approaches.[31-35] In prostate cancer, androgen deprivation therapy (ADT) via gonadotropin-releasing hormone (GnRH) agonists/antagonists remains foundational, and treatment intensification with androgen receptor (AR) pathway inhibitors (e.g., abiraterone, enzalutamide, apalutamide) has reshaped management across hormone-sensitive and castration-resistant disease states.[34,35]

3.6.2. Typical workflow

The workflow begins with confirmation of ER/progesterone receptor (PR)/AR status and clinically relevant context—for example, menopausal status in breast cancer or disease state in prostate cancer. The endocrine backbone is then selected with consideration of evidence-supported intensification, such as CDK4/6 inhibitor-based combinations in ER-positive breast cancer or AR pathway intensification in prostate cancer.[31-35] Long-term monitoring addresses bone health, metabolic profile, and cardiovascular risk throughout treatment.

3.6.3. Mechanisms

The SERD/SERM agents antagonize ER; aromatase inhibitors suppress estrogen synthesis; ADT lowers testosterone; and antiandrogens block AR.[28-35]

3.6.4. Toxicities

Toxicities include hot flashes, fatigue, libido reduction, osteoporosis and fractures, thromboembolism (tamoxifen), and metabolic syndrome and sarcopenia with ADT.[34,35,59]

3.6.5. Drug–drug interactions

Clinically relevant issues include tamoxifen interactions

with anticoagulants (increased bleeding risk) and CYP-mediated interactions with several antiandrogens. Bone-protective co-management with calcium, vitamin D, bisphosphonates, and denosumab when appropriate often accompanies prolonged endocrine suppression (Table 2).[28-35]

3.6.6. Strengths and limitations

Hormone therapy offers tolerability, oral regimens, and durable control. Its limitations include endocrine resistance and metabolic risks.

3.6.7. Validated combinations and sequences

In ER-positive breast cancer, endocrine therapy combined with CDK4/6 inhibitors is validated across PALOMA, MONALEESA, and MONARCH trials.[31-35] In prostate cancer, ADT combined with abiraterone, enzalutamide, or apalutamide is standard in metastatic castration-resistant prostate cancer/metastatic hormone-sensitive prostate cancer.[34,35]

3.7. Genetic and cell-genetic approaches

3.7.1. Definition and principle

Genetic and cell–genetic approaches aim to modify tumor biology or host immunity through gene delivery, silencing, or editing, and personalized immunogenic platforms (e.g., neoantigen vaccination). These strategies seek to restore tumor suppressor functions, suppress oncogenic drivers, or reprogram immune effector cells to recognize tumor antigens more effectively. While proof-of-concept and early clinical signals exist, broad clinical adoption in solid tumors remains limited by delivery constraints, off-target risks, manufacturing complexity, and the current predominance of early-phase evidence.[60-65]

3.7.2. Typical workflow

The workflow proceeds from platform selection (e.g., viral versus lipid/nanoparticle delivery; *ex vivo* versus *ex vivo* engineering) through feasibility and safety screening, delivery/manufacturing and administration, monitoring of expression, immune activity, and toxicity, and finally consideration of combination strategies with ICIs or targeted agents when supported by emerging evidence.[60-65]

3.7.3. Mechanisms

Key mechanisms include tumor suppressor restoration, oncogene silencing, T-cell editing (e.g., *PD1* knockout), and neoantigen-directed immunity via mRNA vaccines.[60-65]

3.7.4. Toxicities and limitations

Toxicities and limitations encompass vector immunogenicity, off-target editing, delivery barriers in solid tumors, and cost and access constraints.

3.7.5. Drug–drug interactions

Concomitant immunosuppression may blunt immune responses. Systemic inflammatory risk exists with ICI and radiotherapy combinations (see Table 2).

3.7.6. Strengths and limitations

Genetic platforms offer novel mechanisms and personalization potential. Their limitations include technological complexity, delivery challenges, and cost.

3.7.7. Validated combinations and sequences

T-VEC combined with ICI in melanoma and early CRISPR-engineered T-cell studies represent current validated and investigational approaches.[61-63,66,67]

3.8. Combined strategies and sequences

3.8.1. Principle

Contemporary oncology increasingly relies on multimodality and combination strategies to improve depth and durability of response, address spatial and temporal heterogeneity, and delay or overcome therapeutic resistance. Local modalities (surgery, radiotherapy) are integrated with systemic platforms (chemotherapy, targeted therapy, endocrine therapy, ICIs, and cellular therapies) within evidence-based sequences that are tailored to tumor biology, disease stage, and patient-level constraints.[1-14] Mechanistically, combinations are pursued to increase tumor cell kill through non-overlapping mechanisms, recondition the tumor microenvironment to improve immune infiltration and antigen presentation, and reduce the probability of clonal escape via pathway redundancy or antigen heterogeneity.

These combinations achieve synergy through complementary mechanisms. Chemotherapy with ICI induces immunogenic cell death, releasing DAMPs that enhance antigen presentation and T-cell priming. Anti-VEGF agents combined with ICI normalize tumor vasculature, enhancing immune cell infiltration and augmenting ICI efficacy. Dual HER2 blockade via complementary mechanisms reduces bypass resistance and delays therapeutic escape. ADCs after HER2 blockade deliver potent cytotoxic payloads directly to HER2-expressing cancer cells, minimizing systemic toxicity.

These rational combinations and sequences demonstrate that synergistic approaches can improve survival outcomes, overcome therapeutic resistance, and enable personalized, biomarker-driven strategies.[1-6,9-14]

3.8.2. Approaches

Synergistic combinations include chemotherapy plus ICI[1,2,57,58], ICI plus anti-VEGF[3], and dual HER2 blockade plus chemotherapy followed by ADCs.[5,6,12-14] Resistance-aware sequences in *EGFR*-mutant NSCLC proceed from osimertinib through re-profiling (e.g., for *MET* amplification) to adding a MET inhibitor or switching to an ADC; in HER2-positive breast cancer, the sequence runs from mAb through T-DM1 to T-DXd. Representative decision pathways for common clinical situations are summarized in Section A1 (Typical clinical scenarios). Oligometastatic strategies combine a systemic platform with SBRT to control disease sites.[23,46]

3.8.3. Safety

The principal limitation of combination and sequence intensification is toxicity amplification and the need for coordinated monitoring across specialties. Clinically relevant risks include pneumonitis with thoracic radiotherapy plus ICI, fistula and necrosis in pelvic radiotherapy combined with anti-VEGF exposure, ILD with trastuzumab deruxtecan, and cardiotoxicity with HER2-directed regimens, underscoring the importance of risk-adapted coordination, early recognition pathways, and supportive-care integration (Table 2).[12-14,19-24] In addition, real-world feasibility is constrained by access to biomarkers, specialized centers (e.g., CAR-T), drug affordability, and longitudinal PRO-informed toxicity management.

4. Discussion

Therapeutic resistance operates through three interconnected pathways: target-level alterations, pathway bypass, and microenvironmental protection.

Target-level resistance includes on-target mutations that prevent drug binding (*EGFR* C797S after osimertinib, *BCR-ABL* T315I in CML), target amplification that overwhelms inhibitor capacity, or target loss (*RB1* deletion eliminating CDK4/6 inhibitor dependency). These mechanisms are often detectable through ctDNA monitoring and may guide selection of next-generation inhibitors or alternative targets.

Pathway bypass involves activation of parallel signaling cascades that circumvent the inhibited pathway. *MET* or *HER2* amplification in EGFR-inhibitor-resistant NSCLC, *PIK3CA* mutations in HER2-positive breast cancer, and MAPK pathway reactivation in *BRAF*-mutant melanoma exemplify this category. Rational combination therapy targeting both the primary driver and common bypass pathways—such as BRAF plus MEK inhibition in melanoma—can delay resistance, though toxicity often limits dosing intensity.

Microenvironmental resistance reflects tumor-stroma interactions that protect cancer cells from therapy. In bone metastases, the CXCL12/CXCR4 axis and mesenchymal stromal cells create a protective niche.[68] In immunotherapy, myeloid-derived suppressor cells, regulatory T cells, and immunosuppressive cytokines (TGF-β, IL-10) establish an immune-excluded phenotype. Strategies targeting the microenvironment—such as VEGF inhibition to normalize vasculature and enhance immune infiltration, or CSF-1R inhibition to reprogram tumor-associated macrophages—are under active investigation.

4.1. Tumor-specific resistance patterns and countermeasures

In *EGFR*-mutated NSCLC, resistance arises from target mutations (C797S in 15–20%), signaling pathway bypass via *MET* amplification (15%) or HER2 activation, and histological transformation to small cell or squamous phenotypes. Management requires molecular re-profiling, ideally with ctDNA monitoring, followed by rational strategies such as combination with MET inhibitors (capmatinib, tepotinib), switching to ADCs, or enrollment in trials of fourth-generation EGFR inhibitors.[9–11,37,51–53]

In *ALK*-rearranged NSCLC, resistance is often mediated by mutations in the kinase domain (G1202R, I1171N/T/S). Sequential ALK TKI therapy (crizotinib → alectinib/brigatinib → lorlatinib) can achieve multi-year disease control by overcoming different resistance mutations. Multi-target blockade strategies combining ALK inhibition with MEK or SHP2 inhibitors are under investigation to suppress parallel escape pathways.[51–53]

In ER-positive breast cancer, endocrine resistance is caused by *ESR1* mutations (30–40% of aromatase inhibitor-resistant cases) and CDK4/6 pathway reactivation. Treatment strategies include novel oral SERDs (elacestrant, camizestrant), continuation or switching of CDK4/6 inhibitors based on RB1 status, PI3K inhibitors in *PIK3CA*-mutant disease, and investigational FGFR inhibitors in *FGFR*-amplified tumors.[31–35]

In HER2-positive breast cancer, resistance reflects HER2 heterogeneity and clonal selection. Sequential strategies have been validated: trastuzumab-based regimens → T-DM1 → T-DXd, with response rates of 60–80% even after multiple prior lines. Novel bispecific antibodies (zanidatamab) and next-generation ADCs are in clinical development.[12–14]

Immune checkpoint inhibitor resistance mechanisms include loss of *B2M* (impaired antigen presentation in 10–15%), upregulation of alternative checkpoints

(LAG-3, TIGIT, TIM-3), and immunosuppressive tumor microenvironment remodeling. Countermeasures include dual checkpoint blockade (anti-PD-1 plus anti-LAG-3 in relatlimab/nivolumab), anti-TGF-β agents to reverse immune exclusion, stimulator of interferon genes (STING) agonists to enhance innate immunity, and radiotherapy to increase tumor immunogenicity through immunogenic cell death.[38,44,45,56]

Clinically, resistance management requires serial tumor profiling (tissue rebiopsy or liquid biopsy), understanding of mechanism-specific vulnerabilities, and access to rational combination or sequential strategies. The emergence of multi-omic profiling may eventually enable predictive modeling of resistance trajectories, allowing preemptive therapeutic adjustments.

4.2. Bone metastases and the tumor microenvironment

Skeletal metastases of unknown primary (SMUP) represent a diagnostically and therapeutically challenging subset of metastatic cancer, accounting for 8–23% of cancer of unknown primary presentations.[68] The bone marrow microenvironment provides a uniquely permissive niche for metastatic colonization through multiple mechanisms. Cancer cells home to bone via CXCL12/CXCR4 chemokine signaling, which guides circulating tumor cells to the endosteal and perivascular niches normally occupied by hematopoietic stem cells. Once lodged in bone, cancer cells interact with mesenchymal stromal cells, osteoblasts, and osteoclasts, hijacking normal bone remodeling processes.[68]

The "vicious cycle" of bone metastasis involves tumor-secreted factors (parathyroid hormone-related protein [PTHrP], IL-6, receptor activator of nuclear factor kappa-B ligand [RANKL]) that stimulate osteoclast activity, leading to bone resorption. Released bone matrix factors (TGF-β, insulin-like growth factor 1 [IGF-1], calcium) in turn promote tumor growth, creating a self-reinforcing loop. Hypoxia within the bone marrow, mediated by HIF-1α and HIF-2α signaling, further supports cancer cell survival and dormancy. Perivascular niches may harbor dormant tumor cells that resist chemotherapy and later emerge as overt metastases.[68]

Diagnostic evaluation of SMUP requires integrated imaging (CT, MRI, bone scintigraphy, or PET-CT), serum bone turnover markers (alkaline phosphatase, C-terminal telopeptide), and tissue biopsy with comprehensive immunohistochemistry. Despite thorough investigation, the primary site remains unidentified in 11–40% of cases even at autopsy. Prognosis is generally poor (median OS 3–11 months), though identification of treatable primaries (prostate, breast) significantly improves outcomes.[68]

Bone-modifying agents—bisphosphonates (zoledronic acid) and the RANKL inhibitor denosumab—are foundational for preventing skeletal-related events (pathologic fractures, spinal cord compression, need for bone radiation). Beyond their anti-resorptive effects, emerging evidence suggests that these agents may modulate the immunosuppressive bone microenvironment, potentially enhancing immunotherapy efficacy.[68] Integration with systemic therapy requires attention to osteonecrosis of the jaw risk (2–5% with long-term use), renal function monitoring, and calcium/vitamin D supplementation. The role of bone-modifying agents in the adjuvant setting remains investigational, with conflicting results across tumor types.

4.3. Quality of life and patient-reported outcomes

In cancer care, systematic collection of PROs represents both standard practice and an ethical imperative. Validated instruments (PRO-CTCAE, EORTC QLQ-C30) and digital platforms enable early detection of symptoms, including nausea, diarrhea, mucositis, fatigue, neuropathy, and psychological distress, facilitating timely intervention. Proactive monitoring enables maintenance of treatment intensity and has been shown to lower emergency room visits and hospital stays.[39–41]

Supportive care standards are central to maintaining quality of life. Prevention of nausea relies on triple-agent regimens for highly emetogenic chemotherapy. Primary prophylaxis with G-CSF is indicated when the risk of febrile neutropenia is ≥20%. Cardiological monitoring is required during HER2-targeted therapy. Early screening for ILD is essential in patients receiving T-DXd. Integration of validated PRO instruments into digital platforms enables a shift from reactive to proactive, patient-centered toxicity management. PRO-guided dose modifications and early supportive interventions improve treatment tolerability, align outcomes with patient experience, and enhance long-term quality of life.

4.4. Global access and health equity

Disparities in cancer care access represent a fundamental ethical challenge. In low- and middle-income countries (LMICs), late-stage diagnosis predominates due to limited screening infrastructure, while restricted availability of biomarker testing (NGS, PD-L1 IHC) prevents precision therapy selection. Even when molecular targets are identified, access to targeted agents and immunotherapy is severely constrained by cost—monthly treatment expenses often exceed annual per-capita gross domestic product (GDP). Radiotherapy capacity is grossly inadequate, with fewer than 30% of LMICs meeting International Atomic Energy Agency-recommended linear accelerator-to-population ratios.[42,43]

Potential solutions include biosimilar adoption (reducing costs 30–70% for trastuzumab, rituximab, and bevacizumab), tiered pricing negotiated through international consortia, and technology transfer for local manufacturing. Diagnostic access may improve through point-of-care testing, telepathology, and centralized reference laboratories. However, sustainable progress requires systemic investment in healthcare infrastructure, oncology workforce training, and essential medicines procurement systems. Without addressing these structural barriers, advances in precision oncology risk deepening rather than resolving global inequities.

4.5. Emerging platforms

Several investigational platforms show early promise but require validation in adequately powered trials before clinical implementation. mRNA-based neoantigen vaccines induce robust and durable T-cell responses against tumor-specific neoantigens. Clinical application awaits demonstration of survival benefit in randomized phase III trials; current evidence is limited to phase I/II immunogenicity and safety data. Bispecific antibodies and natural killer cell-based therapies aim to bridge innate and adaptive immunity, potentially overcoming immune evasion mechanisms. PROTACs induce targeted protein degradation rather than reversible inhibition, expanding the druggable proteome; the technology remains in early clinical development (phase I/II), with challenges including oral bioavailability, tissue distribution, and potential for compensatory protein upregulation.[69] Radioligand treatments, such as those targeting PSMA and SSTR, deliver cytotoxic payloads with high precision, minimizing normal-tissue exposure. STING agonists and anti-TGF-β agents are under investigation to remodel the tumor microenvironment, converting immune-excluded ("cold") tumors to immune-inflamed ("hot") phenotypes. Nanomedicine platforms are under development to enhance drug delivery and reduce systemic toxicity, enabling spatiotemporal control of therapeutic, genetic, or immunomodulatory cargo release.[65]

Collectively, these platforms represent a shift toward mechanistically precise, personalized interventions, expanding both the therapeutic landscape and opportunities for rational combination with established modalities.[61-65]

4.6. Geography and ethics

Global cancer outcomes have improved heterogeneously, creating geographic and ethical disparities. Survival rates have improved more rapidly in high-income countries due to established screening programs, comprehensive surgical and radiation infrastructure, and widespread access to molecular diagnostics (NGS, PD-L1 testing). Healthcare financing structures enable timely access to targeted treatments and ICIs.[24,25]

Low- and middle-income countries face substantial barriers, including inadequate infrastructure, limited diagnostic access, and prohibitive drug costs. Addressing these inequities requires context-adapted solutions balancing innovation with pragmatic implementation. Essential treatment packages represent one approach, focusing on standard treatments, more affordable drugs, and leveraging telemedicine for knowledge dissemination and referral optimization. PRO integration ensures patient-centered, cost-effective care delivery. The global oncology community bears both scientific and ethical responsibility to ensure that advances do not exacerbate inequities but rather improve outcomes across all resource settings.

5. Conclusion

Three principles define optimal cancer care in the precision oncology era. First, molecular profiling must guide therapy selection, with serial tumor assessment enabling adaptive strategies that address evolving resistance. Second, therapeutic decisions require balancing efficacy against toxicity and quality of life; systematic PRO monitoring improves both tolerability and survival. Third, equitable access to effective diagnostics and therapies constitutes an ethical imperative. Current global disparities demand coordinated efforts across biosimilar development, tiered pricing, and healthcare system strengthening. Future progress depends on a mechanistic understanding of resistance, pragmatic trial designs reflecting real-world heterogeneity, and delivery systems capable of implementing personalized care at scale.

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Conflict of interest

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Author contributions

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Appendix

A1. Typical clinical scenarios

The following representative scenarios illustrate how the therapeutic principles discussed throughout this review translate into clinical practice across major tumor types:

(i) Non-small cell lung cancer (NSCLC)

In resectable *EGFR*-mutant disease, surgical resection followed by adjuvant osimertinib represents the current standard of care, with ADAURA demonstrating significant improvement in disease-free survival.[9-11] For metastatic nonsquamous NSCLC, platinum-pemetrexed plus pembrolizumab (KEYNOTE-189) is the established first-line backbone.[1] In squamous NSCLC, platinum-paclitaxel plus pembrolizumab (KEYNOTE-407) is the preferred first-line regimen.[2] For biomarker-agnostic systemic disease, atezolizumab combined with bevacizumab and chemotherapy (IMpower150) provides an alternative platform.[3]

(ii) Melanoma

In advanced melanoma, first-line dual checkpoint blockade with nivolumab plus ipilimumab (CheckMate-067) remains a cornerstone strategy, offering durable long-term survival in a meaningful subset of patients.[4]

(iii) Triple-negative breast cancer (TNBC)

In early-stage TNBC, neoadjuvant pembrolizumab combined with chemotherapy, followed by adjuvant pembrolizumab (KEYNOTE-522), has demonstrated improved event-free survival and is now a standard approach in eligible patients.[57,58]

(iv) HER2-positive breast cancer

The validated sequential strategy proceeds from trastuzumab plus pertuzumab plus docetaxel (CLEOPATRA) through T-DM1 (EMILIA) to trastuzumab deruxtecan (DESTINY-Breast03), with each transition guided by prior response and resistance profiling.[5,6,13,14]

(v) Metastatic colorectal cancer

FOLFOX or FOLFIRI combined with bevacizumab, or with cetuximab in KRAS/NRAS wild-type tumors with left-sided primary, remains the standard first-line framework, with sidedness and RAS/BRAF status guiding biological agent selection.[27]

(vi) Diffuse large B-cell lymphoma (DLBCL)

In relapsed or refractory DLBCL, axicabtagene ciloleucel (axi-cel; ZUMA-1) established CAR-T cell therapy as a potentially curative option in eligible patients after two or more prior lines.[15]

(vii) Pancreatic ductal adenocarcinoma (PDAC)

In the metastatic setting, FOLFIRINOX demonstrated superior overall survival compared with gemcitabine monotherapy and remains the preferred regimen for fit patients.[28] In the adjuvant setting, the PRODIGE-24 trial established modified FOLFIRINOX as the standard of care following resection.[36]

Collectively, these scenarios underscore the central role of biomarker-driven therapy selection, rational combination and sequencing strategies, and adaptive treatment modifications in response to emerging resistance. They illustrate how the integration of local and systemic modalities, guided by molecular profiling and patient-centred outcome assessment, defines contemporary oncology practice.