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Review

Latest Approaches in Cancer Therapy and Remaining Gaps

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Abstract

Cancer remains one of the major global challenges due to its complex and heterogeneous molecular nature across individuals. Recent advances in technology have enhanced the understanding of cancer's molecular mechanisms, paving the way for the development of effective therapeutics. These include small-molecule inhibitors and monoclonal antibodies, used to interfere with the oncogenic signaling pathways. Immunotherapy has also emerged as a promising area in cancer therapy, with approaches such as immune checkpoint inhibitors, immune cell engagers, adoptive T-cell therapies, and cancer vaccines. Besides, stem cell-based approaches are also being assessed for their potential to modulate immune responses and promote tissue repair. Although these advances have improved cancer care, significant challenges remain. The major challenges in cancer therapy may include drug resistance, side effects, and systemic toxicity that diminish therapeutic efficacy. Moreover, the heterogeneous nature of tumors and the immunosuppressive tumor microenvironment (TME) in solid tumors further complicate treatment responses, especially in advanced or aggressive

cancers. Hence, in this review, we highlight the latest approaches in cancer therapy and discuss the remaining gaps and challenges that hinder their full clinical potential.

Keywords
Cancer therapy; targeted therapy; immunotherapy; stem cell therapy; tumor heterogeneity; drug resistance

1. Introduction

Cancer is a complex disease and one of the leading causes of mortality globally [1, 2]. In early 2025, 18.6 million people had a history of cancer, and this number is expected to climb to over 22 million over the next decade in the United States (U.S.) alone [3]. Cancer has various causes, and the prognosis is complex and differs for each patient because the molecular signatures are unique in the human body. Underlying molecular mechanisms, such as genetic heterogeneity and genetic and epigenetic modifications, complicate both diagnosis and treatment [4, 5]. Generally, cancer cells have a less differentiated phenotype than surrounding cells, and most are multidrug-resistant. Therefore, it is not surprising that one of the important questions in cancer research today is to understand the underlying molecular mechanisms that underpin the development of targeted treatments [6, 7].

Conventional cancer therapy, primarily chemotherapy, is generally considered successful but is associated with significant side effects, such as a lack of specificity and adverse side effects. Traditional cancer treatments, therefore, lump patients together and use similar drugs, resulting in variable responses to the treatment [8]. Latest research on cancer treatment and findings have led to the development of precision medicine approaches like basing treatment on the molecular properties of the tumor cell [9-11].

Targeted drug delivery plays a crucial role in precision medicine for cancer treatment. This approach focuses on delivering medication directly to the targeted organ or tissue, thereby systematically increasing the drug concentration at the desired site [12, 13]. The main aim of cancer research is to generate tumor-specific treatment strategies that kill cancer cells while sparing normal healthy cells [2, 10].

Cancer raises multiple mutations in a single cell and its progeny. Affected cells and their progeny accumulate sequential mutations and sustain multiple genetic and epigenetic alterations over decades. Genetic mutations disrupt critical cellular pathways [14, 15].

1.1 Molecular Background of Cancer Development

The development of cancer may require mutations in multiple genes. Mutations may affect different aspects of cellular growth control. Such as cell cycle control/regulatory genes (oncogenes and tumor suppressor genes), DNA repair genes, angiogenesis genes, telomere regulation, cell morphology/metastasis, and immune surveillance [5, 16, 17]. Basically, genes that regulate all these properties, directly and/or indirectly, can contribute to cancer. In addition to alterations in cancer-related genes, telomerase activation is necessary for the sustained growth and development of most cancer types, except those that use alternative pathways for telomeric integrity and repair.

Telomeres are the ends of chromosomes, specialized nucleoprotein structures that maintain chromosome stability and, thus, the genome [18, 19]. When telomeres shorten to a critical level, the cell declines further cellular division. Telomeres normally shorten with each cell division and when damaged. Cancer cells maintain telomere length and stability mainly by reactivating telomerase, unlike normal cells [18, 20].

2. Current Approaches in Cancer Therapy

Cancer remains a global health challenge. Traditional treatment methods, including surgery, chemotherapy, radiotherapy, or their combinations, have long been utilized for cancer management. However, the treatment process remains highly complex and often falls short of achieving the desired level of efficacy [8]. Consequently, several innovative approaches have been introduced, including stem cell therapy, targeted therapy, ablation therapy, nanoparticles, natural antioxidants, radiomics, chemo dynamic therapy, sonodynamic therapy, and ferroptosis-based therapy [21-24].

Stem cell therapy has shown promising efficacy in regenerating and repairing damaged or diseased organs and/or tissues [25]. Recent advances in oncology emphasize the development of safe and effective cancer nanomedicines, with nanoparticles offering new opportunities for both diagnosis and therapy [26, 27]. Targeted therapy has demonstrated significant potential in inhibiting the growth and spread of specific cancer cells while preserving healthy cells [28, 29]. Ablation therapy has gained attention as a minimally invasive technique that destroys cancer cells by freezing or burning them, eliminating the need for open surgery [30]. Additionally, complementary medicine, including natural antioxidants, has been proposed to counteract the harmful effects of free radicals [31, 32]. Moreover, various innovative technologies are currently undergoing clinical trials, with some already approved for clinical use [33-37]. Some of the major therapeutic approaches in cancer treatment are summarized in this section and illustrated in Figure 1.

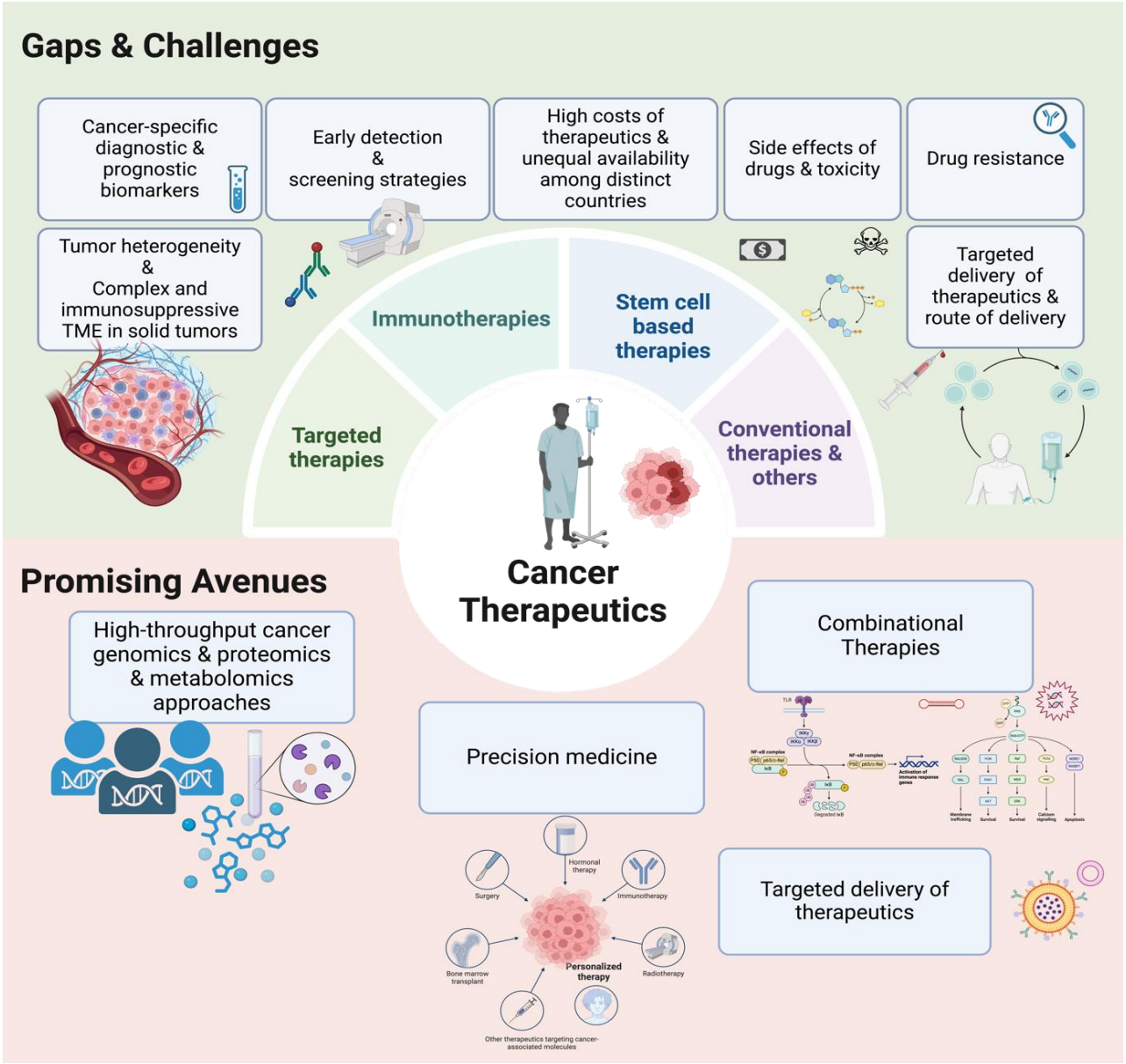

Figure 1 Current landscape of anti-cancer therapeutic approaches. The upper panel summarizes the major challenges that limit the effectiveness of current cancer therapeutic strategies. The lower panel highlights promising future directions to address these limitations. The figure was created with BioRender.com.

2.1 Targeted Therapy

Targeted cancer therapies primarily target a specific mutation or molecular pathway that drives tumor progression. While conventional therapies affect both cancerous and normally dividing cells, therefore all cells that have division potential, targeted therapies only aim to suppress division in cancer cells by limiting the effects of molecules involved in tumor growth, progression, and metastasis. Moreover, targeted therapies generally have fewer side effects for patients because healthy cells are less affected than with conventional cancer treatments.

There are several mechanisms in cancer cells that can be targeted for therapies. One key mechanism of targeted cancer therapies is the inhibition of cancer cell growth by either blocking

protein expression or normalizing their activity. For example, the human epidermal growth factor receptor 2 (HER2) receptor is overexpressed in some breast cancers, leading to aggressive tumor growth. Trastuzumab (Herceptin) is a monoclonal antibody that specifically binds to the HER2 protein, inhibiting its function and preventing further tumor proliferation [38]. Lapatinib, a dual EGFR/HER2 inhibitor, is particularly useful in cases resistant to monoclonal antibody therapy like Trastuzumab [39].

Targeted therapies provide personalized treatments to cancer patients. Some of the U.S. Food and Drug Administration (FDA)-approved targeted therapy drugs are listed in Table 1. Tyrosine kinase inhibitors (TKIs) have proved to be one of the main treatment options. Normally, tyrosine kinases phosphorylate the tyrosine residues on proteins for the regulation of cell cycle progression and signal transduction. The mechanistic action of TKIs is to inhibit the activity of an enzyme involved in tumor growth, neoplastic transformation, cellular survival, and migration. TKIs achieve this by competitively binding to the ATP-binding sites of kinases so that the kinase becomes inactive. TKIs can be both single-kinase-specific or target multiple kinases—the development of next-generation TKIs aimed to overcome resistance mutations and improve selectivity [40].

Table 1 List of Targeted Therapy Drugs Approved by the Food and Drug Administration (FDA) for Different Cancer Types (originally published by the National Cancer Institute; information retrieved and summarized from www.cancer.gov for the selected cancer types).

Cancer Type	Target/Mechanism	Drug Example (s)
Bladder Cancer	PD-L1, PD-1, Enzyme inhibitor, Recombinant protein complex, Antibody-drug conjugate	Atezolizumab, Avelumab, Enfortumab Vedotin-ejfv, Erdafitinib, Nivolumab, Nogapendekin Alfa Inbakicept-pmln, Pembrolizumab
Brain Cancer	HIF-2α, VEGF, BRAF, Enzyme inhibitor, mTOR, MEK1, MEK2	Belzutifan, Bevacizumab, Dabrafenib, Everolimus, Tovorafenib, Trametinib, Vorasidenib
Breast Cancer	CDK4/6, Antibody-drug conjugate, PI3K, mTOR, HER2, Enzyme inhibitor	Abemaciclib, Ado-Trastuzumab Emtansine, Alpelisib, Everolimus, Pertuzumab, Ribociclib, Tucatinib, Palbociclib, Exemestane, Letrozole, Sacituzumab Govitecan-hziy
Cervical Cancer	VEGF, PD-1, Antibody-drug conjugate	Bevacizumab, Pembrolizumab, Tisotumab Vedotin-tftv
Colorectal Cancer	VEGF, EGFR, BRAF, CTLA-4, PD-1, VEGFR-2, Multi-kinase inhibitor, HER2 tyrosine kinase inhibitor	Bevacizumab, Cetuximab, Encorafenib, Ipilimumab, Nivolumab, Panitumumab, Pembrolizumab, Ramucirumab, Regorafenib, Tucatinib
Endocrine and Neuroendocrine Tumors	PD-L1, Radiopharmaceutical, Somatostatin receptors	Avelumab, Iobenguane I 131, Lanreotide Acetate, Lutetium Lu 177-Dotatate
Endometrial Cancer	PD-1, PD-L1, Multi-kinase inhibitor	Dostarlimab-gxly, Durvalumab, Lenvatinib mesylate, Pembrolizumab

Esophageal Cancer	Antibody-drug conjugate, CTLA-4, PD-1, VEGFR-2, HER2	Fam-Trastuzumab Deruxtecan-nxki, Ipilimumab, Nivolumab, Pembrolizumab, Ramucirumab, Tislelizumab-jsgr, Trastuzumab
Gastrointestinal Stromal Tumor	Enzyme inhibitor, Multi-kinase inhibitor	Avapritinib, Imatinib mesylate, Regorafenib, Ripretinib, Sunitinib malate
Head and Neck Cancer	EGFR, PD-1	Cetuximab, Nivolumab, Pembrolizumab, Toripalimab
Leukemia	Enzyme inhibitor, CD52, BCR-ABL, Bi-specific T-cell engager (BiTE), CAR T-cell therapy, PI3K, BCL-2, CD20	Acalabrutinib, Alemtuzumab, Asciminib hydrochloride, Blinatumomab, Bosutinib, Brexucabtagene autoleucel, Dasatinib, Duvelisib, Venetoclax, Rituximab
Liver and Bile Duct Cancer	PD-L1, VEGF, Multi-kinase inhibitor, FGFR, PD-1	Atezolizumab, Bevacizumab, Cabozantinib-s-malate, Futibatinib, Nivolumab, Pembrolizumab, Regorafenib, Sorafenib tosylate
Lung Cancer	Enzyme inhibitor, EGFR, ALK, ROS1, RET, MEK, PD-L1, BRAF, VEGF	Afatinib dimaleate, Alectinib, Bevacizumab, Crizotinib, Dabrafenib mesylate, Durvalumab, Erlotinib hydrochloride, Gefitinib, Osimertinib mesylate, Selpercatinib, Trametinib dimethyl sulfoxide, Pembrolizumab
Lymphoma	BTK, CAR T-cell therapy, Antibody-drug conjugate, CD20, BCL-2	Acalabrutinib, Axicabtagene ciloleucel, Brentuximab vedotin, Ibrutinib, Obinutuzumab, Rituximab, Tisagenlecleucel, Venetoclax, Zanubrutinib
Pancreatic Cancer	HIF-2α, EGFR, mTOR, PARP, Multi-kinase inhibitor	Belzutifan, Erlotinib hydrochloride, Everolimus, Olaparib, Sunitinib malate
Prostate Cancer	CYP17, Androgen Receptor, PARP, GnRH receptor, Microtubule inhibitor, Radiopharmaceutical	Abiraterone acetate, Apalutamide, Darolutamide, Enzalutamide, Olaparib, Talazoparib tosylate, Leuprolide mesylate, Cabazitaxel, Lutetium Lu 177 vipivotide tetraxetan
Stomach (gastric) Cancer	Antibody-drug conjugate, PD-1, VEGFR-2, HER2	Fam-trastuzumab deruxtecan-nxki, Nivolumab, Pembrolizumab, Ramucirumab, Trastuzumab
Skin Cancer	PD-L1, MEK, BRAF, PD-1, CTLA-4	Atezolizumab, Binimetinib, Cemiplimab-rwlc, Cobimetinib fumarate, Dabrafenib mesylate, Ipilimumab, Nivolumab, Pembrolizumab, Trametinib dimethyl sulfoxide, Vemurafenib
Thyroid Cancer	Multi-kinase inhibitor, BRAF, RET	Cabozantinib s-malate, Selpercatinib, Vandetanib, Sorafenib tosylate, Dabrafenib mesylate, Lenvatinib mesylate

A prominent example is the use of Imatinib (Gleevec), a tyrosine kinase inhibitor often used in targeted cancer therapies, to treat chronic myelogenous leukemia (CML). It targets the BCR-ABL

fusion protein, which is formed by a gross chromosomal rearrangement that results in the Philadelphia chromosome, a driver of growth in CML cells. CML can be transformed into a manageable chronic condition with this treatment [41]. Imatinib is also effective in GIST patients with mutations in the KIT or PDGFRA tyrosine kinases, significantly improving survival rates [42]. However, over long-term use, imatinib can be ineffective due to drug resistance. To overcome this problem, second-generation TKIs have been developed. These include Dasatinib and Nilotinib [43].

Additionally, any genetic mutation present in cancer cells can, in principle, serve as a target for cancer therapies, because if the mutation can be targeted, only the cells that harbor it would be subject to the administered drug. In many non-small cell lung cancers (NSCLC), mutations in the epidermal growth factor receptor (EGFR) result in overexpression, increased activity, or increased ligand affinity. Drugs like Erlotinib (Tarceva) and Gefitinib (Iressa) work by inhibiting EGFR signaling downstream of secondary messengers, thereby blocking signal transduction pathways, reducing tumor size, and improving survival outcomes in patients with EGFR mutations [44]. In addition, Osimertinib is particularly effective against T790M resistance mutations. It has become the first-line therapy for EGFR-mutant NSCLC [45].

Moreover, some types of renal cell carcinomas (RCC) can also be targeted by TKIs. RCC is mainly driven by angiogenesis due to mutations in VEGFR. TKIs such as Sunitinib, Sorafenib, and Axitinib inhibit VEGFR and have improved outcomes in RCC patients [46]. Multi-targeted TKIs, including Lenvatinib and Sorafenib, have shown improvements in patients with advanced thyroid cancers, particularly those who do not respond to radioactive iodine therapy [47].

Although there is mounting evidence on the potential of targeted therapies, there are limitations that cannot be ignored. Because cancer cells have a higher mutation rate, alternative signaling pathways can be activated, promoting progression or relapse. In addition, some cancers cannot be targeted because the target mutations are not present. Currently, the potential for targeted therapy can only be increased through new target discoveries, combination therapies, and the development of novel therapies.

2.2 Immunotherapy

Tumor immunology and immunotherapy are among the rapidly evolving fields, significantly contributing to higher treatment success when applied alongside surgery and/or other treatment modalities, including chemotherapy and radiotherapy. Over the past five decades, advancements driven by molecular biology technologies have made cancer immunotherapy emerge as one of the most promising and fast-growing fields [48, 49]. Cancer immunotherapy harnesses the power of the immune system as a transformative approach, redirecting its components to attack and eradicate tumor cells [50]. Unlike other therapeutic strategies, immunotherapy works by stimulating or enhancing the immune system, the body's defense system [49]. Although several immunotherapeutic approaches have been developed and shown to improve treatment outcomes, it is important to note that, not all patients benefit from these strategies, as individual's tumors are highly heterogeneous [51]. This represents a major challenge for scientists in the field, who are striving to understand the mechanisms underlying resistance to immunotherapies [52]. In this section, current tumor immunotherapy strategies will be explored including immune checkpoint inhibitors (ICIs), adoptive cell therapy, cancer vaccines and a more recent approach, immune cell engagers.

2.2.1 Immune Checkpoint Inhibitors

One of the main obstacles to developing effective treatment strategies for solid tumors is the immunosuppressive microenvironment. The suppressive tumor microenvironment (TME) also contributes to tumor cells' escape from immune recognition [53]. Various small molecule-based immunomodulators (inhibitors, agonists, degraders) have been developed to transform the immunosuppressive tumor microenvironment by promoting T-cell infiltration and activating tumor-specific immune responses [54-56]. Therefore, targeting the TME and activating tumor-specific innate and adaptive immune responses. Besides, these small molecules could target intracellular molecules such as stimulator of interferon genes (STING) and indoleamine 2,3-dioxygenase 1 (IDO1), overcoming the challenges with antibody therapies, which can't cross the cell membrane. They could be combined with other therapies for potential synergistic effects [56].

Furthermore, immune checkpoints (ICs) are part of the immune system involved in vital cellular pathways regulating the immune responses and self-tolerance. However, the tumor cells can engage with these ICs to initiate immunosuppression to favor their escape from the immune system. Over the last decade, numerous reports have been published on the mechanisms of tumor escape and T-cell immunobiology [52, 57-61]. To this end, monoclonal antibodies (mAbs) targeting ICs have been developed for the treatment of various cancers. Immune checkpoint inhibitors (ICIs) work by targeting key regulatory molecules such as programmed cell death protein 1 (PD-1), programmed death-ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), which normally suppress T cell activity and contribute to immune tolerance in tumor cells [62]. By blocking these checkpoints, ICIs help to restore the anti-tumor immune responses. Nevertheless, some patients fail to respond to ICIs as a monotherapy regimen [53, 63].

Tumors can develop resistance to ICIs by upregulating alternative immune checkpoint molecules or recruiting additional immunosuppressive cells into the TME, thereby decreasing the therapeutic effectiveness of these drugs. To overcome the current limitations, combinational approaches are being tested in clinical trials [64-67]. These strategies may include combining multiple ICIs, such as anti-PD-1/PD-L1 and anti-CTLA-4 antibodies, and also integrating ICIs with other therapies, such as chemotherapy or radiotherapy, to improve therapeutic efficacy and patient outcomes [60, 68]. Notably, the FDA approved lymphocyte-activation gene 3 (LAG-3) immune checkpoint pathway inhibitor, relatlimab, in March 2022, for use in combination with the anti-PD-1 therapy nivolumab (previously approved) against pediatric and adult patient with advanced unresectable or metastatic melanoma. This highlights the potential of combinatorial approaches to improve outcomes in challenging cancers [68-71].

Nevertheless, overcoming the issues associated with ICIs may require strategies to enhance tumor immunogenicity, reprogram and reverse the immunosuppressive TME, and implement more refined patient selection processes [72].

2.2.2 Immune Cell Engagers

Immune cell engagers (ICEs) are antibody-based molecules, engineered to redirect the immune cells against cancer cells. The majority of ICEs are antibodies with multiple arms, including at least one arm targeting tumor-associated antigens (TAAs) and other arms engaging with effector immune cell surface molecule(s) [73, 74]. By redirecting immune cells toward tumors, ICEs trigger signaling

pathways essential for an effective anti-tumor response by forming an immunological synapse between the tumor and immune cells.

Although the initial generation of bispecific ICE molecules showed promise for treating hematological malignancies, their use was limited by side effects, including neurotoxicity, post-treatment relapse, and systemic inflammatory reactions [73, 75, 76]. In addition, several challenges hinder their therapeutic efficacy in solid tumors, including the immunosuppressive and heterogeneous TME [77]. Nevertheless, the first immune engager developed was the bispecific T-cell engager (BiTE), a groundbreaking innovation that cross-links T cells and cancer cells, enabling targeted immune responses.

In 2014, the FDA approved blinatumomab as consolidation for cluster of differentiation 19 (CD19)-positive Philadelphia chromosome-negative B-cell precursor acute lymphoblastic leukemia, which pioneered the field as the first bispecific antibody [78, 79]. Remarkably, bispecific T cell engager research is rapidly advancing with approximately 100 bispecific T cell engagers in clinical trials [79-81].

Recently, innovative therapeutic strategies have been introduced, including bifunctional checkpoint-inhibitory T cell engagers (CiTEs), simultaneous multiple interaction T cell engagers (SMITEs), trispecific killer engagers (TriKEs), and BiTE-expressing CAR T cells (CART.BiTE cells), which aim to combine multiple immune functions into a single treatment approach [82]. This multifaceted approach aims to improve anticancer effects while minimizing immune-related side effects [79, 83].

2.2.3 Adoptive Cell Therapy/T-Cell Transfer Therapy

Adoptive cell therapy (ACT), also known as T-cell transfer therapy, is among the most promising advances in cancer immunotherapy. This approach uses the patient's or donor's immune cells to combat cancer by enhancing their natural ability to target and kill tumor cells. Over the past decade, ACT has transformed the landscape of oncology, with particular success in hematological malignancies and emerging potential in solid tumors.

ACT is based on the principle of isolating immune cells, *ex vivo* modifying or expanding them, and reinfusing them into the patient. The process begins with the extraction of T cells, either from tumor tissue (for tumor-infiltrating lymphocytes, or TILs) or from the bloodstream. These cells are then activated and expanded in the laboratory or genetically engineered to enhance their tumor-killing capabilities. Once the T-cells are ready, they are infused back into the patient, typically following a lymphodepleting regimen to improve their survival and proliferation in the patient's body.

There are 3 main types of ACT: Tumor-Infiltrating Lymphocytes (TILs), Chimeric Antigen Receptor (CAR) T-Cell Therapy, and T-Cell Receptor (TCR) Therapy. TILs are extracted directly from a patient's tumor. These cells have already demonstrated a natural ability to recognize cancer cells, but are often present in insufficient numbers. By expanding TILs outside the body and reinfusing them into the patient, their therapeutic potential can be maximized. TIL therapy has shown encouraging results in melanoma, with some patients experiencing long-term remission and limited options [84, 85].

On the other hand, CAR T-cell therapy involves genetic engineering to equip T-cells with synthetic receptors that recognize specific tumor antigens. This therapy has been groundbreaking in the treatment of B-cell malignancies, particularly acute lymphoblastic leukemia (ALL) and diffuse large B-cell lymphoma. The success of CAR T-cell therapies, such as tisagenlecleucel, has paved the way

for broader applications in oncology [86]. The CAR T cells have unparalleled distinctiveness that enables cancer cells, including the corresponding tumor-associated antigens (TAAs), to be eliminated. The redundant death of healthy cells is prevented by CAR T-cell therapy. Cell surface molecules can be identified without the need for human leukocyte antigen (HLA) expression. Almost all types of antigens, including lipid, protein, and carbohydrate antigens, that are able to bind with antibodies can be recognized by CAR T-cell therapy [87].

Sudden interference and sole inoculation of CAR T cells are reported as a remarkable benefit of CAR T-cell therapy compared to different cancer therapy methods. CAR T cells can persist for a long time in the host body and retain the ability to detect and destroy cancer cells in the event of recurrence [88].

The CAR T-cell-dependent therapeutic agents can actively home to the disease site, detect the microenvironment, and integrate more than one inlet, leading to the occurrence of complicated and dynamic immunological reactions against cancer tissues. In contrast, conventional cancer medicaments (for instance, antibodies and small molecules) are based on passive targeting. Furthermore, the CAR T cells are qualified for self-enlargement, regeneration, and differentiation to different effector subsets [89].

Furthermore, TCR therapy focuses on enhancing T-cells' ability to recognize intracellular antigens presented on major histocompatibility complexes (MHCs). This approach is particularly promising for targeting solid tumors, where antigen heterogeneity and the tumor microenvironment pose challenges for CAR T cells [90].

There are serious challenges that lie ahead for ACT. One of them is antigen escape. Generation of tumor resistance to the antigen of CAR T cells is called antigen escape, which is defined as one of the major threats to the CAR T-cell therapy [91]. In antigen escape, the CAR T cells are in an inefficient condition, counter to tumor cells [92]. Antigen escape is encountered in cases of single-antigen targeting structures. Even though at the beginning of CAR T-cell therapy, an effective response is analyzed in single-antigen targeting, the target antigen expression can be partially or completely lost in patients who have been treated with CAR T-cell therapy and whose malignant cells [91]. Antigen escape recrudescence is associated with a lack of detectable CD19 on tumor cell surfaces, which can be explained by several mechanisms. For instance, CD19 is present but cannot be recognized by anti-CD19 CAR T cells due to harmful mutations and alternative splicing, leading to a lack of cell-surface fragments, including cognate antigenic determinants [92]. The antigen escape is commonly seen in pediatric patients with B-cell acute lymphoblastic leukemia (B-ALL) after CD19 CAR T-cell therapy. Numerous CD19 splice variants are reported by Sotillo and colleagues to be expressed in B-ALL, including exon 2, which does not include the extracellular antigenic determinant of CD19 recognized by anti-CD19-binder [89]. The elevated level of a CD19 isoform skipping exon 2 was analyzed in two patients; one had a CD19 genetic change, while the other did not. The CD19 mRNA can be alternatively spliced, causing the level of the full-size CD19 isoform to decline and raising the level of the isoform of exon 2. Moreover, the exon 2 isoform of CD19 is established as more stable than the full-length isoform, and the functional impairment associated with complete loss of CD19 expression can be partly rescued while causing the loss of the cognate CD19 antigenic determinant essential for recognition [93].

Furthermore, antigen escape was reported in chronic lymphocytic leukemia (CLL) and primary mediastinal large B-cell lymphoma (PMBCL). In the experiential analysis of solid tumors, the occurrence of antigen escape was also documented, with the HER2 target in a glioblastoma cell line

resulting in the presence of HER2-null tumor cells, in which the expression of nontargeted tumor-related antigens is maintained [92].

One of the most significant challenges of CAR T-cell therapy is managing its toxic side effects, including cytokine release syndrome (CRS) and neurotoxicity. These conditions, resulting from excessive immune activation, can be life-threatening. Advances in CAR design and supportive care protocols aim to mitigate these risks [94]. In addition to this, the treatment of solid tumors using ACT has been less successful compared to hematological malignancies. Issues such as antigen heterogeneity, poor T-cell infiltration into the tumor microenvironment, and immune suppression by the tumor stroma contribute to these challenges [95]. The complexity and cost of ACT also generate a risk for availability to the patients. Because T-cell therapies are personalized and production costs are high, they limit access for many patients [96]. These problems can be overcome when ACT can be more commonly generated.

2.2.4 Cancer Vaccines

Although cancer vaccines have emerged over the last decade, they have been employed for various cancers in both pre-clinical and clinical trial settings [97, 98]. Advances in scientific developments, particularly in genetic engineering and the enhanced mechanistic understanding of the complex pathophysiology of cancer and tumor immunology, have led to the use of biomolecules such as DNA, RNA, and proteins as potent cancer vaccine strategies [97, 99]. Currently, more than 1,000 clinical cancer vaccine trials have been completed using various biologicals and drug molecules, with almost an equal number of studies actively in progress [97, 98, 100]. Numerous cancer vaccine strategies in both pre-clinical and clinical trials aim to induce an antigen-specific T-cell response and restore the ability of immune cells to target tumor cells [99, 101-103].

Among these, the tumor vaccine candidate MNG1601 has completed Phase I/II trials for metastatic renal cell carcinoma (mRCC). It has been designed to include allogeneic, fourfold gene-modified vaccine cells and the toll-like receptor 9 (TLR-9) agonist Double stem-loop immunomodulator (dSLIM). These vaccine cells were derived from renal cell carcinoma tissue expressing various tumor antigens. They were further gene-modified to express co-stimulatory molecules, including CD80 and CD154, as well as cytokines such as GM-CSF and IL-7. This vaccine design shows promise in inducing a robust tumor-specific immune response while bridging innate and adaptive immunity [104] (ClinicalTrials.gov ID NCT01265368).

Hence, the primary targets in vaccine development are tumor-specific antigens (TSAs) and tumor-associated antigens (TAAs), which are essential for initiating a robust anti-tumor response by host immune cells through antigen presentation [102, 105]. TSAs are small molecules uniquely expressed in tumor cells, whereas TAAs are expressed at relatively low levels in both tumor and healthy cells [106, 107]. Importantly, recent studies have focused on targeting TSAs, particularly neoantigens, as they are unique to tumor cells and arise from various tumor-specific alterations [108]. Consequently, novel cancer immunotherapy strategies in recent years have emphasized the significance of neoantigen research, as these tumor-specific neoantigens are highly immunogenic and represent emerging targets for personalized cancer immunotherapies, including cancer vaccines [103, 108, 109]. The list of FDA-approved biologicals functioning as prophylactic or therapeutic vaccines is summarized in Table 2.

Table 2 List of Biologicals Approved by the FDA, Associated with Different Cancer Types. Prophylactic (preventive) cancer vaccines can reduce cancer risk by preventing infections that cause the disease. On the other hand, therapeutic cancer vaccines target tumor antigens to promote an anti-tumor immune response, ultimately destroying malignant cells (www.fda.gov, https://www.mskcc.org/) [97, 110].

Vaccine Name	Relative Disease(s)		Category
Gardasil®	Diseases caused by Human Papillomavirus (HPV) Types 6, 11, 16, and 18	Cervical cancer, Genital warts (condyloma acuminata), and the following precancerous or dysplastic lesions: Cervical adenocarcinoma in situ (AIS), Cervical intraepithelial neoplasia (CIN) grade 2 and grade 3, Vulvar intraepithelial neoplasia (VIN) grade 2 and grade 3, Vaginal intraepithelial neoplasia (VaIN) grade 2 and grade 3, Cervical intraepithelial neoplasia (CIN) grade 1	Prophylactic
Gardasil 9®	Cancers caused by Human Papillomavirus (HPV) types 16, 18, 31, 33, 45, 52, and 58	Cervical, vulvar, vaginal, anal, oropharyngeal, and other head and neck cancers	Prophylactic
	Genital warts caused by HPV types 6 and 11	Condyloma acuminata	
	Precancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58	Cervical intraepithelial neoplasia (CIN) grade 2/3 and cervical adenocarcinoma *in situ* (AIS), Cervical intraepithelial neoplasia (CIN) grade 1, Vulvar intraepithelial neoplasia (VIN) grade 2 and grade 3, Vaginal intraepithelial neoplasia (VaIN) grade 2 and grade 3, and Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3	
Cervarix®	Diseases caused by oncogenic human papillomavirus (HPV) types 16 and 18	Cervical cancer, cervical intraepithelial neoplasia (CIN) Grade 2 or worse, and adenocarcinoma in situ, and cervical intraepithelial neoplasia (CIN) Grade 1	Prophylactic
HEPLISAV-B®	Diseases caused by all known subtypes of the hepatitis B virus	Liver cancer	Prophylactic

Sipuleucel-T (Provenge®)	Metastatic castrate resistant (hormone-refractory) prostate cancer	Therapeutic
Bacillus Calmette-Guérin (BCG)	Vaccination against Mycobacterium tuberculosis (Mtb) infection and treatment option for Non-muscle-invasive bladder cancer (NMIBC)	Prophylactic (for Mtb) Therapeutic (for NMIBC)
Nadofaragene firadonevec (Adstiladrin®)	Early-stage bladder cancers that have progressed despite BCG therapy.	Therapeutic
Talimogene laherparepvec (T-VEC or Imlygic®)	Melanoma (Advanced stage)	Therapeutic

2.3 Stem Cells in Cancer Therapy

Stem cells are characterized as undifferentiated cells that self-renew and can differentiate into more specialized cells throughout the body. Stem cell research gained more focus and impact with the identification of cells with extensive proliferative potential in acute myeloid leukemia (AML) in 1997 by Bonnet and Dick [111]. These isolated cells were further characterized as cancer stem cells (CSCs) with the $CD34^{+}CD38^{-}$ phenotype. This study widely acknowledged the existence of leukemia stem cells, which then led to the development of the theory of "CSCs" in 2001 [112]. The concept of CSCs has since expanded to encompass the identification of various solid tumors. A few years later, Al-Hajj et al. isolated $CD44^{+}CD24^{-/low}$ CSCs from breast tumors in 2003 [113]. This study showed that 200 CSC cells could form tumors in recipient mice within 12 weeks, whereas 10,000 non-special breast cancer cells could not. Late in the same year, $CD133^{+}$ CSC population from diverse brain tumors was purified by Sheila K Singh et al. [114]. These studies suggesting potential CSCs across both hematologic and solid malignancies have substantiated the CSC theory; more research is focused on further understanding the role of stem cells in cancer, as well as on using and targeting stem cells in cancer.

Currently, mesenchymal stem cells (MSCs) are actively being investigated for their potential to regenerate diseased or damaged tissues [115]. These cells are currently utilized in clinical trials and are primarily derived from bone marrow (BM), adipose tissue, and connective tissues. Additionally, hematopoietic stem cells (HSCs) and neural stem cells (NSCs) are significant adult stem cell populations commonly used in cancer therapies [116-118]. HSCs, found in the bone marrow, can generate all mature blood cell types. Notably, the only HSC-based therapy approved by the FDA involves the infusion of HSCs derived from umbilical cord blood for the treatment of hematopoietic system disorders, including hematologic malignancies and inherited blood disorders [119]. Omisirge (omidubicel-onlv) is a nicotinamide-modified, cord blood-derived hematopoietic stem cell transplant therapy. It was approved by the FDA in 2023 for patients with hematologic malignancies [120]. More recently, in 2025, the FDA approved Omisirge, the first allogeneic hematopoietic stem cell transplant therapy, for severe aplastic anemia [100, 121].

MSCs, present in various tissues and organs, play crucial roles in tissue repair and regeneration by differentiating into specific cell types [122]. Stem cells survive much longer than normal somatic

cells, and they are more likely to accumulate genetic mutations over time. Cancer research has shown that only a few mutations may be enough for a cell to lose control of the regular cell cycle and its self-renewal and growth, potentially leading to cancer [123].

Stem cells are responsible for and participate in normal development and health. Embryonic stem cells are the first producers of progenitors that determine how tissues and organs are arranged and form in the body. After these progenitor cells complete their work, they leave behind a guardian population of stem cells that repair each tissue when needed. Thus, these cells will undergo self-renewal and differentiate into specialized cells, allowing the gradual accumulation of mutations that lead to cancer, in line with current theories of the stem cell's role in cancer development. Stem cells' involvement might explain the difficulties of those treatments that aim to reduce tumor mass to cure cancer. This could simply be due to treatments targeting fast-dividing cells; thus, slow-dividing cells, like stem cells, might stay off target and thus untouched [112, 124]. For this reason, cancer stem cells are believed to be responsible for resistance to chemotherapy and the recurrence of disease [112]. Therefore, a new treatment strategy is needed, particularly one that targets cancer stem cells in combination with current treatment approaches. A study by Markus Frank et al. first demonstrated this therapeutic strategy, which identified a class of stem cells that initiate melanomas in an animal model and, at the same time, an antibody that slowed tumor growth by targeting these stem cells [125]. An increasing number of studies are focusing on personalized medicine and targeted therapy as effective approaches to cancer treatment, with particular emphasis on stem cells due to their unique tumor-homing and anti-cancer properties [8, 10]. Research has highlighted the multifaceted roles of mesenchymal stem cells (MSCs) in cellular functions, revealing their dual role as both promoters and suppressors of cancer [126]. Some studies suggest that MSCs can enhance tumor progression by facilitating angiogenesis and suppressing immune responses, thereby promoting tumor growth.

On the other hand, the tumor-homing properties of MSCs have been harnessed for their potential to serve as vectors for delivering anti-cancer agents directly to tumor sites. Furthermore, several studies have demonstrated MSCs' ability to inhibit cancer proliferation and metastasis, primarily by inducing apoptosis [115, 127]. Taken together, this duality underscores the complexity of MSCs in cancer therapy and their potential as tools for innovative therapeutic strategies.

Despite the recent advances, stem cell-based approaches should be rigorously evaluated to establish standardized, clear treatment algorithms and to provide safe, long-term outcome data. Notably, the efficacy and tolerability of stem cell-based modalities are modulated by variables such as patient age, comorbidity burden, disease stage, prior treatment exposure, donor- and tissue-source characteristics. These donor-specific variables could affect cell phenotype, morphology, and function. Moreover, the preparation and manufacturing processes for stem cell-based therapies also introduce additional heterogeneity. Thus, there is a need for comparative clinical studies, harmonized product characterization, and more precise patient-selection frameworks [128-130].

Furthermore, MSCs have been shown to produce extracellular vesicles (i.e., exosomes), which show exceptional potential as drug delivery vehicles due to their biocompatibility, low immunogenicity, and high loading capacity. These advantages promoted the exploration of non-cell-based therapies, particularly exosome-based approaches, as promising alternatives in cancer treatment [21, 131, 132]. For instance, an ongoing clinical trial (NCT03608631) is designed to assess the safety and efficacy of MSC-derived exosomes loaded with KrasG12D siRNA (iExosomes) for the

treatment of pancreatic cancer. This highlights the potential of MSC-derived exosomes as innovative tools for targeted cancer therapy [133].

3. Gaps and Challenges in Cancer Therapy

The current therapeutic advances have improved outcomes in selected cancers. However, the global burden remains high, and survival still varies notably by cancer type and stage. By 2050, it is expected that the number of new cases of cancer will reach 35 million [134]. Despite the comprehensive research on understanding molecular pathology of cancer, cancer being a complex disease individual disease models are not representative of the corresponding cancer types, thus clinical cancer research faces significant barriers to increase understanding of underlying molecular pathology. Treating an individual even before the clinical detection of a tumor with a drug that is effective in treating an established cancer is the driving force behind cancer research.

Furthermore, an interception approach needs to be carefully evaluated as well as investigated to detect the potentially efficient drugs and, at the same time, potentially deleterious effects when used in a preventive setting.

Another important point is that the gaps in current cancer screening policies and regulatory barriers may hinder progress. There is significant variability in regulatory processes across countries. There is a need to streamline and standardize procedures globally.

Cancer is a complex disease, characterized by numerous challenges in developing effective screening, diagnosis, and treatment modalities. Even within the same cancer type, genetic and phenotypic variability can exist, highlighting the importance of precision medicine in the clinical application of current practices. Furthermore, limited early detection and the absence of effective diagnostic and prognostic biomarkers further hinder the application of existing therapies. Although significant advances have been made in cancer therapy in recent years, resistance to treatment, drug toxicity, immune escape of cancer cells, and the lack of personalized approaches further complicate the effective application of current therapies (Figure 1).

3.1 Drug Resistance, Side Effects, and Toxicity

The development of resistance to both traditional chemotherapeutic agents and novel targeted drugs remains a significant challenge and a primary cause of cancer recurrence and mortality. Multidrug resistance refers to the ability of cancer cells to develop resistance to various structurally and functionally distinct cancer therapeutics. This can limit the efficacy of drugs and significantly alter the treatment response [135]. Drug resistance in cancer can arise due to several mechanisms, including genetic mutations, drug efflux pumps, altered drug metabolism, epithelial-mesenchymal transition (EMT), and a dense immunosuppressive tumor microenvironment (TME) [136-138].

Drug resistance was shown to be either intrinsic- existing before treatment or acquired - developed after therapy. Intrinsic resistance arises from genetic mutations present before treatment, variations within the tumor, or the activation of cellular defense mechanisms. As most tumors are multi-clonal and genetically heterogeneous, single-agent therapeutics often result in killing only the drug-sensitive cells, allowing the resistant cells to proliferate. Therefore, implementing combinatorial therapy strategies that target multiple driver genes or pathways simultaneously could reduce the risk of developing drug resistance during treatment [137].

On the other hand, acquired resistance arises from new mutations, alterations in the expression of drug targets, or interactions within the tumor's microenvironment. These different forms of resistance may co-occur, making it critical to design more effective treatment strategies to minimize therapeutic failure. With advancements in next-generation sequencing technologies, genomic analysis before treatment and the adjustment of personalized therapies to prevent acquired resistance are vital for improving patient outcomes.

Traditional cancer treatment regimens have long involved the administration of the highest tolerable doses of drug(s), which led to faster drug resistance due to constant high-dose drug exposure to cancer cells, together with high toxicity and side effects. It has been reported that conventional immunotherapies may also cause severe side effects due to prolonged administration and hyperreactivity in some patients [139]. Nevertheless, this traditional treatment regimen is recently being replaced with intermittent dosing strategies -high and low dose switches- which have been shown to provide prolonged survival and delayed resistance [137].

Overall, while progress is being made in developing combination therapies and novel immunotherapy approaches, several challenges remain. For instance, the high complexity of tumor evolution and progression makes it more difficult to identify the best strategies to overcome drug resistance. Nevertheless, combination therapies generally provide better treatment outcomes compared to single-agent therapies, due to the heterogeneous and multi-clonal nature of tumors. In fact, the reason most single-agent therapies eventually lead to treatment failure is drug resistance, as these therapies selectively kill sensitive cancer cells, allowing the resistant cell population to proliferate and survive [137].

Hence, to improve cancer treatment outcomes with minimal side effects, a mechanistic understanding of an individual's tumor and drug resistance mechanisms is necessary to develop enhanced treatment strategies. Significant advancements have been made in the field, including optimizing treatment combinations and doses, utilizing nanotechnology-based targeted delivery systems, etc. Moreover, to identify driver genes and molecules involved in tumorigenesis and drug resistance, utilizing the big data from high-throughput cancer genomics, proteomics, and metabolomics is critical and promising.

3.2 Early Detection and Diagnosis and Access to Treatment

Along with technological advances in medicine and health sciences, cancer diagnosis has evolved in recent years. Early detection of cancer improves the chances of successful treatment and long-term survival. However, early-stage cancers are often asymptomatic and go undetected until they progress to advanced stages, where treatment options become less effective. Current screening methods face limitations in identifying cancers at their earliest, most treatable stages. To overcome this, there is an urgent need to develop more effective early detection tools, such as liquid biopsies, advanced imaging technologies, and reliable biomarkers, that can detect cancers before they advance. For instance, a recent study by Berahmand et al. developed a Nested Ensemble Deep Learning model for Gynecological Cancer Risk Prediction, demonstrating >98% accuracy on public benchmark datasets [140].

Alongside these technological advancements, it is also critical to address the significant disparities in access to cancer care. From a global health perspective, outcomes depend not only on scientific advances but also on timely access to screening programs, the availability of necessary

infrastructure, and affordability. In low- and middle-income countries, these factors create additional barriers to appropriate cancer care. A cross-sectional study analyzed 36 cancer types across 185 countries and territories from the Global Cancer Observatory database. The authors demonstrated that the global cancer burden is expected to increase substantially by 2050. This increase is greater in low-Human Development Index countries, underlying the enlarging disparities in cancer outcomes and equitable access to prevention, diagnosis, and treatment worldwide [141]. Therefore, people in low- and middle-income countries may struggle with limited healthcare infrastructure, high costs of treatment, and unequal availability of therapies. Closing this gap requires investment in healthcare infrastructure, efforts to reduce treatment costs, and strategies to ensure equal access to life-saving technologies [142].

3.3 Tumor Heterogeneity

The genetic, epigenetic, and metabolic profiles of tumor cells often contribute to heterogeneity within the same tumor. Tumor heterogeneity is therefore used to describe variations among tumors of the same type across patients, the diversity of cancer cells within a single tumor, or differences between a primary and a secondary tumor [143]. Accumulating evidence suggests that a single tumor may contain clonally distinct populations, with no common driver gene alterations, making them difficult to treat and likely to develop resistance to therapeutics [144-148]. Hence, understanding the complex tumor pathophysiology and heterogeneity is vital for developing novel personalized cancer therapies.

Moreover, in metastasis, primary tumor cells spread to distant anatomical sites, posing an additional therapeutic challenge. These metastasized cancer cells exhibit greater phenotypic and molecular heterogeneity than the primary tumor. During metastasis, cancer cells undergo continuous genetic and epigenetic modifications, as well as contributions from the TME. These multiple adaptations drive more cancer cells to become more aggressive, invasive, and to foster therapy resistance. The anatomical and biological differences of metastatic lesions further complicate the treatment [149].

In addition, the dense, highly complex and heterogeneous nature of TME shaped by numerous cell types and tissues (i.e., immune cells, stem cells, blood vessels, and extracellular matrix components) further challenges cancer progression and treatment response. This dynamic TME significantly influences cancer progression and treatment response as the TME is involved in tumor initiation, growth and metastasis representing a challenge for developing effective anti-tumor strategies. For these reasons, there is an urgent need for more studies to fully understand how these interactions between the tumor and its TME contribute to cancer progression and therapy resistance. A deeper understanding could pave the way for innovative treatments targeting tumor cells and the TME, offering a more comprehensive approach to combat solid tumors [138].

4. Conclusion and Future Perspectives

There has been significant progress in cancer treatment strategies in recent years; however, many challenges still limit their clinical potential. Future advances in cancer therapy will also depend on improving the reproducibility and transparency of the studies conducted. For this reason, standardized reporting of methodologies, patient cohorts, endpoints, and data resources is of great importance. Addressing current challenges, including drug resistance, toxicity, and tumor

heterogeneity, is needed for developing effective personalized approaches and improving long-term patient outcomes.

One of the active research field in cancer focus on the development of nanomedicines and drug delivery platforms, including nanoparticles (NPs) for the targeted delivery of therapeutic agents/drugs to specific tissues/organs. Among these, lipid-based NPs containing at least one lipid membrane layer with an internal aqueous compartment offer promising advantages, including simple formulation, self-assembly, high bioavailability and biocompatibility, the ability to carry large cargos, and other physicochemical properties that can be controlled to regulate their biological characteristics [150]. By investigating the physicochemical features of nanocarriers, modifying the associated molecules could enhance the effectiveness of therapies and enable controlled drug release in the target tissue [139]. Consequently, lipid-based NPs are promising for clinical translation in precision therapy, immunotherapy, and gene editing in cancer therapy. Unsurprisingly, lipid-based NPs are among the most common categories of FDA-approved nanomedicines [151].

Furthermore, some solid cancers, including pancreatic cancer, are difficult to treat due to the presence of a tumor-promoting complex tumor microenvironment. These dense tumor niches make drug delivery challenging, as they often block drug entry into tumor cells. Efficient drug-delivery platforms that address current challenges should be developed for these 'undruggable' cancers with complex tumor niches.

Besides, future progress in cancer therapy will depend not only on the development of new agents, but also on improved patient stratification, earlier prediction of treatment response, and more effective management of therapy-related adverse effects. Since the completion of the Human Genome Project and the establishment of genome sequencing technologies, genomic, transcriptomic, and proteomic methods have generated vast amounts of data. However, integrating these data to address current challenges in developing efficient and personalized therapies remains a work in progress.

Enhanced data analysis tools and algorithms could aid in interpreting and translating this big data into effective therapeutic strategies for precision medicine. Thus, an important future direction in oncology is the integration of genomic, transcriptomic, proteomic, imaging, pathology, and real-world clinical data through artificial intelligence (AI)- and machine learning (ML)-based frameworks. Such approaches have increasing potential to support treatment-response prediction, toxicity forecasting, biomarker discovery, clinical trial matching, and personalized therapeutic decision-making. Notably, a recent study by Thalji et al. described an AI-derived electronic tumor marker (e19-9) for pancreatic ductal adenocarcinoma patients who do not produce elevated carbohydrate antigen 19-9 (also known as cancer antigen 19-9, CA19-9). Using routine serum laboratory data, the authors developed a machine-learning model with prognostic and treatment-response value in CA19-9 nonproducers. It highlights the potential of AI-assisted biomarker approaches to complement conventional markers and improve patient stratification [152].

Together, an accumulating number of recent studies highlight the potential of explainable, multimodal AI to refine patient stratification and therapeutic decision-making [153-157]. Future advances in cancer therapy are likely to be increasingly shaped by AI- and ML-based approaches that extend from diagnosis to treatment optimization and drug discovery. Nevertheless, prospective validation and broader clinical implementation of these studies remain necessary. Bridging the current gaps in cancer therapy requires continued innovation, multidisciplinary collaboration, and a focus on personalized therapies to overcome these barriers and maximize the benefits of cutting-

edge cancer treatments. Finally, continued emphasis on cancer prevention strategies remains necessary to reduce the cancer burden and improve socioeconomic outcomes across populations.

Abbreviations

ACT	Adoptive cell therapy
AI	Artificial intelligence
AIS	Adenocarcinoma in situ
AIN	Anal intraepithelial neoplasia
ALK	Anaplastic lymphoma kinase
ALL	Acute lymphoblastic leukemia
AML	Acute myeloid leukemia
ATP	Adenosine triphosphate
B-ALL	B-cell acute lymphoblastic leukemia
BCG	Bacillus Calmette-Guérin
BCL-2	B-cell lymphoma 2
BCR-ABL1	Breakpoint cluster region-Abelson 1 fusion gene
BiTE	Bispecific T-cell engager
BM	Bone marrow
CA19-9	Carbohydrate antigen 19-9
CAR	Chimeric antigen receptor
CART.BiTE	BiTE-expressing chimeric antigen receptor T cells
CDK4/6	Cyclin-dependent kinases 4 and 6
CiTEs	Checkpoint-inhibitory T-cell engagers
CIN	Cervical intraepithelial neoplasia
CLL	Chronic lymphocytic leukemia
CML	Chronic myelogenous leukemia
CRS	Cytokine release syndrome
CSCs	Cancer stem cells
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
CYP17	Cytochrome P450 17
dSLIM	Double-stem loop immunomodulator
EGFR	Epidermal growth factor receptor
EMT	Epithelial-mesenchymal transition
FDA	Food and Drug Administration
FGFR	Fibroblast growth factor receptor
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GIST	Gastrointestinal stromal tumor
GnRH	Gonadotropin-releasing hormone
HER2	Human epidermal growth factor receptor 2
HIF-2α	Hypoxia-inducible factor 2 alpha
HLA	Human leukocyte antigen
HSCs	Hematopoietic stem cells
HPV	Human papillomavirus

ICs	Immune checkpoints
ICEs	Immune cell engagers
ICIs	Immune checkpoint inhibitors
IDO1	Indoleamine 2,3-dioxygenase 1
IL-7	Interleukin 7
KIT	KIT receptor tyrosine kinase
LAG-3	Lymphocyte-activation gene 3
mAbs	Monoclonal antibodies
MEK	Mitogen-activated protein kinase kinase
MHCs	Major histocompatibility complexes
ML	Machine learning
mRCC	Metastatic renal cell carcinoma
MSCs	Mesenchymal stem cells
Mtb	Mycobacterium tuberculosis
mTOR	Mechanistic target of rapamycin kinase
NCI	National Cancer Institute
NMIBC	Non-muscle-invasive bladder cancer
NPs	Nanoparticles
NSCLC	Non-small cell lung cancer
NSCs	Neural stem cells
PARP	Poly(ADP-ribose) polymerase
PD-1	Programmed cell death protein 1
PDGFRA	Platelet-derived growth factor receptor alpha
PD-L1	Programmed death-ligand 1
PI3K	Phosphoinositide 3-kinase
PMBCL	Primary mediastinal large B-cell lymphoma
RCC	Renal cell carcinoma
RET	Rearranged during transfection
ROS1	ROS proto-oncogene 1 receptor tyrosine kinase
siRNA	Small interfering RNA
SMITEs	Simultaneous multiple interaction T-cell engagers
STING	Stimulator of interferon genes
TAAs	Tumor-associated antigens
TCR	T-cell receptor
TKIs	Tyrosine kinase inhibitors
TILs	Tumor-infiltrating lymphocytes
TLR-9	Toll-like receptor 9
TME	Tumor microenvironment
TSAs	Tumor-specific antigens
TriKEs	Trispecific killer cell engagers
U.S.	United States
VaIN	Vaginal intraepithelial neoplasia
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor

VIN Vulvar intraepithelial neoplasia

Author Contributions

N.S. conceived the presented idea and contributed to the writing and editing of the stem cell-related sections. H.Ö.E. took the lead in writing and editing the manuscript. H.Ç. contributed to manuscript writing. All authors reviewed and approved the final version of the manuscript.

Competing Interests

The authors have declared that no competing interests exist.

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