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Review Article

Emerging Trends and Evolving Landscape in Cancer Immunotherapy

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Abstract

Cancer cells are continuously evolving to escape the effect of different treatment strategies and it has become a daunting task to control the cancer adoptive nature by various emerging anti-cancer agents. Cancer immunotherapy is a revolutionary approach for the treatment of cancer through harnessing the immune system to get anti-tumour properties. This review summarizes recent trend, advancements of various categories of immunotherapeutic agents, including immune checkpoint inhibitors, cancer vaccines, and adoptive T cell therapies such as CAR T-cell therapy. Immune checkpoint blockade, particularly targeting CTLA-4 and PD-1/PD-L1 pathways, has shown notable success but remains effective in only a subset of patients. Cancer vaccines and neoantigen-targeted approaches are evolving to overcome tumor immune evasion. Adoptive T cell therapies have achieved remarkable outcomes in hematological cancers, though solid tumors pose ongoing challenges. Combination therapies and novel agents offer potential to enhance efficacy and reduce resistance. The review also addresses major hurdles, such as immune-related adverse events and the immunosuppressive tumor microenvironment. Continued research and clinical trials are essential to optimize these therapies and expand their impact, positioning immunotherapy as a vital component of future personalized cancer treatment strategies. This review analysis reflect a paradigm shift toward immune-centric therapies to address unresolved challenges like immune-related toxicity and tumor microenvironment suppression.

Keywords: Cancer Immunotherapy; Immune Checkpoint Inhibitors; CAR T - Cell Therapy; Cancer Vaccines; Combination Therapy

Introduction

Cancer has become the second most serious and life-threatening disease and evolved as one of the world's one of the top ten leading causes of death. In 2018 and 2022, there were 18.2 and 20 million new cases and 9.6 and 9.7 million deaths reported [1-3]. The uncontrolled cell proliferation and abnormal cell behaviour, such as resistance to apoptosis and sustained angiogenesis in cancer, are caused by several internal and external factors. Internal factors include tumor mutations [4,5] and the patient's immune conditions [6]. External factors include tobacco, alcohol [7], ionizing and non-ionizing radiation [8], viruses [9], and dietary factors [10]. The vast majority of cancer-associated deaths are due to advancing metastases [11].

The treatment modality for cancer depends on the type of cancer, age, stage of cancer, and its origin. The use of chemotherapy began at the start of the 20th century, and the successful treatment of childhood leukemia and advanced Hodgkin's disease in the 1960s and 1970s led to the widespread acceptance of chemotherapy as a cancer treatment [12]. According to a 2017 analysis, among 150 USFDA-approved anti-cancer drugs, 61 are cytotoxic-based drugs, and 89 are target-based drugs belonging to the tyrosine kinase family [13]. By 2024, the number of FDA-approved kinase inhibitors had increased to 80, with 69 prescribed for cancer treatment [14]. Tyrosine kinase inhibitors (TKIs) continue to form the first-line of adjuvant treatment options for various cancers, targeting critical kinase families involved in cancer progression [15]. The evolution of TKIs has led to improved clinical outcomes in terms of safety and efficacy compared to conventional therapies [13]. However, challenges such as drug resistance and si de effects persist, emphasizing the need for more selective inhibitors

and combination therapies to optimize patient-specific cancer treatment [15,16]. However, the TKI forms the baseline of initial treatment options for various cancers (Table 1). The TKI percentage of active recruitments in clinical trials have surged by 100% from 2020 to present (Figure 1a), but the total number of TKI clinical trials has nearly 50% decline of the same period (2020-present) figure 1b. The 50% decline in TKI trials (2020–2025) and 100% surge in CAR-T/OV trials signal a reorientation toward therapies targeting immune evasion mechanisms, though this shift is tempered by translational challenges like trial termination rates (Figure 1a). The TKI involves in cell signalling pathway to block the cancer cell growth and survival (Imatinib - targets BCR-ABL in CML), Erlotinib (targets EGFR in lung cancer), Sorafenib (targets multiple kinases in renal cell carcinoma). Currently, over 70 small-molecule kinase inhibitors have been approved, due to chemotherapeutic drugs have challenges as side effects, high costs, non-specific targeting, limited availability, and drug resistance in cancer cells. On the other hand, methylation shifts in cancer cells induced by chemotherapeutic agents drive drug resistance. [17]. The TKIs now represent ~70% of FDA-approved anti-cancer drugs, underscoring their centrality in precision oncology. While the other cytotoxic agents retain roles in adjuvant/combination settings, TKI innovation continues to redefine first-line standards, albeit with evolving challenges in toxicity and resistance management [18].

Therapeutic Agents	No Results Available	Has Results	Recruiting	Completed	Terminated	Unknown Status	Active not Recruiting	Total Clinical Trails
TKI	614	107	165	220	60	152	56	721
Mabs	4040	1453	917	2339	592	521	593	5493
T-cell therapy	3848	584	1106	1111	377	636	346	4067
NK cell Therapy	907	111	196	336	95	226	46	1080
DC Therapy	631	103	71	329	82	132	48	734
Whole cell tumour	13	3	4	5	3	2	1	16
OV Therapy	192	20	68	60	13	26	20	212

Table 1: Overview of the current status of clinical trials for various therapeutic agents.

While chemotherapy is frequently employed as a standard-of-care in several cancer treatments, other therapies such as monoclonal antibodies (mAbs) and immune checkpoint inhibitors (ICIs) are used in treatment regimens as combination therapy or neoadjuvant therapy to increase progression-free survival (PFS) [19-21]. Moreover, effective and intensive chemotherapy regimens are typically applicable to healthy, young patients, who constitute less than 25% of the cancer patient population [22]. Cytostatic and cytotoxic chemotherapies damage normal cells, leading to immediate side effects such as hair loss, nausea, fatigue, vomiting, neurotoxicity, drug resistance, infertility, complicated infections, and even death [23]. The recent decline of 1.7% in cancer mortality in the American population [24] may not solely be due to the efficacy of approved drugs, as there has been a steady decrease in smoking habits and the availability of advanced diagnostic methodologies for early cancer detection. The decreased mortality rate is particularly evident in major cancer types related to the lung, breast, and prostate. The significant side effects of chemotherapy, irrespective of dosage, have necessitated the need for chemotherapy-free strategies [25,26].

Clinical trials of several new therapeutic agents for cancer are summarized (Table 1), which further highlights the importance of estimating the percentage of trial terminations and active recruitments (Figure 1) across various cancer therapeutic agents. These two factors may help forecast indirect safety features and emerging trends in upcoming cancer therapies. One of the major causes of clinical trial termination is adverse events, translational challenges, patient availability, rare indications, etc. On the other hand, the possibility of an increase in active recruitment might be due to translational feasibility, future need, demand, and patient availability. However, indication-specific historical clinical investigations both warrant and warn about the specific challenges and characteristics of therapeutic agents.

Rationale for therapeutic paradigm shift in modern oncology

The limitations of conventional chemotherapy-including systemic toxicity, drug resistance, and poor tolerability in elderly or comorbid patients-have driven the development of chemotherapy-

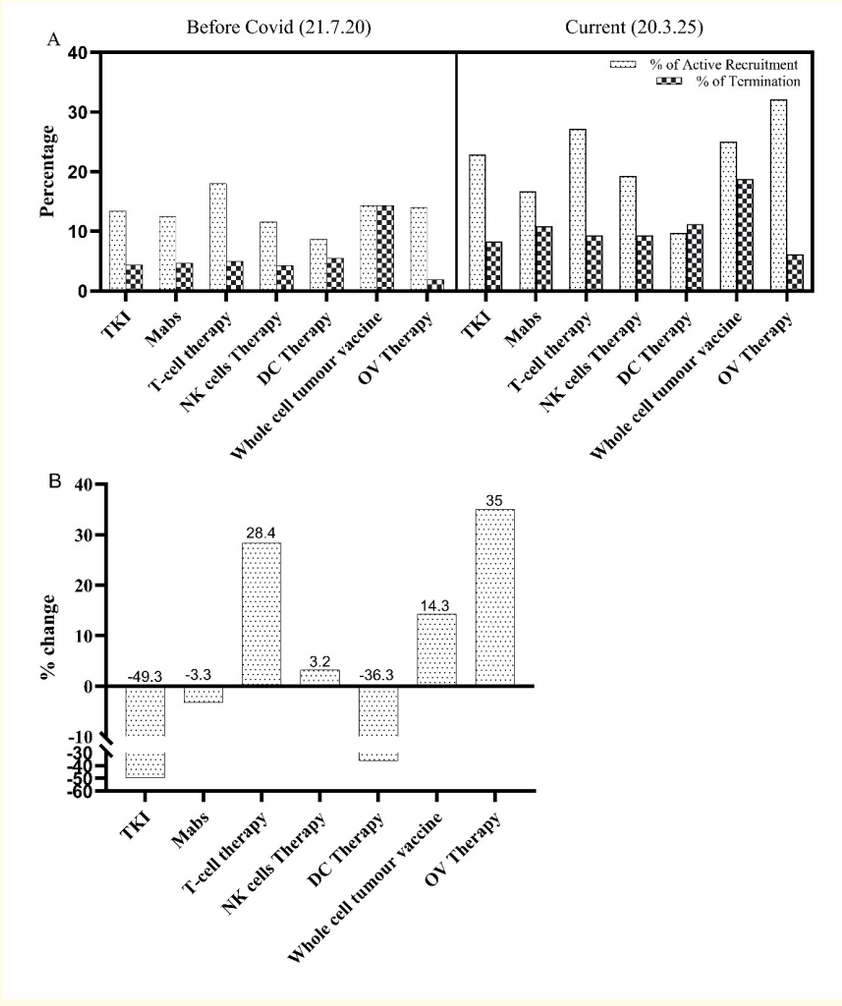

Figure 1: Comparison of Clinical Trial Trends of % active recruitment and % of termination across various therapeutics categories. A. The TKIs, monoclonal antibodies (mAbs), CAR-T therapy, NK cell therapy, DC therapy, whole cell tumor vaccines and OV Therapy) as of 21.7.2020 (pre-COVID-19). The clinical trial termination signals the translational challenges which may arise due to adverse reactions, patient's non-availability etc and rise of active recruitments due to simple products (product scalability) and its safety features; Current status of clinical trials (as of 20.3.2025) showing the percentage of active recruitment and termination across the same therapeutic categories. This figure highlights the significant surge of active recruitment in recent years in CAR-T cell Therapy and OV Therapy due to advanced therapeutics development focus shift. B. Overall changes in total clinical trial activity across therapeutic modalities 1b: represents the percentage change in the number of clinical trials for various therapeutic categories between 21.7.2020 and 20.3.2025, highlighting trends of growth or decline. T-cell Therapy and OV Therapy show significant increases, while TKI and DC Therapy experience notable declines, reflecting shifting priorities in clinical research.

free regimens as a paradigm shift in oncology. Several strategies are in clinical trials to demonstrate clinical efficacy without chemotherapy for various cancers. Recently, the chemotherapy-free strategy for platinum-sensitive recurrent ovarian cancer has received significant attention, as phase III results showed that niraparib maintenance therapy after platinum-based treatment significantly extended progression-free survival (PFS) to 21 months compared to 12.9 months [27]. Currently, six new FDA-approved drugs have shown an increase in overall survival for advanced prostate cancer as part of chemotherapy-free strategies [28] and late stage clinical trial data (Table 2) reflect biomarkers associated with improved progression-free survival (PFS) or toxicity risks under combinational immunotherapy Pooled data from 12 phase clinical trials (2018-2024)reveal that substantial increase in

progression-free survival (approx. 45.81%), but increase grade ≥3 toxicity risks raised by 31.96% compared to conventional therapies, underscoring the need for predictive biomarkersv (Table 2). On contrary, The heterogeneity of tumor microenvironment (TME) dynamics and PD-L1 (ligand) variability further complicates the biomarker reliability. On the other hand, the sipuleucel-T (immunotherapy), abiraterone acetate, enzalutamide (androgen pathway inhibitors), docetaxel, cabazitaxel, and the radionuclide radium-223 also forms the part of chemotherapy free regimens [29]. The overall goal is to reduce side effects without compromising the quality of life (QoL) of patients. However, the heterogeneity of prostate cancer biology limits a unified and harmonized approach, necessitating the identification of compatible biomarkers to determine the clinical benefits of specific drugs and to maximize patient outcomes in chemotherapy-free clinical practice. Another recent report on a non-chemotherapy regimen for mantle cell lymphoma (MCL) treated with lenalidomide-rituximab showed equivalent results to chemotherapy, and various strategies are currently in the clinical development phase [30]. However, it might be too early to establish evidence-based recommendations as a standard practice due to limited data. The combination of Imbruvica (ibrutinib, IBR) and Venclexta (venetoclax, VEN) appears to represent a paradigm shift toward chemo-free treatment as an effective oral regimen for older and high-risk chronic lymphocytic leukemia (CLL) and MCL patients [31,32]. The dose specific toxicity persists during toxicity management (e.g., hematological adverse events like thrombocytopenia) and the need for improved trial design to optimize dosing and reduce side effects. On the other hand, incorporating financial toxicity considerations into clinical trial design is to be a patient centric facilitating approach for decision making in oncology. Financial toxicity refers to the economic burden and distress experienced by patients due to out-of-pocket costs related to cancer treatment and participation in clinical trials [33]. Non-chemotherapy treatments also have side effects, such as an increased risk of secondary cancers observed with long-term exposure to lenalidomide [34,35]. Opportunistic infections, bleeding, atrial fibrillation, and adverse events have been reported, leading to 10% of patients discontinuing ibrutinib use [36-38]. Furthermore, non-chemotherapy drugs can induce acute agranulocytosis in more than 70% of cases [39].

Trial Name	Cancer Type	Predictive Biomarker(s)	Regimen	PFS Improvement	Grade ≥ 3 Toxicity Risk	Reference
CheckMate 067	Advanced Melanoma	PD-L1 expression, Tumor Mutational Burden (TMB)	Nivolumab + Ipilimumab	43%	63%	40-41
KEYNOTE-028	20 Solid Tumors	PD-L1positivy as biomarker	Pembrolizumab	38%	21%	42
IMbrave050	Hepatocellular Carcinoma	Dendritic cell density, T effector cells, CD138+ plasma cells	Atezolizumab + Bevacizumab	24-mo RFS rate 62%	20%	43-44
DESTINY-Breast03	HER2+ Breast Cancer	HER2 amplification (IHC 3+ or ISH+)	Trastuzumab Deruxtecan	45.7%	16.7% (increased risk of interstitial lung disease)"	45
HER2CLIMB	HER2+ Metastatic Breast Cancer	HER2 amplification, Brain metastases	Tucatinib + Trastuzumab + Capecitabine	34%	28%	46-47
CheckMate 649	Gastric/GEJ Adenocarcinoma	PD-L1 combined positive score (CPS)	Nivolumab + Chemotherapy	13%	59%	48-49
IMpassion130	Triple-Negative Breast Cancer	PD-L1 Tumor Proportion Score (TPS)	Atezolizumab + Nab-Paclitaxel	29%	48.7%	50
SU2C-SARC032	Sarcoma (UPS/ Liposarcoma)	PD-L1 expression, Tumor Mutational Burden (TMB) (not yet defined for clinical use)	Pembrolizumab + Radiotherapy	DFS rate was 67%	10%	51
HUDSON (ATM cohort)	NSCLC	ATM alterations, PD-L1 expression	Durvalumab + Ceralasertib (ATR inhibitor)	ORR is 26.1% and 8.4 months	Manageable, exact % not specified	52
SPEARHEAD-1	Synovial Sarcoma	MAGE-A4 expression	Afamitresgene Autoleucel (TCR therapy)	ORR was 39%	+71% (cytokine release syndrome)	53
IGNYTE-ESO	Sarcoma	NY-ESO-1 antigen expression	Letetresgene Autoleucel (TCR therapy)	Median PFS was 5.3 months	Hematologic toxicities (86%)	54-55
Check Mate 459	Hepatocellular Carcinoma	PD-L1 TPS	Nivolumab vs. Sorafenib	Median PFS: 3.8 months (nivolumab) vs. 3.6 months (sorafenib)	22% for nivolumab vs. 49% for sorafenib	56-57

Table 2: Summary of clinical trials and predictive biomarkers in chemotherapy – free regimen (2018-2024) across various cancer types.

Advanced cancer immunotherapies

Monoclonal antibodies and Immune-check point inhibitors (ICIs)

The cell growth and proliferation of the cancer cell indirectly depends on immune suppression. Cancer cells evade the immune system by activating different immune checkpoints targets on tumour cells like, programmed cell death protein-1, programmed cell death ligand-1 (PD-1/PD-L1) and cytotoxic T-Lymphocyte associated protein 4 (CTLA-4), in order to stop the T-cell's recognition and destruction of cancer cells [58]. This T-cell activity inhibition is reactivated by blocking those expressed markers by mabs. These immunomodulatory mabs, which reawaken the suppressed T- cell effector function are called check-point inhibitors [59]. The activated T-cells may destroy normal cells as an auto-immune reaction. Immune-related adverse events are a hallmark of ICIs, including colitis, pneumonitis, hypophysitis, and hypothyroidism [60,61]. The USFDA approved ICIs are Ipilimumab (CTLA-4, 2011), Nivolumab (PD-1, 2014) Pemobrolizumab (PD-1, 2014), Atezolizumab (PD-L1, 2015), Avelumab (PD-L1, 2017), Durvalumab (PD-L1, 2017) for metastatic melanoma, non-squamous cell lung cancer, and urothelial carcinoma [62]. Moreover, Teclistamab (BCMAxCD3 bispecific) got accelerated approval for replapsed/refractory multiple myeloma having 63% ORR in phase-II trials [63].

Currently, there are more than 70 ICI-based clinical trials are under phase III and phase IV clinical trials for various cancer indications after successful USFDA approval of Ipilimumab [64]. Currently, the various types of mabs are extensively investigating its safety and efficacy for cancer treatment at various clinical phases (Figure 2). Recent clinical trial results reveal that the ICIs enhance the efficacy, when combined with chemotherapy over the usage of ICIs alone [65]. Though, the ICIs have better tolerability than chemotherapy, its role as the first-line non-chemotherapy treatment remains unproven yet [66]. The favourable risk-benefit ratio for ICIs needs to be assessed based on durability benefit, PFS, objective response and Immune adverse events. The combination therapy of PD-I inhibitor (ICIs) with hypo-methylating agents provides better clinical results for relapsed/refractory Acute Myeloid Leukemia (AML) patients as a first-line therapy in elderly patients [67]. Recent, preliminary case report of six patients with relapsed or progressive CNS lymphoma showed the promising results with combinational immunotherapy without chemotherapy using PD-1 inhibitor and rituximab [68]. Further hunt of new targets is through single-cell RNA sequencing of PD-1+ TILs in NSCLC patients identifies *TOX* as a key transcriptional regulator of T-cell exhaustion, suggesting that TOX inhibition would improve ICIs efficacy [69] While the 2023 studies confirm TOX's role [70] and suggest ongoing exploration, emphasizing the need for further research to translate these findings into clinical practice. Further advancements are grounding towards the personalized and effective cancer immunotherapy targeting for dual or triple blockade to overcome evasion [71,72]. In another study, aggressive search for new targets is arrived through the TREM2+ macrophages resistance to ICIs in melanoma and other cancers. TREM2, a myeloid receptor expressed on tumor-associated macrophages (TAMs), promotes immunosuppression and supports tumor growth [73]. TREM2 signaling reprograms macrophages to an M2-like, pro-tumorigenic state, secreting IL-10 and impairing dendritic cell antigen presentation.

The single-cell RNA sequencing reveals that TREM2 inhibition reduces immunosuppressive macrophage subsets while expanding immunostimulatory myeloid cells, leading to improved T cell responses [74]. TREM2 signaling reprograms macrophages to an M2-like, pro-tumorigenic state, secreting IL-10 and impairing dendritic cell antigen presentation [75]. Targeting TREM2+ TAMs represents a promising strategy to overcome ICI resistance by modulating the tumor myeloid landscape. Combining TREM2-targeted therapies with ICIs may enhance treatment efficacy in melanoma and other solid tumors. These findings prompted the combinational trials of anti-TREM2 mAbs (NCT05662358) with anti-PD-1 therapy for advanced melanoma [76]. Recent mechanistic understanding of ICI enhancement is need to utilize predictive biomarkers and necessities the deeper understanding of how to overcome tumour immune evasion.

Adoptive cell-based immunotherapy

Adoptive cell therapy (ACT), or cellular immunotherapy, is a novel area of transfusion medicine that involves the infusion of immune cells to enhance the body's cancer-Fighting capacity. This is achieved through in vitro expansion or genetic modification of immune cells. Various types of immune cells, such as T-cells [77], natural killer (NK) cells [78], and dendritic cells [79], are deployed either independently or in combination [80] to restore natural anti-tumor function in cellular immunotherapy.

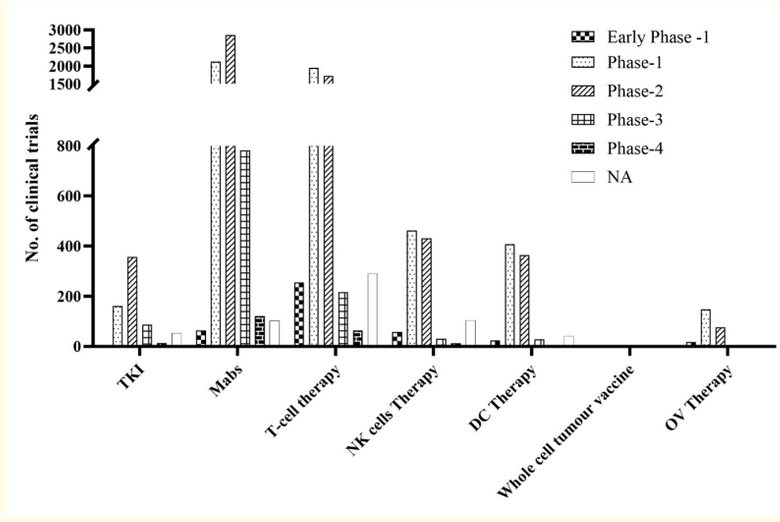

Figure 2: Comparative study of number of clinical trials across 7 therapeutic agents. The extensive deployment of mabs across various clinical phases reveals unprecedented safety profile, scalability and the extensive penetration of various mAbs in Phase 3 and Phase 4 trials, demonstrating their usability as adjuvant and target-based therapeutics.

CAR T - cell therapy

T-cell therapies include tumor-infiltrating lymphocyte (TIL) therapy, T-cell receptor (TCR)-modified T-cell gene therapy, and chimeric antigen receptor (CAR)-modified T-cell therapy (CAR-T cell therapy). Although the first evidence of clinical benefit was reported in 1994, the use of TILs remains limited due to the complexity of producing heterogeneous cell products [81]. Long-lasting complete responses, with an overall survival rate of approximately 21.8 months, have been observed in metastatic melanoma patients treated with TILs and attenuated interleukin-2 (IL-2) [82]. However, this approach requires preconditioning chemotherapy. The 2024 approval of lifileucel, the first TIL therapy for advanced melanoma, achieved durable responses in 32% of patient refractory to anti-PD-1 therapy [83,84]. After 2024 FDA approval of lifileucel, the field are rapidly disrupting the oncology towards expanded application in other solid tumors, novel combinations and technical innovations. The NIH-led trial combined the selected TIL with pembrolizumab in metastatic gastrointestinal cancers (colon, pancreatic, etc.), achieving a 23.5% objective response rate (vs. 7.7% without pembrolizumab) and durable responses up to 3.5 years [85]. The triple the response rate of TILs alone emphasis a new wave of disruption and expanding to NSCLC, ovarian, and head and neck cancers of TIL therapy beyond melanoma signalling a paradigm shift in adoptive cell therapy. Building on this momentum, autologous TCR gene-modified T-cell therapy uses CRISPR-Cas9 to express tumor-specific T-cell receptors (TCRs) is emerging technological innovation that bypassing the limitations of TIL therapy (e.g., dependency on pre-existing tumor-reactive T-cells); These CRISPR-edited TCR-T cells can recognize antigens in an MHC-dependent manner and enable precise targeting of shared tumor antigens (e.g., NY-ESO-1, MAGE-A4), broadening applicability to "cold" tumors and solid cancers with low immune infiltration. The TCR gene-modified T-cell therapy have been used to treat resistant melanoma patients [86]. The objective tumor response rates in clinical trials have ranged from 13% to 30% [87,88]. Various strategies for TCR transgenic lymphocyte therapy are under development and are designed to recognize tumor-specific antigens [89]. Adverse events associated with this therapy include cytokine release syndrome (CRS) and unpredictable off-target cell toxicity. The convergence of TIL success and TCR innovation emphasizes a new wave of immune-oncology revolution, driven by genetic engineering and biomarker-guided patient selection. While these advances expanding the therapeutic edge by building foundational and fundamental insights from first-generation CARs-extracellular fusion proteins derived from antibody-derived single-chain variable fragments (scFvs) coupled to intracellular T-cell signaling domains like CD3ζ. However, the second- and third-generation CARs contain two costimulatory domains linked to CD3ζ. Essentially, CARs are extensions of monoclonal antibodies (mAbs) on T-cells. The CAR-T cell therapy has generated significant enthusiasm due to

the unexpected success of second-generation CAR-T cell therapy in cancer treatment [90-92], despite disappointing outcomes with first-generation CAR-T cells. The CRISPR-Cas9 edited TRAC locus integrated CAR-T cells show improved persistence and reduced tonic signaling, addressing a major limitation of first-generation constructs (clinical trial ID: NCT05757700) [93]. Recent clinical data showed 80% complete remission rate in relapsed/refractory B-ALL patients treated with TRAC-edited (T-cell receptor alpha constant (TRAC) locus) CAR-T cells [94]. The transformative potential of CRISPR-Cas9 edited CAR-T cells needs the ongoing efforts and focus on optimizing gene-editing tools for broader applications. Second-generation CAR-T cell therapy has achieved a 90% objective response rate and long-term remission in B-cell malignancies, such as acute lymphoblastic leukemia (ALL) [95-97]. Adverse events associated with CAR-T cell therapy include CRS and immune effector cell-associated neurotoxicity syndrome (ICANS) [98]. Another groundbreaking innovative approach to enhance CAR-T cell therapy for solid tumors using engineered probiotics, where probiotics were engineered to express CD19 mimotopes, and helps to train the CAR-T cells in the gut to recognize solid tumors. This reduced the effective CAR-T dose by 70% in colorectal cancer models [99]. Probiotic-primed CAR-T therapy is a promising frontier for solid tumors, as it enables dose reduction while improving safety and efficacy. Current research focuses on optimizing probiotic strains, delivery methods, and combination strategies. A breakthrough approach involves knockdown of MYB, HDAC2, and FOXA2 genes to reprogram colorectal cancer cells into normal enterocytes, shifting therapy from cytotoxicity to cell cellular differentiation [100]. For clinical translation, CAR-T cell therapy manufacturing plays a significant role and creation of shorter time frame as little as 24 hours [101], 48-72 hours [102], and 7-8 days [103], compared to traditional 3-6 weeks processes addressing the scalability barrier, allows for fresh cell infusions, potentially improving patient outcomes and reducing overall treatment cost. [105] Further, the allogeneic "off-the-shelf" products (like ALLO-715) and combining novel rapid manufacturing platforms are being explored in multiple myeloma treatment [104]. These transformational developments enhance CAR-T therapy accessibility and effectiveness for a broader patient population. In 2024, the FDA approved fascaratamab, a CD19-directed CAR-T therapy, for refractory lupus and myasthenia gravis-marking the first CAR-T approval outside oncology and signaling immunotherapy's expansion into autoimmunity [105] Further, Anti-CD19 CAR T-cells achieved 100% remission in refractory systemic lupus etythematosus patients [106] by depleting autoreactive CD19+ B cells. The CAR-T cells targeted for fibroblast activated protein, reduces cardiac fibrosis in murine model improving the heart function [107]. Currently more than 2500 clinical trials are underway to evaluate CAR-T cells for various cancers and therapeutics application.

NK cell-based therapy

Natural killer (NK) cells are large granular lymphocytes that play a critical role as the first line of immunological defense against cancer development. The NK cells are CD56-positive and CD3-negative lymphocytes, representing a major component of innate immunity in the early defense against both cancer and certain virus-infected cells [108]. The NK cells secrete cytotoxic granules, effector cytokines, and engage death-inducing receptors to stimulate cancer cell apoptosis. They also serve as the primary mediators of antibody-dependent cell-mediated cytotoxicity (ADCC)v [109-112]. These functional properties of NK cells have been harnessed for cancer immunotherapy, resulting in promising clinical outcomes [78,113].

Various studies have shown that NK cells in cancer patients are often dysfunctional, exhibiting reduced numbers and lower cytotoxic activity. The NK cell function is also a predictor of cancer prognosis. Therefore, the transfusion of activated, functional NK cells can overcome this dysfunction and enhance the immune response against cancer. The NK cells from cancer patients can be expanded in large numbers (up to a few billion) and reactivated using cytokines such as IL-2, IL-12, IL-15, IL-18, and IL-21, as well as agonistic antibodies like CD16, CD56, and NKp46 [114-122]. When reinfused, these reactivated NK cells home to tumor sites, inhibit tumor progression, and may improve progression-free survival [123].

Numerous clinical trials on NK cell therapy are ongoing worldwide. The first autologous NK cell-based clinical trial began in 2008 (NCT00720785) and relied on chemotherapy preconditioning with pentostatin to enhance NK cell therapeutic activity. Since then, advancements in molecular biology, upstream processing, and cryopreservation have enabled scalable, accessible, and cost-effective NK cell-based therapies. The proportion of NK cell-based clinical trials has increased from 23% in 2013 to 33% in 2019 among all cell-based immunotherapies and further raise of 3.2% from 2020 to 2024 (Figure 2b). Recently clinical trials highlight the potential of NK cell therapies for acute myeloid leukemia (AML). Phase I trials of CYNK-001 and haploidentical mbIL-21-expanded

NK cells reported MRD negativity and 58.3% complete remission in refractory AML patients, respectively [124,125]. A phase I/IIa trial of GTA002 and a phase 1/2 trial of memory-like NK cells post-haplo-HCT in high-risk pediatric and young adult AML patients are also underway [126]. These studies highlight the potential of NK cell therapies in improving outcomes for AML patients. The CRISPR-Cas editing has revolutionized NK cell engineering, enabling enhanced tumor-targeting capabilities, persistence, and resistance to immunosuppressive microenvironments The CRISPR-Cas12a editing enables the precise genetic modification of NK cells to enhance their anti-leukemic activity against CLEC12A-positive AML [127]. The CRISPR-edited NK cells are advancing rapidly, with preclinical successes in AML and solid tumors.

Dendritic cancer vaccine

Dendritic cell therapy, or dendritic cancer vaccine, is a promising cell-based immunotherapy for cancer treatment. The observation of tumor regression in some patients following the infusion of bacterial extracts into tumors laid the foundation for the development of cancer vaccines [128]. Since then, clinicians and scientists have explored the use of dendritic cells (DCs) to induce tumor rejection and lysis by the immune system. The efficacy of DC-based treatments was first reported in melanoma patients [129] and later confirmed by several research groups [130,131].

In this approach, cultured DCs are pulsed with tumor lysates or peptides, and these activated DCs are used as dendritic vaccines. The DCs are antigen-presenting cells (APCs) and play a crucial role in both adaptive and innate immunity. The first USFDA-approved anti-cancer vaccine, Sipuleucel-T [Provenge], was approved in 2010 for the treatment of advanced prostate cancer [132]. It was well-tolerated and demonstrated improved overall survival (62.6% vs. 41.6%) when used prior to abiraterone or enzalutamide (androgen pathway inhibitors) in prostate cancer patients [133]. However, Sipuleucel-T, a personalized autologous vaccine, has not been widely adopted due to a lack of public awareness, the need for on-demand manufacturing, and challenges in optimizing patient selection Recent advancements have revitalized interest in DC vaccine because of regulatory breakthrough, precision medicine and combinational approach. The FDA granted fast track designation to DOC1021, an autologous dendritic cell vaccine loaded with tumor lysate and RNA, for pancreatic ductal adenocarcinoma (PDAC) in 2024; following phase I glioblastoma data demonstrating a 75% survival rate (12/16 patients alive at 12.9-month follow-up) and a 7.7-month overall survival (OS) improvement in high-risk glioblastoma patients compared to historical controls [134-136]. The ongoing DECIST trial (NCT04157127) evaluates DOC1021 in PDAC with escalating dendritic cell doses (0.5M–8M cells) combined with peg interferon α 2a to amplify T-cell responses, aiming to establish safety and efficacy in a cohort-based dose-escalation framework. These developments address previous challenges in DC vaccination, such as T-cell dysfunction and inadequate priming [137]. Personalized DC vaccines, combined with other immunotherapies, are emerging as a promising approach to enhance antitumor immunity and improve patient outcomes [138].

Whole cell tumor vaccine and others

The Melacine (Corixa Corp.) is a whole tumor vaccine prepared from an allogeneic melanoma tumor cell lysate, co-administered with Detox adjuvant (containing an altered Mycobacterium cell wall skeleton and monophosphoryl lipid A). It has demonstrated anti-tumor activity in 5-10% of metastatic melanoma cases [139]. The survival rate with Melacine is comparable to chemotherapy regimens, but it exhibits lower toxicity. Currently, personalized cancer vaccine development is emerging as a promising treatment strategy, fueled by recent advances in next-generation sequencing and advanced bioinformatics tools. However, several technical and fundamental challenges must be addressed before these cancer vaccines can be widely translated. These challenges include the diversity of the cancer genome, individual genetic variability, and the highly personalized nature of tumor antigens have historically limited their scalability and broad clinical utility. In contrast, mRNA cancer vaccines avoid these hurdles by leveraging computational neoantigen prediction algorithms and modular design, enabling rapid synthesis of patient-specific or shared tumor antigen sequences. mRNA cancer vaccines overcome the laborious tumor harvesting and scalability limitations of whole-cell approaches by enabling cost-effective *in vitro* synthesis, standardized multi-antigen targeting (e.g., BioNTech's FixVac platform), and adaptability to conserved driver mutations (e.g., KRAS G12D) or heterogeneous neoantigens. Their transient expression enhances safety by avoiding genomic integration while boosting immunogenicity via innate immune activation (e.g., TLR3/7), positioning mRNA as a transformative platform for precision oncology. Encouraging preclinical and clinical trial results have expanded their application to infectious diseases as well as cancers [140]. Complementing this approach, oncolytic viruses (Ovs) are engineered to selectively infect and lyse the tumor cells, simultaneously releasing tumor associated antigen, stimulating innate/adaptive immunity -synergizing with the mRNA vaccine to overcome the immunosuppressive tumor environment. These OVs act as an anti-cancer agents and *in situ*

adjuvant enhancing antigen spread and DC activation. Further, OVs offer the advantage of tumor-specific cell lysis without harming normal cells, while also enhancing immune stimulation and acting as potential in situ tumor vaccines [141]. Currently, more than 60 OV-based clinical trials are in the patient recruitment phase, with the majority involving genetically engineered viruses. Two examples of approved genetically engineered oncolytic viruses are Oncorine (H101, approved in 2005) and talimogene laherparepvec (OncoVEXGM-CSF/T-Vec, approved in 2015 for advanced melanoma). A recent breakthrough in oncolytic virus therapy (IGNYTE phase II trial (NCT03767348)) is the combination of RP1, a genetically engineered HSV-1–based oncolytic virus, with nivolumab in patients with anti–PD-1–failed melanoma achieved a 33.6% objective response rate [142]. The durable responses in both injected and uninjected lesions, including visceral disease and was well-tolerated, with primarily grade 1 or 2 adverse events, and one- and two-year overall survival rates reached 75.3% and 63.3%, respectively. The clinical development of OV therapies requires a focus on viral pharmacokinetics, pharmacodynamics, toxicological studies, and long-term immune status compatibility.

Bridging the translational gap: From preclinical model to clinical realities

The translational gap in adaptive cell-based immunity arises from biological mismatches (e.g., human-specific immune interactions, tumor microenvironment heterogeneity) and methodological shortcomings (e.g., non-predictive animal models, unvalidated biomarkers), are more pronounced in cellular based therapeutics. The translational gap between preclinical research and clinical application-often termed the "valley of death"-remains a critical barrier in drug development, where fewer than 10% of preclinical candidates progress to clinical success [143]. This gap is characterized by having the efficacy in animal models failing to deliver similar benefits in human trials. For instance, in cancer research, mouse models are commonly used but often fail to capture the heterogeneity and microenvironmental factors of human tumors, leading to overestimations of drug efficacy. The murine models suggest NK cell therapy efficacy correlates with NKG2D expression, phase II trials in solid tumors have not demonstrated a consistent association between NKG2D expression and therapeutic efficacy, highlighting the need for humanized models that replicate immunosuppressive microenvironments [144,145].

Methodological challenges in preclinical cancer research, including CAR T-cell therapies, such as inconsistent study designs and non-standardized protocols, impair reproducibility and clinical translatability. Further, these issues with heterogeneous outcomes in preclinical studies, highlighting the need for standardized models to bridge the translational gap in oncology. To address these challenges, there is a growing emphasis on developing more predictive preclinical models, such as patient-derived xenografts and organoids, which better mimic human disease pathology [146]. These models aim to bridge the gap by providing a closer representation of human biology, potentially improving the success rate of translational laboratory results into clinical benefits. Additionally, incorporating biomarkers and translational endpoints in preclinical studies can enhance the predictability of clinical outcomes.

Future Direction and Conclusion

The current standard-of-care for cancer treatment involves surgery, chemotherapy, and radiation, which have shown variable success rates along with associated toxicity, morbidity, and mortality. Tumor antigen heterogeneity and immune escape mechanisms are common features of most cancers, leading to chemotherapy resistance, drug resistance, and the need for diverse mechanisms of action in emerging therapeutics (Figure 3). Future research prospects must prioritize integrating combinatorial epigenetic-CAR-T strategies, such as coupling DNA methyltransferase inhibitors (DNMTis) or histone deacetylase inhibitors (HDACis) with CAR-T cells, to counteract immunosuppressive tumor microenvironments (TMEs) and mitigate T-cell exhaustion. These approaches, validated in preclinical models for enhancing CAR-T persistence and antigen recognition [147], should be paired with multi-omics platforms (e.g., single-cell ATAC/RNA sequencing) to dynamically map epigenetic and transcriptional landscapes during therapy [148]. To address the challenges of PD-L1 heterogeneity, standardized real-world evidence (RWE) frameworks integrating circulating tumor cell (CTC) analyses and longitudinal biomarker monitoring are critical [149,150]. These approaches aim to validate PD-L1 as a dynamic biomarker and mitigate variability arising from tumor biology, testing protocols, and specimen handling. Finally, the successful translation of immunotherapy advancement requires bridging preclinical-clinical gaps through adaptive trial designs that incorporate patient-derived organoids, AI-driven biomarker discovery, and RWE-driven validation of combinatorial regimens (e.g., PD-L1/TMB co-expression). Besides, Machine learning platforms like NeoScanAI (2023) now predict tumor neoantigens with approximately 92% accuracy in ongoing phase II trials for NSCLC [151]. The combination of AI-driven computational system and engineered cell therapies is poised to revolutionize precision cancer immunotherapy, making target oriented, more efficient and patient specific. Advances in cancer

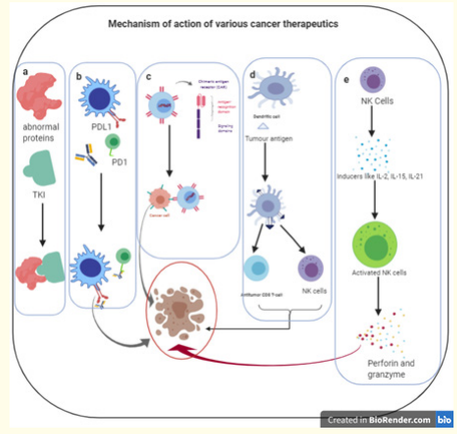

Figure 3: Mechanism of Action of Various Cancer Therapeutics: a) Tyrosine Kinase Inhibitors (TKIs):TKIs are small molecules that block the active sites of abnormal proteins. These abnormal proteins are secreted by chronic myeloid leukemia (CML) cells due to genetic mutations and are responsible for triggering the release of a large number of white blood cells (WBCs) from the bone marrow. By blocking the active sites of these abnormal proteins, TKIs halt disease progression. Example: Gleevec. b) Anti-PD-L1 Monoclonal Antibodies (mAbs):Cancer cells often express PD-L1 to evade recognition by the host immune system. Anti-PD-L1 mAbs block these surface receptors, enabling the host immune cells to recognize and attack tumor cells. This occurs either through antibody-dependent cellular cytotoxicity (ADCC) or by blocking the PD-1 receptor on T-cells, functioning as immune checkpoint inhibitors (ICIs). c) Chimeric Antigen Receptor (CAR) T-Cell Therapy: A targeted response to cancer antigens can be achieved through the generation of CAR T-cells. These are genetically modified T-cells capable of identifying tumor antigens and inducing cytotoxicity against cancer cells. d) Dendritic Cell (DC) Vaccines:Immature dendritic cells (DCs) are pulsed with mutated tumor neo-antigens and presented to CD8+ T-cells and natural killer (NK) cells to stimulate anti-tumor activity.e) Natural Killer (NK) Cell Therapy: NK cells are activated by cytokines such as IL-2, IL-15, and IL-21. Activated NK cells can recognize polyclonal tumor antigens, enabling anti-tumor activity through mechanisms such as ADCC or the release of perforin and granzymes.

diagnostics are progressing toward molecular-level detection of mutations, while new therapeutics are increasingly focused on targeting the root cause of cancer. Combinatorial cancer therapy, combined with molecular diagnostic tools, is paving the way for the development of personalized cancer treatments. Cancer immunotherapy is rapidly evolving, supported by omics-based advanced diagnostic tools that enable precise characterization of cancer. These tools assist clinicians and scientists in developing safe, data-driven combinatorial therapies tailored to individual patients.

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Conflicts of Interest

The authors declare that they have no known financial or non-financial competing interests that could have appeared to influence the work reported in this paper. All authors have reviewed and approved the final manuscript.

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