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A Review of Recent Advances in Cardiothoracic Cancer Immunotherapy

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Abstract. Cardiothoracic malignancies such as lung and esophageal cancer are among the most difficult-to-treat malignancies, being highly lethal with aggressive clinical behaviors. Immunotherapy has become the game-changing method, capitalizing on the natural immune machinery for augmenting the anti-tumor response. Along with considerable successes in the clinical setting, drug resistance, selection of patients through biomarkers, and handling toxicities continue to be principal stumbling blocks to optimal therapeutic management. This review offers an extensive overview of recent developments in immunotherapy of cardiothoracic malignancies, such as immune checkpoint inhibitors (ICIs), cellular therapy, cancer vaccines, and viral-based immunotherapies. We also discuss novel biomarkers, artificial intelligence (AI)-based predictive models, and combination approaches to prevent resistance and maximize efficacy. A comprehensive review of peer-reviewed clinical trials, real-world evidence, and translational studies was performed with a focus on new immunotherapeutic strategies and their clinical significance. Special attention was given to biomarker identification, AI-based treatment choice, and novel combination regimens. The combination of biomarker-guided immunotherapy, predictive modeling with AI, and multimodal treatment modalities has dramatically enhanced patient stratification and rates of therapeutic response. Although PD-1/PD-L1 and CTLA-4 inhibitors continue to be the bedrock of immunotherapy, new approaches like T-cell engineering, oncolytic viruses, and targeted cancer vaccines are demonstrating promising activity in preclinical and clinical environments. In addition, combination treatments, such as ICIs with chemotherapy, targeted therapy, and radiation, have shown increased efficacy in overcoming resistance. Nonetheless, issues like immune-related toxicities, treatment availability, and cost remain.

Keywords: Cardiothoracic cancer, immunotherapy, immune checkpoint inhibitors, biomarkers, artificial intelligence, combination therapy, precision oncology.

I. Introduction

Cardiothoracic cancers, including lung cancer, thymic malignancies, and mesothelioma, represent a significant global health burden with high morbidity and mortality rates. Lung cancer alone accounts for approximately 1.8 million deaths annually, making it the leading cause of cancer-related deaths worldwide [1]. Traditional treatment modalities such as surgery, chemotherapy, and radiotherapy have demonstrated limited long-term efficacy, particularly in cases of advanced or metastatic disease [2]. The emergence of immunotherapy has revolutionized cancer treatment by harnessing the patient's immune system to combat tumour progression, offering durable responses in a subset of patients [3].

Table 1: Summary of Key Immunotherapy Strategies for Cardiothoracic Cancers.

Immunotherapy Strategy	Mechanism of Action	Clinical Applications	Challenges	Reference
Immune Checkpoint Inhibitors (ICIs)	Block inhibitory pathways (e.g., PD-1/PD-L1, CTLA-4) to enhance T-cell activation.	Approved for NSCLC, SCLC, mesothelioma, and other thoracic malignancies.	Resistance mechanisms, immune-related adverse events (irAEs).	[7], [8]
CAR-T and TCR-T Cell Therapy	Genetically modified T cells recognize and attack tumor cells.	Under investigation for solid tumors, including lung cancer and mesothelioma.	Limited efficacy in solid tumors, tumor microenvironment barriers.	[9], [10]
Cancer Vaccines	Stimulate immune system to recognize tumor-specific antigens.	Investigational vaccines targeting mutated proteins and neoantigens in thoracic cancers.	Low immunogenicity, need for patient-specific customization.	[11], [12]
Oncolytic Virus Therapy	Genetically engineered viruses selectively infect and kill cancer cells.	Early trials for lung cancer and mesothelioma.	Immune evasion, viral delivery challenges.	[13], [14]

Immunotherapy encompasses a broad range of therapeutic approaches, including immune checkpoint inhibitors (ICIs), CAR-T and TCR-T cell therapy, cancer vaccines, and oncolytic virus therapy [4]. Among these, ICIs targeting PD-1, PD-L1, and CTLA-4 have demonstrated remarkable clinical success, leading to the approval of agents such

as nivolumab, pembrolizumab, and atezolizumab for lung cancer treatment [5]. Despite these advances, primary and acquired resistance to immunotherapy remains a critical challenge, necessitating the exploration of novel biomarkers, combination therapies, and predictive tools to optimize treatment outcomes [6].

In this review, we present a thorough overview of recent progress in cardiothoracic cancer immunotherapy, with emphasis on several major areas. We first review existing immunotherapeutic approaches, including immune checkpoint inhibitors (ICIs), cellular therapies like CAR-T and TCR-T cell therapy, therapeutic cancer vaccines, and oncolytic virus therapy, all of which have shown great promise in the treatment of cardiothoracic cancers. Second, we discuss new biomarkers and AI-based predictive models that are augmenting the power to forecast patient response to immunotherapy, thus enabling personalized treatment strategies. Finally, we review combination therapy regimens, including ICIs combined with chemotherapy, targeted therapy, or radiation therapy, to evade resistance and enhance treatment effectiveness. Lastly, we underscore future directions in immuno-oncology, such as next-generation immunotherapies and precision medicine strategies, which promise to continue redefining the treatment landscape of cardiothoracic cancers. Through addressing these areas, this review seeks to give important insights into recent advances, current challenges, and future directions of immunotherapy in the treatment of cardiothoracic malignancies.

II. Immunotherapy Modalities in Cardiothoracic Cancer

Immunotherapy has come up as a novel treatment modality for cardiothoracic tumors, such as non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), and malignant pleural mesothelioma (MPM). Amongst these, immune checkpoint inhibitors (ICIs) have shown excellent clinical efficacy and have been approved as standard care in several disease settings [14]. ICIs rejuvenate T-cell anti-tumor immunity by inhibiting immune checkpoint pathways that dampen immunity, including programmed death-1 (PD-1), programmed death-ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) [15]. Though highly promising, ICIs are marred by difficulties such as immune-related adverse events (irAEs), primary and secondary resistance, and a requirement for predictive biomarkers [16].

Immune Checkpoint Inhibitors (ICIs)

- PD-1/PD-L1 and CTLA-4 Inhibitors

PD-1 inhibitors (e.g., nivolumab and pembrolizumab) and PD-L1 inhibitors (e.g., atezolizumab and durvalumab) block the PD-1/PD-L1 axis, preventing tumor-induced immune suppression [17]. CTLA-4 inhibitors, such as ipilimumab, work by amplifying T-cell activation and proliferation at the priming phase of the immune response [18]. These therapies have shown durable clinical responses and have been approved for various cardiothoracic cancers, either as monotherapy or in combination with chemotherapy and radiation [19].

Mechanisms, Clinical Trials, and FDA Approvals

Several landmark clinical trials have established ICIs as a standard treatment for cardiothoracic malignancies. The KEYNOTE-189 trial demonstrated superior overall survival (OS) and progression-free survival (PFS) for pembrolizumab plus chemotherapy

in first-line NSCLC [20]. The PACIFIC trial led to durvalumab approval as a consolidation therapy following chemoradiation in unresectable stage III NSCLC [21]. Additionally, the CheckMate 743 trial supported the approval of nivolumab plus ipilimumab as a first-line therapy for mesothelioma, marking a major advancement in thoracic oncology [22].

Table 2: FDA-Approved ICIs for Cardiothoracic Cancers, Their Indications, and Clinical Trial Outcomes.

Drug	Target	Indication	Key Clinical Trial	Outcome	FDA Approval Year	Reference
Pembrolizumab	PD-1	1L NSCLC (PD-L1 ≥ 1%)	KEYNOTE-189	Improved OS and PFS	2018	[20]
Nivolumab	PD-1	2L NSCLC, SCLC	CheckMate 017, 057	Increased survival	2015	[21]
Atezolizumab	PD-L1	1L SCLC + chemo	IMpower133	Increased OS	2018	[22]
Durvalumab	PD-L1	Stage III NSCLC post-CRT	PACIFIC	Improved PFS and OS	2017	[23]
Ipilimumab + Nivolumab	CTLA-4 + PD-1	Unresectable Mesothelioma	CheckMate 743	OS benefit over chemo	2020	[24]

Challenges: Resistance and Adverse Effects

Though they have been clinically successful, ICIs have some challenges:

Primary and Acquired Resistance

Certain tumors are inherently resistant because of low tumor mutation burden (TMB), bad antigen presentation, or an immunosuppressive microenvironment [25]. Tumors over time can acquire resistance by overexpressing alternative immune checkpoints or depleting T-cell function [26].

Immune-Related Adverse Events (irAEs)

ICIs have the ability to induce autoimmune toxicities that involve the lungs, gastrointestinal system, liver, and endocrine organs. Frequent irAEs are pneumonitis, colitis, hepatitis, and thyroiditis and need immune-modulatory management including corticosteroids [27].

Patient Selection and Biomarkers

The discovery of biomarkers that can predict ICI response, such as PD-L1 expression, TMB, and tumor-infiltrating lymphocytes (TILs), is ongoing. AI-based predictive models and multi-omics strategies are being investigated to improve patient stratification and tailor immunotherapy selection [28].

CAR-T and TCR-T Cell Therapy

Chimeric Antigen Receptor (CAR) T-Cell Therapy

Chimeric Antigen Receptor (CAR) T-cell therapy has transformed hematologic malignancies but is still tricky to apply to solid tumors, such as cardiothoracic cancers [29]. CAR T-cell therapy comprises genetically modifying autologous T cells to target a synthetic receptor that binds tumor-specific antigens [30]. In mesothelioma and lung cancer, mesothelin (MSLN), epidermal growth factor receptor (EGFR), and carcinoembryonic antigen (CEA) have been investigated as suitable CAR targets [31]. Nonetheless, tumor heterogeneity, immunosuppressive tumor microenvironment (TME), and poor T-cell infiltration are still significant challenges [32].

Tumor-Infiltrating Lymphocyte (TIL) Therapy

Tumor-infiltrating lymphocyte (TIL) therapy with ex vivo expansion of autologous lymphocytes from tumor biopsies has been promising in melanoma and NSCLC [33]. TIL therapy boosts the anti-tumor immune response by reinstating highly responsive T cells within the patient, resulting in some instances of tumor regression [34]. Scalability, patient selection criteria, and the requirement of lymphodepletion regimens hold back its broader use in thoracic oncology [35].

Table 3: Cellular Therapies in Cardiothoracic Cancers and Their Clinical Implications.

Cellular Therapy	Target Antigen	Cancer Type	Clinical Trial	Outcome	Reference
CAR T-Cell Therapy	Mesothelin	Mesothelioma, NSCLC	NCT02414269	Partial responses	[36]
CAR T-Cell Therapy	EGFR	NSCLC	NCT01869166	Increased T-cell persistence	[37]
TIL Therapy	Tumor-Specific Neoantigens	NSCLC	NCT03215810	Improved PFS	[38]

(a) The native TCR complex, consisting of CD3 subunits (ε, δ, γ, ζ) and αβ chains, facilitates antigen recognition and signal transduction.
(b) Evolution of CAR designs from first to fourth generation, incorporating scFv-based antigen recognition, hinge/spacer domains, transmembrane regions, and various co-stimulatory molecules.

(c) CAR T-cell mechanism: engineered T-cells recognize tumor-associated antigens (TAA) via scFv, leading to inflammatory cytokine release and tumor cell targeting while balancing immune inhibition.

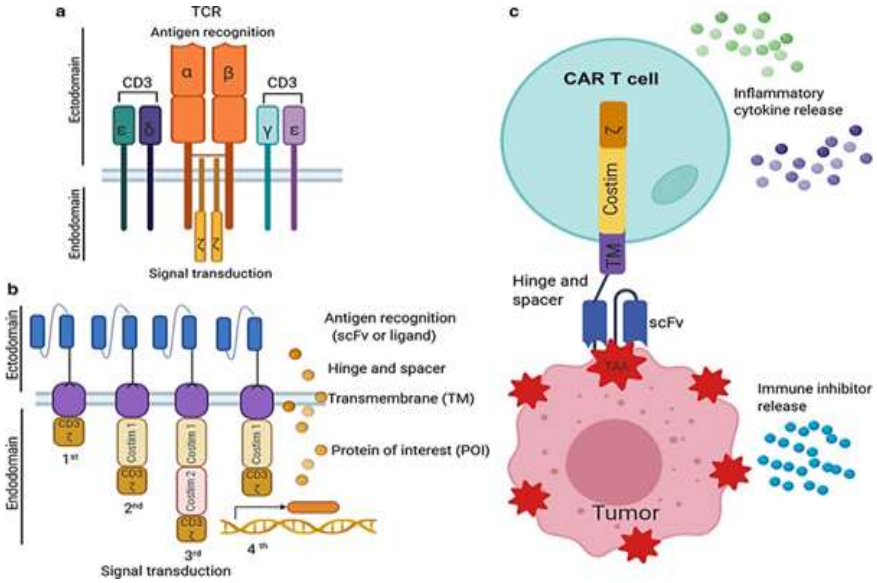

Figure 1. Schematic representation of T-cell receptor (TCR) and chimeric antigen receptor (CAR) structures in T-cell signalling and tumour targeting.

Cancer Vaccines

- Therapeutic Cancer Vaccines

Vaccines in cancer aim to induce an anti-tumor immune response by exposing tumor-associated antigens (TAAs) or neoantigens to the immune system. Vaccines against MAGE-A3, WT1, NY-ESO-1, and KRAS mutations have been investigated in cardiothoracic cancers [39]. The GVAX vaccine, a genetically engineered tumor cell vaccine, has been investigated in mesothelioma [40]. Clinical responses have been disappointing, with only modest outcomes despite robust preclinical evidence, primarily because of inefficient immunogenicity and immune evasion mechanisms [41].

Oncolytic Virus Therapy (OVT)

Oncolytic viruses (OVs) selectively target and kill tumor cells while boosting anti-tumor immune responses. The Talimogene laherparepvec (T-VEC), a genetically modified herpes simplex virus, has been studied in lung cancer [42]. Adenovirus-derived OVs, like CG0070, are being explored in NSCLC for their capacity to induce immunogenic cell death and boost checkpoint inhibitor efficacy [43].

Oncolytic Virus Therapy

Combining ICIs with chemotherapy, radiation, or targeted therapies is a promising strategy to overcome tumor resistance. Chemoimmunotherapy, such as pembrolizumab + platinum-doublet chemotherapy, has shown superior efficacy in NSCLC [44]. Radiotherapy induces immunogenic cell death, increasing tumor antigen presentation and

enhancing ICI response [45]. Additionally, targeted therapies, such as EGFR-TKIs (osimertinib) or VEGF inhibitors (bevacizumab), have been combined with ICIs to improve outcomes in lung cancer patients with specific genetic alterations [46].

Table 4: Combination Immunotherapy Strategies in Cardiothoracic Cancer.

Combination Therapy	Cancer Type	Key Clinical Trial	Outcome	Reference
Pembrolizumab + Chemo	NSCLC	KEYNOTE-189	Improved OS & PFS	[47]
Durvalumab + Radiotherapy	Stage III NSCLC	PACIFIC	Increased DFS	[48]
Osimertinib + PD-1 Inhibitor	EGFR+ NSCLC	TATTON	Enhanced response rate	[49]

III. Novel Biomarkers and Predictive Tools for Immunotherapy Response

The effectiveness of immunotherapy in cardiothoracic malignancies continues to be very heterogeneous among patients, and there is a need for strong predictive biomarkers to better tailor treatment regimens. Novel technologies like liquid biopsy, tumor mutational burden (TMB), microsatellite instability (MSI), and AI-based predictive modeling are revolutionizing the field of personalized immuno-oncology [50].

Liquid Biopsy: Detection of Non-Invasive Biomarkers
Liquid biopsy has become increasingly popular as a minimally invasive approach to tracking tumor dynamics and immunotherapy response prediction. The major components that are being analyzed are circulating tumor DNA (ctDNA), exosomes, and cytokines [51].

Circulating Tumor DNA (ctDNA)
ctDNA fragments shed by tumor cells into the blood offer real-time information on tumor burden, genetic alterations, and resistance mechanisms [52]. Research has shown that levels of ctDNA can predict response to PD-1/PD-L1 inhibitors, with early clearance being associated with improved survival in NSCLC patients [53].

Exosomal Biomarkers
Tumor-derived exosomes contain proteins, RNA, and DNA that affect immune modulation. Certain PD-L1+ exosomes have been linked to ICIs resistance by inhibiting T-cell activity [54].

Cytokine Profiling
Pro-inflammatory cytokines like IFN-γ, IL-6, and TNF-α are biomarkers of immune activation. Increased IL-8 is associated with reduced response to anti-PD-1 therapy in lung cancer [55].

Tumor Mutational Burden (TMB), Microsatellite Instability (MSI), and Other Biomarkers

TMB and MSI have also become important genomic predictors of immunotherapy response.

Tumour Mutational Burden (TMB)

TMB measures the number of mutations per megabase of DNA and correlates with the probability of neoantigen presentation, thus improving immune recognition [56]. It has been demonstrated that high TMB is a predictor of sustained responses to checkpoint inhibitors, especially in NSCLC and mesothelioma [57].

Microsatellite Instability (MSI)

MSI-high (MSI-H) status due to faulty mismatch repair (MMR) genes has been related to increased ICI sensitivity [58]. Whereas MSI is well documented as a biomarker for colorectal carcinoma, its impact on thoracic malignancies has been studied as investigations continue through ongoing trials looking at MSI-H lung cancer [59].

Other Biomarkers

Other predictive markers are PD-L1 expression levels, lactate dehydrogenase (LDH), and immune cell infiltration measures (CD8+ T cells, NK cells) [60].

Table 5: Genomic and Molecular Biomarkers in Immunotherapy Response

Biomarker	Mechanism	Cancer Type	Clinical Significance	Reference
TMB	Increased neoantigen load	NSCLC, Mesothelioma	Predicts response to ICIs	[61]
MSI	Defective MMR pathway	NSCLC	Associated with improved outcomes in ICI therapy	[62]
PD-L1	Immune checkpoint regulation	NSCLC, Mesothelioma	High expression correlates with response to PD-1/PD-L1 inhibitors	[63]
ctDNA	Tumor burden indicator	NSCLC	Reduction in ctDNA correlates with better prognosis	[64]

Artificial Intelligence and Machine Learning in Predictive Modeling

Artificial intelligence (AI) and machine learning (ML) have transformed biomarker discovery and response prediction models in immunotherapy. These computational methods process multi-omics data, such as genomics, transcriptomics, and radiomics, to create personalized predictive tools [65].

Radiomics and Deep Learning

Deep learning radiomics derives high-dimensional features from imaging modalities (CT, MRI, PET) to measure immune signatures and estimate response to checkpoint inhibitors [66]. Deep learning models based on radiomic features have been able to

differentiate responders from non-responders in pembrolizumab-treated NSCLC patients [67].

Multi-Omics Integration
AI combines genomic (TMB, MSI), proteomic, and transcriptomic information to establish predictive models of immunotherapy responses [68]. Machine learning methods, including random forests and deep neural networks, are being utilized to discover new biomarkers of immune checkpoint blockade therapy [69].

Natural Language Processing
Natural Language Processing (NLP) within Electronic Health Records (EHRs): AI software based on NLP reviews real-world clinical information to monitor patient outcomes, toxicities, and long-term survival with immunotherapy [70].

IV. Combination Strategies to Overcome Resistance

Although immune checkpoint inhibitors (ICIs) have enjoyed great success in cardiothoracic oncology, primary and acquired resistance to these drugs constitute a significant burden, confining the long-term effectiveness of mono-therapy regimes [56]. Combination therapies which include chemotherapy, targeted therapy, radiation therapy, and multi-modality immunotherapy have been evolving to augment the anti-tumor response and avoid immune evasion mechanism [57].

ICIs + Chemotherapy
Immune checkpoint inhibitors combined with chemotherapy have been highly effective in non-small cell lung cancer (NSCLC) and mesothelioma, capitalizing on chemotherapy-induced release of tumor antigens to sensitize the immune system [58].
Mechanism: Chemotherapy causes immunogenic cell death (ICD), leading to the release of damage-associated molecular patterns (DAMPs) that stimulate antigen-presenting cells (APCs), making T-cell priming and checkpoint inhibitor effects more pronounced [59].

Clinical Evidence: KEYNOTE-189 trials proved that pembrolizumab (anti-PD-1) in combination with chemotherapy greatly enhanced overall survival (OS) and progression-free survival (PFS) in patients with advanced NSCLC compared to chemotherapy alone [60].
Challenges: The major restrictions are augmented toxicity, myelosuppression, and depletion of tumor-infiltrating lymphocytes (TILs) [61].

Table 6: Key Clinical Trials for ICI + Chemotherapy Combinations

Combination Therapy	Cancer Type	Key Trial	Outcome	Reference
Pembrolizumab + Platinum/ Pemetrexed	NSCLC	KEYNOTE-189	Improved OS & PFS	[62]
Nivolumab + Gemcitabine/ Cisplatin	Mesothelioma	CheckMate-743	Increased median OS	[63]

ICIs + Targeted Therapy

Targeted therapies, such as tyrosine kinase inhibitors (TKIs) and angiogenesis inhibitors, have been used with ICIs to regulate the tumor microenvironment (TME) and promote immune recognition [64].

Anti-VEGF and ICIs: Vascular endothelial growth factor (VEGF) has immunosuppressive functions by blocking T-cell infiltration and enhancing regulatory T cells (Tregs) [65]. Atezolizumab (anti-PD-L1) and bevacizumab (anti-VEGF) has shown improved survival in NSCLC and hepatocellular carcinoma (HCC) [66].

EGFR-TKIs and ICIs: Epidermal growth factor receptor (EGFR) mutation is prevalent in lung adenocarcinoma, but single-agent EGFR-TKIs usually do not provide sustained response. Osimertinib (EGFR-TKI) with ICIs has been encouraging, but with toxicity being the problem [67].

ICIs + Radiation Therapy

Radiation therapy (RT) may serve as an in situ vaccine by causing tumor antigen release and presentation of neoantigens, thus increasing the efficacy of ICI [68].
Abscopal Effect: RT has the ability to stimulate systemic anti-tumor immunity outside the irradiated field, a process enhanced by checkpoint blockade [69].

Clinical Evidence: PACIFIC trial showed that durvalumab (anti-PD-L1) following chemoradiation considerably extended survival in unresected stage III NSCLC [70].
Challenges: Radiation-induced immune suppression (lymphopenia, T-cell exhaustion) remains a barrier [71].

Multi-Modality Immunotherapy Strategies

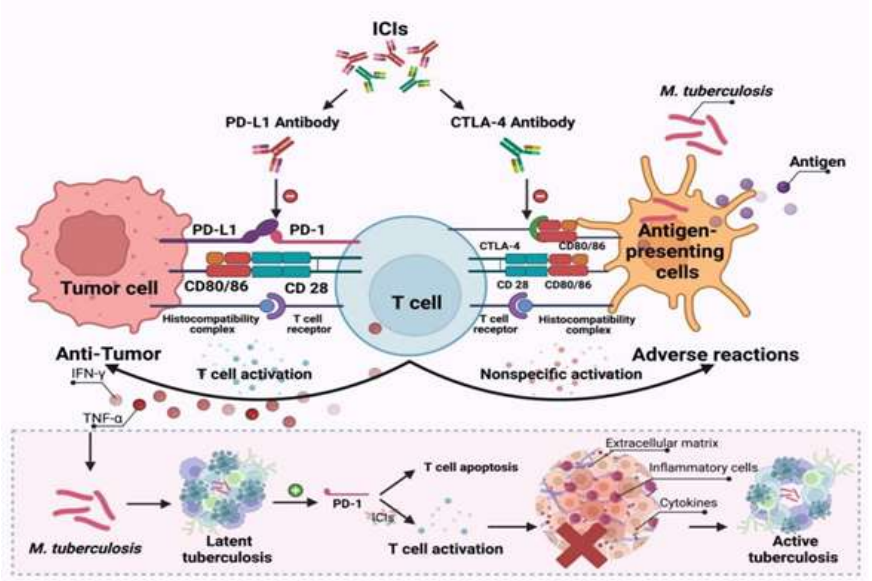

Figure 2. Immune checkpoint inhibitors (ICIs) and their dual effects on anti-tumor immunity and tuberculosis activation.

Multi-modal regimens integrate ICIs, chemotherapy, targeted therapy, and radiation therapy to take advantage of various anti-tumor mechanisms at the same time [72].
Triple Combinations: ICIs + chemotherapy + anti-VEGF therapy have yielded encouraging results in lung cancer [73].
Personalized Strategies: Treatment selection based on AI is being investigated to maximize combination regimens in individual patients [74].

The schematic illustrates how PD-L1 and CTLA-4 antibodies enhance T-cell activation by blocking immune checkpoints, promoting anti-tumor responses through IFN-γ and TNF-α release. However, this immune activation can also lead to adverse reactions, including nonspecific T-cell activation. In the context of Mycobacterium tuberculosis infection, PD-1 blockade may cause reactivation of latent tuberculosis due to increased inflammatory responses, extracellular matrix degradation, and cytokine release, leading to active tuberculosis.

V. Challenges and Future Perspectives

Although immunotherapy has revolutionized cardiothoracic cancer therapy, major obstacles still remain. Mechanisms of resistance, toxicity, cost considerations, and the demand for individually tailored treatment methods are still constraints for broad-based uptake and success [75]. Upcoming progress such as the advent of next-generation immunotherapies, the use of predictive models utilizing artificial intelligence, and new combinations remains essential for maximization of benefit [76].

Immunotherapy Resistance Mechanisms
Primary and secondary resistance are key challenges to long-term success in immunotherapy. Tumors become resistant via immunoediting, alternative immune checkpoint upregulation, antigen presentation loss, and T-cell exhaustion [77].
Tumor-Intrinsic Mechanisms: MHC-I downregulation, tumor neoantigen loss, and oncogenic pathway activation (e.g., WNT, JAK-STAT, and PTEN mutations) account for resistance [78].

Tumor Microenvironment (TME) Impact: Immunosuppressive cell infiltration (Tregs, myeloid-derived suppressor cells (MDSCs), tumor-associated macrophages (TAMs)), and hypoxia induce immune evasion [79].
Bypassing Resistance: Targeting other immune checkpoints (e.g., LAG-3, TIGIT, TIM-3), optimizing antigen presentation, and tilting the TME are attractive approaches [80].

Adverse Effects and Toxicity Management
Although effective, immune checkpoint inhibitors (ICIs) and CAR-T cell therapies have the potential to cause severe immune-related adverse events (irAEs) involving several organ systems [84].
Common Toxicities: ICIs are implicated in colitis, pneumonitis, hepatitis, myocarditis, and endocrinopathies as a result of generalized immune activation [85].
CAR-T Cell Toxicities: Cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) are significant concerns [86].

Management Strategies: Corticosteroids, IL-6 inhibitors (such as tocilizumab), and risk stratification models are important strategies for reducing toxicity [87].

Table 7: Key Challenges and Proposed Solutions in Cardiothoracic Cancer Immunotherapy

Challenge	Mechanism	Proposed Solutions	Reference
Primary Resistance	Tumor antigen loss, upregulated immune checkpoints	Neoantigen-targeted therapies, bispecific T-cell engagers (BiTEs)	[81]
Acquired Resistance	T-cell exhaustion, adaptive immune evasion	LAG-3 and TIGIT inhibitors, cytokine modulation	[82]
TME Immunosuppression	Tregs, MDSCs, hypoxia	TME reprogramming, anti-VEGF therapy	[83]

Cost, Accessibility, and Individualized Treatment Strategies

The expense of immunotherapies is an important obstacle to universal access worldwide, especially among low- and middle-income countries (LMICs) [88].

Economic Burden: The economic burden of ICIs such as nivolumab and pembrolizumab can amount to more than $100,000 annually, with affordability proving to be an enormous challenge [89].

Access Disparities: Limited availability of clinical trials, regulatory obstacles, and biomarker testing disparities further inhibit the equitable distribution of treatment [90].

Solutions: Biosimilars, precision medicine through AI, and value-based pricing schemes can enhance affordability and access [91].

New Research Directions and Prospective Breakthroughs

State-of-the-art research is geared towards next-generation immunotherapies, new immune checkpoints, and AI-based patient stratification [92].

Next-Generation ICIs: Dual-targeting antibodies (e.g., PD-1/CTLA-4 dual inhibitors) and immune agonists (e.g., OX40, GITR, CD40 agonists) are being explored [93].

Personalized Immunotherapy: AI models are refining biomarker-guided selection of treatment, predicting the outcome, and avoiding toxicity [94].

Oncolytic Virus Therapy: Genetically engineered viruses that selectively infect and kill tumor cells and induce immune responses are a promising area [95].

VI. Conclusion

The cardiothoracic cancer immunotherapy landscape has dramatically changed, with immune checkpoint inhibitors (ICIs), cellular therapies, cancer vaccines, and innovative combination regimens showing profound clinical benefits. Notwithstanding these developments, hurdles like tumor resistance, side effects, accessibility concerns, and the requirement for individualized treatment regimens remain. Recent advances such as AI-powered predictive models, liquid biopsy-based biomarkers, and next-generation immunotherapeutic agents promise to overcome these shortcomings and further improve treatment outcomes.

From a clinical and translational view, combined patient selection via biomarkers, real-world data, and combination immune therapies is vital for maximalization of patient outcome. Approvals of the PD-1/PD-L1 and CTLA-4 blockers, along with the maturation of next-generation immune-modulatory agents, confirm the critical necessity of treatment adaptation to both tumor-specific and patient-specific markers. Moreover, novel oncolytic viruses, gene-engineered T-cell strategies, and adaptive immunotherapy strategies have new ways in which patients could be protected against resistance as well as for achieving better rates of response.

In the future, research must continue to clarify immunotherapy resistance mechanisms, discover new immune targets, and incorporate machine learning models to personalize therapy choice. The complementary use of genomics, proteomics, and computational modeling might propel predictive oncology breakthroughs toward more personalized and effective treatment paradigms. Additionally, academia-industry-regulatory collaborations are necessary for expediting clinical translation and achieving wider access to immunotherapy.

Finally, although immunotherapy has transformed cardiothoracic cancer care, ongoing research, innovation, and collaboration are the key to the full realization of its clinical benefit. Through meeting existing challenges and harnessing forthcoming technologies, future generations of immunotherapies can reshape the lives of cancer patients and remake the landscape of precision oncology.

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