

MINI REVIEW

Iran J Allergy Asthma Immunol

In press.

Neoantigens in Cancer Immunotherapy: An Overview with a Focus on Non-small Cell Lung Cancer and Pancreatic Ductal Adenocarcinoma

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Received: 6 July 2025; Received in revised form: 20 September 2025; Accepted: 10 November 2025

ABSTRACT

Non-small cell lung cancer (NSCLC) and pancreatic ductal adenocarcinoma (PDAC) figure prominently in the list of prevalent and resistant cancers that reveal significant differences in response to immunotherapy. Neoantigens, specific antigens resulting from tumor mutations, play an important role in provoking immune responses and the success of immunotherapy. This review scrutinizes the quantitative and qualitative differences in neoantigens in NSCLC and PDAC and their impact on the efficacy of immunotherapy. The evidence suggests that the higher mutational burden, greater diversity, and different quality of neoantigens in NSCLC compared with PDAC are among the key drivers contributing to the enhanced susceptibility to immunotherapy in this cancer. These differences could pave the way for the development of personalized therapies and novel strategies to improve treatment outcomes in resistant cancers.

Keywords: Cancer immunotherapy; Non-small cell lung cancer; Neoantigens; Pancreatic ductal adenocarcinoma

INTRODUCTION

Cancer persists as a globally paramount public health issue, annually affecting millions of individuals. The World Health Organization's 2022 estimates, which documented approximately 20 million new diagnoses and 10 million deaths, coupled with a potential escalation to over 35 million new cases annually by 2050, underscore this reality.¹ This escalating global cancer burden magnifies the need for sustained efforts in

both basic biological research and the therapeutic development of novel modalities.²⁻⁴ Among the vast range of malignant neoplasms, non-small cell lung cancer (NSCLC) and pancreatic ductal adenocarcinoma (PDAC) warrant particular scholarly and clinical attention.⁵⁻⁷ This stepped-up consideration is justified by their marked incidence rates, biologically distinctive and aggressive characteristics, and the exceptionally complex therapeutic challenges they pose. Consequently, a profound and comprehensive understanding of the intricate pathobiological mechanisms underpinning these specific malignancies is an indispensable prerequisite for the rational design and successful clinical translation of effective therapeutic strategies, with a particular emphasis on pioneering immunotherapeutic approaches.⁸⁻¹⁰

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NSCLC, representing approximately 80%–85% of all lung malignancies,¹¹ covers three primary histopathological subtypes—adenocarcinoma, squamous cell carcinoma, and large cell carcinoma—each distinguished by unique hallmarks and differential therapeutic sensitivity.¹² Despite the fact that cigarette smoking is generally reputed to be the primary cause, adenocarcinoma, the principal histological type, often emerges in people who have always abstained from tobacco.¹¹ The initial clinical manifestations, often characterized by a constellation of nonspecific respiratory and systemic symptoms, including chronic cough, pleuritic discomfort, hemoptysis, cachexia, and dyspnea, commonly lead to chronologically late diagnosis and advanced-stage presentation.¹¹ With 5-year survival rates of roughly 64% for locoregionally confined neoplasms and only 9% for distant metastatic involvement, prognostic outcomes are significantly dependent on disease staging at diagnosis.¹³ The therapeutic algorithm for NSCLC, separated based on clinically and pathobiologically stage-specific criteria, integrates surgical resection, platinum-based chemotherapy, thoracic radiotherapy, molecularly targeted agents, and, more recently, immune checkpoint inhibitors (ICIs), thereby constituting a multifaceted treatment paradigm.^{14–16} The advent of ICIs, particularly in patient cohorts exhibiting elevated programmed death-ligand 1 (PD-L1) expression or tumoral mutational burden (TMB), has yielded a paradigm shift in treatment efficacy and patient quality-of-life metrics.^{17,18} Furthermore, the use of neoadjuvant immunotherapeutic regimens before surgery is emerging as a popular standard-of-care strategy.^{19–21}

PDAC, a malignancy originating from the pancreatic ductal epithelium, is the main and deadliest manifestation of pancreatic cancer, constituting over 80% of all identified patients.^{22,23} The exceedingly poor prognosis associated with PDAC can be mostly assigned to its intrinsically and biologically complex tumor microenvironment, characterized by a dense, tissue-remodeled desmoplastic stromal reaction that impedes therapeutic intervention and promotes disease progression.^{24–26} Genetic factors that contribute to the risk of PDAC encompass germline mutations in genes like *BRCA1/2* or *PALB2*. Lifestyle factors that increase the risk include smoking, being overweight, having chronic pancreatic inflammation (chronic pancreatitis), and having long-term uncontrolled diabetes.^{27–29} The insidious nature of early-stage PDAC often manifests

through vague and nonspecific symptomatology, such as icterus, diffuse abdominal discomfort, unintentional cachexia, and various gastrointestinal disturbances, consequently leading to diagnostic deferral in the majority of affected individuals.^{30,31} Compounding these diagnostic challenges is the lack of efficacious screening modalities and the deep anatomical retroperitoneal location of the pancreas, which collectively hinder timely identification. Resultantly, a mere 15%–20% of patients present with disease amenable to surgical resection, and even among this select cohort, the postoperative recurrence rates are high.³² The overall prognosis for PDAC is exceptionally grim, underscored by a 5-year relative survival rate reported at less than 6%.³³ In the context of advanced, unresectable disease, conventional chemotherapeutic regimens offer only palliative benefit with a limited duration of response, while the profound immunosuppressive ‘cold’ immune microenvironment and substantial stromal barriers contribute significantly to the observed resistance to current immunotherapeutic strategies.^{34,35} These multifaceted pathobiological and clinical features collectively render PDAC one of the most formidable oncological challenges, thereby galvanizing intensive research efforts aimed at the development of novel targeted therapeutic paradigms and innovative approaches to beneficially modulate the tumor microenvironment.

In spite of paradigm-shifting progress in oncological treatment modalities, immunotherapeutic response heterogeneity remains a pervasive challenge across a world of different tumor histotypes. The deployment of ICI-based therapeutic protocols within NSCLC management has yielded substantial survival advantages and enhanced patient-reported quality-of-life indices, whereas analogous immunotherapeutic strategies in PDAC treatment frameworks have demonstrated marginal efficacy amid complex tumor microenvironment-associated resistance mechanisms.^{36,37} This stark intertumoral efficacy divergence reflects the intricate tumor-specific immunobiological and molecular complexity underpinning therapeutic responsiveness and underscores the imperative for systematic delineation of cancer-specific immunotherapy response determinants.

Researchers have been investigating the role of genetic and molecular factors, especially TMB and neoantigen diversity, in the success or failure of immune-based therapies in recent years. One of the main

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goals of these studies is to determine how the neoantigens in NSCLC and PDAC differ in terms of quantity and quality, and how these differences affect the immune system and the health of patients.^{23,38-41} A deep understanding of these differences could lead to the creation of targeted and personalized treatments and new ways to overcome therapeutic resistance in cancers like PDAC that do not respond to treatment.

Neoantigens and Importance in Immunotherapy

Neoantigens, peptide sequences not present in the normal somatic cell repertoire, can be traced back to somatic mutations within the genome of cancer cells.⁴² These genetic anomalies extend over a spectrum of alterations, including point mutations, insertions/deletions, and gene rearrangements,^{43,44} which result in the synthesis of atypical proteins characterized by previously nonexistent amino acid sequences. After being broken down by proteolytic enzymes inside cancer cells, these changed proteins yield truncated peptide fragments that are then displayed on the surface of tumor cells by Major Histocompatibility Complex (MHC) class I or class II molecules.⁴⁵⁻⁴⁸ Neoantigens manifest in two primary forms: totally tumor-specific truncal and subpopulation-specific clonal.^{40,45} Truncal neoantigens, ubiquitously expressed across the entire tumor cell population due to their emergence from early oncogenic events, are highly prized targets for immunotherapy, as their engagement opens the door to the potential to eradicate a substantial proportion, if not the entirety, of the malignant cell burden. Conversely, clonal neoantigens, restricted to specific subclones as products of ongoing intratumoral heterogeneity and evolutionary divergence, may, upon targeting, contribute to partial tumor regression, with the inherent risk of immune evasion by surviving, neoantigen-deficient cell populations.^{40,45,49} Owing to their ubiquitous expression in malignant cells, the peptides are recognized as immunologically non-self, particularly by cytotoxic CD8⁺ T lymphocytes (CTLs), eliciting a robust and specific anti-tumor immune response compared with self-antigens, which are subject to immunological tolerance.⁵⁰⁻⁵² This tumor-specificity minimizes the risk of off-target effects and damage to healthy tissues, rendering them exceptionally suitable targets for personalized immunotherapeutic interventions.⁵³

The clinical importance of neoantigens and their nascent therapeutic applications in cancer immunotherapy exhibits a wide array of aspects.

Primarily, their non-self origin means they largely circumvent central immunological tolerance mechanisms, ensuring that T lymphocytes specific for these epitopes maintain their functional reactivity.^{51,54} Second, neoantigens are important biomarkers for predicting how well patients will respond to immunotherapy. In fact, strong evidence shows that people with tumors that have a high TMB and a correspondingly high number of neoantigens have better clinical outcomes when treated with ICIs.^{55,56} Furthermore, the identification and targeting of neoantigens form the basis of the development of highly personalized therapeutic vaccines, a strategy promising greater treatment efficacy alongside a minimized profile of adverse events.^{57,58}

Malignancies with a high TMB, exemplified by NSCLC, typically lead to the development of a proportionately richer repertoire of neoantigens, consequently revealing enhanced sensitivity to immunotherapeutic strategies.⁵⁹⁻⁶¹ In such patients, this neoantigen abundance is instrumental in provoking robust anti-tumor immune surveillance and effector functions.⁶¹ As a result, immunotherapy has become a powerful treatment alternative for many NSCLC patients, and in many cases, the first choice, giving practitioners new hope for better clinical outcomes.^{61,62} Conversely, tumors possessing a reduced TMB, such as PDAC, display a scarcity of neoantigens, thereby eliciting a comparatively attenuated anti-tumor immune response.^{23,63} This inherent immunogenic scarcity in PDAC is exacerbated by a notoriously dense and profoundly immunosuppressive tumor microenvironment (TME), which actively impedes effector immune cell infiltration and dampens efficient antigen presentation. Collectively, these elements result in a significantly reduced anti-tumor immune response in PDAC, significantly reducing the effectiveness of currently used immunotherapeutic techniques.^{64,65}

Targeting Neoantigens: Immunotherapy in PDAC and NSCLC

The tactical targeting of neoantigens is indicative of an emergent and compelling therapeutic paradigm within the scope of NSCLC immunotherapy. Of particular interest are neoantigens originating from specific, well-defined somatic mutations within the epidermal growth factor receptor (*EGFR*) gene, such as L858R, T790M, and the E746_A750 deletion, and also *BRAF*, *MET*, *RET*, *ROS1*, *TP53*, *STK11 (LKB1)*,

PIK3CA, *NRAS*, *HRAS*, *HER2 (ERBB2)*, *MED23*, and *SNTB2*, which are distinguished by their highly tumor-restricted expression and their profound T-cell stimulatory capacity (Table 1).^{66,67} Indeed, clinical studies of personalized neoantigen vaccines (PNVs) have confirmed both their positive safety record and their ability to produce significant clinical responses in groups of patients with advanced NSCLC who have these *EGFR* mutations.⁶⁷ Illustratively, in vitro models provide evidence that vaccination with peptides derived from the T790M mutation sparks a specific CTL against neoplastic cells harboring the neoantigen.⁶⁶ The therapeutic potential of such vaccines appears to be dramatically amplified through synergistic combinations with ICIs, agents like tislelizumab, or with conventional chemotherapeutic regimens. Nevertheless, the clinical translation of these strategies is hampered by challenges that are difficult to surmount, notably the intrinsic heterogeneity among *EGFR* mutant subtypes and the potential for clonal neoantigen attrition set in motion by tyrosine kinase inhibitor (TKI) therapy.^{68,69} Evidence indicating that the co-occurrence of particular HLA allotypes, such as HLA-A*02:01, with *EGFR* mutations correlates with an improved prognostic outlook in affected individuals further adds another layer of complexity to this landscape while also providing opportunities for patient stratification.⁷⁰ Collectively, these observations illuminate a path towards the rational design of highly targeted, personalized combination immunotherapies for NSCLC.

Within the distinct, yet analogously challenging, context of PDAC, investigations have substantiated that even a quantitatively limited repertoire of clonal neoantigens—originating from canonical driver mutations in genes like *KRAS* (notably G12D, G12V, Q61H), *TP53* (e.g., R175H, R273H), *SMAD4*, and *CDKN2A*, supplemented by those from less frequently mutated genes including *ARID1A*, *MLL3*, *RNF43*, *TGFBR2*, and *BRCA2*—hold the potential to be efficacious targets for inducing robust T-cell-mediated anti-tumor immunity (Table 1).^{23,71,72} The precise and specific identification of this neoantigenic landscape has been actualized by sophisticated technological progress in next-generation sequencing (NGS) and advanced bioinformatic algorithms, thereby critically facilitating the rational development of personalized immunotherapeutic modalities, including individualized vaccines and adoptively transferred, genetically engineered T-cells, such as T-cell receptor (TCR)-

engineered T-cells and Chimeric Antigen Receptor (CAR)-T cells.^{73–75} mRNA- and peptide-based neoantigen vaccines have shown a good safety profile and immunogenicity in PDAC cohorts, according to preliminary results from early-phase clinical trials. However, their monotherapeutic clinical efficacy has been limited thus far, highlighting the need for combinatorial regimens that include ICIs and TME-modulating agents.⁷⁶ Furthermore, putting into practice rapid and cost-effective methodologies for neoantigen validation, coupled with a strategic emphasis on high-fidelity clonal neoantigens, is hypothesized to mitigate the risk of immune evasion and thereby augment therapeutic efficacy.⁷² At the same time, cutting-edge platform technologies, such as lipid nanoparticle (LNP)-mediated delivery vehicles and CRISPR-Cas gene-editing systems, are playing crucial roles in enhancing antigen presentation pathways and boosting the resulting adaptive immune responses. Notwithstanding the formidable challenges posed by inherent tumor heterogeneity and the intricate logistical complexities associated with personalized vaccine manufacturing, the strategic targeting of neoantigens in PDAC proffers a golden opportunity for surmounting entrenched therapeutic resistance and substantially improving patient survival outcomes. In the difficult field of treatment-refractory cancers, this therapeutic paradigm, which is distinguished by its highly selective engagement of neoplastic cells and thereby minimizes off-tumor toxicities to healthy tissues, has the profound potential to orchestrate durable anti-tumor immune responses and establish long-lived immunological memory, thereby illuminating a transformative trajectory for personalized medicine.⁷⁶

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Table 1. Neoantigens in NSCLC and PDAC.

Neoantigen	Properties	Applications	References
Shared Neoantigens (NSCLC & PDAC)			
<i>KRAS</i> (G12C, G12D, G12V, G12R, Q61H)	Driver mutation, recurrent, tumor-specific; hotspot differs per cancer type	Peptide/mRNA vaccines, TCR-T, adoptive cell therapy	77–79
<i>TP53</i> mutations (R175H, R273H, others)	Tumor suppressor, immunogenic; heterogeneous; clonal in both cancers	Personalized vaccines, adoptive T-cell therapy	80, 81
Personalized frameshift/indel neoantigens	Unique per patient, predicted by sequencing	mRNA/peptide/DC vaccines	82–84
<i>PIK3CA</i> mutations	Driver, occasionally immunogenic	Personalized peptide vaccines	85
<i>PTEN</i> loss mutations	Tumor suppressor; may produce neoepitopes	Vaccine candidate in combination therapy	86
Enriched Neoantigens in NSCLC			
<i>EGFR</i> (L858R, T790M, E746_A750del)	Oncogenic driver; highly tumor-restricted; T-cell stimulatory; subset-specific	Peptide/mRNA vaccines, TCR-T; adjunct to EGFR inhibitors	87, 88
<i>STK11</i> (<i>LKB1</i>)	Tumor suppressor; affects TME	Vaccine combination strategies; predictive biomarker	89
<i>MET</i>	Oncogenic driver; fusion/overexpression	Peptide/TCR vaccines	90, 91
<i>RET</i>	Fusion-driven oncogenic; rare but immunogenic	Personalized TCR/peptide vaccines	92–95
<i>ROS1</i>	Fusion-driven; highly tumor-specific	Personalized vaccine/TCR therapy	93–95
<i>BRAF</i>	Oncogenic driver; subset-specific	Peptide/mRNA vaccines, TCR-T	96, 97
<i>MED23</i> , <i>SNTB2</i>	Tumor-specific mutations	Candidate for personalized vaccines	98, 99
<i>NRAS</i> , <i>HRAS</i>	Rare driver mutations; immunogenic in subset	Personalized peptide/mRNA vaccines	100–103
Cancer-testis antigens (NY-ESO-1, MAGE-A, XAGE1)	Tumor-restricted expression; immunogenic	Peptide/protein vaccines, TCR/CAR-T	85, 104–106

Table 1. Continued...

Neoantigen	Properties	Applications	References
Enriched Neoantigens in PDAC			
<i>SMAD4</i>	Tumor suppressor loss; patient-specific	Personalized neoantigen vaccines	78, 107, 108
<i>CDKN2A</i>	Tumor suppressor loss; heterogeneous	Personalized peptide/mRNA vaccines	78, 107
<i>BRCA1/2</i> & DNA repair defects	Increase indels → neoantigen load; subset-specific	Neoantigen vaccines + PARP inhibitors or checkpoint blockade	109–111
<i>ARID1A</i>	Less frequent mutation; clonal	Personalized vaccine candidates	82
<i>MLL3 (KMT2C)</i>	Chromatin modifier; neoepitopes in subsets	Candidate for mRNA/DC vaccines	82
<i>RNF43</i>	Frameshift mutation; immunogenic	Personalized vaccine candidates	82
<i>TGFBR2</i>	Frameshift mutation; immunogenic	Peptide/mRNA vaccine	82
Mesothelin, MUC1, CEACAM5	Overexpressed tumor antigens, sometimes neo-epitopic	Protein/peptide vaccines, CAR-T/NK, ADCs	112, 113

ADC: antibody-drug conjugate; ARID1A: AT-rich interaction domain 1A; BRAF: B-Raf proto-oncogene, serine/threonine kinase; BRCA: breast cancer gene; CAR-T: chimeric antigen receptor T-cell; CD: cluster of differentiation; CDKN2A: cyclin dependent kinase inhibitor 2A; CEACAM5: carcinoembryonic antigen related cell adhesion molecule 5; DC: dendritic cell; del: deletion; DNA: deoxyribonucleic acid; EGFR: epidermal growth factor receptor; HRAS: HRas proto-oncogene, GTPase; KMT2C: lysine methyltransferase 2C; KRAS: KRAS proto-oncogene, GTPase; LKB1: liver kinase B1; MED23: mediator complex subunit 23; MET: MET proto-oncogene, receptor tyrosine kinase; MLL3: mixed-lineage leukemia 3; MUC1: mucin 1, cell surface associated; NK: natural killer; NRAS: NRAS proto-oncogene, GTPase; NSCLC: non-small cell lung cancer; NY-ESO-1: New York esophageal squamous cell carcinoma 1; PARP: poly(ADP-ribose) polymerase; PDAC: pancreatic ductal adenocarcinoma; PIK3CA: phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PTEN: phosphatase and tensin homolog; RET: ret proto-oncogene; RNF43: ring finger protein 43; ROS1: ROS proto-oncogene 1, receptor tyrosine kinase; SMAD4: SMAD family member 4; SNTB2: syntrophin beta 2; STK11: serine/threonine kinase 11; TCR-T: T-cell receptor-engineered T-cell; TGFBR2: transforming growth factor beta receptor 2; TME: tumor microenvironment; TP53: tumor protein p53; XAGE1: X antigen family member 1.

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Conclusion and Future Perspectives

This review clearly illustrates that the quantitative and qualitative disparities in neoantigen profiles between NSCLC and PDAC play a crucial role in shaping their differential responses to immunotherapy. The substantial mutational burden and pronounced neoantigenic diversity characteristic of NSCLC support the more potent efficacy of immune-based interventions in this malignancy versus PDAC. Furthermore, a body of literature gives weight to the assertion that the immunogenic quality of NSCLC-derived neoantigens, having their roots in somatic mutations and gene fusions yielding high-affinity binding

MHC molecules, results in a more potent stimulation of anti-tumor immune responses. In fact, new data show that neoantigen quality frequently surpasses quantity, which is a crucial factor in the better immunotherapeutic results seen in NSCLC patients as opposed to those with PDAC (Figure.1). Regular studies show that neoantigens derived from NSCLC are generally very immunogenic and can elicit strong and specific T-cell-mediated effector functions. This has been confirmed in a variety of experimental settings, including in vitro tests and in vivo animal models.

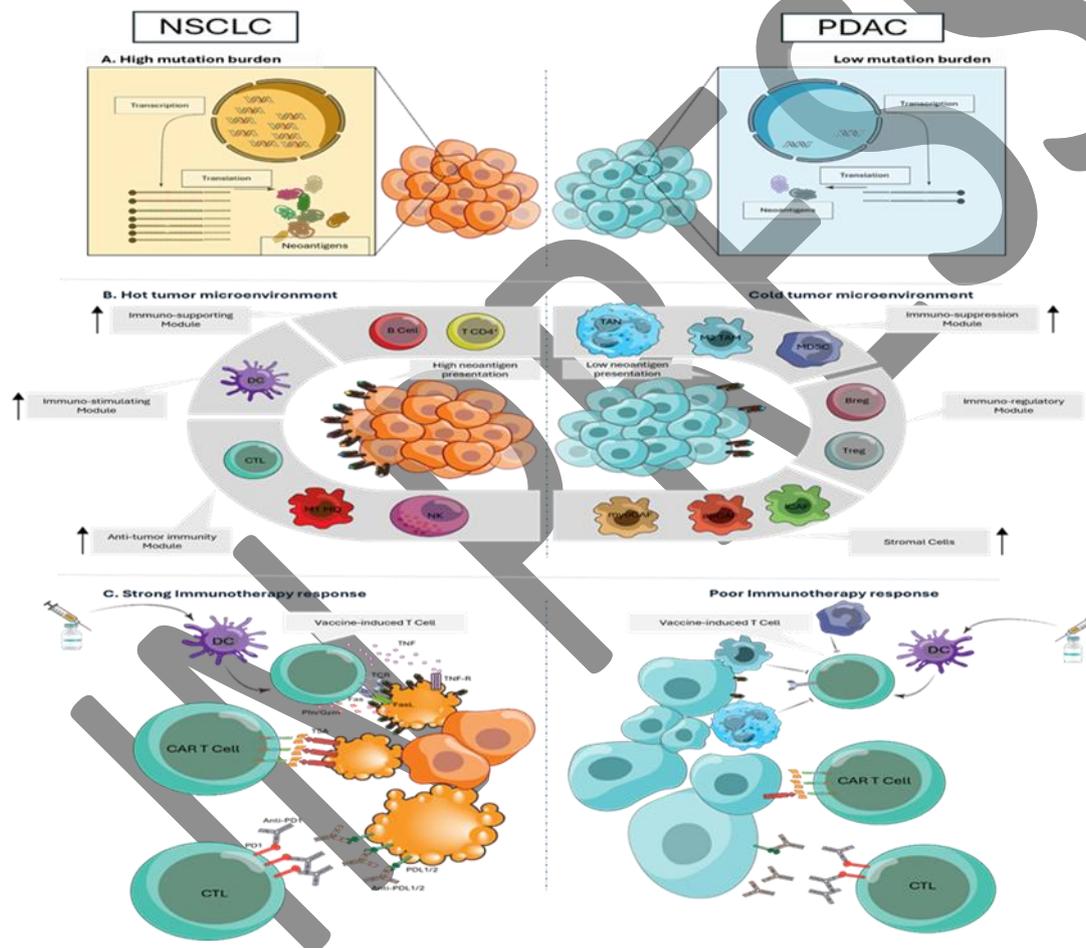


Figure 1. Comparison of molecular and cellular mechanisms affecting immunotherapy response in NSCLC and PDAC. (A) NSCLC shows high mutation burden and increased neoantigen production; PDAC has low mutation burden and fewer neoantigens. (B) NSCLC tumors present more neoantigens and attract active immune cells (“hot” TME); PDAC shows limited presentation and immunosuppressive infiltration (“cold” TME). (C) These differences result in stronger immunotherapy response in NSCLC and poor response in PDAC. NSCLC: Non-Small Cell Lung Cancer, PDAC: Pancreatic Ductal Adenocarcinoma, DC: Dendritic Cell, CTL: Cytotoxic T Lymphocyte, TAN: Tumor-Associated Neutrophil, MDSC: Myeloid-Derived Suppressor Cell, Breg: Regulatory B Cell, Treg: Regulatory T Cell, NK: Natural Killer Cell, MQ: Macrophage, iCAF: Inflammatory Cancer-Associated Fibroblast, myCAF; Myofibroblastic CAF, apCAF: Antigen-Presenting CAF, CAR-T: Chimeric Antigen Receptor T Cell, PD1/PD-L1: Programmed Death 1/Ligand 1.

On the other hand, PDAC manifests a marked and well-established resistance to standard immunotherapeutic approaches, which is exacerbated by the marked deficiency and poor immunogenic quality of its neoantigens as well as an intrinsically immunosuppressive TME. The development of progressively individualized therapeutic interventions has been facilitated by the accurate identification and careful characterization of genuine clonal and subclonal neoantigens driven by significant technological advancements in NGS and advanced bioinformatic algorithms. Additionally, there is significant room for growth in boosting treatment effectiveness in immunotherapeutically resistant cancers like PDAC by carefully combining neoantigen-directed approaches-like customized vaccines or adoptive T-cell therapies-with therapies that target the hostile TME and with well-established immune checkpoint inhibitors.

This quickly developing field is well-positioned to benefit from novel multivalent vaccine formulations and flexible mRNA platforms in the future, thanks to the synergistic integration of cutting-edge genomics, proteomics, and artificial intelligence technologies. These next-generation strategies are being developed to simultaneously target a wide range of patient-specific neoantigens in an effort to overcome the significant obstacles presented by intra- and inter-tumor heterogeneity. In conclusion, all of the evidence points to the urgent need for innovative approaches to neoantigen targeting and calls for more thorough research to overcome the intricate treatment challenges that resistant cancers present. A paradigm where neoantigens play multifaceted roles that go beyond direct therapeutics to include the sensitive monitoring of treatment response, the early detection of incipient relapse, and possibly the accurate prediction of emergent therapeutic resistance in individual patients is envisioned by this perspective, which lays out new and promising avenues for the development of personalized immunotherapy.

STATEMENT OF ETHICS

Not applicable.

FUNDING

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ACKNOWLEDGMENTS

Not applicable.

DATA AVAILABILITY

Not applicable.

AI ASSISTANCE DISCLOSURE

Not applicable.

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