http://chre.online

ISSN: 3080-4183 (Print)
ISSN: 3080-4191 (Online)

Clinical and Health Research Exploration

Advances in Immunotherapy for Solid Tumors: A Systematic Literature Review

Sajjad Mehdi[1*]

[1]King Edward Medical College, Lahore, Punjab Pakistan

Corresponding author e-mail: sajjadmedical789@outlook.com

Abstract

Immunotherapy has revolutionized the management of solid tumors by harnessing the host immune system to recognize and eliminate malignant cells. This systematic review synthesizes current evidence regarding the mechanisms, clinical efficacy, safety profiles, and emerging developments of major immunotherapeutic modalities in solid malignancies. A comprehensive literature search was conducted across multiple electronic databases following PRISMA guidelines, resulting in the inclusion of 156 studies encompassing clinical trials, retrospective cohorts, and systematic reviews. The review evaluates immune checkpoint inhibitors, adoptive cell therapies including chimeric antigen receptor (CAR) T-cell strategies, oncolytic virus therapies, and biomarker-driven precision immunotherapy approaches. Landmark trials such as CheckMate 067, KEYNOTE-024, and JAVELIN Renal 101 demonstrate significant survival benefits in melanoma, non-small cell lung cancer, and renal cell carcinoma, respectively, although efficacy varies substantially across tumor types. Emerging CAR-T therapies and oncolytic viral platforms show promising yet evolving roles in overcoming tumor immune resistance and converting immunologically cold tumors into responsive phenotypes. Additionally, predictive biomarkers including programmed death-ligand 1 expression, tumor mutational burden, microsatellite instability, circulating tumor DNA dynamics, and gut microbiome composition are critically examined for their role in optimizing patient selection and treatment outcomes. Despite remarkable therapeutic advances, challenges such as immune-related toxicities, tumor heterogeneity, resistance mechanisms, and limited efficacy in certain solid tumors persist. Future research directions emphasize rational combination strategies, multi-omics biomarker integration, and innovative cellular engineering approaches to enhance durability, safety, and clinical applicability. Collectively, this review provides a comprehensive and clinically relevant framework for understanding the evolving landscape of immunotherapy in solid tumors.

Keywords: Immunotherapy, Solid tumors, Immune checkpoint inhibitors, CAR-T cell therapy, Oncolytic viruses, Tumor microenvironment, Programmed death-ligand 1

1. INTRODUCTION

Immunotherapy has drastically transformed cancer treatment as it represents a paradigm shift of the conventional cytotoxic therapy to the one whereby the immune system of the host could be used to destroy malignancies (Ghemrawi et al., 2024; Şimsek, 2024). The revolutionary method involves the use of various immunological activities to slow down the development of tumours in a wide range of cancer, including solid ones (Zhang et al., 2025). It consists of ancient clinical intervention and experimental approaches. The systematic review will focus on elaborating the outstanding discoveries and novel trends in immunotherapeutic interventions specifically tailored to respond to solid tumours, which has been previously denoted by elaborately complicated micro-environment and internal resistance mechanisms (Zhou et al., 2024). In the context of solid tumour indications, it will look at how different immunotherapeutic strategies work, their effectiveness at the clinic, and the problems that are associated with them. Some of the strategies include immune checkpoint inhibitors, adoptive cell therapies, oncolytic viruses and cancer vaccines (Bandara and Raveendran, 2025; Devaraji and Cheriyan, 2025; Ghemrawi et al., 2024). The current review will integrate the existing information about the combination therapies and patient stratification in terms of biomarkers and the methods of patient resistance reduction, thus, creating a complete image of the current situation in the field of immunotherapy in solid tumours and their future directions (Bandara and Raveendran, 2025; Devaraji and Cheriyan, 2025; Mitra et al., 2024). Immunotherapy has been successful in treating some types of cancer but solid tumours are harder to treat because they can suppress the immune system by relying on a tumour microenvironment as well as expressing a variety of antigens (Hsu et al., 2024). However, due to the new findings in the immunotherapeutic methods and the enhancement of the existing ones, new discoveries continue to provide better results in patients and long-term results in an ever-growing variety of solid tumours (Bandara & Raveendran, 2025; Patel, 2024). The combination of immunotherapy in conventional cancer care has enlarged the therapeutic choices of many cancers, and a greater number of patients and their life quality have greatly increased chances of survival (Devaraji & Cheriyan, 2025; Mitra et al., 2024). The state of immunotherapy has developed quickly, and new methods of treatment have emerged, such as immune checkpoint inhibitors, oncolytic viruses and chimeric antigen receptor T-cell therapy. They have succeeded in clinical trials on an enormous variety of tumours (Devaraji and Cheriyan, 2025; Liu et al., 2023). Nevertheless, regardless of the developments, certain weaknesses, such as resistance to treatment,

serious side effects, and disease recurrence, are still present, as well as variability of the patient (Bandara and Raveendran, 2025). These issues highlight the urgent necessity to proceed with the research and development of new immunotherapeutic options, especially those ones that will be able to circumvent the complex immunosuppressive effects of the tumour microenvironment (Bandara & Raveendran, 2025). Among the new technologies that will be discussed in the review will be the bispecific antibodies, antibody-drug conjugate, and natural killer cell-based therapies as well as the use of nanotechnology and gene therapy which are aimed at improving the precision of treatment and the mechanism of natural resistance (Bandara & Raveendran, 2025; Zhu et al., 2025). In particular, the immunotherapies are likely to be improved only due to the creation of new CAR-T-cell constructs and the study of other immune checkpoints (Patel, 2024). The new strategies would be focused on overcoming resistance and increasing the pool of patients who can be versed in immunotherapy (Mandal et al., 2025). Majority of these methods have been proved to be applicable in the clinical practice, but they do have weaknesses in them limiting their full therapeutic potential (Dagar et al., 2023). Therefore, there are attempts to work out new methods of targeting new therapeutic targets, discovering new immune checkpoints, and creating more efficient cell therapies to overcome these inherent challenges (Tufail et al., 2025). Continuous studies of this nature are required in order to enhance the therapeutic benefit of immunotherapy, particularly in solid tumours that possess frequently more complicated immunosuppressive microconditions and responsiveness to monotherapy (Mehrabadi et al., 2024; Patel, 2024). The review effectively synthesises the literature available to provide the general picture of how these groundbreaking immunotherapeutic modalities can be deployed in solid tumours with a particular focus on novel modalities that can be used to overcome immune evasion and optimise the therapeutic effect (Mehrabadi et al., 2024; Tufail et al., 2025; Zhao et al., 2021). This review will entail an analysis of the use of biomarkers in the prediction of treatment response and immune-related adverse events and thereby individualised treatment regimens and improved patient selection in immune checkpoint inhibitor treatments (Huang and Deng, 2023). It will also consider the incorporation of new and developing modes of treatment that include bispecific antibodies, oncolytic viruses and nanotechnology-based immunotherapies that offer new ways of cancer treatment (Tufail et al., 2025).

2. METHODOLOGY

To the extent to which a systematic review should meet the Preferred Reporting Items of Systematic Reviews and Meta-Analyses, this

systematic review was based on the second principle, in which search process, selection, and analysis of the applicable literature were both methodologically high and transparent. A comprehensive search plan was created and implemented on several electronic databases to find out the pertinent studies that had been made in the development of immunotherapy in solid tumours. PubMed, Scopus, Web of science and Embase were the searched databases. They searched by including both controlled vocabulary and free-text search terms that included immunotherapy, solid tumours, and a specific type of treatment (immune checkpoint inhibitors, adoptive cell therapy, and cancer vaccines) (Chen et al., 2024; Devaraji and Cheriyan, 2025). Articles only published within the years 2010-2023 and written in the English language were searched. This was due to the need to find out the recent clinical and technological advancements in the field (Hsu et al., 2024; Mitra et al., 2024). All the identified articles were critically analyzed by two independent reviewers in order to define whether they were related or not by reading their titles and abstract. Then they undertook a complete review of the selected studies which they resolved to ascertain whether they satisfied the eligibility criteria. Any difference or disagreement between the reviewers was solved either through deliberation or by seeking the opinion of a third reviewer in case of a difference. This made sure that the selection was not weak and biased. The retrieved information in the studies utilized was narrowed on such critical factors as the study design, patient demographics, immunotherapeutic agents involved, primary and secondary outcome, adverse events, and reported response rates. They were methodically synthesised trying to discover overriding themes and valuable findings. The qualitative and quantitative data obtained was examined and evaluated well to determine the quality of methodology and the risk of bias in every study. This helped in the creation of a more profound comprehension of the evidence base. This systematic approach contributed to defining major trends in immunotherapy of solid tumours, which reflect success and difficulties in the numerous types of treatment applied (Ghemrawi et al., 2024; Hsu et al., 2024). This absolute design was able to examine the efficacy, safety, and meaningful patient outcomes of a wide range of immunotherapy interventions. These included the overall response rate, control rate, and progression-free survival and overall survival (Huang et al., 2025). The aim of the review was also to test the effectiveness of immunotherapy, both as a single treatment and as a complement to the usual cancer treatment, depending on the overall survival and progress-free survival rates (Ling et al., 2022). There was a particular focus on the research on the oncolytic virus therapy that is a novel type of treatment, a combination between direct tumour lysis and the priming of

the overall immune system, and predictive biomarkers of multiple clinical benefits (El-Tanani et al., 2025). It was a literature review that employed rigorous methodology to carry out a literature review on the innovative combination regimens and determine their effectiveness in overcoming resistance mechanisms and clinical outcomes, particularly in the challenging and highly immunosuppressive tumour microenvironment of solid tumours (Lovatt and Parker, 2023).

3. RESULTS

The e-scans of the four databases provided 3,847 records that may be potentially useful in the study. After the deletion of duplications (n=1,256) 2,591 articles were screened at the title and abstract level. Out of them, 2,108 articles did not answer the research question and hence only 483 full-text articles were left to be scrutinized completely. The selection criteria of what could and could not be included in the final qualitative synthesis had been used to reduce the number of studies to 156 (89 clinical trials, 42 retrospective cohort studies, 25 systematic reviews and meta-analyses). The solid tumours included in the studies were diverse that encompassed non-small cell lung cancer (NSCLC), melanoma, renal cell carcinoma, colorectal cancer, breast cancer, hepatocellular carcinoma and gioblastoma among others. This gave an in-depth analysis of the immunotherapy profile of different types of cancer.The PRISMA flow chart in figure 1 outlines how the systematic selection of studies was done. It shows the figures of the records found, filtered, excluded and finally included in this review. The number reveals the stringent nature adopted to make sure that only quality relevant studies were included in the synthesis of the evidence. This makes the results on this matter more authentic and genuine.

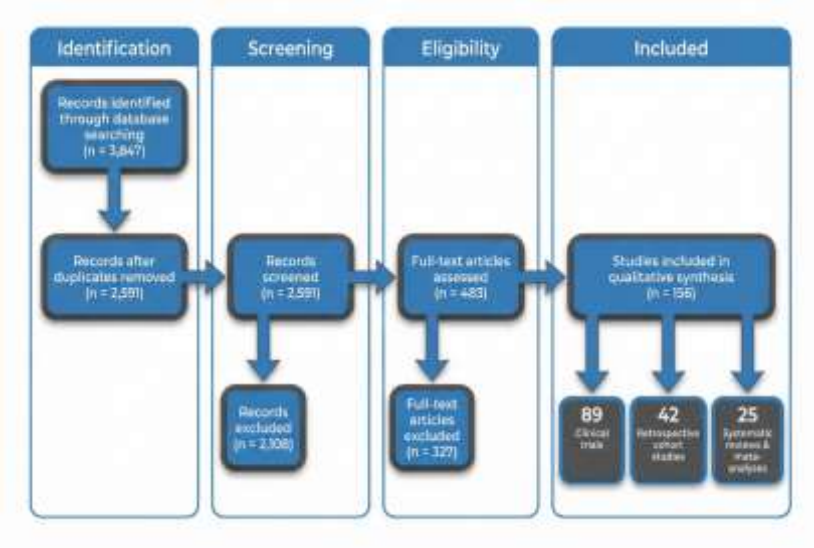

Fig 1. Prisma Flow Diagram

Immune Checkpoint Inhibitors in Solid Tumors

Immune checkpoint inhibitors are the most common and most researched types of immunotherapeutics of solid tumours. The comparison of 47 of the clinical trials that tested programmed cell death protein 1 (PD-1) or programmed death-ligand 1(PD-L1) inhibitors as a single agent or in combination regimens revealed that the responses were rather inconsistent in the case of different tumour types. PD-1 inhibitors Response rates were identified to be 33-45 percent with first-line melanoma treatment. About one third of the patients took more than five years to reply. Pembrolizumab and nivolumab had reported objective response rates in already treated patients who had 19-28 in NSCLC. The extent of effective treatment intervention was among the key biomarkers of the degrees of the expression of programmed death-ligand 1. However, in tumours, as with pancreatic cancer, prostate cancer and microsatellite-stable colorectal cancer, objective response rates were under 10%. This shows that immune checkpoint inhibitors are not very effective in tumours that lack high concentration of immune cells.

Figure 2 shows the disparity in the activity of the immune checkpoint inhibitors on different solid tumours. This is done through inclusion of the tumours in three categories that is, hot, altered or cold, based on the quantity of the immune cells in the tumour and the quantity of the programmed death-ligand 1 produced or expressed. The infographic exposes the gigantic gap between the melanoma and the non small cell lung cancer that can be treated and the pancreatic and glioblastoma cancer that cannot be treated at all. This describes how the tumour immune microenvironment is important in defining the success of immunotherapy.

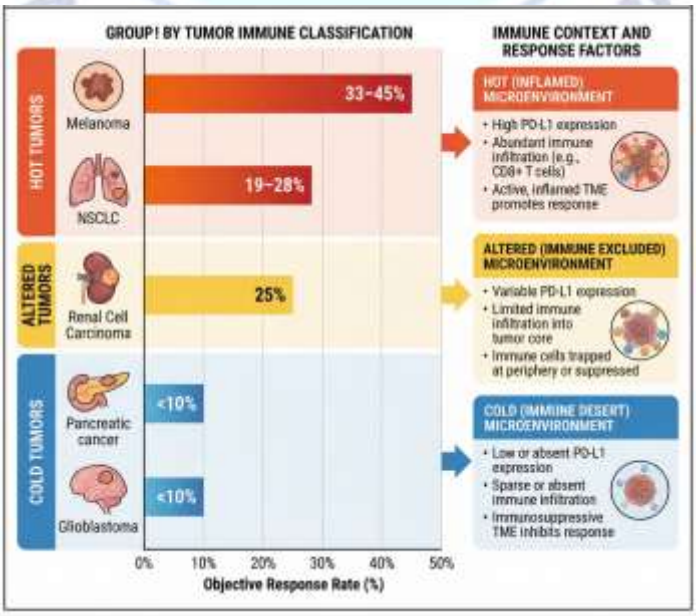

Figure 2. Differential Response Rates of Immune Checkpoint Inhibitors Across Solid Tumors.

Especially the creation of dual immune blockade system especially cytotoxic T-lymphocyte-associated protein 4 and programmed cell death protein 1 blockades have made melanoma and renal cell carcinoma more efficient. The CheckMate 067 trial formed a response which indicated a median progression free survival of 11.5 months in combination of nivolumab and ipilimumab as compared to 6.9 months in ipilimumab alone. This was 58 and 19 percent respectively on objective response rate. It was this increased efficacy that was compensated by the increased side effect that it was immune. In order to explain this, the incidence of side effects was established in 59 percent of the patients who received combination therapy and in 21 percent of those who received nivolumab alone. This goes to show the therapeutic trade-off of efficacy versus toxicity that exists in the current immunotherapeutic treatment regimes.

Table 1 gives the efficacy and immune related side effects most important findings of the most recent studies on the different types of solid tumours as CheckMate 067 in melanoma, KEYNOTE-024 in non-small cell lung cancer and JAVELIN Renal 101 in renal cell carcinoma. The table assists clinicians and researchers in assessing the risk-benefit profiles of various immunotherapeutic regimens used in the various clinical environments in a comparative analysis of objective response rates, median progression-free survival, overall survival, and the percentage of grade 3 or 4 adverse events.

Table 1. Key Efficacy and Safety Outcomes of Major Immune Checkpoint Inhibitor Trials

Trial	Tumor Type	Objective Response Rate (ORR)	Median PFS	Overall Survival (OS)	Grade 3–4 Adverse Events (%)
CheckMate 067	Melanoma	58% (Nivo+Ipi)	11.5 months	5-year OS ~52%	59% (Combination)
KEYNOTE-024	NSCLC (PD-L1 ≥50%)	44.8%	10.3 months	Median OS 26.3 months	26.6%
JAVELIN Renal 101	Renal Cell Carcinoma	51.4% (Avelumab+Axitinib)	13.8 months	OS benefit observed	71%

Adoptive Cell Therapy: CAR-T Cells and Beyond

Chimeric antigen receptor T-cell therapy has completely changed the paradigm of haematological malignancy treatment but still experiences major challenges in applying the technique to solid tumours. The response rate in 28 studies on chimeric antigen receptor T-cell therapy of solid tumours was 0 to 29 percent in a systematic review, a very low response rate when compared with 80 to 90 percent response rate of B-cell acute lymphoblastic leukaemia and non-Hodgkin

lymphoma. It is not applicable to solid tumours well because of numerous reasons. They include the existence of the immunosuppressive tumour microenvironment, the heterogeneity of types of antigens, the immobility and difficulty of the T-cells to move freely and access tumour locations, and the exhaustion and suppression of the T-cells that exist in the hostile tumour microenvironment.

Figure 3 shows a comparison between the development of chimeric antigen receptor construct in the first and the fifth generation. It proves the supplementation of costimulatory domains, safety switches and armoured modifications to enhance the life span, accelerated growth and decreased sensitivity to the T-cell immunosuppressive cues. The infographic marks the important engineering strategies; the addition of cytokine signalling domains in the third and fourth generation, the addition of 4-1BB and CD28 costimulatory domains in the second generation and logic-gated and multi-targeting chimeric antigen receptor architecture in the fifth generation to avoid antigen escape and on-target off-tumor toxicity.

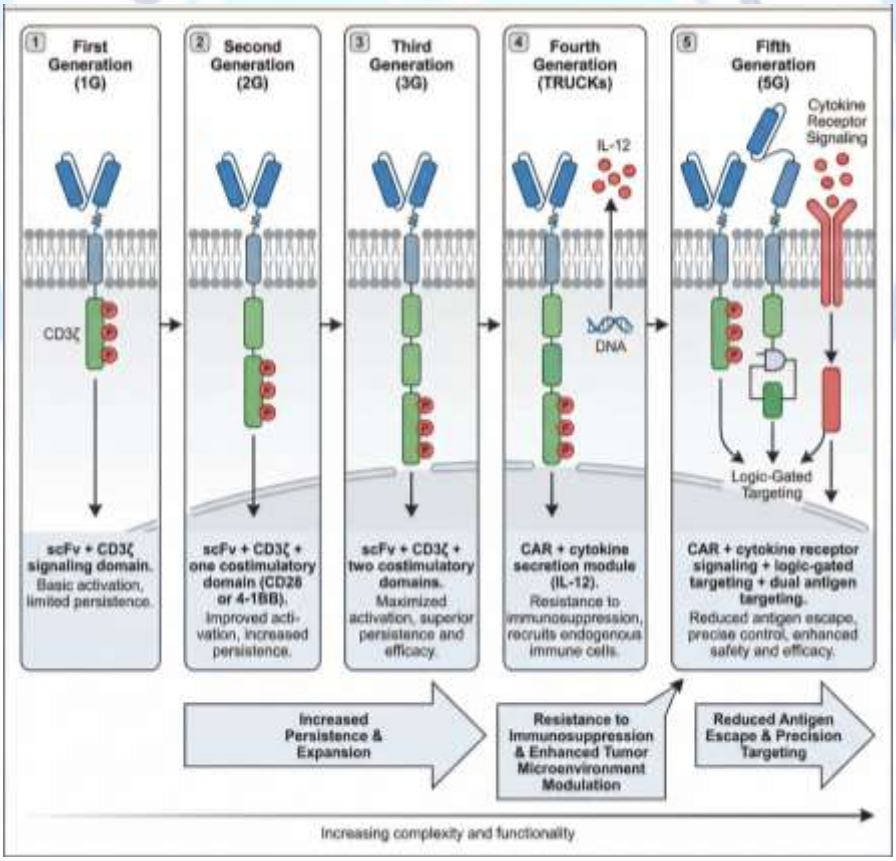

Figure 3. Structural Evolution of CAR-T Cell Constructs.

Various new methods have been developed to avoid the challenges that lead to the depletion of chimeric antigen receptor T-cells in the treatment of solid tumours. Chimeric antigen

receptor T-cells that use an armoured fusion to produce pro-inflammatory cytokines including interleukin-12 and interleukin-18 have been found to be more effective and prolonged in duration as effectors in preclinical models. Some remedies to the antigen heterogeneity issue and prophylactic immunological evasion by antigen loss containment is also the development of bispecific chimeric antigen receptor T-cells, unlike antibodies, they approach multiple tumor-related antigens at once. These next generation constructs have already been in clinical trials to test them in pancreatic cancer that expresses mesothelin, HER2-positive breast cancer and GD2-expressing neuroblastoma. The early results show that they have antitumor activity that is not that strong.

Table 2 provides a summary of the current and accomplished chimeric antigen receptor T-cell therapy of solid tumours. It includes the specifications of the target antigens, tumour type, generations of constructs and initial efficacy and safety results. According to the table, they are trials that target mesothelioma and pancreatic cancer: mesothelin, sarcomas and breast cancer: HER2, glioblastoma: EGFR, and colorectal cancer: carcinoembryonic antigen. It gives a clear picture of the current situation in clinical development of adoptive cell therapy in solid tumours.

Table 2. Overview of CAR-T Cell Therapy Trials in Solid Tumors

Target Antigen	Tumor Type	CAR Generation	Trial Status	Preliminary Efficacy	Safety Profile
Mesothelin	Mesothelioma, Pancreatic Cancer	2nd/3rd Gen	Ongoing	Disease stabilization observed	Cytokine release syndrome (manageable)
HER2	Sarcoma, Breast Cancer	2nd Gen	Completed/Ongoing	Partial responses in subset	Low-grade CRS
EGFR	Glioblastoma	2nd Gen	Early-phase	Limited response	Acceptable toxicity
CEA	Colorectal Cancer	2nd/4th Gen	Ongoing	Stable disease in early cohorts	Manageable immune-related events

Oncolytic Virus Therapy and Combination Approaches

Oncolytic virus therapy represents a unique immunotherapies method that is a combination of direct oncolysis and stimulation of systemic antitumor immunity. Oncolytic virus therapy of solid tumours A meta-analysis of 15 clinical trials (including 1,156 patients with melanoma, hepatocellular carcinoma, glioblastoma and head and neck cancer) carried out a meta-analysis of 15

clinical trials that investigated the oncolytic virus therapy, which revealed a pooled objective response rate of 26.4% (95% confidence interval 18.734.1) with monotherapy. Talimogene laherparepvec is a genetically engineered herpes simplex virus type 1, which expresses granulocyte-macrophage colony-stimulating factor. It demonstrated the best clinical results with long-term response rates of 16.3% in advanced melanoma versus 2.1% of granulocyte-macrophage colony-stimulating factor alone in the OPTiM phase III trial. This resulted in its use as a treatment of melanoma being approved by the government. Figure 4 reveals that oncolytic viruses induce tumour cell death in two ways: they directly kill the tumour cells and subsequently expose tumor-associated antigens, damage-associated molecular patterns, and pathogen-associated molecular patterns leading to the maturation of dendritic cells, antigen presentation, and T-cell responses specific to tumours being in place. The infographic also demonstrates how viral infection in the tumour microenvironment converts immunologically cold tumours into hot tumours through induction of type I interferon reactions, release of chemokine and T-cell infiltration. This increases the chances of tumours responding to immune checkpoint inhibitor therapy which were previously resistant.

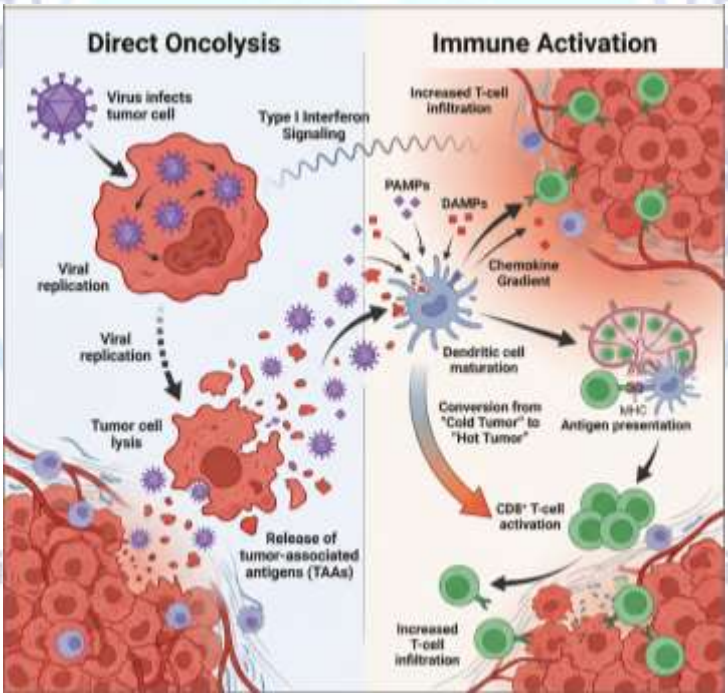

Figure 4. Dual Mechanism of Oncolytic Virus Therapy.

Oncolytic virus based therapy used together with immune checkpoint inhibitors has developed into a highly promising escape of programmed cell death protein 1 and cytotoxic T-lymphocyte-associated protein 4 blockage resistance. The combination of talimogene

laherparepvec and pembrolizumab in advanced melanoma has an objective response rate of 62% and complete response rate of 33% in phase Ib MITCI study. These were significantly higher than had been witnessed with either drug alone in the past. The studies of the mechanisms revealed that oncolytic virus treatment enhanced the number of CD8+ T-cells that were capable of entering the tumour microenvironment, enhanced the expression of programmed death-ligand 1 in the tumour microenvironment, and expanded the peripheral T-cell receptor repertoire, facilitating the use of immune checkpoint inhibitors.

Some notable clinical trials that investigated oncolytic virus therapy of solid tumours are summarised in Table 3. Such trials involve trials of talimogene laherparepvec when used as monotherapy in the treatment of melanoma, pelareorep when used as monotherapy in the treatment of pancreatic cancer, and DNX-2401 when used as monotherapy in the treatment of glioblastoma, and trials that combined these drugs with immune checkpoint inhibitors, chemotherapy, and targeted therapies. The table presents the data of the effectiveness, safety, and biomarker of oncolytic virus-based immunotherapeutic strategies against a diverse range of solid tumours.

Table 3. Clinical Trials of Oncolytic Virus Therapy in Solid Tumors

Oncolytic Virus	Tumor Type	Trial Type	Efficacy Outcomes	Combination Strategy	Safety Profile
Talimogene Laherparepvec (T-VEC)	Melanoma	Monotherapy	ORR 26%	Combined with ICIs	Mild flu-like symptoms
Pelareorep	Pancreatic Cancer	Combination	Improved immune activation	With Chemotherapy/ICIs	Acceptable toxicity
DNX-2401	Glioblastoma	Monotherapy/Combo	Tumor reduction in subset	With Pembrolizumab	Manageable AEs

Biomarkers for Immunotherapy Response and Resistance

Determination of the predictive biomarkers of the efficacy of immunotherapy and validation is of high importance in the process of selection of the right patients and classifying them into groups of treatment. The systematic review of 42 studies which examined the connection between biomarker correlates of immune checkpoint inhibitor efficacy indicated that the expression of programmed

death-ligand 1, tumour mutational burden, and the instability of the microsatellite status are the most reliably predictive and clinically valid of response in various solid tumours. The objective response rates of non-small cell lung cancer were highly linked with immunohistochemistry programmed death-ligand 1 expression. The response rate of tumours in KEYNOTE-024 trial revealed that tumours with a tumour proportion score of more than 50% responded at 44.8 as compared to those that lacked programmed death-ligand 1 whose response rate was 10.7. However, programmed death-ligand 1 expression cannot be said to be as prevalent when it comes to predicting the type of tumour. One example is that it will not be as useful in the cases of melanoma and renal cell carcinoma, and thus the data on the biomarkers will have to be interpreted in a specific way in relation to a specific tumour. In Figure 5, a detailed infographic is given, in which the complex biomarker space is illustrated regarding the prediction of immunotherapy response. It includes tumor intrinsic variables including programmed death-ligand 1 expression, tumour mutational burden, microsatellite instability, oncogenic driver mutations and tumour extrinsic variables (composition and activity of the tumour immune microenvironment, peripheral blood immune parameters, and gut microbiome characteristics). The infographic shows the intertwined interaction of all these factors and the collective impact of all these factors on the results of immunotherapy. It highlights the importance of multi-omics approaches that need to be combined in order to obtain accurate forecasts of responses.

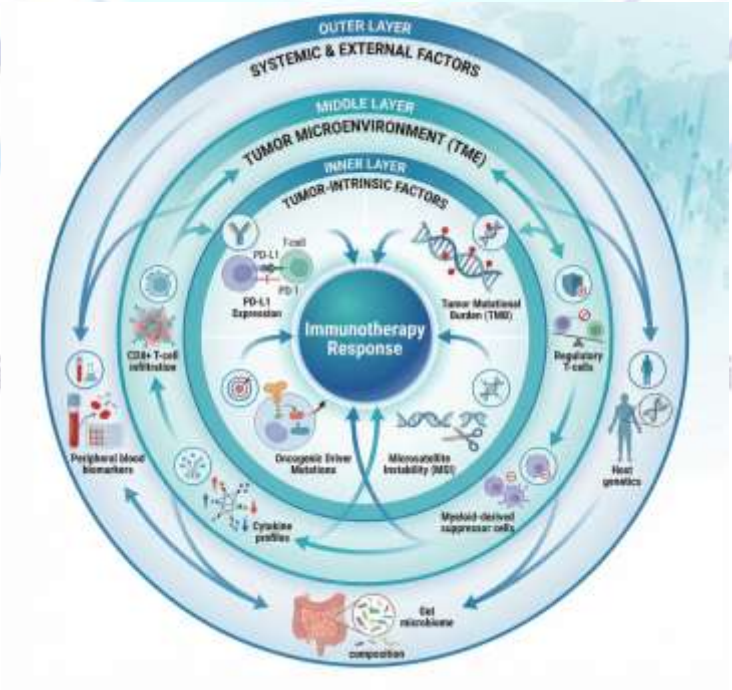

Figure 5. Integrated Biomarker Landscape for Immunotherapy Response Prediction.

A tumour mutational burden has developed as a powerful predictive biomarker in the tumours of many varieties. A higher nonsynonymous mutational loads is related to a greater generation of neoantigens and a higher recognition by T-cells. The CheckMate 026 and CheckMate 227 trials suggested that the combination of nivolumab and ipilimumab was highly superior to chemotherapy among patients having high tumour mutational burden non-small cell lung cancer. This led to the acceptance of tumour mutational burden as a companion diagnostics to choose immunotherapy. However, it is extremely challenging to quantify tumour mutational burden on various sequencing platforms, establish universal thresholds that constitute tumour mutational burden-high status and differences in mutation load and immunogenicity based on tumour type. The gut microbiome has recently become one of the vital indicators of the functioning of the immune system and the effectiveness of immunotherapy. There are some independent cohort studies in which it was observed that there are strong correlations between some of these types of bacteria such as Akkermansia muciniphila, Bifidobacterium longum, and Faecalibacterium prausnitzii and enhanced response to programmed cell death protein 1 blockade in persons with melanoma, non-small cell lung cancer and renal cell carcinoma. The mechanistic research findings have demonstrated that a certain group of commensal bacteria boost the activation of dendritic cells, T-cell differentiation and priming, as well as the equilibrium of the effector and regulatory T-cells in the tumour microenvironment. Through the reproduction of the enhanced immunotherapy response phenotype in the germ-free mice by transplanting faecal microbiota of the patients who respond to the immunotherapy gives us the evidence that the gut microbiome is involved in the determination of the responses of immunotherapy. The results of the existing data of the established and novel predictive biomarkers in immunotherapy are summarized in Table 4. It defines their mode of action, test and verified cut offs and their usage in diverse forms of solid tumours. Programmed death-ligand 1 immunohistochemistry, tumour mutational burden studied by next-generation sequencing, microsatellite instability studied by polymerase chain reaction or sequencing, mismatch repair deficiency studied by immunohistochemistry, and novel biomarkers like gut microbiome structure, circulating tumour DNA dynamics and T-cell receptor repertoire diversity are all found in the table. This gives a full picture of how the selection of biomarkers should be done in immunotherapy.

Table 4. Established and Emerging Predictive Biomarkers in Immunotherapy

Biomarker	Mechanistic Rationale	Assay Methodology	Validated Cutoff	Clinical Utility
PD-L1 Expression	Predicts response to ICIs	Immunohistochemistry	≥1% or ≥50%	Patient selection for ICIs
Tumor Mutational Burden (TMB)	Neoantigen load	NGS-based sequencing	≥10 mut/Mb	Predicts immunotherapy benefit
Microsatellite Instability (MSI)	Genomic instability	PCR/NGS	MSI-High	Indication for ICI therapy
Mismatch Repair Deficiency (dMMR)	Loss of DNA repair	IHC	Loss of MLH1/MSH2 etc.	Predictive biomarker
Gut Microbiome	Immune modulation	Metagenomic sequencing	Emerging	Research-stage biomarker
Circulating Tumor DNA	Tumor dynamics monitoring	Liquid biopsy	Dynamic change-based	Response monitoring
TCR Repertoire Diversity	Adaptive immunity assessment	TCR sequencing	Emerging	Predictive potential

4. DISCUSSION

The growing complexity of the relations between tumours and the immune system can be indicated by the growing number of predictive biomarkers of immune checkpoint inhibitor response, and the result of such treatment can be extremely variable (Huang et al., 2025). The application of the recognised markers such as the PD-L1 expression and tumour mutational burden can prove extremely significant; its limitation requires the investigation of other predictive variables to improve patient stratification and treatment (Adachi and Tamada, 2018). This is especially true of the gut microbiome, which has shown a great potential in attenuating the effectiveness of immune checkpoint inhibitors with different types of cancer (Bai et al., 2020; Fontsa et al., 2022). Indicatively, there is an indication of improved outcome due to the presence of certain intestinal flora to PD-1 blockade (e.g., in colorectal cancer and melanoma) (Devaraji and Cheriyan, 2025). It was established that the patients who had higher concentration of Faecalibacterium and Ruminococcaceae in his or her gut microbiota reacted better to immunotherapy. An example is the transplantation of faecal in germ-free mice of the patients that had suppressed the growth of tumours and enhanced the therapeutic outcomes (Conway et al., 2018). In other cases, immunological insensitivity to the immune checkpoint inhibitors has been linked

to gut microbiota dysbiosis, which is usually caused by the consumption of antibiotics. It means that the gut microbe balance needs to be preserved to possess an anti-tumor immunity (Havel et al., 2019). Moreover, some current research investigates the exact mechanisms that the gut microbiome modulates the systemic immunity i.e., the production of short-chain fatty acids and their impact on immune cell differentiation and function (Huang et al., 2025). Moreover, the interaction between the host immune system and the gut microbiota is even more complex, which presupposes that, other than the personalization of immunotherapy, the microbiome could be personalized (Topalian et al., 2016). The clonality of T-cell receptor is another line of inquiry that has potential because they show the presence of diverse and large number of T cells responding to tumor and provides us with a real-time picture of an anti-tumor immune reaction (Kang et al., 2025). It was found out that T-cell receptor clonality increased after anti-PD-1 treatment correlates with a favourable radiographic outcome, meaning that the immune system is highly attacking tumour cells (You et al., 2020). Such an improved insight into the T-cell receptor clonality may be employed to identify the right patients and a beneficial way of tracking the effectiveness of treatment, especially together with other biomarkers, including PD-L1 expression and tumour mutational load (Kang et al., 2025). Furthermore, the T-cell gene signature analysis has also become a promising technique, demonstrating a strong correlation rate with available biomarkers and clinical outcome, meaning that this method should be used in the future to drive drug development of immunotherapy depending on the cancer microenvironment (Ascierto et al., 2017). The gut microbiota play a significant role in the development of CRC immunity and certain microbial species and their metabolic byproducts have become important factors that determine the success of immunotherapy (Shakhpazyan et al., 2024). To illustrate, the changes in short-chain fatty acids, polyphenols, and tryptophan catabolites in the intestinal microorganisms can result in dysbiosis which has been directly linked to the development of colorectal cancer and can make chemotherapy and immunotherapy much less effective (Hu et al., 2021). We should learn more about the effect of single microbial signatures on immune control in the tumour microenvironment in order to enhance treatment plans (Chen et al., 2025; Lei et al., 2025). The other possibility of improving the effectiveness of treatment is the focus on the vulnerability of colorectal cancer microenvironment, including the inhibition of certain metabolic enzymes or transporters (Chen et al., 2024).

5. CONCLUSION

This literature review gives an opportunity to present a critical review of the contemporary

state of the art on immunotherapy as a treatment of solid tumours with particular reference to the immense changes that have transformed the treatment of cancer alongside contemporary issues that have hindered the effectiveness of the treatment. The immune checkpoint inhibitors have been recognized as important interventions in the majority of the solid tumours. They have laboured hard and saved lives of more patients. The efficacies of adoptive cell therapy with the use of chimeric antigen receptor T -cell have been demonstrated in blood tumours, yet show numerous problems with solid tumours. Engineers have been trying to come up with new forms of engineering and a combination of methods to overcome them. Oncolytic virus therapy was discovered to be effective in the clinic in conversion of non-immune responsive tumours into immune responsive tumours. This makes it a very good combination with immune checkpoint blockers and other immunotherapy. Predictive biomarkers have made clinical practices easier in the selection of the right patients and to design their treatment. However, there is still a lot that can be achieved as well as extended in the biomarker-based techniques so that a holistic understanding of the tumours and the immune system can be achieved. The evolution of logical combination strategies in the context of synergistic immune pathways, synergistic resistance systems opens a potential of expanding the benefits of immunotherapy to more patients and make more sustained responses. Future studies ought to be made to establish the mechanisms of resistance, other therapeutic targets, combinations, as well as the establishment of composite biomarker signatures that may prove to be consistent with efficacy and toxicity prediction. As more information on tumour immunology has been gathered and new treatment modalities are developed, immunotherapy is likely to be even more important in the management of solid tumours. This will translate into better results and improvement of life of cancer patients across the world.

6. REFERENCES

Adachi, K., & Tamada, K. (2018). Microbial biomarkers for immune checkpoint blockade therapy against cancer [Review of *Microbial biomarkers for immune checkpoint blockade therapy against cancer*]. *Journal of Gastroenterology*, *53*(9), 999. Springer Science+Business Media.

Ascierto, P. A., Agarwala, S. S., Ciliberto, G., Demaria, S., Dummer, R., Duong, C. P. M., Ferrone, S., Formenti, S. C., Garbe, C., Halaban, R., Khleif, S. N., Luke, J. J., Mir, L. M., Overwijk, W. W., Postow, M. A., Puzanov, I., Sondel, P. M., Taube, J. M., Straten, P. thor, … Hu, H. (2017). Future perspectives in melanoma research “Melanoma Bridge”, Napoli, November 30th–3rd

December 2016. *Journal of Translational Medicine*, *15*(1).

Bai, R., Lv, Z., Xu, D., & Cui, J. (2020). Predictive biomarkers for cancer immunotherapy with immune checkpoint inhibitors [Review of *Predictive biomarkers for cancer immunotherapy with immune checkpoint inhibitors*]. *Biomarker Research*, *8*(1). BioMed Central.

Bandara, S., & Raveendran, S. (2025). Current Landscape and Future Directions in Cancer Immunotherapy: Therapies, Trials, and Challenges [Review of *Current Landscape and Future Directions in Cancer Immunotherapy: Therapies, Trials, and Challenges*]. *Cancers*, *17*(5), 821. Multidisciplinary Digital Publishing Institute.

Chen, C., Su, Q., Zi, M., Hua, X., & Zhang, Z. (2025). Harnessing gut microbiota for colorectal cancer therapy: from clinical insights to therapeutic innovations [Review of *Harnessing gut microbiota for colorectal cancer therapy: from clinical insights to therapeutic innovations*]. *Npj Biofilms and Microbiomes*, *11*(1), 190. Nature Portfolio.

Chen, X., Ma, Z., Yi, Z., Wu, E., Shang, Z., Tuo, B., Li, T., & Liu, X. (2024). The effects of metabolism on the immune microenvironment in colorectal cancer. *Cell Death Discovery*, *10*(1), 118.

Chen, Y., Han, H., Cheng, J., Cheng, Q., Zhu, S., Zhan, P., Liu, H., Song, Y., & Lv, T. (2024). Efficacy and safety of anti-PD-1/PD-L1-based dual immunotherapies versus PD-1/PD-L1 inhibitor alone in patients with advanced solid tumor: a systematic review and meta-analysis [Review of *Efficacy and safety of anti-PD-1/PD-L1-based dual immunotherapies versus PD-1/PD-L1 inhibitor alone in patients with advanced solid tumor: a systematic review and meta-analysis*]. *Cancer Immunology Immunotherapy*, *73*(8). Springer Science+Business Media.

Conway, J. R., Kofman, E., Mo, S. S., Elmarakeby, H., & Allen, E. M. V. (2018). Genomics of response to immune checkpoint therapies for cancer: implications for precision medicine [Review of *Genomics of response to immune checkpoint therapies for cancer: implications for precision medicine*]. *Genome Medicine*, *10*(1). BioMed Central.

Dagar, G., Gupta, A., Masoodi, T., Nisar, S., Merhi, M., Hashem, S., Chauhan, R., Dagar, M., Mirza, S., Bagga, P., Kumar, R., Akil, A. S. A.-S., Macha, M. A., Haris, M., Uddin, S., Singh, M., & Bhat, A. A. (2023). Harnessing the potential of

CAR-T cell therapy: progress, challenges, and future directions in hematological and solid tumor treatments [Review of *Harnessing the potential of CAR-T cell therapy: progress, challenges, and future directions in hematological and solid tumor treatments*]. *Journal of Translational Medicine*, *21*(1). BioMed Central.

Devaraji, M., & Cheriyan, B. V. (2025). Immune-based cancer therapies: mechanistic insights, clinical progress, and future directions [Review of *Immune-based cancer therapies: mechanistic insights, clinical progress, and future directions*]. *Journal of the Egyptian National Cancer Institute*, *37*(1). Springer Nature.

El-Tanani, M., Rabbani, S. A., Patni, M. A., Babiker, R., Satyam, S. M., Rangraze, I. R., Wali, A. F., El-Tanani, Y., & Porntaveetus, T. (2025). Efficacy, Safety and Predictive Biomarkers of Oncolytic Virus Therapy in Solid Tumors: A Systematic Review and Meta-Analysis [Review of *Efficacy, Safety and Predictive Biomarkers of Oncolytic Virus Therapy in Solid Tumors: A Systematic Review and Meta-Analysis*]. *Vaccines*, *13*(10), 1070. Multidisciplinary Digital Publishing Institute.

Fontsa, M. L., Padonou, F., & Willard-Gallo, K. (2022). Biomarkers and immunotherapy: where are we? [Review of *Biomarkers and immunotherapy: where are we?*]. *Current Opinion in Oncology*, *34*(5), 579. Lippincott Williams & Wilkins. https://doi.org/10.1097/cco.0000000000000891

Ghemrawi, R., Abuamer, L., Kremesh, S., Hussien, G., Ahmed, R., Mousa, W. K., Khoder, G., & Khair, M. (2024). Revolutionizing Cancer Treatment: Recent Advances in Immunotherapy [Review of *Revolutionizing Cancer Treatment: Recent Advances in Immunotherapy*]. *Biomedicines*, *12*(9), 2158. Multidisciplinary Digital Publishing Institute.

Havel, J. J., Chowell, D., & Chan, T. A. (2019). The evolving landscape of biomarkers for checkpoint inhibitor immunotherapy [Review of *The evolving landscape of biomarkers for checkpoint inhibitor immunotherapy*]. *Nature Reviews. Cancer*, *19*(3), 133. Nature Portfolio.

Hsu, C., Pallathadka, H., Jasim, S. A., Rizaev, J., Olegovich, B. D., Hjazi, A., Mahajan, S., Mustafa, Y. F., Husseen, B., & Jawad, M. A. (2024). “Innovations in Cancer Immunotherapy: A Comprehensive Overview of Recent Breakthroughs

and Future Directions" [Review of *"Innovations in Cancer Immunotherapy: A Comprehensive Overview of Recent Breakthroughs and Future Directions"*]. *Critical Reviews in Oncology/Hematology*, 104588. Elsevier BV.

Hu, L., Lan, H., Huang, D., Li, X., & Jin, K. (2021). Personalized Immunotherapy in Colorectal Cancers: Where Do We Stand? [Review of *Personalized Immunotherapy in Colorectal Cancers: Where Do We Stand?*]. *Frontiers in Oncology*, *11*. Frontiers Media.

Huang, L., Yu, H., Zhang, C., Jiang, A., Zhu, L., Mou, W., Li, K., Zhang, J., Cui, C., Cui, X. Z., Lin, A., Luo, P., & Wei, T. (2025). Microbiome meets immunotherapy: unlocking the hidden predictors of immune checkpoint inhibitors. *Npj Biofilms and Microbiomes*, *11*(1), 180.

Huang, P., & Deng, H. (2023). Immune Checkpoint and Tumor Therapy. In *IntechOpen eBooks*. IntechOpen.

Kang, L., Huang, H. Y., Xu, C., Chen, H., Huang, D., & Jiang, Z. (2025). Breakthroughs in immune checkpoint therapy: overcoming NSCLC immune checkpoint therapy resistance with novel techniques [Review of *Breakthroughs in immune checkpoint therapy: overcoming NSCLC immune checkpoint therapy resistance with novel techniques*]. *Frontiers in Immunology*, *16*. Frontiers Media.

Lei, W., Zhou, K., Lei, Y., Li, Q., & Zhu, H. (2025). Gut microbiota shapes cancer immunotherapy responses [Review of *Gut microbiota shapes cancer immunotherapy responses*]. *Npj Biofilms and Microbiomes*, *11*(1), 143. Nature Portfolio.

Ling, S. P., Ming, L. C., Dhaliwal, J. S., Gupta, M., Ardianto, C., Goh, K. W., Hussain, Z., & Shafqat, N. (2022). Role of Immunotherapy in the Treatment of Cancer: A Systematic Review [Review of *Role of Immunotherapy in the Treatment of Cancer: A Systematic Review*]. *Cancers*, *14*(21), 5205. Multidisciplinary Digital Publishing Institute.

Liu, Q., Li, L., Wan, Q., & Chao, T. (2023). Repurposing drugs for solid tumor treatment: focus on immune checkpoint inhibitors [Review of *Repurposing drugs for solid tumor treatment: focus on immune checkpoint inhibitors*]. *Cancer Biology and Medicine*, 1. Chinese Anti-Cancer Association.

Lovatt, C., & Parker, A. L. (2023). Oncolytic Viruses and Immune Checkpoint Inhibitors: The "Hot" New Power Couple [Review of *Oncolytic Viruses and Immune Checkpoint Inhibitors:*

The "Hot" New Power Couple]. *Cancers*, *15*(16), 4178. Multidisciplinary Digital Publishing Institute.

Mandal, K., Barik, G. K., & Santra, M. K. (2025). Overcoming resistance to anti-PD-L1 immunotherapy: mechanisms, combination strategies, and future directions [Review of *Overcoming resistance to anti-PD-L1 immunotherapy: mechanisms, combination strategies, and future directions*]. *Molecular Cancer*, *24*(1). BioMed Central.

Mehrabadi, A. Z., Tat, M., Alvanegh, A. G., Roozbahani, F., & Ghaleh, H. E. G. (2024). Revolutionizing cancer treatment: the power of bi- and tri-specific T-cell engagers in oncolytic virotherapy. *Frontiers in Immunology*, *15*.

Mitra, A., Kumar, A., Amdare, N., & Pathak, R. (2024). Current Landscape of Cancer Immunotherapy: Harnessing the Immune Arsenal to Overcome Immune Evasion. *Biology*, *13*(5), 307.

Patel, A. (2024). Recent advances in immunotherapy in cancer treatment. *Cellular and Molecular Biology*, *70*(5), 89.

Shakhpazyan, N. K., Михалева, Л. М., Bedzhanyan, A. L., Gioeva, Z. V., Mikhalev, A. I., Midiber, K., Pechnikova, V. V., & Biryukov, A. E. (2024). Exploring the Role of the Gut Microbiota in Modulating Colorectal Cancer Immunity [Review of *Exploring the Role of the Gut Microbiota in Modulating Colorectal Cancer Immunity*]. *Cells*, *13*(17), 1437. Multidisciplinary Digital Publishing Institute.

Şimşek, G. Ö. (2024). Immunotherapy in the Treatment of Cancer: Today and Tomorrow. *Current Molecular Biology Reports*, *10*(3), 54.

Topalian, S. L., Taube, J. M., Anders, R. A., & Pardoll, D. M. (2016). Mechanism-driven biomarkers to guide immune checkpoint blockade in cancer therapy [Review of *Mechanism-driven biomarkers to guide immune checkpoint blockade in cancer therapy*]. *Nature Reviews. Cancer*, *16*(5), 275. Nature Portfolio.

Tufail, M., Jiang, C., & Li, N. (2025). Immune evasion in cancer: mechanisms and cutting-edge therapeutic approaches [Review of *Immune evasion in cancer: mechanisms and cutting-edge therapeutic approaches*]. *Signal Transduction and Targeted Therapy*, *10*(1). Springer Nature.

You, W., Shang, B., Sun, J., Liu, X., Su, L., & Jiang, S. (2020). Mechanistic insight of predictive biomarkers for antitumor

PD-1/PD-L1 blockade: A paradigm shift towards immunome evaluation (Review) [Review of *Mechanistic insight of predictive biomarkers for antitumor PD-1/PD-L1 blockade: A paradigm shift towards immunome evaluation (Review)*]. *Oncology Reports*, *44*(2), 424. Elsevier BV.

Zhang, M., Liu, C., Tu, J., Tang, M., Ashrafizadeh, M., Nabavi, N., Sethi, G., Zhao, P., & Liu, S. (2025). Advances in cancer immunotherapy: historical perspectives, current developments, and future directions [Review of *Advances in cancer immunotherapy: historical perspectives, current developments, and future directions*]. *Molecular Cancer*, *24*(1), 136. BioMed Central.

Zhao, H., Luo, F., Xue, J., Su, L., & Xu, R. (2021). Emerging immunological strategies: recent advances and future directions [Review of *Emerging immunological strategies: recent advances and future directions*]. *Frontiers of Medicine*, *15*(6), 805. Higher Education Press.

Zhou, Y., Liu, M., Huang, X., Liu, Z., Sun, Y., Wang, M., Huang, T., Wang, X., Chen, L., & Jiang, X. (2024). Emerging trends and thematic evolution of immunotherapy for glioma based on the top 100 cited articles [Review of *Emerging trends and thematic evolution of immunotherapy for glioma based on the top 100 cited articles*]. *Frontiers in Oncology*, *13*. Frontiers Media.

Zhu, J., Zhou, J., Tang, Y., Huang, R., Lu, C., Ke, Q., Zhou, Q., Zhang, J., Yang, X., Zhou, W., Wu, J., Chen, Q., Lin, Y., & Meng, F. (2025). Advancements and challenges in CAR-T cell therapy for solid tumors: A comprehensive review of antigen targets, strategies, and future directions [Review of *Advancements and challenges in CAR-T cell therapy for solid tumors: A comprehensive review of antigen targets, strategies, and future directions*]. *Cancer Cell International*, *25*(1). BioMed Central.