

Review article

Cancer Immunotherapy: A Review of Recent Advances, Clinical Challenges and Future Directions

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Abstract: Cancer immunotherapy has reshaped clinical oncology by directing the patient's own immune system against malignant cells. Recent advances include immune checkpoint inhibitors, chimeric antigen receptor T-cell (CAR-T) therapy, tumor-infiltrating lymphocyte (TIL) therapy, and bispecific T-cell-engaging antibodies, and these approaches have widened the treatment options available to selected patients with hematological malignancies and solid tumors. Therapeutic benefit nonetheless varies considerably according to tumor biology, immune status, prior treatment and the composition of the tumor microenvironment. Immune-related adverse events, cytokine release syndrome, primary and acquired resistance, manufacturing complexity and unequal access remain substantial clinical challenges. This narrative review summarises recent developments in cancer immunotherapy, examines its clinical applications and treatment-related toxicities, and considers emerging strategies for improving therapeutic precision. Literature published between January 2020 and October 2025 was prioritized, with emphasis on clinically relevant reviews and regulatory developments. The evidence supports individualized treatment selection, biomarker-guided patient assessment, early recognition of toxicity, and multidisciplinary management. Further progress will depend on more reliable predictive biomarkers, rationally designed combination regimens, safer cellular products and improved access to treatment. Although immunotherapy has altered the management of several cancers, it is not universally effective, and its role must be judged within the context of tumor type, disease stage and established clinical evidence.

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Introduction

Cancer arises through the progressive accumulation of genetic and epigenetic alterations that allow cells to proliferate without restraint, invade adjacent tissue and evade immune surveillance. The immune system is capable of recognising tumour-associated antigens and eliminating transformed cells, and this capacity operates continuously in healthy tissue. Malignant cells that become clinically apparent are, by definition, those that have escaped it (Emens et al., 2024).

The relationship between a developing tumour and the host immune system is conventionally described in three phases. During elimination, immune effector cells recognise and destroy transformed cells before a tumour becomes established. In equilibrium, immune pressure contains the lesion without eradicating it, while selecting for variants that are progressively less visible to immune recognition (Esfahani et al., 2020). In escape, the surviving population proliferates unchecked. This framework explains an

observation central to the whole field: by the time a tumour presents clinically it has already been shaped by immune selection, and the mechanisms that permitted its escape are the same mechanisms that immunotherapy must now overcome.

These mechanisms act in combination: inhibitory checkpoint signalling dampens T-cell activity at the tumour site; loss or downregulation of target antigens removes the structures on which recognition depends; defects in antigen processing prevent display of those that remain; regulatory T cells, myeloid-derived suppressor cells and tumour-associated macrophages suppress effector function; and metabolic conditions within the tumour impair the immune cells that do arrive (Hegde and Chen, 2020).

Cancer immunotherapy seeks to restore, redirect or amplify antitumour immunity. It differs from conventional cytotoxic chemotherapy in a fundamental respect: chemotherapy acts directly on dividing cells, whereas immunotherapy acts on the immune system and relies on that system to act on the tumour. The therapeutic target is therefore the host response rather than the malignant cell itself, and this distinction accounts for much of what is distinctive about immunotherapy in practice, including its delayed patterns of response, its potential for durable disease control after treatment has stopped, and its characteristic autoimmune toxicities (Kumar et al., 2021).

Immune checkpoint inhibitors targeting programmed cell death protein 1 (PD-1), its ligand PD-L1, and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) are now established treatments for several malignancies. Cellular therapies have expanded in parallel, particularly in selected hematological cancers (Ghemrawi et al., 2024). In February 2024, the United States Food and Drug Administration granted accelerated approval to lifileucel, a tumor-infiltrating lymphocyte therapy for certain patients with advanced melanoma, representing the first approval of a cellular therapy for a solid tumor and an important development in the treatment of non-hematological malignancy (Kochenderfer, 2024; Zhou et al., 2025).

Substantial limitations nonetheless persist. Response is heterogeneous and frequently unpredictable; resistance develops in many patients who initially respond; immune-mediated toxicity can be severe and occasionally fatal; and the cost and infrastructural demands of cellular therapy restrict availability to a minority of the patients who might benefit. This review examines recent progress in cancer immunotherapy together with the clinical considerations that govern its safe and effective application (Yi et al., 2023).

Scope and literature selection

This is a narrative review. Literature published between January 2020, and October 2025 was prioritized, with emphasis on clinically oriented reviews, regulatory determinations and studies reporting outcomes relevant to practice. Sources were identified through searches of PubMed and the published regulatory record, supplemented by the reference lists of retrieved articles. Preference was given to work addressing clinical application, toxicity and implementation rather than preclinical mechanistic studies. A narrative rather than systematic approach was adopted because the platforms reviewed differ in mechanism, evidence base and stage of development, such that quantitative synthesis would not yield an interpretable estimate; the resulting limitations are addressed before the conclusions (Gao et al., 2021).

Major approaches to cancer immunotherapy

Immune checkpoint inhibitors

Immune checkpoints are regulatory pathways that govern the magnitude and duration of immune responses and that exist to prevent excessive or self-directed immune activation. PD-1 signalling reduces T-cell activity when PD-1 engages PD-L1 or PD-L2, and CTLA-4 limits T-cell activation through competitive interaction with B7 molecules on antigen-presenting cells. Many tumours exploit these physiological pathways to reduce immune-mediated destruction, either by expressing checkpoint ligands directly or by inducing their expression within the surrounding stroma (Habib et al., 2021).

The two principal targets act at different points in the immune response, and this difference has clinical consequences. CTLA-4 operates predominantly during the priming phase, within lymphoid tissue, where it restrains the initial activation and expansion of T cells. PD-1 operates principally during the effector phase, within peripheral tissue and the tumour itself, where it attenuates the activity of T cells that have

already been primed. Blockade of CTLA-4 therefore broadens the repertoire of responding T cells, whereas blockade of PD-1 or PD-L1 restores the function of T cells already directed at the tumour. The broader immunological effect of CTLA-4 blockade is reflected in a correspondingly higher burden of immune-related toxicity, and combined blockade of both pathways increases response rates in some settings at the cost of substantially greater toxicity (Gröger, 2022).

Antibodies blocking PD-1, PD-L1 or CTLA-4 can restore aspects of antitumour T-cell activity, and are administered alone or with chemotherapy, targeted therapy, radiotherapy or other immunotherapeutic agents according to the indication. Their adoption across multiple tumour types, in the metastatic, adjuvant and neoadjuvant settings, has made checkpoint blockade a central component of contemporary practice. Interest has extended to further inhibitory receptors, including LAG-3, TIM-3 and TIGIT, on the expectation that blocking complementary pathways may benefit patients who do not respond to PD-1-directed treatment (Yi et al., 2022).

Response is nonetheless far from uniform. Tumour mutational burden, mismatch-repair deficiency, PD-L1 expression, the integrity of antigen presentation and the extent of immune-cell infiltration may inform treatment selection in defined clinical settings, but no single biomarker reliably predicts benefit for every patient or every tumour type. Clinical decisions must therefore incorporate the cancer type, disease stage, validated testing criteria and the relevant disease-specific guidelines rather than relying on any individual marker in isolation (Keam et al., 2024).

Chimeric antigen receptor T-cell therapy

CAR-T therapy involves collecting the patient's T lymphocytes by leukapheresis, genetically modifying them *ex vivo* to express a receptor recognising a selected tumour-associated antigen, expanding the modified cells to a therapeutic dose, and reinfusing them following lymphodepleting chemotherapy. Recognition of the target antigen through the engineered receptor triggers T-cell activation, proliferation and tumour-cell killing, independently of major histocompatibility complex presentation (Dasyam et al., 2020).

The receptor itself has evolved through successive designs. First-generation constructs linked an antigen-binding domain to the CD3 zeta chain alone and persisted poorly. Second-generation receptors added a single co-stimulatory domain, most commonly CD28 or 4-1BB, markedly improving expansion and persistence; these underlie the products now in use. Third-generation designs combine two such domains, and armoured constructs additionally secrete cytokines intended to modify the local environment. The choice of co-stimulatory domain is not merely technical, influencing the kinetics of expansion, the durability of persistence and the character of the toxicity observed (Chung et al., 2024).

CAR-T therapies have established important treatment options for selected B-cell malignancies and for multiple myeloma, with CD19 and B-cell maturation antigen the principal validated targets. Their extension to solid tumours has proved considerably more difficult. Heterogeneous antigen expression means that no single target is present on all malignant cells within a lesion. Inadequate trafficking limits the number of transferred cells that reach the tumour. Local immunosuppression and progressive T-cell exhaustion impair the function of those that do arrive. Antigen loss under therapeutic pressure permits escape from recognition even where initial activity was substantial (Wala and Hanna, 2023).

A further constraint is the scarcity of genuinely tumour-restricted targets. Most tumour-associated antigens in solid tumours are also expressed on essential normal tissue, and a receptor of sufficient affinity to recognise the tumour may recognise that tissue too. In haematological malignancy this is tolerable, because the normal counterpart population can be depleted and the resulting immunoglobulin deficiency replaced; no comparable tolerance exists for the loss of lung, cardiac or neural tissue (Tantalo et al., 2021).

The important toxicities are cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), prolonged cytopenias, infection and hypogammaglobulinaemia. Early recognition, structured monitoring and access to experienced multidisciplinary teams are essential to safe delivery. Tocilizumab and corticosteroids are used in defined circumstances according to toxicity grade and established management protocols, and treatment must be individualised to the patient and the severity of the event (Brudno and Kochenderfer, 2024).

Tumour-infiltrating lymphocyte therapy

TIL therapy differs from CAR-T therapy in a conceptually important respect: rather than engineering a receptor of defined specificity, it harvests and expands the lymphocytes that have already entered the tumour and therefore already recognise it. Tumour tissue is surgically obtained, lymphocytes are isolated and expanded *ex vivo* over several weeks, and the resulting cell population is reinfused following lymphodepleting conditioning, typically with interleukin-2 support (Klobuch et al., 2024).

The infused product is therefore polyclonal and recognises multiple tumour-associated antigens, including patient-specific neoantigens that could not have been identified in advance. This confers a theoretical advantage over single-target engineered approaches, since loss of any one antigen is less likely to abolish the response entirely, but it also means the product cannot be characterised as a defined engineered receptor can, and that its composition varies between patients (Sarnaik et al., 2021).

The United States approval of lifileucel in February 2024 introduced a TIL-based cellular therapy for eligible adults with unresectable or metastatic melanoma following specified prior treatment. The approval was granted under the accelerated pathway on the basis of objective response rate, with continued approval potentially contingent upon verification of clinical benefit in confirmatory study. This regulatory distinction matters and is frequently lost in secondary reporting: accelerated approval establishes that a treatment produces measurable tumour responses in a defined population, not that it prolongs survival, and it should not be interpreted as evidence that TIL therapy is effective across solid tumours generally (Shaik et al., 2025; Suárez Formigo et al., 2025).

The limitations of the approach are substantial. It requires tumour tissue of sufficient quantity and quality, which presupposes a surgically accessible lesion. Manufacturing is specialised and prolonged, and patients with rapidly progressive disease may deteriorate before the product is available. Lymphodepleting conditioning and interleukin-2 administration are themselves toxic and demand an inpatient setting with intensive care support. The characteristics of the cell product vary, which complicates both standardisation and the interpretation of trial results. Current research is examining how cell selection, expansion conditions and combination with checkpoint blockade might improve the consistency and durability of response (Shaik et al., 2025).

Bispecific antibodies and T-cell engagers

Bispecific antibodies are engineered to bind two targets simultaneously, most often linking a tumour-associated antigen to a receptor on an immune effector cell. T-cell-engaging constructs typically bind CD3 on the T cell and a selected antigen on the malignant cell, bringing the two into close apposition and inducing immune-mediated killing without requiring prior antigen priming or MHC-restricted recognition. Other bispecific molecules engage two tumour-associated pathways, or combine tumour targeting with immune modulation (van de Donk and Zweegman, 2023).

These agents occupy a distinctive position relative to cellular therapy. Manufactured as pharmaceutical products rather than generated from each patient's own cells, they avoid the delay, cost and infrastructural burden of bespoke manufacture and can be given in centres without cell-therapy capability. The corresponding disadvantage is that their effect depends on continued administration rather than on a persisting, self-renewing cell population (Tian et al., 2021).

Clinical development has expanded considerably in haematological cancers and, more recently, in selected solid tumours. Efficacy remains dependent on adequate target expression, physical accessibility of the tumour and the presence of functional effector cells, the last of which may be compromised in heavily pre-treated patients. CRS, neurotoxicity and on-target activity against normal tissue expressing the same antigen remain important concerns, and step-up dosing schedules are now widely used to reduce the severity of cytokine-mediated toxicity during treatment initiation (Gu and Zhao, 2024; Zhou et al., 2025).

Other and emerging platforms

Additional approaches include therapeutic cancer vaccines, engineered T-cell receptor therapies, natural killer cell-based treatments and oncolytic viral platforms, frequently in combination with checkpoint inhibitors. Engineered T-cell receptor therapy is of particular interest in solid tumours because, unlike a chimeric antigen

receptor, a T-cell receptor can recognise intracellular antigens presented on MHC molecules, greatly widening the range of accessible targets; the corresponding constraint is that the therapy must be matched to the patient's HLA type (Liu et al., 2024).

Natural killer cell therapies offer the prospect of allogeneic, off-the-shelf products, carrying a lower risk of graft-versus-host disease than allogeneic T cells. Therapeutic vaccines, including individualised neoantigen approaches delivered on messenger RNA platforms, aim to generate or broaden tumour-specific responses rather than restore existing ones. Several of these platforms remain investigational or narrowly indicated; their common promise lies in broadening immune recognition and addressing the mechanisms that cause established treatments to fail (Alard et al., 2020).

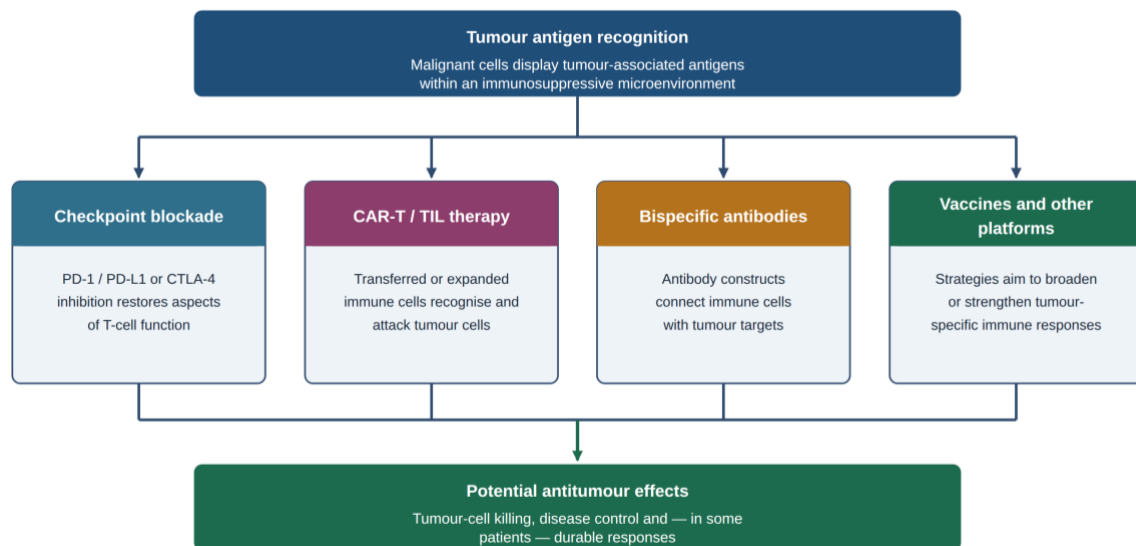


Figure 1. Major mechanisms of cancer immunotherapy. Malignant cells display tumour-associated antigens within an immunosuppressive microenvironment. Checkpoint blockade, adoptive cellular therapy, bispecific antibodies and vaccine-based platforms act through distinct mechanisms that converge on tumour-cell killing, disease control and, in some patients, durable responses. Figure 1 represents an original conceptual synthesis of major immunotherapeutic mechanisms; outcomes vary by tumour type, treatment and patient characteristics.

Clinical applications and comparative considerations

Immunotherapy is now used in selected cancers including melanoma, non-small cell lung cancer, renal cell carcinoma, urothelial carcinoma, head and neck squamous cell carcinoma, mismatch-repair-deficient colorectal cancer and several haematological malignancies. The optimal approach differs according to histology, disease stage, molecular characteristics, prior treatment and patient fitness. Treatment selection should follow current disease-specific evidence rather than presuming that any one immunotherapeutic platform is universally superior; the platforms are not interchangeable, and a strategy validated in one tumour type carries no implication for another (Adhikary et al., 2024). Table 1 summarises the principal approaches together with their practical limitations.

Combination strategies

Combining immunotherapy with chemotherapy, radiotherapy, targeted agents or other immune therapies may improve tumour control in selected settings. The mechanistic rationale varies with the partner: cytotoxic chemotherapy and radiotherapy may increase the release and presentation of tumour antigens, targeted agents may modify the composition and vascular supply of the tumour microenvironment, and combined checkpoint blockade may address complementary routes of immune escape. In several indications, combination regimens have replaced single-agent immunotherapy as standard first-line treatment (Petroni et al., 2022).

Table 1. Major cancer immunotherapy approaches and clinical considerations.

Approach	Main mechanism	Important application	Key limitation
Checkpoint inhibitors	Release inhibitory signals acting on T cells	Selected solid tumours and other malignancies	Immune-related organ toxicity; primary or acquired resistance
CAR-T cells	Engineered T cells recognise defined surface antigens	Selected haematological malignancies	CRS, ICANS, antigen escape, manufacturing demands
TIL therapy	Expanded tumour-derived lymphocytes attack cancer cells	Selected advanced melanoma settings	Tumour-tissue requirement; complex and prolonged treatment pathway
Bispecific antibodies	Connect immune effectors to tumour targets, or engage two targets	Selected haematological cancers and emerging solid-tumour indications	CRS, target-related toxicity, variable solid-tumour activity
Cancer vaccines and related platforms	Promote tumour-antigen-specific immunity	Selected established or investigational settings	Immune suppression, antigen heterogeneity, variable efficacy

Abbreviations: CAR-T, chimeric antigen receptor T cell; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; TIL, tumour-infiltrating lymphocyte.

Combination nonetheless carries costs. Toxicity may be additive, overlapping or qualitatively new, and attributing an adverse event to one component of a regimen is often difficult in practice, which complicates the decision of what to withhold and what to continue. Financial cost and treatment complexity both increase. A systematic review and meta-analysis published in 2024 examined the toxicity of checkpoint inhibitor and tyrosine kinase inhibitor combinations in solid tumours and underlined the need to evaluate safety alongside efficacy rather than as a secondary consideration (O'Reilly et al., 2024).

Combination regimens should accordingly be supported by evidence from the relevant cancer population and line of therapy. Mechanistic plausibility is not sufficient to establish clinical benefit, and the field contains several rationally designed combinations that proved more toxic without proving more effective (Li et al., 2023).

Safety, resistance and barriers to treatment

Immune-related adverse events

Checkpoint inhibition can provoke inflammatory reactions in virtually any organ system, including the skin, gastrointestinal tract, liver, lungs, endocrine glands, kidneys, joints, nervous system and heart. Some events are mild and self-limiting; others are severe, life-threatening or productive of permanent organ dysfunction. Endocrine events such as hypophysitis and primary thyroid failure frequently require lifelong hormone replacement even after the inflammatory process has resolved, and immune-mediated myocarditis, although uncommon, carries disproportionate mortality (Li et al., 2023).

Timing is clinically important. Cutaneous and gastrointestinal toxicity tends to appear within the first weeks to months, whereas endocrine and some neurological events emerge considerably later and may present after treatment has stopped; a patient who has tolerated several cycles cannot be regarded as no longer at risk (Suijkerbuijk et al., 2024).

Clinical evaluation should consider the timing of symptom onset, plausible alternative diagnoses, intercurrent infection, concurrent medication and the possibility of immune-mediated injury, with the recognition that infection and immune toxicity may coexist and that treatment of one may worsen the other. Depending on severity and the organ affected, management may involve interruption of treatment, corticosteroids, additional immunosuppression and early specialist referral. Decisions regarding resumption of immunotherapy require individualised assessment balancing the degree of toxicity resolution against the anticipated oncological benefit, and some toxicities preclude rechallenge altogether [4,8].

Toxicities of cellular and T-cell-engaging therapies

The toxicity profile of cellular and T-cell-engaging therapies differs in character from that of checkpoint blockade. Cytokine release syndrome arises from the systemic inflammatory response accompanying large-scale immune activation, and presents with fever, hypotension and hypoxia along a spectrum from self-limiting illness to a picture resembling septic shock with multi-organ failure. Severity is broadly related to disease burden at the time of treatment, and cytoreduction before infusion is one approach to risk reduction (Shanshal et al., 2023).

Immune effector cell-associated neurotoxicity syndrome presents with impaired attention, dysgraphia, expressive dysphasia, confusion and, in severe cases, seizures or cerebral oedema. Its pathophysiology is incompletely understood but appears to involve endothelial activation and disruption of the blood-brain barrier. It frequently follows CRS but may occur independently, and because its early manifestations are subtle, structured bedside assessment at defined intervals is more reliable than clinical impression alone (Chohan et al., 2023).

Both syndromes are now subject to consensus grading systems, and graded management algorithms specifying thresholds for tocilizumab and corticosteroid administration have improved their safety considerably. Prolonged cytopenias, hypogammaglobulinaemia and consequent infection risk extend well beyond the acute period and require sustained follow-up (Brudno and Kochenderfer, 2024).

Mechanisms of resistance

Resistance to immunotherapy may be present before treatment begins, in which case the tumour fails to respond at all, or may develop during treatment in a patient who initially responded. The distinction matters because the underlying mechanisms, and the therapeutic implications, differ. Described mechanisms include deficient presentation of tumour antigen, loss of target antigen expression, impaired interferon signalling, intrinsic T-cell dysfunction and exhaustion, and active suppression by regulatory T cells and myeloid-derived suppressor cells (Said and Ibrahim, 2023). Acquired resistance in particular frequently reflects immune selection: effective therapy eliminates the recognisable fraction of the tumour and thereby selects for variants that are not recognised, so that the response itself generates the conditions for its eventual failure (Wala and Hanna, 2023).

CAR-T approaches encounter analogous difficulties. Where target antigens are heterogeneously expressed, cells lacking the antigen survive selectively; where antigens are shared with essential normal tissue, the therapeutic window may be too narrow to exploit. Strategies under investigation include simultaneous targeting of multiple antigens and the design of receptors whose activation depends on the combined presence or absence of several surface markers (Dobosz et al., 2022).

The tumour microenvironment

The tumour microenvironment is a principal determinant of response, particularly in solid cancers, and encompasses the stromal cells, vasculature, extracellular matrix, soluble mediators and metabolic conditions surrounding malignant cells. Its influence is exerted at several distinct stages: it may prevent immune cells from entering the tumour, impair their function once they arrive, or actively promote their exhaustion and death.

Dense desmoplastic stroma presents a physical barrier to infiltration, and abnormal tumour vasculature limits delivery while sometimes selectively excluding effector cells. Within the tumour, competition for glucose and essential amino acids, hypoxia, acidification and inhibitory metabolites such as adenosine impair effector function, a state reinforced by suppressive signalling through transforming growth factor beta and interleukin-10 (Baghy et al., 2023).

Tumours are frequently characterised as immunologically inflamed, excluded or desert, according to whether effector cells are present within the tumour, confined to the surrounding stroma, or largely absent. This classification carries therapeutic implications: restoring the function of cells already present is a different problem from importing cells that were never there, and checkpoint blockade addresses the former far more readily than the latter. Strategies aimed at modifying the microenvironment therefore remain an active and necessary area of investigation (Wala and Hanna, 2023).

Biomarkers and personalised treatment

Biomarkers can improve patient selection and spare patients exposure to treatments unlikely to confer meaningful benefit, together with their attendant toxicity and cost. Depending on the clinical indication, relevant assessments may include PD-L1 expression, mismatch-repair or microsatellite-instability status, tumour mutational burden and defined molecular alterations. These markers are not interchangeable, and their predictive value is conditional rather than absolute. PD-L1 expression illustrates the difficulty: it is assessed by different antibody clones on different platforms, scored by different algorithms, and interpreted against different thresholds depending on the tumour type and the agent concerned, so that a result reported for one indication cannot be transferred to another. Expression is additionally heterogeneous within a tumour and variable over time, so that a single biopsy may not represent the lesion as a whole, still less the disease (Jazieh et al., 2022). Tumour mutational burden presents a related problem. A greater mutational load should generate more neoantigens and therefore more opportunity for recognition, but the relationship between burden and benefit is neither linear nor consistent across tumour types, and measured values depend on the sequencing panel and pipeline used. Mismatch-repair deficiency and high microsatellite instability are more robust tissue-agnostic predictors, but identify only a small proportion of patients.

Longitudinal sampling and emerging approaches, including circulating tumour DNA and spatial immune profiling, may assist in detecting residual disease or identifying evolving resistance earlier than radiological assessment permits. Spatial methods are of particular conceptual interest because they capture not merely which immune cells are present but where they are situated in relation to malignant cells, which bears directly on the inflamed, excluded and desert distinction. The clinical use of all such approaches must nonetheless be supported by validated evidence of analytical reliability and demonstrated clinical utility, rather than by biological plausibility alone (Normanno et al., 2022).

Access and implementation

Cellular immunotherapies require specialised laboratory facilities, coordinated manufacturing and logistics, trained clinical teams and institutions capable of managing severe complications, including critical care provision. The practical consequences extend beyond cost. Autologous manufacture requires that cells be collected, transported, modified, expanded, released and returned, an interval of several weeks during which disease continues to progress. Patients referred late, or living far from an accredited centre, may deteriorate into ineligibility before treatment can be delivered. Equity of access is therefore determined not only by funding but by the timeliness of referral pathways and the distribution of capability (Pillai et al., 2020). Improving access will require investment in clinical services, standardised referral pathways, training in toxicity recognition beyond specialist centres, and research evaluating affordability and outcomes in diverse populations. Allogeneic off-the-shelf products and T-cell-engaging antibodies, which avoid bespoke manufacture altogether, may prove as important to access as to efficacy. The availability of a treatment in one jurisdiction establishes neither its approval nor its affordability in another (Gotti et al., 2020).

Table 2. Major challenges and potential strategies for improvement.

Challenge	Clinical consequence	Potential direction
Unreliable prediction of response	Patients may receive ineffective treatment and incur avoidable toxicity	Validate biomarkers and integrate clinical with molecular data
Antigen loss or immune escape	Disease progression following an initial response	Investigate multi-antigen targeting and rational combinations
Immunotherapy-related toxicity	Treatment interruption or serious organ injury	Early recognition, standardised monitoring, specialist management
Suppressive tumour microenvironment	Reduced immune-cell activity in solid tumours	Investigate microenvironment-modifying strategies
Complex cellular manufacturing	Delays, high cost and limited availability	Improve manufacturing efficiency and develop off-the-shelf products
Unequal access to specialist care	Differences in treatment availability and outcomes	Strengthen referral networks, infrastructure and equitable funding

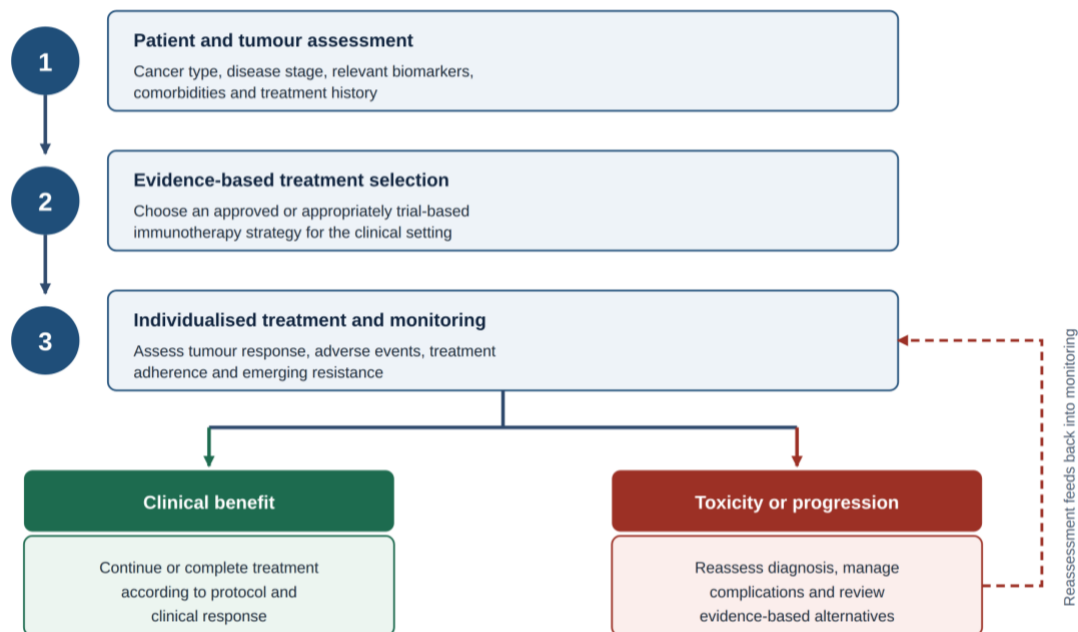


Figure 2. Translational pathway toward safer, more personalised immunotherapy. Assessment of the patient and tumour informs evidence-based selection of an approved or appropriately trial-based strategy, which is then delivered with individualised monitoring of response, toxicity, adherence and emerging resistance. Clinical benefit supports continuation or completion of treatment according to protocol; toxicity or progression prompts reassessment of the diagnosis, management of complications and review of evidence-based alternatives, with findings feeding back into ongoing monitoring. Figure 2 represents an original conceptual framework for personalised immunotherapy; the pathway is illustrative and does not replace disease-specific guidelines or clinical judgment.

Future directions

Future research should address why some patients experience durable responses while others develop primary or acquired resistance. Better integration of genomic, transcriptomic, immune and clinical data may support more accurate stratification, and computational approaches to such multimodal data are advancing rapidly. Any new biomarker must nonetheless demonstrate reproducibility across laboratories and genuine clinical utility before adoption, rather than statistical association in a single retrospective cohort. Next-generation cellular therapies are being designed to incorporate improved persistence, resistance to immunosuppressive signalling, recognition of multiple antigens and controllable safety mechanisms such as inducible suicide genes permitting rapid elimination of the infused product. Allogeneic products derived from healthy donors or induced pluripotent stem cells would remove the delay and expense of autologous manufacture if the associated immunological barriers can be overcome, and approaches generating engineered cells directly within the patient, rather than *ex vivo*, would represent a more fundamental simplification still. Bispecific and multispecific antibodies continue to be engineered for improved target selectivity, pharmacological properties and effector engagement.

Therapeutic cancer vaccines and individualised neoantigen approaches remain important areas of investigation, and messenger RNA platforms have shortened the interval between sequencing a tumour and manufacturing a corresponding product to a clinically practicable period. Their value will depend on demonstrating meaningful clinical outcomes in adequately designed and adequately powered trials, rather than on immunological response alone, a distinction that has repeatedly proved decisive in this field.

Limitations of this review

Several limitations should be acknowledged. The review is narrative rather than systematic; studies were not selected against pre-specified criteria, screening was not duplicated, and the possibility of selection favouring prominent or confirmatory work cannot be excluded. Emphasis on literature from 2022 to 2026 captures current practice but may understate foundational earlier work. Regulatory determinations are cited for a

single jurisdiction and do not describe approval status elsewhere. Finally, the field is advancing quickly enough that specific statements regarding approvals, indications and investigational agents should be verified against current sources at the time of reading.

Conclusions

Cancer immunotherapy has substantially expanded the therapeutic options available in selected malignancies. Checkpoint inhibitors, CAR-T cells, TIL therapy and bispecific antibodies employ distinct mechanisms to improve immune recognition and destruction of cancer cells, and in a minority of patients they achieve durable disease control that was not previously attainable. Tumour biology, resistance, patient selection and the composition of the tumour microenvironment nonetheless continue to determine their effectiveness, and serious immune-related toxicity together with inequitable access remain pressing concerns. Progress will depend on integrating validated biomarkers with individualised treatment decisions, improving the recognition and management of toxicity, developing more effective approaches for solid tumours and strengthening the quality of clinical research. Immunotherapy is best regarded as a diverse and rapidly evolving group of treatments rather than a universal solution to cancer. High-quality comparative trials and long-term follow-up remain essential to establishing which patients benefit most, and how those who do not might be helped.

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