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REVIEW ARTICLE

IMMUNE CHECKPOINT INHIBITORS IN CANCER THERAPY: FROM MONOTHERAPY TO COMBINATION AND PERSONALISED STRATEGIES

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ABSTRACT

Immune checkpoint inhibitors (ICIs) have transformed oncological practice by generating durable antitumour responses across a broad spectrum of malignancies. However, meaningful clinical benefit accrues to only a fraction of patients, and resistance remains a persistent challenge. This review examines the evolution of ICI-based therapy from single-agent checkpoint blockade through multimodal combination regimens to biomarker-directed, personalised strategies. Combination approaches pairing ICIs with cytotoxic chemotherapy, radiotherapy, molecularly targeted agents, and emerging platforms such as oncolytic viruses and therapeutic vaccines exploit mechanistic synergies and have demonstrated improved immunological and clinical endpoints. The expanding repertoire of predictive biomarkers encompassing PD-L1 expression, tumour mutational burden (TMB), microsatellite instability (MSI) status, and transcriptomic immune signatures has refined patient stratification. The tumour immune microenvironment and the gut microbiome are increasingly recognised as modulable determinants of treatment response, offering avenues aligned with integrative oncology. Artificial intelligence and machine learning applied to multi-omics datasets are advancing response prediction and resistance identification. Key challenges include immune-related adverse events (irAEs), treatment costs, and biomarker standardisation. Future priorities encompass next-generation checkpoint targets, bispecific antibodies, liquid biopsy-guided surveillance, and microbiome-directed interventions. The convergence of immunological precision, integrative patient-centred care, and computational decision-making defines the next chapter of cancer immunotherapy.

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INTRODUCTION

The human immune system constitutes a highly coordinated defence network capable of distinguishing self from non-self. Central to this discrimination are immune checkpoints – molecular regulatory circuits governing the amplitude and duration of immune activation. By modulating T-cell responsiveness, these pathways protect peripheral tissues from immune injury and preserve immunological self-tolerance (12,13). In malignant disease, tumour cells co-opt these checkpoint mechanisms to escape immunological detection. By hijacking inhibitory signalling pathways, neoplastic cells engineer an immunosuppressive microenvironment that shields them from cytotoxic T-cell attack. Recognition of this strategy provided the conceptual basis for developing immune checkpoint inhibitors (ICIs) engineered monoclonal antibodies that interrupt inhibitory receptor-ligand interactions, thereby reactivating endogenous antitumour immunity (1,3,4). The clinical introduction of ICIs marked a paradigm shift in oncology, generating prolonged responses in patients with tumours historically refractory to standard systemic treatments. Yet therapeutic gains are not universally distributed; only a proportion of patients experience clinically meaningful benefit. Inter-patient variability in tumour immunogenicity, adaptive resistance, and immune-mediated organ toxicities collectively constrain the broad applicability of single-agent ICI therapy. Overcoming these obstacles demands strategies that augment response rates without disproportionately amplifying adverse effects. Accordingly, multimodal regimens combining ICIs with chemotherapy, radiotherapy, molecularly targeted agents, and novel immunological platforms have been developed. Concurrently, progress in biomarker discovery, tumour immune microenvironment characterisation, gut microbiome science, and

computational analytics has laid the groundwork for personalised immunotherapy. The gut microbiome and dietary modulation core concerns of integrative medicine are now recognised as clinically relevant modulators of ICI response, linking precision oncology to integrative patient-centred care (21,22). This review systematically examines single-agent ICI therapy, multimodal combination strategies, and the growing contribution of personalised and integrative approaches to improving outcomes in patients with cancer.

MECHANISM OF ACTION OF IMMUNE CHECKPOINT INHIBITORS: At the molecular level, immune checkpoints function as regulatory rheostats that maintain immunological balance and curtail pathological immune overactivation (12,13). Prominent members include programmed cell death protein 1 (PD-1), cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), lymphocyte-activation gene 3 (LAG-3), and T-cell immunoglobulin and mucin domain-containing protein 3 (TIM-3), together with their cognate ligands. Neoplastic cells selectively leverage these checkpoint axes as a strategy of immune escape (12). A principal example is upregulation of PD-L1 on tumour cell surfaces, engaging PD-1 on infiltrating T cells and inducing functional exhaustion characterised by attenuated cytokine secretion and diminished cytolytic capacity. CTLA-4 competes with the co-stimulatory receptor CD28 for occupancy of B7 ligands (CD80/CD86) on antigen-presenting cells, suppressing the early priming phase of T-cell activation. Collectively, these mechanisms generate an immunosuppressive tumour microenvironment permissive for neoplastic growth.

ICIs are engineered monoclonal antibodies that interrupt these inhibitory receptor-ligand interactions, releasing the brakes on T-cell-mediated antitumour killing. Disruption of the PD-1/PD-L1 axis reinstates cytotoxic T-cell function and restores tumour-cell recognition. CTLA-4 blockade exerts its principal effect at the T-cell priming stage in lymphoid organs, fostering greater clonal expansion. Notably, PD-L1 expression is subject to dynamic transcriptional regulation via IFN-γ signalling and is commonly heterogeneous across intratumoral sites, limiting its utility as a universally applicable predictive marker. Beyond PD-1/PD-L1 and CTLA-4, co-inhibitory receptors including LAG-3, TIM-3, and TIGIT are frequently co-expressed on exhausted CD8+ T cells within the tumour microenvironment. Their co-expression suggests that single checkpoint blockade is often insufficient to fully reverse T-cell exhaustion, providing mechanistic rationale for combination checkpoint strategies (13,23,24).

IMMUNE CHECKPOINT INHIBITORS AS MONOTHERAPY

Clinical Applications: As single agents, ICIs have yielded substantial and in some cases lasting clinical benefit across multiple tumour types, with the most pronounced activity observed in immunologically active neoplasms (1,3,4). Regulatory approvals now span melanoma, advanced non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), urothelial carcinoma, head and neck squamous cell carcinoma, and classical Hodgkin lymphoma. For metastatic NSCLC, first-line pembrolizumab monotherapy is guideline-endorsed in patients whose tumours express PD-L1 in at least 50% of cells, having demonstrated superior overall survival over platinum-based chemotherapy (4). Anti-PD-1 antibodies nivolumab and pembrolizumab have similarly transformed outcomes in advanced melanoma (1,2).

Efficacy across Tumour Types: Therapeutic responses are profoundly shaped by the immunological architecture, mutational landscape, and intrinsic biology of each tumour. Objective response rates diverge sharply: highly immunogenic tumours such as melanoma and MSI-H colorectal cancer respond in 30-50% of cases, while immunologically inert tumours such as pancreatic and prostate cancers respond in fewer than 10%. This heterogeneity reflects differences in neoantigen load, baseline T-cell infiltration, and the degree of pre-existing immune activation within the tumour microenvironment. Tumours characterised by high tumour mutational burden (TMB) or microsatellite instability (MSI-H) tend to respond more favourably (6,7) owing to increased neoantigen formation and enhanced immune recognition (8,9).

Table 1. Efficacy of ICI Monotherapy Across Tumour Types

Cancer Type	Response Rate	Key Determinant
Melanoma	30-45%	High immunogenicity
NSCLC	20-40%	PD-L1 expression
RCC	20-30%	Immune-responsive tumour
MSI-H Colorectal Cancer	40-50%	High mutation load
Pancreatic/Prostate Cancer	<10%	Immune-cold tumours

Limitations of Monotherapy: Despite its success, ICI monotherapy is associated with several important limitations. Only a subset of patients derive meaningful clinical benefit, with many tumours exhibiting primary resistance attributable to low neoantigen load and absent T-cell infiltration. Acquired resistance is equally pressing: tumours can adapt by upregulating alternative inhibitory checkpoints such as LAG-3 or TIM-3, or by losing antigen visibility through downregulation of MHC class I molecules via loss of beta-2 microglobulin (B2M) or JAK1/JAK2 mutations abrogating IFN-γ signalling (25). Immune-related adverse events (irAEs) resulting from systemic immune activation affect multiple organ systems, including the skin, gastrointestinal tract, liver, and endocrine glands. These limitations highlight the need for combination strategies and biomarker-guided personalised approaches.

COMBINATION STRATEGIES WITH IMMUNE CHECKPOINT INHIBITORS

The conceptual foundation of combination therapy rests on co-targeting distinct but interconnected pathways governing tumour growth and immune regulation (6,15). While monotherapy concentrates on relieving inhibitory checkpoint pressure, combination approaches pursue augmented tumour antigen release, enhanced T-cell priming, and reprogramming of the immunosuppressive tumour microenvironment. Several therapeutic modalities have been combined with ICIs to achieve synergistic effects, as detailed below.

ICI + Chemotherapy: Contrary to their historical reputation as globally immunosuppressive agents, select cytotoxic drugs can meaningfully potentiate immune responses in the context of ICI co-administration. The primary mechanism is induction of immunogenic cell death (ICD), which promotes release of tumour antigens and danger-associated molecular patterns (DAMPs), leading to dendritic cell activation and T-cell priming. Chemotherapy can additionally deplete immunosuppressive cells such as regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), further enhancing immune-mediated tumour destruction. Importantly, these immunostimulatory effects are highly dose- and schedule-dependent: low-dose metronomic regimens preferentially deplete Tregs while sparing

effector T cells, whereas high cytotoxic doses may cause lymphodepletion. Optimal sequencing continues to be evaluated in clinical trials.

Table 2. ICI + Chemotherapy Clinical Trials

Trial	Cancer Type	Combination Therapy	Key Outcome
KEYNOTE-189	NSCLC	Pembrolizumab + platinum-based chemotherapy	Improved OS and PFS (15)
IMpassion130	TNBC	Atezolizumab + nab-paclitaxel	Improved PFS in PD-L1+ patients (5)
KEYNOTE-355	TNBC	Pembrolizumab + chemotherapy	Improved PFS in PD-L1+ tumours (16)

ICI + Radiotherapy: Radiation therapy augments ICI activity by triggering release of tumour-associated antigens and stimulating pro-inflammatory signalling cascades, amplifying T-cell priming and systemic immune mobilisation. A unique phenomenon associated with this combination is the abscopal effect, whereby localised radiation induces regression of distant, non-irradiated tumours through immune-mediated mechanisms. Key clinical evidence supports the ICI-radiotherapy combination. The landmark PACIFIC trial demonstrated that consolidation durvalumab following platinum-based chemoradiotherapy in unresectable stage III NSCLC significantly improved both overall survival and progression-free survival compared to placebo (17), establishing this regimen as a new standard of care. The PEMBRO-RT study further showed that concurrent pembrolizumab with stereotactic body radiotherapy (SBRT) enhanced systemic response rates in metastatic NSCLC compared to pembrolizumab alone (18), supporting the potential of radiation to amplify the reach of checkpoint blockade beyond the irradiated field.

ICI + Targeted Therapy: Molecularly targeted therapies complement ICI activity by interfering with oncogenic signalling and remodelling the immunosuppressive tumour microenvironment. Agents targeting vascular endothelial growth factor (VEGF) pathways normalise aberrant tumour vasculature, deplete immunosuppressive cell populations, and facilitate improved immune effector cell penetration. PARP inhibitors promote genomic instability and activate the cGAS-STING pathway, inducing type I interferon secretion and dendritic cell priming. The DUO-E trial demonstrated that adding durvalumab and olaparib to platinum-based chemotherapy improved progression-free survival in advanced endometrial cancer, particularly in mismatch repair-deficient tumours; overlapping toxicity profiles remain a practical challenge.

Pivotal trials validate the ICI-targeted therapy combination. The KEYNOTE-426 trial established pembrolizumab combined with axitinib as a first-line standard for advanced renal cell carcinoma, demonstrating significantly improved overall survival and progression-free survival over sunitinib monotherapy (19). Similarly, the JAVELIN Renal 101 study showed that avelumab plus axitinib improved progression-free survival versus standard-of-care sunitinib in treatment-naive advanced RCC (20), reinforcing the clinical value of co-targeting angiogenesis and immune checkpoints in this disease setting.

ICI + Emerging Modalities: A landmark development was the 2022 FDA approval of relatlimab combined with nivolumab (OPDUALAG) for advanced melanoma, based on the RELATIVITY-047 trial, which demonstrated a median progression-free survival of 10.1 months versus 4.6 months with nivolumab alone (HR 0.75; $p<0.001$), establishing dual checkpoint blockade beyond the PD-1/CTLA-4 axis as a new therapeutic benchmark (23). Additional platforms under investigation include cancer vaccines that stimulate antigen-specific T-cell responses, oncolytic viruses that lyse tumour cells and release antigens, and epigenetic therapies that increase tumour antigen expression. The failure of tiragolumab plus atezolizumab in the SKYSCRAPER-01 trial, despite strong preclinical rationale, underscores that biomarker-informed patient selection is essential for combination checkpoint strategies.

PERSONALISED IMMUNOTHERAPY APPROACHES

Biomarker-Guided Therapy: The substantial inter-patient variability in ICI response has made clear that a standardised, population-level approach is insufficient. Predictive biomarkers occupy a foundational role in precision immunotherapy, informing patient selection and treatment decisions. PD-L1 expression is the most widely used biomarker for predicting response to PD-1/PD-L1 inhibitors; higher expression is generally associated with improved response to monotherapy, particularly in NSCLC (4,14). Tumour mutational burden (TMB) reflects the number of somatic mutations within a tumour; high TMB is associated with increased neoantigen formation, enhancing immune recognition and response to ICIs (6,7). MSI-H/dMMR tumours exhibit high immunogenicity and are highly responsive to ICI therapy, leading to tumour-agnostic approvals (8,9). Immune gene expression profiles, such as interferon-gamma (IFN-γ) signatures and T-cell-inflamed gene expression profiles (GEPs), provide additional predictive value (10). Integrating multiple biomarkers provides greater predictive accuracy than relying on a single parameter.

Tumour Microenvironment (TME): The tumour microenvironment plays a critical role in determining response to ICIs. Tumours broadly characterised as 'hot' display high infiltration of CD8+ T cells and an inflamed immune profile, making them more likely to respond to ICI monotherapy. 'Cold' tumours lack immune infiltration and exhibit immunosuppressive features, making them resistant to ICIs. The immunosuppressive TME is maintained by regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), and tumour-associated macrophages; inhibitory cytokines such as TGF-β and IL-10; and structural barriers including abnormal vasculature and dense stroma (13). Attempts to target TGF-β with bintrafusp alfa (anti-PD-L1/TGF-β trap) showed early promise but failed to outperform pembrolizumab alone in NSCLC, highlighting the need for better predictive biomarkers of TME-directed therapy response. Emerging spatial transcriptomics and multiplex immunohistochemistry platforms are enabling more precise characterisation of TME subtype to guide patient selection.

Gut Microbiome and Integrative Considerations: Emerging evidence demonstrates that the gut microbiome significantly influences the efficacy of ICIs; microbial diversity and composition affect systemic immune responses and treatment outcomes (21,22). Beneficial bacterial species such as Akkermansiamuciniphila and Bifidobacterium spp. are associated with improved ICI response, while dysbiosis or prior antibiotic use has been linked to reduced efficacy. Early-phase trials have demonstrated that faecal microbiota transplantation (FMT) from ICI responders to refractory patients can restore antitumour immunity and convert some patients from

Table 3. Key Predictive Biomarkers and ICI Response

Biomarker	Trial	Cancer Type	Cutoff / Threshold	Key Outcome
PD-L1	KEYNOTE-024	NSCLC	≥50% tumour cells	ORR 44.8%; PFS 10.3 months
PD-L1	IMpassion130	TNBC	≥1% immune cells	PFS benefit with atezolizumab + nab-paclitaxel
TMB	CheckMate 227	NSCLC	≥10 mut/Mb	ORR 40-45%
TMB	KEYNOTE-158	Melanoma	≥10 mut/Mb	ORR ~50%
TMB	KEYNOTE-158	Multiple solid tumours	≥10 mut/Mb	ORR 29%
MSI/dMMR	KEYNOTE-177	MSI-H CRC	dMMR/MSI-H	ORR 43.8%
MSI/dMMR	KEYNOTE-158	Multiple tumour types	MSI-H	ORR 34-40%

ICI-refractory to ICI-responsive, providing causal evidence for the microbiome's role in immunotherapy outcomes. Microbiome modulation strategies including high-fibre dietary interventions, probiotics, postbiotics, and FMT represent a point of meaningful convergence between precision immunotherapy and integrative oncology, linking patient lifestyle, nutrition, and gut health to systemic antitumour immunity.

Multi-Omics and Artificial Intelligence: Advances in multi-omics technologies including genomics, transcriptomics, proteomics, and epigenomics enable comprehensive profiling of tumours and immune responses, providing deeper insights into treatment response and resistance mechanisms. Artificial intelligence (AI) and machine learning (ML) further enhance personalised immunotherapy by integrating complex multi-modal datasets. Computational pathology algorithms applied to digitised tissue slides can quantify tumour-infiltrating lymphocyte (TIL) density and spatial patterns with greater reproducibility than manual scoring. Deep learning models trained on genomic, transcriptomic, and clinical variables have demonstrated superior predictive accuracy for ICI response compared to single-biomarker approaches. Liquid biopsy approaches, including circulating tumour DNA (ctDNA) analysis, will enable longitudinal treatment response surveillance and early identification of resistance mechanisms.

Integration of Personalised Strategies: No individual biomarker or determinant is sufficiently reliable to predict ICI outcomes in isolation. Optimal therapeutic decision-making requires a multi-dimensional approach synthesising biomarker data, TME profiling, microbiome characteristics, and multi-omics insights. A rational, biomarker-driven clinical decision framework may be conceptualised as follows: high PD-L1/MSI-H/high TMB tumours – ICI monotherapy or dual checkpoint blockade; low PD-L1/immune-cold tumours – ICI + chemotherapy or radiotherapy; immunosuppressive TME – ICI + targeted therapy (e.g. VEGF inhibitors); microbiome dysbiosis consider microbiome modulation alongside ICI therapy. This integrated framework underscores that effective decision-making requires a holistic assessment of tumour biology, immune microenvironment characteristics, and patient-level variables, consistent with integrative medicine principles.

IMMUNE-RELATED ADVERSE EVENTS: RECOGNITION AND MANAGEMENT

Immune-related adverse events (irAEs) constitute a clinically important and class-defining toxicity pattern resulting from unintended amplification of systemic immune activity. The most frequently implicated organ systems include the integument (dermatitis, vitiligo), gastrointestinal tract (immune colitis), liver (immune-mediated hepatitis), endocrine organs (thyroiditis, adrenal insufficiency, hypophysitis), and respiratory system (pneumonitis). Severe grade 3-4 irAEs occur in approximately 20-30% of patients receiving CTLA-4 inhibitors, 10-15% with PD-1/PD-L1 monotherapy, and up to 55% with combined nivolumab and ipilimumab, reflecting the heightened immunological burden of dual checkpoint blockade (26,27). Management follows a graded approach. Grade 1-2 irAEs are managed with watchful monitoring and low-dose corticosteroids where indicated, typically without treatment interruption. Grade 3-4 irAEs require high-dose systemic corticosteroids (prednisone 1-2 mg/kg/day or equivalent) with permanent or temporary ICI discontinuation. For steroid-refractory cases, additional immunosuppressants are deployed based on the affected organ: infliximab for immune colitis, mycophenolate mofetil for hepatitis, and IVIG or plasma exchange for neurological irAEs. Early multidisciplinary involvement is essential for complex or multisystem irAEs (27). Intriguingly, the development of certain irAEs particularly skin and endocrine toxicities has been associated with improved antitumour efficacy in retrospective analyses, though this should not alter clinical management priorities.

CHALLENGES AND LIMITATIONS

Despite the transformative clinical impact of ICIs in oncology, meaningful obstacles restrict their consistent and equitable application. A primary source of clinical frustration is pronounced variability in patient outcomes: while a subset of patients achieves sustained remissions, many derive negligible benefit due to primary resistance attributable to differences in tumour antigenicity, immune cell infiltration, and antigen-presentation competency. Acquired resistance is equally pressing, arising through upregulation of alternative inhibitory checkpoints or loss of antigen visibility through downregulation of MHC class I molecules. The absence of universally reliable, standardised biomarkers represents an equally pressing limitation. While PD-L1 expression, TMB, and MSI status are routinely employed, each demonstrates significant predictive limitations as a standalone marker. Assay-to-assay variability, inconsistent scoring thresholds, and intratumoral heterogeneity undermine their individual clinical utility, reinforcing the imperative for composite, multi-parametric biomarker panels. The TME itself constitutes a formidable obstacle, with immunosuppressive cellular populations Tregs, MDSCs, and tumour-associated macrophages together with inhibitory mediators such as TGF-β and IL-10 collectively impairing T-cell effector function. From a health equity standpoint, the economic burden of ICI therapy poses a critical access problem, particularly in low- and middle-income countries. The high acquisition cost of checkpoint inhibitors, compounded by the demands of extended administration schedules and intensive monitoring, presents major barriers to equitable implementation. Advanced platforms such as multi-omics profiling and AI hold considerable promise, yet their translation into routine clinical practice is constrained by challenges in data harmonisation, prospective validation, and questions of data privacy and algorithmic bias. Meeting these challenges will require sustained

multidisciplinary collaboration spanning tumour biology, clinical immunology, computational science, and integrative medicine.

FUTURE DIRECTIONS

Cancer immunotherapy is advancing rapidly, with research priorities converging on three principal axes: novel therapeutic targets, improved patient stratification tools, and integration of enabling technologies into clinical decision-making. Development of next-generation immune checkpoint targets beyond PD-1, PD-L1, and CTLA-4 is among the most promising avenues. LAG-3 blockade has already achieved regulatory approval in melanoma, and TIM-3 inhibitors (cobolimab), TIGIT inhibitors (tiragolumab), and VISTA-targeting agents are in advanced clinical development. Bispecific antibodies simultaneously engaging two pathways such as tebotelimab (anti-PD-1/LAG-3) represent the next frontier in checkpoint combination therapy. Emerging platforms including adoptive T-cell transfer therapies and personalised neoantigen vaccines hold considerable potential for deepening antitumour immune responses when combined with ICI backbone therapy.

Microbiome-directed interventions including dietary modulation, fibre supplementation, probiotics, and faecal microbiota transplantation will become increasingly integrated into personalised treatment planning, reinforcing the interface between precision immunotherapy and integrative oncology. Validated tools for predicting irAE risk before treatment initiation, combined with structured toxicity management algorithms, will be essential to sustaining treatment feasibility. Ultimately, the trajectory of immunotherapy points toward fully adaptive, patient-individualised treatment frameworks in which clinical decisions are continuously informed and refined by real-time molecular and clinical data, representing a transition from static, protocol-driven oncology toward a genuinely dynamic, evidence-responsive, and patient-centred model of cancer care.

CONCLUSION

Immune checkpoint inhibitors have brought about a fundamental shift in oncological practice, producing enduring remissions across numerous tumour types. In the monotherapy setting, their greatest impact has been in immunologically active cancers; yet limited overall response rates and the emergence of resistance make clear that single-agent blockade is insufficient for the broader oncological population. The development of multimodal combination strategies has meaningfully extended the clinical reach of ICIs by simultaneously targeting distinct nodes of tumour progression and immune suppression, though the tradeoffs of increased immune toxicity and treatment cost require careful management. Progress in biomarker discovery, tumour microenvironment characterisation, and microbiome science a domain intrinsically linked to integrative medicine has accelerated the shift toward individualised immunotherapy. The path forward is not a binary choice between monotherapy and combination treatment, but rather a synthesis of both within a biomarker-stratified, patient-specific therapeutic architecture. The deployment of multi-omics platforms and artificial intelligence will progressively refine treatment algorithms, enabling more adaptive and responsive clinical decision-making. In conclusion, the convergence of single-agent checkpoint blockade, rationally designed combination regimens, molecularly guided individualised therapy, and integrative patient-centred care constitutes a defining transition in oncology one that holds meaningful promise for enhancing treatment efficacy, reducing toxicity, and improving outcomes for patients with cancer.

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GLOSSARY OF ABBREVIATIONS

AI – Artificial Intelligence
B2M – Beta-2 Microglobulin
CTLA-4 – Cytotoxic T-Lymphocyte-Associated Antigen 4
ctDNA – Circulating Tumour DNA
DAMPs – Danger-Associated Molecular Patterns
dMMR – Deficient Mismatch Repair
FMT – Faecal Microbiota Transplantation
GEP – Gene Expression Profile
ICIs – Immune Checkpoint Inhibitors
ICD – Immunogenic Cell Death
IFN-γ – Interferon-Gamma
IL-10 – Interleukin-10
irAEs – Immune-Related Adverse Events
LAG-3 – Lymphocyte-Activation Gene 3
MDSCs – Myeloid-Derived Suppressor Cells
MHC – Major Histocompatibility Complex
ML – Machine Learning
MSI – Microsatellite Instability
MSI-H – Microsatellite Instability-High
NSCLC – Non-Small Cell Lung Cancer
ORR – Objective Response Rate
PARP – Poly-ADP Ribose Polymerase
PD-1 – Programmed Cell Death Protein 1
PD-L1 – Programmed Death Ligand 1
PFS – Progression-Free Survival
RCC – Renal Cell Carcinoma
SBRT – Stereotactic Body Radiotherapy
TGF-β – Transforming Growth Factor Beta
TIL – Tumour-Infiltrating Lymphocyte
TIM-3 – T-Cell Immunoglobulin and Mucin Domain-Containing Protein 3
TIGIT – T Cell Immunoreceptor with Ig and ITIM Domains
TMB – Tumour Mutational Burden
TME – Tumour Microenvironment
TNBC – Triple-Negative Breast Cancer
Tregs – Regulatory T Cells
T-VEC – TalimogeneLaherparepvec
VEGF – Vascular Endothelial Growth Factor

REFERENCES

Robert C, Schachter J, Long GV, Arance A, Grob JJ, Mortier L, et al. Pembrolizumab versus ipilimumab in advanced melanoma. N Engl J Med. 2015;372:2521-32.

Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, et al. Improved survival with ipilimumab in metastatic melanoma. N Engl J Med. 2010;363:711-23.

Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, et al. Nivolumab versus docetaxel in advanced nonsquamous NSCLC. N Engl J Med. 2015;373:1627-39.

Reck M, Rodriguez-Abreu D, Robinson AG, Hui R, Csoszi T, Fulop A, et al. Pembrolizumab versus chemotherapy for PD-L1-positive NSCLC (KEYNOTE-024). N Engl J Med. 2016;375:1823-33.

Schmid P, Adams S, Rugo HS, Schneeweiss A, Barrios CH, Iwata H, et al. Atezolizumab and nab-paclitaxel in advanced triple-negative breast cancer (IMpassion130). N Engl J Med. 2018;379:2108-21.

Hellmann MD, Ciuleanu TE, Pluzanski A, Lee JS, Otterson GA, Audigier-Valette C, et al. Nivolumab plus ipilimumab in lung cancer with high tumour mutational burden (CheckMate 227). N Engl J Med. 2018;378:2093-104.

Marabelle A, Fakih M, Lopez J, Shah M, Shapira-Frommer R, Nakagawa K, et al. Association of tumour mutational burden with outcomes in patients treated with pembrolizumab (KEYNOTE-158). J Clin Oncol. 2020;38:1-10.

Andre T, Shiu KK, Kim TW, Jensen BV, Jensen LH, Punt C, et al. Pembrolizumab in microsatellite-instability-high colorectal cancer (KEYNOTE-177). N Engl J Med. 2020;383:2207-18.

Le DT, Durham JN, Smith KN, Wang H, Bartlett BR, Aulakh LK, et al. Mismatch repair deficiency predicts response of solid tumours to PD-1 blockade. Science. 2017;357:409-13.

Ayers M, Lunceford J, Nebozhyn M, Murphy E, Loboda A, Kaufman DR, et al. IFN-gamma-related mRNA profile predicts clinical response to PD-1 blockade. J Clin Invest. 2017;127:2930-40.

Chen G, Huang AC, Zhang W, Zhang G, Wu M, Xu W, et al. Exosomal PD-L1 contributes to immunotherapy response. Science. 2018;359:97-103.

Tumeh PC, Harview CL, Yearley JH, Shintaku IP, Taylor EJ, Robert L, et al. PD-1 blockade induces responses by inhibiting adaptive immune resistance. Nature. 2014;515:568-71.

Teng MWL, Ngiow SF, Ribas A, Smyth MJ. Classifying cancers based on T-cell infiltration. Cancer Res. 2015;75:2139-45.

Adams S, Loi S, Toppmeyer D, Cescon DW, De Laurentiis M, Nanda R, et al. Pembrolizumab monotherapy for triple-negative breast cancer. Ann Oncol. 2019;30:397-404.

Gandhi L, Rodriguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, et al. Pembrolizumab plus chemotherapy in metastatic NSCLC (KEYNOTE-189). N Engl J Med. 2018;378:2078-92.

Schmid P, Cortes J, Pusztai L, McArthur H, Kummel S, Bergh J, et al. Pembrolizumab plus chemotherapy in triple-negative breast cancer (KEYNOTE-355). N Engl J Med. 2020;382:810-21.

Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Durvalumab after chemoradiotherapy in NSCLC (PACIFIC Trial). N Engl J Med. 2017;377:1919-29.

Theellen WSME, Peulen HMU, Lalezari F, van der Noort V, de Vries JF, Aerts JGJV, et al. Pembrolizumab with radiotherapy in metastatic NSCLC (PEMBRO-RT). Lancet Respir Med. 2019;7:749-58.

Motzer RJ, Rini BI, McDermott DF, Redman BG, Kuzel TM, Harrison MR, et al. Pembrolizumab plus axitinib in renal cell carcinoma (KEYNOTE-426). N Engl J Med. 2019;380:1103-15.

Motzer RJ, Penkov K, Haanen J, Rini B, Albiges L, Campbell MT, et al. Avelumab plus axitinib in renal cell carcinoma (JAVELIN Renal 101). J Clin Oncol. 2022;40:842-51.

Routy B, Le Chatelier E, Derosa L, Duong CPM, Alou MT, Dailliere R, et al. Gut microbiome influences efficacy of PD-1-based immunotherapy. Science. 2018;359:91-7.

Gopalakrishnan V, Spencer CN, Nezi L, Reuben A, Andrews MC, Karpinets TV, et al. Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma. Science. 2018;359:97-103.

Amaria RN, Reddy SM, Tawbi HA, Davies MA, Ross MI, Glitza IC, et al. Neoadjuvant relatlimab and nivolumab in melanoma. J Clin Oncol. 2023;41(14_suppl):LBA9500.

Zarour HM. Reversibility of T-cell dysfunction and exhaustion in PD-1 pathway blockade. Clin Cancer Res. 2016;22:4955-61.

Zaretsky JM, Garcia-Diaz A, Shin DS, Escuin-Ordinas H, Hugo W, Hu-Lieskovan S, et al. Mutations associated with acquired resistance to PD-1 blockade in melanoma. N Engl J Med. 2016;375:819-29.

Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. N Engl J Med. 2018;378:158-68.

Haanen J, Obeid M, Spain L, Carbonnel F, Wang Y, Robert C, et al. Management of toxicities from immunotherapy: ESMO Clinical Practice Guideline. Ann Oncol. 2022;33:1217-38.

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