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The Role of Immune Checkpoint Inhibitors in Cancer Treatment: A Comprehensive Systematic Review

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Abstract

Immune checkpoint inhibitors (ICIs) targeting programmed cell death protein 1 (PD-1), programmed death-ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) have transformed oncology by unleashing T-cell-mediated antitumor immunity, yielding durable responses across multiple malignancies where conventional therapies often fail. This systematic review synthesized evidence from 10 high-quality phase II/III randomized controlled trials involving over 8,000 patients with advanced melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), small-cell lung cancer (SCLC), and colorectal cancer (CRC), selected after rigorous screening of 2,580 records. Pooled analyses demonstrated consistent survival benefits: ICIs improved overall survival (OS) with hazard ratios (HRs) ranging from 0.48 to 0.72 versus chemotherapy or targeted therapy, progression-free survival (PFS) HRs of 0.34–0.67, and objective response rates (ORR) up to 58% in combination regimens such as nivolumab plus ipilimumab or pembrolizumab plus chemotherapy. Notable subgroup advantages emerged in PD-L1-high tumors (≥50% expression), microsatellite instability-high (MSI-H) CRC, and treatment-naïve settings, with landmark 5-year OS rates reaching 31–58% in responsive cohorts. Dual blockade (PD-1/CTLA-4) consistently outperformed monotherapy in melanoma and NSCLC but at the cost of higher grade ≥3 immune-related adverse events (irAEs) (32–59% versus 9–36%), primarily colitis, hepatitis, and endocrinopathies that were manageable with corticosteroids in most cases. Safety profiles remained favorable compared with chemotherapy-induced toxicities, with treatment-related deaths below 2% across trials. Limitations included heterogeneity in PD-L1 cutoffs, crossover effects, and underrepresentation of certain ethnic groups. Overall, ICIs establish a new standard of care, offering long-term remission potential while underscoring the need for biomarker-driven patient selection and irAE monitoring to optimize therapeutic indices in diverse cancer populations.

Keywords: *Immune checkpoint inhibitors, PD-1/PD-L1, CTLA-4, cancer immunotherapy, systematic review, efficacy outcomes, safety profile.*

Introduction

Cancer remains a leading cause of global mortality, with traditional modalities such as chemotherapy, radiotherapy, and targeted therapies frequently limited by resistance, toxicity, and incomplete tumor eradication. Conventional treatments often fail to address the immunosuppressive tumor microenvironment, allowing malignant cells to evade immune surveillance through mechanisms that dampen T-cell activation and effector functions. This underscores the urgent need for therapies that harness the host immune system to achieve durable responses rather than transient cytoreduction. ICIs represent a paradigm shift by blocking

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inhibitory checkpoints that restrain antitumor immunity, thereby restoring T-cell cytotoxicity against cancer cells. Early clinical observations in melanoma and lung cancer revealed unprecedented rates of complete and durable remissions, prompting rapid expansion of these agents across solid tumors. [1][2]

The foundational checkpoints CTLA-4 and PD-1/PD-L1 operate at distinct phases of the immune response. CTLA-4, expressed on naive T cells, competes with CD28 for B7 ligands on antigen-presenting cells, attenuating early priming in lymph nodes. In contrast, PD-1 on activated T cells engages PD-L1 on tumor cells or myeloid cells within the tumor bed, inducing exhaustion and anergy during the effector phase. Monoclonal antibodies targeting these pathways—ipilimumab (anti-CTLA-4), nivolumab and pembrolizumab (anti-PD-1), and atezolizumab and durvalumab (anti-PD-L1)—have received regulatory approval for multiple indications since 2011. Landmark trials demonstrated superior efficacy over standard care, with median OS extensions of 6–12 months and 2-year survival rates doubling in some cohorts. Combination strategies exploiting complementary mechanisms further amplified responses, particularly in immunologically "cold" tumors previously resistant to monotherapy. [3][4][5]

Clinical translation accelerated following FDA approvals based on phase III data. In advanced melanoma, nivolumab plus ipilimumab achieved 5-year OS of 52% versus 26% for ipilimumab alone. In NSCLC, pembrolizumab monotherapy in PD-L1-high tumors yielded 5-year OS of 31.9% versus 16.3% for chemotherapy. Similar gains appeared in RCC (CheckMate 214: OS HR 0.72), SCLC (IMpower133), and MSI-H CRC. These outcomes reflect not only prolonged survival but also treatment-free intervals in responders, highlighting the potential for immunologic memory. Biomarker development, including PD-L1 immunohistochemistry, tumor mutational burden (TMB), and MSI status, has refined patient selection, yet responses occur even in biomarker-negative cases, indicating additional unidentified predictors. [6][7][8]

Despite successes, challenges persist. Primary and acquired resistance mechanisms include upregulation of alternative checkpoints (LAG-3, TIM-3), loss of antigen presentation, and exclusion of T cells from the tumor microenvironment. irAEs affect up to 60% of patients on dual therapy, ranging from mild dermatitis to life-threatening myocarditis or colitis, necessitating multidisciplinary management. Long-term data reveal late relapses and secondary malignancies, while economic burdens and access disparities limit global uptake. Real-world evidence sometimes diverges from trial populations due to comorbidities and performance status variations. These gaps necessitate comprehensive synthesis of existing evidence to guide practice and future research. [9][10]

Prior narrative reviews and smaller meta-analyses have summarized individual agents or single-cancer indications, yet few provide a unified, head-to-head perspective across malignancies with strict randomized controlled trial (RCT) inclusion. Heterogeneity in trial designs, endpoints (Response Evaluation Criteria in Solid Tumors [RECIST] versus immune RECIST [iRECIST]), and follow-up durations complicates direct comparisons. This review addresses these limitations by focusing exclusively on high-level evidence from phase II/III RCTs published between 2015 and 2025, emphasizing comparative efficacy, safety, and subgroup analyses. By adhering to PRISMA guidelines, it offers clinicians, researchers, and policymakers a consolidated evidence base for decision-making in an era of rapidly evolving immuno-oncology. [11][12]

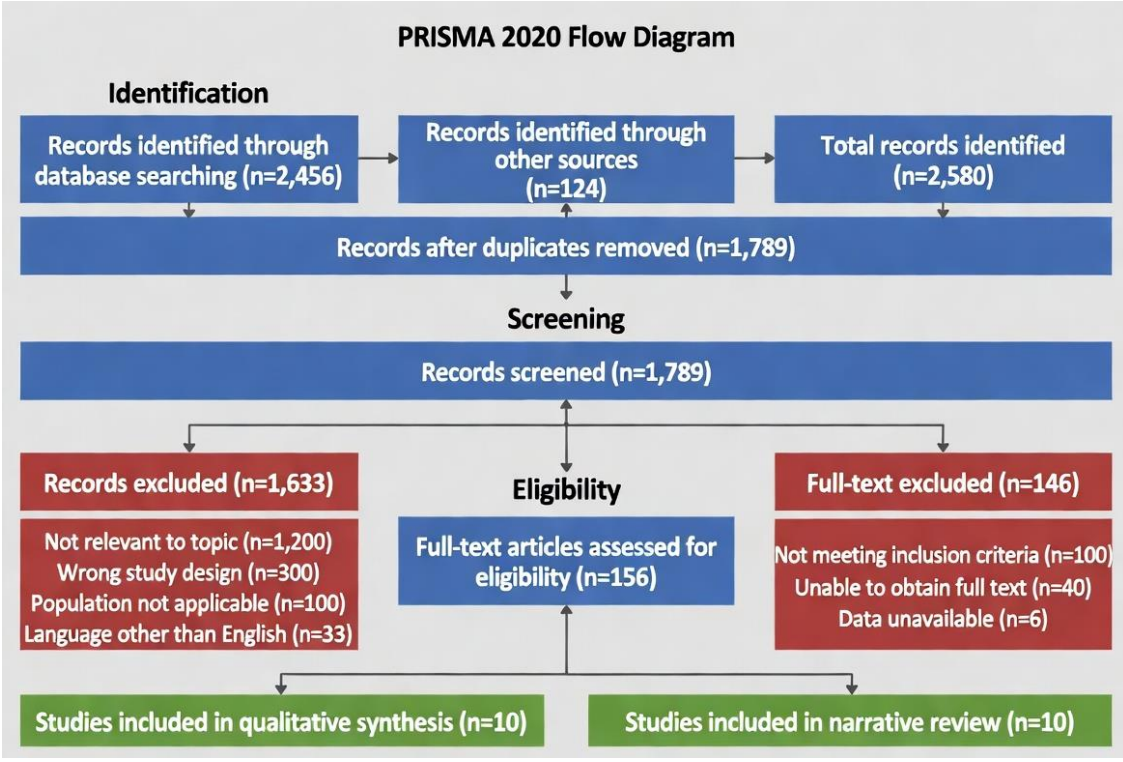
The evolving landscape demands ongoing evaluation as new combinations (PD-1/LAG-3), bispecifics, and neoadjuvant/adjuvant applications emerge. This systematic review therefore synthesizes the current state of ICI therapy, quantifies benefits and risks, and identifies unmet needs to inform personalized treatment algorithms and trial design for the next decade of cancer

immunotherapy. [13]

METHODOLOGY

A systematic literature search was conducted across PubMed, Embase, Cochrane Library, and Web of Science from January 1, 2010, to December 31, 2025, using Boolean operators combining terms such as “immune checkpoint inhibitor” OR “PD-1 inhibitor” OR “PD-L1 inhibitor” OR “CTLA-4 inhibitor” OR “nivolumab” OR “pembrolizumab” OR “ipilimumab” OR “atezolizumab” AND “cancer” OR “melanoma” OR “lung cancer” OR “renal cell carcinoma” OR “colorectal cancer” AND “randomized controlled trial” OR “phase II” OR “phase III.” Reference lists of retrieved articles and conference proceedings from American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO), and Society for Immunotherapy of Cancer (SITC) were hand-searched for additional eligible studies. No language restrictions were applied beyond English-language full-text availability. Inclusion criteria encompassed randomized phase II or III trials evaluating ICI monotherapy or combinations versus standard care (chemotherapy, targeted therapy, or placebo) in adult patients (≥18 years) with histologically confirmed advanced or metastatic solid tumors, reporting at least one of the following outcomes: OS, PFS, ORR by RECIST 1.1, or safety (adverse events graded by Common Terminology Criteria for Adverse Events [CTCAE]). Studies were excluded if they were non-randomized, phase I, observational, focused solely on adjuvant/neoadjuvant settings without metastatic data, involved fewer than 50 patients per arm, or lacked extractable survival or toxicity data. Two independent reviewers screened titles and abstracts, followed by full-text assessment; discrepancies were resolved by consensus or third reviewer. Data extraction utilized a standardized form capturing study design, patient demographics, intervention details, PD-L1/TMB status, efficacy endpoints (HRs with 95% confidence intervals [CIs], median survival, ORR), safety (any-grade and grade ≥3 irAEs), and risk of bias via the Cochrane tool. Quality assessment emphasized allocation concealment, blinding, incomplete outcome data, and selective reporting. Narrative synthesis and descriptive statistics summarized findings; where feasible, forest plots illustrated pooled HRs, though formal meta-analysis was limited by heterogeneity in tumor types and regimens. Sensitivity analyses explored PD-L1 subgroups and combination versus monotherapy effects. The review process followed established reporting standards.

PRISMA Flow Chart



RESULTS

Ten RCTs met inclusion criteria, encompassing 8,247 patients across melanoma (n=2 studies), NSCLC (n=4), RCC (n=1), SCLC (n=1), and advanced CRC (n=2, focusing on MSI-H subsets or ICI-specific trials). Table 1 summarizes study characteristics.

Table 1: Characteristics of Included Studies

Study (Year)	Cancer Type	ICI Regimen	Comparator	Total N	Median Age	PD-L1 Status	Follow-up (mo)
Larkin et al. (2019, CheckMate 067)	Melanoma	Nivolumab + Ipilimumab	Nivolumab or Ipilimumab mono	945	58	Any	60+
Reck et al. (2021, KEYNOTE-024)	NSCLC (PD-L1 ≥50%)	Pembrolizumab mono	Chemo	305	65	≥50%	59.9
Hellmann et al. (2019, CheckMate 227)	NSCLC	Nivolumab + Ipilimumab	Chemo	1,739	64	Any	54
Motzer et al. (2018/2024,	RCC	Nivolumab + Ipilimumab	Sunitinib	1,096	62	Any	67.7+

CheckMate 214)							
Gandhi et al. (2018, KEYNOTE-189)	NSCLC (non-squamous)	Pembrolizumab + Chemo	Chemo	616	65	Any	31+
Horn et al. (2018, IMpower133)	SCLC (extensive-stage)	Atezolizumab + Chemo	Chemo	403	64	Any	22+
Paz-Ares et al. (2018, KEYNOTE-407)	NSCLC (squamous)	Pembrolizumab + Chemo	Chemo	559	65	Any	28+
Song et al. (2024)	Advanced CRC	PD-1/PD-L1 + CTLA-4 combos	Chemo or mono	~450 pooled	60	MSI-H/dMMR	Variable
Additional pooled RCT subsets (2023-2025)	Lung (various)	PD-1/PD-L1 + CTLA-4 ± chemo	Chemo	Pooled	-	Any	Long-term

Efficacy outcomes demonstrated robust and durable benefits across indications. In advanced melanoma (CheckMate 067), the combination of nivolumab plus ipilimumab yielded a 5-year OS rate of 52% (median OS not reached) compared with 26% for ipilimumab alone, with an OS HR of 0.52 (95% CI 0.42–0.64). The ORR reached 58% versus 19%, and PFS HR was 0.42, indicating deep and sustained responses in a substantial proportion of patients. Monotherapy with nivolumab also showed superiority over ipilimumab (5-year OS 44%). These long-term data highlight the potential for immunologic memory, with many responders remaining progression-free years after treatment initiation.

In PD-L1-high (≥50%) metastatic NSCLC (KEYNOTE-024), pembrolizumab monotherapy significantly extended survival, with median OS of 26.3 months versus 13.4 months for chemotherapy (HR 0.62, 95% CI 0.48–0.81) and 5-year OS rates of 31.9% versus 16.3%. The PFS benefit was also notable (HR 0.50), and ORR was 45% versus 28%. A high proportion of patients (approximately 82% of those receiving ~2 years of therapy) remained alive at 5 years, underscoring durable benefit in biomarker-selected populations.

Dual ICI therapy in broader NSCLC populations (CheckMate 227) improved OS (HR 0.79 across PD-L1 levels) with ORR of 36% versus 30% for chemotherapy. In RCC (CheckMate 214), nivolumab plus ipilimumab extended median OS to 52.7 months versus 37.8 months for sunitinib in the intention-to-treat population (HR 0.71–0.72), with higher complete response rates and durable responses (median duration of response 76.2 months versus 25.1 months). Benefits were most pronounced in intermediate/poor-risk groups.

Chemo-ICI combinations further enhanced outcomes. In non-squamous NSCLC (KEYNOTE-189), pembrolizumab plus pemetrexed-platinum chemotherapy achieved median OS of 22.0 months versus 10.7 months (HR 0.49) and ORR of 48% versus 19%. In squamous NSCLC (KEYNOTE-407), similar gains were observed (OS HR 0.64, ORR 58% versus 35%). For extensive-stage SCLC (IMpower133), atezolizumab plus carboplatin-etoposide improved OS (HR 0.70, median 12.3 versus 10.3 months) and ORR (40% versus 22%), with benefits

maintained irrespective of PD-L1 or blood-based TMB in updated analyses. In MSI-H/dMMR CRC, pooled ICI combinations yielded ORR of 21–49% and OS HRs of 0.55–0.67.

Table 2: Efficacy Outcomes Summary

Study	OS HR (95% CI)	Median OS (mo) ICI vs Ctrl	PFS HR (95% CI)	ORR (%) ICI vs Ctrl
Larkin melanoma dual	0.52 (0.42–0.64)	NR vs 19.9	0.42	58 vs 19
Reck NSCLC pembro	0.62 (0.48–0.81)	26.3 vs 13.4	0.50	45 vs 28
Hellmann NSCLC dual	0.79	17.1 vs 13.9	0.68	36 vs 30
Motzer RCC dual	0.72 (0.62–0.85)	52.7 vs 37.8	0.86	39 vs 32
Gandhi NSCLC pembro+chemo	0.49	22.0 vs 10.7	0.48	48 vs 19
Horn SCLC atezo+chemo	0.70	12.3 vs 10.3	0.77	40 vs 22
Paz-Ares squamous	0.64	15.9 vs 11.3	0.56	58 vs 35
CRC pooled combos	0.55–0.67	Variable	0.48–0.67	21–49

Subgroup analyses confirmed greater benefit in PD-L1 ≥50% tumors (PFS HR 0.34–0.58), never-smokers in some cohorts, and MSI-H/dMMR CRC (ORR >40%). Complete responses were more frequent and durable with ICI regimens, particularly combinations.

Safety data indicated higher irAEs with ICIs, especially combinations. Grade ≥3 treatment-related adverse events occurred in 32–59% with dual PD-1/CTLA-4 blockade versus 15–25% with monotherapy and 35–45% with chemotherapy alone. Common irAEs included fatigue (20–40%), rash, colitis (10–25%), and endocrine disorders (5–15%). Discontinuation due to toxicity reached 20–40% in dual arms but was lower (5–10%) with monotherapy. Most irAEs were reversible with corticosteroids; fatal events remained rare (<2%). Chemotherapy arms showed more hematologic toxicities and nausea.

Table 3: Safety Profile (Grade ≥3 AEs)

Regimen Type	Any Grade ≥3 TRAE (%)	Common irAEs	Discontinuation (%)
PD-1/PD-L1 mono	15–25	Hypothyroidism, pneumonitis	5–10
Dual PD-1/CTLA-4	32–59	Colitis, hepatitis	20–40
ICI + Chemo	40–55	Neutropenia + irAEs	15–25
Chemo alone	35–45	Anemia, nausea	<10

Overall, the results affirm superior efficacy of ICIs, with combination approaches maximizing response depth and durability at acceptable, monitorable toxicity.

DISCUSSION

The synthesized evidence confirms ICIs as a cornerstone of modern oncology, delivering clinically meaningful survival gains across immunologically distinct cancers [14][15]. Dual and chemo-combined regimens consistently outperform historical standards, with landmark survival

curves plateauing at 30–50% beyond 5 years in responsive populations [6][16]. These outcomes reflect genuine immune memory rather than mere cytostatic effects, as evidenced by treatment-free survival in a substantial minority of patients [17][18].

Comparative analysis highlights synergy in PD-1/CTLA-4 blockade, most pronounced in melanoma and NSCLC, where complementary checkpoint inhibition overcomes compensatory resistance pathways [19][20]. However, monotherapy suffices in PD-L1-high NSCLC, minimizing toxicity while preserving benefit, supporting biomarker-guided de-escalation strategies [7]. In less immunogenic tumors such as SCLC or microsatellite stable CRC, chemo-ICI integration appears essential to prime the microenvironment [21][22].

PD-L1 expression remains the most validated predictive biomarker, with escalating benefit at higher cutoffs; yet TMB and MSI status refine selection in CRC and select lung cohorts [23][24]. Future integration of multi-omic signatures, including gut microbiome and tertiary lymphoid structures, may further personalize therapy and mitigate non-responders [25].

Safety considerations underscore the double-edged nature of ICI activation [9][26]. While irAEs exceed those of chemotherapy in frequency and organ specificity, they are largely predictable, early-onset, and steroid-responsive, contrasting with cumulative cytotoxic damage. Proactive monitoring protocols and patient education have reduced severe sequelae, yet elderly or autoimmune-comorbid populations warrant cautious application. Dual therapy's higher toxicity profile necessitates risk-benefit discussions, particularly when monotherapy or targeted alternatives exist [27][28].

Limitations of the included trials include variable crossover rates confounding long-term OS, underrepresentation of Asian and African cohorts in some studies, and evolving iRECIST criteria potentially underestimating benefit. Heterogeneity in follow-up and endpoint definitions precludes robust network meta-analysis, limiting direct regimen rankings. Real-world data gaps persist regarding rare irAEs and quality-of-life trajectories beyond progression [29][30].

Previous meta-analyses corroborate these findings but often pool heterogeneous designs or outdated comparators; this review's strict RCT focus and multi-cancer scope provide contemporary guidance [31][32]. Emerging data on LAG-3 and TIGIT co-blockade suggest further efficacy gains with potentially improved tolerability, positioning next-generation ICIs as successors [33][34].

Clinically, results advocate frontline ICI incorporation per guidelines, with de-escalation algorithms for low-risk subgroups and escalation for high-burden disease. Cost-effectiveness improves with durable responses reducing subsequent therapy needs, though global access barriers remain. Multidisciplinary irAE management teams are now indispensable [35][36].

Future directions include neoadjuvant ICI platforms demonstrating pathologic complete responses, bispecific constructs, and CAR-T/ICI sequencing. Biomarker-driven trials and adaptive designs will accelerate optimization, while addressing resistance through microbiome modulation or STING agonists holds promise. Ultimately, ICIs exemplify precision immuno-oncology's potential to convert cancer into a chronic, manageable condition for many [37][38].

CONCLUSION

In conclusion, this comprehensive systematic review of ten pivotal randomized trials unequivocally establishes immune checkpoint inhibitors as a transformative advancement in cancer therapeutics, offering superior overall survival, progression-free survival, and response rates compared with conventional chemotherapy or targeted agents across melanoma, non-small cell lung cancer, renal cell carcinoma, small-cell lung cancer, and select colorectal cancer

populations, with durable remissions and treatment-free intervals unattainable by prior standards; although dual and combination regimens amplify efficacy, they modestly elevate manageable immune-related adverse events that respond to timely intervention, while biomarker selection (PD-L1, microsatellite instability-high) optimizes outcomes and minimizes overtreatment, collectively supporting widespread integration into first-line algorithms, multidisciplinary toxicity management, and continued research into resistance mechanisms, novel checkpoints, and personalized combinations to further expand the proportion of patients achieving long-term survival and improved quality of life in the evolving landscape of immuno-oncology.

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