Review Article

Efficacy and Safety of CTLA-4, PD-1, and LAG-3 Immune Checkpoint Inhibitors as Monotherapy and Combination Therapy in Advanced Melanoma: A Systematic Review and Meta-Analysis

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Background: Advanced unresectable melanoma has a poor prognosis, with limited benefit from chemotherapy and low responsiveness to radiotherapy. Immune checkpoint inhibitors (ICIs) targeting PD-1, CTLA-4, and LAG-3 have significantly improved outcomes, but comparative efficacy and safety remain uncertain.

Aim: To systematically assess and compare the efficacy and safety of PD-1 and CTLA-4 monotherapies, and dual regimens including PD-1 + CTLA-4 and PD-1 + LAG-3, in patients with advanced unresectable melanoma.

Methods: A systematic search of PubMed and Cochrane CENTRAL was conducted on March 18, 2025. Eligible studies were randomised controlled trials comparing ICIs to conventional therapies or other ICI regimens. Primary outcomes included overall survival (OS), progression-free survival (PFS), objective response rate (ORR), and grade ≥3 adverse events (AEs). A random-effects meta-analysis was performed, and risk of bias was assessed using the Cochrane RoB 2.0 tool.

Results: Eleven trials (n = 4,111) were included. The PD-1 + CTLA-4 combination showed the strongest improvements in OS (HR = 0.59), PFS (HR = 0.45), and ORR (RR = 3.11), but with the highest toxicity (RR = 2.14 for grade ≥3 AEs). PD-1 + LAG-3 showed a moderate but significant efficacy advantage over PD-1 monotherapy (OS HR = 0.80) with improved tolerability. PD-1 monotherapy outperformed CTLA-4 monotherapy across all endpoints and had the lowest toxicity.

Conclusion: PD-1 + CTLA-4 provides the most substantial clinical benefit but with considerable toxicity. PD-1 + LAG-3 appears to offer a more balanced alternative. PD-1 monotherapy remains the safest option, though less effective than combination strategies.

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Introduction

Melanoma arises from the malignant transformation of melanocytes, which originate from the neural crest. They are not only limited to the skin but can also develop in other parts of the body where neural crest cells migrate, such as mucosal membranes, the brain, and the uveal tract of the eye. This transformation results from the accumulation of genetic mutations leading to uncontrolled proliferation of the malignant melanocytes. Contributing factors include genetic predisposition, ultraviolet radiation, and other environmental influences[1]. As a result, melanoma has become a global health concern, with more than 330,000 new cases and 58,000 deaths reported worldwide in 2022. Melanoma continues to rise in high-income regions like Australia, Europe, and North America[2].

Early diagnosis of melanoma at stage 0 or 1 is often curable with surgical resection, providing five-year survival rates in approximately 97% of patients. However, survival outcomes deteriorate significantly in the advanced stage of the disease (unresectable or metastatic melanoma); the five-year survival rate in advanced melanoma is around 30%[3][1].

Traditional treatments, such as chemotherapy (e.g., dacarbazine) and radiotherapy, have not provided consistent survival benefits in advanced unresectable melanoma, primarily serving palliative purposes[4]. The introduction of targeted therapies, including BRAF and MEK inhibitors, led to notable improvements in patients with specific mutations. However, these benefits are often short-lived due to acquired resistance, mainly through MAPK pathway reactivation or alternative survival mechanisms, resulting in disease progression[5].

Over the past decade, immune checkpoint inhibitors, particularly those targeting PD-1, CTLA-4, and LAG-3, have significantly improved overall and progression-free survival in patients with advanced unresectable melanoma. The immune system can recognize and eliminate abnormal cells, including tumours, through T-cell activation. This process requires two signals: antigen recognition via the T-cell receptor (TCR) and co-stimulation, typically through CD28 binding to CD80/CD86 on antigen-presenting cells (APCs). To avoid excessive immune activation, this process is regulated by immune checkpoints[6]. CTLA-4 (cytotoxic T-lymphocyte-associated protein-4) is an inhibitory receptor on activated T-cells that binds CD80/CD86 with higher affinity than CD28, blocking co-stimulation and dampening T-cell activation. CTLA-4 inhibitors (e.g., ipilimumab) are IgG1 monoclonal antibodies that block this interaction, allowing CD28-mediated signalling and full T-cell activation[7].

PD-1 (programmed cell death protein-1) is another inhibitory receptor on activated T-cells. It binds PD-L1 or PD-L2, which are often overexpressed on tumour and antigen-presenting cells. Persistent PD-1 signalling leads to T-cell exhaustion, marked by reduced proliferation, cytokine production, and cytotoxic activity, enabling tumour immune evasion. PD-1 inhibitors (e.g., nivolumab, pembrolizumab) are monoclonal antibodies that block PD-1, restoring T-cell function and enhancing tumour elimination[7].

All antigen-presenting cells (APCs), including dendritic cells, macrophages, and B-cells, express MHC class II molecules, which present extracellular antigens to CD4+ T-helper cells, leading to their activation. Upon recognizing an antigen–MHC-II complex via the T-cell receptor (TCR) and receiving co-stimulatory signals, CD4+ T-cells proliferate and secrete cytokines that drive broader immune responses, including B-cell antibody production and indirect activation of cytotoxic T-cells. Through these pathways, CD4+ T-cell activation contributes to the detection and elimination of abnormal cells, including tumours[8].

LAG-3 (lymphocyte activation gene-3) is an inhibitory receptor on activated T-cells. It binds MHC class II with higher affinity than CD4, delivering inhibitory signals that reduce T-cell proliferation, cytokine release, and effector function. In the tumour microenvironment, LAG-3 is often co-expressed with other inhibitory receptors like PD-1, and their combined activity leads to T-cell exhaustion and immune evasion[9]. LAG-3 inhibitors (e.g., relatlimab) are monoclonal antibodies that block this interaction, sustaining T-cell activation and enhancing anti-tumour responses[10].

Current evidence

Previous systematic reviews like Hao et al., 2017, Karlsson and Saleh[11] and Yun et al.[12]. assessed immune checkpoint inhibitors using interim results from early trials such as CheckMate 066 (Robert et al., 2015) and CheckMate 067[13]. However, updated long-term follow-up data, including outcomes up to 10 years, now provide more mature insights into safety and efficacy[14]. Earlier reviews also did not incorporate newer checkpoint inhibitors targeting LAG-3, such as relatlimab evaluated in the RELATIVITY-047 trial[15]. Therefore, a new, comprehensive systematic review is needed to assess and compare the safety and efficacy of immune checkpoint inhibitors in advanced melanoma.

Aim

This systematic review aims to evaluate and compare the efficacy (OS, PFS, ORR) and safety (grade ≥3 AEs) of immune checkpoint inhibitors, including PD-1 and CTLA-4 monotherapies, PD-1 + CTLA-4, and PD-1 + LAG-3 combinations in advanced unresectable melanoma.

Research Questions

- Do PD-1 or CTLA-4 inhibitor monotherapies provide better efficacy and safety compared to traditional therapies (e.g., chemotherapy, vaccines) in advanced unresectable melanoma?
- Does combination immune checkpoint blockade provide superior efficacy and safety compared with monotherapy?
- Is the PD-1 + LAG-3 combination more effective and better tolerated than the PD-1 + CTLA-4 combination?

Objectives

To address the research questions in this review, we will assess and compare the efficacy (OS, PFS, ORR) and safety (grade ≥3 AEs) of the following treatment regimens:

- CTLA-4 and PD-1 vs. traditional treatments (chemotherapy or vaccine)
- Combination of PD-1+CTLA-4 vs. CTLA-4 alone
- Combination of PD-1+CTLA-4 vs. PD-1+LAG-3

Methods

Inclusion Criteria

Population (P): Adults with advanced unresectable or metastatic melanoma.

Intervention (I): Immune checkpoint inhibitors (ICI) targeting Programmed cell death protein-1 (PD-1), Cytotoxic T-lymphocyte associated protein-4 (CTLA-4), or Lymphocyte activation gene-3 (LAG-3) pathways, administered as monotherapy or in combination.

Comparator (C): Traditional therapies (e.g., chemotherapy, vaccines), monotherapy versus combination therapy.

Outcomes (O): Overall survival (OS), progression-free survival (PFS), objective response rate (ORR), and treatment-related adverse events (AEs).

Studies were included if they enrolled adults with advanced unresectable melanoma and evaluated immune checkpoint inhibitors (ICIs) as monotherapy or in combination, compared to traditional therapies or other ICI regimens. Eligible studies had to report at least one key clinical outcome: overall survival (OS), progression-free survival (PFS), objective response rate (ORR), or adverse events (AEs). Only English-language randomised controlled trials (RCTs) were considered. When multiple publications existed for the same trial, the most recent analysis was prioritised. Exclusion criteria included non-randomised studies, observational designs, case reports, reviews, adjuvant-only trials, or those lacking relevant survival or safety outcomes.

Search Strategy

A final systematic literature search was conducted on 18 March 2025 across PubMed and the Cochrane Central Register of Controlled Trials (CENTRAL) databases. Medical Subject Headings (MeSH) terms and related keywords were used, including "Melanoma," "Programmed Cell Death 1 Receptor (PD-1)," "CTLA-4 Antigen," "LAG-3 Protein," as well as drug names such as "nivolumab," "pembrolizumab," "ipilimumab," "tremelimumab," and "relatlimab." Boolean operators were applied to combine terms appropriately. The full search string was:

("Melanoma"[Mesh] OR melanoma[tiab]) AND (("Programmed Cell Death 1 Receptor"[Mesh] OR PD-1[tiab] OR PD1[tiab] OR nivolumab[tiab] OR pembrolizumab[tiab]) OR ("CTLA-4 Antigen"[Mesh] OR CTLA-4[tiab] OR CTLA4[tiab] OR ipilimumab[tiab] OR tremelimumab[tiab]) OR ("Lymphocyte Activation Gene-3"[Mesh] OR LAG-3[tiab] OR LAG3[tiab] OR relatlimab[tiab]))

Studies published from 2006 to 18 March 2025 (PubMed) and from database inception to 18 March 2025 (CENTRAL) were considered. The

PubMed search, filtered for randomised controlled trials (RCTs), identified 213 records, while the Cochrane CENTRAL search identified 1,721 records after applying an English language filter.

Study Selection

Following title and abstract screening, 63 studies were assessed in full text. During full-text screening, 52 studies were excluded for the following reasons: duplicate or older versions (n = 20), non-RCT studies (n = 15), studies evaluating resectable melanoma (n = 11), and other reasons (n = 6). The selection process is summarised in the PRISMA flow diagram *(Figure 1)*.

Data Extraction

Data extraction was conducted using a standardised form. Two summary tables were created: one described study and patient characteristics (study name, region, median age by arm, sample sizes, intervention/control treatments, ECOG performance status, and BRAF mutation status); the other summarised clinical outcomes. Outcomes were extracted separately for experimental and control arms, including median OS with 95% CIs, HRs for OS and PFS, median PFS with 95% CIs, ORR, and incidence of grade ≥3 AEs. The hazard ratio is a measure of how often a particular event happens in one group compared to how often it happens in another group, while a risk ratio is a measure of the risk of a certain event happening in one group compared to the risk of the same event happening in another group[16]. For trials with multiple publications, the most recent and complete datasets were prioritised to ensure mature data. Where key outcomes such as survival outcomes or AE profiles were incomplete, earlier interim reports were used to supplement missing information.

Risk of Bias Assessment

Risk of bias was assessed using the Cochrane Risk of Bias 2.0 (RoB 2) tool, which evaluates five domains: randomisation process, deviations from intended interventions, missing outcome data, outcome measurement, and selection of reported results. Each domain was rated as “low risk,” “some concerns,” or “high risk” following Cochrane Handbook guidelines. An overall judgment was assigned based on domain-level ratings. Assessments were summarised narratively and tabulated using a colour-coded system: green for low risk, yellow for some concerns, and red for high risk as detailed in *Table 1.*

Data Synthesis

Data synthesis was conducted using Review Manager (RevMan) version 5.4.1. Hazard ratios (HRs) with 95% confidence intervals (CIs) were pooled for time-to-event outcomes (OS and PFS), and risk ratios (RRs) for binary outcomes (ORR and grade ≥3 AEs). A random-effects model was used to account for clinical and methodological heterogeneity. Statistical heterogeneity was assessed using the I^2 statistic, with values >50% indicating substantial heterogeneity. Where meta-analysis was not feasible due to limited or inconsistent data, results were summarised narratively.

Results

Characteristics and quality assessment of included studies

A total of 11 randomised controlled trials were included in this systematic review and meta-analysis, as illustrated in the PRISMA flow diagram (*Figure 1*).

The included studies enrolled adults with advanced unresectable or metastatic melanoma and evaluated immune checkpoint inhibitors as monotherapy or in combination. Three studies assessed CTLA-4 inhibitors (ipilimumab or tremelimumab) versus traditional therapies such as chemotherapy or vaccines. Three evaluated PD-1 inhibitors (nivolumab or pembrolizumab) against chemotherapy. Five investigated combination therapies: four assessed nivolumab plus ipilimumab (dual PD-1 and CTLA-4 blockade) versus ipilimumab alone,

and one evaluated nivolumab plus relatlimab (dual PD-1 and LAG-3 inhibition) versus nivolumab. Sample sizes ranged from 53 to 714, with median ages typically between 56 and 64. Most studies included patients with ECOG performance status 0–1, and BRAF-mutated melanoma was present in 0–42% of participants. Study characteristics are summarised in *Table 2*.

Risk of bias was assessed using the Cochrane Risk of Bias 2.0 (RoB 2) tool for RCTs across five domains. Five studies[17][18][19][14][15] were rated as low risk across all domains. Four[20][21][22][23] were high risk, mainly due to deviations from intended interventions and lack of blinding or selective reporting. Two[24][25] had some concerns, primarily related to randomization or outcome assessment. Detailed assessments are presented in *Table 1*.

PRISMA Diagram

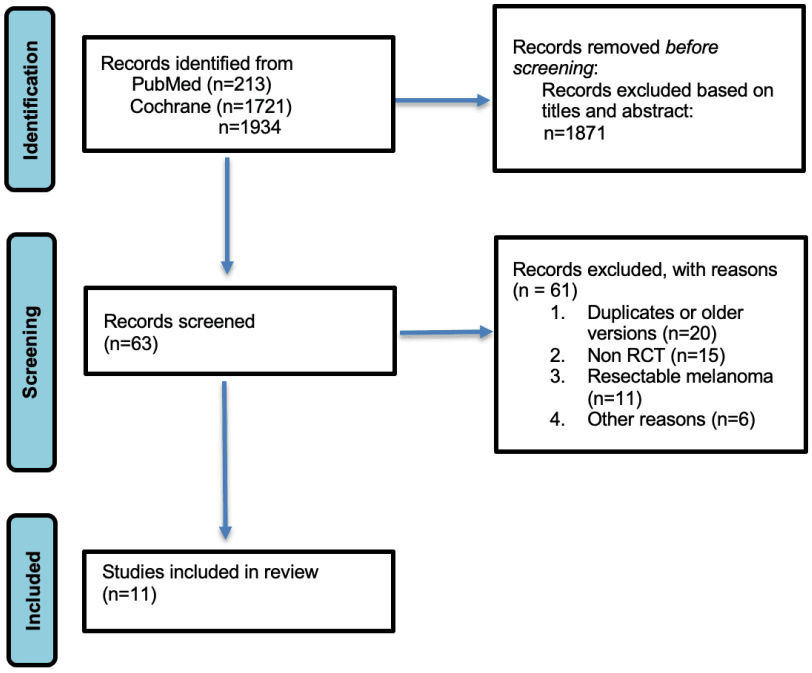

Figure 1. *Flowchart of search and selection of studies.*

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Study (Author, Year)	Randomization Process	Deviations from Intended Interventions	Missing Outcome Data	Measurement of Outcome	Selection of Reported Results	Overall Risk of Bias
[24]	LOW	LOW	LOW	LOW	SOME CONCERN	SOME CONCERN
[17]	LOW	LOW	LOW	LOW	LOW	LOW RISK
[20]	LOW	HIGH	LOW	SOME CONCERN	SOME CONCERN	HIGH RISK
[18]	LOW	LOW	LOW	LOW	LOW	LOW RISK
[19]	LOW	LOW	LOW	LOW	LOW	LOW RISK
[22]	LOW	HIGH	LOW	LOW	LOW	HIGH RISK
[14]	LOW	LOW	LOW	LOW	LOW	LOW
[15]	LOW	LOW	LOW	LOW	LOW	LOW
[25]	LOW	SOME CONCERNS	LOW	SOME CONCERNS	LOW	SOME CONCERNS
[23]	LOW	HIGH	LOW	LOW	LOW	HIGH RISK
[21]	LOW	HIGH	LOW	LOW	SOME CONCERN	HIGH RISK

Table 1. Risk of bias assessment

Study	Region	Age Exp/Ctrl		Sample size (Exp/Ctrl)	Intervention arm	Control arm	ECOG status	BRAF mutation (%)
[21]	Multinational	59 (23–88)	62 (29–85)	405 (272/133)	Nivolumab (3 mg/kg)	Dacarbazine or paclitaxel	0: 246 1: 158	89 (22%)
[22]	Multinational	62 (15–87)	63 (27–87)	540 (361/179)	Pembrolizumab (2 mg/kg or 10 mg/kg)	Chemotherapy	0: 296 1: 242	126 (23%)
[24]	Multinational	56.2 (NR)	57.4 (NR)	676 (540/136)	Ipilimumab (3 mg/kg) ± gp100	gp100	0: 374 1: 291 2: 9 3: 1	NR
[17]	Multinational	57.5 (NR)	56.4 (NR)	502 (250/252)	Ipilimumab (10 mg/kg) + Dacarbazine	Placebo + Dacarbazine	0: 356 1: 146	NR
[20]	Multinational	57 (22–90)	56 (22–90)	655 (328/327)	Tremelimumab (15 mg/kg)	Dacarbazine + Temozolomide	0: 449 1: 191	NR
[14]	Multinational	59 (18–88)	61 (18–89)	629 (314/315)	Nivolumab (1 mg/kg) + Ipilimumab (3 mg/kg)	Ipilimumab 3 mg/kg	0: 454 1: 174	198 (31%)
[19]	Multinational	≥18 (NR)	≥18 (NR)	142 (95/47)	Ipilimumab (3 mg/kg) + nivolumab (1 mg/kg)	Ipilimumab (3 mg/kg) + Placebo	0–1: 142	33 (23%)
[23]	Italy	56 (25–79)	60 (31–74)	53 (27/26)	Ipilimumab (3 mg/kg) + nivolumab (1 mg/kg)	Ipilimumab (10 mg/kg) + Fotemustine	0: 40 1: 13	22 (42%)
[18]	Multinational	64 (18–86)	66 (26–87)	418 (210/208)	Nivolumab (3 mg/kg) + placebo	Dacarbazine + Placebo	0: 269 1: 144 2: 4	0
[25]	USA	63 (NR)	63 (NR)	91 (68/23)	Ipilimumab (3 mg/kg) + nivolumab (1 mg/kg)	Ipilimumab (3 mg/kg)	NR	NR
[15]	Multinational	63 (20–94)	62 (21–90)	714 (355/359)	Relatlimab (160 mg) + Nivolumab (480 mg)	Nivolumab (480 mg)	0: 478 1: 236	275 (38.5%)

Table 2. Characteristics of included studies

Abbreviations: ECOG, Eastern Cooperative Oncology Group; Exp, experimental arm; Ctrl, control arm; NR, not reported; BRAF, B-Raf proto-oncogene.

Study	Exp arm	Ctrl arm	Overall survival (OS)			Progression-free survival (PFS)			Objective response rate (ORR) in %		Grade ≥3 Adverse events (AEs) in %	
			Median (95% CI), in months		HR (95% CI)	Median (95% CI), in months		HR (95% CI)	Exp	Ctrl	Exp	Ctrl
			Exp	Ctrl		Exp	Ctrl					
[21]	Nivolumab	**Chemotherapy**	15.7 (12.9-19.9)	14.4 (11.7-18.2)	0.95 (0.73-1.24)	3.1 (2.3-3.5)	3.7 (2.3-5.3)	1 (0.78-1.436)	74 (27%)	13 (10%)	126 (47%)	46 (45%)
[22] (Keynote-002)	Pembrolizumab	**Chemotherapy**	14.05 (11.2-18.0)	11 (8.9-13.8)	0.80 (0.67-0.96)	NR	NR	0.52 (0.44-0.62)	90 (25%)	8 (4%)	53 (15%)	45 (26.3%)
[18] (CheckMate-066)	Nivolumab	**Chemotherapy**	37.3 (25.4-51.6)	11.2 (9.6-13.0)	0.5 (0.40-0.63)	5.1 (3.5-12.2)	2.2 (2.1-2.5)	0.4 (0.33-0.54)	89 (42%)	30 (14%)	70 (34%)	78 (38%)
[24]	Ipilimumab ± gp100	**Gp100 (vaccine)**	10.1 (8-13.8)	6.4 (5.5-8.7)	0.67 (0.57-0.80)	2.78 (2.76-3.02)	2.76 (2.73-3.02)	0.74 (0.63-0.87)	38 (8.86%)	2 (1.5%)	233 (45.59%)	62 (47%)
[17]	Ipilimumab+dacarbazine	**Chemotherapy**	11.2 (9.4-13.6)	9.1 (7.8-10.5)	0.72 (0.59-0.87)	2.8 (2.6-2.9)	2.8 (2.5-2.9)	0.76 (0.63-0.93)	38 (15.2%)	26 (10.3%)	139 (56.3%)	69 (27.5%)
[20]	Tremelimumab	**Chemotherapy**	12.6 (10.8-14.3)	10.7 (9.36-11.96)	0.88 (0.75-1.04)	NR	NR	NR	36 (11%)	32 (10%)	170 (52%)	119 (37%)
[14] (CheckMate-067)	Nivolumab+Ipilimumab	Ipilimumab	71.9 (38.2-114.4)	19.9 (16.8-24.6)	0.53 (0.44-0.65)	11.5 (8.9-20.0)	2.9 (2.8-3.1)	0.42 (0.35-0.51)	183 (58%)	59 (19%)	184 (59%)	86 (28%)
[19] (CheckMate-069)	Nivolumab+Ipilimumab	Ipilimumab	NR	NR	0.74 (0.43-1.26)	NR	3 (2.7-5.1)	0.36 (0.22-0.56)	56 (59%)	5 (11%)	51 (55%)	9 (19%)
[23] (NIBIT-M2 trial)	Nivolumab+Ipilimumab	Ipilimumab+Futemustine	29.2 (0-69.9)	8.2 (2.1-14.3)	0.45 (0.22-0.91)	8.7 (0-19.9)	3.3 (1.2-5.4)	NR	12 (44.4%)	5 (19.2%)	14 (52%)	22 (85%)

Study	Exp arm	Ctrl arm	Overall survival (OS)			Progression-free survival (PFS)			Objective response rate (ORR) in %		Grade ≥3 Adverse events (AEs) in %	
			Median (95% CI), in months		HR (95% CI)	Median (95% CI), in months		HR (95% CI)	Exp	Ctrl	Exp	Ctrl
			Exp	Ctrl		Exp	Ctrl					
[25]	Nivolumab+Ipilimumab	Ipilimumab	NR	NR	0.83 (0.50-1.39)	NR	NR	0.63 (0.41-0.97)	19 (28%)	2 (9%)	39 (57%)	8 (35%)
[15] (Relativity-047)	Nivolumab+Relatlimab	Nivolumab	51 (NR)	34.1 (24.2-44.7)	0.8 (0.66-0.99)	10.2 (6.5-15.4)	4.6 (3.5-6.5)	0.79 (0.66-0.95)	155 (43.7%)	121 (33.7%)	164 (46.2%)	141 (39.3%)

Table 3. Safety and efficacy

Abbreviations: OS, overall survival; PFS, progression-free survival; ORR, objective response rate; AEs, adverse events; HR, hazard ratio; RR, risk ratio; CI, confidence interval; Exp, experimental arm; Ctrl, control arm; NR, not reported; PD-1, programmed cell death protein 1; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; LAG-3, lymphocyte activation gene 3; BRAF, B-Raf proto-oncogene.

Efficacy

Overall Survival (OS)

Ten randomised controlled trials involving 4,111 patients were included. Six studies (n = 3,196) comparing single ICIs to traditional therapies significantly improved OS in favour of ICIs (HR = 0.74; 95% CI: 0.63–0.87; p = 0.0003), though heterogeneity was substantial (I^2 = 77%) *(Figure A)*. Subgroup analysis showed benefit with CTLA-4 inhibitors (HR = 0.75; 95% CI: 0.64–0.89; I^2 = 66%) and a favourable trend with PD-1 inhibitors (HR = 0.72; 95% CI: 0.51–1.03; I^2 = 87%), though not statistically significant. The difference between subgroups was not significant (p = 0.83). Four additional trials (n = 915) comparing combination therapy to monotherapy demonstrated a clear survival advantage with dual ICIs (HR = 0.59; 95% CI: 0.47–0.75; p < 0.0001), with low heterogeneity (I^2 = 25%) *(Figure A)*.

Three trials evaluated PD-1 inhibitors versus chemotherapy *(Table 3)*. Robert et al.[18] reported median OS of 37.3 months with nivolumab compared to 11.2 with dacarbazine (HR = 0.50; 95% CI: 0.40–0.63). Hamid et al.[22] noted a modest benefit with pembrolizumab (14.05 vs. 11.0 months; HR = 0.80; 95% CI: 0.67–0.96). In contrast, Larkin et al.[21] reported no significant difference (15.7 vs. 14.4 months; HR = 0.95; 95% CI: 0.73–1.24).

Three trials assessed CTLA-4 inhibitors *(Table 3)*. Hodi et al.[24] reported ipilimumab improved median OS to 10.1 months vs. 6.4 with gp100 (HR = 0.67; 95% CI: 0.57–0.80). Robert et al.[17] showed improved OS with ipilimumab plus dacarbazine (11.2 vs. 9.1 months; HR = 0.72; 95% CI: 0.59–0.87). Ribas et al.[20] reported no significant difference between tremelimumab and chemotherapy (12.6 vs. 10.7 months; HR = 0.88; 95% CI: 0.75–1.04).

Four trials assessed PD-1 + CTLA-4 combinations versus ipilimumab alone *(Table 3)*. Wolchok et al.[14] reported OS of 71.9 vs. 19.9 months (HR = 0.53; 95% CI: 0.44–0.65), while Maria et al.[23] reported 29.2 vs. 8.2 months (HR = 0.45; 95% CI: 0.22–0.91). Hodi et al.[19] and VanderWalde et al.[25] favoured the combination, though results were not statistically significant (HR = 0.74 and 0.83, respectively). Tawbi et al.[15] evaluated PD-1 + LAG-3 (nivolumab + relatlimab) vs. nivolumab, reporting OS of 51.0 vs. 34.1 months (HR = 0.80; 95% CI: 0.66–0.99).

Progression-Free Survival (PFS)

Eight randomised controlled trials involving 3,403 patients were included. Five studies (n = 2,541) comparing single ICIs to traditional therapies significantly improved PFS (HR = 0.65; 95% CI: 0.49–0.86; p = 0.003), though heterogeneity was high (I^2 = 92%) *(Figure B)*. Subgroup analysis showed consistent benefit with CTLA-4 inhibitors (HR = 0.75; 95% CI: 0.66–0.85; I^2 = 0%) and PD-1 inhibitors (HR = 0.59; 95% CI: 0.37–0.94; I^2 = 94%), with no significant subgroup difference (p = 0.33). Three additional trials (n = 862) comparing dual ICIs to monotherapy reported a pooled HR of 0.45 (95% CI: 0.34–0.59; p < 0.00001) with moderate heterogeneity (I^2 = 44%) *(Figure B)*.

Three studies evaluated PD-1 monotherapy *(Table 3)*. Robert et al.[18] reported median PFS of 5.1 months with nivolumab vs. 2.2 with dacarbazine (HR = 0.40; 95% CI: 0.33–0.54). Hamid et al.[22] reported similar benefit with pembrolizumab (HR = 0.52; 95% CI: 0.44–0.62), though median PFS was not reported. Larkin et al.[21] reported no significant difference (3.1 vs. 3.7 months; HR = 1.00; 95% CI: 0.78–1.44).

Two trials assessed CTLA-4 inhibitors *(Table 3)*. Hodi et al.[24] reported slightly longer PFS with ipilimumab (2.78 vs. 2.76 months; HR = 0.74; 95% CI: 0.63–0.87). Robert et al.[17] showed no difference in median PFS (2.8 months in both arms), though the HR favoured ipilimumab (0.76; 95% CI: 0.63–0.93).

Five studies examined combination therapy *(Table 3)*. Wolchok et al.[14] reported median PFS of 11.5 months with nivolumab + ipilimumab vs. 2.9 with ipilimumab alone (HR = 0.42; 95% CI: 0.35–0.51). Maria et al.[23] showed a similar trend (8.7 vs. 3.3 months), though the HR was not reported. Hodi et al.[19] and VanderWalde et al.[25] reported HRs of 0.36 and 0.63, respectively. Tawbi et al.[15] reported PFS of 10.2 vs. 4.6 months with PD-1 + LAG-3 vs. PD-1 alone (HR = 0.79; 95% CI: 0.66–0.95).

Objective Response Rate (ORR)

Ten randomised controlled trials involving 4,111 patients were included. Among six studies comparing single ICIs with traditional therapies, pooled analysis demonstrated significantly higher ORR with immunotherapy (RR = 2.28; 95% CI: 1.44–3.59; p = 0.0004), though heterogeneity was substantial (I^2 = 76%) *(Figure C)*. Subgroup analysis showed significant benefit with PD-1 inhibitors (RR = 3.01; 95% CI: 1.85–4.89; I^2 = 62%), while CTLA-4 inhibitors did not reach statistical significance (RR = 1.51; 95% CI: 0.91–2.51; I^2 = 50%). No significant subgroup difference was detected (p = 0.06).

Four trials comparing combination therapy to monotherapy reported significantly higher ORR with dual ICIs (RR = 3.11; 95% CI: 2.48–3.89; p < 0.00001) with no heterogeneity (I^2 = 0%) *(Figure C)*.

Three trials evaluated PD-1 inhibitors *(Table 3)*. Hamid et al.[22] reported an ORR of 25% with pembrolizumab vs. 4% with chemotherapy. Robert et al.[18] found 42% with nivolumab vs. 14%. Larkin et al.[21] reported 27% vs. 10%.

Three trials assessed CTLA-4 inhibitors *(Table 3)*. Hodi et al.[24] reported 8.9% with ipilimumab vs. 1.5% with gp100. Ribas et al.[20] found similar response rates (11% vs. 10%). Robert et al.[17] reported 15.2% vs. 10.3% with ipilimumab plus dacarbazine vs. dacarbazine alone.

Five trials evaluated combination therapy *(Table 3)*. Wolchok et al.[14] reported 58% with nivolumab + ipilimumab vs. 19%. Maria et al.[23] reported 44.4% vs. 19.2%. Hodi et al.[19] reported 59% vs. 11%, and VanderWalde et al.[25] 28% vs. 9%. Tawbi et al.[15] found 43.7% vs. 33.7% with PD-1 + LAG-3 vs. PD-1 alone.

Safety

Grade ≥3 Adverse Events (AEs)

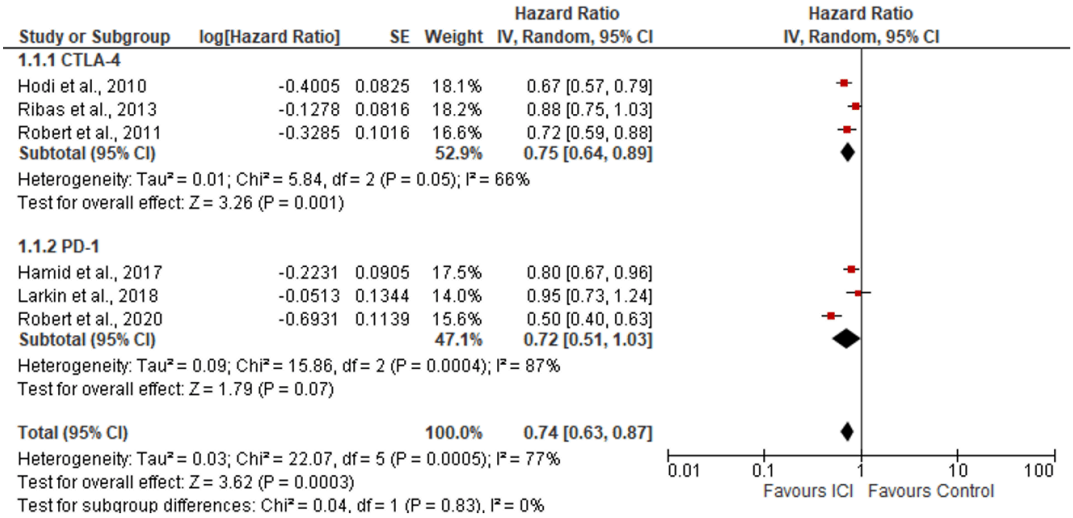
Nine randomised controlled trials involving 4,058 patients were included. Six trials (n = 3,196) comparing single ICIs with traditional therapies reported no significant difference in grade ≥3 AEs (RR = 1.08; 95% CI: 0.79–1.47; p = 0.62), with high heterogeneity (I^2 = 90%) *(Figure D)*. Subgroup analysis indicated a higher, though non-significant, AE risk with CTLA-4 inhibitors (RR = 1.40; 95% CI: 0.94–2.08; I^2 = 91%), and a non-significant trend toward lower risk with PD-1 inhibitors (RR = 0.82; 95% CI: 0.59–1.14; I^2 = 75%). The subgroup difference was significant (p = 0.04), suggesting distinct toxicity profiles. Three trials comparing combination therapy vs. monotherapy reported significantly higher AE rates with dual ICIs (RR = 2.14; 95% CI: 1.78–2.57; p < 0.00001), with no heterogeneity (I^2 = 0%) *(Figure D)*.

Three trials evaluated PD-1 inhibitors *(Table 3)*. Hamid et al.[22] reported grade ≥3 adverse events in 15% of pembrolizumab-treated patients vs. 26.3% with chemotherapy. Robert et al.[18] found 34% with nivolumab vs. 38% for dacarbazine. Larkin et al.[21] reported a slightly higher rate with nivolumab (47%) than chemotherapy (45%).

Three trials assessed CTLA-4 inhibitors *(Table 3)*. Hodi et al.[24] reported grade ≥3 AEs in 45.6% with ipilimumab vs. 47% with the gp100 vaccine. Ribas et al.[20] observed 52% with tremelimumab vs. 37% with chemotherapy. Robert et al.[17] found 56.3% with ipilimumab plus dacarbazine vs. 27.5% with dacarbazine alone.

Five trials evaluated combination therapy *(Table 3)*. Wolchok et al.[14] reported 59% with nivolumab plus ipilimumab compared to 28% with ipilimumab alone. Hodi et al.[19] observed 55% vs. 19%, VanderWalde et al.[25] reported 57% vs. 35%, and Maria et al.[23] found 52% with the combination and 85% with ipilimumab plus fotemustine. In contrast, Tawbi et al.[15] reported 46.2% with nivolumab plus relatlimab versus 39.3% with nivolumab alone, indicating a modest increase in toxicity but lower than the CTLA-4+PD-1 combination.

Single ICI vs Traditional therapy



Combination therapy vs Monotherapy

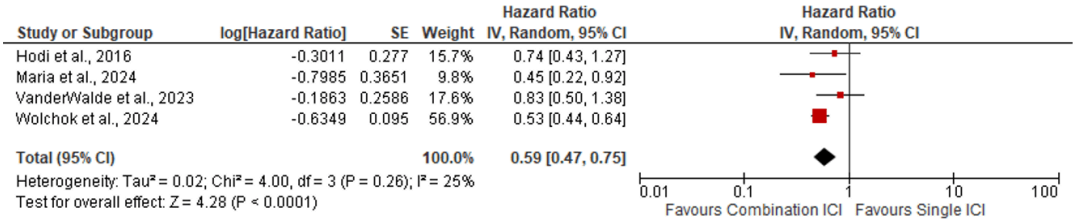
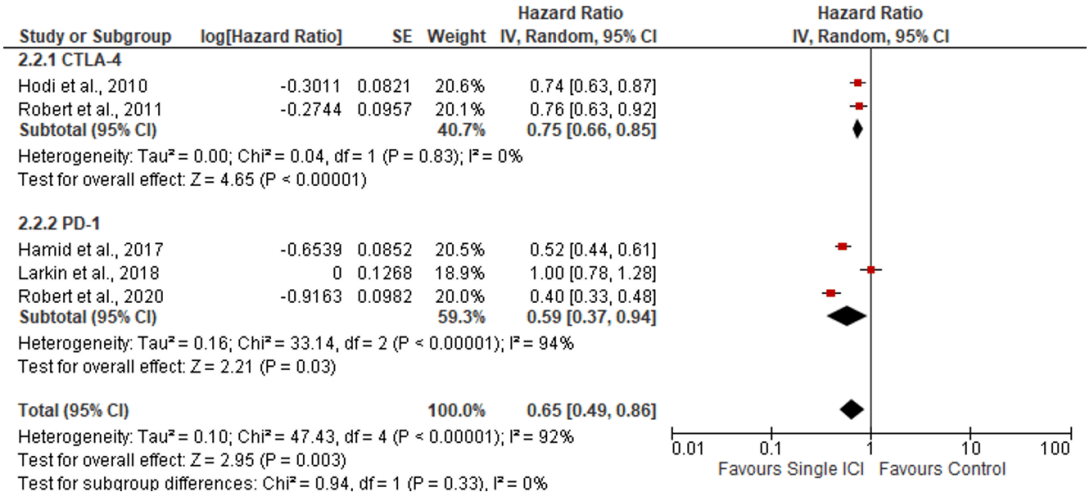


Figure (A). Overall survival (OS)

doi.org/10.32388/4AAZYE

Single ICI vs Traditional therapy



Combination therapy vs Monotherapy

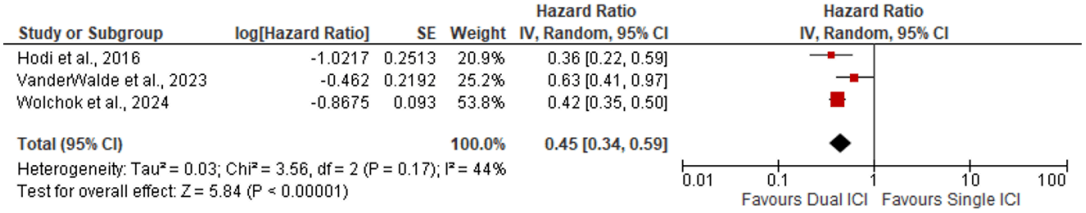


Figure (B). Progression-free survival (PFS)

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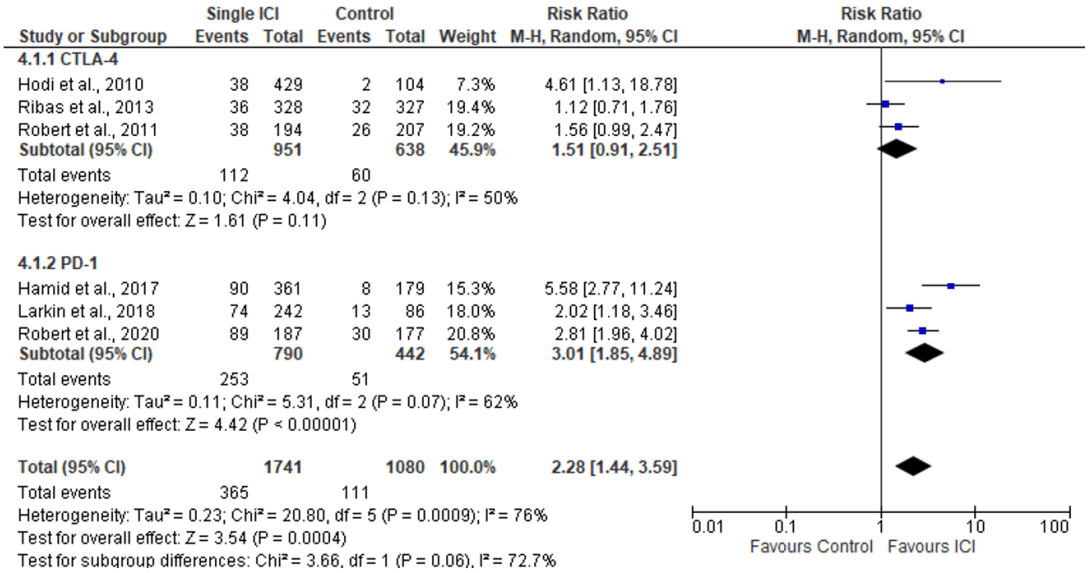
Single ICI vs Traditional therapy



Combination therapy vs Monotherapy

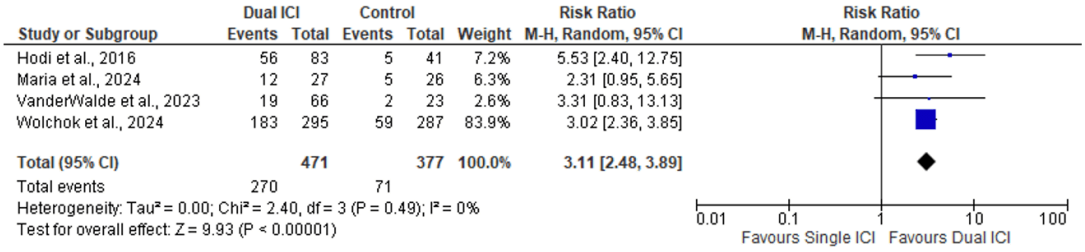


Figure (C). Objective response rate (ORR)

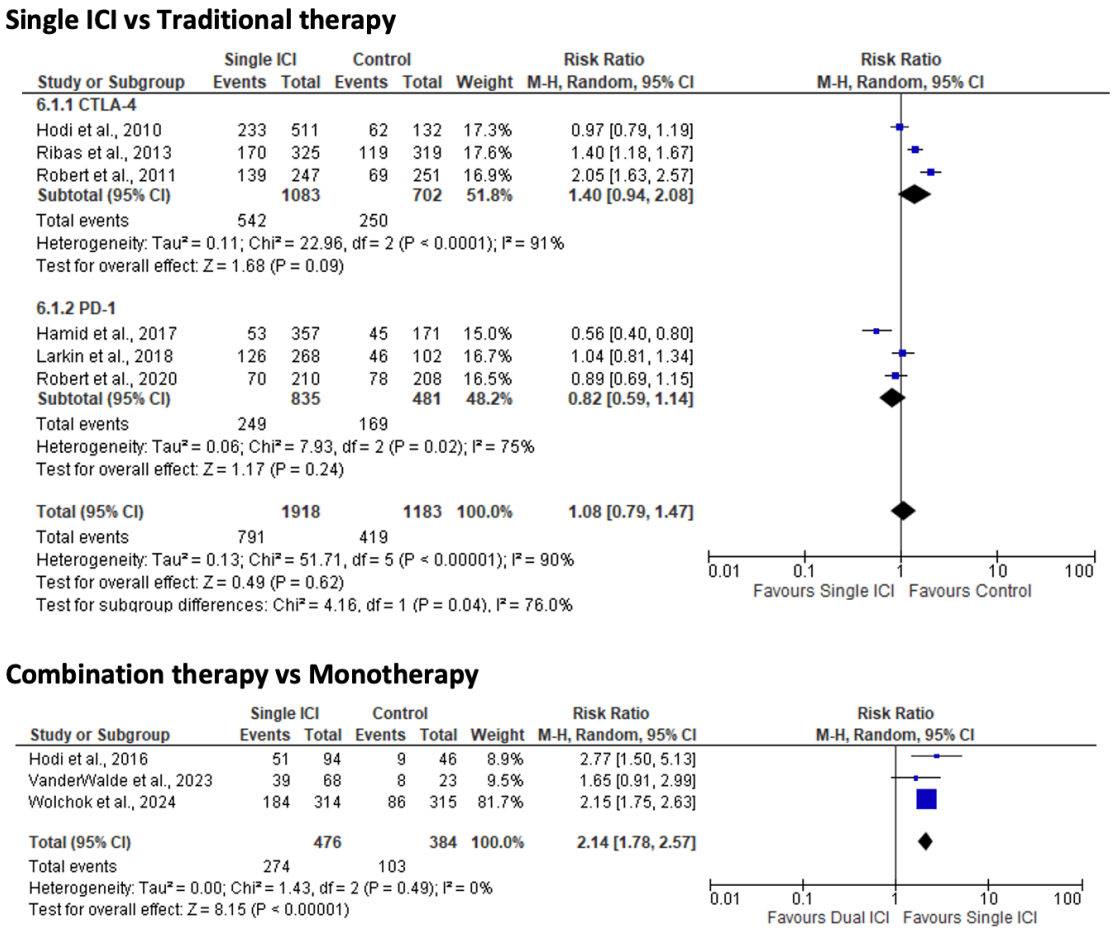


Figure (D). Adverse events (AEs)

Discussion

Efficacy

Immune checkpoint inhibitors showed clear efficacy advantages over traditional treatments in advanced melanoma. Among monotherapy regimens, PD-1 inhibitors consistently demonstrated improved progression-free survival and objective response rates across trials. While the pooled overall survival result did not reach statistical significance, a narrative synthesis of the included studies showed generally favourable outcomes with PD-1 treatment compared to the control. This discrepancy may be explained by considerable heterogeneity among studies. In Hamid et al., post-progression crossover to PD-1 therapy was allowed in the control arm, likely reducing the measurable survival difference between groups. Still, the consistency of direction across individual studies supports a meaningful clinical effect of PD-1 monotherapy. In contrast, CTLA-4 inhibitors showed more mixed results. While pooled analyses indicated significant improvement in PFS and OS, the ORR did not reach statistical significance, and the results across trials were variable. Some studies showed only modest gains with CTLA-4 monotherapy, suggesting a less predictable therapeutic impact. These inconsistencies may reflect both clinical and biological factors, including trial population differences and the broader mechanism of immune activation associated with CTLA-4 inhibition. PD-1 and CTLA-4 inhibitors differ in their immune targets and functional effects, which may account for the differences observed in clinical performance. PD-1 blockade reactivates previously primed, antigen-experienced T cells within the

tumour microenvironment, restoring localised cytotoxic immune activity against tumour cells. This targeted mechanism is more likely to produce sustained and tumour-specific responses. In contrast, CTLA-4 inhibition acts earlier in the immune response by promoting the expansion of naïve T cells in lymphoid tissues. While this broadens immune activation, it may result in less focused anti-tumour activity and contribute to the variability in treatment outcomes observed with CTLA-4 monotherapy[26].

Blocking two immune checkpoints simultaneously has emerged as a powerful strategy to improve treatment outcomes in advanced melanoma. Combination regimens consistently outperformed monotherapy across key efficacy endpoints, providing stronger and more durable clinical benefit. Dual inhibition of PD-1 and CTLA-4 produced particularly robust improvements, reflecting the synergy achieved by targeting different stages of the T-cell activation cycle. While PD-1 plus LAG-3 also demonstrated improved outcomes compared to PD-1 monotherapy, the survival advantage was statistically significant but more modest in scale. Nonetheless, both approaches underscore the therapeutic advantage of disrupting multiple immunosuppressive pathways rather than relying on a single mechanism.

The enhanced efficacy of PD-1 and CTLA-4 combination therapy reflects their complementary roles in immune regulation, targeting distinct stages of T-cell activation. This dual approach enables broader and more durable anti-tumour responses. In contrast, PD-1 and LAG-3 are often co-expressed on exhausted CD8+ T cells within the tumour microenvironment, where they suppress immune function through parallel pathways. LAG-3 primarily reduces cytotoxicity and cytokine production, while PD-1 limits T-cell proliferation. Blocking both pathways reactivates effector function by enhancing TCR signalling, increasing IFN-γ production, and restoring cytolytic activity. These mechanistic distinctions help explain why PD-1 + CTLA-4 blockade produces the most robust efficacy, while PD-1 + LAG-3 offers a more moderate, yet meaningful, clinical benefit[27][28].

Safety

In terms of safety, the pooled analysis for grade ≥3 adverse events was not statistically significant in either the PD-1 or CTLA-4 subgroup. Both subgroups showed high heterogeneity, particularly CTLA-4. This likely reflects differences in trial design, especially background therapies. For instance, ipilimumab was combined with dacarbazine in Robert et al.[17] and with the gp100 vaccine in Hodi et al.[24], both of which are independently associated with toxicity and may have inflated adverse event rates in CTLA-4 arms. Narrative synthesis indicated that CTLA-4 monotherapy was more frequently associated with severe immune-related adverse events, whereas PD-1 inhibitors tended to be better tolerated across trials. As previously discussed, CTLA-4 blockade promotes broad immune activation by enhancing naïve T-cell priming in lymphoid tissues. This widespread stimulation increases the likelihood of off-target inflammation, particularly in barrier organs like the gastrointestinal tract, where immune-related colitis is common. In contrast, PD-1 inhibition acts locally within the tumour microenvironment, reactivating exhausted T cells without broadly stimulating the immune system. This tumour-specific reactivation contributes to the lower incidence of systemic immune-related adverse events observed with PD-1[29]. Given these mechanistic differences, combining PD-1 and CTLA-4 blockade amplifies immune activation both during early T-cell priming in lymphoid tissues (CTLA-4) and at the tumour site where PD-1 regulates exhausted T cells, which likely accounts for the significantly increased toxicity observed in pooled analyses. No heterogeneity was detected, suggesting this effect was consistent across studies. In contrast, PD-1 plus LAG-3 demonstrated a more favourable safety profile. As outlined previously, LAG-3 and PD-1 blockade acts more selectively on exhausted T cells in the tumour microenvironment, which may limit systemic immune activation. These findings support a clear toxicity gradient, with PD-1 in monotherapy being the most tolerable, followed by PD-1 + LAG-3 in the combination therapy[29][30].

Summary of findings

The findings of this systematic review and meta-analysis demonstrate that immunotherapy is more effective than traditional treatments in advanced melanoma. Single ICIs improved OS, PFS, and ORR, with PD-1 inhibitors consistently outperforming CTLA-4 inhibitors in both efficacy and safety. CTLA-4 inhibitors were associated with modest clinical benefits and a higher rate of severe adverse events, while

PD-1 inhibitors showed greater improvements across all endpoints with a comparatively better safety profile. Combination therapy with PD-1 and CTLA-4 inhibitors provided the most substantial benefit in terms of survival and response, but this came with significantly increased toxicity. The PD-1 + LAG-3 combination, which represents a more recent approach targeting a novel immune checkpoint, demonstrated favourable efficacy while being better tolerated than PD-1 + CTLA-4. This suggests that PD-1 + LAG-3 may offer a more clinically viable option, especially for patients who may not tolerate the high toxicity associated with dual PD-1 and CTLA-4 blockade. These findings are consistent with previous studies reporting similar trends for PD-1 and CTLA-4 inhibitors[11][12] (Hao et al., 2017).

Strengths and Limitations

The key strength of this systematic review with meta-analysis is the inclusion of only randomised controlled trials with a generally low risk of bias. It captured the most widely used immune checkpoint inhibitors in melanoma—CTLA-4 and PD-1—as well as the newer PD-1 + LAG-3 combination, offering a broad and clinically relevant evaluation of current treatment strategies. The analysis included long-term follow-up where available, including studies with survival data up to 10 years, such as Wolchok et al., enabling a more complete understanding of treatment durability. Efficacy and safety were comprehensively assessed through key outcomes including OS, PFS, ORR, and grade ≥3 AEs. Subgroup analyses enabled direct comparison across ICI classes.

While the findings are clinically meaningful and largely consistent with previous evidence, several limitations should be noted. Some outcomes, including OS for PD-1 monotherapy, did not reach statistical significance despite favourable trends. In Hamid et al., two pembrolizumab doses (2 mg/kg and 10 mg/kg) were pooled, which may have introduced variability. Post-progression crossover occurred in multiple trials, including Hamid et al. and Ribas et al., potentially diluting treatment effects and underestimating survival benefit. Some monotherapy trials included ICIs with chemotherapy, such as ipilimumab with dacarbazine[17] and nivolumab versus dacarbazine[18], possibly confounding the interpretation of ICI-only effects. Only 11 trials were included, limiting statistical power for subgroup analyses. Sensitivity analyses were not performed due to the small number of studies, and funnel plots were not generated, so publication bias could not be formally assessed. Heterogeneity was substantial in several analyses, particularly among single-agent comparisons, due to differences in trial design, treatment protocols, and patient populations. In the analysis of grade ≥3 AEs, the study by Maria et al. was excluded as all other included studies were of high quality and showed consistent findings (I^2 = 0%), while Maria et al. used an uncommon comparator (ipilimumab plus fotemustine) and reported a distinct toxicity profile, which would have introduced unnecessary heterogeneity. Lastly, the meta-analysis relied on published aggregate data rather than patient-level data, limiting the ability to conduct adjusted or stratified analyses.

Future implications and research

The results of this systematic review and meta-analysis support the use of PD-1 inhibitors as the preferred monotherapy option in advanced melanoma, given their consistent efficacy and favourable safety profile compared to CTLA-4 inhibitors. Dual checkpoint blockade with PD-1 and CTLA-4 provides the most substantial survival benefit but is associated with high toxicity, which limits its use in many patients. The PD-1 + LAG-3 combination showed promising results with meaningful survival benefit and improved tolerability and may be a more suitable alternative for patients who are unable to tolerate the toxicity of PD-1 + CTLA-4 therapy.

Future research should focus on optimising treatment sequencing, identifying reliable predictive biomarkers, and developing strategies to overcome resistance. Not all patients benefit from immune checkpoint inhibition, as these therapies only block certain immune pathways that may not be active in all tumours. A large proportion of patients continue to show no meaningful clinical response, even with combination therapy, which exposes them to unnecessary toxicity. This highlights the need to better understand why some patients do not respond and to expand treatment options beyond the currently available targets. Improving biomarker-based selection could help personalise therapy, reduce exposure to adverse effects in non-responders, and ultimately lead to better outcomes across a wider group of

patients. Further clinical trials are also needed to evaluate LAG-3–based combinations across different melanoma subtypes, confirm their long-term benefit, and define their role within first-line treatment strategies.

Conclusion

This systematic review with meta-analysis evaluated the comparative efficacy and safety of immune checkpoint inhibitors in advanced unresectable melanoma, including monotherapies and combination regimens across the CTLA-4, PD-1, and LAG-3 pathways. The findings clearly demonstrate that immune checkpoint inhibitors offer superior efficacy compared to traditional therapies such as chemotherapy and vaccines, with improved overall survival, progression-free survival, and response rates. However, safety profiles varied. PD-1 inhibitors were associated with a lower incidence of grade ≥3 adverse events compared to traditional therapies, while CTLA-4 inhibitors, particularly ipilimumab, were linked to a higher rate of toxicity. Among monotherapies, PD-1 inhibitors provided the most favourable balance between efficacy and safety. Combination therapy with PD-1 and CTLA-4 yielded the most substantial improvement in efficacy but was associated with significantly increased toxicity, limiting its use in many patients. The PD-1 + LAG-3 combination showed promising results, with meaningful survival benefit and improved tolerability, suggesting it may serve as a more balanced alternative for patients unable to tolerate standard dual therapy. These findings directly address the clinical questions posed at the outset of this review and provide a clear comparative overview of current immunotherapy strategies in advanced melanoma.

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