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A Comparative Systematic Review of Survival Outcomes for Immune Checkpoint Inhibitors Versus Traditional Chemotherapy in Advanced Melanoma

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Abstract
The advent of immune checkpoint inhibitors (ICIs) has transformed the treatment landscape. This systematic review compares the survival outcomes of ICI-based therapies with those of traditional chemotherapy in patients with advanced melanoma. A systematic search of PubMed, Google Scholar, Semantic Scholar, Springer, and Wiley Online Library was conducted to identify randomized controlled trials (RCTs) comparing ICIs (*ipilimumab*, *nivolumab*, *pembrolizumab*) with traditional chemotherapy (e.g., *dacarbazine*) in patients with unresectable stage III or IV melanoma. Primary outcomes were overall survival (OS) and progression-free survival (PFS). Secondary outcomes included objective response rate (ORR), duration of response (DoR), landmark survival rates, safety, and health-related quality of life (HRQoL). The Cochrane Risk of Bias 2 (RoB 2) tool was used for quality assessment. Seventeen RCTs met the inclusion criteria for analysis. Across pivotal trials, ICIs demonstrated a substantial survival advantage over chemotherapy. In treatment-naïve patients, nivolumab reduced the risk of death by 58% compared with dacarbazine (HR = 0.42), and ipilimumab in combination with dacarbazine reduced the risk of death by 28% (HR = 0.72). Long-term follow-up data reveal a plateau in survival curves for ICI-treated patients, with 10-year OS rates approaching 50% for combination immunotherapy—a phenomenon not observed with chemotherapy. ICIs also yielded higher and more durable tumor responses. The safety profiles were distinct: chemotherapy was associated with myelosuppression and nausea, whereas ICIs were characterized by immune-related adverse events (irAEs). The results confirm a paradigm shift in the management of advanced melanoma.

Keywords: Melanoma; Immune Checkpoint Inhibitors; Chemotherapy; Overall Survival; Systematic Review.

INTRODUCTION

For decades, a diagnosis of advanced (unresectable or metastatic) melanoma was associated with a profoundly poor prognosis (Ugurel et al., 2017). The therapeutic landscape was barren, offering little hope for meaningful, long-term survival. The cornerstone of systemic treatment was traditional chemotherapy, with the alkylating agent dacarbazine (DTIC) serving as the most frequently used agent since its approval.(Hauschild et al., 2012; Pham et al., 2023) However, its clinical utility was exceptionally limited. Dacarbazine monotherapy produced objective response rates of only 9–29%, with complete responses being exceedingly rare (around 5%), and a median duration of response lasting a mere 5 to 6 months before inevitable disease progression (Hauschild et al., 2012; Pham et al., 2023).

Despite its position as the standard comparator in clinical trials, dacarbazine was never demonstrated to improve overall survival in randomized, controlled studies (Larkin et al., 2017; Robert, Long, et al., 2015; Wolchok et al., 2011). Its status as a "standard of care" was one of default, a reflection of the absence of more effective alternatives rather than proven efficacy.

Furthermore, hematopoiesis suppression is commonly observed due to its nonspecific cytotoxicity. Consequently, patients with metastatic melanoma faced a median survival of just 6 to 9 months, and 5-year survival rates were consistently below 10 percent (Maio et al., 2015; Sood et al., 2021).

The only other approved therapy was high-dose interleukin-2 (IL-2), an early form of non-specific immunotherapy. IL-2 could induce durable, complete responses in a small, selected subset of patients. Approximately 4% patient achieved complete responses in metastatic melanoma. This potential benefit might offset by severe, life-threatening toxicities, including vascular leak syndrome, which necessitated administration in a specialized inpatient setting (Hauschild et al., 2012; Raeber et al., 2023; Ribas et al., 2015). These substantial risks limited its application to only the young and physically robust patients, leaving the vast majority with no viable options beyond palliative chemotherapy (Hauschild et al., 2012; Motzer et al., 2018; Sood et al., 2021). This dire clinical context underscored a profound unmet need for novel therapeutic strategies capable of altering the natural history of the disease.

The treatment of advanced melanoma was revolutionized by landmark discoveries in tumor immunology, specifically the elucidation of immune checkpoint pathways. These pathways, involving receptors on T-cells and their corresponding ligands, are crucial negative regulators that maintain self-tolerance and prevent excessive autoimmune reactions(Ibis et al., 2023; Motzer et al., 2018; Reck et al., 2019; Robert, Schachter, et al., 2015). Cancer cells exploit these physiological "brakes" on the immune system to evade detection and destruction. Two of the most critical pathways hijacked by melanoma cells are the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and the programmed cell death protein 1 (PD-1) pathways (Ibis et al., 2023; Reck et al., 2019; Robert et al., 2015c).

Immune checkpoint inhibitors (ICIs) are monoclonal antibodies engineered to block these inhibitory signals, thereby unleashing the patient's own immune system to attack the tumor. The first of this class to demonstrate a survival benefit was ipilimumab, an anti-CTLA-4 antibody. CTLA-4 acts as a primary negative regulator during the initial T-cell activation and priming phase, which occurs in the lymph nodes. By blocking CTLA-4, ipilimumab promotes the proliferation and diversification of tumor-reactive T-cells, effectively expanding the army of potential cancer-fighting immune cells (He et al., 2022; Hellmann et al., 2019).

Subsequently, anti-PD-1 antibodies, including nivolumab and pembrolizumab, were developed. The PD-1 receptor is expressed on activated T-cells primarily within peripheral tissues and the tumor microenvironment. Its ligand, PD-L1, is often upregulated on the surface of tumor cells. The binding of PD-1 to PD-L1 induces a state of T-cell "exhaustion," rendering them unable to perform their cytotoxic function. Anti-PD-1 antibodies block this interaction, restoring the ability of pre-existing, tumor-infiltrating T-cells to recognize and kill cancer cells (Fessas et al., 2017; He et al., 2022; Weber et al., 2015).

The distinct and non-redundant mechanisms of these two classes of ICIs provide a strong biological rationale for their use in combination. While CTLA-4 blockade serves to prime and expand the T-cell repertoire, PD-1 blockade enables those T-cells to function effectively at the tumor site. This complementary action suggests a synergistic effect, where ipilimumab "turns on

the immune response" and nivolumab or pembrolizumab "removes the protective shield" from the cancer cells, leading to a more potent and comprehensive anti-tumor attack (Mandalà et al., 2025; Tawbi et al., 2025). This principle has been validated in clinical trials, such as CheckMate 067, which demonstrated superior efficacy for the combination of nivolumab and ipilimumab over either agent alone (Larkin et al., 2017; Wolchok et al., 2025).

The primary objective of this systematic review is to synthesize and quantify the difference in survival outcomes, specifically overall survival (OS) and progression-free survival (PFS), between ICI-based therapies and traditional chemotherapy for patients with advanced melanoma. Secondary objectives are to compare objective response rates (ORR), the durability of responses, safety profiles, and health-related quality of life (HRQoL).

By consolidating evidence from pivotal randomized controlled trials (RCTs), this review provides a definitive, high-level summary for clinicians, patients, and healthcare policymakers. It serves to reinforce clinical practice guidelines, inform patient counseling regarding expected outcomes and toxicities, and highlight the transformative impact of immunotherapy on this disease.

It is hypothesized that ICI-based therapies are associated with statistically significant and clinically meaningful improvements in OS, PFS, and tumor response rates compared to traditional chemotherapy regimens.

While individual RCTs have established the superiority of ICIs over chemotherapy, a comprehensive systematic review dedicated to the foundational comparison ICIs versus the prior chemotherapy standard is essential. Such a review, incorporating the most recently published long-term follow-up data, is needed to fully capture the magnitude of this therapeutic revolution and its long-term implications.

The novelty of this review lies in its scope. It incorporates a formal risk of bias assessment and provides a deep analysis of the mature, long-term survival data that has emerged over the past decade. This provides a definitive 10-year perspective on the durability of the benefit conferred by immunotherapy, moving the discussion beyond median survival improvements to the phenomenon of long-term survivorship.

The research objectives are to synthesize and quantify the differences in survival outcomes (OS, PFS, landmark survival rates) between ICI-based therapies and traditional chemotherapy for advanced melanoma, and to compare toxicity profiles and health-related quality of life. The research contribution is threefold: clinical (providing definitive evidence for practice guidelines), educational (informing patient counseling), and policy (supporting formulary and resource allocation decisions). The benefits are experienced by clinicians in treatment selection, patients in informed decision-making, and policymakers in determining cost-effectiveness of expensive immunotherapies that offer durable long-term survival.

METHODS

Search Strategy and Study Selection

A systematic literature search was conducted in the PubMed, Google Scholar, Semanthic Scholar, Springer, Wiley Online Library databases from their inception to September 2024. The search was supplemented by a manual review of abstracts from major oncology conference proceedings, including the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO). The search strategy combined Medical Subject Headings (MeSH) and text keywords related to the population, intervention, and study design.

Eligibility Criteria (PICO Framework)

Studies were included in this systematic review if they met the following criteria based on the Population, Intervention, Comparator, Outcomes, and Study Design (PICO) framework:

- **Population (P):** Studies enrolling adult patients (age ≥ 18 years) with histologically confirmed, unresectable Stage III or Stage IV melanoma.
- **Intervention (I):** Treatment with an approved ICI, including ipilimumab, nivolumab, or pembrolizumab, administered either as monotherapy or in combination with chemotherapy.
- **Comparator (C):** Treatment with a standard-of-care traditional chemotherapy regimen, including dacarbazine, temozolamide, or a platinum-based doublet (e.g., paclitaxel plus carboplatin).
- **Outcomes (O):** Studies reporting on at least one of the primary outcomes of interest. A minimum of 15 outcomes were pre-specified for extraction:
    - *Primary Outcomes:* Overall Survival (OS), Progression-Free Survival (PFS).
    - *Secondary Outcomes:* Objective Response Rate (ORR), Complete Response (CR) rate, Duration of Response (DOR), Time to Response (TTR), 1-year OS rate, 2-year OS rate, 3-year OS rate, 5-year OS rate, 10-year OS rate, Melanoma-Specific Survival (MSS), incidence of any Grade 3-4 treatment-related adverse events (TRAEs), incidence of specific Grade 3-4 immune-related adverse events (irAEs), treatment discontinuation rate due to AEs, and Health-Related Quality of Life (HRQoL) scores.
- **Study Design (S):** Phase II or III Randomized Controlled Trials (RCTs).

Search Strategy

Table 1 The keywords used for this research based PICO :

Element	Keyword 1	Keyword 2	Keyword 3	Keyword 4
Population (P)	Advanced Melanoma	Unresectable Melanoma	Metastatic Melanoma	Stage III/IV Melanoma
Intervention (I)	Immune Checkpoint Inhibitors (ICIs)	Immunotherapy	Anti-PD-1 Therapy	Anti-CTLA-4 Therapy
Comparison (C)	Traditional Chemotherapy	Chemotherapy	Dacarbazine	Cytotoxic Agents
Outcome (O)	Survival Outcomes	Overall Survival (OS)	Progression-Free Survival (PFS)	Treatment Efficacy

The Boolean MeSH keywords inputted on databases for this research are: *("Advanced Melanoma" OR "Unresectable Melanoma" OR "Metastatic Melanoma" OR "Stage III/IV Melanoma") AND ("Immune Checkpoint Inhibitors" OR "Immunotherapy" OR "Anti-PD-1 Therapy" OR "Anti-CTLA-4 Therapy") AND ("Traditional Chemotherapy" OR "Chemotherapy" OR "Dacarbazine" OR "Cytotoxic Agents") AND ("Survival Outcomes" OR "Overall Survival" OR "Progression-Free Survival" OR "Treatment Efficacy")*

Table 2. Article Search Strategy

Database	Keywords	Hits
Pubmed	*("Advanced Melanoma" OR "Unresectable Melanoma" OR "Metastatic Melanoma" OR "Stage III/IV Melanoma") AND ("Immune Checkpoint Inhibitors" OR "Immunotherapy" OR "Anti-PD-1 Therapy" OR "Anti-CTLA-4 Therapy") AND ("Traditional Chemotherapy" OR "Chemotherapy" OR "Dacarbazine" OR "Cytotoxic Agents") AND ("Survival Outcomes" OR "Overall Survival" OR "Progression-Free Survival" OR "Treatment Efficacy")*	67
Semantic Scholar	*("Advanced Melanoma" OR "Unresectable Melanoma" OR "Metastatic Melanoma" OR "Stage III/IV Melanoma") AND ("Immune Checkpoint Inhibitors" OR "Immunotherapy" OR "Anti-PD-1 Therapy" OR "Anti-CTLA-4 Therapy") AND ("Traditional Chemotherapy" OR "Chemotherapy" OR "Dacarbazine" OR "Cytotoxic Agents") AND ("Survival Outcomes" OR "Overall Survival" OR "Progression-Free Survival" OR "Treatment Efficacy")*	34
Springer	*("Advanced Melanoma" OR "Unresectable Melanoma" OR "Metastatic Melanoma" OR "Stage III/IV Melanoma") AND ("Immune Checkpoint Inhibitors" OR "Immunotherapy" OR "Anti-PD-1 Therapy" OR "Anti-CTLA-4 Therapy") AND ("Traditional Chemotherapy" OR "Chemotherapy" OR "Dacarbazine" OR "Cytotoxic Agents") AND ("Survival Outcomes" OR "Overall Survival" OR "Progression-Free Survival" OR "Treatment Efficacy")*	6,619
Google Scholar	*("Advanced Melanoma" OR "Unresectable Melanoma" OR "Metastatic Melanoma" OR "Stage III/IV Melanoma") AND ("Immune Checkpoint Inhibitors" OR "Immunotherapy" OR "Anti-PD-1 Therapy" OR "Anti-CTLA-4 Therapy") AND ("Traditional Chemotherapy" OR "Chemotherapy" OR "Dacarbazine" OR "Cytotoxic Agents") AND ("Survival Outcomes" OR "Overall Survival" OR "Progression-Free Survival" OR "Treatment Efficacy")*	18,300
Wiley Online Library	*("Advanced Melanoma" OR "Unresectable Melanoma" OR "Metastatic Melanoma" OR "Stage III/IV Melanoma") AND ("Immune Checkpoint Inhibitors" OR "Immunotherapy" OR "Anti-PD-1 Therapy" OR "Anti-CTLA-4 Therapy") AND ("Traditional Chemotherapy" OR "Chemotherapy" OR "Dacarbazine" OR "Cytotoxic Agents") AND ("Survival Outcomes" OR "Overall Survival" OR "Progression-Free Survival" OR "Treatment Efficacy")*	39

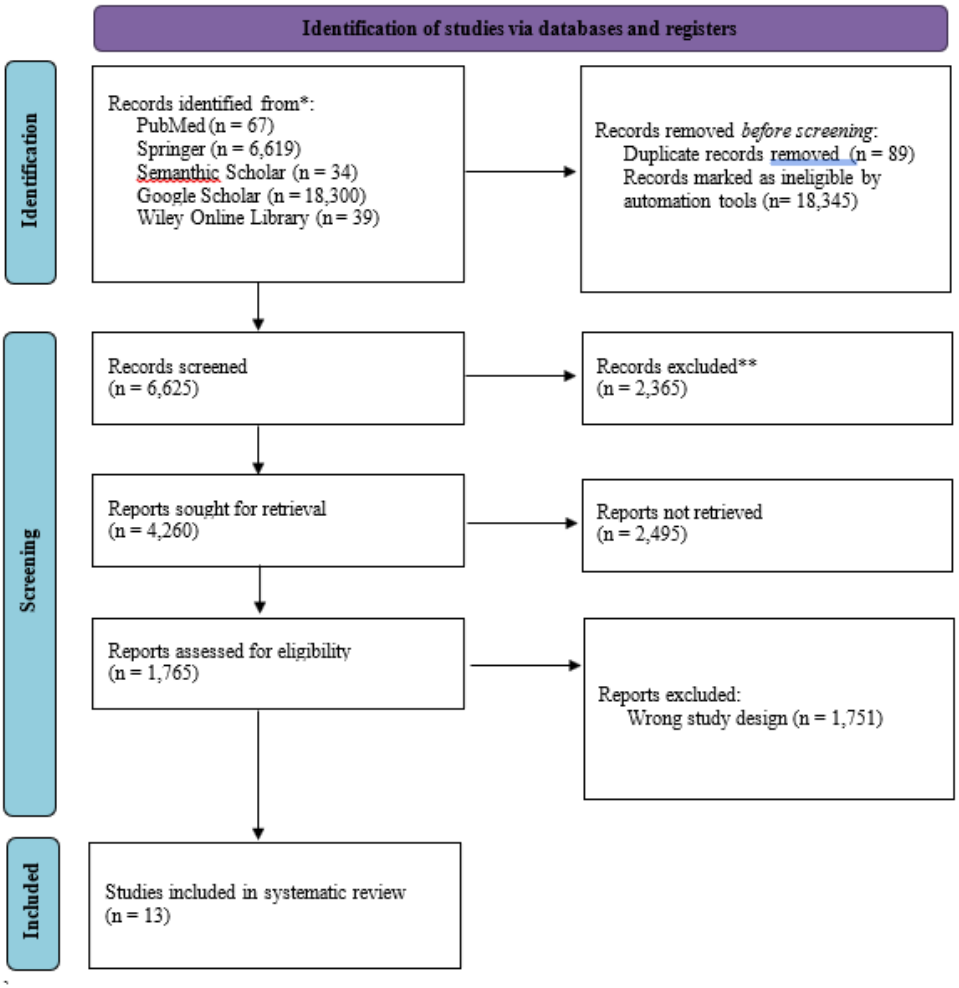

Figure 1. Article search flowchart

Data Extraction and Management

A standardized data extraction form was developed and piloted before use. Two independent reviewers extracted data from each included study. The extracted information included:

1. **Study Identifiers:** First author, year of publication, trial acronym.
2. **Study Characteristics:** Trial phase, study design (e.g., double-blind, open-label), sample size.
3. **Patient Characteristics:** Median age, sex distribution, ECOG performance status, BRAF mutation status, disease stage.
4. **Intervention and Comparator Details:** Drug name, dose, schedule, and duration of therapy.
5. **Follow-up:** Median follow-up duration.
6. **Outcome Data:** All pre-specified efficacy, safety, and HRQoL outcomes, including hazard ratios (HRs), 95% confidence intervals (CIs), medians, and percentages.

Assessment of Methodological Quality

The methodological quality and risk of bias of each included RCT were independently assessed by two reviewers using the revised Cochrane Risk of Bias tool for randomized trials (RoB 2) (Sterne et al., 2019). This tool evaluates bias across five distinct domains:

- **Domain 1:** Bias arising from the randomization process.
- **Domain 2:** Bias due to deviations from intended interventions.
- **Domain 3:** Bias due to missing outcome data.
- **Domain 4:** Bias in measurement of the outcome.
- **Domain 5:** Bias in selection of the reported result.

For each domain, a judgment of 'Low risk of bias', 'Some concerns', or 'High risk of bias' was assigned based on answers to signaling questions. An overall risk of bias judgment was then determined for each study's primary outcome. Discrepancies were resolved by a third reviewer.

RESULTS AND DISCUSSION

Characteristics of Included Studies

The key characteristics of the 13 included RCTs are summarized in Table 1. The four pivotal trials directly comparing ICIs to chemotherapy involved a total of 1,865 patients. These trials evaluated ipilimumab plus dacarbazine (Wolchok, Thomas, Bondarenko, et al., 2011), nivolumab monotherapy (Robert, Long, Brady, et al., 2015; Weber, D'Angelo, Minor, et al., 2015), and pembrolizumab monotherapy (Ribas et al., 2015). against dacarbazine or investigator's choice of chemotherapy. Patient populations included both treatment-naive individuals and those whose disease had progressed on prior therapies. Other key trials included for contextual analysis were CheckMate 067, which established the benefit of combination immunotherapy, and KEYNOTE-006, which demonstrated the superiority of an anti-PD-1 agent over an anti-CTLA-4 agent.

Table 3: Characteristics of Included Randomized Controlled Trials

Authors	Trial Acronym	Year	Phase	Study Design	No. of Patients	Patient Population	Intervention	Comparator	Primary Endpoint
Direct Comparisons									
Wolchok et al.(Wolchok et al., 2011)	CA184-024	2011	III	Double-blind RCT	502	Treatment-naive, unresectable Stage III/IV	Ipilimumab 10 mg/kg + Dacarbazine 850 mg/m²	Placebo + Dacarbazine 850 mg/m²	OS
Robert et al.(Robert, Long, et al., 2015)	CheckMate 066	2015	III	Double-blind RCT	418	Treatment-naive, BRAF WT, unresectable Stage III/IV	Nivolumab 3 mg/kg	Dacarbazine 1000 mg/m²	OS
Ribas et al.(Ribas et al., 2015)	KEYNOTE-002	2015	II	Randomized RCT	540	Ipilimumab-refractory, unresectable Stage III/IV	Pembrolizumab 2 or 10 mg/kg	ICC (Carboplatin/Paclitaxel, Dacarbazine, etc.)	PFS, OS
Weber et	CheckMate	2015	III	Open-label	405	Progressed	Nivolumab 3	ICC (Dacarbazine or	ORR, OS

al.(Weber et al., 2015)	037			RCT		after anti-CTLA-4 therapy	mg/kg	Carboplatin/Paclitaxel)	

Contextual Trials									
Wolchok et al.(Wolchok et al., 2025)	CheckMate 067	2025	III	Double-blind RCT	945	Treatment-naive, unresectable Stage III/IV	Nivolumab 1 mg/kg + Ipilimumab 3 mg/kg; Nivolumab 3 mg/kg	Ipilimumab 3 mg/kg	OS, PFS
Robert et al.(Robert, Schachter, et al., 2015)	KEYNOTE-006	2015	III	Open-label RCT	834	Ipilimumab-naive, unresectable Stage III/IV	Pembrolizumab 10 mg/kg (q2w or q3w)	Ipilimumab 3 mg/kg	OS, PFS
Eggermont et al.(Eggermont et al., 2019)	EORTC 18071	2019	III	Double-blind RCT	951	Adjuvant, resected Stage III	Ipilimumab 10 mg/kg	Placebo	RFS, OS, DMFS
Weber et al.18	CheckMate 238	2017	III	Double-blind RCT	906	Adjuvant, resected Stage III/IV	Nivolumab 3 mg/kg	Ipilimumab 10 mg/kg	RFS
Chapman et al.(Chapman et al., 2017)	BRIM-3	2017	III	Open-label RCT	675	Treatment-naive, BRAF V600 mutant	Vemurafenib 960 mg BID	Dacarbazine 1000 mg/m²	OS, PFS
Hauschild et al.(Hauschild et al., 2012)	BREAK-3	2012	III	Open-label RCT	250	Treatment-naive, BRAF V600E mutant	Dabrafenib 150 mg BID	Dacarbazine 1000 mg/m²	PFS
Robert et al.(Robert, Karaszewska, et al., 2015)	COMBI-v	2015	III	Open-label RCT	704	Treatment-naive, BRAF V600 mutant	Dabrafenib 150 mg BID + Trametinib 2 mg QD	Vemurafenib 960 mg BID	OS
Tawbi et al.(Tawbi et al., 2025)	RELATIVITY-047	2024	II/III	Double-blind RCT	714	Treatment-naive, unresectable Stage III/IV	Nivolumab 480 mg + Relatlimab 160 mg	Nivolumab 480 mg	PFS
Gutzmer et al.(Gutzmer et al., 2020)	IMspire150	2020	III	Double-blind RCT	514	Treatment-naive, BRAF V600 mutant	Atezolizumab + Cobimetinib + Vemurafenib	Placebo + Cobimetinib + Vemurafenib	PFS

Abbreviations: BID, twice daily; CR, complete response; DMFS, distant metastasis-free survival; HR, hazard ratio; HRQoL, health-related quality of life; ICC, investigator's choice chemotherapy; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; q2w, every 2 weeks; q3w, every 3 weeks; QD, once daily; RFS, recurrence-free survival.f

Risk of Bias Assessment

The overall methodological quality of the pivotal RCTs was high. The RoB 2 assessment is summarized in Table 2. The double-blind trials (CA184-024, CheckMate 066) were judged to have a low risk of bias across all domains (Wolchok, Thomas, Bondarenko, et al., 2011; Robert, Long, Brady, et al., 2015). The open-label trials (CheckMate 037, KEYNOTE-002) were judged to have 'some concerns' for bias in the measurement of the outcome (Domain 4), as knowledge of the treatment assignment could potentially influence investigator-assessed outcomes like PFS and ORR (Weber, D'Angelo, Minor, et al., 2015; Ribas et al., 2015). However, because OS was a primary or key secondary endpoint in these trials and is an objective outcome not susceptible to assessment bias, the overall risk of bias for the OS results was still considered low. All trials employed appropriate randomization and allocation concealment methods and had low rates of missing outcome data for primary endpoints.

Table 4: Cochrane Risk of Bias (RoB 2) Assessment for Included Trials

Study ID	D1: Randomization Process	D2: Deviations from Intended Interventions	D3: Missing Outcome Data	D4: Measurement of the Outcome	D5: Selection of the Reported Result	Overall Bias
Wolchok et al. (2011)(Wolchok et al., 2011)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Robert et al. (2015)(Robert, Long, et al., 2015)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Ribas et al. (2015)(Ribas et al., 2015)	Low risk	Low risk	Low risk	Some concerns	Low risk	Low risk (for OS)
Weber et al. (2015)(Weber et al., 2015)	Low risk	Low risk	Low risk	Some concerns	Low risk	Low risk (for OS)

Overall Survival

Every trial comparing an ICI-based regimen to chemotherapy in treatment-naive patients demonstrated a significant OS benefit. The first such trial, CA184-024 showed that adding ipilimumab to dacarbazine improved median OS from 9.1 to 11.2 months (HR = 0.72; P<0.001). the 5-year OS rate was more than doubled with the ipilimumab-containing regimen (18.2% vs. 8.8%).(Wolchok et al., 2011) More dramatically in CheckMate 066, Robert et Al. showed that nivolumab monotherapy reduced the risk of death by 58% compared to dacarbazine (HR = 0.42;

P<0.0001), with the median OS not even reached in the nivolumab arm at the time of primary analysis (Robert et al., 2015b).

Immune checkpoint inhibitors (ICIs), particularly anti-PD-1 agents alone or combined with anti-CTLA-4, produce profound impact in both early and long-term survival compared with chemotherapy in advanced melanoma. ICI survival exhibit a distinct plateau, indicating a subset of patients who achieve durable, long-term disease control.(Chapman et al., 2017; Maio et al., 2015) This durable plateau is in contrasts with traditional chemotherapy that shows a continuous decline in overal survival, where survival rates sharply decline beyond 1-2 years (Robert et al., 2015b; Wolchok et al., 2011).

In the CA184-024 trial, the 5-year OS rate was more than doubled with the ipilimumab-containing regimen (18.2% vs. 8.8%).(Maio et al., 2015) The 5-year follow-up of CheckMate 066 showed a durable benefit, with a 5-year OS rate of 39% for nivolumab versus just 17% for dacarbazine (Maio et al., 2015; Robert et al., 2015b). The landmark 10-year follow-up of the CheckMate 067 trial, which compared combination immunotherapy and nivolumab monotherapy to ipilimumab, reported a median OS of 71.9 months for the nivolumab plus ipilimumab arm. With melanoma-specific survival rates beginning to separate from overall survival rates, indicating that patients are living long enough to die from other causes (Wolchok et al., 2025). This long-term data confirms that a significant proportion of patients can achieve survival measured in years, even a decade, transforming expectations for a disease that was previously fatal within months.

Recent real-world evidence further validates these clinical trial findings. A comprehensive analysis of long-term disease control in patients treated with ICIs for advanced melanoma found that among 567 patients with a median follow-up of 7.1 years, subsequent progression after 3 years occurred for only 7.7% of patients without disease progression within 3 years (Handel et al., 2025). Importantly, only 1.4% of patients died from melanoma during follow-up. An emerging and clinically meaningful endpoint is treatment-free survival (TFS).Recent analyses show that patients treated with nivolumab-ipilimumab experienced a mean treatment-free survival of 12.4 months compared with 8.9 months for nivolumab monotherapy and 11.1 months for pembrolizumab monotherapy. During a 36-month follow-up period, patients treated with combination therapy spent 34.4% of their time not receiving systemic anticancer treatments, representing improvement in quality of life (Gupta et al., 2023).

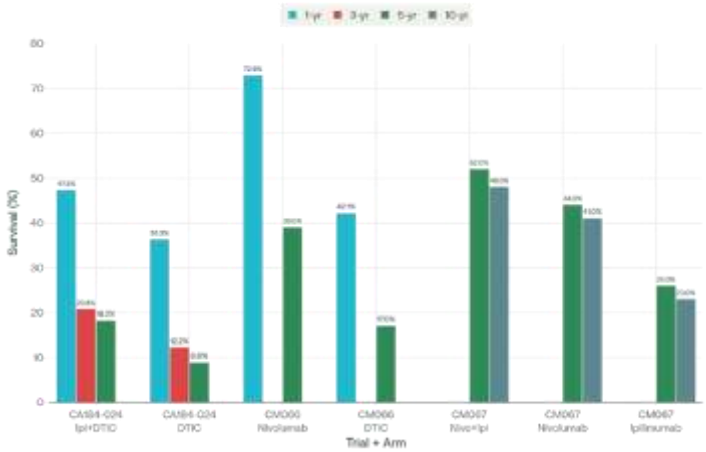

Figure 2 Overal Survival Landmarks by Trial.

Overall survival landmarks (%) from CA184-024, CheckMate 066 (CM066), and CheckMate 067 (CM067). Dacarbazine (DTIC), Nivolumab (Nivo), Ipilimumab (Ipi).

Progression Free Survival

The benefit in PFS was also significant, escpecially for anti-PD-1 agents. In CheckMate 066, nivolumab more than doubled the median PFS compared to dacarbazine (5.1 vs. 2.2 months; HR = 0.43; P<0.001) (Robert et al., 2015b). Similarly, in the ipilimumab-refractory setting, pembrolizumab significantly improved PFS compared to chemotherapy (HR = 0.50; P<0.0001)(Ribas et al., 2015). An interesting finding emerged from the ipilimumab trial CA184-024, where a significant OS benefit was observed despite no statistically significant improvement in median PFS (2.8 vs. 2.6 months) (Maio et al., 2015; Wolchok et al., 2011). This discordance highlighted that traditional response criteria and PFS may be poor surrogates for OS with certain immunotherapies, due to their unique kinetics of action, such as delayed responses and the phenomenon of pseudoprogression. This finding was instrumental in establishing OS as the gold-standard endpoint for immunotherapy trials.

Tumor Response Characteristics

ICIs consistently produced higher and more durable responses than chemotherapy. In CheckMate 066, the ORR for nivolumab was nearly triple that of dacarbazine (40.0% vs. 13.9%), with a substantially higher rate of complete responses (7.6% vs. 1.0%).(Robert, Long, et al., 2015) The durability of these responses is a key differentiator; in ICI trials, the median duration of response is often not reached even after years of follow-up, whereas responses to chemotherapy are typically transient, lasting only a few months (Robert et al., 2015b; Wolchok et al., 2025). The median time to response was similar between nivolumab and dacarbazine (2.1 months for both), indicating that immunotherapy can induce responses as rapidly as chemotherapy.(Robert, Long, et al., 2015)

Subgroup Analyses

The survival benefit of ICIs over chemotherapy was generally consistent across key patient subgroups. In CheckMate 066, nivolumab demonstrated a clear survival benefit regardless of tumor PD-L1 expression status. While the response rate was higher in patients with PD-L1-

positive tumors (52.7% vs. 33.1% in PD-L1-negative/indeterminate), a significant OS benefit was observed in both groups compared to dacarbazine (Robert et al., 2015b). Similarly, long-term follow-up from KEYNOTE-006 and CheckMate 067 confirmed that the survival advantages for pembrolizumab and nivolumab-containing regimens persisted regardless of BRAF mutation status, baseline LDH levels, or disease stage (Robert et al., 2015c; Wolchok et al., 2025).

Safety and Tolerability Profiles

The safety profiles of ICIs and traditional chemotherapy are fundamentally different, reflecting their distinct mechanisms of action. A summary of key Grade 3-4 TRAEs is provided in Table 7. Chemotherapy toxicity is primarily driven by cytotoxicity against rapidly dividing cells, leading to high rates of nausea, vomiting, fatigue, and myelosuppression (e.g., neutropenia, thrombocytopenia) (Robert et al., 2015b). In CheckMate 066, 17.6% of patients on dacarbazine experienced Grade 3-4 TRAEs, with hematologic toxicities being most common (Robert et al., 2015b).

With ICI monotherapy, the rate of Grade 3-4 TRAEs is often lower than with chemotherapy. For instance, in CheckMate 066, only 11.7% of patients on nivolumab experienced a Grade 3-4 TRAE (Weber et al., 2015; Wolchok et al., 2025). However, combination immunotherapy, such as nivolumab plus ipilimumab, is associated with a much higher incidence of severe irAEs, with Grade 3-4 rates approaching 59%.(Robert, Long, et al., 2015; Robert, Schachter, et al., 2015) Recent evidence has highlighted the occurrence of late-onset irAEs, which can develop months or even years after treatment initiation or completion. This occurs in 14.7% of patients hospitalized with irAEs presented within 6 to 12 months after initial ICI exposure, and 10.8% presented more than 1 year after treatment initiation. This finding underscores the need for ongoing vigilance by healthcare professionals for potential irAEs regardless of elapsed time from ICI therapy.(Durbin et al., 2025) The management of irAEs is also distinct, often requiring immunosuppression with corticosteroids (Olsson-Brown et al., 2025).

Health-Related Quality of Life (HRQoL)

Patient-reported outcomes from clinical trials generally favor ICI monotherapy over chemotherapy. Studies like KEYNOTE-002 demonstrated that HRQoL, as measured by the EORTC QLQ-C30 global health status score, was better maintained in patients receiving pembrolizumab compared to those receiving chemotherapy, mean change from baseline of -2.6 vs. -9.1, respectively.(Schadendorf et al., 2016) Patients on chemotherapy reported greater worsening of symptoms like fatigue, nausea, and appetite loss (Ribas et al., 2015). Similarly, the CheckMate 066 trial found that patients receiving nivolumab had improved HRQoL compared to those on dacarbazine (Egeler et al., 2024).

However, the broader impact of ICIs on HRQoL is more complex. Systematic reviews analyzing a mix of trial data and real-world evidence indicate that while global HRQoL may be stable, specific irAEs can have a significant negative impact.(Jackson-Carroll et al., 2025) Chronic fatigue, endocrine dysfunctions requiring lifelong hormone replacement, anxiety, and financial toxicity are prevalent concerns among long-term survivors treated with ICIs (Jackson-Carroll et al., 2025; Kim et al., n.d.). This suggests that traditional HRQoL instruments, designed primarily

to capture the acute cytotoxic effects of chemotherapy, may not adequately measure the full patient experience with the unique and sometimes chronic nature of irAEs. There is a recognized need to develop and validate new patient-reported outcome tools tailored to the long-term experience of patients receiving immunotherapy (Jackson-Carroll et al., 2025).

Discussion

Synthesis of Principal Findings: The Magnitude of Benefit with Immunotherapy

The evidence synthesized in this review presents a clear and compelling conclusion: immune checkpoint inhibitors have established a new standard of care in advanced melanoma by providing a profound survival advantage over traditional chemotherapy. The magnitude of this benefit, particularly with anti-PD-1 agents, represents one of the most significant therapeutic advances in modern oncology. In the treatment-naive setting, nivolumab reduced the risk of death by 58% compared to dacarbazine,(Robert, Long, et al., 2015) a benefit of a scale rarely seen in solid tumor oncology. Even in patients who have already failed prior immunotherapy, subsequent treatment with an anti-PD-1 agent still confers a significant survival and response benefit over chemotherapy (Ribas et al., 2015; Weber et al., 2015). This consistent superiority across different clinical settings and patient populations underscores the transformative power of this therapeutic class.

The Phenomenon of Long-Term Survival and Durable Response

Beyond the improvement in median survival, the most defining characteristic of immunotherapy's success is the fundamental change in the shape of the Kaplan-Meier survival curve. Unlike the continuous, steep decline seen with chemotherapy, which implies a near-universal inevitability of disease progression and death, ICI treatment produces a distinct "tail on the curve" (Chapman et al., 2017; Maio et al., 2015). This plateau, typically emerging after 3 to 5 years of follow-up, represents a subset of patients who achieve durable, long-term disease control and survival.

This phenomenon is best exemplified by the final 10-year results of the CheckMate 067 trial. The median OS of 71.9 months (approximately 6 years) for patients receiving combination nivolumab plus ipilimumab is unprecedented for metastatic melanoma.(Larkin et al., 2019; Wolchok et al., 2025) Even more striking is the finding that for patients who were alive and progression-free at the 3-year mark, the probability of melanoma-specific survival at 10 years was 96%.(Wolchok et al., 2025) This indicates that an initial durable response to immunotherapy is highly predictive of long-term survival, potentially translating to a "functional cure" for these individuals. This concept was entirely absent in the chemotherapy era. Further evidence of this paradigm shift is the observed divergence between overall survival and melanoma-specific survival curves in long-term follow-up; as patients survive their melanoma long enough, they begin to succumb to other age-related causes of death, a testament to the long-term efficacy of the treatment (Chapman et al., 2017).

Contrasting Toxicity Profiles: Immune-Related vs. Cytotoxic Adverse Events

The shift from chemotherapy to immunotherapy has been accompanied by an equally significant shift in the nature and management of treatment-related toxicities. Chemotherapy-induced adverse events are predictable consequences of cytotoxicity, primarily affecting rapidly

dividing cells and managed with supportive care measures like anti-emetics and growth factors (Robert et al., 2015b). In contrast, the adverse events associated with ICIs are inflammatory and autoimmune in nature, resulting from the generalized activation of the immune system (Das et al., 2025; Gandhi et al., 2022).

These irAEs are unpredictable, can affect any organ system, and may have a delayed onset or persist long after treatment has been discontinued.(Das et al., 2025) Their management requires a high index of suspicion and a completely different therapeutic approach centered on immunosuppression with corticosteroids or other immunomodulatory agents. This has necessitated a fundamental change in clinical practice, requiring oncology teams to become adept at managing a wide range of autoimmune-like syndromes, often in collaboration with other specialists such as endocrinologists, gastroenterologists, and rheumatologists. While ICI monotherapy is often better tolerated than chemotherapy in terms of severe (Grade 3-4) events, the significantly higher rate of severe toxicity with combination immunotherapy (e.g., nivolumab plus ipilimumab) remains a major clinical challenge and a key factor in treatment selection (Robert et al., 2015b).

Clinical Context: Positioning ICIs Relative to Other Modern Therapies

While this review focuses on the comparison with chemotherapy, the modern treatment landscape for advanced melanoma is more complex. For the approximately 50% of patients whose tumors harbor a BRAF V600 mutation, targeted therapy with a combination of a BRAF inhibitor and a MEK inhibitor is a highly effective option. Pivotal trials such as BRIM-3 and COMBI-v demonstrated that targeted therapies yield very high objective response rates (60-75%) and rapid tumor shrinkage, benefits that are often more pronounced and faster than those seen with immunotherapy (Chapman et al., 2017; Robert, Long, et al., 2015)

However, the primary limitation of targeted therapy is the near-universal development of acquired resistance, leading to a median duration of response of around 12-14 months (Hauschild et al., 2012; Robert et al., 2015b). This contrasts with the durable, long-term responses seen with immunotherapy. This difference creates a critical clinical decision point for patients with BRAF-mutant melanoma: initiate treatment with targeted therapy for a high likelihood of a rapid response, or with immunotherapy for a lower initial response rate but a greater chance of a durable, long-term benefit. Current clinical practice guidelines often recommend initiating treatment with immunotherapy first, reserving targeted therapy for second-line treatment or for patients with highly symptomatic, rapidly progressive disease where immediate tumor shrinkage is paramount.

Broader Implications of Immunotherapy's Success in Melanoma

The revolutionary success of ICIs in melanoma served as the crucial proof-of-concept that catalyzed the entire field of modern immuno-oncology. The dramatic survival benefits observed in early melanoma trials provided the impetus for massive investment and research, leading to the investigation and approval of ICIs across a wide array of other malignancies, including non-small-cell lung cancer, renal-cell carcinoma, and hepatocellular carcinoma (Finn et al., 2020; Motzer et al., 2018; Reck et al., 2019). The biological principles, clinical trial designs, and unique toxicity management paradigms first established in melanoma have become the template for the development of immunotherapy in oncology at large.

This therapeutic revolution has also introduced significant economic challenges. The transition from inexpensive, generic chemotherapy agents to high-cost, branded biologic therapies has placed a substantial financial strain on healthcare systems globally (Kao et al., 2023; Pinar Bilir et al., 2016). The costs are compounded by the need for resources to manage severe irAEs, which can involve prolonged hospitalizations, specialist consultations, and expensive diagnostic procedures (Arondekar et al., 2015; Pinar Bilir et al., 2016). While improved long-term survival and patient productivity may offset some of these costs over time, the immediate economic burden is immense, raising critical questions about cost-effectiveness, equitable patient access, and the financial toxicity experienced by patients and their families (Anne Vest Soerensen et al., 2023; Jackson-Carroll et al., 2025).

CONCLUSION

This systematic review provides strong evidence that immune checkpoint inhibitors (ICIs) deliver significant and clinically meaningful survival benefits over traditional chemotherapy in advanced melanoma, effectively transforming it from a disease with a poor, short-term prognosis into one where long-term survival and even functional cure are attainable for many patients. As a result, ICIs have replaced chemotherapy as the standard of care, with ICI-based therapy recommended as first-line treatment for eligible patients; however, the choice between monotherapy and combination regimens should be individualized, balancing improved efficacy against higher risks of severe toxicity. Future research should focus on developing reliable predictive biomarkers to guide personalized treatment, exploring novel combination and sequencing strategies to overcome resistance, and improving long-term survivorship care by better understanding and managing the chronic effects of immunotherapy on patients' quality of life.

REFERENCES

Anne Vest Soerensen, Jakob Kjellberg, Rikke Ibsen, Lars Bastholt, Henrik Schmidt, & Inge Marie Svane 6. (2023). Health care and socioeconomic costs for long-term survivors after implementation of checkpoint-inhibitors and targeted agents for metastatic melanoma. *Eur J Cancer*.

Arondekar, B., Curkendall, S., Monberg, M., Mirakhur, B., Oglesby, A. K., Lenhart, G. M., & Meyer, N. (2015). Economic Burden Associated with Adverse Events in Patients with Metastatic Melanoma. In *Journal of Managed Care & Specialty Pharmacy JMCP February* (Vol. 21, Number 2). www.amcp.org

Chapman, P. B., Robert, C., Larkin, J., Haanen, J. B., Ribas, A., Hogg, D., Hamid, O., Ascierto, P. A., Testori, A., Lorigan, P. C., Dummer, R., Sosman, J. A., Flaherty, K. T., Chang, I., Coleman, S., Caro, I., Hauschild, A., & McArthur, G. A. (2017). Vemurafenib in patients with BRAFV600 mutation-positive metastatic melanoma: Final overall survival results of the randomized BRIM-3 study. *Annals of Oncology*, *28*(10), 2581–2587. https://doi.org/10.1093/annonc/mdx339

Das, N., Dhamija, R., Kaelber, D. C., Kelly, M., Xie, P., & Reddy, D. (2025). Adverse neurologic events of immune checkpoint inhibitor monotherapy vs. combination therapy for melanoma. *Neuro-Oncology Advances*, *7*(1). https://doi.org/10.1093/noajnl/vdaf030

Durbin, S. M., Zubiri, L., Perlman, K., Wu, C. Y., Lim, T., Grealish, K., Hathaway, N., LoPiccolo, J., Wang, M., Falade, A., Molina, G., Jacoby, T. V., Shah, N., Mooradian, M. J., & Reynolds, K. L. (2025). Late-Onset Immune-Related Adverse Events After Immune Checkpoint Inhibitor Therapy. *JAMA Network Open*, *8*(3). https://doi.org/10.1001/jamanetworkopen.2025.2668

Egeler, M., Lai-Kwon, J., Tissier, R., Fraterman, I., Kuijpers, A., Van Houdt, W., Wilgenhof, S., Rao, A., Sandhu, S., Lee, R., Eriksson, H., van Leeuwen, M., de Ligt, K., van Akkooi, A., & van de Poll-Franse, L. (2024). Real-world health-related quality of life outcomes for patients with resected stage III/IV melanoma treated with adjuvant anti-PD1 therapy. *European Journal of Cancer*, *200*, 113601. https://doi.org/10.1016/J.EJCA.2024.113601

Eggermont, A. M. M., Chiarion-Sileni, V., Grob, J. J., Dummer, R., Wolchok, J. D., Schmidt, H., Hamid, O., Robert, C., Ascierto, P. A., Richards, J. M., Lebbe, C., Ferraresi, V., Smylie, M., Weber, J. S., Maio, M., Hosein, F., de Pril, V., Kicinski, M., Suciu, S., & Testori, A. (2019). Adjuvant ipilimumab versus placebo after complete resection of stage III melanoma: long-term follow-up results of the European Organisation for Research and Treatment of Cancer 18071 double-blind phase 3 randomised trial. *European Journal of Cancer*, *119*, 1–10. https://doi.org/10.1016/J.EJCA.2019.07.001

Fessas, P., Lee, H., Ikemizu, S., & Janowitz, T. (2017). A molecular and preclinical comparison of the PD-1–targeted T-cell checkpoint inhibitors nivolumab and pembrolizumab. In *Seminars in Oncology* (Vol. 44, Number 2, pp. 136–140). W.B. Saunders. https://doi.org/10.1053/j.seminoncol.2017.06.002

Finn, R. S., Qin, S., Ikeda, M., Galle, P. R., Ducreux, M., Kim, T.-Y., Kudo, M., Breder, V., Merle, P., Kaseb, A. O., Li, D., Verret, W., Xu, D.-Z., Hernandez, S., Liu, J., Huang, C., Mulla, S., Wang, Y., Lim, H. Y., … Cheng, A.-L. (2020). Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. *New England Journal of Medicine*, *382*(20), 1894–1905. https://doi.org/10.1056/nejmoa1915745

Gandhi, A., Taylor, J., Morici, M., Reid, A., Meniawy, T., Adnan Khattak, M., Gray, E., Millward, M., & Zaenker, P. (2022). *Autoantibodies as potential biomarkers of immune-related adverse events in patients with advanced cutaneous melanoma treated with immune checkpoint inhibitors*.

Gupta, M., Stukalin, I., Meyers, D., Goutam, S., Heng, D. Y. C., Cheng, T., Monzon, J., & Navani, V. (2023). Treatment-Free Survival after Nivolumab vs Pembrolizumab vs Nivolumab-Ipilimumab for Advanced Melanoma. *JAMA Network Open*, *6*(6), E2319607. https://doi.org/10.1001/jamanetworkopen.2023.19607

Gutzmer, R., Stroyakovskiy, D., Gogas, H., Robert, C., Lewis, K., Protsenko, S., Pereira, R. P., Eigentler, T., Rutkowski, P., Demidov, L., Manikhas, G. M., Yan, Y., Huang, K. C., Uyei, A., McNally, V., McArthur, G. A., & Ascierto, P. A. (2020). Atezolizumab, vemurafenib,

and cobimetinib as first-line treatment for unresectable advanced BRAFV600 mutation-positive melanoma (IMspire150): primary analysis of the randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet*, *395*(10240), 1835–1844. https://doi.org/10.1016/S0140-6736(20)30934-X

Handel, E. E., McKeown, J., Wei, J., Kankaria, R. A., Burnette, H., Johnson, D. B., Lawless, A., Czapla, J., Sullivan, R. J., Albrecht, L. J., Zimmer, L., Mangana, J., Dummer, R., Kessels, J. I., Neyns, B., Allayous, C., Lebbe, C., Boatwright, C., Mehnert, J. M., … Carlino, M. S. (2025). Outcomes following long-term disease control with immune checkpoint inhibitors in patients with advanced melanoma. *European Journal of Cancer*, *215*. https://doi.org/10.1016/j.ejca.2024.115171

Hauschild, A., Grob, J. J., Demidov, L. V., Jouary, T., Gutzmer, R., Millward, M., Rutkowski, P., Blank, C. U., Miller, W. H., Kaempgen, E., Martín-Algarra, S., Karaszewska, B., Mauch, C., Chiarion-Sileni, V., Martin, A. M., Swann, S., Haney, P., Mirakhur, B., Guckert, M. E., … Chapman, P. B. (2012). Dabrafenib in BRAF-mutated metastatic melanoma: A multicentre, open-label, phase 3 randomised controlled trial. *The Lancet*, *380*(9839), 358–365. https://doi.org/10.1016/S0140-6736(12)60868-X

He, R., Zhao, X., Liu, J., Zhou, Y., Zhang, X., & Cheng, F. (2022). PD-1 and CTLA-4 inhibitors in combination vs. alone for the treatment of advanced melanoma: A systematic review and meta-analysis. In *Medicine (United States)* (Vol. 101, Number 41, p. E30561). Lippincott Williams and Wilkins. https://doi.org/10.1097/MD.0000000000030561

Hellmann, M. D., Paz-Ares, L., Bernabe Caro, R., Zurawski, B., Kim, S.-W., Carcereny Costa, E., Park, K., Alexandru, A., Lupinacci, L., de la Mora Jimenez, E., Sakai, H., Albert, I., Vergnenegre, A., Peters, S., Syrigos, K., Barlesi, F., Reck, M., Borghaei, H., Brahmer, J. R., … Ramalingam, S. S. (2019). Nivolumab plus Ipilimumab in Advanced Non–Small-Cell Lung Cancer. *New England Journal of Medicine*, *381*(21), 2020–2031. https://doi.org/10.1056/nejmoa1910231

Ibis, B., Aliazis, K., Cao, C., Yenyuwadee, S., & Boussiotis, V. A. (2023). Immune-related adverse effects of checkpoint immunotherapy and implications for the treatment of patients with cancer and autoimmune diseases. In *Frontiers in Immunology* (Vol. 14). Frontiers Media S.A. https://doi.org/10.3389/fimmu.2023.1197364

Jackson-Carroll, N., Whisenant, M., Crane, S., & Johnson, C. (2025). Impact of Immune Checkpoint Inhibitor Therapy on Quality of Life in Patients With Advanced Melanoma: A Systematic Review. In *Cancer Nursing* (Vol. 48, Number 4, pp. 261–279). Lippincott Williams and Wilkins. https://doi.org/10.1097/NCC.0000000000001299

Kao, S. Y. Z., Ekwueme, D. U., Holman, D. M., Rim, S. H., Thomas, C. C., & Saraiya, M. (2023). Economic burden of skin cancer treatment in the USA: an analysis of the Medical Expenditure Panel Survey Data, 2012–2018. *Cancer Causes and Control*, *34*(3), 205–212. https://doi.org/10.1007/s10552-022-01644-0

Kim, H., Hyung, C., Park, K., Kim, Y., & Joo, Y. (n.d.). *Original Research Article Correlates of Psychological Distress in Patients With Cancer*.

Larkin, J., Chiarion-Sileni, V., Gonzalez, R., Grob, J.-J., Rutkowski, P., Lao, C. D., Cowey, C. L., Schadendorf, D., Wagstaff, J., Dummer, R., Ferrucci, P. F., Smylie, M., Hogg, D., Hill, A., Márquez-Rodas, I., Haanen, J., Guidoboni, M., Maio, M., Schöffski, P., … Wolchok, J. D. (2019). Five-Year Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma. *New England Journal of Medicine*, *381*(16), 1535–1546. https://doi.org/10.1056/nejmoa1910836

Larkin, J., Minor, D., Angelo, S. D. ', Neyns, B., Smylie, M., Miller, W. H., Gutzmer, R., Linette, G., Chmielowski, B., Lao, C. D., Lorigan, P., Grossmann, K., Hassel, J. C., Sznol, M., Daud, A., Sosman, J., Khushalani, N., Schadendorf, D., Hoeller, C., … Weber, J. (2017). JOURNAL OF CLINICAL ONCOLOGY Overall Survival in Patients With Advanced Melanoma Who Received Nivolumab Versus Investigator's Choice Chemotherapy in CheckMate 037: A Randomized, Controlled, Open-Label Phase III Trial. *J Clin Oncol*, *36*, 383–390. https://doi.org/10.1200/JCO

Maio, M., Grob, J. J., Aamdal, S., Bondarenko, I., Robert, C., Thomas, L., Garbe, C., Chiarion-Sileni, V., Testori, A., Chen, T. T., Tschaika, M., & Wolchok, J. D. (2015). Five-year survival rates for treatment-naive patients with advanced melanoma who received ipilimumab plus dacarbazine in a phase III trial. *Journal of Clinical Oncology*, *33*(10), 1191–1196. https://doi.org/10.1200/JCO.2014.56.6018

Mandalà, M., Amaral, T., Rutkowski, P., Sergi, M. C., Rasch, M. L., Benannoune, N., Serra, P., Vitale, M. G., Giannarelli, D., Arance, A. M., Couselo, E. M., Neyns, B., Dirven, I., Tucci, M., Guida, M., Spagnolo, F., Rossi, E., Queirolo, P., Quaglino, P., … Ascierto, P. A. (2025). Combined immunotherapy with nivolumab and ipilimumab with and without sequential or concomitant stereotactic radiotherapy in patients with melanoma brain metastasis: An international retrospective study. *European Journal of Cancer*, *225*. https://doi.org/10.1016/j.ejca.2025.115567

Motzer, R. J., Tannir, N. M., McDermott, D. F., Arén Frontera, O., Melichar, B., Choueiri, T. K., Plimack, E. R., Barthélémy, P., Porta, C., George, S., Powles, T., Donskov, F., Neiman, V., Kollmannsberger, C. K., Salman, P., Gurney, H., Hawkins, R., Ravaud, A., Grimm, M.-O., … Escudier, B. (2018). Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma. *New England Journal of Medicine*, *378*(14), 1277–1290. https://doi.org/10.1056/nejmoa1712126

Olsson-Brown, A., Jain, A., Frazer, R., Farrugia, D., Carser, J., Houghton, J., Lewis, R. D., D'Mello, S., & Emanuel, G. (2025). Clinical Management and Outcomes of Immune-Related Adverse Events During Treatment with Immune Checkpoint Inhibitor Therapies in Melanoma and Renal Cell Carcinoma: A UK Real-World Evidence Study. *Oncology and Therapy*. https://doi.org/10.1007/s40487-025-00349-z

Pham, J. P., Joshua, A. M., da Silva, I. P., Dummer, R., & Goldinger, S. M. (2023). Chemotherapy in Cutaneous Melanoma: Is There Still a Role? In *Current Oncology Reports* (Vol. 25, Number 6, pp. 609–621). Springer. https://doi.org/10.1007/s11912-023-01385-6

Pinar Bilir, S., Ma, Q., Zhao, Z., Wehler, E., Munakata, J., & Barber, B. (2016). *Economic Burden of Toxicities Associated with Treating Metastatic Melanoma in the United States* (Vol. 9). www.AHDBonline.com

Raeber, M. E., Sahin, D., Karakus, U., & Boyman, O. (2023). A systematic review of interleukin-2-based immunotherapies in clinical trials for cancer and autoimmune diseases. *EBioMedicine*, *90*. https://doi.org/10.1016/j.ebiom.2023.104539

Reck, M., Schenker, M., Lee, K. H., Provencio, M., Nishio, M., Lesniewski-Kmak, K., Sangha, R., Ahmed, S., Raimbourg, J., Feeney, K., Corre, R., Franke, F. A., Richardet, E., Penrod, J. R., Yuan, Y., Nathan, F. E., Bhagavatheeswaran, P., DeRosa, M., Taylor, F., … Brahmer, J. (2019). Nivolumab plus ipilimumab versus chemotherapy as first-line treatment in advanced non–small-cell lung cancer with high tumour mutational burden: patient-reported outcomes results from the randomised, open-label, phase III CheckMate 227 trial. *European Journal of Cancer*, *116*, 137–147. https://doi.org/10.1016/j.ejca.2019.05.008

Ribas, A., Puzanov, I., Dummer, R., Schadendorf, D., Hamid, O., Robert, C., Hodi, F. S., Schachter, J., Pavlick, A. C., Lewis, K. D., Cranmer, L. D., Blank, C. U., O'Day, S. J., Ascierto, P. A., Salama, A. K. S., Margolin, K. A., Loquai, C., Eigentler, T. K., Gangadhar, T. C., … Daud, A. (2015). Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomised, controlled, phase 2 trial. *The Lancet Oncology*, *16*(8), 908–918. https://doi.org/10.1016/S1470-2045(15)00083-2

Robert, C., Karaszewska, B., Schachter, J., Rutkowski, P., Mackiewicz, A., Stroiakovski, D., Lichinitser, M., Dummer, R., Grange, F., Mortier, L., Chiarion-Sileni, V., Drucis, K., Krajsova, I., Hauschild, A., Lorigan, P., Wolter, P., Long, G. V., Flaherty, K., Nathan, P., … Schadendorf, D. (2015). Improved Overall Survival in Melanoma with Combined Dabrafenib and Trametinib. *New England Journal of Medicine*, *372*(1), 30–39. https://doi.org/10.1056/nejmoa1412690

Robert, C., Long, G. V., Brady, B., Dutriaux, C., Maio, M., Mortier, L., Hassel, J. C., Rutkowski, P., McNeil, C., Kalinka-Warzocha, E., Savage, K. J., Hernberg, M. M., Lebbé, C., Charles, J., Mihalcioiu, C., Chiarion-Sileni, V., Mauch, C., Cognetti, F., Arance, A., … Ascierto, P. A. (2015). Nivolumab in Previously Untreated Melanoma without BRAF Mutation . *New England Journal of Medicine*, *372*(4), 320–330. https://doi.org/10.1056/nejmoa1412082

Robert, C., Schachter, J., Long, G. V., Arance, A., Grob, J. J., Mortier, L., Daud, A., Carlino, M. S., McNeil, C., Lotem, M., Larkin, J., Lorigan, P., Neyns, B., Blank, C. U., Hamid, O., Mateus, C., Shapira-Frommer, R., Kosh, M., Zhou, H., … Ribas, A. (2015). Pembrolizumab versus Ipilimumab in Advanced Melanoma. *New England Journal of Medicine*, *372*(26), 2521–2532. https://doi.org/10.1056/nejmoa1503093

Schadendorf, D., Dummer, R., Hauschild, A., Robert, C., Hamid, O., Daud, A., van den Eertwegh, A., Cranmer, L., O'Day, S., Puzanov, I., Schachter, J., Blank, C., Salama, A., Loquai, C., Mehnert, J. M., Hille, D., Ebbinghaus, S., Kang, S. P., Zhou, W., & Ribas, A. (2016). Health-related quality of life in the randomised KEYNOTE-002 study of pembrolizumab versus

chemotherapy in patients with ipilimumab-refractory melanoma. *European Journal of Cancer*, *67*, 46–54. https://doi.org/10.1016/J.EJCA.2016.07.018

Sood, S., Jayachandiran, R., & Pandey, S. (2021). Current Advancements and Novel Strategies in the Treatment of Metastatic Melanoma. In *Integrative Cancer Therapies* (Vol. 20). SAGE Publications Inc. https://doi.org/10.1177/1534735421990078

Sterne, J. A. C., Savović, J., Page, M. J., Elbers, R. G., Blencowe, N. S., Boutron, I., Cates, C. J., Cheng, H. Y., Corbett, M. S., Eldridge, S. M., Emberson, J. R., Hernán, M. A., Hopewell, S., Hróbjartsson, A., Junqueira, D. R., Jüni, P., Kirkham, J. J., Lasserson, T., Li, T., … Higgins, J. P. T. (2019). RoB 2: A revised tool for assessing risk of bias in randomised trials. *The BMJ*, *366*. https://doi.org/10.1136/bmj.l4898

Tawbi, H. A., Hodi, F. S., Lipson, E. J., Schadendorf, D., Ascierto, P. A., Matamala, L., Castillo Gutiérrez, E., Rutkowski, P., Gogas, H., Lao, C. D., Janoski De Menezes, J., Dalle, S., Arance, A. M., Grob, J. J., Ratto, B., Rodriguez, S., Mazzei, A., Dolfi, S., & Long, G. V. (2025). Three-Year Overall Survival With Nivolumab Plus Relatlimab in Advanced Melanoma From RELATIVITY-047. *Journal of Clinical Oncology*, *43*(13), 1546–1552. https://doi.org/10.1200/JCO.24.01124

Ugurel, S., Röhmel, J., Ascierto, P. A., Flaherty, K. T., Grob, J. J., Hauschild, A., Larkin, J., Long, G. V., Lorigan, P., McArthur, G. A., Ribas, A., Robert, C., Schadendorf, D., & Garbe, C. (2017). Survival of patients with advanced metastatic melanoma: the impact of novel therapies–update 2017. *European Journal of Cancer*, *83*, 247–257. https://doi.org/10.1016/J.EJCA.2017.06.028

Weber, J. S., D'Angelo, S. P., Minor, D., Hodi, F. S., Gutzmer, R., Neyns, B., Hoeller, C., Khushalani, N. I., Miller, W. H., Lao, C. D., Linette, G. P., Thomas, L., Lorigan, P., Grossmann, K. F., Hassel, J. C., Maio, M., Sznol, M., Ascierto, P. A., Mohr, P., … Larkin, J. (2015). Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): A randomised, controlled, open-label, phase 3 trial. *The Lancet Oncology*, *16*(4), 375–384. https://doi.org/10.1016/S1470-2045(15)70076-8

Wolchok, J. D., Chiarion-Sileni, V., Rutkowski, P., Cowey, C. L., Schadendorf, D., Wagstaff, J., Queirolo, P., Dummer, R., Butler, M. O., Hill, A. G., Postow, M. A., Gaudy-Marqueste, C., Medina, T., Lao, C. D., Walker, J., Márquez-Rodas, I., Haanen, J. B. A. G., Guidoboni, M., Maio, M., … Larkin, J. (2025). Final, 10-Year Outcomes with Nivolumab plus Ipilimumab in Advanced Melanoma. *New England Journal of Medicine*, *392*(1), 11–22. https://doi.org/10.1056/nejmoa2407417

Wolchok, J. D., Thomas, L., Bondarenko, I. N., O'Day, S., Weber, J. S., Garbe, C., Francis, S., Ibrahim, R. A., Hoos, A., & Robert, C. (2011). Phase III randomized study of ipilimumab (IPI) plus dacarbazine (DTIC) versus DTIC alone as first-line treatment in patients with unresectable stage III or IV melanoma. *Journal of Clinical Oncology*, *29*(18_suppl), LBA5–LBA5. https://doi.org/10.1200/jco.2011.29.18_suppl.lba5