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Project thesis

A Comparative Analysis of Monotherapy with PD-1/PD-L1 Inhibitors and Combination Therapy with PD-1/PD-L1 and CTLA-4 Inhibitors in Cancer Treatment

A systematic overview

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Abstract

Background: The advent of immune checkpoint inhibitors, particularly the inhibitors of PD-1/PD-L1 and CTLA-4, has marked a paradigm shift in cancer treatment. While monotherapy with these inhibitors has shown promise, the exploration of combination therapy involving PD-1/PD-L1 and CTLA-4 inhibitors has gained substantial attention.

Purpose: This article aims to provide a comprehensive comparative analysis of the efficacy and safety profiles of monotherapy with PD-1/PD-L1 inhibitor against combination therapy incorporating PD-1/PD-L1 and CTLA-4 inhibitors in the context of cancer treatment.

Method: A systematic literature search was conducted on PubMed, identifying relevant studies published up to the knowledge cutoff date in January 2024. Twelve clinical studies were found after using search strings and going through an assessment based on title, abstract and full text.

Results: The studies cover the cancer subtypes: melanoma, small cell lung carcinoma (SCLC), non-small cell lung carcinoma (NSCLC), oral cavity squamous cell carcinoma, sarcoma, pleural mesothelioma, glioblastoma and urothelial carcinoma. Combination therapy yielded significant superior efficacy in terms of both response rate and survival, exceptions being in glioblastoma and SCLC. Combination therapy exhibited higher frequency in grade 3-4 adverse effects in all studies.

Conclusion: Combination therapy has demonstrated greater effectiveness in enhancing overall response rates and survival rates; nevertheless, it warrants cautious consideration due to its association with more frequent and severe adverse effects. Variability in response is observed and thus necessitates further research in understanding the biomarkers and tumor microenvironment.

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Introduction

Cancer treatment has witnessed transformative advances with the advent of immune checkpoint inhibitors, particularly those targeting PD-1/PD-L1 and CTLA-4 pathways. The prospect of synergistic effects and enhanced efficacy in combining PD-1 and CTLA-4 inhibitors piqued my curiosity, motivating me to delve into this avenue of research. This exploration is not just a theoretical inquiry but a practical investigation into numerous clinical studies that scrutinize the effectiveness and safety profiles of both monotherapy with PD-1/PD-L1 inhibitors and combination therapy with PD-1/PD-L1 and CTLA-4 inhibitors.

This systematic review aims to conduct a comparative analysis of monotherapy with PD-1 inhibitors and combination therapy with PD-1 and CTLA-4 inhibitors in the context of cancer treatment.

Background

What is cancer?

"Cancer is a disease in which some of the body's cells grow uncontrollably and spread to other parts of the body" (1). Today, it is understood that cancer is a genomic disease, marked by genomic instability that results in the accumulation of numerous point mutations and structural changes during tumor progression (2,3). Arising from mutated cellular genes, cancer cells exhibit antigens that distinguish them from their nontransformed counterparts. These antigens manifest in various forms, including differentiation antigens, mutational antigens, overexpressed cellular antigens, viral antigens, and unsilenced antigens (4). Recognition of these antigens by the immune system can induce a cascade of immune responses, perceiving the cancer cells as foreign entities.(4–6). This process is generally known as, immunosurveillance, where immune cells from both the adaptive and innate immune systems invade the tumor microenvironment (TME) and contribute to the regulation of tumor progression (7). The innate immune system includes cells such as: granulocytes (eosinophils, basophils, and neutrophils), natural killer cells (NK), mast cells, monocytes, macrophages, and dendritic cells (8). They contribute in tumor suppression by directly eliminating tumor cells or by signalling the adaptive immune system (9). The adaptive immune system consists of lymphocytes, such as B-cells and T-cells (8). B- and T-cells contribute in tumor suppression through humoral immune responses and cell-mediated immune responses, respectively (5,6).

In a state of optimal functionality, the immune system is adept at recognizing and eliminating cancer cells, thereby disrupting their phenotypes and functions. However, cancer cells have evolved and implemented mechanisms to evade both immunosurveillance and immunomediated destruction. This evasion may occur by exploiting defects in the antigen-presenting mechanism, recruiting immunosuppressive cell populations, or activating negative regulatory pathways, allowing them to circumvent immune recognition (3,10). As our comprehension of the immune system and its surveillance capabilities advanced, there has been growing interest in leveraging immune cells for the eradication of cancer. Consequently, numerous approaches have been devised and immunotherapy has proven to be a promising treatment option (11,12).

One of the earliest approaches in cancer treatment within immunotherapy was the use and administration of interleukin-2 (IL-2), a cytokine known for stimulating T-cell proliferation, thus exerting immune-stimulatory properties (3). Nevertheless, the initial wave of immunotherapies faced limitations, including low response rates and a high occurrence of severe adverse events (3,13,14). The pursuit of reliable targets for immune response modulation led to the identification of checkpoints in T-cell activation, paving the way for the creation of monoclonal antibodies targeting these checkpoints. Notably, cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1) emerged as the most dependable targets. Drugs designed to target CTLA-4 and PD-1 have had a profound impact on the outcomes of advanced cancer treatments, revolutionizing the field.

CTLA-4 inhibitors

For a T-cell to become activated, it requires >1 stimulatory signals when interacting with an antigen presenting cell (APC). Binding of the T-cell receptor (TCR) to major histocompatibility complex confers specificity for T-cell activation but it requires additional costimulatory signals (15–17)**.** Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) is a co-inhibitory receptor found on the surface of activated T-cells (CD4+ and CD8+), and functions to negatively regulate T-cell activation (3,17). CD28 is homologous to CTLA-4 and is also expressed by T-cells, but functions to positively regulate T-cell activation, thus mediating opposing functions. Both CTLA-4 and CD28 compete for ligand binding with B7 ligands (B7-1/CD80 dimer and B7-2/CD86 monomer) presented on APCs. However, CTLA-4 receptors have a higher affinity to B7 ligands but lower surface density, thereby outcompeting CD28 receptors. The sum of stimulatory signals from CD28-B7 binding and

inhibitory signals from CTLA4-B7 binding, determines the path of anergy or activation in T-cells (3,13,15–18). Furthermore, the CTLA-4 receptor has been shown to sequester B7 ligand from the surface of APCs, significantly depleting the surface of the ligand and consequently mediating an enhanced inhibitory function (13).

One could hypothesize that blocking this pathway could aid in immunosurveillance and eliminate cancer cells, hence CTLA-4 inhibitors were developed. CTLA-4 inhibitors are monoclonal antibodies (mAbs) that function by blocking the inhibitory signals transmitted by CTLA-4, essentially removing the brakes on the immune system. This induces effective immune responses by activating and inducing proliferation of T-cells, and empowering the immune system to better recognize and eliminate cancer cells, thus leading to tumor regression. After some years of clinical trials and efficacy evaluations, Ipilimumab, was finally approved by the FDA in 2011 for cancer treatment (3,10,13).

PD-1/PD-L1 inhibitors

Like CTLA-4, programmed cell death protein 1 (PD-1/CD279) is also a co-inhibitory cell surface receptor of the B7/CD28 family (13,16,17). PD-1 is minimally expressed on resting cells of the immune system. However, upon activation, PD-1 expression is widely induced in T-cells, B-cells and NK cells. The receptor is also expressed on Tregs, NKT cells, activated monocytes and myeloid DCs (17,19).

PD-1 has two distinct ligands: PD-L1 (B7-H1/CD274) and PD-L2 (B7-DC/CD273), which are also members of the B7 family. In contrast to “normal” B7 ligands, PD-L1 is expressed on both hematopoietic and nonhematopoietic cells, including DCs, macrophages, mast cells, B-cells, T-cells, endothelial cells, and several types of epithelial cells. Expression of these ligands are enhanced by inflammatory signals, such as TNF-α, IFN-γ, GM-CSF, and IL-4 (17). PD-1 binding to its ligand results in suppression of TCR-mediated lymphocyte proliferation, cytokine secretion and cytotoxic ability of effector immune cells, and thereby reducing the immune response (20) PD-L2 is less understood, as studies show that PD-L2-deficient mice have been reported both enhanced (21) or impaired in T-cell response (22).

Cancer cells exploit this pathway by abnormally expressing PD-L1 on their cell surface, thus sequestering themselves from immunosurveillance and effectively inactivating further immune responses (3). PD-1 and PD-L1 inhibitors are monoclonal antibodies (mAbs) and are designed to block the interaction between PD-1 and its ligands (PD-L1 and PD-L2). By doing so, these inhibitors release the brakes on the immune system, allowing T-cells to mount a

more robust and effective attack against cancer cells. This approach is aimed at overcoming the immune evasion mechanisms employed by tumors. To date, the FDA has approved several PD-1/PD-L1 inhibitors, and the first one was Nivolumab (Opdivo) in 2014 (23).

Table 1 - List of FDA approved drugs targeting CTLA-4 and PD-1 (current as January 2024)

Drug	Brand name	Year of first approval	Indication
PD-1 inhibitors			
- **Pembrolizumab**	Keytruda	2014	Metastatic melanoma, surgically resectable 'high-risk melanoma (adjuvant setting), metastatic NSCLC, classical Hodgkin's lymphoma, primary mediastinal B-cell lymphoma (PMBCL), HNSCC, gastric cancer, solid tumors with MSI-H and MMR aberrations, metastatic urothelial carcinoma, Merkel cell carcinoma, renal cell carcinoma, cervical cancer, hepatocellular carcinoma, biliary tract cancer (BTC)
- **Nivolumab**	Opdivo	2014	Metastatic or unresectable melanoma, metastatic non-small-cell lung cancer (NSCLC), small-cell lung cancer (SCLC), renal cell carcinoma (RCC), classical Hodgkins's lymphoma, metastatic head and neck squamous cell carcinoma, metastatic urothelial carcinoma, hepatocellular carcinoma (HCC), colorectal cancer with MSI-H and MMR aberrations
- **Cemiplimab**	Libtayo	2018	Metastatic cutaneous squamous cell carcinoma (CSCC) or locally advanced CSCC who are not candidates for curative surgery or curative radiation
- **Dostarlimab**	Jemperli	2021	Endometrial cancer
PD-L1 inhibitors			
- **Atezolizumab**	Tecentriq	2016	Metastatic urothelial carcinoma, metastatic NSCLC (monotherapy and in combination with chemotherapy), metastatic SCLC (in combination with chemotherapy) and metastatic triple negative breast cancer (in combination with paclitaxel), unresectable or metastatic alveolar soft part sarcoma (ASPS), unresectable or metastatic hepatocellular carcinoma (in combination with bevacizumab)
- **Avelumab**	Bavencio	2017	Merkel cell carcinoma, metastatic urothelial carcinoma
- **Durvalumab**	Imfinzi	2017	Metastatic urothelial carcinoma, unresectable stage III NSCLC, hepatocellular carcinoma (in combination with tremelimumab), metastatic biliary tract carcinoma (in combination with tremelimumab), extensive-stage small cell lung cancer (ES-SCLC) (in combination with etoposide and either carboplatin or cisplatin)
CTLA-4 inhibitors			
- **Ipilimumab**	Yervoy	2011	Metastatic or unresectable melanoma in adults and pediatric patients
- **Tremelimumab**	Imjuno	2022	Hepatocellular carcinoma
Combination of CTLA-4 and PD-1 inhibitor - **Ipilimumab + nivolumab**	Yervoy + Opdivo	2015	Metastatic melanoma, metastatic renal cell carcinoma, colorectal cancer with MSI-H and MMR aberration, hepatocellular carcinoma (HCC), non-small cell lung cancer (NSCLC), unresectable malignant pleural mesothelioma

Updates gathered via: https://www.fda.gov/drugs/resources-information-approved-drugs/oncology-cancer-hematologic-malignancies-approval-notifications

Materials and Methods

Literature search strategy

The search was conducted on PubMed during two separate periods: from the 17th of June, 2023, to the 6th of July, 2023, and from the 30th of November, 2023, to the 20th of December, 2023.

A comprehensive search strategy was developed using the following keywords: ((PD-1 inhibitors) OR (programmed cell death protein 1 inhibitors) OR (PD-L1 inhibitors) OR (Programmed death-ligand 1)) AND ((CTLA-4 inhibitors) OR (cytotoxic T-lymphocyte-associated protein 4 inhibitors)) AND (monotherapy) AND (combination therapy) AND (cancer treatment).

Study selection

The inclusion criteria and exclusion criteria were determined prior to the search.

Inclusion Criteria:

1. Studies investigating PD-1 inhibitors in monotherapy
2. Studies exploring combination therapy with both PD-1 and CTLA-4 inhibitors
3. Clinical studies, retrospective studies, real-life studies, and other types of studies

Exclusion Criteria:

1. Studies not related to monotherapy with PD-1 inhibitors or combination therapy with PD-1 and CTLA-4 inhibitors in cancer treatment
2. Studies lacking information on relevant outcomes
3. Studies using a combination of other drugs with immune check inhibitors
4. Articles covering reviews, guidelines, and editorials
5. Virtual patients

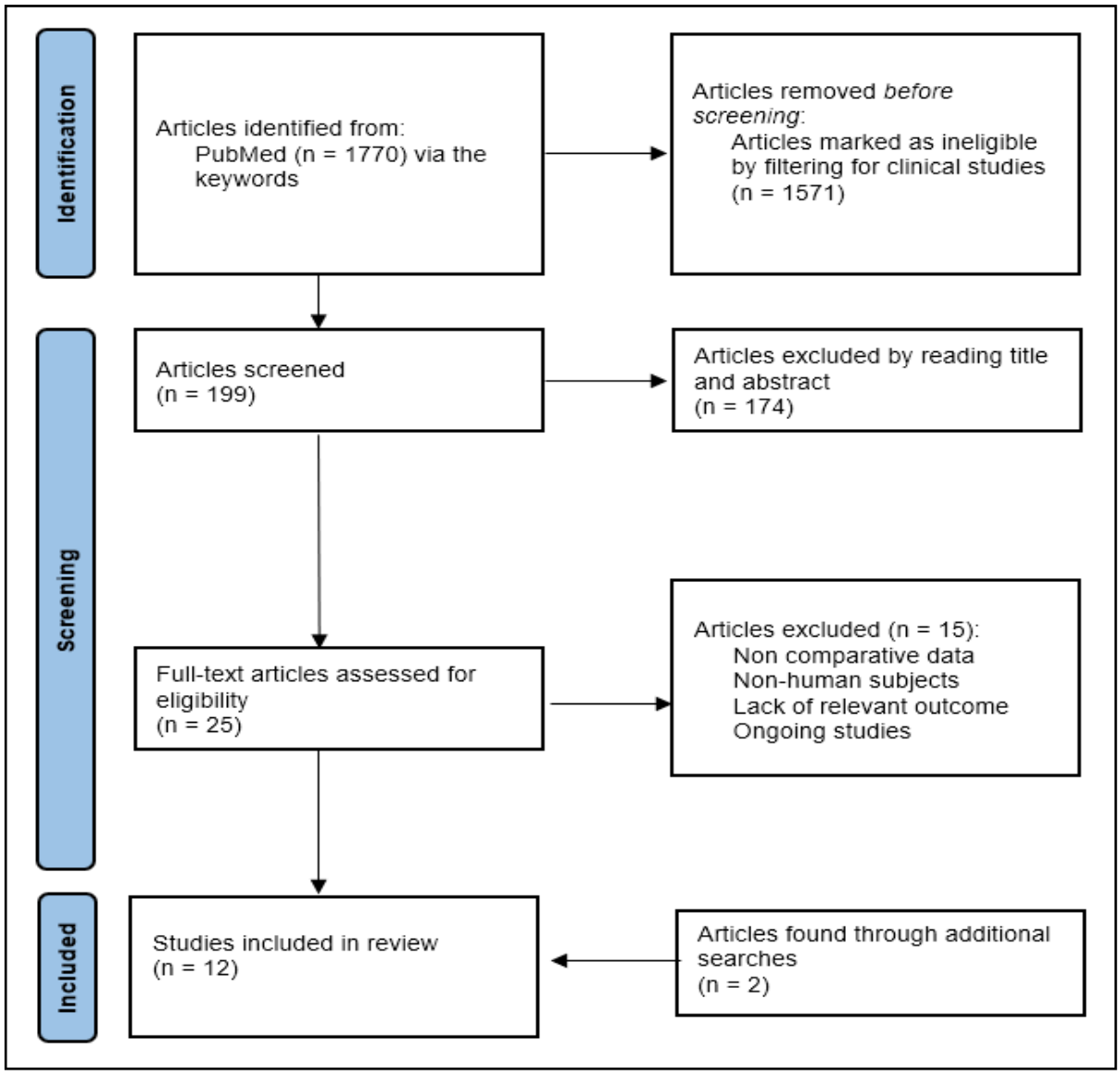
Additional Searches:

To ensure representation across different cancer types, additional searches were conducted for specific cancer types. These searches were performed separately for monotherapy and combination therapy. The goal was to identify articles that focused exclusively on a certain cancer type if only combinational or monotherapeutic approaches were published.

Search Results:

The initial search yielded 1770 results. To prioritize recent studies, the search was sorted chronologically. The results were then refined by filtering for clinical studies, resulting in 199 articles. A detailed screening process, involving a review of titles and abstracts, was conducted, leading to the selection of 25 probable articles. A thorough examination of the full texts was performed, ultimately identifying 10 articles that met the criteria for inclusion. The additional search yielded 2 articles and a total of 12 articles were used in preparation of this comparative analysis.

Figure 1 – Visualization of the search conducted



Results

Table 2 - Clinical studies in melanoma

Patient group and number of participants	Treatment	Trial, ID	Outcomes		Reference
			Monotherapy	Combination therapy	
High-risk resectable melanoma, n=23 (nivo=12, nivo+ipil=11)	Nivolumab ± ipilimumab	Phase 2, NCT02519322	**ORR:** 25% **17,2 months PFS:** 58% **pCR rates:** 25% **23 months OS rate:** 76% **Grade 3 AEs:** 8%	**ORR:** 73% **17,2 months PFS:** 82% **pCR rates:** 45% **23 months OS rate:** 100% **Grade 3 AEs:** 73%	Amaria et al 2018
Previously untreated advanced melanoma, n=945 (nivo=316, nivo+ipil=314, ipil=315)	Nivolumab ± ipilimumab	Phase 3, NCT01844505	**ORR:** 43.7% **Median PFS:** 6.9 months **12 months PFS rate:** 48% **Grade 3-4 AEs:** 16.3%	**ORR:** 57.6% **Median PFS:**11.5 months **12 months PFS rate:** 53% **Grade 3-4 AEs:** 55.0%	Larkin et al 2015
Previously untreated advanced melanoma	Nivolumab ± ipilimumab	Phase 3, NCT01844505	**ORR:** 45% **Complete response:** 18% **Median PFS:** 6.9 months **4 year PFS rate:** 31% **Median OS:** 36.9 months **4 year OS rate:** 46% **Grade 3-4 AEs:** 22%	**ORR:** 58% **Complete response:** 21% **Median PFS:**11.5 months **4 year PFS rate:** 37% **Median OS:** Not reached **4 year OS rate:** 53% **Grade 3-4 AEs:** 59.0%	Hodi et al 2018
Previously untreated advanced melanoma	Nivolumab ± ipilimumab	Phase 3, NCT01844505	**ORR:** 45% **Median PFS:** 6.9 months **6 year PFS:** 23% **Median OS:** 36.9 months **6.5 years OS rate:** 43% **Grade 3-4 AEs:** 22%	**ORR:** 58% **Median PFS:**11.5 months **6 year PFS:** 38% **Median OS:** 72.1 months **6.5 years OS rate:** 57% **Grade 3-4 AEs:** 59.0%	Wolchok et al 2021

AE = adverse effects, ORR = overall response rate, OS = overall survival, pCR = pathological complete response, PFS = progression-free survival

Melanoma

A randomized phase II trial conducted by Amaria *et al* (24) at a single institution, as an investigator-initiated study with 23 participants, aimed to assess the efficacy and safety of PD-1 inhibitor alone or in combination with CTLA-4 inhibitor in patients with high-risk resectable melanoma (Table 2). Neoadjuvant administration was provided to participants in the form of either nivolumab monotherapy (3 mg/kg IV every 14 days for up to 4 doses) or a combination of ipilimumab with nivolumab (ipilimumab 3 mg/kg and nivolumab 1 mg/kg IV every 21 days for up to 3 doses). The study yielded notable outcomes, revealing an impressive overall response rate (ORR) of 73% in the combination therapy arm, as opposed to 25% in the monotherapy arm. Additionally, a pathologic complete response (pCR) rate of 45% was observed in the combination therapy arm, while it was 25% in the monotherapy arm. The progression-free survival (PFS) at 17.2 months showed rates of 82% and 58% for the combination therapy and monotherapy arms, respectively. The overall survival (OS) rate at 23 months was 100% for the combination therapy arm and 76% for the monotherapy arm. Regrettably, the combination therapy arm exhibited a higher incidence of grade 3 adverse events (AEs) at 73%, compared to 8% in the monotherapy arm. Based on these findings, the authors inferred that the combination therapy demonstrates efficacy. However, they also underscored the imperative need for cautious consideration of associated adverse events.

A multicentre, randomised, phase 3 trial was conducted to investigate the efficacy and safety of PD-1 inhibitor alone, CTLA-4 inhibitor alone or as in combination in patients with untreated melanoma (Table 2). However, this review will only extract data that concurs with my study, and thus only include results from PD-1 inhibitor monotherapy and combination therapy of PD-1 inhibitor and CTLA-4 inhibitor. Participants were administered either nivolumab alone (at a dosage of 3 mg/kg every 2 weeks) or a combination of nivolumab (at a dosage of 1 mg/kg every 3 weeks) and ipilimumab (at a dosage of 3 mg/kg every 3 weeks for 4 doses). Larkin *et al* (25) published their study two years after the initiation of treatment, revealing an ORR of 45% in the nivolumab arm and 58% in the nivolumab and ipilimumab arm. The median PFS was reached at 6.9 months in the monotherapy group and extended to 11.5 months in the combination therapy group. Although the 12-month PFS rates were relatively close at 48% and 53%, respectively, a long-term assessment at 4 years by Hodi *et al* (26) and at 6.5 years by Wolchok *et al* (27) revealed a significantly better PFS rate in the combination therapy arm. The 4-year PFS rate was 31% and 37%, while the 6.5-year PFS rate was 23% and 37%. Moreover, the latter two studies demonstrate a notable contrast in median OS, with 36.9 months observed in the monotherapy arm and an extended 72.1 months in the combination therapy arm. The 6.5-year OS rates were also distinctive at 43% for monotherapy and 57% for combination therapy, respectively. Across all these investigations, the authors consistently observed a substantial percentage of participants experiencing grade 3-4 AE in the combination therapy arm, reaching 55%, compared to 16.3% in the monotherapy arm. All the authors concurred in their conclusion that the study indicates a substantial advantage for combination therapy (nivolumab plus ipilimumab) over monotherapy (nivolumab alone) in the first-line treatment of advanced melanoma. Nevertheless, they emphasized the importance of considering safety profiles in future studies.

Table 3 - Clinical studies in lung cancer

Patient group and number of participants	Treatment	Trial, ID	Outcomes		Reference
			Monotherapy	Combination therapy	
Recurrent SCLC, n=243(nivolumab=147, nivolumab+ipilimumab=96)	Nivolumab ± ipilimumab	Phase 1 / 2, NCT01928394	**ORR:** 11.6% **Median PFS:** 1.4 months **12 months PFS rate:** 9.5% **Median OS:** 5.7 months **24 months OS rate:** 17.9% **Grade 3-4 AEs:** 12.9%	**ORR:** 21.9% **Median PFS:** 1.5 months **12 months PFS rate:** 11.9% **Median OS:** 4.7 months **24 months OS rate:** 16.9% **Grade 3-4 AEs:** 37.5%	Ready et al 2020
Untreated advanced NSCLC n = 1274	Pembrolizumab	Phase 3, NCT02220894	**ORR**: 39% **Median PFS:** 7.1 months **Median OS**: 20 months **24-months OS rate:** 45% **Grade 3-4 AEs:** 18%		Mok et al 2019
Untreated advanced NSCLC n = 77	Nivolumab + ipilimumab	Phase 1, NCT01454102		**ORR:** 47% **Median PFS:** 8.1 months **24-week PFS rate:** 68% **Median OS:** Not reached after 2 years **1 year OS rate:** 69% **Grade 3-4 AEs:** 37%	Hellmann et al 2017

AE = adverse effects, NSCLC = non-small cell lung carcinoma, ORR = overall response rate, OS = overall survival, PFS = progression-free survival, SCLC = small cell lung carcinoma

Lung cancer

Small cell lung carcinoma (SCLC)

The efficacy of PD-1 blockade alone or in combination with CTLA-4 blockade was evaluated in a multicenter, open-label, phase 1/2 trial involving patients with recurrent small cell lung cancer after one-to-two-year prior chemotherapy regimens (Table 3). Participants were given either nivolumab 3 mg/kg every 2 weeks or nivolumab 1 mg/kg plus ipilimumab 3 mg/kg every 3 weeks for four cycles followed by nivolumab 3 mg/kg every 2 weeks. Analysis of the outcomes revealed an ORR of 11.6% in the monotherapy arm and 21.9% in the combination therapy arm. Despite the higher response rate, median PFS and 12-month PFS rates were relatively comparable, albeit slightly better in the combination therapy arm. Similarly, OS was relatively similar, with a slightly worse outcome in the combination therapy arm. Specifically, the median PFS was 1.4 months and 1.5 months, the 12-month PFS rates were 9.5% and 11.9%, the median OS was 5.7 months and 4.7 months, and the 24-month OS rates were 17.9% and 16.9%, respectively. Additionally, a heightened frequency of grade 3-4 treatment related adverse effect (TRAE) was observed in the combination therapy arm, accounting for 37.5%, in contrast to 12.9% in the monotherapy arm. The authors concluded that monotherapy may exhibit a slight advantage in terms of toxicity and OS, yet emphasized that both arms remain clinically significant. (28)

Non-small cell lung carcinoma (NSCLC)

Mok *et al* (29) conducted a randomized, open-label, phase 3 study investigating the efficacy of PD-1 inhibitor monotherapy in patients with untreated metastatic non-small-cell lung cancer and a programmed death ligand 1 (PD-L1) tumor proportion score (TPS) of 50% or greater (Table 3). Participants received pembrolizumab at a dosage of 200 mg every 3 weeks for up to 35 cycles. The results demonstrated an ORR of 39%, with a median PFS of 7.1 months. The median OS was reported as 20 months, and the 24-month OS rate reached 45%. Notably, grade 3-4 TRAE were observed in 18% of the participants.

In a separate study led by Hellmann *et al* (30), an open-label, phase 1, multicohort investigation evaluated the efficacy of combination therapy involving a PD-1 inhibitor and a CTLA-4 inhibitor in patients with untreated metastatic non-small-cell lung cancer, administered as a first-line treatment (Table 3). The study reported an impressive ORR of 47%. Median PFS was extended to 8.1 months, with a 24-week PFS rate of 68%. Remarkably, the median OS could not be reached after 2 years, and the 1-year OS rate reached 69%. The study also observed that 37% of participants experienced grade 3-4 adverse events (AEs).

Comparatively, the monotherapy approach showed a lower ORR (39%) and a shorter median PFS (7.1 months) but reported a favorable safety profile with lower incidence of grade 3-4 AEs (18%). In contrast, the combination therapy demonstrated a higher ORR (47%), an extended median PFS (8.1 months), and an impressive 1-year OS rate (69%), but with a higher frequency of grade 3-4 AEs (37%). The choice between monotherapy and combination therapy may hinge on balancing efficacy outcomes and safety considerations based on individual patient characteristics and preferences.

Table 4 - Clinical studies in other cancer types

Patient group and number of participants	Treatment	Trial, ID	Outcomes		Reference
			Monotherapy	Combination therapy	
Untreated oral cavity squamous cell carcinoma, n=29 (nivo=14, nivo+ipil=15)	Nivolumab ± ipilimumab	Phase 2, NCT02919683	**Volumetric response:** 50% **ORR:** 13% **Pathologic downstaging:** 69% **Pathologic response:** PTR1: 38% PTR2: 15% Near complete or complete: 1 (8%) **Grade 3-4 AEs:** 14% Adjuvant radio- or chemotherapy **1 year PFS:** 85% **OS rate:** 89%	**Volumetric response:** 53% **ORR:** 38% **Pathologic downstaging:** 53% **Pathologic response:** PTR1: 40% PTR2: 33% Near complete or complete: 3 (20%) **Grade 3-4 AEs:** 33% Adjuvant radio- or chemotherapy **1 year PFS:** 85% **OS rate:** 89%	Schoenfeld et al 2020
Metastatic sarcoma, n=83 (nivo=42, nivo+ipil=41)	Nivolumab ± ipilimumab	Phase 2, NCT02500797	**ORR**: 5% **Median** PFS: 1.7 months **Median OS**: 10.7 months **12 months OS rate**: 40.4% **Grade 3-4 AEs**: 7%	**ORR**: 16% **Median PFS**: 4.1 months **Median OS**: 14.3 months **12 months OS rate**: 54.6% **Grade 3-4 AEs**: 14%	D'angelo et al 2018
Relapsed malignant pleural mesothelioma, n=125 (nivo=63, ipil=62)	Nivolumab ± ipilimumab	Phase 2, NCT02716272	**ORR:** 18.5% **Median PFS:** 4.0 months **12 months PFS rate**: 15.9% **Median OS:** 11.9 months **12 months OS rate:** 49.2% **Grade 3-4 AEs:** 14.3%	**ORR:** 27.8% **Median PFS:** 5.6 months **12 months PFS rate:** 22.6% **Median OS:** 15.9 months **12 months OS rate:** 58.1% **Grade 3-4 AEs:** 26.2%	Scherpereel et al 2019
Recurrent glioblastoma, n=40 (nivo3=10, nivo1+ipi3=10, nivo3+ipi1=20)	Nivolumab ± ipilimumab	Phase 1, NCT02017717	**ORR:** 11% **Median PFS:** 1.9 months **Median OS:** 10.4 months **Grade 3-4 AEs:** 0%	NIVO1+IPI3 / NIVO3+IPI1 **ORR:** 0% / 10% **Median PFS:** 1.5 months / 2.1 months **Median OS:** 9.2 months / 7.3 months **Grade 3-4 AEs:** 90% / 30 %	Omuro et al 2018
Previously treated metastatic urothelial carcinoma, n= 274 (nivo3=78, nivo3+ipi1=104, nivo1+ipi3=92)	Nivolumab ± ipilimumab	Phase 1 / 2, NCT01928394.	**ORR:** 25,6% **Median PFS:** 2.8 months **12 months PFS rate:** 17.9% **Median OS:** 9.9 months **12 months OS rate:** 47.3% **Grade 3-4 AEs:** 26.9%	NIVO1+IPI3 / NIVO3+IPI1 **ORR:** 26.9% / 38% **Median PFS:** 2.6 months / 4.9 months **12 months PFS rate:** 22.6% / 25.9% **Median OS:** 7.4 months / 15.3 months **12 months OS rate:** 38.3% / 56.9% **Grade 3-4 AEs:** 30.8% / 39.1%	Sharma et al 2019

AE = adverse effects, IPI1 = ipilimumab 1 mg/kg, IPI3 = ipilimumab 3 mg/kg, NIVO1 = nivolumab 1 mg/kg, NIVO3 = nivolumab 3 mg/kg, ORR = overall response rate, OS = overall survival, PFS = progression-free survival, PTR1 – Pathologic tumor response grade 1 (≥10% and <50% response), PTR2 – Pathologic tumor response grade 2 (≥50% response)

Oral cavity cancer

A randomized phase 2 trial by Schoenfeld *et al* (31) with 29 participants, investigated the safety and efficacy of PD-1 inhibitor alone or in combination with CTLA-4 inhibitor in patients with untreated squamous cell carcinoma of the oral cavity (≥T2, or clinically node positive) (Table 4). The treatment was given as neoadjuvant nivolumab alone 3 mg/kg, weeks 1 and 3, or nivolumab 3mg/kg and ipilimumab in combination (ipilimumab, 1 mg/kg, given week 1 only). The study reported an ORR of 13% in patients receiving nivolumab alone and

38% in patients that received treatment in combination with ipilimumab. Pathological downstaging was reported in 69% and 53% of the patients, respectively. Authors noted promising pathological responses in both arms: PTR1: 38% with nivolumab, 40% with nivolumab and ipilimumab; PTR2: 15% with nivolumab, 33% with nivolumab and ipilimumab. More importantly, pathologic near complete or complete responses were observed in 4 patients – 1 in the nivolumab arm (8%) and 3 in the nivolumab and ipilimumab arm (20%). It was also noted that a higher frequency of patients experienced grade 3-4 TRAE in the combination therapy arm (33%) compared to the monotherapy arm (14%). Authors concluded that both arms deemed promising, with the combination therapy demonstrating superior efficacy, but further neoadjuvant studies are needed to balance the severe toxic effects and lack of proven benefit in the metastatic setting. (31)

Sarcoma

Efficacy of PD-1 blockade alone or in combination with CTLA-4 blockade was evaluated in a multicenter, open label, randomized, non-comparative phase 2 trial in patients with advanced or metastatic sarcoma who received at least one systemic therapy (Table 4). Patients were either given nivolumab 3mg/kg alone every 2 weeks, or nivolumab 3mg/kg and ipilimumab 1mg/kg every three weeks for four doses followed by nivolumab 3mg/kg every two weeks thereafter. Analysis of the outcomes revealed that ORR were seen in 5% of the patients receiving nivolumab alone and in 16% receiving nivolumab and ipilimumab in combination. Median PFS was 1.7 months and 4.1 months, median OS was 10.7 months and 14.3 months, and 12 months OS rate was 40.4% and 54.6%, respectively. Authors also observed that grade 3-4 TRAE occurred with higher frequency with the combination therapy arm (14% of 42 patients) compared to the monotherapy arm (7% of 42 patients). The authors concluded that nivolumab monotherapy exhibited limited efficacy in sarcoma patients, while the results of the combination therapy were promising. Consequently, the prospect of further clinical trials is deemed of interest for more comprehensive evaluation (32).

Mesothelioma

A multicenter randomized non-comparative, open-label phase 2 trial by Scherpereel *et al* (33) was conducted to investigate efficacy and safety of PD-1 inhibitor alone or in combination with CTLA-4 inhibitor in patients that had histologically-proven malignant pleural mesothelioma progressing after 1st-/2nd-line treatments involving pemetrexed or platinum based treatments (Table 4). Patients were either given nivolumab alone (3 mg/kg bodyweight intravenously) every 2 weeks), or nivolumab plus ipilimumab (3 mg/kg every 2 weeks plus 1

mg/kg, every 6 weeks, intravenously). The study revealed that combination therapy had a higher ORR of 27.8% compared to an ORR of 18.5% in monotherapy treatment. A similar trend was seen in other efficacy measurements: median PFS was 5.6 months and 4.0 months, 12 months PFS rate was 22.6% and 15.9%, median OS was 15.9 months and 11.9 months, and 12 months OS rate was 58.1% and 49.2%, respectively. It was also noted that 14.3% of the patients in the monotherapy arm and 26.2% of the patients in the combination therapy arm reported a grade 3-4 AEs. The authors concluded that both therapeutic approaches yielded commendable responses, with the combination therapy suggesting potentially superior efficacy. However, a more comprehensive assessment of toxicity warrants further investigation through larger-scale trials.

Glioblastoma

The safety and efficacy of PD-1 inhibitor alone or in combination with CTLA-4 inhibitors was evaluated in a prospective phase 1 clinical trial in patients with recurrent grade IV glioblastoma (Table 4). The study was designed to test multiple dose regimens of the combination therapy, concurrently comparing with monotherapy. The doses were: nivolumab 3 mg/kg every 2 weeks (Q2W; NIVO3) or nivolumab 1 mg/kg + ipilimumab 3 mg/kg every 3 weeks (Q3W) for 4 doses, then nivolumab 3 mg/kg Q2W (NIVO1+IPI3) or nivolumab 3 mg/kg + ipilimumab 1 mg/kg Q3W for 4 doses, then nivolumab 3 mg/kg Q2W (NIVO3+IPI1). The analyses of the outcomes per investigator revealed that ORR of 11% was seen in the monotherapy arm, 0% in the NIVO1+IPI3 arm, and 10% in the NIVO3+IPI1 arm. Median PFS was 1.9 months, 1.5 months and 2.1 months, and median OS was 10.4 months, 9.2 months and 7.3 months, respectively. Notably, within the monotherapy cohort, there were no instances of grade 3-4 TRAE. In contrast, both combination regimens, namely NIVO1+IPI3 and NIVO3+IPI1, exhibited occurrences of such events at rates of 90% and 30%, respectively. Authors concluded that monotherapy was better tolerated and responded overall better compared to combination therapy. (34)

Urothelial carcinoma

In a multicenter, open-label, multiarm, phase I/II trial, the safety and efficacy of PD-1 blockade alone or in combination with CTLA-4 blockade was evaluated in patients with previously treated unresectable locally advanced or metastatic urothelial carcinoma (Table 4). The study was structured to investigate three distinct regimens: nivolumab monotherapy (administered at a dosage of 3 mg/kg every 2 weeks) denoted as NIVO3, and two nivolumab plus ipilimumab combination regimens—NIVO3+IPI1, involving nivolumab at 3 mg/kg and

ipilimumab at 1 mg/kg every 3 weeks for four doses followed by nivolumab monotherapy maintenance; and NIVO1+IPI3, comprising nivolumab at 1 mg/kg and ipilimumab at 3 mg/kg every 3 weeks for four doses followed by nivolumab monotherapy maintenance. The analyses of the outcomes as per investigator assessment revealed an ORR of 25.6% in the monotherapy arm, 26.9% in the NIVO1+IPI3 arm, and 38% in the NIVO3+IPI1 arm. The median PFS durations were 2.8 months, 2.6 months, and 4.9 months for the respective groups. The 12-month PFS rates were 17.9%, 22.6%, and 25.9%. Regarding OS, the median OS values were 9.9 months, 7.4 months, and 15.3 months, with corresponding 12-month OS rates of 47.3%, 38.3%, and 56.9%, respectively. The authors noted marginal distinctions in the incidence of grade 3-4 TRAE among the treatment groups, with rates of 26.9% for the monotherapy arm, 30.8% for the NIVO1+IPI3 arm, and 39.1% for the NIVO3+IPI1 arm. The authors reached the conclusion that NIVO1+IPI3 exhibited the most pronounced antitumor activity among all regimens, accompanied by a manageable safety profile. This outcome not only advocates for further investigation of NIVO1+IPI3 in metastatic urothelial carcinoma (mUC) but also underscores the potential advantages of immunotherapy combinations in addressing this disease. (35)

Discussion

Efficacy

The studies incorporated in this analysis (24–35) indicate that the combined use of PD-1/PD-L1 inhibitors and CTLA-4 inhibitors has proven effective in elevating overall response rates and survival rates when compared to the solitary use of PD-1/PD-L1 inhibitors across various cancer subtypes. Nevertheless, it is noteworthy that two specific studies in this review demonstrated a potential superior outcome associated with monotherapy in SCLC and glioblastoma (28,34).

Melanoma

The findings presented in four papers (24–27), which detailed outcomes in high-risk resectable and advanced melanoma, uniformly affirmed that combination therapy exhibited superior effectiveness, particularly in a neoadjuvant setting, regarding response rates and overall survival. Participant numbers in these studies varied from 23 to 945 individuals. It is noteworthy to acknowledge the potential biases introduced by the exclusive inclusion of two trials in this discussion. This is particularly relevant because one trial featured a limited sample size, while the other boasted a more substantial participant pool. The potential impact of these disparate sample sizes on the overall assessment of melanoma treatment outcomes is

a noteworthy consideration in the interpretation of the results. Despite the diversity in sample sizes and possible bias, the conclusions across all studies remained consistent and combination therapy is seen as a promising treatment choice.

The long-term outcomes of combination therapy and monotherapy was observed over a period of 6.5 years post-treatment, with documented assessments at 1 year, 4 years and 6.5 years (25–27). However, it is essential to acknowledge a limitation in the form of potential biases, as the data emanates from a singular source despite the substantial participant cohort. Despite this bias, the consistent findings underscore the preferential efficacy of combination therapy over monotherapy. This preference is highlighted by a discernible divergence in the overall survival rate observed throughout the extended 6.5-year duration, thereby emphasizing the sustained and superior effectiveness of combination therapy, thus providing further support to this approach.

Lung cancer

Small-cell lung carcinoma (SCLC)

According to the findings by Ready *et al* (28), their study concluded that combination therapy exhibited a generally higher response rate. However, monotherapy demonstrated a slightly superior overall survival, though the difference was marginal, and thus could be the preferred approach. A significant constraint in this analysis is the reliance on data from a singular source, introducing the potential for selection bias. Nevertheless, it is worth noting that the study included a substantial sample size of 243 participants, which, while not exhaustive, is considered reasonably robust, offering indicative insights. It is crucial to recognize that the observation of overall survival rates and other efficacy outcomes was limited to a relatively short duration. Consequently, there is a pressing need for additional studies to elucidate the long-term effects and sustainability of these therapeutic approaches.

Non-small cell lung carcinoma (NSCLC)

The comparative analysis between the studies conducted by Mok *et al* (29) and Hellmann *et al* (30) underscores that combination therapy exhibits a superior response and overall survival when contrasted with monotherapy. However, it is crucial to approach the interpretation of these findings with caution due to several limitations inherent in the comparison.

One notable limitation is the indirect nature of the comparison, introducing potential heterogeneity in study designs. Divergent follow-up durations and the risk of confounding variables are plausible limitations that may influence the reliability of the conclusions drawn. Moreover, a critical consideration is the use of different PD-1 inhibitors in the two studies,

pembrozulimab in one and nivolumab in the other, a factor that poses a limitation in the comparison. In the monotherapy study, participants were required to have a PD-L1 expression of 1% or greater. In contrast, the combination therapy study did not employ biomarker analyses for participant selection, introducing another variable that complicates the comparison. Additionally, the substantial variation in sample sizes, with 1274 participants in the monotherapy study compared to only 77 participants in the combination therapy study, adds an additional layer of complexity.

Despite these challenges, a pivotal phase 3 trial, NCT02477826, was undertaken to rigorously evaluate the efficacy, safety, and long-term effects of nivolumab plus ipilimumab compared to chemotherapy as first-line treatment for metastatic non-small cell lung carcinoma. Encouragingly, this study yielded promising results, demonstrating the potential of nivolumab and ipilimumab to enhance 5-year survival rates and provide durable clinical benefits, irrespective of PD-L1 expression (36). Such compelling findings underscore and lend robust support to the utilization of combination therapy as a valuable and effective approach in the treatment paradigm for NSCLC.

Other cancers

One significant common limitation across all these cancer subtypes is the reliance on data from a single study for representation, thus potentially introducing bias.

Oral cavity cancer

Schoenfeld *et al* (31) showcased promising outcomes for both treatment arms, highlighting the superior efficacy of combination therapy in terms of overall response rate and pathological response. However, it is essential to consider several limitations inherent in this study. These limitations encompass a restricted follow-up duration, thus limited knowledge of long-term effects, and a relatively modest sample size, consisting of only 29 participants. Despite the small sample size, the study yields indicative data pointing towards the promising effects of both therapies and hints at the potential superiority of combination therapy. To address these findings comprehensively, an ongoing phase 2 study (NCT02919683) is currently underway. This study employs the same treatment arms and is anticipated to offer additional insights into the use of monotherapy versus combination therapy in the context of oral cavity squamous cell carcinoma, providing a more comprehensive understanding of the treatment landscape for this particular condition.

Sarcoma

The investigation conducted by D'angelo *et al* (37) brought to light that monotherapy lacks clinical benefit. In contrast, combination therapy demonstrated promising responses, potentially surpassing the effectiveness of standard chemotherapy agents. Moreover, it exhibited superior overall survival outcomes when compared to monotherapy. Notably, this combination approach showed particular promise in specific sarcoma subtypes, including undifferentiated pleomorphic sarcoma, leiomyosarcoma, myxofibrosarcoma, and angiosarcoma. However, it is important to acknowledge the study's limitations, such as the absence of an evaluation of long-term effects and small sample size. Despite a relatively small sample size of 83 participants, the study provides indicative insights into the therapeutic effects. Additionally, further studies are imperative to comprehensively understand the enduring impact of these therapies. Currently, the combination of PD-1 and CTLA-4 is under extensive investigation in sarcoma, with several ongoing phase 2 and 3 studies. Examples include NCT03219671, NCT02982486, and NCT04741438. These endeavors aim to contribute additional data to the evolving landscape of sarcoma treatment and shed light on the potential benefits of combining immune checkpoint inhibitors in this context.

Mesothelioma

Findings from the study conducted by Scherpereel *et al* (33) indicated commendable responses for both therapeutic approaches, with combination therapy suggesting potentially superior efficacy. Despite drawing conclusions from a single source, the involvement of 125 participants lends weight to the results, offering suggestive and indicative evidence. The exploration of combination therapy is currently a focal point of extensive research, with multiple phase 2 and 3 randomized trials underway. One such phase 3 trial, NCT02899299, compared combination therapy to standard chemotherapy and concluded that the combination of nivolumab plus ipilimumab outperformed standard chemotherapy, providing long-term survival benefits and respectable responses (38). This compelling evidence not only supports the potential efficacy of combinatory immunotherapeutics for mesothelioma but also underscores the significance of ongoing research in refining treatment approaches for improved patient outcomes.

Glioblastoma

Omuro *et al* (34) reported that in the treatment of glioblastoma, monotherapy demonstrated a slightly superior response and overall survival compared to combination therapy. It is noteworthy, however, that the study's sample size was modest, consisting of only 40

participants. Despite the limited sample size, the results prompted the advancement of the study to a phase 3 trial (NCT02017717) to assess the efficacy of monotherapy in comparison to a VEGF inhibitor. Unfortunately, the outcomes of this trial did not meet the specified endpoints (39). Given the inconclusive nature of the primary trial and its inherent limitations, multiple ongoing studies are being conducted, reflecting the substantial interest in immune checkpoint inhibitors within the field. NCT04606316 is one such trial currently in progress, aiming to evaluate the efficacy and safety of a combination therapy involving nivolumab and ipilimumab. These continued investigations are vital for gaining a more comprehensive understanding of the optimal treatment approaches for glioblastoma and addressing the limitations encountered in previous trials.

Urothelial carcinoma

The study conducted by Sharma *et al* (35) elucidated that the combination therapy employing the NIVO1+IPI3 regimen exhibited superior response rates and survival outcomes compared to monotherapy. Despite drawing conclusions from a single source, the inclusion of a substantial number of participants of 274, lends robust support to the data. It is important to note, however, that the existence of multiple regimens introduces a potential limitation due to a comparatively small sample size per arm. Notably, the study also underscored the notable efficacy of combination therapy in patients with poor prognoses, adding a valuable dimension to its potential clinical applicability. Nevertheless, recognizing the promising outcomes, the NIVO1+IPI3 combination is currently under scrutiny in a phase 3 trial, NCT03036098. This trial aims to compare its efficacy to chemotherapy in patients with previously untreated metastatic urothelial carcinoma (mUC). To comprehensively assess the long-term efficacy and safety of the NIVO1+IPI3 combination, extended follow-up periods are crucial, emphasizing the need for ongoing research to refine treatment strategies for patients with mUC.

Adverse effects

While combination therapy with PD-1 and CTLA-4 inhibitors has demonstrated superior overall response rates and overall survival, it is not without its trade-offs, primarily manifesting in a higher frequency of adverse effects. Despite the substantial variation in sample sizes across all the studies, the consistency of outcomes is noteworthy. In the monotherapy arms, the occurrence of grade 3-4 adverse events (AEs) ranged from 0% to 26.9%, whereas in the combination therapy arms, this range extended from 14% to 90%.

Comparatively, monotherapy was generally found to be better tolerated, with fewer severe adverse effects. The presentation of adverse effects was similar in both therapies, with monotherapy typically associated with milder grades. Commonly reported any-grade adverse effects included fatigue, rash, diarrhea, and pruritus. Among grade 3-4 TRAE, rash, hypothyroidism, hyperthyroidism, pneumonitis, diarrhea, infusion-related reactions, and elevated serum aminotransferase levels were prevalent. While most immune-mediated adverse effects responded to corticosteroid treatment, there were instances of discontinuation due to adverse effects, though the incidence was significantly low, making direct comparisons challenging.

Notably, eight deaths suspected to be treatment-related occurred across the included studies, with several linked to pneumonitis, raising concerns about potential induction of lung toxicity. However, as of now, no studies have conclusively confirmed this suspicion. Another review exploring the possibility of immune checkpoint inhibitors inducing cardiac toxicity yielded inconclusive results (40). While both pneumonitis and cardiac toxicity are rare, they have the potential for fatal outcomes, necessitating further research to enhance understanding and prevent potential fatalities. The incidence of treatment related death was significantly low, making direct comparisons difficult.

The dosage of monotherapy using nivolumab remained consistent across all the studies, eliminating the observation of dose-related effects. However, in the context of combination therapy with nivolumab and ipilimumab, studies focusing on glioblastoma (34) and urothelial carcinoma (35) introduced a variable by comparing two distinct dosage regimens: NIVO1 + IPI3 or NIVO3 + IPI1. Interestingly, adjusting the dosage and regimen demonstrated a partial mitigation of the severity and incidence of adverse effects. It is noteworthy that the dose of nivolumab and ipilimumab associated with limited toxicity appeared to vary between the glioblastoma and urothelial carcinoma studies. Glioblastoma participants experienced limited toxicity with the NIVO3 + IPI1 regimen, whereas urothelial carcinoma participants preferred the NIVO1 + IPI3 regimen. This discrepancy could potentially be attributed to differences in sample sizes, introducing a degree of unreliability or bias into the observations. Interestingly, a separate review echoed a similar trend, noting that in melanoma and esophagogastric cancer, the NIVO1 + IPI3 regimen was preferred, while in renal cancer, colorectal cancer, and sarcoma, the NIVO3 + IPI1 regimen was favored (13).

Future perspectives

In 2011, Ipilimumab received FDA approval for the treatment of melanoma, and shortly thereafter, in 2014, Nivolumab obtained approval for the same indication (Table 1). The success attained with these treatments has paved the way for the approval of therapies for diverse cancer subtypes over the years, including pulmonary, gastric, renal, lymphatic, hepatic, and more. Nevertheless, the benefits of monotherapy were hindered by the limitation of low response rates.

The notion that combination therapy involving PD-1/PD-L1 and CTLA-4 inhibitors may exhibit greater efficacy compared to monotherapy with immune checkpoint inhibitors stems from the concept that CTLA-4 inhibitors serve as T-cell activators. This activation, in turn, facilitates PD-1/PD-L1 inhibitors in enhancing immune responses directed at the tumor.

Numerous studies have explored the synergistic potential of combining nivolumab and ipilimumab, leading to recent FDA approvals for their combined use in treating melanoma, renal cell carcinoma, hepatocellular carcinoma, colorectal cancer, pleural mesothelioma, and non-small cell lung cancer (Table 1). Representing a revolutionary advancement in immunotherapy, ongoing research is extending this combination's evaluation to various other cancer types, with the anticipation of yielding promising results.

Nevertheless, the question of why certain individuals exhibits better responses than others, and why particular cancer types demonstrate more favorable responses, remains unclear. Thus, the search for reliable biomarkers is of significant interest.

Studies suggest that a high tumor mutational load holds promise as a potential biomarker, exhibiting correlation with favorable responses to checkpoint blockade agents in melanoma and lung cancers. However, it's important to note the existence of outliers in these observations. (41,42).

Research has also indicated that the presence of tumor-infiltrating lymphocytes (TILs) and the expression of programmed death-ligand 1 (PD-L1) on the tumor tissue as potentially significant biomarkers predictive of treatment benefit in specific malignancies (41). Notably, studies conducted in untreated melanoma by Larkin *et al* (25) and in NSCLC by Mok *et al* (29) highlight this phenomenon. The results demonstrated a notably heightened response in tumors expressing PD-L1, particularly within the combination therapy group, compared to tumors with non-expressive PD-L1. These findings establish a clear association between elevated tumor PD-L1 expression and enhanced efficacy of immune checkpoint inhibitors.

On the contrary, the reasons behind monotherapy yielding a marginally superior outcome and the lack of correlation between tumor PD-L1 expression and clinical activity in the glioblastoma study by Omuro *et al* (34), remain unexplained. A significant limitation is the small sample size employed in the study.

The variations in effective doses and responses underscore the intricate distinctions in the tumor microenvironment among different cancer subtypes. The findings from future studies have the potential to offer additional insights into the immunosuppressive mechanisms within the tumor microenvironment (TME) and highlight the importance of combining CTLA-4 and PD-1 inhibition in specific types of cancer.

Summary and Conclusions

In conclusion, combination therapy involving PD-1/PD-L1 and CTLA-4 inhibitors has proven to be more effective in elevating overall response rates and survival rates. However, notable exceptions, such as superior outcomes associated with monotherapy in SCLC and glioblastoma, were observed.

Despite the success and approvals of immune checkpoint inhibitors like ipilimumab and nivolumab, challenges persist. The higher frequency of adverse effects with combination therapy, though consistent across varying sample sizes, poses a trade-off. Notable grade 3-4 adverse events were reported, and while most immune-mediated adverse effects responded to corticosteroids, cases of discontinuation were rare but noteworthy. The incidence of treatment-related deaths, particularly linked to pneumonitis, highlights the need for continued research on potential toxicities.

Dosage variations in combination therapy regimens exhibited differences in adverse effects, with ongoing reviews emphasizing the preference for specific regimens based on cancer types. The successes in melanoma, renal cell carcinoma, hepatocellular carcinoma, colorectal cancer, pleural mesothelioma, and non-small cell lung cancer highlight the transformative potential of immune checkpoint inhibitors. Nevertheless, the variability in patient responses necessitates the quest for reliable biomarkers and the understanding of diverse tumor microenvironments in order to refine treatment strategies and optimizing patient outcomes in the dynamic field of cancer treatment.

Limitations

The research papers were selected from one database by one person, and therefore this review might be affected by selection bias. The inclusion and exclusion criteria for this review were made by one person with limited knowledge and experience in the field of oncology and immunotherapy. The majority of the studies included in this review tested the combination of nivolumab and ipilimumab, and the evaluation of other PD-1/PD-L1 and CTLA-4 inhibitors is therefore not eligible. Further studies may be needed to confirm the efficacy of other PD-1/PD-L1 inhibitors and combinations with CTLA-4 inhibitors.

Abbreviations:

AE = adverse events; APC = antigen-presenting cell; CTLA-4 = cytotoxic T-lymphocyte associated protein 4; DC = dendritic cell; FDA = Food and Drug Administration; GM-CSF = granulocyte-macrophage colony-stimulating factor; HNSCC = head and neck squamous cell carcinoma; IFN-γ = interferon gamma; IL-4 = interleukin-4; IPI1 = ipilimumab 1 mg/kg; IPI3 = ipilimumab 3 mg/kg; MMR = Mismatch repair; MSI-H = Microsatellite-Instability–High; mUC = metastatic urothelial carcinoma; NIVO1 = nivolumab 1 mg/kg; NIVO3 = nivolumab 3 mg/kg; NK = natural killer cells; NKT = Natural killer T-cell; NSCLC = non-small-cell lung cancer; ORR = Overall response rate; OS = Overall survival; pCR = pathologic complete response; PD-1 = Programmed cell death protein – 1; PD-L1 = Programmed death ligand 1; PD-L2 = programmed death ligand 2; PFS = Progression free survival; PTR1 – Pathologic tumor response grade 1 (≥10% and <50% response); PTR2 – Pathologic tumor response grade 2 (≥50% response); SCLC = small-cell lung cancer; TCR = T-cell receptor; TME = tumor microenvironment; TNF-α = Tumor necrosis factor alpha; TPS = tumor proportion score; TRAE = treatment-related adverse events; Tregs = Regulatory T-cells; VEGF = Vascular endothelial growth factor

References:

1. What Is Cancer? - NCI [Internet]. 2007 [cited 2024 Jan 8]. Available from: https://www.cancer.gov/about-cancer/understanding/what-is-cancer

2. Stratton MR, Campbell PJ, Futreal PA. The cancer genome. Nature. 2009 Apr 9;458(7239):719–24.

3. Zhang Y, Zhang Z. The history and advances in cancer immunotherapy: understanding the characteristics of tumor-infiltrating immune cells and their therapeutic implications. Cell Mol Immunol. 2020 Aug;17(8):807–21.

4. Schreiber RD, Old LJ, Smyth MJ. Cancer immunoediting: integrating immunity's roles in cancer suppression and promotion. Science. 2011 Mar 25;331(6024):1565–70.

5. Gajewski TF, Schreiber H, Fu YX. Innate and adaptive immune cells in the tumor microenvironment. Nat Immunol. 2013 Oct;14(10):1014–22.

6. Mellman I, Chen DS, Powles T, Turley SJ. The cancer-immunity cycle: Indication, genotype, and immunotype. Immunity. 2023 Oct 10;56(10):2188–205.

7. Seager RJ, Hajal C, Spill F, Kamm RD, Zaman MH. Dynamic interplay between tumour, stroma and immune system can drive or prevent tumour progression. Converg Sci Phys Oncol. 2017;3:034002.

8. Stuge TB. immunsystemet. In: Store medisinske leksikon [Internet]. 2023 [cited 2024 Jan 11]. Available from: https://sml.snl.no/immunsystemet

9. Woo SR, Corrales L, Gajewski TF. Innate immune recognition of cancer. Annu Rev Immunol. 2015;33:445–74.

10. Seidel JA, Otsuka A, Kabashima K. Anti-PD-1 and Anti-CTLA-4 Therapies in Cancer: Mechanisms of Action, Efficacy, and Limitations. Front Oncol. 2018 Mar 28;8:86.

11. Hargadon KM, Johnson CE, Williams CJ. Immune checkpoint blockade therapy for cancer: An overview of FDA-approved immune checkpoint inhibitors. International Immunopharmacology. 2018 Sep 1;62:29–39.

12. Lee JB, Kim HR, Ha SJ. Immune Checkpoint Inhibitors in 10 Years: Contribution of Basic Research and Clinical Application in Cancer Immunotherapy. Immune Network [Internet]. 2022 Feb 21 [cited 2024 Jan 11];22(1). Available from: https://doi.org/10.4110/in.2022.22.e2

13. Rotte A. Combination of CTLA-4 and PD-1 blockers for treatment of cancer. J Exp Clin Cancer Res. 2019 Jun 13;38:255.

14. Dobosz P, Dzieciątkowski T. The Intriguing History of Cancer Immunotherapy. Front Immunol. 2019 Dec 17;10:2965.

15. Hosseini A, Gharibi T, Marofi F, Babaloo Z, Baradaran B. CTLA-4: From mechanism to autoimmune therapy. International Immunopharmacology. 2020 Mar 1;80:106221.

16. Buchbinder EI, Desai A. CTLA-4 and PD-1 Pathways. Am J Clin Oncol. 2016 Feb;39(1):98–106.

17. Intlekofer AM, Thompson CB. At the Bench: Preclinical rationale for CTLA-4 and PD-1 blockade as cancer immunotherapy. J Leukoc Biol. 2013 Jul;94(1):25–39.

18. Rowshanravan B, Halliday N, Sansom DM. CTLA-4: a moving target in immunotherapy. Blood. 2018 Jan 4;131(1):58–67.

19. Ghosh C, Luong G, Sun Y. A snapshot of the PD-1/PD-L1 pathway. J Cancer. 2021 Mar 5;12(9):2735–46.

20. Yi M, Zheng X, Niu M, Zhu S, Ge H, Wu K. Combination strategies with PD-1/PD-L1 blockade: current advances and future directions. Mol Cancer. 2022 Jan 21;21:28.

21. Keir ME, Liang SC, Guleria I, Latchman YE, Qipo A, Albacker LA, et al. Tissue expression of PD-L1 mediates peripheral T cell tolerance. J Exp Med. 2006 Apr 17;203(4):883–95.

22. Shin T, Yoshimura K, Shin T, Crafton EB, Tsuchiya H, Housseau F, et al. In vivo costimulatory role of B7-DC in tuning T helper cell 1 and cytotoxic T lymphocyte responses. J Exp Med. 2005 May 16;201(10):1531–41.

23. Jiang Y, Chen M, Nie H, Yuan Y. PD-1 and PD-L1 in cancer immunotherapy: clinical implications and future considerations. Hum Vaccin Immunother. 2019 Mar 19;15(5):1111–22.

24. Amaria RN, Reddy SM, Tawbi HA, Davies MA, Ross MI, Glitza IC, et al. Neoadjuvant Immune Checkpoint Blockade in High-Risk Resectable Melanoma. Nat Med. 2018 Nov;24(11):1649–54.

25. Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, et al. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. N Engl J Med. 2015 Jul 2;373(1):23–34.

26. Hodi FS, Chiarion-Sileni V, Gonzalez R, Grob JJ, Rutkowski P, Cowey CL, et al. Nivolumab plus ipilimumab or nivolumab alone versus ipilimumab alone in advanced melanoma (CheckMate 067): 4-year outcomes of a multicentre, randomised, phase 3 trial. Lancet Oncol. 2018 Nov;19(11):1480–92.

27. Wolchok JD, Chiarion-Sileni V, Gonzalez R, Grob JJ, Rutkowski P, Lao CD, et al. Long-Term Outcomes With Nivolumab Plus Ipilimumab or Nivolumab Alone Versus Ipilimumab in Patients With Advanced Melanoma. J Clin Oncol. 2022 Jan 10;40(2):127–37.

28. Ready NE, Ott PA, Hellmann MD, Zugazagoitia J, Hann CL, de Braud F, et al. Nivolumab Monotherapy and Nivolumab Plus Ipilimumab in Recurrent Small Cell Lung Cancer: Results From the CheckMate 032 Randomized Cohort. Journal of Thoracic Oncology. 2020 Mar 1;15(3):426–35.

29. Mok TSK, Wu YL, Kudaba I, Kowalski DM, Cho BC, Turna HZ, et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally

advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. The Lancet. 2019 May 4;393(10183):1819–30.

30. Hellmann MD, Rizvi NA, Goldman JW, Gettinger SN, Borghaei H, Brahmer JR, et al. Nivolumab plus ipilimumab as first-line treatment for advanced non-small-cell lung cancer (CheckMate 012): results of an open-label, phase 1, multicohort study. Lancet Oncol. 2017 Jan;18(1):31–41.

31. Schoenfeld JD, Hanna GJ, Jo VY, Rawal B, Chen YH, Catalano PS, et al. Neoadjuvant Nivolumab or Nivolumab Plus Ipilimumab in Untreated Oral Cavity Squamous Cell Carcinoma: A Phase 2 Open-Label Randomized Clinical Trial. JAMA Oncol. 2020 Oct 1;6(10):1563–70.

32. D'Angelo SP, Mahoney MR, Van Tine BA, Atkins J, Milhem MM, Jahagirdar BN, et al. A non-comparative multi-center randomized phase II study of nivolumab +/− ipilimumab for patients with metastatic sarcoma (Alliance A091401). Lancet Oncol. 2018 Mar;19(3):416–26.

33. Scherpereel A, Mazieres J, Greillier L, Lantuejoul S, Dô P, Bylicki O, et al. Nivolumab or nivolumab plus ipilimumab in patients with relapsed malignant pleural mesothelioma (IFCT-1501 MAPS2): a multicentre, open-label, randomised, non-comparative, phase 2 trial. The Lancet Oncology. 2019 Feb 1;20(2):239–53.

34. Omuro A, Vlahovic G, Lim M, Sahebjam S, Baehring J, Cloughesy T, et al. Nivolumab with or without ipilimumab in patients with recurrent glioblastoma: results from exploratory phase I cohorts of CheckMate 143. Neuro Oncol. 2018 Apr;20(5):674–86.

35. Sharma P, Siefker-Radtke A, de Braud F, Basso U, Calvo E, Bono P, et al. Nivolumab Alone and With Ipilimumab in Previously Treated Metastatic Urothelial Carcinoma: CheckMate 032 Nivolumab 1 mg/kg Plus Ipilimumab 3 mg/kg Expansion Cohort Results. J Clin Oncol. 2019 Jul 1;37(19):1608–16.

36. Brahmer JR, Lee JS, Ciuleanu TE, Bernabe Caro R, Nishio M, Urban L, et al. Five-Year Survival Outcomes With Nivolumab Plus Ipilimumab Versus Chemotherapy as First-Line Treatment for Metastatic Non–Small-Cell Lung Cancer in CheckMate 227. J Clin Oncol. 2023 Feb 20;41(6):1200–12.

37. D'Angelo SP, Mahoney MR, Van Tine BA, Atkins J, Milhem MM, Jahagirdar BN, et al. Nivolumab with or without ipilimumab treatment for metastatic sarcoma (Alliance A091401): two open-label, non-comparative, randomised, phase 2 trials. Lancet Oncol. 2018 Mar;19(3):416–26.

38. Peters S, Scherpereel A, Cornelissen R, Oulkhouir Y, Greillier L, Kaplan MA, et al. First-line nivolumab plus ipilimumab versus chemotherapy in patients with unresectable malignant pleural mesothelioma: 3-year outcomes from CheckMate 743. Ann Oncol. 2022 May;33(5):488–99.

39. Reardon DA, Brandes AA, Omuro A, Mulholland P, Lim M, Wick A, et al. Effect of Nivolumab vs Bevacizumab in Patients With Recurrent Glioblastoma: The CheckMate 143 Phase 3 Randomized Clinical Trial. JAMA Oncol. 2020 Jul 1;6(7):1003–10.

40. Cozma A, Sporis ND, Lazar AL, Buruiana A, Ganea AM, Malinescu TV, et al. Cardiac Toxicity Associated with Immune Checkpoint Inhibitors: A Systematic Review. Int J Mol Sci. 2022 Sep 19;23(18):10948.

41. Sun Q, Hong Z, Zhang C, Wang L, Han Z, Ma D. Immune checkpoint therapy for solid tumours: clinical dilemmas and future trends. Sig Transduct Target Ther. 2023 Aug 28;8(1):1–26.

42. Negrao MV, Skoulidis F, Montesion M, Schulze K, Bara I, Shen V, et al. Oncogene-specific differences in tumor mutational burden, PD-L1 expression, and outcomes from immunotherapy in non-small cell lung cancer. J Immunother Cancer. 2021 Aug 1;9(8):e002891.

43. Research C for DE and. Oncology (Cancer) / Hematologic Malignancies Approval Notifications. FDA [Internet]. 2024 Jan 19 [cited 2024 Jan 27]; Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/oncology-cancer-hematologic-malignancies-approval-notifications