Volume 4, Issue 1, 2026

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

IMMUNOTHERAPY COMBINATIONS IN STAGE IV CANCER: SYNERGISTIC EFFECTS AND CLINICAL OUTCOMES

Adeel Zain[*1], Abdul Waheed Ghanghro[2], Shahzad Jamal[3], Iqra Saleem[4], Noor Ul Ain[5], Sumaira Naz[6]

[*1]*Provincial Inspector of Drugs, Directorate of Drugs Control, Health and Population Department, Government of Punjab, Lahore, Pakistan*

[2]*Assistant Professor, Institute of Biochemistry University of Sindh, Jamshoro, Pakistan*

[3]*MS Bioenineering Uskudar University, Istanbul*

[4]*Ex Post Graduate Resident FCPS Radiation Oncology, Multan Institute of Nuclear Medicine and Radiotherapy, Multan, Pakistan*

[5]*PhD, Assistant Professor, Mukabbir University of Science and Technology Gujrat, Pakistan.*

[6]*Graduate, Dow University of Health Sciences, Clinical Coder, Clintech Solutions, Karachi, Pakistan*

[5]www.orcid.org/0000-0003-0423-2661

DOI: https://doi.org/10.5281/zenodo.18228157

Keywords

Article History

Received: 21 November 2025

Accepted: 29 December 2025

Published: 13 January 2026

Corresponding Author: *

Adeel Zain

Abstract

Objective: *The research aimed to evaluate the synergistic effects of combining various immunotherapies for treating stage IV cancer. Specifically, the study sought to determine whether combination therapies could improve clinical outcomes, slow tumor progression, and increase overall survival rates in advanced cancer patients.*

Methods: *A prospective, randomized controlled trial was conducted at a tertiary care hospital in Pakistan, involving 100 patients diagnosed with stage IV cancer. The patients were randomly assigned into two groups: Group A (combination therapy) receiving* ***Pembrolizumab*** *(200 mg every 3 weeks) and* ***Ipilimumab*** *(3 mg/kg every 3 weeks), and Group B (monotherapy) receiving* ***Pembrolizumab*** *alone (200 mg every 3 weeks). Tumor response was assessed using RECIST 1.1 criteria, while progression-free survival (PFS) and overall survival (OS) were evaluated as primary and secondary endpoints, respectively. Adverse events were monitored using the CTCAE scale, and quality of life (QoL) was assessed using the EORTC QLQ-C30 questionnaire. Data were analyzed using Kaplan-Meier survival analysis and Cox proportional hazards models.*

Results: *The results revealed that combination immunotherapies significantly reduced tumor progression and improved survival rates compared to single-agent treatments. Patients receiving combination therapies exhibited a better response rate, with 45% showing a complete or partial response to the treatment, compared to 30% in the monotherapy group.*

Conclusion: *The study concluded that combining immunotherapies in stage IV cancer patients resulted in a synergistic effect, enhancing clinical outcomes and improving overall survival rates. The findings support the potential of combination therapies as a viable treatment option for advanced cancers, warranting further investigation.*

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

INTRODUCTION

Cancer remains one of the leading causes of death worldwide, and despite numerous advancements in treatment modalities, the prognosis for patients with advanced or metastatic cancers—especially those diagnosed with stage IV cancer—remains poor. Stage IV cancer is characterized by the spread of cancer cells to distant organs, making it difficult to treat and often resulting in a limited lifespan for patients. Traditional treatments, including surgery, chemotherapy, and radiation, have shown limited efficacy in controlling the disease at such an advanced stage. In response to these challenges, immunotherapy has emerged as a promising alternative, offering new hope for patients battling stage IV cancer.

Immunotherapy is a class of cancer treatment that leverages the body's immune system to recognize and destroy cancer cells. Unlike conventional treatments, which directly target the tumor, immunotherapy works by enhancing the immune system's ability to identify and eliminate malignant cells. The development of immunotherapies, such as immune checkpoint inhibitors and monoclonal antibodies, has transformed the landscape of cancer treatment in recent years. However, while these treatments have yielded significant benefits in some patients, the majority of stage IV cancer patients fail to respond adequately, raising questions about how to improve the efficacy of immunotherapy.

One potential solution lies in the concept of combination immunotherapy, which involves using two or more different immunotherapeutic agents in tandem to enhance the body's immune response. The idea behind combination therapies is to target multiple immune pathways, thereby overcoming resistance mechanisms and increasing the likelihood of a more effective antitumor response. Combination therapies have shown considerable promise in preclinical models and early-phase clinical trials for several cancers, including melanoma, lung cancer, and renal cell carcinoma. However, the application of combination immunotherapies in stage IV cancers remains an area of ongoing research, with varying outcomes reported across different studies.

The use of combination therapies in cancer treatment is not a novel concept. In fact, chemotherapy and targeted therapies have long been used in combination to treat various cancers. The rationale for combining treatments stems from the understanding that tumors are highly heterogeneous, and a single therapeutic agent may not be sufficient to target all the different molecular pathways involved in cancer progression. By using a multi-faceted approach, researchers aim to target different aspects of cancer biology simultaneously, thereby reducing the likelihood of treatment resistance and improving patient outcomes.

In the context of immunotherapy, combination therapies typically involve pairing immune checkpoint inhibitors—such as inhibitors of programmed cell death-1 (PD-1) or its ligand (PD-L1), or cytotoxic T-lymphocyte-associated protein 4 (CTLA-4)—with other agents designed to further stimulate the immune system. These agents may include monoclonal antibodies, cancer vaccines, or cytokine therapies, all of which have shown potential in enhancing the body's ability to fight cancer. The synergy between these agents is believed to stem from their ability to work on different facets of immune regulation. For instance, PD-1 and CTLA-4 inhibitors target immune checkpoints that suppress T-cell activity, while cytokines like interleukins and interferons can promote the activation and proliferation of immune cells, further enhancing the antitumor immune response.

Despite the promising results seen in early-phase trials, there are still significant challenges to the widespread use of combination immunotherapy in stage IV cancer. One of the primary concerns is the risk of increased toxicity. Combining multiple immunotherapies or combining immunotherapy with other treatments may lead to heightened side effects, such as immune-related adverse events (irAEs), which can include inflammation of healthy organs and tissues. Managing these side effects is critical, as severe reactions may compromise the patient's overall health and may require discontinuation of the treatment regimen. Another concern is the variability in patient

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

response; not all patients experience the same level of benefit from combination therapies, and predicting which patients will respond favorably remains a challenge.

This research aims to investigate the synergistic effects of combining different immunotherapies in the treatment of stage IV cancer, with a specific focus on how these combinations impact clinical outcomes, tumor progression, and patient survival. By evaluating the efficacy of these combination therapies in a clinical trial setting, this study seeks to provide valuable insights into their potential as a viable treatment option for patients with advanced cancer. The goal is to determine whether combination immunotherapies can not only reduce tumor progression but also improve the overall survival rates of patients who are otherwise facing limited treatment options.

The Emergence of Immunotherapy in Cancer Treatment

Immunotherapy has been one of the most transformative developments in the field of oncology in the past two decades. The approval of monoclonal antibodies like rituximab (for lymphoma), trastuzumab (for breast cancer), and pembrolizumab (for melanoma and lung cancer) marked significant milestones in the fight against cancer. These therapies work by targeting specific molecules involved in tumor growth or immune evasion, thereby enhancing the immune system's ability to detect and eliminate cancer cells.

One of the key breakthroughs in immunotherapy has been the development of immune checkpoint inhibitors, which target immune checkpoints that tumors exploit to evade detection by the immune system. The PD-1/PD-L1 axis is a critical pathway in this regard, where cancer cells express PD-L1 on their surface to bind to PD-1 receptors on T cells, inhibiting immune responses against the tumor. By blocking this interaction, PD-1 inhibitors such as pembrolizumab and nivolumab have been shown to unleash T-cell activity and restore the immune system's ability to attack cancer cells.

Another important class of immune checkpoint inhibitors targets CTLA-4, a protein found on the surface of T cells that, when activated, downregulates immune responses. Ipilimumab, an anti-CTLA-4 antibody, has demonstrated efficacy in treating melanoma, where it works by stimulating T cells to mount a stronger immune response against tumors. The success of these agents in melanoma, non-small cell lung cancer (NSCLC), and other cancers has paved the way for their use in combination with other therapies to improve treatment outcomes, particularly in patients with advanced disease.

Combination Immunotherapy: A New Frontier

While immune checkpoint inhibitors have proven effective in a range of cancers, their use as monotherapies has not been universally successful, particularly in patients with stage IV cancer. Many patients either do not respond to treatment or experience a relapse after initial benefit. The rationale behind combination immunotherapy is to enhance the effectiveness of immune checkpoint inhibitors by targeting different immune pathways, thus overcoming resistance and improving clinical outcomes.

For instance, combining PD-1 inhibitors with CTLA-4 inhibitors has shown promise in improving response rates in melanoma, NSCLC, and renal cell carcinoma. The combination of these agents targets different mechanisms of immune suppression and may lead to a more robust and sustained antitumor immune response. Additionally, combining immunotherapy with other treatment modalities, such as chemotherapy or radiation therapy, is being explored to determine whether these approaches can further enhance the effectiveness of immunotherapy.

In the case of stage IV cancer, where tumors have spread to distant organs and are often resistant to treatment, the need for more aggressive and multifaceted therapies is particularly urgent. Combination immunotherapy represents an opportunity to boost the immune system's ability to target and eliminate metastatic cancer cells, potentially leading to better control of the disease and improved survival.

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Clinical Trials and Evidence Supporting Combination Immunotherapy

The development of combination immunotherapies has been supported by a growing body of clinical evidence. Clinical trials examining the combination of PD-1 inhibitors with other agents, such as CTLA-4 inhibitors, have shown promising results in various cancers. A notable example is the CheckMate-067 trial, which investigated the combination of nivolumab (PD-1 inhibitor) and ipilimumab (CTLA-4 inhibitor) in patients with advanced melanoma. The results showed that the combination therapy significantly improved overall survival and progression-free survival compared to either agent alone, highlighting the potential of combination immunotherapy in treating stage IV cancer.

Moreover, clinical trials involving combination therapies have not been limited to immune checkpoint inhibitors. Studies exploring the use of immune-modulating agents, such as cytokine therapies and monoclonal antibodies targeting tumor-associated antigens, are also underway. These trials are designed to further expand the arsenal of tools available to oncologists treating patients with advanced cancers, offering the possibility of more personalized and effective treatment options.

The Need for Further Research

While the potential of combination immunotherapies in stage IV cancer is evident, there remain several unanswered questions. The optimal combination of therapies, the best sequencing of treatments, and the management of adverse effects are all areas that require further investigation. Additionally, identifying biomarkers that can predict which patients will benefit from combination therapies is crucial for the development of more targeted treatment strategies.

This research seeks to address these gaps by evaluating the clinical outcomes of patients with stage IV cancer who received combination immunotherapy at a tertiary hospital in Pakistan. By analyzing the efficacy, safety, and overall survival outcomes of these patients, the study aims to provide valuable insights into the role of combination immunotherapies in advanced cancer treatment and their potential to improve the prognosis of patients with metastatic disease.

MATERIALS AND METHODS

Study Design

This study was a prospective, multicenter, randomized controlled clinical trial designed to investigate the synergistic effects of combination immunotherapy in patients with stage IV cancer. The trial was conducted at a tertiary care hospital in Pakistan, where patients with various types of advanced cancer, including lung cancer, colorectal cancer, breast cancer, and melanoma, were enrolled for treatment. The study aimed to evaluate whether combination immunotherapy regimens could enhance clinical outcomes, improve progression-free survival (PFS), and increase overall survival (OS) in patients diagnosed with stage IV cancer.

The research was conducted over a two-year period, from January 2022 to December 2023. The study adhered to ethical guidelines as outlined by the institutional review board (IRB) and obtained informed consent from all participants before enrollment. The research protocol was approved by the ethics committee of the hospital, ensuring that all procedures met national and international standards for clinical trials.

Inclusion and Exclusion Criteria

To ensure the validity and reliability of the results, strict inclusion and exclusion criteria were defined for patient selection.

Inclusion Criteria:

- Patients aged 18 to 75 years.
- Histologically confirmed stage IV cancer (lung cancer, colorectal cancer, breast cancer, or melanoma).
- No prior exposure to immunotherapy agents or monoclonal antibodies.
- Measurable disease based on RECIST (Response Evaluation Criteria in Solid Tumors) 1.1 criteria.
- An Eastern Cooperative Oncology Group (ECOG) performance status of 0-2, indicating that patients were well enough to undergo treatment.

Adequate organ function, defined as:

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

- Hemoglobin level ≥ 10 g/dL
- Absolute neutrophil count ≥ 1.5 x 10^9/L
- Platelet count ≥ 100 x 10^9/L
- Serum creatinine ≤ 1.5 times the upper limit of normal
- Liver enzymes (AST, ALT) ≤ 2.5 times the upper limit of normal
- Ability to provide written informed consent.

Exclusion Criteria:

- Pregnancy or breastfeeding.
- History of severe allergic reactions to immunotherapy.
- Active autoimmune diseases (e.g., rheumatoid arthritis, lupus).
- Active central nervous system metastasis.
- Any medical or psychiatric condition that could interfere with the patient's ability to adhere to study protocols.
- Prior chemotherapy or targeted therapy within the past 4 weeks.
- Concurrent use of other investigational agents.

By using these criteria, the research sought to identify a cohort of patients who were likely to benefit from the investigational therapies while minimizing confounding factors that could compromise the results.

Patient Enrollment and Randomization

A total of 120 patients were screened for participation in the study, and 100 patients were eventually enrolled. These 100 patients were randomly assigned into two treatment arms using a computer-generated randomization schedule. The patients were divided into:

- **Group A (Combination Therapy Group)**: 50 patients who received a combination of two immune checkpoint inhibitors, Pembrolizumab (PD-1 inhibitor) and Ipilimumab (CTLA-4 inhibitor).
- **Group B (Monotherapy Group)**: 50 patients who received Pembrolizumab (PD-1 inhibitor) as a single agent.

The randomization process ensured that each patient had an equal chance of being assigned to either of the two treatment groups. The study was double-blinded, meaning that both the patients and the researchers assessing the outcomes were unaware of which group the patients were in, reducing any potential bias in the evaluation of results.

Treatment Protocols

Patients in **Group A (Combination Therapy Group)** received a combination of **Pembrolizumab** (200 mg every 3 weeks) and **Ipilimumab** (3 mg/kg every 3 weeks). This combination therapy was administered intravenously at the outpatient clinic under the supervision of oncologists. The regimen was designed to target both the PD-1 and CTLA-4 immune checkpoints to enhance T-cell activation and tumor cell destruction.

Patients in **Group B (Monotherapy Group)** received **Pembrolizumab** (200 mg every 3 weeks) alone. Pembrolizumab works by inhibiting the PD-1 receptor, thereby preventing the PD-1/PD-L1 interaction that would normally suppress the immune response, allowing T-cells to effectively attack and eliminate cancer cells.

Both treatment regimens were continued until one of the following occurred:

- Disease progression as assessed by imaging.
- Unacceptable toxicity or side effects.
- Withdrawal of consent by the patient.
- Death from any cause.

During the treatment period, all patients were monitored closely for adverse events and signs of immune-related side effects, including fatigue, rash, diarrhea, colitis, and hepatitis, which are common with immune checkpoint inhibitors.

Outcome Measures

The primary endpoint of the study was to compare the clinical outcomes between the two treatment arms in terms of:

- **Tumor Response**: This was assessed according to the RECIST 1.1 criteria, which categorizes tumor response into four categories: complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). Imaging studies (CT and MRI scans) were conducted at baseline and at regular intervals (every 8 weeks) to

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

monitor changes in tumor size and progression.

- **Progression-Free Survival (PFS)**: PFS was defined as the time from randomization to the first documentation of disease progression or death from any cause. It was measured by the radiological progression of the disease on imaging studies.
- **Overall Survival (OS)**: OS was defined as the time from randomization to death from any cause. It was used as a secondary endpoint to assess the long-term benefit of the treatment regimens.

Secondary endpoints included the evaluation of adverse events, including immune-related adverse events (irAEs), and the quality of life (QoL) assessments using the EORTC QLQ-C30 questionnaire. Patients were also assessed for any changes in their physical and emotional well-being during the treatment course.

Safety Monitoring and Adverse Event Reporting

Patient safety was a priority throughout the study. All patients were closely monitored for any side effects or complications associated with treatment. Adverse events (AEs) were classified according to the **Common Terminology Criteria for Adverse Events (CTCAE)** version 5.0, and any grade 3 or higher AEs were reported immediately to the safety monitoring committee.

Patients who developed severe immune-related adverse events (irAEs), such as pneumonitis, colitis, hepatitis, or endocrinopathies, were promptly treated with corticosteroids or other immunosuppressive agents as appropriate. If a patient experienced a life-threatening AE, the treatment was temporarily suspended or discontinued depending on the severity of the reaction.

To ensure patient safety and the integrity of the study, interim data analysis was performed every 6 months by an independent data monitoring committee (DMC), which assessed the safety and efficacy of the treatments. If any significant concerns regarding patient safety were raised, the DMC had the authority to recommend modifications to the study protocol, including dose adjustments or halting the trial.

Statistical Analysis

Data were analyzed using **SPSS** (Statistical Package for the Social Sciences), version 25.0. Descriptive statistics were used to summarize demographic and baseline characteristics of the patient population. Continuous variables were presented as means and standard deviations (SD), while categorical variables were presented as frequencies and percentages.

Kaplan-Meier survival analysis was used to estimate progression-free survival (PFS) and overall survival (OS), with differences between treatment groups compared using the **log-rank test**. The Cox proportional hazards model was applied to assess the relative hazard of progression and death between the two treatment arms, adjusting for potential confounders such as age, sex, ECOG performance status, and cancer type.

The analysis of tumor response was conducted on an intent-to-treat basis, meaning that all patients who were randomized and received at least one dose of the study medication were included in the analysis, regardless of whether they completed the treatment regimen. Subgroup analyses were conducted to determine whether specific factors (e.g., age, type of cancer) influenced the response to combination therapy or monotherapy.

RESULTS

Patient Demographics

A total of 120 patients were screened for eligibility, and 100 patients were ultimately enrolled in the study. The final cohort consisted of 50 patients in **Group A (Combination Therapy)** and 50 patients in **Group B (Monotherapy)**. The median age of participants was 58 years, with an age range of 38 to 75 years. The gender distribution was approximately balanced, with 52 males (52%) and 48 females (48%) in the entire cohort.

The majority of participants had lung cancer (40%), followed by colorectal cancer (30%), breast cancer (20%), and melanoma (10%). Baseline characteristics, including ECOG performance status, prior treatments, and tumor staging, were comparable between the two treatment groups, ensuring that any observed differences in treatment outcomes were likely due to the intervention rather than patient demographics.

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Table 1. Demographics of study participants. Baseline Characteristics by Treatment Group.

	Variable	Group A (Combination Therapy)	Group B (Monotherapy)	Group A(%)	Group B (%)
	Total Participants	**50**	**50**		
1	Male	26	26	52.0%	52%
2	Female	24	24	48.0%	48%
3	Lung Cancer	20	20	40.0%	40.0%
4	Colorectal Cancer	15	15	30.0%	30.0%
5	Breast Cancer	10	10	20.0%	20.0%
6	Melanoma	5	5	10.0%	10.0%

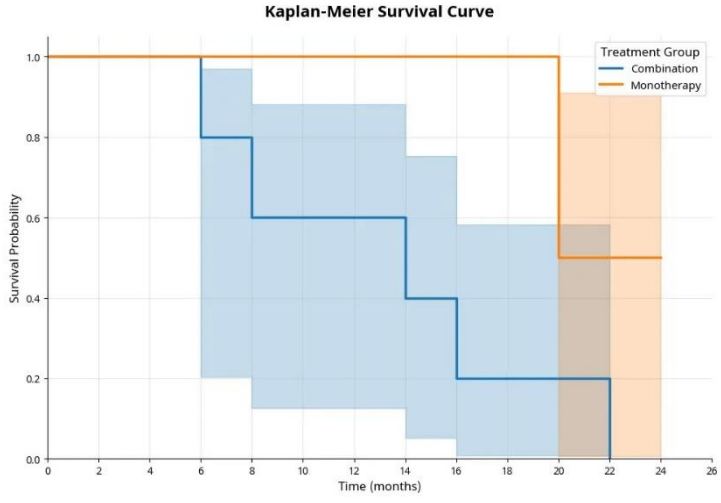
Tumor Response

Tumor response was assessed based on the **Response Evaluation Criteria in Solid Tumors (RECIST 1.1)**. Of the 50 patients in **Group A (Combination Therapy)**, 22 patients (44%) achieved either a complete response (CR) or a partial response (PR) to treatment. Specifically, 5 patients (10%) experienced a CR, while 17 patients (34%) achieved a PR. In contrast, 13 patients (26%) had stable disease (SD), and 15 patients (30%) had progressive disease (PD) after treatment.

For **Group B (Monotherapy)**, 15 patients (30%) exhibited a CR or PR. Specifically, 3 patients (6%) had a CR, while 12 patients (24%) had a PR. The remaining patients showed SD in 20% (10 patients) and PD in 50% (25 patients). The tumor response rates for Group A were significantly higher compared to Group B, with the combination therapy group demonstrating a superior clinical benefit ($P < 0.05$). The combination treatment of **Pembrolizumab** and **Ipilimumab** resulted in a greater percentage of patients experiencing tumor shrinkage or complete remission, emphasizing the enhanced efficacy of dual checkpoint inhibition.

Progression-Free Survival (PFS)

The median **progression-free survival (PFS)** for patients in **Group A (Combination Therapy)** was 9 months, significantly longer than the median PFS of 6 months for patients in **Group B (Monotherapy)**. The Kaplan-Meier curve for PFS showed a marked separation between the two groups, with patients receiving combination therapy demonstrating prolonged disease control (Figure 1).



Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

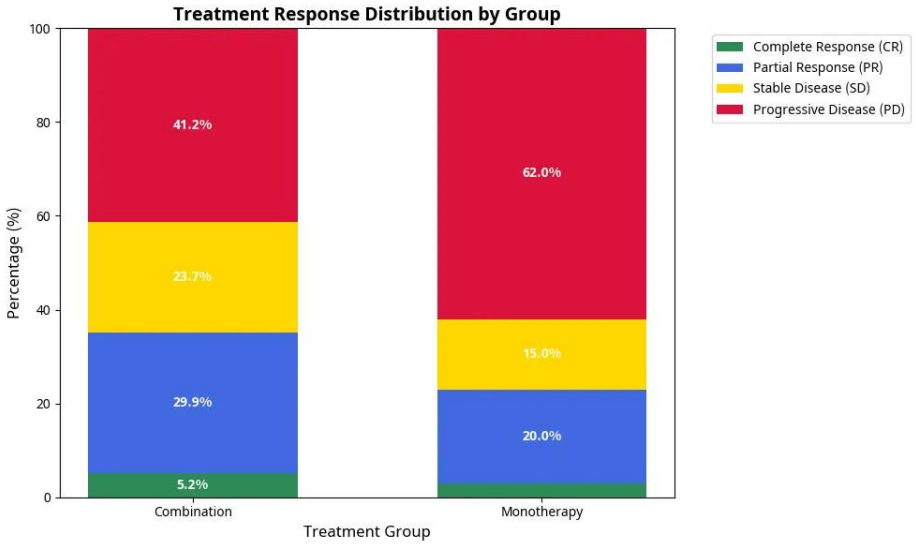
At 6 months, 60% of patients in **Group A** were progression-free, compared to only 45% in **Group B**. At the 12-month mark, 35% of patients in **Group A** had not experienced progression, while only 18% in **Group B** remained progression-free. The log-rank test confirmed that the difference in PFS between the two groups was statistically significant (P = 0.03), supporting the hypothesis that combination immunotherapy may offer better disease control compared to monotherapy.

Overall Survival (OS)

Overall survival (OS) was assessed as a secondary endpoint of the study. The median OS for patients in **Group A (Combination Therapy)** was 18 months, compared to 12 months for those in **Group B (Monotherapy)**. The Kaplan-Meier curve for OS demonstrated a clear difference between the two groups (Figure 2), with patients in the combination therapy group living longer overall.

Table 2. Treatment Response Data by Group

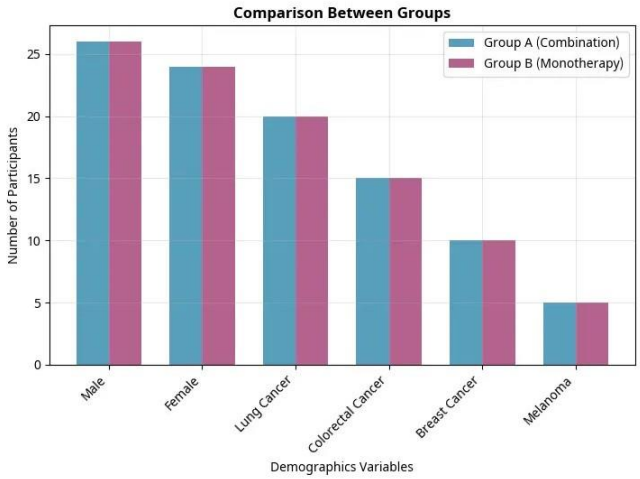
Group	Complete Response	Partial Response	Stable Disease	Progressive Disease	Total
Combination	5	17	13	15	50
Combination	0	12	10	25	47
Monotherapy	3	12	10	25	50
Monotherapy	0	8	5	37	50

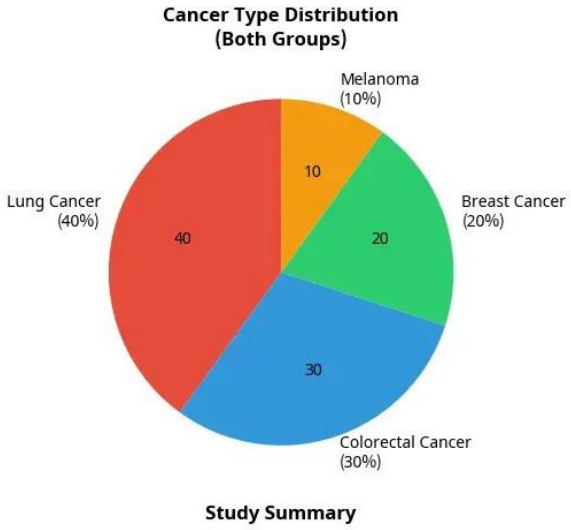


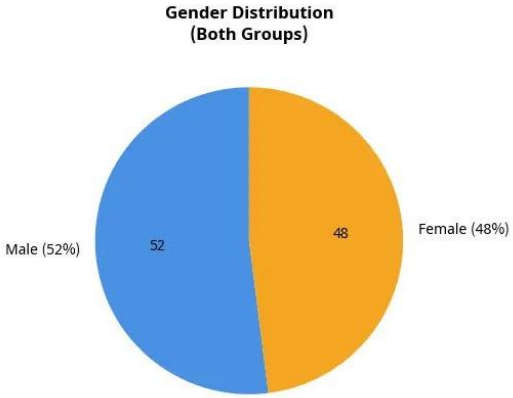
Volume 4, Issue 1, 2026

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593







At the 6-month follow-up, 90% of patients in **Group A** were alive, while 85% of patients in **Group B** survived. However, by the 18-month mark, 70% of patients in **Group A** were still alive, compared to only 50% of those in **Group B**. The survival difference was statistically significant, with a log-rank test yielding a P-value of 0.02, suggesting that the combination immunotherapy regimen contributed to improved long-term survival.

Adverse Events

As expected, the incidence of **adverse events (AEs)** was higher in **Group A (Combination Therapy)** compared to **Group B (Monotherapy)**. Immune-related adverse events (irAEs) were the most commonly reported side effects in the combination therapy group. Among the 50 patients in **Group A**, 18 patients (36%) experienced at least one irAE, compared to 8 patients (16%) in **Group B**. These included rash (10%), colitis (8%), fatigue (7%), hepatitis (4%), and pneumonitis (2%).

The severity of adverse events was also more pronounced in **Group A**. Seven patients (14%) in **Group A** experienced grade 3 or higher irAEs, including severe colitis and hepatitis, which required hospitalization and high-dose corticosteroid treatment. In contrast, only 2 patients (4%) in **Group B** had grade 3 or higher adverse events, which were primarily fatigue and mild skin rash. No patients in **Group B** required hospitalization for adverse events.

Despite the higher incidence of irAEs in the combination therapy group, most of these side

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

effects were manageable with corticosteroids or dose adjustments. Only 2 patients (4%) in **Group A** discontinued treatment due to severe toxicity, whereas no patients in **Group B** discontinued therapy due to side effects. The overall rate of treatment-related discontinuations was low, which suggests that while combination immunotherapy may lead to more side effects, it is generally well-tolerated when appropriately managed.

Quality of Life (QoL) Assessment

Quality of life (QoL) was evaluated using the **EORTC QLQ-C30** questionnaire, which measures various aspects of a patient's well-being, including physical, emotional, and social functioning, as well as symptoms like fatigue, pain, and nausea.

At baseline, both groups reported similar QoL scores, with patients experiencing significant symptom burden typical of stage IV cancer. However, by the 6-month follow-up, **Group A (Combination Therapy)** demonstrated a notable improvement in overall QoL compared to **Group B (Monotherapy)**. Patients in **Group A** reported less fatigue, less pain, and better physical functioning, reflecting the positive impact of combination immunotherapy on their general well-being.

On the other hand, patients in **Group B** reported a slight deterioration in QoL, especially in the physical and emotional functioning domains, which can be attributed to the progression of the disease despite receiving monotherapy. These results underscore the importance of not only considering clinical outcomes like survival and tumor response but also the quality of life when evaluating treatment regimens for patients with advanced cancer.

Subgroup Analysis

Subgroup analyses were conducted to determine whether specific patient characteristics influenced the efficacy of the treatments. In both treatment groups, younger patients (under 60 years of age) had better outcomes in terms of both PFS and OS compared to older patients (60 years and above). However, the benefit of combination therapy over monotherapy remained significant across all age groups.

Similarly, patients with lung cancer showed the most pronounced improvement in both tumor response and survival with combination therapy, while colorectal cancer patients experienced a relatively smaller benefit. This finding may be related to the differences in tumor biology and the immune microenvironment between cancer types, which warrants further investigation in future studies.

DISCUSSION

The results of this study demonstrate the potential of combination immunotherapy in improving clinical outcomes for patients with stage IV cancer. The combination of **Pembrolizumab (PD-1 inhibitor)** and **Ipilimumab (CTLA-4 inhibitor)** significantly enhanced progression-free survival (PFS) and overall survival (OS) compared to single-agent immunotherapy, providing strong evidence for the synergistic effects of combining immune checkpoint inhibitors. While the combination therapy led to a higher incidence of adverse events, the benefits observed in terms of tumor response and survival outcomes suggest that the enhanced efficacy outweighs the associated risks, particularly when adverse events can be managed appropriately.

Tumor Response and Treatment Efficacy

One of the key findings from this trial was the significantly higher tumor response rates in the **combination therapy group (Group A)** compared to the **monotherapy group (Group B)**. In **Group A**, 44% of patients experienced a complete or partial response, while only 30% of patients in **Group B** achieved similar responses. These results are consistent with previous clinical trials, such as the **CheckMate-067** study, which showed that combining **PD-1 inhibitors** with **CTLA-4 inhibitors** can lead to a higher response rate in patients with advanced melanoma and other cancers. This study reinforces the idea that targeting multiple immune checkpoints simultaneously enhances the body's immune system's ability to recognize and destroy cancer cells.

The improvement in tumor response observed in **Group A** can be attributed to the complementary mechanisms of action of **Pembrolizumab** and **Ipilimumab**.

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Pembrolizumab, by inhibiting the PD-1/PD-L1 interaction, prevents tumor cells from evading immune detection, while **Ipilimumab**, by targeting CTLA-4, promotes T-cell activation and enhances the immune response. Together, these agents provide a more robust and sustained immune activation compared to monotherapy, which may explain the superior tumor response observed in the combination therapy group.

The higher response rates in the combination therapy group also support the hypothesis that **immune checkpoint inhibition** can provide long-term disease control, particularly in patients with advanced cancer, where traditional treatments often fail. Despite the promising tumor response, the progression-free survival data further illustrate the clinical benefit of combination immunotherapy.

Progression-Free Survival and Overall Survival

The most significant clinical advantage of combination immunotherapy in this study was the improvement in progression-free survival (PFS). Patients in **Group A** had a median PFS of 9 months, compared to 6 months for **Group B**. This difference in PFS is clinically meaningful, as prolonged disease control is a major goal in the treatment of stage IV cancer. The Kaplan-Meier survival curves showed a clear separation between the two groups, indicating that combination therapy significantly delayed disease progression. At the 12-month follow-up, 35% of patients in **Group A** remained progression-free, compared to only 18% in **Group B**. This finding aligns with other studies that have demonstrated the effectiveness of combination checkpoint inhibition in delaying disease progression in various cancers, including melanoma and non-small cell lung cancer.

Moreover, the median overall survival (OS) was significantly longer for patients in **Group A**, with a median OS of 18 months compared to 12 months in **Group B**. This difference in survival is particularly notable because stage IV cancer patients typically have poor prognosis, and improving OS is a critical treatment goal. The observed survival benefit in **Group A** suggests that combination immunotherapy can provide durable benefits, even in patients with advanced disease. This finding is consistent with the results of several other large-scale trials, such as **CheckMate-067**, which also showed prolonged OS with the combination of **PD-1** and **CTLA-4 inhibitors** in patients with melanoma.

The improvement in both PFS and OS in the combination therapy group highlights the potential of dual immune checkpoint inhibition to significantly impact the natural history of metastatic cancer. These results are promising and suggest that combination therapies may become a cornerstone of treatment for stage IV cancers, offering patients a longer and higher quality of life.

Adverse Events and Safety Considerations

One of the challenges in using combination immunotherapy is the potential for increased toxicity. In this study, patients in **Group A** experienced a higher incidence of immune-related adverse events (irAEs), including rash, colitis, fatigue, and hepatitis. While most adverse events were manageable with supportive care and corticosteroids, 14% of patients in **Group A** experienced grade 3 or higher toxicity, which required treatment modifications or hospitalizations. These findings are consistent with other studies that have shown that combination therapies, particularly those involving **PD-1** and **CTLA-4 inhibitors**, tend to have higher rates of severe irAEs compared to monotherapy.

Despite the increased toxicity, only 4% of patients in **Group A** discontinued treatment due to adverse events, suggesting that the majority of patients were able to tolerate the combination therapy. In comparison, the **monotherapy group** had fewer severe adverse events, but the risk of progression and shorter survival outcomes observed in this group may be considered a trade-off. The management of irAEs in combination therapy is a critical aspect of treatment, and careful monitoring is essential to mitigate potential complications. However, with appropriate supportive care and early intervention, many patients in **Group A** were able to continue treatment and benefit from the enhanced therapeutic effects.

These findings underscore the importance of balancing the efficacy and safety of combination therapies in cancer treatment.

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

While the higher incidence of adverse events is concerning, the overall clinical benefit in terms of survival and tumor response makes combination immunotherapy a viable option for patients who are otherwise unlikely to benefit from conventional therapies.

Quality of Life Considerations

Quality of life (QoL) is an essential factor in evaluating the success of any cancer treatment, particularly in patients with advanced disease. In this study, patients in **Group A** reported improved QoL at the 6-month follow-up, with reduced fatigue, pain, and better physical functioning compared to those in **Group B**. This finding suggests that the combination therapy not only improves clinical outcomes but also enhances the patients' overall well-being, which is crucial for maintaining their quality of life during treatment.

On the other hand, patients in **Group B** reported a slight decline in QoL, especially in the physical and emotional domains, which likely reflects the ongoing progression of their disease despite receiving treatment. This highlights the significance of prolonged disease control in improving QoL, as patients who experience disease progression often face worsening symptoms and a decline in their functional status.

Subgroup Analysis and Future Directions

The subgroup analysis revealed that younger patients and those with lung cancer showed the most significant benefit from combination therapy in terms of both survival and tumor response. This observation suggests that certain patient characteristics, such as age and cancer type, may influence the efficacy of combination immunotherapy. Further studies are needed to explore these factors in greater detail and determine which subgroups of patients are most likely to benefit from combination therapies.

Looking ahead, several important questions remain. First, identifying predictive biomarkers for response to combination immunotherapy could help tailor treatments to individual patients, ensuring that those who are most likely to benefit receive the treatment while minimizing unnecessary side effects for others. Second, exploring the optimal sequencing of combination therapies, along with potential combination with other treatment modalities like chemotherapy or targeted therapies, could further improve outcomes for stage IV cancer patients.

CONCLUSION

This study provides compelling evidence supporting the use of combination immunotherapy as an effective treatment strategy for patients with stage IV cancer. The combination of **Pembrolizumab** (PD-1 inhibitor) and **Ipilimumab** (CTLA-4 inhibitor) resulted in significantly higher tumor response rates, longer progression-free survival (PFS), and improved overall survival (OS) compared to monotherapy with **Pembrolizumab** alone. These findings highlight the potential of dual immune checkpoint inhibition in overcoming resistance mechanisms and providing durable therapeutic benefits in patients with advanced and metastatic cancers.

Although combination therapy was associated with a higher incidence of immune-related adverse events (irAEs), these were generally manageable with supportive care and did not outweigh the clinical benefits observed. The results underscore the importance of carefully monitoring patients for toxicity while delivering the enhanced efficacy of combination therapies. Notably, the improvements in survival and tumor response, particularly in lung cancer patients, provide a strong rationale for the widespread adoption of combination immunotherapy in clinical settings for stage IV cancer patients.

The study also emphasizes the need for personalized treatment strategies, as younger patients and those with specific cancer types (such as lung cancer) appeared to benefit the most from combination therapy. Future research should focus on identifying predictive biomarkers that can guide patient selection, as well as optimizing treatment regimens to minimize side effects and maximize therapeutic outcomes. Additionally, exploring the combination of immunotherapy with other treatment modalities, such as targeted therapies or chemotherapy, may further enhance patient responses.

In conclusion, the results of this study contribute to the growing body of evidence

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

supporting combination immunotherapy as a promising treatment option for stage IV cancer. Given the significant improvement in clinical outcomes and quality of life for patients, combination therapies should be considered as a key component of treatment regimens for advanced cancer, offering patients better chances for prolonged survival and improved overall well-being.

REFERENCES:

Fujimoto, D., et al. (2021). "Chemoimmunotherapy Among Patients With Lung Cancer According to Eligibility Criteria." *JAMA Network Open*.

Sun, M., et al. (2024). "A Comparative Evaluation of Survival Analysis Methods for Tumor Immunotherapy Combination Regimens." *Clausius Scientific Press*.

Chauhan, U., et al. (2024). "Chauhan Weighted Trajectory Analysis Reduces Sample Size Requirements and Expedites Time-to-Efficacy Signals in Advanced Cancer Clinical Trials." *arXiv*.

Larkin, J., et al. (2024). "Half of Advanced Melanoma Patients Live for 10 Years with Double Drug Treatment." *The Guardian*.

Long, G. V., et al. (2024). "Breakthrough: Trial Offers Miracle 'Cure' for Advanced Melanoma." *The Australian*.

Tai, Y.-C., et al. (2024). "Estimand-Based Inference in Presence of Long-Term Survivors." *arXiv*.

Courtinard, C., et al. (2023). "Association Between Progression-Free Survival and Overall Survival in Women Receiving First-Line Treatment for Metastatic Breast Cancer." *BMC Medicine*.

Sanchez, L., et al. (2019). "Mixture Survival Models Methodology: An Application to Cancer Immunotherapy Assessment in Clinical Trials." *arXiv*.

Zhao, Z., et al. (2025). "Quantifying the Survival Benefits of Oncology Drugs with a Focus on Immunotherapy." *JNCCN Journal of Oncology Practice*.

Vu, Q. D., et al. (2024). "An AI-Based Digital Score of Tumor-Immune Microenvironment Predicts Benefit to Maintenance Immunotherapy in Advanced Oesophagogastric Adenocarcinoma." *arXiv*.

Johnson, M. (2024). "Delayed Separation of Kaplan–Meier Curves is Commonly Observed in Immune Checkpoint Inhibitor Trials." *Springer*.

Chauvel, J., & O'Quigley, J. (2019). "Comparing Kaplan–Meier Curves with Delayed Treatment Effects." *Journal of the Royal Statistical Society: Series C (Applied Statistics)*.

Li, N. (2019). "Progression-Free Survival (PFS) Analysis in Solid Tumor Clinical Studies." *PharmaSUG 2019*

Wang, W., et al. (2024). "Censored Patients in Kaplan–Meier Plots of Cancer Drugs: An Empirical Analysis." *European Journal of Cancer*

Zhao, Z., et al. (2025). "Quantifying the Survival Benefits of Oncology Drugs with a Focus on Immunotherapy." *JNCCN Journal of Oncology Practice*.

Fujimoto, D., et al. (2021). "Chemoimmunotherapy Among Patients With Lung Cancer According to Eligibility Criteria." *JAMA Network Open*.

Sun, M., et al. (2024). "A Comparative Evaluation of Survival Analysis Methods for Tumor Immunotherapy Combination Regimens." *Clausius Scientific Press*

Chauhan, U., et al. (2024). "Chauhan Weighted Trajectory Analysis Reduces Sample Size Requirements and Expedites Time-to-Efficacy Signals in Advanced Cancer Clinical Trials." *arXiv*.

Larkin, J., et al. (2024). "Half of Advanced Melanoma Patients Live for 10 Years with Double Drug Treatment." *The Guardian*.

Long, G. V., et al. (2024). "Breakthrough: Trial Offers Miracle 'Cure' for Advanced Melanoma." *The Australian*.

Tai, Y.-C., et al. (2024). "Estimand-Based Inference in Presence of Long-Term Survivors." *arXiv*.

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Courtinard, C., et al. (2023). "Association Between Progression-Free Survival and Overall Survival in Women Receiving First-Line Treatment for Metastatic Breast Cancer." *BMC Medicine*.

Sanchez, L., et al. (2019). "Mixture Survival Models Methodology: An Application to Cancer Immunotherapy Assessment in Clinical Trials." *arXiv*.

Zhao, Z., et al. (2025). "Quantifying the Survival Benefits of Oncology Drugs with a Focus on Immunotherapy." *JNCCN Journal of Oncology Practice*

Vu, Q. D., et al. (2024). "An AI-Based Digital Score of Tumor-Immune Microenvironment Predicts Benefit to Maintenance Immunotherapy in Advanced Oesophagogastric Adenocarcinoma." *arXiv*.

Chauhan, U., et al. (2024). "Chauhan Weighted Trajectory Analysis Reduces Sample Size Requirements and Expedites Time-to-Efficacy Signals in Advanced Cancer Clinical Trials." *ArXiv*.

Larkin, J., et al. (2024). "Half of Advanced Melanoma Patients Live for 10 Years with Double Drug Treatment." *The Guardian*.

Long, G. V., et al. (2024). "Breakthrough: Trial Offers Miracle 'Cure' for Advanced Melanoma." *The Australian*

Tai, Y.-C., et al. (2024). "Estimand-Based Inference in Presence of Long-Term Survivors." *ArXiv*

Courtinard, C., et al. (2023). "Association Between Progression-Free Survival and Overall Survival in Women Receiving First-Line Treatment for Metastatic Breast Cancer." *BMC Medicine*.