A Review on Metastatic Melanoma Combination Therapy

Ipilimumab-Nivolumab

By

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A project submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy (Hons.)

School of Pharmacy
BRAC University
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Declaration

It is hereby declared that

1. The project submitted is my own original work while completing degree at BRAC University.
2. The project does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The project does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

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Approval

The project titled “A Review on Metastatic Melanoma Combination Therapy Ipilimumab-Nivolumab” submitted by Anupama Chakraborty (19346043), of Summer,2023 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy.

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Ethics Statement

This is a review work which did not include any human or animal subjects. The authors acknowledge the contributions of all relevant sources of information, and any discrepancies or limitations in the data are reported in a transparent and honest manner.

Abstract

Chemotherapy, radiation therapy, surgery, and other treatments have proven to be ineffective for a patient suffering with metastatic melanoma. Recently, immunotherapy has become a potential method for treating the condition. Combination therapy, which focuses on various immune system components, has grabbed the attention of the scientific world. The treatment of metastatic melanoma with the immune checkpoint inhibitors Ipilimumab and Nivolumab has been demonstrated to be very successful.

This review aims to analyze the current literature and articles from PubMed and Google Scholar and ClinicalTrials.gov on the use of Ipilimumab and Nivolumab in treating metastatic melanoma. Moreover, this work focuses at some clinical trial results for this combination therapy. The findings demonstrate that Ipilimumab and Nivolumab combination therapy substantially increases patient survival.

In conclusion, Ipilimumab and Nivolumab in combination is a very promising treatment for metastatic melanoma. However, there are several clinical and practical issues that must be resolved to maximize the effectiveness of this combination therapy more research in the field is required.

Keywords: Metastatic Melanoma, Combination Therapy, Ipilimumab, Nivolumab.

Dedication

To my friends and family.

Acknowledgment

I extend my heartfelt appreciation to all those who have contributed to the completion of this research. I am deeply grateful to Allah for providing me the opportunity to work with such wonderful people from the School of Pharmacy, BRAC University. I am honored to have been guided by my esteemed supervisor, Farzana Islam, Lecturer at the School of Pharmacy, whose support, guidance, dedication, and expertise have driven me to excel in this field. I would like to extend my gratitude to Professor Dr. Hasina Yasmin, Program Director and Assistant Dean at the School of Pharmacy, for imparting valuable knowledge, and to Professor Dr. Eva Rahman Kabir, Dean at the School of Pharmacy, for her unwavering support and motivation. I also want to acknowledge the efforts of all the faculty members at the School of Pharmacy, BRAC University, and express my gratitude to my friends and seniors for their guidance and my family members for their unwavering support.

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List of Acronyms

Metastatic Melanoma	MM
Food and Drug Administration	FDA
World Health Organization	WHO
Combination Therapy	CT
Methotrexate, 6-Mercaptopurine, Vincristine and Prednisone	POMP
National Cancer Institute's	NCI
Surveillance, Epidemiology and End Results	SEER
Cytotoxic T-Lymphocyte Associated Protein-4	CTLA-4
Cluster of Differentiation 28	CD-28
T-Cell Receptor	TCR
Major Histocompatibility Complex	MHC
Acyl Carrier Protein	ACP
Area Under Curve	AUC
Maximum Concentration	C-max
European Medicine Agency	EMA
Programmed Cell Death-1	PD-1
estimated Glomerular Filtration Rate	e-GFR
Immune Checkpoint Inhibitors	ICIs
Interleukin-2	IL-2
Median Progression-Free Survival	mPFS
Intracranial Response	IR

Intracranial Clinical Response	ICR
Intracranial Clinical Benefit	ICB
Complete Response	CR
Partial Response	PR
Objective Response	OR
Progression Free Survival	PFS
Overall Survival	OS
Median Overall Survival	MOS

Chapter 1

Introduction

1.1 Metastatic Melanoma

Metastatic melanoma is the result of the dissemination of cancerous cells from the primary tumor, which subsequently undergo free movement and migration via lymphatic or hematogenous routes and ultimately establish a secondary metastatic tumor at a distant site. Typically, this melanoma type shows symptoms in stages 3 or 4 (Cancercenter.n.d.2023). Melanoma the lethal variant of cutaneous malignancies, arises due to genetic defect in melanocytes, the specialized cells responsible for producing pigment in the integumentary system, ocular structures, and the auditory apparatus (Gray-Schopfer et al., 2007). Although melanoma has the potential to arise in any tissue that contain melanocytes, it predominantly manifests in the integumentary system (Tolleson 2005).

The anatomical origin of the tumor largely determined the early classification of melanoma. During the 1960s, an influential dermatologist named Wallace Clark proposed a reclassification approach for melanoma, emphasizing the significance of histological characteristics (Rebecca et al., 2012). Subsequently, the author proceeded to delineate three distinct histological dissimilarities of melanoma (Lee et al., 2013; Scolyer et al., 2011).This cancer ranks as the third most prevalent form of malignancy affecting the skin. Moreover, for the male patient's melanoma has the fifth position of most prevalent malignancy and ranks the sixth most prevalent malignancy in females.

Recently, the approach to therapy has changed significantly for metastatic melanoma. In contemporary times, medical interventions are employed for the treatment and encompass surgical procedures, immunotherapy, targeted therapy and chemotherapy (Sundararajan. 2022). Based on specifics of the tumor, such as its location, stage, and genetic profile, a number of therapies been

received authorization from the Food and Drug Administration (FDA) (Batus et al. 2013; Miller et al. 2022; van Zeijl et al., 2017). Throughout the preceding three decades, there has been a noteworthy increase in the occurrence of metastatic melanoma, accompanied by a more rapid rise in mortality rates compared to most other malignancies (Gray-Schopfer et al., 2007b) (Jemal et al., 2009). In line with the World Health Organization (WHO), according to estimates, 66,000 people worldwide die each year from skin cancer.

1.2 Combination Therapy in Oncology

Oncology is the field of study that encompasses the examination of cancer, including its treatment, prevention, and early detection (Oncology: Types, Diagnosis, Treatment, n.d.). The combination therapy is a strategy that includes the simultaneous administration of two or more therapeutic drugs, and it is widely recognized as the cornerstone for cancer treatment (Blagosklonny, 2004; Yap et al., 2013). This therapy's idea was first put forth by Emil Frei, James F. Holland, and Emil J. Freireich in 1965. These researchers suggested a possible scenario of employing a combination of chemotherapeutic agents in order to combat with severe leukemia (Karon et al., 1966). The treatment regimen, referred to as the POMP regimen, comprises a combination of Methotrexate, 6-Mercaptopurine, Vincristine, and Prednisone. A therapeutic intervention was employed in order to treat infants found to have acute lymphocytic leukemia, which demonstrated efficacy in lowering tumor load and extending the duration of remission (Karon et al., 1966). The POMP regimen’s effectiveness has led to more focused-on cancer therapy research and examining drug combinations that target several pathways to have a synergistic effect (Quinn et al., 2011). Many combinations of two or more molecularly targeted medications have recently been approved, and many more are in the last phases of clinical development (Webster, 2016).

Now mentionable advantages of combination therapy: it targets important pathways in a manner that is typically synergistic (Blagosklonny, 2004; Yap et al., 2013). The price of cancer research and its financial burden are increasing (Baselga et al., 2015). And only a small percentage of this improvement is attributable to newer drugs (Garattini, 2003). Because of the lengthy and costly procedure of creating new pharmaceutical anti-cancer medications, that includes in vitro, in vivo, and clinical trials before FDA clearance. It takes 15 years to launch a new drug (DiMasi et al., 2003). Monotherapy kills all actively replicating cells, including healthy ones. Damage to bone marrow cells weakens the patient's immune system and makes them more susceptible to host infections (Lebaron et al., 1988; Partridge et al., 2001). Monotherapy increases medication resistance because cancer cells are repeatedly treated with one chemical (Gottesman et al., 2002; Khdair et al., 2010). Combination therapy reduces resistance since it works faster and better (Hanahan et al., 2000; Tschanz et al., 2021).

1.3 Survival Rate of Metastatic Melanoma

Metastatic melanoma patients' survival is often estimated in months rather than years. The median lifespan is six to eight months. 45 percent survive one year, and less than ten percent survive five years (Shields et al., 2000). As per American Cancer Society, the five-year survival rate is delineated across three distinct categories:

Table 1: Adapted from the five-year survival rate of patients with diagnosed melanoma from 2012 to 2018

SEER Stages	5 Years Survival rate
• Local Cancer	• The percentage exceeds 99.
• Regional Cancer	• 71 percent of the population falls into the specified category.
• Distant Cancer	• The percentage of interest is 32 percent.
• Combine of all Stages	• 94 percent of the population falls into the specified category.

To calculate mortality rates for various forms of cancer, data from the National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results (SEER) database is used. The SEER database keeps track of how many people with melanoma skin cancer in the United States are still alive after 5 years based on how far the cancer has spread (Melanoma Survival Statistics, n.d.)

1.4 Ipilimumab

Ipilimumab belongs to a monoclonal antibody of human origin, where Cytotoxic T-Lymphocyte Associated Protein-4 (CTLA-4) is the target and blocks CTLA-4's ligand interactions. Research is currently done on the application of Ipilimumab in the management of various cancers like, prostate, lung, and bladder cancer and depending on the cancer type Ipilimumab can be administered alone or with other drugs (Carthon et al., 2010; Lynch et al., 2012).

1.4.1 Mechanism of Actions of Ipilimumab

The Immunological Checkpoint Protein (ICIs) means CTLA-4 is the target of this monoclonal antibody. It takes two commands or signals to activate T-cells: the initial is T Cell Receptor (TCR) recognizes antigen after antigen presentation done by Major Histocompatibility Complex (MHC) class II molecules and next one is the signal of co-stimulation. It is generally accomplished through the interaction of Cluster of Differentiation 28 (CD28) (Hodi et al., 2008). When trying to bind to B7-1 or B7-2 to modify T-cell response, CTLA-4 competes with CD28 onto the T-cell surface. This slows down T-cell activation and stops the T cells from becoming primed to recognize tumor cells. As a result, they cannot eradicate tumor cells from the body (Hodi et al., 2008). This inhibiting signal is taken away by an ICIs that prevents B7-1/B7-2 from attaching to CTLA-4, activating the T cells and destroying tumor cells (Agarwala, 2010).

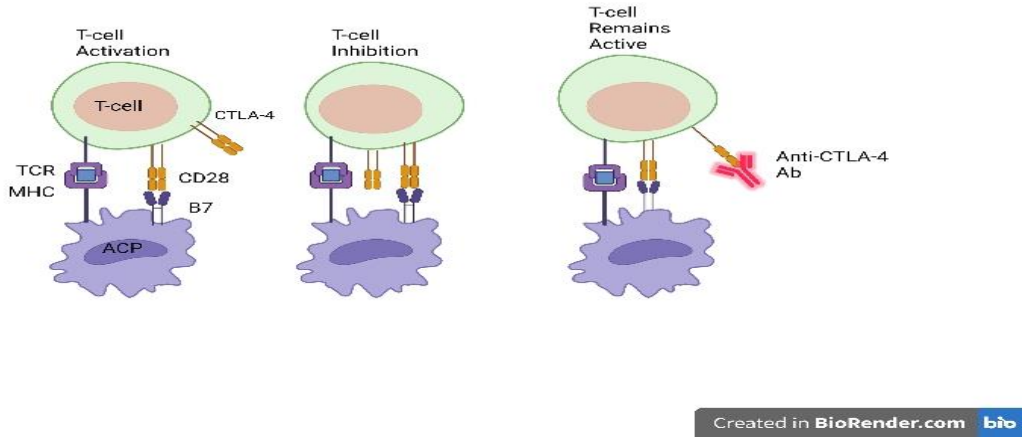

Figure 1: Mechanism of Action of Ipilimumab

1.4.2 Pharmacokinetics of Ipilimumab

According to a report published in 2012, the pharmacokinetics of Ipilimumab demonstrated a direct relationship between the administered dose and maximum concentration(C-max), the minimum concentration and area under the curve (AUC) of the drug. The administration of Ipilimumab as a third dose at a frequency of once every three weeks resulted in an elevation of the level to 80. In the initial state, there was a positive correlation observed between body and both lactate dehydrogenase and Ipilimumab clearance and it is unaffected by age, gender, hepatic function, concomitant budesonide use, renal function, performance status, HLA-A2*0201 status, or systemic anticancer therapy (Weber et al., 2008)

Ipilimumab is frequently administered by a medical expert in a therapeutic setting. Ipilimumab is distributed throughout the body after being administered. It attaches to T-cells, which are found in many tissues, including lymphoid organs and tumor microenvironments, and specifically to CTLA-4 on T-cells. Because of this distribution, ipilimumab can target and control the immune response in these areas. Ipilimumab's metabolism is not fully understood, however it is assumed that it degrades by a process similar to that of endogenous immunoglobulins. Ipilimumab's specific breakdown mechanisms and enzymes have not been thoroughly investigated. Moreover, Ipilimumab's excretion has also not been completely explained. The substance is thought to be removed from the body by typical physiological mechanisms. (Weber et al., 2008) (Lynch et al., 2012)

Single 20 mg/kg and repeated 10 mg/kg doses on days 1, 57, and 85 were well tolerated. However, Ipilimumab therapy on days 1, 22, 43, and 64 enhanced immune-related adverse events, notably at 10 mg/kg. Ipilimumab was suggested for ongoing research at 10 mg/kg every three weeks for four doses due to its tolerability and the positive correlation among immune-related undesirable

effects and therapeutic benefit. Ipilimumab had no significant PK or PD interactions with dacarbazine or carboplatin/paclitaxel (Weber et al., 2008) (Lynch et al., 2012)

1.4.3 Dose and Administration of Ipilimumab

People with advanced melanoma get Ipilimumab intravenously for over ninety minutes once on a weekly basis for a total of four doses (*Yervoy | European Medicines Agency*, n.d.). Before figuring out how the tumor is responding, patients should go through the whole induction procedure, if they can. In the US, Ipilimumab carries a black box warning for immune-mediated side effects and should be withheld in moderately severe cases (FDA, 2015; FDA & cder, n.d.-b)

1.4.4 Regulatory Status of Ipilimumab

In 2011, the FDA authorized it for late-stage melanoma (Small et al., 2007; Yang et al., 2007). FDA and European Medicine Agency (EMA) have approved Ipilimumab to be administered as an adjuvant therapy in cutaneous melanoma patients. In metastatic or unresectable melanomas, the FDA and EMA authorized OPDIVO® (Nivolumab) with Ipilimumab (FDA, 2015; FDA & cder, n.d.-b)

1.5 Nivolumab

Nivolumab is derived from Chinese hamster ovary cells. This monoclonal antibody functions as an inhibitor of Programmed Cell Death-1 (PD-1), thereby exhibiting anti-tumor properties. Notably, its administration has demonstrated enhanced patient survival rates relating to malignant melanoma (Yano et al., 2018). It is also known as ICIs. It works by attaching to the PD-1. This prevents cancer cells from reducing the immune system's efficiency. Notice published by FDA that, Nivolumab or in combination with Ipilimumab can be used to treat several types of cancer.

1.5.1 Mechanism of action of Nivolumab

The PD-1 receptor, predominantly found on T cells, serves as the specific binding site for Nivolumab. The interplay between mature T cells and tumor cells is contingent upon various chemical factors, among which the PD-1 receptor plays a crucial role. The PD-1 protein categorised as a type I transmembrane protein, consisting of a singular immunoglobulin chain, a transmembrane domain, an extracellular variable-like domain known as IgV and along with a cytoplasmic tail that has two tyrosine motifs (Boussiotis, 2016). It works along with PD-L1 and PD-L2 ligands, produced by tumor cells and macrophages that are connected to tumors. This interaction makes it hard for the T cells to react. Nivolumab blocks the connection between PD-1 and PD-L1 and PD-L2 via binding strongly to the PD-1 receptor (Wang et al., 2014). Nivolumab aids in T cells immunological function recovery by blocking the PD-1 receptor. This lets T cells fight cancer cells (Wong, 2007).

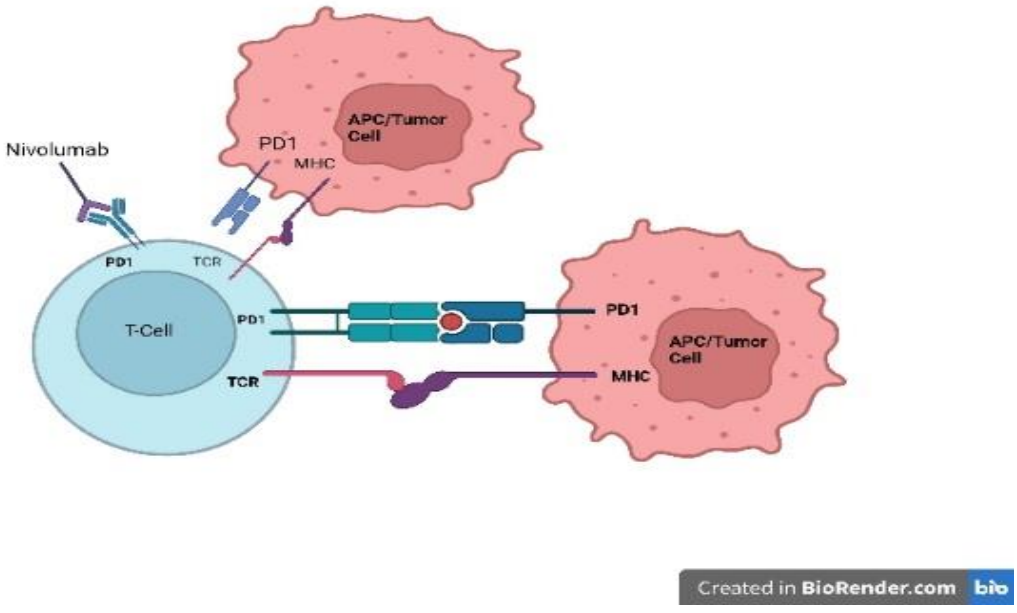

Figure 2: Mechanism of Action of Nivolumab

1.5.2 Pharmacokinetics of Nivolumab

The standardized dose range for Nivolumab is between 0.3 and 10 mg/kg. (Bajaj et al., 2017) It changes over time and depends on things like the patient's performance level at the start, body weight, estimated Glomerular Filtration Rate (eGFR), race, and sex. When used with Ipilimumab after the baseline, ADAs can boost clearance by 14%. The typical half-life of Nivolumab is 25 days and a coefficient of variation of 77.5% after 12 weeks (about 3 months), the amount of the drug in the body stays the same (Bajaj et al., 2017).

According to population PK analysis, Nivolumab's distribution volumes are 3.63 L (IIV 35%) and 2.78 L (IIV 35.1%) (Myers Squibb, n.d.).

1.5.5 Regulatory status of Nivolumab

On December 20, 2017, the FDA certify Nivolumab (OPDIVO, Bristol-Myers Squibb Company), an anti-PD1 monoclonal antibody, for adjuvant treatment of melanoma patients who go through complete resection (FDA, n.d.).

1.6 Ipilimumab-Nivolumab as combination therapy

Melanoma is staged depending on factors like, tumor width, ulceration, lymph node involvement, and metastasis. The initial therapeutic approach of melanoma involved the utilization of Interleukin-2 (IL)-2 therapy, which can be administered as a standalone treatment or in conjunction with other pharmaceutical interventions. The intake of large amount of IL-2 is currently not employed as a treatment approach for individuals with melanoma, primarily due to the progress made when it comes to immunotherapy and the growth of ICIs like PD-1 and CTLA-4 inhibitors (Marabondo & Kaufman, 2017). Several clinical studies has been found to be effective in treating

melanoma patients with metastases from Ipilimumab either by itself or in combination with Nivolumab. Like in one research the median Progression-Free Survival (mPFS) for Nivolumab plus Ipilimumab was 11.5 months, 2.9 months for Ipilimumab alone, and 6.9 months for Nivolumab alone (Kooshkaki et al., 2020a; Shankar et al., 2014).

However, in another research, found that Nivolumab and Ipilimumab combination therapy for metastatic melanoma is effective (Wolchok et al., 2017). After more than 33 months (about 3 years) of follow-up in a phase 1 dose-finding study, metastatic melanoma patients treated with Nivolumab and Ipilimumab had a three-year overall survival rate of sixty- eight percent, regardless of previous therapy. Whereas in phase 2 study of previously untreated patients, combined treatment had a 2-year survival rate of 64% and Ipilimumab alone 54%. The phase 3 trial shows that priorly untreated advanced melanoma patients, Nivolumab with Ipilimumab and Nivolumab alone exhibited more reliable response rates than Ipilimumab alone (Hodi et al., 2010; Kooshkaki et al., 2020).

1.7 Aim

Primary goal of this inquiry is to comprehensively examine the utilization of combination therapy in ongoing trials targeting metastatic melanoma, while also offering a comprehensive analysis of their underlying mechanisms of action to elucidate their efficacy against cancerous cells. This study aims to

1.8 Objective

The objective of this work is to provide comprehensive insights into the combination therapy of Ipilimumab and Nivolumab, focusing on its:

- toxicity and efficacy rates,
- various approaches,
- advantages,
- and limitations.

This study aims to present the information in a simplified manner, ensuring comprehensibility for a wide range of individuals.

Chapter 2

Methodology

The review task included the selection of relevant literature, the analysis of scientific articles and summary of this paper. This review's facts and statistics were gathered from many scientific articles that were important to the topic. An online search was done in order to compile all of the journals that are relevant to this subject. Following an analysis of the information collected from the recently published articles of choice, a plan was prepared to convey the gleaned material in accordance with the requirements of the project objectives. The main objective of this review is to gather more information about Ipilimumab and Nivolumab as a combination therapy and it is ongoing trials targeting metastatic melanoma, while also offering a comprehensive analysis of their underlying mechanisms of action to elucidate their efficacy against cancerous cells. The scientific articles are being selected according to their information about Ipilimumab, Nivolumab, their mechanism of action, clinical trials and adverse effects.

Research conducted a comprehensive search of the PubMed, Google Scholar, ScienceDirect for studies. The time frame of the search will be from 1999 to 2022, and the language of the articles will be limited to English. All studies that met the inclusion criteria, including observational studies, randomized controlled trials have been selected for further analysis.

Chapter 3

Result

3.1 Clinical trials

Table 2: Adapted from paper compilation of finding of several phase II clinical trials- (January 2020) (Kooshkaki et al., 2020)

Study Arms	Primary Indicators	Findings	Reference
1.Induction phase: Nivolumab 1 mg/kg (3 weeks) with Ipilimumab 3 mg/kg (3 weeks) for four doses. **Maintenance phase:** 3mg/kg of Nivolumab (2 weeks)	Rate of Intracranial Clinical Benefit (ICB) of (at least six months)	▪ ICB rate = 57 % ▪ Complete Response (CR) rate = 26% ▪ Partial Response rate (PR) = 30% ▪ Stable Disease rate for six months = 2%	(Tawbi et al., 2018)
2. Combination group: 1mg/kg of Nivolumab plus 3mg/kg Ipilimumab (three weeks for four doses) **Monotherapy group of Ipilimumab:** Ipilimumab plus Placebo.	Objective Response (OR) percentage at 6 months in the randomized, BRAF wild-type population.	▪ OR rate for combination group = 61% ▪ OR rate for monotherapy group of Ipilimumab = 11% ▪ CR for combination group = 22% ▪ CR for monotherapy group of Ipilimumab = absence of patients	(Postow et al., 2015)
3. Group A or combination group: received 3mg/kg of	The major outcome measure assessed in this study was the Intracranial	▪ IR in Group A = 46% ▪ IR in Group B = 20%	(Long et al., 2018a)

Ipilimumab with 1mg/kg of Nivolumab (once every 3 weeks) **Group B or monotherapy group of Nivolumab:** 3mg/kg of Nivolumab (once every 2 weeks) **Group C individuals with neurological symptoms, leptomeningeal illness, or local therapeutic failure:** 3mg/kg of Nivolumab	Response (IR) of 3 years.	▪ IR in Group C = 6% ▪ Intracranial Clinical Response (ICR) in Group A = 17% ▪ ICR in Group B = 12% ▪ ICR in Group C = none	

In the first box, individuals who had metastatic melanoma and a minimum of one quantifiable, nonirradiated brain metastasis and no neurological complications are selected for this phase two clinical trials. 94 patients in all were enrolled and received Nivolumab with Ipilimumab first. Then, only Nivolumab one time every 14 days (about 2 weeks) until any kind of development or intolerable toxic effects. The principal goal was the amount of intracranial clinical benefit, which was narrated as a few patients whose disease was stable for a minimum 6 months, all-discovered confirmation of cancer is gone means had a complete response, or who had a depletion a of minimum thirty percent quantifiable tumor means partial response.

The second section describes a double-bind study comprised 142 treatment-naïve patients with metastatic melanoma. Patients were randomly chosen to get either with Ipilimumab combined with

Nivolumab or Placebo. Here, treatment was administered every 21 days for four doses, next came Ipilimumab or Placebo every 14 days.

Third box presents the study of a multicenter open-label randomized phase two experiment conducted at four distinct locations in Australia. The trial has three distinct categories of patients who were at least eighteen years or older who were immunotherapy-naive and diagnosed with melanoma brain metastases. The study chose individuals who had asymptomatic brain metastases and did not get any earlier local brain treatment. These patients were randomly selected to either group A (Nivolumab plus Ipilimumab) or group B (Nivolumab). Stratification by site was performed, and the allocation ratio was 30:24. Prior to the main study, a safety run-in phase with six patients was conducted. The study included individuals who had brain metastases and had experienced treatment failure with local therapy, exhibited neurological symptoms, or had a leptomeningeal illness. These patients were registered in non-randomized group C, which involved the administration of Nivolumab. The primary and safety findings were conducted based on an intention-to-treat approach, including all patients who received at least one dosage of the trial medication.

Table 3: Adapted from paper compilation of finding of several phase III clinical trials - (January 2020) (Kooshkaki et al., 2020b)

Study Arms	Primary Indicators	Findings	Reference
1. **Combination group:** Nivolumab combined with Ipilimumab with the addition of a Placebo for nivolumab. **Monotherapy group:** Nivolumab plus Placebo (paired with ipilimumab) plus Placebo for nivolumab.	The study's main objectives were to assess Progression-Free Survival (PFS) and Overall Survival (OS) in both the nivolumab-plus-ipilimumab group and the nivolumab group compared to the ipilimumab group**.**	▪ The rate of OS in 3 years for the combination group = 58% ▪ The rate of OS in 3 years for nivolumab= 52% ▪ The rate of OS in 3 years for ipilimumab = 34%	(Long et al., 2018b)
2. **Combination group:** Nivolumab combined with Ipilimumab with the addition of Placebo for nivolumab. **Monotherapy group:** Nivolumab plus Placebo (paired with ipilimumab) plus Placebo for nivolumab.	The study's major goals were PFS and OS in the nivolumab-plus-ipilimumab group and the nivolumab group compared to the ipilimumab group.	3. Median Overall Survival for ipilimumab and nivolumab = 60.0 months (about 5 years) 4. Median overall survival for nivolumab = 36.9 months 5. Median overall survival for ipilimumab = 19.9 months (about 1 and a half years). 6. The overall survival rate at 5 years for nivolumab and ipilimumab = 52% 7. The overall survival rate at 5 years for nivolumab = 44% 8. The overall survival rate at 5 years for ipilimumab = 26%.	(Wolchok et al., 2017b)

The first box participants in the study were adults with stage III or stage IV melanoma and BRAF V600 mutation. They had not been treated before and had a low level of disability according to performance status measure. All eligibility criteria for the study were documented. The patients with advanced melanoma who had not received any therapy before were randomly assigned to one of two treatment groups: receiving Nivolumab and Ipilimumab, or receiving Nivolumab alone. The dosages were determined based on body weight and given at specific intervals. The randomization was based on factors such as PD-L1 presence, BRAF mutation, and stage of spread. The prime outcomes of interest were progression-free survival and overall survival in the different treatment groups.

In the second scenario, the phase 3 trial included people who were assigned to one of three treatment regimens in equal proportions. The first regimen involved receiving Nivolumab and Ipilimumab at specific dosages and intervals. The second regimen included Nivolumab and a Placebo that matched Ipilimumab. The third regimen consisted of Ipilimumab and a Placebo that matched Nivolumab.

3.2 Adverse Effects

Adverse effects of nivolumab and ipilimumab, when used for treating metastatic melanoma, can vary depending on the individual patient and the specific treatment regimen. In one research, it is stated that around 40% of patients discontinued their treatment after receiving combination therapy in the induction phase because of adverse events (Schadendorf et al., 2017). Incidence of adverse effects can be different, here are some commonly reported adverse effects:

Table 4: *I*ncidence of adverse events adapted from *(Somekawa et al., 2022)*

Type of AEs	**Example**	**Incidence (95% Confidence interval)**
1. Gastrointestinal	- Amylase - Diarrhea - Colitis - Nausea - Vomiting	- 9.4 (6.2-12.7) - 26.0 (21.5-30.5) - 8.2 (5.5-18) - 15.1 (12.1-18.1) - 8.6 (5.9-11.4)
2. Dermatological	- Rash - Vitiligo	- 24.0 (19.3-28.7) - 7.1 (5.3-8.8)
3. Hormonal	- Hypothyroidism - Hyperthyroidism - Adrenal insufficiency	- 13.1 (11.2-15.1) - 11.0 (7.7-14.4) - 4.8 (2.8-6.7)
4. Others	- Fatigue - Pyrexia - Headache	- 27.9 (22.6-33.3) - 14.8 (10.7-18.9) - 13.5 (9.9-17.1)

Chapter 4

Discussion

Metastatic melanoma is a dangerous subtype of skin cancer that has very poor outcomes and limited treatment options (Cancercenter.n.d.2023).However, recently has been shifted to new treatment strategy and emergence of ICIs like, Ipilimumab and Nivolumab has reform the management of this disease (Sundararajan et al., 2022).

This review study aims to understand how Ipilimumab and Nivolumab has been found to be a potential way to treat metastatic melanoma. Considering the results from the different clinical trials, it is quite difficult to understand the direct impact on survival of patients because of heterogeneity of individuals makes it difficult to come up on conclusions. Next, individual response and disease progression could be another reason like, some of patients may experience improvements in survival, while some of the patients may not respond well (Kent & Hayward, 2007; Kooshkaki et al., 2020; Rekkas et al., 2020).

It was found that, these clinical trials mainly focus on indicators for example, Intracranial Clinical Benefit (ICB), Complete Response (CR) rate, Partial Response (PR) rate, Objective Response (OR) percentage, Intracranial Response and Stable Disease rate. These indicators give insights into the effectiveness of different treatment options in terms of disease control and tumor response.

In the first study, it was found that the combination treatment showed promising outcomes in terms of CR rate, PR rate and ICB rate, which suggests that the combination therapy may have a great impact on tumor control and overall disease management. Whereas, the stable disease rate for six months was comparatively low, indicating that significant percentage of patients failed to experience the disease stabilization as mentioned in the reference (Tawbi et al., 2018). In the

second study of table 2, monotherapy was compared with combination therapy and the OR rate was bit high in case of combination group than the monotherapy group and that indicates, the combination therapy may show a greater tumor response and may give a better survival result (Postow et al., 2015). Furthermore, in the third portion of study, various treatment groups were compared and implies that the IR and ICR rates were higher in combination group and indicating a better control of intracranial tumors. However, monotherapy group of Nivolumab suggesting a less favorable response in case of intracranial disease control as per the reference (Long et al., 2018).

In table 3, findings suggest that combination therapy may provide a better chance of long-term survival for patients. This could be due to a synergistic effect of two drugs. The longer median survival rate and greater overall survival rate in combination group point to possible patient treatment alternatives that may be more successful (Long et al., 2018).

However, the ideal treatment strategy may depend on numbers of factors, including the characteristics of the patients and the kind of tumor. It is crucial to keep in mind that these findings are based on particular studies. So, in order to confirm these findings and assess the safety and effectiveness of this combination more clinical trials and research are required.

Chapter 5

Conclusion

Ipilimumab plus Nivolumab is a combination therapy that has been shown to be successful in treating metastatic melanoma, and the review study has shed light on its efficacy and possible patient advantages. The review of prior studies and clinical trials revealed encouraging findings, including increased overall survival rates. Like, in the timeframe of 3 years combination groups shows 58% overall survival rate, but monotherapy group means Ipilimumab shows 34% of and Nivolumab has 52% OR rate (Kooshkaki et al., 2020). Moreover, this combination therapy gives the synergistic effects and enhance anti-tumor immune response by blocking two different pathways (Gray-Schopfer et al., 2007). Also, this study helps to observes that this therapy may increase the level of toxicity compared to monotherapy. Which can damage patient's different organs (Hodi et al., 2008).

However, there are still a number of areas that call for more study and might be used as future paths for this type of research. To optimise the therapeutic process's efficacy, it is essential to comprehend the molecular processes behind the synergy between Ipilimumab and Nivolumab. Or discovering biomarkers that may forecast how an individual patient would react to an Ipilimumab and Nivolumab combination therapy will enable the development of more specialized treatment plans. In patients who are unlikely to benefit, this can increase therapy effectiveness and reduce unneeded toxicity.

Finally, investigating innovative treatment approaches, such as the combination of Ipilimumab and Nivolumab with immunomodulatory drugs, vaccines, or adoptive cell therapies, may open up new possibilities for enhancing patient outcomes. Therefore, more clinical trials and research needed

for this combination drug or to find a new drug combination which may shows a greater efficacy or strategy to serve the patient to get a better life.

In conclusion, even though Ipilimumab and Nivolumab combination therapy has shown encouraging outcomes for metastatic melanoma, more investigation into molecular causes, biomarkers, combination techniques, and innovative therapeutic methods is required. As a result, treatment results will be improved, patients will be better chosen, and ultimately, more effective treatments for metastatic melanoma will be developed.

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