Combination Therapies of Metastatic Melanoma and Melanoma Brain Metastases

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Abstract: Melanoma is a fatal cancer that develops in melanocytes and has the highest mortality rates in all types of skin cancers. It generally starts as a primary tumor, spreads to adjacent lymph nodes, migrates to distant sites of body through bloodstream, and becomes metastatic in this case. Melanoma brain metastases occur when melanoma cancer cells disperse to the brain. However, compared to the survival rate of melanoma that is localized (stage I, II) or regional (stage III), the survival rate in metastatic melanoma (stage IV) decreases a lot, and it is imperative to find an effective treatment to prolong the survival. As immunotherapy has been developed, one of the methods, checkpoint inhibitors provide higher overall survival and more enduring objective response, which can be both used as monotherapies and combination therapies. In this review, we will focus on the combination of checkpoint inhibitors as an impressive therapy for metastatic melanoma and melanoma brain metastases and summarize its effect on the overall survival and response rate in different clinical trials. The combination of radiotherapy and checkpoint inhibitors for treating melanoma brain metastases is also explored. These combination therapies serve as potent treatments of metastatic melanoma and its brain metastases.

1 INTRODUCTION

Ultraviolet rays (UV) from the sunlight are the major cause of melanoma. Excessive sunlight exposure leads to mutations in DNA in the skin cells, and the mutation in the BRAF oncogene is the most common one that found in almost half of the melanomas. NRAS, CDKN2A, and NF1 are the other genes affected by UVs. When mutations occur, they keep turning on the oncogenes and make melanocytes grow and divide abnormally, which stimulates them to become cancerous (*What Causes Melanoma?*, n.d.).

Melanoma develops from a primary tumor and then propagate to distant sites of the body, such as lymph nodes, the skin, brain, lungs, bones, and liver, and such condition is called metastatic melanoma. Symptoms are shown when there are metastases in distant sites of the body. Melanoma is lethal, and metastatic melanoma is the one that has extremely poor survival rate in contrast to the melanoma that is localized. Conventionally, surgery was utilized when the tumor is dispersed to only one or several sites of the body, and they were resectable. However, for metastatic melanoma, surgery is impotent, and the treatments of chemotherapy, radiotherapy, and immunotherapy have become more appropriate. Chemo drugs are applied in chemotherapy for slowing the growth of cancer cells, such as dacarbazine (DTIC) and temozolomide (Temodar). Radiotherapy is given when the tumors are in the location that can't be moved easily, such as brain, or in many sites of the body, and it is able to shrink tumors. As the field of immunotherapy advances, it has become the preferred treatment for metastatic melanoma. Immune checkpoint inhibitors (ICI), ipilimumab and nivolumab, are one of them that are helpful and provide improved survival and prolonged responses. Nivolumab and pembrolizumab are anti-PD-1 checkpoint inhibitors, which both can be employed as monotherapies or in combination with ipilimumab. Ipilimumab is an anti-CTLA-4 immune checkpoint inhibitor that triggers the immune system to attack melanoma cells, but it is less efficient than nivolumab and pembrolizumab when it is using alone. Many studies have stated the

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beneficial effects of using ipilimumab or nivolumab monotherapy as treatments for metastatic cancers. However, these monotherapies are not effective for all patients with metastatic melanoma and melanoma brain metastases. Therefore, in this review, we will not only discuss the combination of nivolumab and ipilimumab for treating metastatic uveal melanoma and mucosal melanoma and its effect on patients in clinical trials, but also explore the effect of radiotherapy plus anti-PD-1 inhibitors or anti-CTLA-4 inhibitors for treating melanoma brain metastases.

2 MELANOMA

Melanoma is the deadliest form of skin cancer, and it is brought about by the malignant tumor derive from melanocytes which is a type of cell derived from neural crest stem cells (NCSCs) that produces and contains a UV absorbing pigment called melanin. There are two forms of melanin generated by melanocytes. One is, a black or brown pigment, eumelanin. Since this pigment is dark, it serves as a great shield for UV radiation, and that is why people with darker skin have lower risk of skin cancer. Indeed, the risk of getting skin cancer is related to the color of skin, hair, and eyes. People who have light skin, blond or red hair, and light eyes has higher risk of gaining skin cancer than those with darker ones. The other pigment is called pheomelanin, which is red or yellow. Compared to eumelanin, it offers less protection against UV radiation, and the yielding of pheomelanin stimulates the advent of cancer. This is due to pheomelanin give more ultraviolet-A-induced reactive oxidative species (ROS) which results in more DNA damage reacting to UV radiation (Davis et al., 2019).

2.1 Mortality Rates, Pathology, and Clinical Manifestations of Melanoma

Skin cancer is one of the most common cancers. Although melanoma only occupies 1% of the skin cancer, more than 75% mortalities was induced by it among all types of skin cancers. According to National Cancer Institute and SEER Database, there are approximately 106,110 new cases of melanoma in 2021, and 7,180 people will die due to this disease (*Melanoma of the Skin - Cancer Stat Facts*, n.d.). Melanoma is caused by the mutations in DNA which are induced by excessive sun exposure. It can be metastatic when melanocytes become malignant and start to disperse to distant body parts, including soft tissues (skin, muscle, and lymph nodes) and major organs (liver, lung, and brain) (DiCaprio et al., 2020; Rebecca et al., 2020). The first step of metastases is to disseminate from the primary tumor to nearby lymph nodes, and then the cancer cells enter the bloodstream and travel to other body parts to form new tumors (*Melanoma Cells That Pass through Lymph More Likely to Spread - National Cancer Institute*, 2020). Symptoms of melanoma that has spread to other sites of body, for example, are hardened lumps under skin, swollen or painful lymph nodes, trouble breathing, bone pain, and swelling of liver (Peri, n.d.). The survival rate of metastatic melanoma is much lower than that of melanoma that doesn't spread based on statistics from Cancer.Net, which drops from 80% to 27% in metastatic melanoma (*Melanoma - Statistics*, 2012).

2.2 Conventional Treatments of Melanoma

Conventional melanoma treatments include surgery, chemotherapy, and radiation therapy. However, surgery is not robust enough to treat metastatic melanoma due to too many sites of tumors throughout the body. Chemotherapy and radiotherapy are more useful as the treatments for metastatic melanoma. As Table 1 showed, there are six chemotherapeutic drugs that are primarily used. Dacarbazine (DTIC) was granted by Food and Drug Administration (FDA) in 1975. However, when it works as a single agent, it has poor efficacy on treating metastatic melanoma, thus it doesn't have much effect on increasing the OS of patients. The other chemotherapeutic drug temozolomide is a substitute of DTIC and can be taken orally. There is no significant difference on the effect of utilizing DTIC and temozolomide. The major problem that induces such low effectiveness is that melanoma cells are intrinsically resistant to chemotherapy (Mishra et al., 2018). Radiotherapy is mainly utilized when melanoma spreads to the brain, which is effective in shrinking the tumors. For melanoma brain metastases, one of the radiotherapies called stereotactic radiation therapy applies to only parts of the brain that have tumor while preventing it from damaging the surrounding normal brain cells (*Patient Education: Melanoma Treatment; Advanced or Metastatic Melanoma (Beyond the Basics) - UpToDate*, n.d.). As the field of immunology gets developed, the better understanding of immune systems leads to a novel

method of treating metastatic cancers, which is employing immune cells against cancers.

Table 1: The Chemo Drugs that Used to Treat Metastatic Melanoma. (Commissioner, 2021).

Drug Name (Brand Name)	Years Approved by FDA
Dacarbazine (DTIC)	May 1975 and January 1998
Temozolomide (Temodar)	August 11th, 1999
Nab-paclitaxel (Abraxane)	January 2005
Paclitaxel (Abraxane)	January 25th, 2002
Cisplatin (Platinol)	December 19th, 1978
Carboplatin (Paraplatin)	July 14th, 2003

3 MONOTHERAPIES OF MELANOMA

3.1 Nivolumab

Nivolumab is a fully human immunoglobulin (Ig) G4 monoclonal antibody that binds to programmed cell death protein 1(PD-1), a T-cell surface receptor, and prevents it from being activated by the programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Activated PD-1 down regulates T-cell activation, helps tumors evade from the immune attack, and promotes its growth. By exploiting nivolumab, PD-1 remains inactivated which enables T cell activation against the tumors. Nivolumab is commonly used as a remedy for melanoma, especially for the situation when the tumor is unresectable or has metastasized. (National Cancer Institute).

As a monotherapy, nivolumab improves the objective response rate (ORR), progression free survival (PFS), and overall survival (OS) compared to chemotherapy. As Figure 1 showed, Larkin et al. compared the overall survival in patients with advanced melanoma using nivolumab versus chemotherapy as a treatment in a phase III trial (CheckMate 037). There were 272 patients treated with nivolumab, and 133 patients were involved in chemotherapy. The median OS was 16 months for nivolumab and 14 months for chemotherapy. The median PFS was 3.1 months in patients with nivolumab and 3.7 months with chemotherapy. Besides, the ORR was higher in nivolumab than in chemotherapy (27% vs. 10%) (Larkin et al., 2018). Another phase III trial, CheckMate 066, also justified the increment in survival. There were 418 patients with metastatic melanoma, the ORR was 40% in those who had nivolumab and 13.9% for patients with dacarbazine, a chemotherapy drug. The median PFS was 5.1 months in nivolumab and 2.2 months in people with chemotherapy (O'Reilly & Larkin, 2017). Figure 2 demonstrated that the overall response rate was higher in melanoma patients treated with nivolumab than those of treated with chemotherapy in both phase III trials. Due to the nivolumab's durable response, this indication has been approved by authorities, such as Food and Drug Administration (FDA) and European Union (EU). On December 20, 2017, nivolumab was approved by FDA as a treatment for melanoma. (Food and Drug Administration). Nivolumab was also granted for treating advanced melanoma in adults in EU. (European Medicines Agency).

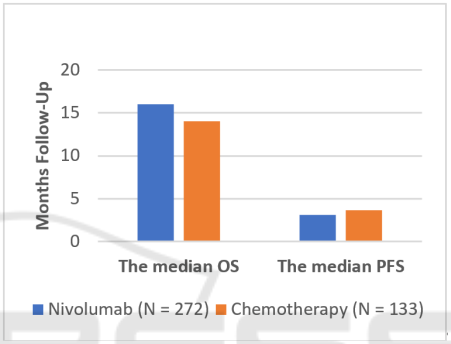

Figure 1: The Overall Survival of Advanced Melanoma Patients Using Nivolumab vs. Chemotherapy in CheckMate 037.

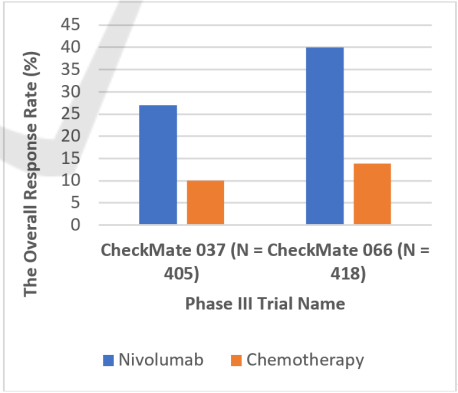

Figure 2: The Overall Response Rate (ORR) of Melanoma Patients Treating with Nivolumab or Chemotherapy in CheckMate 037 vs. CheckMate 066.

3.2 Ipilimumab

Ipilimumab is a recombinant human immunoglobulin (Ig) G1 monoclonal antibody that targets cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), a surface receptor on T-cell. Since

CTLA-4 down regulates the immune system, ipilimumab binds to and inhibits it in order to activate the immune responses. Ipilimumab also shuts down the inhibitory mechanisms on cytotoxic T lymphocytes (CTLs), which kill cancer cells, thus immune responses against cancer are boosted up. Ipilimumab can be favorable for patients who have had surgery for removing melanoma, in which it can work as an adjuvant therapy. Similar to nivolumab, it can also be effective for adults who have metastatic melanoma. (National Cancer Institute).

In contrast to nivolumab monotherapy, ipilimumab monotherapy has shorter PFS and ORRs. In a phase III trial, CheckMate 238, there were 906 patients who were undergone IV melanoma. At 18 months follow-up, the 12 months recurrence-free survival was 70.5% in patients with nivolumab and 60.8% in ipilimumab (Weber et al., 2017). As Figure 3 displayed, a phase III trial (CheckMate 067) conducted by Hodi et al. also proved that nivolumab had greater overall survival than ipilimumab. There were 945 patients involved in the study. Three hundred and sixteen patients were assigned with nivolumab, 315 patients were given ipilimumab, and other patients gained nivolumab plus ipilimumab. The median OS was 36.9 months in the nivolumab group and 19.9 months in the ipilimumab group. The median PFS was 6.9 months in nivolumab while the ipilimumab group was much lower (2.9 months) (Hodi et al., 2018). Ipilimumab was approved by FDA as a therapy for melanoma prior to nivolumab. (Food and Drug Administration). Many recent studies illustrated that nivolumab plus ipilimumab as first-line therapy can achieve a more durable and continuous survival benefit in patients with advanced melanoma.

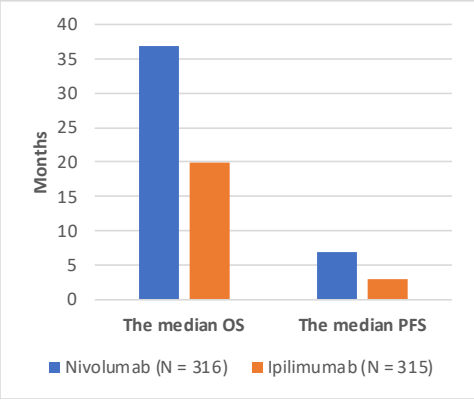

Figure 3: The Overall Survival of Advanced Melanoma Patients Treated with Nivolumab vs. Ipilimumab in CheckMate 067.

4 COMBINATION OF ANTI-CTLA-4 ANTIBODY AND ANTI-PD-1 ANTIBODY

To minimize adverse events and increase the response rate using immunotherapies, it is vital to discover decent checkpoints to adjust the immune response and monoclonal antibodies that target the checkpoints. CTLA-4 and PD-1 are the two potent checkpoints, and there are drugs that are developed modulate the effect of CTLA-4 and PD-1 for treating metastatic melanoma, including CTLA-4 blockers ipilimumab, PD-1 blockers nivolumab, and PD-1 blockers pembrolizumab (Rotte, 2019). The two antibodies ipilimumab and nivolumab are approved on December 22, 2014, by Food and Drug Administration (FDA) for treating metastatic melanoma (Hazarika et al., 2017). Anti-CTLA-4 and anti-PD-1 antibodies can generate durable response and their adverse events are manageable. However, these advantages can't be demonstrated when utilizing either CTLA-4 blockers or PD-1 blockers as monotherapies. Patients with metastatic melanoma are rarely respond to monotherapy (Rotte, 2019). In this case, combination therapies become significance because they activate anti-tumor response, increase response rates, and provide rapid and considerable tumor regression. There are many clinical studies focused on combination therapies for treating melanoma. For instance, when phase I studies received the combination of nivolumab and ipilimumab, they displayed that tumor regression appeared in approximately 50% patients with metastatic melanoma, and 85% of them still survive after 1-year treatment (Koppolu, n.d.).

4.1 CTLA-4 Inhibitor Plus PD-1 Inhibitor for Metastatic Uveal Melanoma and Mucosal Melanoma

The addition of CTLA-4 inhibitor and PD-1 inhibitor can also be useful in treating subtypes of melanoma. For example, it can be impressive for metastatic uveal melanoma. Uveal melanoma arises from melanocytes in the iris. It is very rare, and only five of one million people getting this type of melanoma each year (Afzal et al., 2018). Traditionally, metastatic uveal melanoma (MUM) was treated with chemotherapy alone, but most patients had poor response or no response to it. In a systematic review, 841 patients from 40 different reports were investigated. The overall response rate (ORR) is only 4.6%, and there were 22 studies that demonstrated no response to chemotherapy (Buder

et al., 2013). Compared to employing chemotherapy alone, the efficacy of combining nivolumab and ipilimumab on treating MUM is greater based on the data listed in the prospective phase II GEM1402 trial (NCT02626962). The ORR was 12%, the median progression free survival (PFS) was 3.3 months, and the median OS was 12.7 months (Piulats Rodriguez et al., 2018). Heppt et al. also analyzed the effect of utilizing both PD-1 inhibitors only and the combination of ipilimumab and PD-1 inhibitors in a clinical trial with 96 MUM patients. For PD-1 inhibitor monotherapy, pembrolizumab was given in 54 patients (25 females and 29 males), and nivolumab was in 32 patients (13 females and 19 males). The ORR was 4.7% with four patients demonstrated a PR, and there was no complete response observed. The median PFS was 3.1 months in patients with pembrolizumab and 2.8 months with nivolumab. The median OS was 14.0 months for pembrolizumab and 10.0 months for nivolumab. Combining ipilimumab and PD-1 inhibitors leads to higher ORR compared to monotherapy. Fifteen patients were investigated, and twelve patients developed response. There was still no complete response and only two PRs. The ORR was 16.7%, which is much larger than the 4.7% ORR in monotherapy (Heppt et al., 2017).

The potency of the combination of ipilimumab and nivolumab is also compelling in treating patients with mucosal melanoma (MM). It is a rare and aggressive disease with insufficient prognosis. Only 1.5 per million people every year are diagnosed with MM. The common sites for MM are head and neck (41%). The cutting of surgery is the primary method for head and neck MMs, and radiotherapy is always applied for local control after the surgery (Ascierto et al., 2017). Even though immune checkpoint inhibitors have become a promising option for MMs, the clinical use for it still remains inadequate (Li et al., 2020). In a pooled analysis, Sandra et al. reported the competence of nivolumab alone and the mix with ipilimumab. In clinical studies, 889 patients were received only nivolumab. Among them, 86 (10%) were mucosal melanoma patients and 665 (75%) had cutaneous melanoma. For the addition of nivolumab and ipilimumab, there were 35 mucosal melanoma patients and 326 patients with cutaneous melanoma. The outcome illustrated that the median PFS was 3.0 months, and Figure 4 showed that the ORR was 23.3% for MM patients who accepted nivolumab monotherapy. Combining nivolumab and ipilimumab manifested a higher median PFS in patients that was 5.9 months. As Figure 4 displayed, the ORR was also boosted to 37.1% (D'Angelo et al., 2017). The performance of the combo seems to be more superior than that of the agent using alone. Another case report by Fujimura et al. confirmed the efficiency of this combination method again. The patient was an 81-year-old Japanese woman who had anti-PD-1 Ab-resistant recurrent malignant melanoma of nasal cavity. They found out that denosumab could enhance the anti-tumor effects of incorporating nivolumab and ipilimumab and successfully resolve the advanced anti-PD-1 Ab-resistant mucosal melanoma by blending denosumab, nivolumab, and ipilimumab as a second-line therapy (Fujimura et al., 2020).

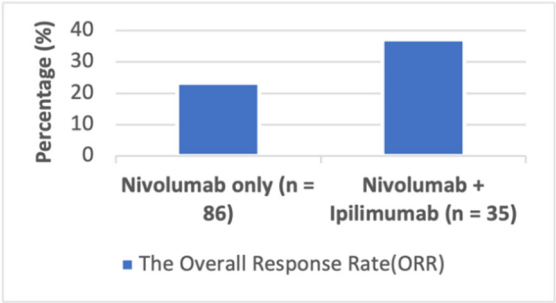

Figure 4: The Overall Response Rate in Mucosal Melanoma Patients Treated with Nivolumab Monotherapy vs. Nivolumab and Ipilimumab Combination Therapy.

5 COMBINED TREATMENTS FOR MELANOMA BRAIN METASTASES

Approximately 20% patients with cancer will develop brain metastases. Melanoma brain metastases (MBM) is one of the major ones (7% - 16%) (Berghoff et al., 2016). Brain metastases occur when tumor cells disperse from a primary tumor through the blood to the brain microvasculature. The microenvironment of the brain microvasculature bolsters the growth of tumors. Among different ethnic groups, African Americans who are 50 to 59-year-old with melanoma tended to have larger probability getting brain metastases. For various subsets of brain metastases, people with melanoma have the highest likelihood of obtaining leptomeningeal metastases, the one in the lining of brain or spine (Achrol et al., 2019).

Treatments for brain metastases include surgery if it is in a surgically accessible region, whole brain radiotherapy (WBRT) for multiple symptomatic brain metastases, stereotactic radiosurgery (SRS) treating metastatic lesions without damaging the surrounding brain tissues, systemic therapy that conjugates with local therapy and provides greater intracranial control, cytotoxic therapy, targeted therapy, and immunotherapy (Rishi & Yu, 2020).

5.1 Nivolumab Plus Ipilimumab Treatment

Within immunotherapy, the combination of nivolumab and ipilimumab presented an essential efficaciousness in patients who had melanoma brain metastases. According to a phase II study (NCT02320058) with 94 melanoma patients who had at least one brain metastasis (tumor diameter 0.5 to 3 cm). The trial indicated that the intracranial clinical benefit rate (CBR) was 57%, the complete response was 26%, and partial response was 30%. This study affirmed that adding nivolumab and ipilimumab was impressive for melanoma patients who had untreated brain metastases (*Combined Nivolumab and Ipilimumab in Melanoma Metastatic to the Brain | NEJM*, n.d.). Recently, this phase II study (NCT02320058) updated their data for asymptomatic patients. The intracranial CBR was 58.4% for 101 asymptomatic patients, and the PFS and OS were still investigating. Due to the reliable clinical benefits in asymptomatic MBM patients, nivolumab plus ipilimumab was considered as the first-line therapy (Tawbi et al., 2021).

5.2 Radiotherapy Plus PD-1 or CTLA-4 Blockers

Moreover, except for conjoining the immune checkpoint inhibitors, stereotactic radiosurgery (SRS) along with nivolumab or ipilimumab can also serve as a way for patients with MBM. Giuseppe et al. examined the adequacy of concurrent SRS plus nivolumab or ipilimumab for patients with untreated MBM. Eighty patients with 326 MBM were engaged in the study. There were 45 patients gained the SRS and ipilimumab, and 35 patients got SRS and nivolumab. The median follow-up was 15 months. Among the 45 patients with SRS and ipilimumab, 32 of them (71%) obtained an intracranial progression event while 20 patients (57%) in the SRS and nivolumab group got such advancement. The median OS was 22.0 months for the SRS and nivolumab group and 14.7 months in patients with SRS and ipilimumab. Besides, the 12-month and 24-month survival probabilities were 78% and 42% for the SRS and nivolumab patients. Compared to that, the SRS and ipilimumab group had lower rate, which were 68% and 20% individually. Both groups exhibited valid intracranial activities, and the combo of SRS and nivolumab had more excellent intracranial control (Minniti et al., 2019).

6 CONCLUSIONS

Combination therapies of immune checkpoint inhibitors have the bright future for treating metastatic melanoma and melanoma brain metastases. As I mentioned before, immune checkpoint inhibitors, anti-PD-1 and anti-CTLA-4 inhibitors target the checkpoint proteins and turn on the immune response against the melanoma cells. However, no matter checkpoint inhibitors are used as individual therapy or combing with one another, all of them can generate immune-related adverse events (irAEs), which can be life-threatening. For ICIs that combines with another existing therapy, this may cause severe immune related adverse events happen more frequently. For instance, therapies that involve anti-CTLA-4 inhibitors have higher incidence of irAEs occurring in the gastrointestinal tract, renal system, and endocrine system. Most irAEs of anti-PD-1 therapies appear at endocrine system, gastrointestinal tract, musculoskeletal system, and hepatobiliary system. Thus, it is necessary for future research to identify predictive biomarkers for irAEs which can not only help patients with metastatic melanoma and select the therapy that has optimal benefits, but also avoid the toxicities. There's also a need for next generation research to investigate and evaluate the drugs that can improve the response to ICIs, such as microbiota modifiers, drugs targeting co-inhibitory receptors, and oncolytic viruses.

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