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## **Immunotherapy versus Chemotherapy: Which Treatment Offers Better Survival to Adults with Advanced Melanoma?**

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Immunotherapy versus Chemotherapy: Which Treatment Offers Better Survival to Adults with  
Advanced Melanoma?

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Abstract

Background: Melanoma is the most serious type of skin cancer that can lead to metastasis. The main treatment for melanoma is surgical removal — a wide excision. Patients with advanced melanoma require further treatment such as chemotherapy or immunotherapy due to the concern of continuous spread.

Purpose: Literature review of studies to examine if patients with advanced melanoma, treated with immunotherapy, enjoy better overall survival rates than patients treated with chemotherapy?

Methods: A comprehensive literature review was conducted using <Pub Med> using the search terms <(advanced melanoma) AND (immunotherapy)) AND (chemotherapy)) AND (skin cancer)>. Inclusion criteria were studies that were related to immunotherapy and chemotherapy among advanced melanoma patients. Exclusion criteria were studies that were completed more than five years ago, free text was available, other languages besides English, non-human species, and any patient under the age of 18 years old.

Conclusions: Immunotherapy is a more sustainable option for treating patients with advanced melanoma. It has been proven that immunotherapy offers patients better outcomes versus treating advanced melanoma with chemotherapy.

Key Words: “advanced melanoma”, “immunotherapy”, “chemotherapy”, “skin cancer”

## Introduction

Among skin cancers, melanoma represents the most aggressive type and is responsible for the majority of deaths among skin cancer patients. Melanoma is especially fearsome as it often spreads to other parts of the body. According to the American Academy of Dermatology (AAD), more than 197,000 Americans will be diagnosed with advanced melanoma in 2022, affecting slightly more women than men, yet more men will die from melanoma.<sup>1</sup> When detected early, and before it spreads to lymph nodes, melanoma has a ninety-nine percent five-year survival rate.<sup>1</sup> However, that figure falls to sixty-eight percent if melanoma spreads to nearby lymph nodes, and then plummets to thirty percent once it spreads to distant lymph nodes and other organs.<sup>1</sup> The AAD estimates nearly twenty Americans die each day from melanoma-related complications.<sup>1</sup>

Melanoma may show itself on the skin in many ways: as a mole that changes shape or color, a spot that may resemble a mole or freckle or age spot but appears slightly different, spots with jagged borders and changing colors, or a dome-shaped growth that is firm to the touch and looks like a sore that may bleed.<sup>1</sup> Melanoma may also appear as a dark-brown or black vertical line beneath a fingernail or toenail, or a band of darker skin around a fingernail or toenail.<sup>1</sup>

Examining the efficacy of melanoma treatments is important as the incidence of melanoma, according to the American Cancer Society (ACS), has been increasing in recent decades.<sup>2</sup> This alarming fact is due to the use of artificial sun lamps and prolonged exposure to ultraviolet light. And despite pleading from health officials and their own physicians and healthcare providers, people continue to engage in unsafe behaviors exposing their skin to potentially damaging ultra violet (UV) radiation.<sup>2</sup> Of course, climate change contributes to these unsafe practices, with summers becoming increasingly hotter; just this summer heat records are

being shattered across the globe, and millions of people are seeking relief outdoors, millions of people often unaccustomed to such sun exposure.

So, new beachgoers, and even those who traditionally worship the sun, must be aware that even one blistering sunburn as a child, or five or more between the ages of fifteen and twenty, increases melanoma risk by up to eighty percent. The message, often repeated, is this: “Unprotected exposure to the sun’s UV rays remains the most preventable risk factor for skin cancer.”<sup>2</sup>

Despite healthcare professionals’ pleading with everyone to apply sunscreen, incidents of melanoma march on. But, early detection can prevent complications. This means performing self-exams to check the skin for signs (as above) of melanoma, and then seeing a physician for a definitive diagnosis. Unfortunately, the messages, the self-exams, the use of sunscreens are either forgotten or ignored, leading to diagnoses of stage III and state IV melanoma.

When melanoma is classified as stage III, this means it has spread to one or more lymph glands and nearby skin.<sup>1</sup> And by stage IV, the most advanced stage, it means melanoma has spread to one or multiple parts of the body including non-adjacent skin or lymph nodes, and to internal organs including the lungs or brain.<sup>1</sup> Thus, when a patient is diagnosed with stage III or stage IV melanoma, they and their physician face a choice: which treatment will offer greatest chance of survival with minimal side effects, traditional chemotherapy, or any of the newer immunotherapies or, perhaps a combination of both? This literature review will examine treatment therapies for advanced melanoma to determine if patients will have greater survival rates with immunotherapy, chemotherapy, or a therapy protocol combining the two. Further, a comprehensive discussion will lead to conclusions, including next steps, as well as potential for future research.

## Methods

A comprehensive literature review was conducted using <Pub Med> using the search terms <(advanced melanoma) AND (immunotherapy)) AND (chemotherapy)) AND (skin cancer)>. Inclusion criteria were studies that were related to immunotherapy and chemotherapy among advanced melanoma patients. Exclusion criteria were studies that were completed more than five years ago, free text was available, other languages besides English, non-human species, and any patient under the age of eighteen-years-old.

The abstract includes sources relevant because the death rate associated with melanoma is increasing annually and there is generally a lack of awareness among people about melanoma risk factors. Sources were obtained through Pub Med, and then they were analyzed, with special attention paid to survival rates. From this analysis, a recognizable trend emerged in terms of which treatment may be most effective.

Further, studies were limited to those conducted within the previous five years to ensure the most accurate and current data to propose effective treatment for patients with advanced melanoma. The age limit — only patients eighteen years of age and older — was selected as adults report far greater incidence of melanoma than children. And, only English-language studies were reviewed to allow for a complete understanding of the data. Treatment options for advanced melanoma are becoming more advanced, so a comparison of these options is useful and may lead to future studies.

Pub Med  
((advanced melanoma) AND  
(chemotherapy) AND  
(immunotherapy) AND (skin  
cancer))  
n=804

Exclude articles outside of the last  
five years and free text available  
n=214

Exclude any other languages aside  
from English and non- human  
species  
n=185

Exclude participants under 18 years  
old  
n=95

Inclusion of participants with advanced  
melanoma (Stage III and IV).  
n=35

### **Literature Review**

In a study published in 2019 by Larkin et al patients were randomly assigned in a 1:1:1 ratio to receive a different combination of immunotherapy – nivolumab plus ipilimumab, nivolumab, and ipilimumab.<sup>3</sup> This study included adult patients with confirmed stage III or stage IV advanced melanoma.<sup>3</sup> Participants were selected between July 2013 through March 2014 where a total of 1296 patients were enrolled, but only 945 underwent randomization.<sup>3</sup> The



patients were followed-up at a minimum of sixty months. This study revealed that the overall survival was longer in patients who were treated with nivolumab- containing groups than in the ipilimumab group.<sup>3</sup> This study also incorporated the quality of life among patients that receive melanoma therapy.<sup>3</sup> The EQ-5D-3L results from this five-year analysis did not show significant deterioration in health-related quality of life among the nivolumab groups but did acknowledge that there was meaningful deterioration that was observed among the patients that used ipilimumab.<sup>3</sup> Overall, patients with advanced melanoma in this study had a greater long-term survival at five years and quality of life by using the nivolumab plus ipilimumab or nivolumab alone than those who received ipilimumab.<sup>3</sup>

Similarly, a study published two years later by Najjar et al, enrolled thirty-one patients (only thirty were evaluated) and examined neoadjuvant pembrolizumab, an immunotherapy drug, and high dose IFN $\alpha$ -2b therapy in patients with reseceptable advanced melanoma.<sup>4</sup> Yet, Larkin and Chiarion-Sileni found that the specific use of nivolumab immunotherapy allowed for a better quality of life in their 2019 study that followed sixty-eight patients for five years.<sup>3</sup> Overall, the patient would undergo about one year of treatment including a definitive surgery to remove the melanoma.<sup>4</sup> High dose IFN $\alpha$ -2b and pembrolizumab were discontinued in seventy-three and 43% of the patients that were enrolled in the trial.<sup>4</sup> The immunotherapy drug and HDI medication that were used concurrently demonstrated promising clinical activity regardless of the high rates of discontinuation.<sup>4</sup> Although there are different types of immunotherapy, they do not all act similarly. Indeed, many patients in this study discontinued their therapy but still were left with promising results.

Tarhini et al found that neoadjuvant therapy was classified as fairly safe and portrayed a significant impact on T-cell fraction.<sup>5</sup> This study examined both male and female adult patients

diagnosed with advanced melanoma.<sup>5</sup> This study used neoadjuvant immunotherapy – ipilimumab because it has capabilities to revamp the overall standard of care for advanced melanoma.<sup>5</sup> The safety and efficacy of the therapy were both evaluated while also examining T-cell fractions in the heme and tumor. <sup>5</sup> However, only twenty-eight patients were evaluated, and of those eleven relapsed and five died.<sup>5</sup>

One other study by Kleef at al examined reported deaths. This research study is a retrospective that examines both the safety and efficacy of a new therapy in more than 100 stage IV cancer patients with various types of cancer who have reached the end point in terms of available conventional therapies.<sup>6</sup> Although immunotherapy has made significant improvement in the overall survival of patients with advanced melanoma, at times it comes with a cost of adverse events — moderately elevated serum glutamic oxaloacetic transaminase (GOT) and serum glutamic pyruvic transaminase (GPT), , diarrhea, skin rash — that later occur.<sup>6</sup> These adverse events lead to patients having to discontinue the immunotherapy. In this study, fifty-nine percent of patients had suffered from some type of adverse event leading to a discontinuation of therapy in 24.5% of patients and one death.<sup>6</sup> As mentioned from Larkin et al, an immunotherapy combination of ipilimumab and nivolumab treatment has achieved a three-year survival rate of sixty-three percent for patients with advanced melanoma.<sup>3</sup>

The efficacy of immunotherapy as an effective treatment for melanoma, which included less frequent hospitalization, was further demonstrated in a study.<sup>7</sup> This is a cohort study that evaluates hospitalization rates in patients with advanced melanoma receiving either pembrolizumab therapy or ipilimumab plus nivolumab therapy.<sup>7</sup> Both of these therapies are approved by the Food and Drug Administration in patients who acquire advanced melanoma. The duration of the study was twelve months.<sup>7</sup> The patients selected were from various U.S.

academic centers. This study is important in that it examines patients with advanced melanoma who underwent chemotherapy and had a particularly low survival rate and high toxicity.<sup>7</sup> The patient population was greater than or equal to eighteen-years-old.<sup>7</sup> This study concluded that patients on the pembrolizumab therapy had a much lower chance of being admitted into the hospital as compared to patients receiving the dual therapy, ipilimumab plus nivolumab.<sup>7</sup> The results support the pembrolizumab as it is proven to decrease hospitalizations as compared to the dual therapy or chemotherapy alone.<sup>7</sup>

Further, a retrospective study focuses on patients with advanced melanoma taking the nivolumab therapy beyond progression.<sup>8</sup> The individuals in this study were treated with nivolumab after first degree progression.<sup>8</sup> The goal of the study was to examine possible benefits, as well as efficacy and safety, of nivolumab therapy. Long et al concluded that the majority of selected patients treated with this therapy had clinical benefits and tolerated the drug.<sup>8</sup>

Likewise, Yamazaki et al conducted a study where patients were also being treated with Nivolumab. This study examines postmarketing data of the antibody nivolumab in patients of Japanese descent who have acquired advanced melanoma.<sup>9</sup> The type of melanoma in this specific population was so advanced in nature that it was unresectable.<sup>9</sup> In the study, the patients were to take nivolumab at various dosages for a duration of every two to three weeks.<sup>9</sup> The goal was to evaluate the responsive and survival rate at this particular population. The results indicated that in the 124 patients observed, the most common melanoma type was mucosal melanoma.<sup>9</sup> The average survival duration was roughly fifteen months.<sup>9</sup> This study concluded that those using nivolumab had lower survival rates and the efficacy of nivolumab therapy does not show highly promising results in clinical practice.<sup>9</sup>

Skudaslski et al provides more information about systemic therapies for patients with melanoma. While melanoma deaths continue to be on the rise, systemic therapies are often approached first due to the difficulty of surgical clearance. Chemotherapy was the gold standard.<sup>10</sup> Yet, that changed after 2011 because of the lack of positive response and survival rates. Since that time, various systemic therapies have come into play, some even being approved by the FDA, including nivolumab.<sup>10</sup> Therapies such as nivolumab have been shown to have favorable results in treating advanced melanoma.<sup>10</sup> Thus, practitioners such as dermatological oncologists should implement newer therapies such as these in hopes for favorable results for their patients. While more testing and research must be completed, it is more evident that these therapies have shown much favorable results as compared to chemotherapy.

Finally, the case report published by Gorayski et al reviewing treatment on a 71-year-old male showed how immunotherapy compares to other treatments and discusses the eradication of micro-metastases wherever it is in the body.<sup>11</sup> The patient ignored fungating and bleeding malignant melanoma. Surgical options were considered, but due to severe complications and significant morbidity, a conjoined decision was made against surgical intervention.<sup>11</sup> The untreated melanoma led to the patient adapting a condition where he lacked healthy red blood cells which normally would carry enough oxygen to your body's tissues as well as debilitated cardiac issues including heart failure.<sup>11</sup> This patient was treated with combined radiotherapy and immunotherapy for four weeks.<sup>11</sup> The combination therapy resulted in a response, but after the fifth round of immunotherapy the patient developed colitis and the immunotherapy was discontinued.<sup>11</sup> Immunotherapy has made significant improvements in total survival within the last decade and has increased the survival to more than three years compared to a six-month survival with chemotherapy.

## Immunotherapy and Chemotherapy

Jenkins et al evaluates various treatments for advanced melanoma in 2020 and beyond. In recent years, new therapies have been introduced to significantly benefit patients with advanced melanoma. These therapies have shifted from chemotherapy, traditionally the gold standard of care.<sup>12</sup> Though there is progress in advanced melanoma, other therapeutic approaches are available that are required for patients that do not respond to current therapies. Because of the target of molecular therapies, there has been an outstanding improvement in the overall survival in people suffering from advanced melanoma. As time progresses, this study and others emphasize the importance of seeking advancements that can overcome resistance with current therapies to combat advanced melanoma and significantly decrease the mortality rate.<sup>12</sup> Chemotherapy is analyzed within studies in combination or versus immunotherapy alone, but there are many elements when patients and providers agree on a treatment plan.

Many patients rely solely on insurance or out-of-pocket expenses to cover the cost of treatment. Immunotherapy and chemotherapy fall among different price points and this can be a factor as to why patients delay, refuse, and or choose different therapy. Ipilimumab was the first systemic agent to prolong survival in 2011 for advanced melanoma patients.<sup>13</sup> Alternative therapies such as target therapy and surgical interventions were less than \$50,00, while ipilimumab was more than \$80,000 dollars.<sup>13</sup> In subsequent years, as other immunotherapy drugs were approved, there was a continued concern of cost. Between 2013 and 2015, the annualized melanoma spending increased 21% leading to an increase of \$61 million.<sup>13</sup> The cost of immunotherapy was \$153 million in 2015.<sup>13</sup> Although the immunotherapy drugs have offered promise to patients, the prices are soaring.<sup>13</sup> Patients may avoid costly immunotherapy by scheduling early detection and prevention exams.

A randomized clinical study published by Hamid et al in 2017, focused on the final analysis of the survival of the therapy pembrolizumab versus chemotherapy in patients who have acquired advanced melanoma.<sup>14</sup> Patients eligible to participate in this study acquired advanced melanoma and had been treated with two or more ipilimumab immunotherapy doses or MEK inhibitors.<sup>14</sup> This particular study had 180 patients randomized to pembrolizumab and 179 patients randomized to chemotherapy.<sup>14</sup> After the follow-up of twenty-eight months, it was unfortunate that a total of 368 patients died.<sup>14</sup> The study also concluded that the survival rate with pembrolizumab therapy was not more significant at either dose when compared to chemotherapy. Although pembrolizumab did not indicate a significant difference compared to chemotherapy in this specific study, Larkin et al concluded that immunotherapy options such as nivolumab provide beneficial results to patients diagnosed with advanced melanoma.<sup>3</sup>

This randomized control study, published by Weber et al examines both safety and adequacy of nivolumab, and compares it to chemotherapy as a second option treatment in patients with advanced melanoma. Participating patients had to be at least eighteen-years-old with metastatic melanoma that could not be treated with surgery.<sup>15</sup> In the study, patients were randomly selected to receive an IV therapy of nivolumab containing 3mg per kg bi-weekly, or chemotherapy every three weeks in combination with carboplatin.<sup>15</sup> A total of 631 patients were screened. There were zero fatalities among participants. The study showed that nivolumab had the best responses as compared to chemotherapy with patients that had advanced melanoma.<sup>15</sup>

Larkin et al controlled, open-label phase III trial evaluated the survival of patients with advanced melanoma who received chemotherapy versus nivolumab therapy. A total of 272 people were given nivolumab at random and a total of 133 were given chemotherapy at random.<sup>16</sup> The average survival rate for those on nivolumab with advanced melanoma was

sixteen months as compared to fourteen months for patients on the chemotherapy regimen.<sup>16</sup> The results of this study made clear that nivolumab therapy had significantly better response rates as compared to the chemotherapy.<sup>16</sup> However, this study indicated that there was no difference in survival rate. Yet, the dropout rate of this study was significant: 233 patients on nivolumab were discontinued from their treatment and 102 patients were discontinued from the chemotherapy treatment.

Furthermore, a study published by Robert et al analyzes ipilimumab plus dacarbazine for previously untreated metastatic melanoma patients. Five-hundred-two patients were assigned to this study and received either ipilimumab plus dacarbazine or dacarbazine plus placebo given over a span over several months.<sup>17</sup> Dacarbazine has never been shown to improve survival in any randomized, controlled studies, but it is the drug that has been compared with new therapies, such as immunotherapy.<sup>17</sup> Eligible patients were required to be at least eighteen-years-old with untreated stage III or stage IV melanoma. If the patients received any treatments prior to enrollment in this study, they were considered ineligible. Between August 2006 and January 2008, 250 patients were randomly assigned to the immunotherapy plus chemotherapy combination and 252 patients were assigned to the chemotherapy plus placebo combination.<sup>17</sup> There was a significant increase in disease progression in both groups, but more significant in the chemotherapy plus placebo group.<sup>17</sup> For the ipilimumab-dacarbazine group, survival was 11.2 months and 9.1 months for the dacarbazine group.<sup>17</sup> The most common adverse effect was elevated liver functions.<sup>17</sup> This trial showed that there was much better improvement in overall survival among patients with previously untreated metastatic melanoma that received the ipilimumab therapy plus the dacarbazine compared to the dacarbazine alone.<sup>17</sup>

## Chemotherapy

Hamid et al is an open-label, randomized, phase III trial and it focuses on patients with advanced NRAS-mutant melanoma. The study examines the efficacy of binimetinib versus dacarbazine.<sup>18</sup> This study looks at both the effectiveness and safety of both therapies. This study was conducted in more than 100 hospitals globally and its patients had advanced NRAS-mutant melanoma unable to be surgically resected.<sup>18</sup> The study concluded that binimetinib had a positive survival by reducing progression compared to the other therapy, dacarbazine.<sup>18</sup> Binimetinib, then, can be a possible promising treatment modality for patients with advanced melanoma who did not have success or cannot afford other therapies.<sup>13</sup>

Ribas et al conducted a phase III randomized trial evaluated the survival rate, including safety and effectiveness, in patients with advanced melanoma who received the tremelimumab therapy. The study included 655 patients all randomly assigned.<sup>19</sup> The results concluded that the overall survival rate for the therapy of tremelimumab was 12.6 months versus 10.7 months for those on chemotherapy treatments.<sup>19</sup> Researchers concluded that there was no significant benefit in terms of overall survival when comparing tremelimumab to chemotherapy because of various similar results.<sup>19</sup> Additional research is needed to find a more definitive conclusion.

Because chemotherapy has shown a negative effect for those suffering with advanced melanoma focused on discovering the effects of other therapies such as paraoxonase-2, part of a paraoxonase gene family proven to equip many antioxidant properties in parts of the body such as the small intestine and central nervous system.<sup>20</sup> It also has properties of attacking oxidative stress that is difficult on the body.<sup>20</sup> The data shows that paraoxonase-2 could have beneficial results in targeting those who have advanced melanoma.<sup>20</sup> More investigation and further studies would be needed to provide insight and efficacy of this therapy.



Although therapies are beneficial they do come with side effects. People with advanced melanoma usually have been treated with dacarbazine, a chemotherapy. Yet, dacarbazine has many side effects, including phototoxic dermatitis.<sup>21</sup> Treudler et al focuses on patients that have received dacarbazine and have had this reaction, and examines a different chemotherapy agent called temozolomide in hopes to eliminate the phototoxic dermatitis reaction.<sup>21</sup> This study evaluated ten patients who were diagnosed with malignant melanoma. The patient population aged between thirty-four and seventy-five years of age.<sup>21</sup> Of the five patients that received the temozolomide chemotherapy, not one encountered the phototoxic reaction.<sup>21</sup> Thus, not only does temozolomide prevent phototoxic dermatitis reaction, it is a beneficial treatment for those suffering from advanced melanoma.<sup>21</sup>

Patients that have advanced melanoma use different types of therapies: immunotherapy, chemotherapy, radiation, and surgical methods. Since 2011, immunotherapy has made a drastic change in medicine especially with advanced melanoma patients. Chemotherapy was no longer the first line treatment.<sup>13</sup> Overall, according to multiple studies, immunotherapy offers patients the best outcome and survival rate compared to chemotherapy. The quality of life for patients experiencing advanced melanoma that are on immunotherapy versus other treatments is better. Although there are several different immunotherapy options and the patients are at risk for side effects, the outcome is overall more beneficial for their health than chemotherapy is due to the survival rate. In a study within this literature review, a patient had a combination therapy of immunotherapy and radiation which both provided the patient with promising results even though the patient developed colitis and the immunotherapy was therefore discontinued.<sup>11</sup>

#### Discussion/Analysis

Based on the literature interpreted above, immunotherapy is a secure option for treating advanced melanoma. The studies have showcased that there has been minimal benefit to chemotherapy for the use of advanced melanoma in the last decade. Although there are differences to each of the medications and the way they target the body of patients that suffer advanced melanoma - patients that use immunotherapy have shown greater signs of survival compared to immunotherapy.

Larkin et al established that there is a greater long-term survival at five years and the quality of life by using nivolumab compared to other immunotherapy drugs.<sup>3</sup> Since 2011, immunotherapy has impacted patients diagnosed with advanced melanoma in numerous ways. Chemotherapy used to be the gold standard and now it is not.<sup>10</sup> The incidence of melanoma is on the rise and the gold standard that was chemotherapy is losing its place among treatment protocols to immunotherapies and combination treatments. Chemotherapy still can play a role within a specific group of patients that suffer from advanced melanoma, but it is not as common. There are patients that do not qualify for any type of immunotherapy treatments and or have undergone multiple treatments and were unsuccessful so now chemotherapy is the last option. It does not have a significant and beneficial survival rate when compared to immunotherapy.

Although chemotherapy can be an option for patients that do not qualify for specific treatments that suffer from advanced melanoma, the efficacy of the treatment is extremely low when compared to immunotherapy. In addition to chemotherapy not having an overall high survival rate it comes with a variety of side effects including , but not limited to hair loss, vomiting, nausea, fatigue, and increased infection. The goal of the chemotherapy treatment is to shrink the cancer, but it has been shown that several months later it typically returns and sometimes even more aggressively.<sup>22</sup>

Immunotherapy's overall survival rate offers patients and their families much more time of survival than chemotherapy. Indeed, there are adverse effects that can potentially affect a patient's everyday life such as colitis, fatigue, nausea, and skin rash. Despite the list of side effects and what the advanced melanoma patient may experience, there have been promising results for the patient's overall survival. A study done by Larkin et al patients with advanced melanoma had a greater long-term survival at five years and quality of life using immunotherapy drugs, specially nivolumab or a combination of nivolumab and ipilimumab.<sup>3</sup> The use of immunotherapy drugs has been on the rise over the last decade and has become the primary form of treatment for patients with advanced melanoma. This study has been a primary example of how immunotherapy has been beneficial for patients that have been diagnosed with advanced melanoma.

Cancer cells typically avoid the immune system including melanoma cells. This allows the immunotherapy drugs to offer patients better potential for survival. The immunotherapy therapies help to increase the immune response and while doing this it increases the response of the immune system in order for the cells to recognize and destroy melanoma cells.

As mentioned, the immunotherapy drugs do offer the best overall survival, but there is still more research among the types of immunotherapy medications that need to be done. It would be beneficial to compare individual and combination immunotherapies among the same group of advanced melanoma patients. This would allow researchers, providers, and patients to succeed at a longer overall survival rate now that the primary treatment has been shifted to immunotherapy for advanced melanoma patients.

With this all means that patients are able to increase their life expectancy and with this be able to enjoy life to its fullest and complete things and spend quality time with their loved ones

while also surviving a terrible disease, advanced melanoma. The immunotherapy drugs will additionally provide less abuse on the body compared to chemotherapy. As mentioned, there are a list of side effects and at times the therapies have to be discontinued due to this. When analyzing the different side effects immunotherapy still offers the body more tolerable side effects compared to chemotherapy. There overall is less abuse on the body and the patient will be able to continue with their everyday life even while they are undergoing treatment.

Overall, the most beneficial treatment for patients suffering from advanced melanoma is immunotherapy. Multiple studies throughout this literature have analyzed immunotherapy, chemotherapy, and both treatments in combination and the overall analysis is that immunotherapy is the best treatment for patients that are suffering from advanced melanoma.

### **Conclusion**

The goal of this literature review is to examine studies for patients diagnosed with advanced melanoma and determine the lead therapies that provide better survival - specifically comparing immunotherapy versus chemotherapy. The studies overall showed that the immunotherapy treatment is a better alternative compared to the chemotherapy. The overall decision of therapies for the patients are individualized and include a multitude of factors that should be considered such as: efficacy, cost, and benefit towards the patients survival. Between both therapy options there is a list of adverse reactions that should be considered and/or the patient should be made aware of prior to beginning treatment. Immunotherapy is the most considered therapy treatment against advanced melanoma.

The analyzed studies investigated the overall survival, safety, efficacy, and other therapies that can benefit patients that suffer from advanced melanoma. Based on the literature, immunotherapy provided patients a better outcome than chemotherapy did, making

immunotherapy the gold standard for patients with advanced melanoma. Immunotherapy drugs for advanced melanoma patients do have considerable side effects, but the overall survival provides hope to patients and their families.

Luckily patients have been able to see a tremendous amount of results from the immunotherapy drugs and are able to have a better survival. There is still an opportunity within this topic to evaluate in more specific which immunotherapy types are most beneficial. Being able to provide research can help providers and patients decide which immunotherapy drug would be best fit to treat their advanced melanoma. All in all, the review of the literature shows that immunotherapy is more beneficial and provides an overall better survival compared to chemotherapy.

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## Appendix A

Author	Title	Design	Source	Findings	Year Published
Larkin, Chiarion-Sileni	Five-Year Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma.	RCT	Pub Med	This is a randomized control trial that discusses the five-year survival among immunotherapeutic agents - nivolumab and ipilimumab amongst advanced melanoma patients	2019
Joseph RW, Shillington AC, Lee TA, et al.	Hospitalization and emergency department utilization in patients with advanced melanoma receiving pembrolizumab versus ipilimumab plus nivolumab in US academic centers	Retrospective study	Pub Med	This is a retrospective study that analyzes patients with advanced melanoma and the use of immunotherapy drugs in correlation with hospitalization and emergency department utilization.	2020
Long GV, Weber JS, Larkin J, et al.	Nivolumab for patients with advanced melanoma treated beyond progression	Retrospective study	Pub Med	This is a retrospective study that discusses treatment beyond progression for patients that have advanced melanoma and	2017

				are being treated with immunotherapy.	
Gorayski P, Dzienis M.	Complete clinical response of a neglected cutaneous melanoma with combined radiotherapy and immunotherapy.	Case report		This case report discusses an individual patient's experience with immunotherapy treatment after leaving an advanced stage melanoma untreated.	2020
Kleef R, Nagy R, Baierl A, et al.	Low-dose ipilimumab plus nivolumab combined with IL-2 and hyperthermia in cancer patients with advanced disease: exploratory findings of case series of 131 stage IV cancers	Retrospective study	Pub Med	This is a retrospective study that compares a single institution's advanced melanoma patients immunotherapy treatments.	2022
Hamid O, Puzanov I, Dummer R, et al.	Final analysis of randomised trial comparing pembrolizumab versus-investigator-choice chemotherapy for ipilimumab-refractory advanced melanoma	RCT	Pub Med	This is a randomized control trial with patients that suffer from either BRAF or MEK inhibitor advanced melanoma that used immunotherapy for treatment.	2017
Weber JS, D'Angelo SP, Minor D, et al.	Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment.	RCT	Pub Med	This is a randomised controlled open-label phase 3 trial that	2015

				investigates and compares immunotherapy and chemotherapy treatments with patients that have advanced melanoma.	
Larkin J, Minor D, D'Angelo S, et al.	Overall survival in patients with advanced melanoma who received nivolumab versus investigators choice chemotherapy in checkmate 037.	RCT	Pub Med	This is a randomized controlled open label phase III trial that discusses and evaluates the overall survival in patients with advanced melanoma that had been given nivolumab versus chemotherapy.	2017
Robert C, Thomas L, Bondarenko I, et al.	Ipilimumab plus dacarbazine for previously untreated metastatic melanoma	RCT	Pub Med	This study is a randomized control trial that randomly assigned 502 patients to a chemotherapy and immunotherapy therapy or a chemotherapy agent and placebo.	2011
Dummer R, Schadendorf D, Ascierto PA, et al.	Binimetinib versus dacarbazine in patients with advanced NRAS-mutant melanoma (NEMO)	RCT	Pub Med	This study is a randomized control trial that analyzes patients with advanced	2017

				NRAS-mutant melanoma within the different chemotherapy treatments.	
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