Project On

"A Review on the Progress and Potential Treatment of Melanoma by EMA & FDA in the Past Decade"

Submitted To

The Department of Pharmacy,

Faculty of Allied Health Sciences,

Daffodil International University.

In the partial fulfillment of the requirements for the degree of Bachelor of Pharmacy

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Date of Submission: April 2023

APPROVAL

The research article titled "A Review on the Progress and Potential Treatment of Melanoma by EMA & FDA in the Past Decade" has been reviewed and submitted by the Department of Pharmacy, Faculty of Allied Health Sciences, Daffodil International University. It has been deemed satisfactory for the partial fulfillment of the requirements for the Bachelor of Pharmacy degree, and approved for its style and content.

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DECLARATION

I hereby declare that I am carrying out this thesis study in accordance with the requirements for the Bachelor of Pharmacy degree (B. Pharm) under the guidance of "Ms. Nazneen Ahmeda Sultana", Assistant Professor in the Department of Pharmacy at the Faculty of Allied Health Sciences, Daffodil International University. This project is one that I created entirely on my own. I further certify that I have not previously submitted this project or any portion of it for a degree award from another institution .

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ACKNOWLEDGEMENT

I am grateful to Allah for granting me good health and wellbeing, which were crucial in completing this work. I would like to extend my heartfelt thanks to Professor Dr. Muniruddin Ahamed, Head of the Department of Pharmacy at Daffodil International University, for providing me with all the necessary facilities for my research.

I would also like to express my sincere appreciation to Professor Dr. Md. Bellal Hossain, Dean and Faculty of Allied Health Sciences at Daffodil International University, for his constant encouragement and support.

I am deeply grateful to my research supervisor "Ms. Nazneen Ahmeda Sultana", Assistant Professor at the Department of Pharmacy, Daffodil International University, for sharing his expertise, offering invaluable guidance, and providing continuous encouragement throughout my project.

I would also like to take this opportunity to express my gratitude to all the faculty members of the Department for their support and assistance. I extend my thanks to my parents for their unwavering encouragement, support, and attention. Furthermore, I am grateful to my partner who has been supportive throughout this endeavor.

Lastly, I would like to express my sincere appreciation to all those who have directly or indirectly contributed to the success of this project.

Sumyea Harun

Author

Abstract:

In the past decade, remarkable advancements have been made in the treatment of melanoma, a type of skin cancer caused by the uncontrolled growth of pigment-producing cells in the skin. Over the past decade, the development of immunotherapies and targeted therapies has drastically changed the treatment of stage IV melanoma patients. Both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have played pivotal roles in this progress by approving numerous new treatments.One of the most significant developments in melanoma treatment has been the use of immunotherapy drugs, which utilize the body's immune system to combat cancer cells. Some of the FDA-approved immunotherapy drugs for melanoma include checkpoint inhibitors targeting CTLA-4, PD-1, and PD-L1 such as ipilimumab and nivolumab, as well as immune system boosters like interleukin-2. These drugs have demonstrated impressive results in treating advanced melanoma, with some patients experiencing long-term remission.Another promising avenue of melanoma treatment is targeted therapy, which concentrates on specific molecular pathways that contribute to the growth and spread of cancer cells. Some of the FDAapproved targeted therapies for melanoma include BRAF inhibitors like vemurafenib and dabrafenib, as well as MEK inhibitors such as trametinib. These drugs target specific genetic mutations commonly found in melanoma cells and have proven effective in slowing the progression of the disease. The EMA approved dabrafenib to treat melanoma with a mutant BRAF protein, specifically the BRAF V600 genetic mutation, that cannot be surgically removed, is unresectable, or has metastasized to other areas of the body. In conclusion, over the past decade, great strides have been taken in the treatment of melanoma. The FDA and EMA have been instrumental in this progress by approving innovative treatments that have improved the prognosis for melanoma patients.

Keywords : Melanoma , FDA , EMA , immunotherapy , targeted therapy , BRAF inhibitors.

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Chapter-1 Introduction

1. Introduction:

Melanoma is the most lethal type of skin cancer, and rates are rising more quickly than those of any other disease that is now curable (American Cancer Society, 2019) .One of the most dangerous malignant tumors of the skin and mucosa, melanomas are malignant tumors that develop from melanocytes (Figure 1) (Diepgen & Mahler, 2002). Melanoma is a cancer that develops in melanocytes, neuroectodermal cells with a dendritic appearance. Genetic and molecular changes are assumed to accumulate sequentially to cause melanocytosis to change (Miller & Mihm Jr, 2006)(Palmieri et al., 2009) .

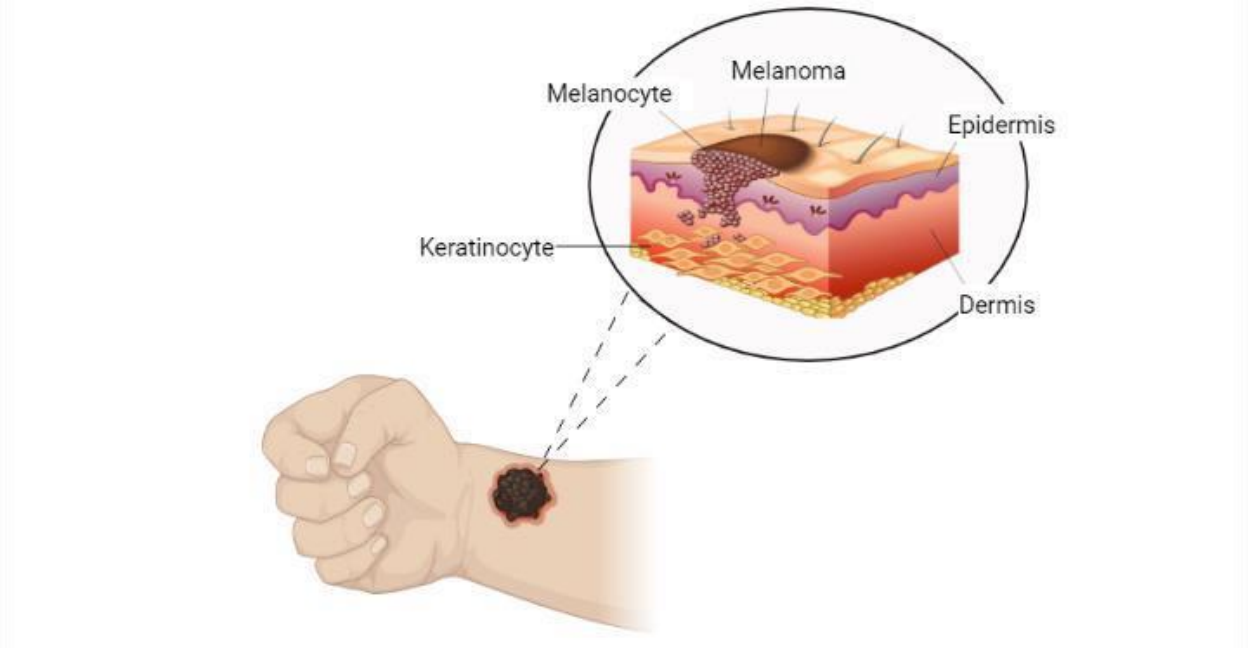

Figure 1: Melanoma Skin Cancer (Diepgen & Mahler, 2002) .

The majority of melanocytes are found in the skin's basal layer of the epidermis, separated from one another by keratinocytes (Elder, 2014). The uveal tract of the eye and different mucosal surfaces, such as the sinonasal mucosa, oral mucosa, and vulva, are additional locations where melanocytes may be present and melanomas may developed (Piepkorn et al., 2014) . It is the third most prevalent malignancy in teenagers and young adults aged 15 to 39, yet most instances affect the elderly(Weir et al., 2011). Melanoma incidence rates vary over the world as a result of population genetic diversity and UV radiation exposure. White (fairskinned) populations living in high UV intensity places have the highest rates of melanoma incidence; in particular, Australia and the USA have greater incidences than Europe (except Sweden) (de Vries & Coebergh, 2005). In the US, melanoma additionally ranks as the fifth most prevalent cancer in males and the seventh most common cancer in women (CDC & NIH, 2017).

Recent statistics show that melanoma is now the most prevalent cancer in young adults in the USA between the ages of 25 and 29. The lifetime chance of having melanoma in Caucasians is currently estimated to be one in fifty(Rigel, 2010) . The incidence of melanoma moves along a gradient across Europe, from northern countries (where incidence is higher) to southern geographic regions (consistently Italian standardized rates per year per 100,000 inhabitants are 10.5–13.5 in North Italy and 3.5–4.5 in South Italy) (Curado, M. P. ; Edwards, B. ; Shin, H. R. ; Storm, H. ; Ferlay, J. ; Heanue, M. ; Boyle, 2007).

The word melanoma, which is derived from the Greek words melas, "black," and oma, "tumor," was originally used by Hippocrates of Cos in the fifth century BC. Later, it was used by the Greek physician Rufus of Ephesus (Urteaga & Pack, 1966). Australian mathematician Henry Lancaster established the first link between exposure to UV radiation from sunshine and the occurrence of melanoma in 1956 (LANCASTER, 1956). Treatments for melanoma in the middle to late 19th century included ligation, excision with a knife or scissors, chloride of zinc, extirpation, amputation, or burning the tumor with caustic substances (Pereira et al., 2020). Inhibitory receptors or checkpoints, such as the CTLA-4 and PD-1 proteins developed by Allison and Honjo, are involved in the paradigm-shifting developments in cancer immunotherapy (Lv et al., 2022)(Filin et al., 2023).

Almost a decade of clinical research in checkpoint immunotherapy has been sparked by promising early results of trials using PD-1 inhibition with nivolumab or pembrolizumab and CTLA-4 blockade with ipilimumab (Lv et al., 2022),(Jandova et al., 2022)(Villani et al., 2022). The only FDA-approved CTLA-4 inhibitor for unresectable or metastatic melanoma in both adults and children is ipilimumab (Postow et al., 2015). One of the three RAF protein family members, BRAF, is the target of the most common mutation in this pathway. BRAF is present in about 50% of all melanomas. One of the three RAS protein (H-, K-, and N-RAS family members) members that is mutated in about 25% of melanomas is NRAS, which is located further downstream in the MAPK pathway (Rabbie et al., 2019)(Tsao et al., 2012). Currently, there are three *MEK* inhibitors that are FDA & EMA-approved for the treatment of cancers. These include: trametinib for *BRAF*-mutant melanoma (approved in 2013&2014), cobimetinib for *BRAF*-mutant melanoma (approved in 2015), and binimetinib for *BRAF*-mutant melanoma (approved in 2018). This review highlights recent advances in the treatment of melanoma in the past decade by FDA & EMA, including changes in staging, surgical management, and advances in systemic therapy for high-risk and advanced melanoma.

Chapter-2
Objective of the Study

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2. Objective of the Study

"A Review on the Progress and Potential Treatment of Melanoma by EMA & FDA in the Past Decade" aims to provide-

- a summary of the developments in the treatment of melanoma over the previous ten years, with a focus on the medications that have been authorized by the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA).
- The purpose of this article is to discuss potential future avenues for the development of novel treatments while also summarizing the advancements made in the field of melanoma treatment.
- This review could explore the clinical trials, research plans, and statistical techniques employed in determining the efficacy and safety of these therapies.
- The review's main objective is to give clinicians and researchers a thorough and current overview of melanoma treatment so they can make informed decisions.

Chapter-3
Melanoma & It's Pathophysiology

3. Melanoma & It's Pathophysiology

3.1. History of Melanoma

The word melanoma, which is derived from the Greek words melas, "black," and oma, "tumor," was originally used by Hippocrates of Cos in the fifth century BC. Later, it was used by the Greek physician

Rufus of Ephesus (Urteaga & Pack, 1966). Despite the generally paucity of archeological evidence of cancer, tumors can be identified in the skeletons of people who had bony osteosarcomas or osteolytic bone metastases. The extensive melanotic metastasis discovered in the skeletons of pre-Colombian mummies from Chancay and Chingas in Peru, which have been radiocarbon dated to be B2400 years old, are the earliest physical proof of melanoma (Urteaga & Pack, 1966).

Dr. William Norris, a medical practitioner from Stourbridge, UK, published one of the earliest in-depth and perceptive observations concerning the etiology and course of "melanosis" in 1820 under the heading of "fungoid illness" (Norris, 1820). Norris followed a 59-year-old male patient with melanoma for three years in his study, recording the disease's development and making specific anatomical observations after the patient's postmortem (Norris, 1857). Most importantly, almost 50 years before Mendel presented his results on heredity, Norris was the first to observe that some melanomas are heritable (Rebecca et al., 2012). He was one of the first to suggest a connection between nevi and melanoma as well as a potential link between exposure to environmental variables (such industrial pollution), and he also noted that the majority of his patients had light-colored hair and fair skin (Norris, 1857). A Case of Melanosis, with General Remarks on the Pathology of the Intriguing Disease was published by Thomas Fawdington in 1826. In it, he described a 30-year-old patient who had developed an ocular melanoma following an eye injury (Fawdington, 1826). In 1837, Isaac Parrish noted the first melanoma case in North America (Morton et al., 2006).

The First Paragraph of "the Theory and Practice of Surgery," published in 1844 by a British surgeon by the name of Samuel Cooper, acknowledged that melanomas in their mature stages were incurable and declared, "The sole opportunity for benefit depends upon the early removal of the illness" (Azzola et al., 2003). The transition of melanoma from a radial growth phase to a vertical growth phase was described by Sir James Paget, Consulting Surgeon to St. Bartholomew's Hospital, London, in a report on 25 cases of melanoma in 1853. "In some cases the growth is superficial, and the dark spot captures a larger area and appears to be slightly raised by some growth beneath it. In other cases the mole rises and becomes very prominent," he wrote (Sondak et al., 2004). Oliver Pemberton described the clinical features and sites of metastases of 60 melanoma cases he had collected between 1820 and 1857 in detail in 1858. Also, he was the first to describe melanoma in a patient who was black and from the island of Madagascar (Viros et al., 2008). Australian mathematician Henry Lancaster identified the first link between exposure to UV radiation from sunlight and the prevalence of melanoma in 1956 (LANCASTER, 1956).

3.2. Pathophysiology :

A malignant neoplasm generated from melanocytes is a simple definition for malignant melanoma. The mass of melanocytes in the skin are found in the basal layer of the epidermis, which is separated by keratinocytes (Elder, 2014). The uveal tract of the eye and different mucosal surfaces, such as the sinonasal mucosa, oral mucosa, and vulva, are additional locations where melanocytes may be located and melanomas may originate (Pereira et al., 2020). Four major histogenetic subgroups of cutaneous melanomas have been identified: nodular, lentiginous, lentigo maligna, and superficial spreading (Figure2) (Viros et al., 2008). Despite the fact that these specific melanoma subtypes are clinically and histopathologically unique, a categorization of this kind lacks independent prognostic significance (Viros et al., 2008).

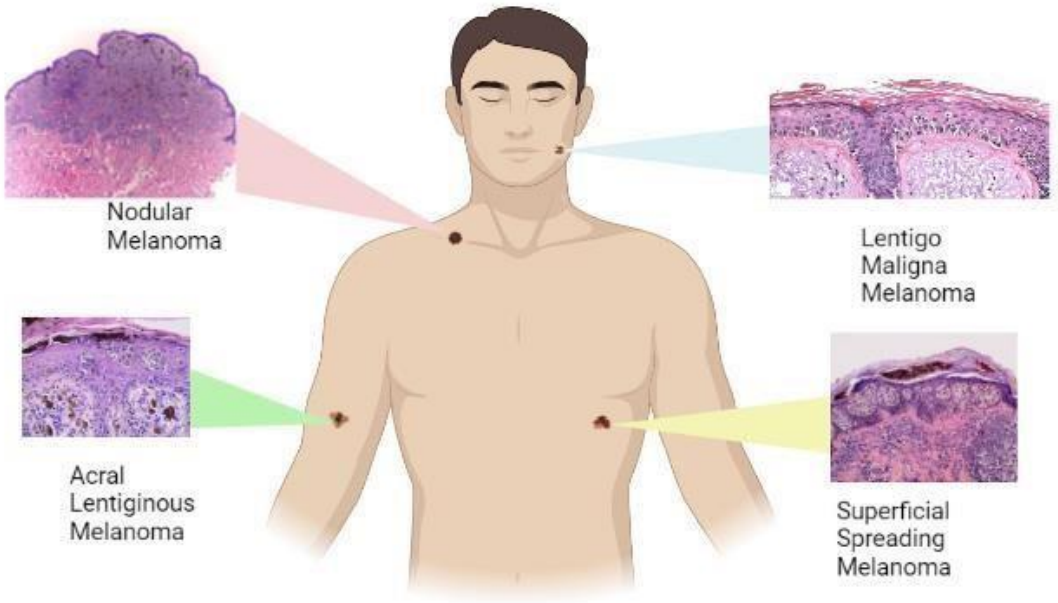

Figure 2 : Microscopic image of different types of melanoma (Viros et al., 2008).

Briefly, those between the ages of 30 and 50 are more likely to develop superficial spreading melanoma, the most commonly diagnosed form of the disease (70–80% of all instances) (Cabrera & Recule, 2018). Typically, it starts out as a macula and progresses into a palpable papule or nodule with uneven edges and a wide spectrum of colors. In intraepidermal tissues, malignant melanocytes frequently spread in a pagetoid and nested pattern according to histology. Intradermal nests of melanocytic proliferation are also executed (Garbe et al., 2016)(Duncan, 2009). Despite the fact that it can occur anywhere, men and women are more likely to experience it on their trunks or lower extremities. Horizontal intraepidermal growth can persist for a long period before becoming invasive (Cabrera & Recule, 2018),(Ammirati & Hruza, 2005). The second most common kind of melanoma (15–30%) is nodular melanoma. It can potentially manifest everywhere, however the trunk, head, and neck are the areas where it occurs most frequently. The most aggressive form of cancer is this one (Cabrera & Recule, 2018). This sort of tumor's brown, black, or even blue-black lesions can manifest in a variety of ways. It might take the form of a smooth-surfaced cutaneous nodule, a conspicuous plaque with uneven forms, or a polypoid exophytic tumor. Histologically, intradermal nests and clusters of tumor cells are seen, but the dermal tumor is covered by limited intraepidermal melanocytic growth (Duncan, 2009).The dramatic variance among diverse melanoma types has resulted in a variety of categorization techniques being used to categorise them. The progression of melanoma from a skin patch or plaque known as the "radial growth phase" (RGP) to a tumorigenic proliferation known as the "vertical growth phase" (VGP), with an increasing risk of metastasis, forms the basis for an important component of

the classification of melanomas (Thapa et al., 2018).The RGP, a name derived from clinical morphology but more frequently used histologically, refers to melanomas that typically start as a patch or plaque in the skin that spreads along the radius of an increasingly irregular circle in the skin. Clinically, the lesions often develop characteristics that have been recorded by several algorithms (Dolianitis et al., 2005), the most well-known of these is the "A, B, C, D, and E" rule, where A stands for asymmetry, B for border irregularity, C for color variegation, D for diameter larger than 4 mm, and E can be either "elevation" or "evolution." Of course, the gross pathology of the melanoma is represented by this clinical morphology(Guerry et al., 1993).

Skin keratinocytes produce the melanocyte stimulating hormone (MSH) in response to UV-induced DNA damage, which binds to the melanocortin receptor 1 (MC1R) on melanocytes to cause them to manufacture and release melanin. In the end, the melanin pigment protects DNA from additional alterations by acting as a shield against UV radiation (Lin & Fisher, 2007). The primary genetic causes of melanoma include mutations in the neurofibromin 1 (NF1), NRAS, and B-Raf proto-oncogene (BRAF), and melanoma associated with prolonged sun exposure typically has a high mutational impact due to UV exposure (Figure 3) (Candido et al., 2014)(Curtin et al., 2005)(Bastian, 2014). On the other hand, incidences of melanoma linked to intermittent sun exposure develop in people under the age of 55, on less exposed parts like the trunk and proximal extremities, and are typically linked to BRAFV600E and a lower mutational impact (Curtin et al., 2005)(Bastian, 2014).

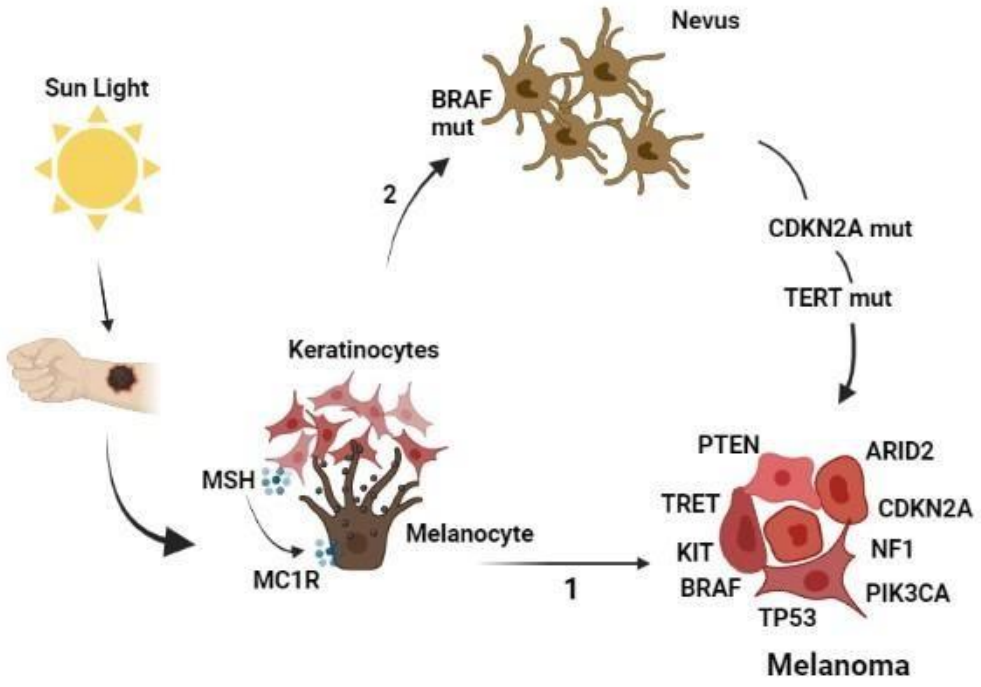

Figure 3: Melanocyte malignant transformation.UV-A irradiation induces melanocytes malignant transformation through two different mechanisms (Leonardi, Falzone, et al., 2018) .

The direct transformation of normal melanocytes in neoplastic cells through the occurrence of several mutations affecting both proto-oncogene and tumor suppressor genes (TP53, NF1, PTEN, etc.). The transformation of melanocytes into benign nevi that in 80% of cases harbor the mutation BRAFV600E.

The biology and development of melanoma have been better understood in recent years. It has become evident that there is no single evolutionary pattern that describes how pre-neoplastic lesions progress into fully-evolved melanoma. Each subtype of melanoma can develop from a different underlying lesion, and it can also entail a different gene mutation and degree of transformation (Shain & Bastian, 2016). An intriguing discovery is that BRAF is mutated in up to 80% of benign nevi, which limits melanocyte growth by activating cell apoptosis through oncogenes (Pollock et al., 2003)(Leonardi, Accardi, et al., 2018). Due to immunological monitoring, these nevi have remained dormant for decades (Speeckaert et al., 2011). Consequently, the oncogenic BRAF mutation alone is insufficient for the formation of melanoma, and benign nevi sporadically proceed to melanoma (Shain & Bastian, 2016),(Gray-Schopfer et al., 2007). When this happens typically, it's linked to the development of later mutations in important genes like TERT or CDKN2A. However, the melanomas that are connected to long-term sun exposure typically develop from dysplastic lesions or melanomas in situ rather than pre-existing nevi and have a different set of alterations (Shain & Bastian, 2016). To diagnose melanocytic neoplasia and determine their malignant potential, histological characterization is currently the gold standard. Yet, histopathology is occasionally connected to the ambiguous identification of these lesions, resulting in their incorrect risk classification (Farmer et al., 1996).

Additionally, an important step is to stage the tumor accurately. As a result, the doctor will be able to determine the patient's prognosis and choose the ideal and most effective therapeutic approach (Lopes et al., 2022a). The American Joint Committee on Cancer(AJCC) has developed the most used cutaneous melanoma staging system .The TNM staging system is based on an evaluation of three characteristics, each of which has several criteria: (T) Breslow tumor thickness of the main tumor and presence or absence of ulceration; (N) number of involved lymph nodes and presence or absence of in-transit, satellite, and/or microsatellite metastasis; and (M) anatomic site of distant metastasis and LDH concentrations. Following analysis, patients are categorized into groups according to their pathological stage, which are as follows: 0, I (IA and IB), II (IIA, IIB, and IIC), III (IIIA, IIIB, IIIC, and IIID), and IV. In stages I and II, tumors are categorized based on their thickness and degree of ulceration, but in stage 0 cancer cells are only seen in

the epidermis. When lymphatic tissues are involved or when there is dissemination to one or more essential organs, respectively, stages III and IV classification are given (Gershenwald et al., 2017).

Chapter-4
Methodology

4. Methodology

Data for this article were collected from PubMed and Google Scholar using the keywords Melanoma , FDA , EMA , immunotherapy , targeted therapy , BRAF inhibitors, Pathophysiology , Prevalence, Treatment etc.I have also used Microsoft Word , Excel , BioRender & Mendeley. The literature search was not limited to a small timescale but 20% of the accumulated data were published before 2000 and the remaining 80% were limited to the timescale of 10 years. I was started collecting the data from January until April 2023.

Around 400 papers were read to find the appropriate information, and after primary screening, 121 papers were selected and critically scrutinized. They were then summarized for the current review.

Chapter-5

Literature Review

5. Literature Review

5.1. Melanoma Management: From Epidemiology to Treatment and Latest Advances (Lopes et al., 2022a) .

Melanoma is the deadliest skin cancer, whose morbidity and mortality indicators show an increasing trend worldwide. In addition to its great heterogeneity, melanoma has a high metastatic potential, resulting in very limited response to therapies currently available, which were restricted to surgery, radiotherapy and chemotherapy for many years. Advances in knowledge about the patho- physiological mechanisms of the disease have allowed the development of new therapeutic classes, such as immune checkpoint and small molecule kinase inhibitors. However, despite the incontestable progress in the quality of life and survival rates of the patients, effectiveness is still far from desired. Some adverse side effects and resistance mechanisms are the main barriers. Thus, the search for better options has resulted in many clinical trials that are now investigating new drugs and/or combinations. The low water solubility of drugs, low stability and rapid metabolism limit the clinical potential and therapeutic use of some compounds. Thus, the research of nanotechnology-based strategies is being explored as the basis for the broad application of different types of nanosystems in the treatment of melanoma. Future development focus on challenges understanding the mechanisms that make these nanosystems more effective.

5.2. Cutaneous melanoma: From pathogenesis to therapy (Review) (Leonardi, Falzone, et al., 2018).

Tyrosine kinase inhibitors and immune checkpoint inhibitors, which have been proven to have a significant influence on patients' prognoses for melanoma, have been approved, revolutionizing melanoma treatment in less than 10 years. In research labs, this transformation's initial stages have been conducted. Through numerous genomic alterations on various components of these pathways, the mitogen-activated protein kinase (MAPK) pathway and the phosphoinositol 3-kinase (PI3K) pathway promote the development of melanoma. Additionally, the tumor microenvironment and immune system have strong interactions with melanoma cells. The discovery of new therapeutic targets and therapeutic approaches has resulted from this knowledge. The epidemiological characteristics of cutaneous melanoma and the biological processes behind its occurrence and development are outlined in this paper. The state-of-the-art in advanced stage melanoma therapy approaches as well as the most recent data on the use of prognostic and predictive biomarkers are also covered.

5.3. Recent Advances in the Treatment of Melanoma (Curti & Faries, 2021) .

Melanoma is a type of skin cancer that arises from the pigment-producing cells of the skin. It is the most deadly form of skin cancer and has been on the rise in recent years. This paper provides an abstract of recent advances in the treatment of melanoma. The paper focuses on new drugs, immunotherapies, and targeted therapies that have shown promise in the treatment of melanoma. In particular, the paper highlights the use of checkpoint inhibitors, BRAF and MEK inhibitors, and combination therapies. The paper also discusses the challenges that remain in the treatment of melanoma, including resistance to therapy and the need for biomarkers to guide treatment decisions. Overall, the paper provides an overview of the latest developments in the treatment of melanoma and the potential impact of these advances on patient outcomes.

Chapter-6
Result & Discussion

6. Result & Discussion

6.1. Prevalence :

6.1.1. Result:

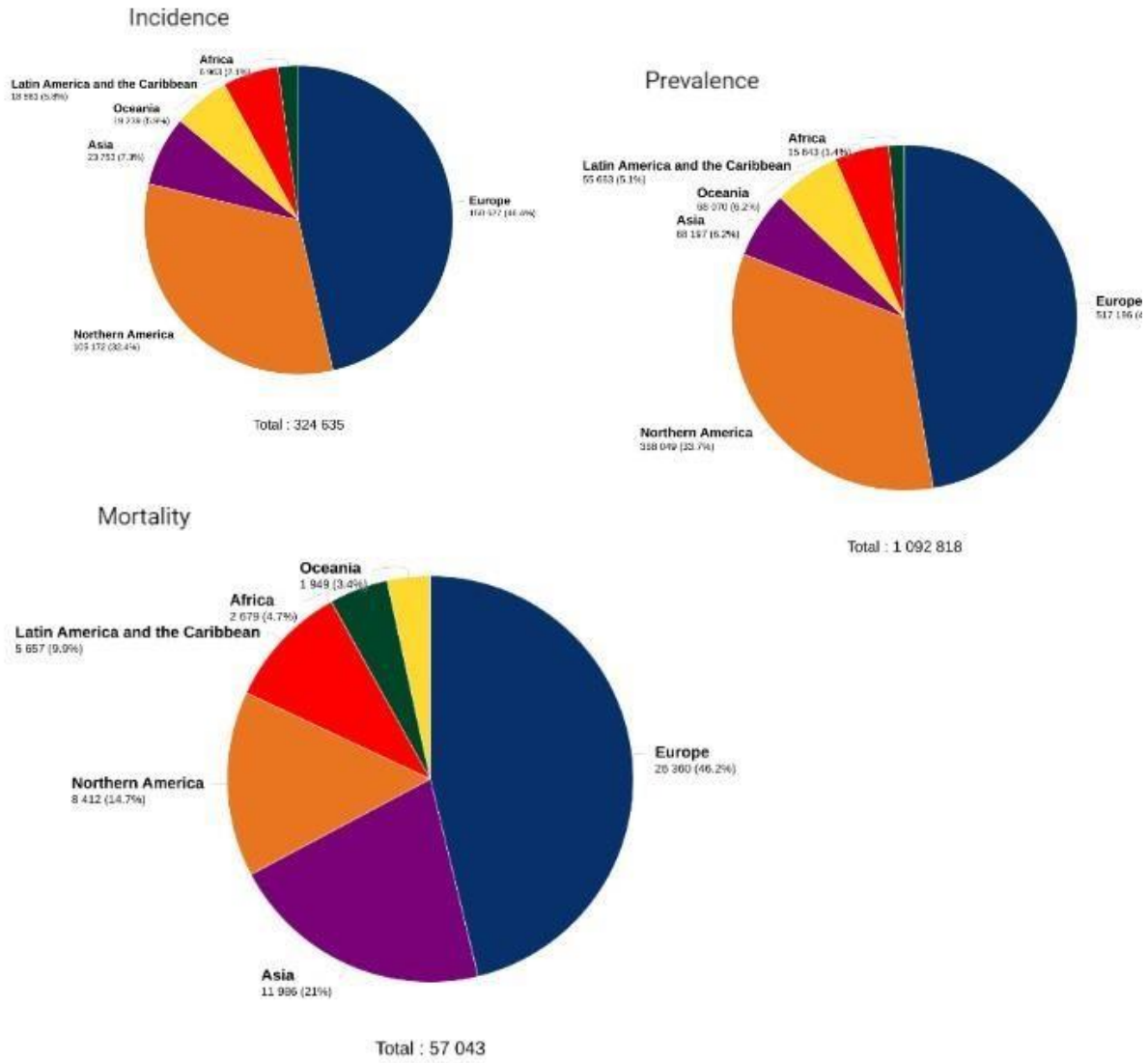

Figure 4: Estimated number of new cases and deaths from cutaneous melanoma in 2020, across all age groups and genders. Data collected from the Global Cancer Observatory (International Agency for Research on Cancer Cancer Today., 2020)

6.1.2. Discussion

Over the past few decades, the incidence rate of melanoma, a type of cancer, has been rising quite quickly throughout the world (Matthews et al., 2017)(Apalla et al., 2017). The annual incidence of melanoma has increased by 4-6% in light-skinned populations such as those in North America, Northern Europe, Australia, or New Zealand (Matthews et al., 2017) . IARC expects that there were approximately 325,000 new cases of cutaneous melanoma in 2020 (International Agency for Research on Cancer Cancer Today., 2020). Melanoma, which accounts for 1.7% of all cancer diagnoses and likely caused 57,000 deaths in the same period, is one of the most prevalent cancers in the world (Sung et al., 2021)(International Agency for Research on Cancer, 2020). The same organization anticipated an increase in new cases and deaths attributable to them until 2040 of around 57 and 68%, respectively (International Agency for Research on Cancer Cancer Tomorrow., n.d.). Therefore, it is not surprising that the highest rates of melanoma incidence are verified in the equatorial regions, where the hours of sunshine exposure are higher (Davey et al., 2021). With an age-standardized rate (ASR) per 100,000 inhabitants of 36.6 and 31.6, respectively, Australia and New Zealand had the highest incidence rates of melanoma in 2020, according to the IARC. In contrast, the following nations—Denmark, the Netherlands, Norway, Sweden, Switzerland, and Germany—had significant incidences of ASR and were all situated at higher latitudes (International Agency for Research on Cancer Cancer Today., 2020). The southern European countries had a lower incidence than the northern ones, which can be attributed to the people' different skin tones, which also reflect the patterns of incidence by ethnicity that will be covered further on. The low ASR levels in other groups living close to the equator, as is the case in many Asian and African countries, are also explained by the frequency of darker pigmentation(Figure 4) (Matthews et al., 2017)(Lopes et al., 2022a).

6.2. Treatment with medication:

6.2.1. Result:

Table 1. Melanoma treatment drugs and respective years of approval by Food and Drug Administration (FDA) and European Medicines Agency (EMA) (Food and Drug Administration., n.d.)European Medicines Agency, n.d.).

Drug Name	Mechanism	Treatment Type	FDA Approval		EMA Approval	
			Date	Manufacturer	Date	Manufacturer

Dabrafenib	BRAF inhibitor	Targeted therapy	29 May, 2013	Novartis Pharmaceuticals Corporation.	2 Aug, 2013	Novartis Europharm Ltd.
Trametinib	MEK inhibitor	Targeted therapy	29 May, 2013	GlaxoSmithKline LLC	29 Aug,2013	GlaxoSmithKline

Pembrolizumab	Monoclonal antibody anti-PD-1	Immunotherapy	4 Sept, 2014	Merck & Co., Inc.	23 July,2015	Merck & Co., Inc.
Nivolumab	Monoclonal antibody anti-PD-1	Immunotherapy	22 Dec ,2014	Bristol-Myers Squibb	19 June , 2015	BristolSquibb yers EEIG Pharma
Dabrafenib +Trametinib	BRAF & MEK inhibitor	Targeted therapy (Combinatorial approaches)	8 Jan , 2014	_	2015	_
Talimogene Laherparepvec	Oncolytic herpes virus	Immunotherapy	27 Oct , 2015	Amgen Inc.	18 Dec , 2015	Amgen B.V. Europe
Cobimetinib	MEK inhibitor	Targeted therapy	10 Nov , 2015	Genentech	20 Nov , 2015	Roche
Cobimetinib + Vemurafenib	BRAF & MEK inhibitor	Targeted therapy (Combinatorial approaches)	10 Nov , 2015	Genentech	22 Dec , 2015	Roche
Nivolumab + Ipilimumab	CTLA-4 & PD-1 blocker	Immunotherapy (Combinatorial approaches)	30 Sept ,2015	Bristol Myers Squibb	29 June , 2016	Bristol Myers Squibb
Binimetinib	MEK inhibitor	Targeted therapy	27 June , 2018	Array BioPharma Inc	3 Sept ,2018	Pierre Fabre Médicament
Encorafenib	BRAF inhibitor	Targeted therapy	27 June , 2018	Array BioPharma Inc	21 Sept ,2018	Pierre Fabre Médicament

Binimetinib + Encorafenib	BRAF & MEK inhibitor	Targeted therapy (Combinatorial approaches)	27 June , 2018	Array BioPharma Inc	21 Sept ,2018	Pierre Fabre Médicament
Atezolizumab	Monoclonal antibody anti-PD-L1	Immunotherapy	30 July, 2020	Tecentriq, Genentech, Inc.)	_	_
Cobimetinib + Vemurafenib + Atezolizumab	MAPK pathway blocker	Targeted therapy + Immunotherapy	30 July, 2020	Tecentriq, Genentech, Inc.)	_	_
Relatlimabrmbw	Monoclonal antibody anti-LAG-3	Immunotherapy	2022	Regeneron Pharmaceuticals, Inc.	_	_
Nivolumab + Relatlimabrmbw	Monoclonal antibody anti-PD-1 & anti-LAG-3	Immunotherapy (Combinatorial approaches)	18 March , 2022	Bristol-Myers Squibb	_	_

In addition, these drugs have other therapeutic uses other than melanoma and they are listed in Table 2.

Table 2. FDA &EMA approved drugs dosage form , therapeutic use(other use), & adverse effects (Food and Drug Administration., n.d.)(European Medicines Agency, n.d.).

Drug Name	**Dosage Form**	**Therapeutic Use**	**Adverse Effects**
Dabrafenib	Capsule	Unresectable or metastatic melanoma, melanoma, metastatic non-small cell lung cancer, metastatic anaplastic thyroid cancer.	Rash, photosensitivity, and hyperkeratosis
Trametinib	Tablet	Melanoma	Rash, renal failure, pneumonitis, and diarrhea

Pembrolizumab	IV Injection	melanoma, lung cancer, head and neck cancer, Hodgkin lymphoma, stomach cancer, cervical cancer, and certain types of breast cancer	Inflammation of the pituitary gland, thyroid (causing both hypothyroidism and hypert hyroidism in different people), and pancreatitis that caused Type
			1 diabetes and diabetic ketoacidosis;
Nivolumab	IV Injection	Melanoma, lung cancer, malignant pleural mesothelioma, renal cell carcinoma, Hodgkin lymphoma, head and neck cancer, urothelial carcinoma, colon cancer, esophageal squamous cell carcinoma, liver cancer, gastric cancer,	Pneumonitis, thyroiditis, hepatitis, pruritus, vitiligo, and diarrhea
Talimogene Laherparepvec	Injection, Suspension	Melanoma	Cellulitis, edema.
Cobimetinib	Tablet	Melanoma	Diarrhea, nausea, vomiting, rash, photosensitivity, and pyrexia.
Binimetinib	Tablet	Unresectable melanoma	Fatigue, nausea, and diarrhea
Encorafenib	Capsule	Melanoma and colorectal cancers	Fatigue, nausea, diarrhea, vomiting, abdominal pain, and arthralgia
Atezolizumab	IV Injection	Urothelial carcinoma, nonsmall cell lung cancer (NSCLC), triplenegative breast cancer (TNBC), small cell lung cancer (SCLC), hepatocellular carcinoma, and alveolar soft part sarcoma.	Fatigue, decreased appetite, nausea, and infections. Urinary tract infection.

Nivolumab + Relatlimab	IV Injection	Unresectable or metastatic melanoma.	Musculoskeletal pain, fatigue, rash, pruritus, and diarrhea.

6.2.2. Discussion The prognosis may be favorable in the early stages of the illness, and the patient may be effectively treated surgically (Garbe et al., 2022). But as the illness gets worse, survival rates sharply decline (O'Neill & Scoggins, 2019). Until 2010, the only alternatives to surgery were radiation and chemotherapy (Mozzillo & Ascierto, 2014),(Davis et al., 2019),(Eddy & Chen, 2020). Later, the identification of new targets was made possible by the expanding understanding of the disease's etiology, the immune system's function, and the capacity for genome sequencing (Eddy & Chen, 2020)(Merlino et al., 2016)(Michielin et al., 2020). Consequently, various medications and/or combinations of drugs have been given marketing authorization (Merlino et al., 2016 - Switzer et al., 2022). Surgery, radiation, chemotherapy, immunotherapy, and targeted therapy are the current methods for treating melanoma (Table 1). The most appropriate therapeutic approach is chosen based on the patient's age and general health status in addition to the anatomic location, stage, and genetic profile of the tumor (Kozar et al., 2019)

A kinase inhibitor called dabrafenib is approved for the treatment of metastatic or incurable melanomas with the BRAF V600E or V600K mutation as well as for use as an adjuvant therapy in patients with melanomas combined with lymph node involvement (Bakkes et al., 2022). A kinase inhibitor called trametinib, which targets MEK1 and MEK2, is approved for the treatment of metastatic or unresectable melanoma with the BRAF V600E or V600K mutation, as well as for use as adjuvant therapy at a dose of 2 mg per day orally (European Medicines Agency (EMA), 2021) . The combination of BRAF and MEK inhibition is a novel melanoma management approach. In fact, compared to monotherapy, combination therapy produced noticeably greater results (Saif et al., 2022). In two randomized controlled studies (COMBI-d study and COMBI-v study), the effects of dabrafenib (150 mg twice daily) and trametinib (2 mg once daily) were assessed in patients with metastatic or incurable BRAF V600E- or V600K-mutated cutaneous melanoma (European Medicines Agency, n.d.).

Anti-PD-1 molecule pembrolizumab is now authorized for the management of patients with metastatic or unresectable melanoma as well as for the adjuvant therapy of patients with melanoma and with lymph node involvement at a dosage of 200 mg every three weeks (Q3W) or 400 mg every six weeks (Bakkes et al., 2022). Its effectiveness and safety in the treatment of metastatic or incurable melanoma, as well as as adjuvant therapy, have been demonstrated in numerous clinical trials (Bakkes et al., 2022)(Chanal et al., 2019). Finally, a recent study evaluating the effectiveness and safety of pembrolizumab in patients older than 85 years revealed that pembrolizumab treatment in elderly people may be associated with a high risk

of toxicity and diminished autonomy (Chanal et al., 2019). In this case, a phase I trial revealed that pembrolizumab at the recommended dosage in combination with ipilimumab at a lower dose would be an effective therapeutic choice for metastatic melanoma (Long et al., 2017). Nivolumab is an immunotherapy drug that has been licensed for the treatment of metastatic or unresectable melanoma as well as for use as adjuvant therapy in patients with lymph node involvement. It does this by preventing the binding of programmed cell death 1 ligand 1 (PD-L1) to PD-1, which permits the immune system to respond to cancer cells. It is permitted to be used alone (240 mg Q2W or 480 mg Q4W intravenous infusions) or in combination with ipilimumab (nivolumab 1 mg/kg followed by ipilimumab 3 mg/kg Q3W up to four doses followed by nivolumab as a single agent) (Bakkes et al., 2022). Ipilimumab is an anti-CTLA-4 antibody that inhibits CTLA-4 activity, encouraging the health and development of T cells. It is permitted in four doses at a dosage of 3 mg/kg Q3 ("Annex I," 2011). Encorafenib is a kinase inhibitor that has been licensed for the treatment of metastatic or unresectable melanoma with the BRAF V600E or V600K mutation. Its recommended dosage is 450 mg (six 75 mg capsules) once day when combined with binimetinib's recommended dosage of 45 mg twice daily ("Annex I," 2018). When combined with encorafenib at a dosage of 45 mg twice daily, binimetinib(a MEK inhibitor) was approved for the management of metastatic or BRAF V600E-mutated unresectable melanoma. In Study CMEK162B2301, patients receiving binimetinib plus encorafenib demonstrated a statistically significant improvement in Progression Free Survival and Overall Survival ("Annex I," 2018). Herpes simplex virus type 1 is the source of the oncolytic immunotherapy talimogene laherparepvec (T-VEC). It works by specifically replicating inside tumors, producing granulocyte macrophage colony-stimulating factor (GM-CSF), which triggers a systemic immune response against the tumor (Johnson et al., 2015) . Only T-VEC has been tested as an oncolytic viral treatment in a clinical trial (Senzer et al., 2009). Nivolumab with relatlimab-rmbw (Opdualag), which the FDA approved on March 18, 2022, for patients with metastatic or unresectable melanoma from the age of 12, was one of the most recent combinations that received approval (Table 1)(Food and Drug Administration., n.d.) .

6.3. Alternative Treatment

6.3.1. Surgical Incision

Whenever possible, surgical removal with adequate margins is the first-line treatment of melanoma (Garbe et al., 2022). Although it is mainly applied in patients up to stage II melanoma, it is also often an option for stage III patients (Henriques et al., 2018)(Kozovska et al., 2016) or even when the disease has already metastasized to other organs (stage IV)(Garbe et al., 2020) . However, especially in some patients at stages II and patients at stages III and IV, surgery alone has limited curative potential. Thus, radiotherapy,

chemotherapy, immunotherapy or targeted therapy are often used as adjuvant treatments (Lopes et al., 2022b)

6.3.2. Radiotherapy

Melanoma is a relatively radioresistant tumor as it has the ability to effectively repair DNA damage caused by radiation (Oliveira Pinho et al., 2019). Therefore, the choice of radiotherapy as a first-line treatment is applied for exceptional cases, for example, given the impossibility of performing surgery or as a complement to some situations where there is a high risk of recurrence. On the other hand, radiotherapy is widely used as a palliative treatment for metastatic melanoma (stage IV). New techniques such as stereotactic radiosurgery and stereotactic body radiotherapy have commonly been used in the treatment of brain, lung or liver metastases. Compared with whole-brain radiotherapy in the case of treatment of brain metastases, promising results and less severe adverse side effects have been observed](Garbe et al., 2020),(Shi, 2017),(Sayan et al., 2021). Nonetheless, the combination of radiotherapy with systemic therapeutic options is currently under study in some clinical trials (NCT02858869 and NCT04902040) (*United States National Institutes of Health. ClinicalTrials.Gov Database*, n.d.).

6.3.3. Chemotherapy

Although chemotherapy remains a therapeutic option for melanoma management, especially in palliative or relapsed situations, in metastatic advanced stages of the disease, new therapeutic choices are preferred (Wilson & Schuchter, 2016). The main disadvantages associated with chemotherapy are the lack of specificity for tumor cells and consequent low drug accumulation at the tumor microenvironment. Thus, therapeutic benefits are limited and the incidence of adverse side effects is prominent (Wilson & Schuchter, 2016)(Beiu et al., 2020). To the best of our knowledge, the DNA alkylating agent dacarbazine (DTIC) remains the only drug approved both by FDA and EMA (Gupta et al., 2017). Generally, in the various clinical trials conducted, DTIC response rate was around 10 to 20%, with most responses being partial and not sustained over time. In addition, nausea, vomiting and myelosuppression are the most common adverse side effects (Wilson & Schuchter, 2016)(Luke & Schwartz, 2013). In addition to DTIC and despite not being officially approved, many other chemotherapeutic agents have been used off-label, namely, temozolomide (TMZ), nitrosoureas, paclitaxel, docetaxel and cis/carboplatin (Davis et al., 2019)(Gupta et al., 2017).

6.3.4. Immunotherapy

Immunotherapy has as its primordial objective the stimulation and activation of the immune system. It started with the FDA approval of interleukin 2 (IL-2) and interferon alfa-2b in the 1990s, with the latter being also approved by EMA. Since 2011, there has been an important shift in the role of immunotherapy

in melanoma like immunological checkpoint inhibitors (ICIs) (Jenkins & Fisher, 2021)(Kuryk et al., 2020). Interestingly, melanoma was the first malignancy to take advantage of ICIs (Queirolo et al., 2019). There are four classes of ICIs monoclonal antibodies approved for the treatment of melanoma, namely, ipilimumab, an antagonist of cytotoxic-T lymphocytes antigen 4 (CTLA-4); nivolumab and pembrolizumab, antagonists of programmed cell death protein 1 (PD-1); atezolizumab, an antagonist of programmed cell death ligand 1 (PD-L1) (Eddy & Chen, 2020); and more recently, in 2022, relatlimabrmbw, an antagonist of lymphocyte activation gene-3 (LAG-3) (Food and Drug Administration., n.d.). These last two drugs are already approved for melanoma indication by FDA but not by EMA.

CTLA-4, PD1, PD-L1 and LAG-3 are immune checkpoint proteins expressed on T cells membrane and involved in the signaling pathways that lead to its suppression. T cells are physiologically essential in the maintenance of immune tolerance. However, these immunological checkpoints are often used by cancer cells for immune evasion by down-regulation of their antitumor responses. ICIs, by selectively binding to these proteins, allow overcoming tumor-induced inhibition of T cell functions, re-establishing the antitumor immune responses (Figure5) (Zhang & Zhang, 2020),(Onitilo & Wittig, 2020),(Kennedy & Salama, 2020),(Bagchi et al., 2021),(Chocarro et al., 2021).

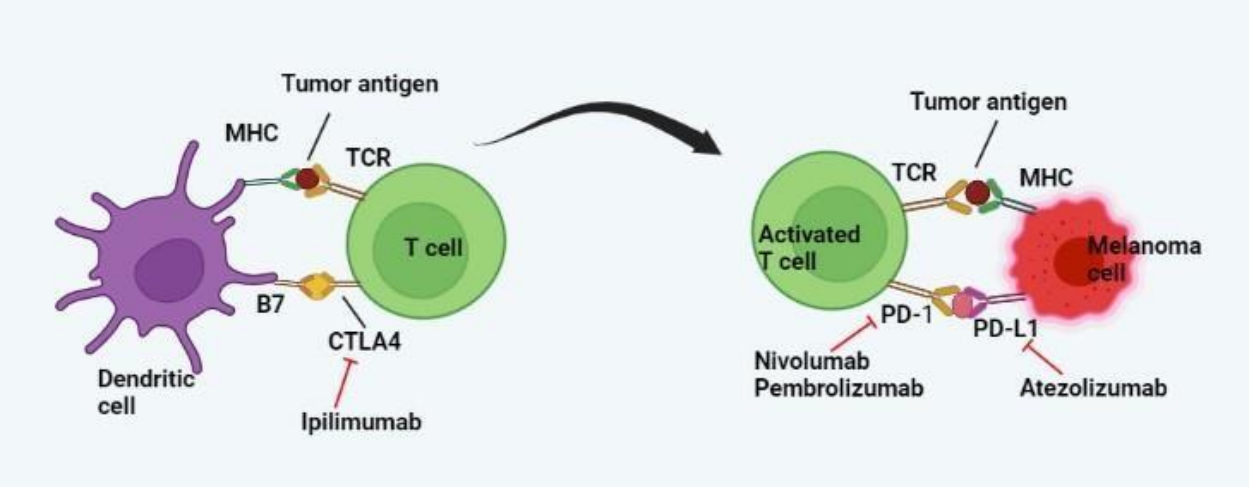

Figure 5 : The RAS-RAF-MEK1/2-ERK1/2 pathway is often upregulated in melanoma, with a consequent increase in cell proliferation and survival. Pharmacological inhibition of mutant BRAF or kinase MEK1/2 blocks the MAPK pathway (LoRusso et al., 2020) .

Another relatively recent immunotherapeutic strategy approved for the treatment of advanced melanoma is talimogene laherparepvec (T-VEC or Imlygic®), the first oncolytic virus approved in the cancer treatment field. T-VEC is a herpes simplex virus type 1 genetically modified to reduce pathogenicity and increase immunogenicity (Bommareddy et al., 2017),(Larocca et al., 2020).

6.3.5 Targeted Therapy

Cutaneous melanoma has a high rate of genetic alterations, with 7 out of 10 diagnosed cases having mutations in genes of the main signaling pathways. These oncogenic mutations promote the activation of cell signaling pathways, leading to the proliferation of malignant cells without any type of control (Domingues et al., 2018),(Tanda et al., 2020). The aim of target therapy is precisely to stop this widespread proliferation through the inhibition of the mutated genes (Onitilo & Wittig, 2020),(Eddy & Chen, 2020). The mitogen-activated protein kinase (MAPK) cascade is the most frequently mutated in melanoma, being composed of a receptor tyrosine kinase(RTK) as well as RAF, RAS, MEK and ERK proteins (Figure 6) (Amaral et al., 2017). Mutations in the BRAF, NRAS and NF1 genes are the most frequent and occur in approximately 50, 25 and 14% of melanoma cases, respectively (Czarnecka et al., 2020),(Mackiewicz & Mackiewicz, 2018). As previously mentioned, there are already several molecules of this therapeutic class used for clinical management of melanoma, such as vemurafenib, dabrafenib and encorafenib (BRAF inhibitors), and trametinib, cobimetinib and binimetinib (MEK inhibitors). Although they are distinct between different BRAF and MEK inhibitors, arthralgia; fatigue; diarrhea; pyrexia; photosensitivity; and skin, cardiovascular and ocular toxicity are the main adverse effects associated with this type of therapy (Mackiewicz & Mackiewicz, 2018),(Kasakovski et al., 2021). Finally, the main limitation inherent in this type of treatment is related to the development of resistance (Kozar et al., 2019),(Kasakovski et al., 2021),(Czarnecka et al., 2020),(Lee et al., 2020).

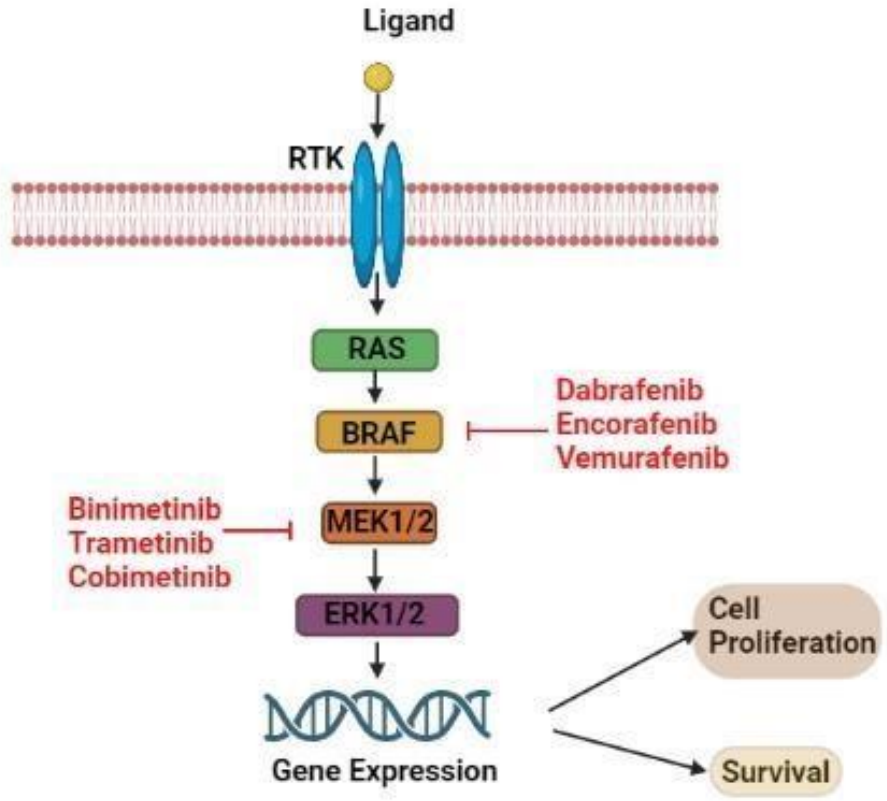

Figure 6 : Melanoma cells can express receptor on the T cells, causes a reduction in T cell function. Blockade of the PD-L1/PD-1 axis with anti-PD-1 or anti-PD-L1 checkpoint inhibitors restores the ability of T cells to recognize and destroy melanoma cells (LoRusso et al., 2020).

6.4 Ongoing Clinical Trials

6.4.1. Result

Table 3. Examples of melanoma treatments undergoing clinical trials (*United States National Institutes of Health. ClinicalTrials.Gov Database*, n.d.).

Trial ID	**Melanoma Stage**	**Interventions**	**Estimated or Starting Completion Date**	**Sponsor**
NCT03543969	IIIC-IV	Encorafenib, Binimetinib, Nivolumab	2018-2022	H. Lee Moffitt Cancer Center and Research Institute
NCT03715205	III/IV	Pembrolizumab	2019-2026	Merck Sharp & Dohme LLC

NCT04020809	I/II	Atezolizumab	2020-2025	The Methodist Hospital Research Institute
NCT04356729	III/IV	Atezolizumab, Bevacizumab	2020-2023	Elizabeth Buchbinder
NCT04330430	IIIB/C/D/IVM1a	T-VEC	2020-2023	The Netherlands Cancer Institute
NCT05002569	III/IV	Nivolumab + Relatlimab	2021-2025	Bristol-Myers Squibb
NCT05492682	Inoperable or metastatic	PeptiCRAd-1, Cyclophosphamide, Pembrolizumab	2022-2024	Valo Therapeutics Oy
NCT05034536	III/IV	Pembrolizumab, Infliximab , Placebo	2022-2025	Massachusetts General Hospita
NCT05466474	III/IV	Tislelizumab Injection	2022-2024	Henan Cancer Hospital
NCT05270044	IIB/C	Encorafenib and Binimetinib . Placebo to match Encorafenib ; Placebo to match Binimetinib	2022–2035	Pierre Fabre Medicament

6.4.2. Discussion

As described so far, the last few years have been marked by tremendous efforts regarding the development of new therapeutic strategies for the treatment of melanoma (Villani et al., 2022). Nevertheless, and as a result of the highly aggressive and heterogeneous nature of this malignancy, existing therapies remain limited (Davis et al., 2019). Hereupon, new drugs and/or combinations are being tested to find more and better therapeutic options as described in Table 3. According to the ClinicalTrials.gov database, there are currently 853 clinical trials worldwide focusing on melanoma as an object of study (Health, n.d.). Our research was restricted to ongoing interventional studies, listed as “not yet recruiting”, “recruiting”, “enrolling by invitation” and “active, not recruiting”.

Chapter-7
Conclusion

7. Conclusions

Treatment and survival for patients with localized or metastatic melanoma have improved dramatically in the past 10 years. Initial surgical treatment is more precise and less invasive, with a lower morbidity.

Systemic therapy has undergone remarkable changes.

The review highlights the progress made in the past decade in the treatment of melanoma, a type of skin cancer, by the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA). The use of targeted therapy and immunotherapy has revolutionized the treatment of melanoma, resulting in increased survival rates and improved quality of life for patients. The review also discusses the challenges associated with these treatments, including drug resistance, adverse effects. Additionally, the review emphasizes the need for continued research to develop new treatments and improve patient outcomes.

However, there are still challenges to be addressed, such as the development of resistance to these therapies and the need for more effective treatments for patients with advanced disease.

Chapter-8
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