Genetic and Molecular Mechanisms of Melanoma Progression: Role of BRAF, NRAS and KIT Mutations

Vijay Sharma[1]*, Pooja Singh[2], Gyanendra Kumar Sharma[3], Maneesh Kumar Singh[4], Saurabh Singh[5], Pankaj Kumar Shankhdhar[6]. Navneet Verma[1], Saurabh Sharma[7]

[*1]Pharmacy Academy, Faculty of Pharmacy, IFTM University, Moradabad, Uttar Pradesh, India
[2]Deprtment of Pharmacy, Quantum University, Roorkee, Uttarakhand, India
[3]Sharda School of Pharmacy, Sharda University Agra, Agra, Uttar Pradesh, India
[4]Department: Pharmaceutics, IIMT University, Meerut, U.P. India
[5]Dayanand Dinanath College, Institute of Pharmacy, Kanpur, U.P. India
[6]BIU College of Pharmacy, Bareilly International University, Bareilly, Uttar Pradesh, India
[7]College of Pharmacy, Vivek College of Technical Education, Bijnor, Uttar Pradesh, India

Corresponding Author:
Vijay Sharma
[*1]Pharmacy Academy,
Faculty of Pharmacy,
IFTM University, Moradabad, Uttar Pradesh, India
***Email:** vijaysrampur@gmail.com
Contact: +91-9045537375

Abstract
Melanoma is a type of cancerous disese that may affect skin and is one of the highly aggressive form of skin cancer. Authors aimed to transfer the knowledge to readers about the genetic and molecular mechanisms of melanoma as well as its progression. This review also focused on mechanism of mutations in B-Rapidly Accelerated Fibrosarcoma (BRAF), Neuroblastoma RAS Viral Oncogene Homolog (NRAS) and Stem Cell Factor Receptor (KIT) genes. B-Rapidly Accelerated Fibrosarcoma (BRAF) mutations is associated with V600E variant of BRAF gene which causes activation of Mitogen-Activated Protein Kinase / Extracellular Signal-Regulated Kinase (MAPK/ERK) signaling pathway resulting in uncontrolled cell proliferation. NRAS mutations is associated with gene alteration in N-Ras protein which on activation causes uncontrolled prolificationn and cancer cell development. KIT mutations are rare in other melanoma subtypes like superficial spreading melanoma lead to persistent activation of downstream signaling pathways, including MAPK and PI3K/AKT.

By controlling vital tumor functions such cell proliferation, survival, energy consumption, and treatment resistance, the PI3K/Akt/mTOR pathway plays a crucial part in melanoma. The development of more individualized therapy strategies that specifically target these altered pathways has improved patient outcomes because to advancements in genetic profiling and molecular analysis. The interaction of genetic changes, important signaling pathways, and the tumor microenvironment in the development of melanoma is examined in this study, which highlights both persistent difficulties and new prospects for successful targeted treatments.

Keyword
Melanogenesis, Metastasis, Oncogenes, Immunotherapy, Tumor microenvironment
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Introduction

1. Overview of melanoma

Melanoma is a cancer that comes from melanocytes and is very aggressive. It is a major problem in oncology because it is very likely to spread through the body and has poor outcomes in advanced stages. Melanoma continues to play a significant role in global morbidity and mortality despite advancements in diagnostic methods and treatment options, highlighting its ongoing clinical significance[1]. Recent data from the GLOBOCAN report show that in 2022, approximately 3.3 lakh new cases of and nearly 60 thosand deaths occurred worldwide. These figures are likely underestimated given limited epidemiological surveillance in many parts of the world, which results from barriers like inadequate healthcare access and inconsistent reporting practices[2]. The molecular biology of melanoma has been dramatically improved by advances in genomic

technology, which have revealed intricate connections between the progression of the disease and genetic mutations. Contemporary research, therefore, aims to integrate the latest genetic insights along with breakthroughs in therapy to provide a holistic view of melanoma, highlighting both progress and ongoing hurdles in effectively treating this aggressive form of skin cancer (Figure 1 and Table 2)[3,4].

Melanoma is an highly aggressive form of cancer which originates from melanocytes and poses significant issue in oncology because of its high tendency for metastasis and poor outcomes in advanced stages. Even with improvements in diagnostic techniques and therapeutic options, melanoma continues to contribute substantially to global morbidity and mortality, underscoring its ongoing clinical significance[1]. Recent data from the GLOBOCAN report show that in 2022, approximately 3.3 lakh new cases of and nearly 60 thosand deaths occurred worldwide. These figures are likely underestimated given limited epidemiological surveillance in many parts of the world, which results from barriers like inadequate healthcare access and inconsistent reporting practices[2].Advances in genomic technology have dramatically enhanced the understanding of melanoma's molecular biology, revealing complex relationships between genetic mutations and disease progression. Contemporary research, therefore, aims to integrate the latest genetic insights along with breakthroughs in therapy to provide a holistic view of melanoma, highlighting both progress and ongoing hurdles in effectively treating this aggressive form of skin cancer (Figure 1 and Table 2)[3,4].

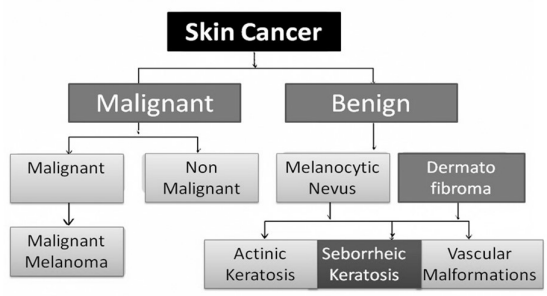

Figure 1: Skin Cancer Classification Highlighting Malignant Melanoma

Table 1: Overview of melanoma[4]

Aspect	Details
Incidence (2025, US)	Estimated 212,200 melanoma cases diagnosed (107,240 noninvasive/in situ, 104,960 invasive)
Incidence by Gender	60,550 cases in men; 44,410 cases in women
Mortality (2025, US)	Approximately 8,430 deaths (5,470 men; 2,960 women)
Survival Rates	5-year relative survival overall: 94%; Localized: >99%; Regional: 75%; Distant: 35%
Lifetime Risk	Approx 3percent for White skin individuals; 0.1% for Black skin individuals; 0.5% for Hispanic individuals
Major Risk Factors	Ultraviolet (UV) radiation exposure, fair skin, genetic predisposition
Common Melanoma Subtypes	Superficial spreading, nodular, acral lentiginous, mucosal
Global Incidence (2022)	Around 3.3 lakh new cases of melanoma cases globally, nearly 60 thousand deaths
Geographic Distribution	Largest Number of Cases in Europe (46.0% of global cases), North America (32.0%)
Trends	Increasing incidence in older adults; stabilized or declining in younger adults
Racial Disparities	Lower incidence but poorer outcome in people of color due to late-stage diagnosis

2. Different types of melanoma

Melanoma represents a cancerous growth that develops from melanocytes, the cells responsible for skin pigmentation.. Although most common form of melanoma is cutaneous melanoma,, its clinical behavior, histopathologyand molecular drivers vary among subtypes. Based on anatomical site, morphologyand molecular alterations, melanoma can be classified into the following main types (Figure 2):

2.1 Superficial Spreading Melanoma

The most common type of melanoma, representing approximately 70% of cases, is superficial spreading melanoma.It grows outward across the top layer of skin before potentially growing deeper. Usually appears as flat or slightly raised patches with irregular borders and multiple colors. Superficial spreading melanoma commonly occurs on the trunk in male and on the legs in female.

2.2 Nodular Melanoma

Nodular melanoma is second most occurring type of melanoma, about 15-20 percent patients were observed suffering with this type of melanoma. . It grows downward rapidly into deeper skin layers and often appears as a raised, dark bump. It is more aggressive and commonly found on the face, chest, or back.

2.3 Hutchingson's melanotic Frackle

This melanoma is also known as Lentigo Maligna Melanoma. This is the less common (10-15%) type of melanoma and occurs mainly in older adults which are exposed themselves to sun. It starts as a large, flat, brown patch with uneven edges, primarily on sun-exposed areas like the face and neck. It grows slowly across the skin surface before invading deeper.

2.4 Acral Melanoma

This type of melanoma is rare overall but mostly occurs in people with darker skin tones. Typically appears on the palms, e. soles, or under nails. Not related to sun exposure and often diagnosed late.

2.5 Mucosal Melanoma

Occurs on mucous membranes inside the body (e.g., nasal passages, mouth, genitals). It is rare, often aggressiveand not linked to sun exposure.

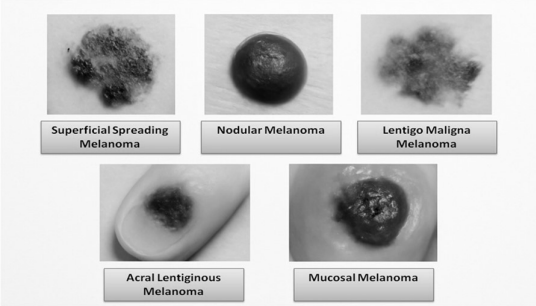

Figure 2: Types of melanoma

3. Incidence and determinants of Melanoma

The mechanisms of melanoma plasticity, explaining how melanoma cells change their behavior and identity to survive, growand spread. At the center is the cancer stem cell (CSC) niche, where cells can self-renew, differentiate, or revert to a stem-like state (figure 3). Melanoma plasticity arises from genetic mutations, epigenetic changesand cell fusion, which together allow cells to shift between different phenotypes. The epithelial–mesenchymal transition (EMT) and its reverse (MET) enable cells to alternate between stationary and invasive forms, promoting metastasis. Through these processes, melanoma develops distinct tumor cell populations with varying functions, leading to tumor heterogeneity, therapy resistanceand metastasis. In short, melanoma plasticity is driven by genetic, epigeneticand cellular factors that help cancer cells adapt and survive.

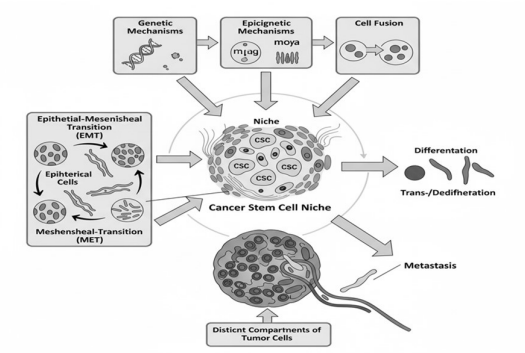

Figure 3: Mechanism of Melanoma

Factors Affecting Risk Including Photo-Type Nevus Count and Ultraviolet Rays

Epidemiologic studies show that cutaneous melanoma risk arises from both environmental and genetic factors. Skin pigmentation plays a major role, particularly through MC1R gene variants that reduce melanin production and increase UV sensitivity, as seen in fair-skinned and red-haired individuals. Lighter phototypes (I and II), numerous acquired nevi, red-hair phenotype, and MC1R "R" alleles are independent risk factors. Research from Queensland reports that people with 20 or more nevi (≥5 mm) and the MC1R R/R genotype have a 25-fold higher melanoma risk, with lifetime risk up to 23.3% in men and 19.3% in women by age 75. These findings highlight the strong interaction between genetic susceptibility and UV exposure in melanoma development[11,12].

Table 2: Major Risk Factors Associated with Melanoma: Phototype, Nevus Countand Ultraviolet (UV) Exposure

Risk Factor	Description / Classification	Mechanistic Basis	Relative Risk / Association	Clinical / Epidemiological Notes	Key References
Skin Phototype (Fitzpatrick I–VI)	Type I–II: very fair skin, burns easily, never tans; Type V–VI: dark skin, rarely burns	Low melanin protection → increased DNA photodamage and mutagenesis (esp.	Risk increases 10–20× for Type I–II compared to Type V–VI	Lighter phototypes have higher BRAF mutation prevalence and superficial spreading melano	Gandini *et al.*, 2005; Whiteman *et al.*, 2016

		C→T transitions in BRAF gene)		ma	
Nevus Count (Common & Atypical)	>100 common nevi or >5 atypical nevi = high-risk group	Each nevus represents clonal proliferation of melanocytes prone to oncogenic transformation (often via BRAF/NRAS mutations)	>5-fold increased risk vs individuals with <15 nevi	High total nevus count correlates with earlier onset and BRAF-mutant melanoma	Olsen *et al.*, 2010; Thomas *et al.*, 2019
Ultraviolet Radiation (UVA & UVB)	Chronic and intermittent exposure (especially childhood sunburns)	UVB causes cyclobutane pyrimidine dimers → C>T transitions; UVA causes oxidative DNA damage and immune suppression	Strong positive correlation; intermittent intense exposure is most carcinogenic	Promotes BRAF V600E mutations; triggers MAPK activation and melanocyte dysregulat	

4. Genetic Factors

A family history and genetic factors, including skin phenotype, increase melanoma risk, with 5–10% of cases being familial. Hereditary syndromes like FAMMM and DNS carry very high lifetime risk, often linked to CDKN2A mutations. Many nevi—especially over 100—or dysplastic nevi further elevate risk. High-risk individuals are monitored with regular dermatoscopy, and risk-assessment models using age, sex, nevus count, and sun exposure guide prevention and early detection, though genetic data add limited predictive value[22-27].

6.1 Molecular Basis of Melanoma Carcinogenesis

Melanoma carcinogenesis is driven by a series of genetic alterations and dysregulated signaling pathways that transform normal melanocytes into malignant melanoma cells. This process involves abnormal activation of pathways controlling cell proliferation, survival, differentiationand invasion, such as MAPK and PI3K/AKT, often because of gene alteration in key genes like BRAF, NRASand CDKN2A. The molecular events lead to uncontrolled growth, resistance to apoptosis, metastatic potentialand therapy resistance[29].

6.2 Normal melanocyte biology and signaling pathways

Normal melanocytes originate from the neural crest and depend on tightly regulated signaling pathways for their development, survival, proliferationand pigment production. Important pathways include[30]:

- MC1R signaling: Binding of α-MSH to the MC1R receptor increases cAMP, which stimulates the transcription factor MITF, a critical regulator of melanocyte survival and melanin synthesis.
- c-KIT/SCF pathway: The stem cell factor (SCF) activates the c-KIT receptor tyrosine kinase promoting melanocyte proliferation, differentiationand survival.
- WNT/β-catenin pathway: Important in early melanocyte lineage specification and differentiation.
- MAPK pathway: Activated by growth factors, controls melanocyte proliferation and survival.
- MITF acts as the master transcriptional regulator orchestrating melanocyte lineage specification, pigment production, cell cycle controland anti-apoptotic functions.

Figure 4 shows how BRAF regulates MITF and drives phenotype switching in melanoma. BRAF activates MEK/ERK, which phosphorylates MITF, controlling its transcriptional activity and nuclear localization. BRAF and ERK signaling can reduce MITF levels via degradation, promoting dedifferentiation and invasiveness. MITF levels determine cell behavior: high promotes

differentiation, intermediate drives proliferation, low enhances invasion, and very low triggers senescence or apoptosis[31, 32].

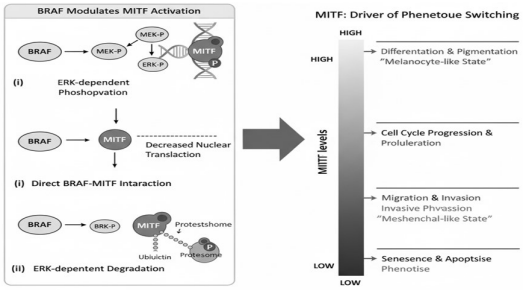

Figure 4: Regulation of MITF activity by BRAF and its role in phenotype switching in melanoma.

5. BRAF Mutations in Melanoma

6.1 Prevalence and types of BRAF mutations (V600E, V600K, others)

BRAF mutations occur in approximately 40-55% of melanomas, predominantly in cutaneous subtypes (Figure 5). The most common mutation is the V600E mutation, taking into account for around 75% of BRAF-mutated melanomas. The V600K mutation is the second most frequent, comprising about 15-20%. Other less common mutations include V600R, V600Dand mutations in codons 594, 597and 601. BRAF mutations are rare in mucosal and uveal melanomas[38].

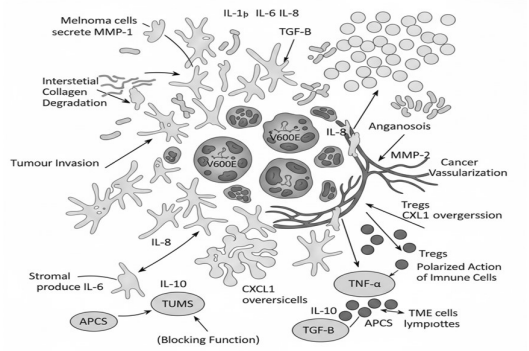

Figure 5: Schematic representation of melanoma tumor microenvironment and progression mechanisms

7.2 Oncogenic signaling and downstream effects

BRAF mutations persistently stimulatethe MAPK/ERK signaling pathway, resulting in unregulted cell proliferation, survivaland tumor growth. This activation bypasses normal regulatory signals, promoting oncogenesis. BRAF V600E mutation results in increased kinase activity, driving melanoma cell proliferation and resistance to apoptosis[39].

7.3 Therapeutic implications (BRAF inhibitors, resistance mechanisms)

he identification of **BRAF mutations** has paved the way for **targeted treatments**, including **BRAF inhibitors** such as **vemurafenib and dabrafenib**, which selectively block the activity of the **mutated BRAF kinase**. These drugs improve survival in patients with BRAF-mutant melanoma. However, resistance frequently develops, often due to reactivation of the MAPK pathway or activation of alternative pathways like PI3K/AKT. Combinedn treatment with MEK inhibitors as well as ongoing research into overcoming resistance are major focuses in treatment[40].

6. NRAS Mutations in Melanoma

The figure 6 illustrates the complex **BRAF-mediated regulation of the MITF transcription factor** and its role as a "rheostat" in determining melanoma cell fate. Within the cell, the constitutively active BRAF/MEK/ERK pathway (i) phosphorylates and activates MITF to regulate target genes, while simultaneously enacting inhibitory control. This control is achieved through two counteracting mechanisms: (ii) a direct interaction between BRAF and MITF that decreases MITF's nuclear translocationand (iii) ERK-mediated phosphorylation that tags MITF for ubiquitin-dependent degradation. This delicate, opposing regulation ensures that MITF protein levels are maintained within the optimal range necessary for malignancy[41].

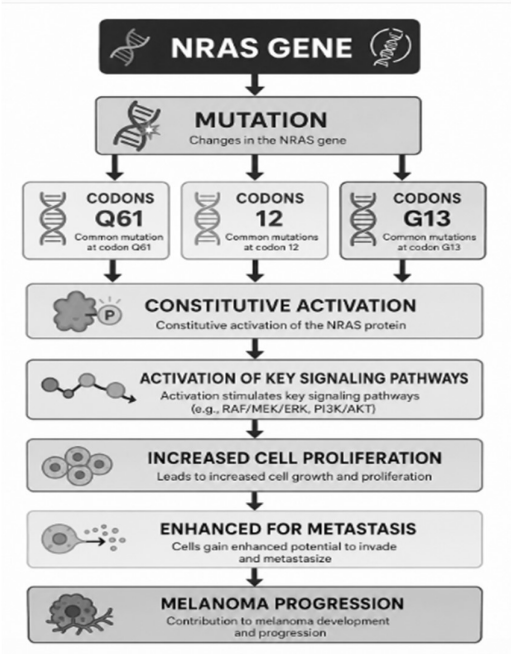

Figure 6: NRAS Mutations in Melanoma

The resulting MITF level then dictates the cell's phenotype: high levels promote a differentiated, melanocyte-like state and proliferation; low levels drive an invasive, mesenchymal-like state, a crucial process called phenotype switching that facilitates metastasis and drug resistance; and very low levels trigger senescence or apoptosis. This dynamic control over MITF is a key driver of melanoma's aggressive nature and plasticity.

8.1 Frequency and mutation subtypes

NRAS mutations are present in approximately 15-25% of melanomas, making them the second most common oncogenic driver after BRAF mutations. The most frequent NRAS mutations occur at codon 61 (Q61R, Q61K), accounting for over 80% of NRAS mutations in melanoma. Less common mutations are found at codons 12 and 13. NRAS mutations occur across melanoma subtypes, particularly in nodular melanomaand are less frequent in benign nevi compared to BRAF mutations[42].

8.2 Role in MAPK and PI3K pathways

Mutations in NRAS constitutively trigger downstream signaling process which includes the RAS-RAF-MEK-ERK (MAPK) pathway and the PI3K-AKT pathway. This leads to increased cell proliferation, survivaland resistance to apoptosis. NRAS mutations triggers MAPK to a equal extent as BRAF mutations and additionally stimulate the PI3K-AKT pathway, promoting aggressive tumor behavior[43].

8.3 Therapeutic challenges and potential strategies

Unlike BRAF-mutant melanomas, NRAS-mutant tumors currently lack direct targeted inhibitors. MEK inhibitors have shown modest efficacy but limited clinical benefit. Therapeutic resistance, pathway redundanciesand lack of effective direct RAS inhibitors complicate management. Combination strategies targeting multiple pathways, immunotherapyand novel approaches such as pan-RAF inhibitors and SHP2 inhibitors are under investigation to improve outcomes in NRAS-mutant melanoma[44].

7. KIT Mutations in Melanoma

9.1 Mutation hotspots and prevalence in acral and mucosal melanoma

KIT mutations occur predominantly in acral lentiginous melanoma (around 15-25%) and mucosal melanoma (15-39%), with a lower frequency in cutaneous melanomas related to chronic sun damage (8-17%). Mutation hotspots include exons 11, 13and 17, with exon 11 mutations like L576P being most common. KIT mutations are rare in other melanoma subtypes like superficial spreading melanoma[45].

9.2 Functional role in tumor initiation and progression

KIT is a receptor tyrosine kinaseand mutations in this gene lead to persistent activation of downstream signaling pathways, including MAPK and PI3K/AKT, which drive melanocyte proliferation, survivaland migration. In melanoma, these gain-of-function mutations play a key role in tumor initiation and progression by stimulating cell growth and preventing apoptosis.[46].

9.3 Targeted therapies (imatinib, sunitinib, others) and limitations

Drugs like imatinib and sunitinib, which inhibit tyrosine kinases, act against dysregulated KIT signaling and have shown clinical benefits in melanomas harboring KIT mutations (Figure 7). However, responses can be variable and resistance often develops. Limitations include mutation heterogeneity, alternative pathway activationand incomplete KIT inhibition. Ongoing research aims

to improve targeting strategies and overcome resistance mechanisms[47].

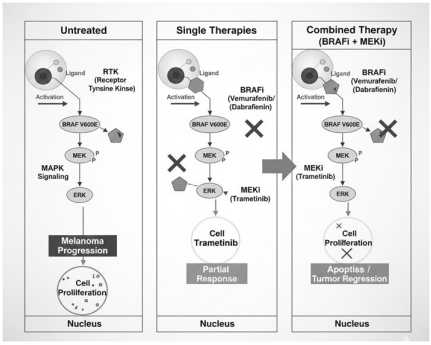

Figure 7: Targeted Therapy (Single and Combined) for Metastatic Melanoma

10.Cross-talk Between BRAF, NRASand KIT Pathways

10.1 Interaction of signaling cascades

Mutations in BRAF, NRAS, and KIT hyperactivate MAPK and PI3K/AKT pathways, with NRAS promoting RAF dimerization, BRAF constitutively activating downstream effectors, and KIT signaling via its receptor tyrosine kinase. These mutations create tumor heterogeneity by altering signaling intensity and cellular behavior, with MITF-driven phenotype switching influencing progression and metastasis. Cross-talk among these pathways also drives intrinsic and acquired drug resistance, highlighting the need for combination therapies targeting multiple signaling nodes.

8. Other Emerging Genetic Alterations in Melanoma

TERT promoter mutations (60–70% of melanomas) increase telomerase expression, enabling cellular immortality. PTEN loss (20–35%) activates PI3K/AKT signaling, promoting survival, growth, metastasis, and therapy resistance, often alongside BRAF mutations. CDKN2A and p53 pathway alterations disrupt cell cycle control and apoptosis, contributing to melanoma initiation, progression, and treatment resistance.

9. Clinical Implications and Therapeutic Advances

Personalized medicine in melanoma uses tumor molecular profiling (e.g., BRAF, NRAS, KIT) to guide targeted therapies and minimize toxicity. Combination therapies targeted inhibitors with immunotherapy enhance efficacy by addressing tumor signaling and immune evasion. Biomarkers like mutation signatures, PD-L1, and tumor mutational burden help predict therapy response and support precision oncology through tailored treatment strategies.

13. Future Perspectives

Recent advances include the development of innovative therapies such as radioactive alpha-particle–emitting drugs targeting melanocortin-1 receptors (MC1R) on melanoma cells, showing promising preclinical efficacy against metastatic melanoma. Additionally, antibody-drug conjugates (ADCs) targeting antigens like HER3, ROR2and KIT are under clinical evaluation, alongside small molecule inhibitors against kinases, CDK4/6and epigenetic modulators. Numerous clinical trials are ongoing testing these novel agents and combination therapies to improve outcomes in advanced and refractory melanoma[57].

14 Conclusion

Melanoma treatment has undergone a remarkable transformation with advances in targeted therapies and immunotherapies, leading to significantly improved patient outcomes. Molecular profiling of tumors has enabled personalized medicine, allowing clinicians to tailor treatments based on specific genetic mutations like BRAF, NRASand KIT. Combination therapies, pairing targeted inhibitors with immune checkpoint blockade, have become standard care for advanced disease, enhancing response rates and survival. Emerging therapies such as mRNA vaccines and tumor-infiltrating lymphocyte (TIL) treatments show promise for further improving efficacy and durability. Despite breakthroughs, challenges persist, including therapeutic resistance and tumor heterogeneity. Future directions focus on novel drug targets, multi-omics driven precision oncologyand artificial intelligence-assisted biomarker discovery to optimize treatment selection. Adaptive combination regimens that address resistance mechanisms hold the potential to transform melanoma into a manageable chronic disease, offering hope for long-term control and improved quality of life. Thus, the current landscape reflects a dynamic era of melanoma care driven by deep molecular insights, innovative therapiesand precision approaches aiming to maximize patient benefit while minimizing toxicity.

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