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REVIEW

Emerging Advances in the Molecular Landscape of Melanoma and Their Implications for Precision Medicine

Azhar Ahmed [1], **Mohammed Alahmadi** [2,*], **Zakaria Khawaji** [3] **and Sara Alghamdi** [4]

[1] Department of Dermatology, King Faisal Specialist Hospital and Research Center, Medina, Saudi Arabia
[2] Department of Dermatology, King Fahad General Hospital, Medina, Saudi Arabia
[3] Department of Internal Medicine, Prince Mohammed Bin Abdulaziz National Guard Hospital, Medina, Saudi Arabia
[4] Department of Dermatology, King Fahad Hospital, Al-Baha, Saudi Arabia

Abstract: Cutaneous melanoma is among the most aggressive skin cancers, with rising incidence and substantial mortality. Advances in molecular profiling have revealed diverse genetic alterations and dysregulated signaling pathways that drive tumor progression and therapeutic resistance, supporting precision oncology and targeted treatment strategies. This narrative review synthesizes current clinical and translational evidence on key molecular determinants of melanoma, emphasizing their roles in pathogenesis, treatment response, and resistance. Major areas include the MAPK and PI3K/AKT/mTOR pathways, NRAS and KIT mutations, CDK4/6 and SHP2 signaling, immunotherapy resistance, and emerging targets such as NTRK fusions and GNAQ/GNA11 alterations. The MAPK pathway remains central in BRAF-mutant melanoma, where combined BRAF and MEK inhibition improves outcomes, although resistance frequently develops. The PI3K/AKT/mTOR axis contributes to intrinsic and acquired resistance and is a key target for combination strategies. In NRAS-mutant melanoma, MEK and CDK4/6 inhibition show therapeutic promise despite the lack of direct inhibitors. Overall, advances in melanoma biology have reshaped treatment paradigms, but resistance continues to limit long-term efficacy. Defining genetic drivers and optimizing rational combination therapies remain essential for durable responses in advanced disease.

Keywords: Melanoma, BRAF, MAPK, PI3K/AKT/mTOR, NRAS, immunotherapy resistance.

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***Corresponding author:**
✉ Mohammed Alahmadi
mohammedaalahmadi20@gmail.com

1 Introduction

Melanoma is a malignant tumor arising from melanocytes, and while making up less than 5% of all skin cancers, its aggressiveness and high potential for metastasis cause the great majority of skin cancer-related fatalities (1). The understanding of melanoma pathogenesis has undergone a significant transformation over the past two decades, driven by major developments in molecular biology and genomic technology, which have shifted the emphasis from conventional histopathological categorization to a genetically driven framework. Precision medicine approaches that address certain genetic abnormalities have been made possible by this shift, which has improved clinical outcomes for patients with advanced illness (2).

Genetic changes largely influence melanoma genesis and development in important carcinogenic pathways, namely mutations in V-Raf murine sarcoma viral oncogene homolog B1 (BRAF), Neuroblastoma RAS Viral Oncogene Homolog (NRAS), Neurofibromin 1 (NF1), and KIT (3). BRAF and Mitogen-Activated Protein Kinase Kinase (MEK) inhibitors have been developed in response to the finding that activating BRAF mutations, most often the V600E substitution, are present in around 40–60% of cutaneous melanomas. This has significantly altered the treatment landscape (4). Although they have had less success, mutations in NRAS (found in about 15–20% of patients) and KIT (found more frequently in acral and mucosal subtypes) have also been identified as potential therapeutic targets (5).

Additionally, melanoma has been thoroughly characterized at the genomic, transcriptomic, and epigenomic levels thanks to developments in next-generation sequencing and The Cancer Genome Atlas (TCGA) initiative. This has resulted in a

more accurate classification of melanoma subtypes according to their mutational signatures and pathway involvement (6). In addition to enhancing treatment stratification, these molecular discoveries are exposing drug resistance pathways and possible biomarkers for immunotherapy response (7).

This narrative review aims to summarize the state of current knowledge about the molecular and genetic causes of melanoma, highlight new genomic findings, and comment on how they could be applied in the Precision oncology maturity.

2 Molecular Landscape of MelanomaSearch Strategy

V-Raf murine sarcoma viral oncogene homolog B1 (BRAF) mutation: BRAF is a RAS-regulated serine/threonine protein kinase that is necessary for activation of the mitogen-activated protein kinase (MAPK) signaling pathway (8, 9). In physiological conditions, MAPK is activated through the interaction between growth factor signaling to receptor tyrosine kinase (RTK). This interaction activates the RAS protein, which in turn activates members of the RAF kinase family, including BRAF. The activation of RAF leads to a set of intracellular cascades that will activate and phosphorylate mitogen-Activated Protein Kinase 1/2 (MEK1/2) and subsequently extracellular Signal-Regulated Kinase 1/2 (ERK1/2). This cascade promotes cell survival, proliferation, differentiation, and inhibits apoptosis (10-12). The BRAF mutation is present in approximately 50% of melanoma cases, with BRAFV600 representing the most prevalent mutation. This mutation occurs within exon 15, whereby glutamic acid is substituted by valine at codon 600. Such a modification results in the BRAF protein being constitutively active, leading to continuous MAPK pathway activation independent of RTK-ligand interactions. This aberrant activation exemplifies the oncogenic hallmark of sustained proliferative signaling, driving melanomagenesis (10, 11). BRAF mutation has been associated with worse prognosis and survival outcomes. Patients harboring BRAF mutations have a 1.7-fold increased risk of mortality compared to those with BRAF wild-type melanoma (95% CI, 1.37–2.12) (13). Additionally, these mutations are more frequently observed in younger patients, those with non-chronically sun-damaged skin, and are associated with more advanced stages of melanoma (14). BRAFV600 has been implicated in increasing the risk of brain metastases compared to patients with BRAF wild-type (WT) melanoma as determined by multivariate analysis. However, treatment with BRAF inhibitors appears to mitigate this risk, resulting in comparable rates of metastasis to those observed in BRAF WT patients (15). Vemurafenib was the first approved BRAF inhibitor for the treatment of metastatic melanoma in 2011 by the Food and Drug Administration (FDA) (16). The mechanism of action of these novel second-generation RAF inhibitors (which include vemurafenib, dabrafenib, and encorafenib) is based upon their selective capacity to bind to the ATP-binding site of the active conformation of one BRAF protomer. This stabilizes the alpha-C helix in the outward conformation. This binding hinders the movement of the alpha-C helix in the second protomer, effectively locking it into the inward conformation and leading to negative allostery. These agents have reduced affinity for the second protomer, therefore limited efficacy to dimeric RAF (e.g. BRAF-WT). This property increases the specificity of these agents to BRAFV600-mutant cell lines, therefore leading to inhibition of MEK/ERK signaling pathway (17, 18). BRIM-3 constituted the landmark phase III trial that substantiated the clinical efficacy of vemurafenib. In this trial, patients with untreated metastatic BRAFV600-mutated melanoma were enrolled and assigned to receive dacarbazine or vemurafenib. Compared to dacarbazine, vemurafenib was associated with significant improvement in overall survival (OS) and progression-free survival (PFS). Furthermore, vemurafenib has decreased the risk of death by 64% (19). Despite its proven clinical benefit, the acquired resistance to BRAF inhibitors has limited its effectiveness, with a median duration of PFS of 6-7 months (20, 21). In the BRIM8 phase III clinical trial, which aimed to compare vemurafenib versus placebo in resected stages II and III, the primary endpoint, which constitutes the disease-free survival, was not met in the study (22). In light of this trial, European Society for Medical Oncology (ESMO) guidelines do not recommend the use of BRAF inhibitors as monotherapy in BRAFV600-mutant melanoma except in the case of absolute contraindication to MEK inhibitors (23). Therefore, understanding the molecular mechanisms behind this resistance is necessary to develop effective strategies to overcome such an obstacle.

Mechanisms of Resistance of BRAF inhibitors, and the role of MEK inhibitors The emergence of resistance of melanoma cells to BRAF inhibitors could be divided into two categories: intrinsic and acquired resistance. Intrinsic or primary resistance refers to the

failure to attain any clinical benefit after initiation of therapy. On the other hand, secondary or acquired resistance refers to the observation of progression of melanoma following an initial clinical benefit (24). The majority of patients would have a dramatic clinical benefit, within the initial course of therapy, although this effectiveness is short-lived, with multiple studies suggesting that resistance would develop within months (25-27). Figure 1 summarizes the mechanisms of resistance to BRAF inhibitors. The reactivation of the MEK/ERK pathway is a major cause of acquired resistance. Several mechanisms have been implicated. For example, the spliced BRAFV600E variant was expressed by melanoma cells resistant to vemurafenib, p61BRAF(V600E). This specific variant showed enhancement of dimerization of cells with low levels of RAS. Other splicing variants were found to lack the RAS-binding domain in tumors resistant to vemurafenib. These variants that can dimerize in a RAS-independent path, therefore mediate the constitutive activation of the ERK pathway (28).

Another significant mutation that was commonly observed in patients diagnosed with melanoma (approximately 20% of cases) was the NRAS mutation. However, the underlying mechanism responsible for this resistance remains to be elucidated. One study postulated that the Q16K NRAS mutation specifically mediates unrestrained reactivation of the MEK signaling pathway by inducing heterodimerization of BRAF and CRAF, thereby bypassing the inhibition of BRAF V600E. Additional NRAS mutations, such as Q12 and Q13, have also been implicated in resistance to BRAF inhibition (30, 31). BRAFV600E amplification has likewise been identified as a mechanism of acquired resistance, diminishing the sensitivity to vemurafenib. This overexpression leads to saturable reactivation of the extracellular signal-regulated kinase (ERK) pathway, wherein higher doses of vemurafenib result in the downregulation of the signaling cascade and enhanced sensitivity of melanoma cells. In contrast to NRAS mutations, amplification-mediated resistance has been found to be independent of CRAF (32). These mechanisms, which consecutively reactivate the MEK/ERK pathway, alongside other mechanisms such as activation of the PI3K-AKT pathway (33), have been proposed as a major driver for resistance. Consequently, the incorporation of selective MEK1/MEK2 inhibitors, which directly target the MEK proteins, is warranted to inhibit the phosphorylation of ERK, thus preventing the paradoxical reactivation of the proliferative signaling cascade. Targeting MEK has been demonstrated to effectively suppress the proliferation of both BRAF-mutant and NRAS-mutant melanoma cells in vivo. Moreover, the extent of inhibition observed in BRAF melanoma cell lines was significantly greater than the efficacy of BRAF inhibitors (34). The first approved drug was trametinib, which is an ATP-non-competitive selective inhibitor of MEK1 and MEK2, in 2013 for patients with unresectable or metastatic BRAF V600E or V600K melanoma (35). The METRIC (MEK114267) trial served as the foundation for this approval; it was a phase III open-label study that assigned 322 patients with metastatic melanoma to receive either dacarbazine (chemotherapy) or trametinib in a 2:1 ratio. The findings of the study indicated a prolonged PFS in the trametinib group compared to the dacarbazine group (4.8 months versus 1.5 months, hazard ratio [HR] for disease progression or mortality in the trametinib group, 0.45; 95% confidence interval [CI], 0.33 - 0.63; P<0.001). The six-month OS rate was 81% in the trametinib group compared to 67% in the dacarbazine group (HR for mortality, 0.54; 95% CI, 0.32 to 0.92; P=0.01) (36). Another significant mutation that was commonly observed in patients diagnosed with melanoma (approximately 20% of cases) was the NRAS mutation. However, the underlying mechanism responsible for this resistance remains to be elucidated. One study postulated that the Q16K NRAS mutation specifically mediates unrestrained reactivation of the MEK signaling pathway by inducing heterodimerization of BRAF and CRAF, thereby bypassing the inhibition of BRAF V600E. Additional NRAS Q12 and Q13 mutations have also been implicated in resistance to BRAF inhibition (30, 31). BRAFV600E amplification has likewise been identified as a mechanism of acquired resistance, diminishing the sensitivity to vemurafenib. This overexpression leads to saturable reactivation of the extracellular signal-regulated kinase (ERK) pathway, wherein higher doses of vemurafenib result in the downregulation of the signaling cascade and enhanced sensitivity of melanoma cells. In contrast to NRAS mutations, amplification-mediated resistance has been found to be independent of CRAF (32). These mechanisms, which consecutively reactivate the MEK/ERK pathway, alongside other mechanisms such as activation of the PI3K-AKT pathway (33), have been proposed as a major driver for resistance. Consequently, the incorporation of selective MEK1/MEK2 inhibitors, which directly target the MEK proteins, is warranted to inhibit the phosphorylation of ERK, thus preventing the paradoxical reactivation of

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One of the possible plausible combination therapies is the incorporation of immunotherapy and the targeted therapy in BRAF-mutant melanoma. For instance, KEYNOTE-022 phase II trial enrolled 120 patients with advanced BRAFV600 melanoma (stages III or IV), evaluating the efficacy of pembrolizumab, dabrafenib, and trametinib triple combination. Within a follow-up for more than 3 years, the 24-month PFS rate for the triplet group was 41% with a median PFS of 16.9 months. Also, the 24-month OS of the triplet group was higher than that of other groups, with a rate of 63%. Despite these improvements in PFS and OS, Grade 3 and above adverse events were much higher in the triplet group compared to the double group (40). IMspire150, is a phase 3 trial that investigated the PD-L1 inhibitor (atezolizumab) when combined with vemurafenib and cobimetinib in stage IIIC-IV BRAFV600 mutant melanoma, compared with a control group (who were not assigned to immunotherapy). The study found that patients who received atezolizumab had a median OS of 39 months compared to 25.8 months in the control group, however this difference is not statistically significant (HR: 0·84 [95% CI 0·66-1·06]; p=0·14). The safety profile was comparable between the groups. The result of the final analysis is unavailable yet, to determine the significance of adding atezolizumab in clinically relevant benefits, including OS and PFS (41). These trials offer an optimistic value for promoting more research efforts to establish the role of immunotherapy in improving outcomes of advanced BRAFV600-mutant melanomas (42). Table 1 summarizes the mechanisms of resistance to BRAF inhibitors.

PI3K/AKT/MTOR Pathway The progression of genuine melanoma harboring BRAF or NRAS mutations requires additional cooperative events, many of which involve components of PI3K-lipid signaling (43). The PI3K/AKT/mTOR pathway is a crucial intracellular signaling network that regulates cell growth, quiescence, and survival under stress. Its activation provides melanoma cells with a proliferative advantage, promotes metastasis, and stimulates angiogenesis (44). Mutations that enhance PI3K/AKT pathway activity have been observed in 22% of melanomas that acquire resistance to BRAF inhibitors. Additionally, increased AKT protein expression has been reported within days after initiating BRAF inhibitor therapy (45).

The most frequent mechanism by which this pathway is altered in melanoma involves mutational inactivation of PTEN, a key tumor suppressor that primarily functions as a PI3K-lipid phosphatase but also exhibits protein tyrosine phosphatase activity (46). PTEN alterations commonly co-occur with mutant BRAF in roughly 20% of melanomas, whereas they are rarely seen in NRAS-mutated melanomas, likely because RAS proteins can directly bind and activate certain PI3'-kinase isoforms (47, 48). The identification of PIP3 as PTEN's primary substrate by Jack Dixon and colleagues established a critical link between PI3'-kinase signaling and human cancers (49, 50). Functional loss of PTEN is often

caused by frameshift mutations leading to intragenic microdeletions or premature truncation, and epigenetic silencing of PTEN is also frequent (51). In some melanomas, both the BRAFV600E>MEK>ERK and PI3'-kinase signaling pathways are concurrently activated (52). Dankort et al. (2009) demonstrated that BRAFV600E expression alone in melanocytes does not initiate melanoma, whereas its combination with PTEN silencing led to tumor formation in all mice tested, with rapid onset and signs of metastasis (53). In contrast, NRAS mutations inherently activate PI3'-kinase signaling, making NRAS mutations and PTEN alterations mutually exclusive (54). Furthermore, Damsky et al. showed that combining BRAFV600E expression with inactivation of tumor suppressors such as INK4A-ARF or LKB accelerates melanoma development in mice via mTORC1/2 activation, suggesting a role for PI3K-lipid signaling in the transformation of benign nevi into melanoma (55). Interestingly, normal melanocytes are not affected by mutational expression of PI3K alpha H1047R or melanocyte-specific PTEN silencing, unlike BRAFV600E (56). Therefore, PI3K-lipid signaling primarily drives melanoma progression rather than initiating its genesis.

Because ERK and PI3K/AKT pathways are interlinked, inhibition of one can enhance the activity of the other. Suppression of ERK signaling leads to adaptive overactivation of PI3K/AKT, which compensates for BRAF inhibition and contributes to acquired resistance to BRAFi. Aberrant PI3K/AKT signaling is a hallmark of melanoma cells, promoting resistance through activation of alternative downstream pathways and reducing dependence on ERK signaling for proliferation (57-59). Preclinical evidence suggested that cells with gain-of-function mutations experience strong selective pressure during BRAFi/MEKi therapy, resulting in heightened PI3K/AKT pathway activity alongside MAPK pathway activation. Cells with such mutations retain proliferative and survival advantages even under BRAF inhibition, explaining tumor regrowth in patients who initially respond to BRAF inhibitors but later develop secondary resistance. Growth factors such as PDGFR-beta and IGF-1R, which bind to RTKs, can also activate PI3K/AKT signaling. In vitro and in vivo studies associate acquired vemurafenib resistance with high RTK expression on melanoma cell surfaces. Expression of PDGFR-beta and IGF-1R enhances cell survival by triggering PI3K/AKT signaling and inhibiting apoptosis. Activating mutations in PI3K and AKT further amplify AKT pathway signaling, enhancing antiapoptotic signaling and promoting genes involved in proliferation. Activated AKT phosphorylates over 9,000 substrates, including forkhead box O3 (Foxo3a), Bim, Bad, XIAP, p21 (Cip1), ASK1, among others (60). These modifications enable melanoma cells to survive and proliferate despite BRAF inhibition, leading to clinical acquired resistance (59, 61, 62).

NRAS mutant melanoma represents a distinct molecular subtype of cutaneous melanoma, accounting for roughly 15–20% of cases. This subtype is associated with aggressive behavior, including early metastasis and worse clinical outcomes compared with other molecular subtypes, such as BRAF-mutant or wild-type melanoma (43).

Located at 1p13.2, the NRAS gene encodes a small GTPase that functions as a molecular switch within intracellular signaling networks (63). Under physiological conditions, NRAS alternates between an inactive GDP-bound state and an active GTP-bound state (64). NRAS activation occurs when upstream signals, such as growth factor receptors, trigger carcinogenic signaling cascades regulating apoptosis, proliferation, and differentiation (65). In NRAS-mutant melanomas, gain-of-function mutations—most frequently at codon 61 (Q61R, Q61K, Q61L)—impair intrinsic GTPase activity, resulting in persistent GTP binding and constitutive downstream signaling (66).

Key downstream effectors include the MAPK/ERK pathway, operating via RAF, MEK, and ERK, which drives uncontrolled proliferation, tumorigenesis, and therapeutic resistance (67); the PI3K/AKT/mTOR pathway, promoting cell survival, angiogenesis, and metabolic reprogramming (68); and the Ral-GDS pathway, which modulates cytoskeletal dynamics, migration, and metastasis (69). The concurrent activation of these pathways renders NRAS-mutant melanoma biologically complex and resilient, characterized by intricate cross-talk and feedback loops that complicate targeted interventions (70). NRAS mutations are mutually exclusive with BRAF mutations but may co-occur with alterations in TP53, CDKN2A, or PTEN, adding further oncogenic signaling and potential for therapeutic resistance (71).

Clinically, NRAS-mutant melanoma more frequently exhibits locoregional nodal involvement, in-transit metastases, and visceral spread (72). Patients typically have shorter disease-specific survival and derive limited benefit from standard chemotherapy and

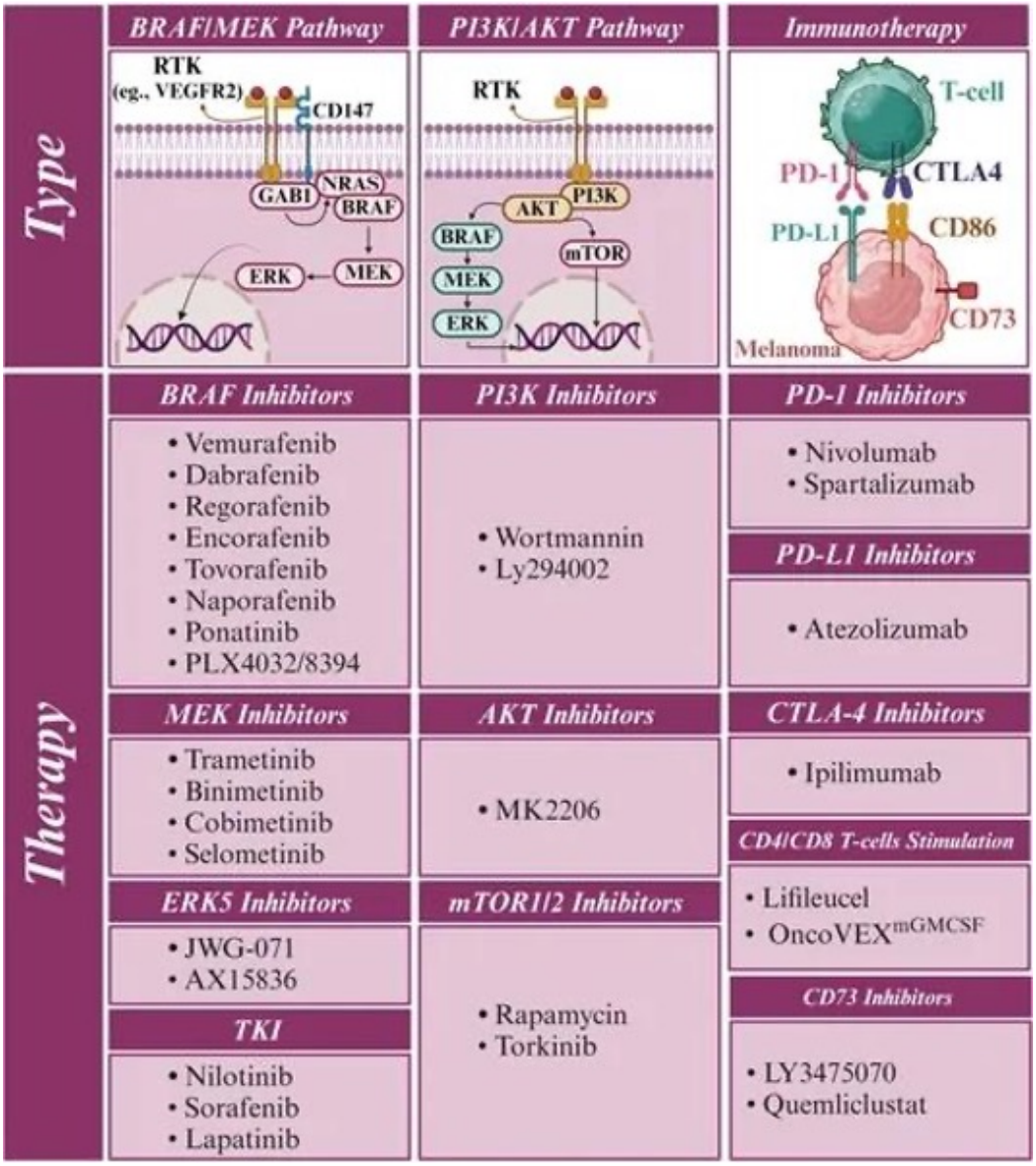

Figure 1. Normal MAPK pathway, B) Resistance mechanisms to BRAF inhibitors; 1) Upregulation of RTK, 2) Amplification of BRAF, 3) BRAF splicing, 4) Loss of NF1. 5) COT overexpression, 6) Reactivation of ERK, 7) Loss of PTEN, 8) Alternative pathway activation (e.g. PI3K/AKT/mTOR). MAPK: Mitogen-Activated Protein Kinase. BRAF: v-Raf Murine Sarcoma Viral Oncogene Homolog B1. RTK: Receptor Tyrosine Kinase. NF1: Neurofibromin 1. COT: Cancer Osaka Thyroid. ERK: Extracellular Signal-Regulated Kinase. PTEN: Phosphatase and Tensin Homolog. PI3K: Phosphoinositide 3-Kinase. AKT: RAC-alpha serine/threonine-protein kinase. mTOR: Mechanistic Target of Rapamycin (29).

targeted therapies (73). Transcriptomic analyses have revealed that NRAS-mutant melanomas often overexpress immune evasion markers, such as PD-L1, IDO1, and LAG-3, alongside T-cell exclusion signatures (74). These findings support the rationale for immunotherapy-based combination strategies, despite overall modest efficacy observed in immune checkpoint inhibitor trials (75).

At present, no FDA-approved therapies directly target mutant NRAS (76). The high-affinity GTP/GDP binding and lack of a suitable druggable pocket make NRAS a challenging target (77). Consequently, therapeutic approaches focus on indirect inhibition via downstream effectors, synthetic lethal partners, or immunomodulation (78). For example, the NEMO trial, a phase III study of the MEK inhibitor binimetinib in adults with NRAS-mutant metastatic melanoma, demonstrated an objective response rate (ORR) of 15.2% and a median progression-free survival (PFS) of 2.8 months, compared to a PFS of 1.5 months with dacarbazine (78, 79). Although statistically significant, the clinical benefit was modest, and MEK inhibitor monotherapy has not received regulatory approval due to limited response duration and rapid emergence

Table 1. Mechanisms of resistance to BRAF inhibitors in melanoma

Resistance Category	Key Mechanisms	Reference
Reactivation of MAPK pathway	BRAF spliced variants.	(28–31, 35)
-	NRAS upregulation.	(28–31, 35)
-	BRAF amplification.	(28–31, 35)
-	C-RAF activation.	(28–31, 35)
PI3K–AKT Pathway Activation	PTEN loss.	(33, 36, 37)
-	IGF-1R/PI3K signaling enhancement.	(33, 36, 37)
MEK1/2 Mutations	Gain-of-function mutations in MEK maintain MAPK activity despite BRAF inhibition.	(38)
Microenvironment-Mediated Resistance	Stromal HGF secretion activates c-MET leading to activation of the MAPK pathway.	(39)

MAPK: Mitogen-activated protein kinase; BRAF: B-Rapidly Accelerated Fibrosarcoma; C-RAF: C-Rapidly Accelerated Fibrosarcoma; NRAS: Neuroblastoma RAS viral oncogene homolog; PI3K–AKT: Phosphoinositide 3-kinase–Protein Kinase B pathway; PTEN: Phosphatase and Tensin Homolog; MEK: Mitogen-activated protein kinase kinase; HGF: Hepatocyte growth factor; C-MET: Mesenchymal–epithelial transition factor.

of resistance (80). Another phase Ib trial utilized the combination of BRAF/CRAF inhibitor (naporafenib) in conjunction with Trametinib (MEK inhibitor) in patients with either advanced KRAS- or BRAF-mutant non–small-cell lung cancer or NRAS-mutant melanoma. The trial aimed to investigate the safety and tolerability of such a combination. The trial found that 16.7% of included patients experienced 3rd grade adverse event or more, including dermatitis acneiform, Steven-Johnson syndrome and increased lipase. In regard to efficacy, the ORR was 46.7%, the median PFS was 3.75 months, and the median OS was 5.52 months. This trial showed that the combination of Naporafenib plus trametinib may hold antitumor activity, however a prophylactic strategy is necessary to limit the dose-limitation toxicity that were found in the study (81). Combination strategies, such as MEK plus CDK4/6 inhibition, are also under investigation. NRAS mutations activate MAPK signaling and upregulate cyclin D1 and CDK4/6, rendering tumor cells dependent on cell cycle machinery (82). Preclinical studies demonstrate synergistic growth inhibition with MEK inhibitors (e.g., trametinib or cobimetinib) combined with CDK4/6 inhibitors (palbociclib or ribociclib) (83). Results from ongoing phase I/II trials are awaited to determine tolerability and clinical efficacy (84). Figure 2 illustrates how NRAS mutations initiate a cascade through MAPK-driven cyclin D1 overexpression, CDK4/6 activation, and Rb phosphorylation, ultimately driving melanoma cell proliferation and providing a rationale for dual inhibition strategies (85, 86). Simultaneous inhibition of MEK, PI3K/mTOR, and CDK4/6 has shown preclinical synergy, reflecting the complex network of signaling pathways utilized by NRAS in melanoma (87, 88).

Beyond traditional pathways, alternative synthetic lethal strategies are being pursued, including the inhibition of SHP2, a non-receptor phosphatase essential for RAS-GTP loading; targeting autophagy and stress-response proteins that are upregulated in NRAS-mutant tumors; and the development of RAS-mimetic peptides and direct KRAS G12C inhibitors, which, although inapplicable to NRAS Q61 mutations, conceptually drive the design of new compounds (89). Two novel RAF inhibitor agents have been recently evaluated in the clinical setting, LXH254 (a Selective ARAF-Sparing Inhibitor of BRAF and CRAF) and Belvarafenib (pan-RAF inhibitor). A phase II, open-label trial, enrolled melanoma patients with BRAFV600 or NRAS mutations, to investigate the role of LXH254 in different combinations (LXH254 + LLTT46, LXH254 + trametinib or LXH254 + ribociclib). The agent did not demonstrate efficacy in BRAFV600 mutations based on RECIST 1.1 criteria. However, the anti-tumor response was more obvious in NRAS-mutated melanoma, with a disease control rate (DCR) reaching 71% among LXH254 + trametinib group. The safety of these combinations was tolerable, with the cutaneous adverse events (e.g. rash, acneiform dermatitis, or pruritus) being the most common (90). A phase Ib of belvarafenib in combination with cobimetinib among 32 patients with advanced NRAS melanoma to evaluate the regimen safety and appropriate dosage. The regimen

showed an acceptable safety profile with the following common side effects: dermatitis acneiform, diarrhea, constipation, and an increase in blood creatine phosphokinase. In regard to efficacy, 38.5% of NRAS melanoma patients reached partial response with a median PFS of 7.3 months (91). On the surface, these current data showed modest benefits of these agents; however, meaningful clinical benefit can be subtle, therefore limiting their role in improving outcomes. A prominent example is the dual inhibition of MEK/AKT pathways with trametinib and GSK2141795 in either NRAS-mutant or wild-type melanomas. The study revealed that no objective responses were observed in either groups with median PFS and OS of only 2.8 months and 3.5 months, respectively. This study indicated that the biological plausibility of the mechanism of the drugs does not necessarily translate to significant clinical benefit, especially when accompanied by the risk of higher grades of adverse events (92). Therefore, further investigation is necessary to establish the safety profiles of these novel agents and the true meaningful clinical outcomes in the metastatic setting.

CDK4/6 Pathway in Melanoma The CDK4/6 axis is a critical regulator of G1-S phase progression, acting downstream of all mitogens to control Rb phosphorylation. Pathway dysregulation is common in melanoma and often shares mutual exclusivity to upstream activation of the RAS pathway (especially NRAS), creating a functional oncogenic loop of unrestricted cell cycle progression (93). Active mutations in NRAS are associated with the enhanced transcription of D-type cyclins (i.e. cyclin D1) from sustained (and active) MAPK pathway activity which ultimately allows for cyclin D-CDK4/6 complexes to form to hyperphosphorylate Rb, effectively silencing its tumor suppressive activity, and releasing E2Fs to promote a synthesis phase of the cell cycle (94). CDKN2A loss has been shown to occur in as many as 40% of melanomas, which promotes a release of the inhibitory brake on CDK4/6 (loss of p16INK4A), further increases phosphorylation of Rb and makes the tumor very reliant towards the CDK4/6 axis. The interplay between NRAS and CDK4/6 signaling supports dual-targeted approaches involving co-inhibition of MAPK pathway activity (via MEK inhibitors) and cell cycle progression (via CDK4/6 inhibitors). The successful use of CDK4/6 inhibitors (e.g. palbociclib, ribociclib, abemaciclib) in HR+/HER2- breast cancer has raised the question of their utility in melanoma. Although single-agent activity has been limited—primarily due to redundancy in signaling pathways and resistance—combination therapies have demonstrated greater benefits (83). CDK4/6 inhibitors combined with MEK inhibitors have shown promising results in preclinical models of NRAS-mutant melanoma, where simultaneous inhibition of both pathways produced significantly greater activity than either drug alone. In these models, the combination resulted in cell cycle arrest, apoptosis, and decreased tumor growth, particularly in tumors with CDKN2A deletions (95) (Figure 3).

SHP2 mutation: Role and current therapeutic potential Tyrosine-protein phosphatase non-receptor type 11 (SHP-2) is encoded by the PTPN11 gene. The two tandem SH2 domains of SHP-2 act as phospho-tyrosine-binding motifs, facilitating interactions between substrates and the tyrosine phosphatase (98). At rest, SHP-2 remains auto-inhibited because the N-terminal SH2 domain binds to the PTP domain's catalytic cleft, blocking substrate access to the active site. Catalytic activation occurs when the N-terminal SH2 domain disengages from the PTP domain upon binding to target phospho-tyrosine residues, restoring the active conformation (99). SHP-2 is ubiquitously expressed and plays essential roles in diverse cellular processes, including transcriptional regulation, metabolic control, mitogenic signaling, and cell migration (100). SHP-2 was the first tyrosine phosphatase identified as an oncogene in hematologic malignancies such as acute myeloid leukemia, myelodysplastic syndromes, and juvenile myelomonocytic leukemia (101). Importantly, overexpression of SHP-2 is critical in melanoma and serves as both a prognostic and predictive marker in multiple cancers (102-110). Melanoma patient samples frequently exhibit SHP-2 overexpression and mutations, which correlate with aggressive metastatic behavior and poorer outcomes (111-113). Kaplan–Meier analyses have further confirmed a significant association between elevated SHP-2 levels and reduced overall survival in melanoma patients (114, 115). Given its central role in oncogenic signaling, particularly through growth factor-mediated pathways such as Ras/ERK1/2, SHP-2 inhibition has broad therapeutic potential across cancers, including melanoma (116). The PTP inhibitor sodium stibogluconate (SSG), initially used to treat leishmaniasis (117) and capable of inhibiting both SHP-1 and SHP-2 (118), enhances interferon-alpha (IFN-alpha)-induced STAT1 tyrosine phosphorylation

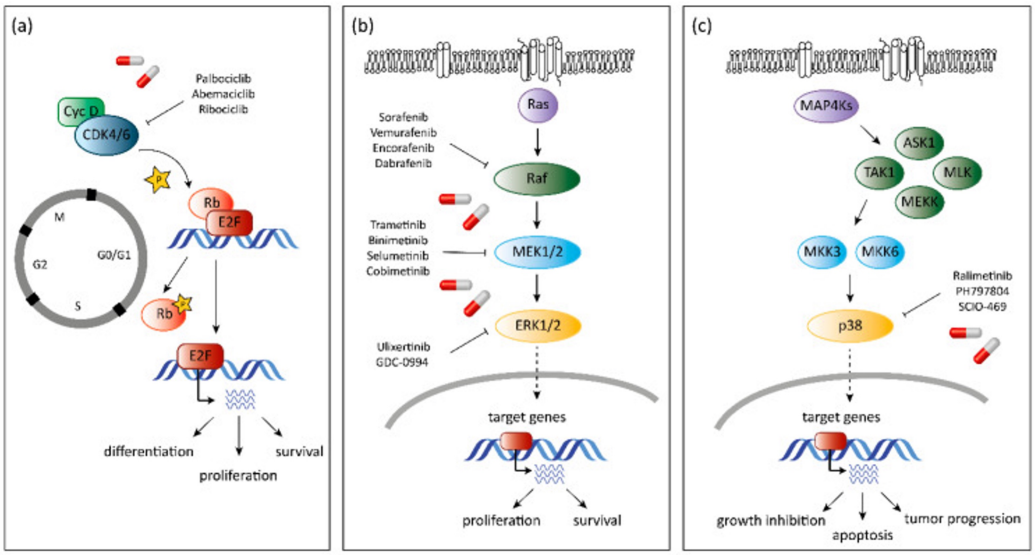

Figure 2. : NRAS mutations activate the MAPK pathway, leading to cyclin D1 overexpression, CDK4/6 activation, and Rb phosphorylation, which promotes cell proliferation. CDK4/6 inhibitors (a) block Rb phosphorylation, ERK inhibitors (b) target MAPK-driven growth, an and p38 inhibitors (c) have mixed effects depending on cancer stage (86).

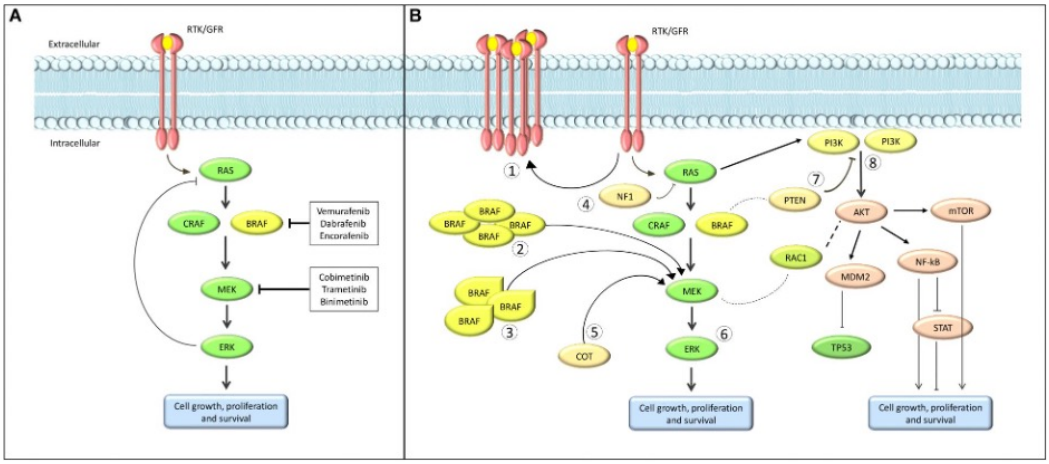

Figure 3. Potential druggable targets and therapeutic strategies for melanoma treatment. This diagram illustrates inhibitors targeting the BRAF/MEK and PI3K/AKT pathways, as well as various immunotherapies including checkpoint inhibitors (PD-1, PD-L1, CTLA-4), CD73 blockers, and oncolytic virus therapies (97).

and synergizes with IFN-alpha to suppress WM9 human melanoma tumor growth in nude mice (119). Similarly, Win-Piazza et al. demonstrated that SHP-2 inhibition potentiates IFN-alpha2b's anticancer effects in A375 melanoma xenografts. Since SHP-2 negatively regulates STAT1/STAT2 phosphorylation, inhibiting SHP-2 with SPI-112 increases IFN-alpha2b-stimulated STAT1 activity and reduces A375 cell proliferation (120). Moreover, Soong and colleagues identified an unusual function of SHP-2 in melanocytes. Semaphorin-4D (Sema4D) strengthens the receptor complex formed by Plexin B1 and the MET tyrosine kinase in melanocytes, with MET activation being associated with melanocyte transformation into melanoma (121). HGF-induced activation of MAPK and AKT pathways requires SHP-2, which mediates downstream effects of MET (122, 123). Inhibition of SHP-2 phosphatase activity using NSC-87877 reduces HGF-stimulated MET activation and downstream ERK1/ERK2 and AKT phosphorylation, suggesting that targeting SHP-2 may prevent melanocyte transformation into melanoma (121). In BRAF wild-type or NRAS-mutant melanoma cells, SHP-2 acts as an oncogene. Silencing the activated SHP-2 E76K mutant or treating with the allosteric SHP-2 inhibitor SHP099 leads to tumor regression, indicating its potential as a therapeutic target for BRAF wild-type melanoma (124). In BRAF-mutant cells, HGF is known to confer resistance to the BRAF inhibitor vemurafenib (125), and recent evidence highlights SHP-2's role in this resistance. For instance, SHP-2 knockout in SK-Mel888 BRAF(V600E)

Table 2. Mechanisms of resistance to BRAF inhibitors.

Target	Mutation/Subtype	Therapeutic Approach	Agents or Combinations	Efficacy Summary
NRAS	Q61 mutations (15–20% of melanomas)	Downstream pathway inhibition	MEK inhibitors (binimetinib), MEK + CDK4/6 inhibitors	ORR ∼15%; modest PFS gains; combination improves efficacy
CDK4/6 Pathway	CDKN2A loss, cyclin D1 overexpression	Cell cycle inhibition	Palbociclib + trametinib, abemaciclib + ICIs	Synergistic tumor regression in preclinical/early clinical models
TME & Immune Evasion	PD-L1, LAG-3, IDO1 expression	Checkpoint inhibition & modulation	Anti-PD-1 (nivolumab, pembrolizumab), T-VEC + PD-1 blockade	High ORR in TIL-rich tumors; low in immune-desert tumors

melanoma cells prevented HGF-, FGF9-, and SCF-induced vemurafenib resistance (126). SHP-2 has also been implicated in adaptive resistance to MEK inhibitors and RAF-targeted therapies across multiple tumor types (127). Collectively, these findings strongly suggest that SHP-2 represents a targetable molecule in melanoma, given its correlation with poor survival outcomes. Consequently, SHP-2 inhibitors are proposed as novel therapeutic approaches for melanoma management (114). Clinical trials are currently evaluating TNO155, an orally bioavailable SHP-2 inhibitor, which has demonstrated antitumor activity in xenograft models, including melanoma (128).

Other Genetic Alterations in Melanoma: GNAQ/GNA11, NTRK Fusions, and VEGF-Associated Pathways In addition to the well-characterized driver mutations in BRAF, NRAS, and KIT, melanoma harbors other less frequent but clinically relevant genetic changes. These include kinase fusions involving NTRK1, mutations in GNAQ and GNA11, and pathway-level activations—such as MAPK and PI3K/AKT—that regulate downstream effectors including VEGF. Characterizing these alterations improves our understanding of melanoma subtypes and highlights potential therapeutic targets, particularly in tumors lacking common mutations (129). Histological subtypes, such as blue nevi, which are pigmented lesions derived from melanocyte precursors, support this molecular stratification. Compared with congenital and acquired melanocytic nevi, blue nevi exhibit a higher prevalence of somatic mutations in GNAQ (extasciitilde80%) and GNA11 (3–5%), with lower rates of BRAF mutations. These mutations, which predominantly affect glutamine 209, result in constitutive MAPK activation. Additional mutations may include KRAS (15–20%), CYSLTR2 (3%), as well as BAP1, SF3B1, and EIF1AX in blue nevus–like melanomas. Despite these molecular alterations, the risk of malignant transformation in blue nevi remains relatively low (129, 130). The G proteins GNAQ, encoding the GTP-binding q subunit commonly altered in malignant blue nevi and uveal melanoma, and GNA11, which also encodes a GTP-binding q subunit mutated in uveal melanoma, are specifically implicated in Subtype 3 melanomas. These mutations promote melanomagenesis by inducing constitutive activation of downstream pathways, including MAPK (130, 131). Further evidence for the presence of GNAQ and GNA11 mutations in the Triple Wild-Type melanoma subtype—defined by the absence of BRAF, RAS, or NF1 mutations—comes from TCGA's integrative genomic analyses. Alternative driver mutations frequently observed in these cancers (extasciitilde15% of cases) include KIT, CTNNB1, and EZH2. Copy number alterations are also common in KIT, PDGFRA, CDK4, CCND1, MDM2, and TERT (132). Spitz nevi, a distinct subset of melanocytic tumors, display a unique spectrum of genetic events. These lesions, composed of large epithelioid or spindle-shaped melanocytes, range from benign to malignant. Kinase fusions occur in approximately 55% of Spitz nevi, most commonly involving ROS1, ALK, and NTRK1, whereas BRAF and RET fusions are less frequent. These fusions drive oncogenic signaling and are mutually exclusive with HRAS alterations. Atypical Spitz tumors, which have intermediate malignant potential, may also exhibit BAP1 allelic loss alongside BRAF mutations. These genetic findings have therapeutic implications, particularly for the use of TRK inhibitors in tumors harboring NTRK fusions, although most Spitz tumors have a low likelihood of melanoma transformation (128). While VEGF itself has not been specifically addressed in these studies, upstream pathways such as MAPK and PI3K/AKT—which are frequently dysregulated in melanoma—significantly influence its transcriptional regulation. For instance, melanomas with KIT mutations often show constitutive activation

of these pathways, promoting tumor growth and survival. Concurrent activation of cyclin-dependent kinase (CDK), AKT/PI3K, and MAPK signaling is commonly observed in subtype 1 melanomas (128, 130).

3 Conclusion

The molecular understanding of melanoma has advanced significantly, revealing key genetic drivers and resistance mechanisms that shape treatment outcomes. The MAPK and PI3K/AKT/mTOR pathways remain central, particularly in BRAF-mutant melanoma, where combined BRAF and MEK inhibition improves survival but is limited by resistance. NRAS- and KIT-mutant melanomas pose additional challenges, with downstream targets like MEK, CDK4/6, and SHP2 showing therapeutic potential. Immunotherapy has transformed melanoma care, yet resistance due to factors like PTEN loss, JAK/STAT mutations, and antigen presentation defects necessitates innovative combination strategies. Emerging alterations such as NTRK fusions, GNAQ/GNA11 mutations, and VEGF-related changes expand the landscape, especially in rare subtypes. These insights highlight the importance of integrating genomic profiling to personalize treatment and guide therapeutic decisions. As research continues, targeting molecular heterogeneity and resistance pathways will be key to improving durability and achieving more effective, individualized care for patients with advanced melanoma.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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