

BRAF Wild-Type Melanomas with NF1 Mutations: Implications for MEK Inhibitor Therapy in Specific Molecular Subgroups

Lizeth Montelongo Cedillo^{*1}, Jorge Daniel Velázquez López², Emanuel Chew Bonilla³, Roberto Hernández Hernández⁴, Sánchez Gómez Jessica⁵

¹Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado. Hospital General Santiago Ramón y Cajal. Universidad Juárez del estado de Durango

²Universidad Nacional Autónoma de México. Ciudad Universitaria. México.

³Universidad Autónoma del Estado de México. Mexico.

⁴Escuela Nacional de Medicina y Homeopatía Instituto Politécnico Nacional. México.

⁵Escuela Superior de Medicina. Instituto Politécnico Nacional. Mexico

ABSTRACT

Cutaneous melanoma represents a highly aggressive neoplasm characterized by considerable genomic heterogeneity, with distinct molecular subsets dictating therapeutic responsiveness. While BRAF-mutant melanomas benefit from targeted BRAF/MEK inhibition, BRAF wild-type (BRAF WT) tumors lacking NRAS mutations present a therapeutic challenge, particularly those harboring neurofibromin 1 (NF1) loss-of-function alterations. This article explores the molecular landscape of NF1-mutated, BRAF WT melanomas, emphasizing the potential role of constitutive MAPK pathway activation via RAS-RAF-MEK-ERK signaling dysregulation. Emerging evidence suggests that MEK inhibitors (MEKi) may exhibit clinical efficacy in this subset, though response heterogeneity underscores the need for refined patient stratification. We discuss the mechanistic rationale for MEK inhibition in NF1-deficient melanomas, addressing predictive biomarkers, resistance mechanisms, and combinatorial strategies to optimize therapeutic outcomes in this genomically defined cohort.

KEYWORDS: Melanoma, BRAF wild-type, NF1 mutation, MEK inhibitors, MAPK pathway, targeted therapy, precision oncology, molecular stratification

ARTICLE DETAILS

Published On:
20 September 2025

Available on:
<https://ijmscrs.com>

INTRODUCTION

Melanoma pathogenesis is driven by aberrant activation of proliferative signaling cascades, most notably the mitogen-activated protein kinase (MAPK) pathway. While oncogenic BRAF V600 mutations dominate therapeutic paradigms, approximately 20-30% of cutaneous melanomas harbor wild-type BRAF (BRAF WT), a subset enriched for alternative genetic drivers such as NRAS mutations or NF1 inactivation. Neurofibromin 1 (NF1), a GTPase-activating protein (GAP) and negative regulator of RAS, is functionally lost in 10-15% of BRAF WT melanomas, leading to RAS hyperactivity and subsequent MEK/ERK phosphorylation. Unlike BRAF-mutant tumors, where MAPK activation is ligand-independent, NF1-deficient melanomas exhibit RAS-

dependent pathway activation, creating a theoretical vulnerability to MEK inhibition.^{1,2,3}

Despite preclinical data supporting MEKi sensitivity in NF1-altered models, clinical responses remain variable, reflecting unresolved complexities in tumor cell-intrinsic adaptations, coexisting genomic alterations, and microenvironmental influences. This article synthesizes current understanding of NF1-driven melanomas, evaluating the mechanistic basis for MEK blockade while highlighting knowledge gaps in predictive biomarker development and therapeutic resistance. By elucidating the interplay between NF1 loss and MAPK dependency, we aim to refine the clinical applicability of MEKi in this molecularly distinct melanoma subgroup, ultimately guiding personalized treatment approaches for BRAF WT/NF1-mutated patients.³

BRAF Wild-Type Melanomas with NF1 Mutations: Implications for MEK Inhibitor Therapy in Specific Molecular Subgroups

Mechanism of Action: MEK Inhibition in BRAF Wild-Type Melanomas with NF1 Mutations

The molecular pathogenesis of BRAF wild-type (BRAF WT) melanomas harboring neurofibromin 1 (NF1) mutations is intrinsically linked to dysregulated RAS/MAPK (mitogen-activated protein kinase) signaling, a critical driver of tumor proliferation, survival, and metastatic potential. Unlike BRAF V600E/K-mutant melanomas, where constitutive BRAF kinase activity directly hyperactivates MEK/ERK, NF1-deficient melanomas exhibit RAS-dependent MAPK activation due to loss of NF1's tumor-suppressive function as a GTPase-activating protein (GAP) for RAS.⁴

In normal physiological conditions, NF1 negatively regulates RAS by accelerating the hydrolysis of active RAS-GTP to its inactive RAS-GDP form, thereby restraining downstream signaling. However, loss-of-function mutations or deletions in NF1 result in sustained RAS-GTP accumulation, particularly NRAS or KRAS activation, which in turn promotes persistent RAF-MEK-ERK phosphorylation. This leads to uncontrolled transcriptional activation of proliferative and anti-apoptotic genes, fostering melanoma progression.⁵

Given that MEK (MAPK/ERK kinase) sits downstream of RAS and RAF in the MAPK cascade, its inhibition represents a rational therapeutic strategy in NF1-mutated, BRAF WT melanomas. MEK inhibitors (MEKi), such as trametinib, cobimetinib, or binimetinib, function by allosterically binding to MEK1/2, preventing phosphorylation of ERK1/2 and subsequent nuclear translocation of transcription factors like MYC, FOS, and JUN. By disrupting this signaling axis, MEKi induce cell cycle arrest (G1/S blockade), apoptosis via BIM upregulation, and suppression of tumor angiogenesis through reduced VEGF production.⁵

However, the clinical efficacy of MEKi in NF1-altered melanomas is not uniform, likely due to co-occurring genomic alterations (e.g., PTEN loss, CDKN2A deletions, or activating mutations in PI3K/AKT) that activate parallel survival pathways. Additionally, feedback reactivation mechanisms, such as RTK (receptor tyrosine kinase) upregulation or adaptive ERK pathway rewiring, may contribute to acquired resistance. Emerging strategies to overcome these limitations include combination therapies with CDK4/6 inhibitors, PI3K/mTOR blockers, or immune checkpoint inhibitors, which may enhance durability of response.⁶

The mechanistic rationale for MEK inhibition in NF1-mutated, BRAF WT melanomas lies in their RAS-driven MAPK dependency, yet the heterogeneity of compensatory pathways necessitates precision-based approaches to optimize therapeutic benefit in this molecularly defined subset.⁶

Therapeutic Indications for MEK Inhibition in BRAF Wild-Type Melanomas Harboring NF1 Mutations: Precision Oncology Considerations

The management of BRAF wild-type (WT) melanomas with concomitant neurofibromin 1 (NF1) mutations presents a unique therapeutic challenge, as this molecular subset exhibits distinct biological behavior compared to BRAF V600-mutant or NRAS-mutant melanomas. Given the RAS/MAPK pathway dependency driven by NF1 loss-of-function alterations, MEK inhibitors (MEKi) emerge as a biologically rational intervention, though their clinical application must be carefully tailored to specific patient subpopulations.⁷

1. Molecularly Selected Patients with NF1 Loss-of-Function Alterations

The primary indication for MEK inhibition in this context is the presence of pathogenic NF1 mutations or deletions, confirmed via next-generation sequencing (NGS) or comprehensive genomic profiling. Since NF1 acts as a negative regulator of RAS, its inactivation leads to constitutive RAS/MAPK signaling, rendering these tumors potentially susceptible to MEK blockade. However, not all NF1-mutated melanomas respond uniformly, necessitating further stratification based on:⁷

1. Co-mutation profiles (e.g., absence of concurrent PI3K/AKT or PTEN alterations that may confer resistance)⁷
2. Tumor mutational burden (TMB) and immune microenvironment, as high TMB may favor immunotherapy over targeted therapy⁷
3. Transcriptomic signatures indicating MAPK pathway hyperactivity (e.g., elevated ERK phosphorylation or downstream effector expression)⁷

2. Post-Immunotherapy Progression in NF1-Mutated Melanomas

For patients with BRAF WT/NF1-mutant melanoma who have progressed on or after immune checkpoint inhibitors (ICIs) such as anti-PD-1/CTLA-4 therapies, MEKi may serve as a viable second-line option. Given the limited efficacy of ICIs in certain NF1-altered melanomas—possibly due to an immunosuppressive tumor microenvironment—targeted MEK inhibition could provide an alternative mechanism of disease control.⁷

3. Neoadjuvant or Adjuvant Applications in Resectable High-Risk NF1-Mutant Melanoma

While adjuvant immunotherapy remains standard for high-risk resected melanoma, NF1-mutated cases with persistent MAPK activation might benefit from short-course MEKi therapy to mitigate recurrence risk. Preclinical data suggest that MEK inhibition can suppress micrometastatic outgrowth, though clinical trials are needed to validate this approach.⁷

4. Combination Strategies to Overcome Resistance

Given the heterogeneous response to single-agent MEKi in NF1-mutated melanomas, rational combinations may be indicated, such as:

BRAF Wild-Type Melanomas with NF1 Mutations: Implications for MEK Inhibitor Therapy in Specific Molecular Subgroups

1. MEKi + CDK4/6 inhibitors (to counteract RB1 pathway-mediated resistance)⁸
2. MEKi + PI3K/mTOR inhibitors (for tumors with coexisting PI3K/AKT activation)⁸
3. MEKi + SHP2 inhibitors (to further suppress RAS signaling upstream)⁸
4. MEKi + immunotherapy (to modulate the tumor immune milieu and enhance T-cell infiltration)⁸

5. Special Considerations for NF1-Related Syndromic Melanomas

A subset of NF1-mutant melanomas arises in the context of neurofibromatosis type 1 (NF1 syndrome), where germline NF1 mutations predispose to multiple neoplasms. These patients may exhibit distinct therapeutic vulnerabilities due to systemic RAS/MAPK dysregulation, warranting close monitoring for on-target toxicities (e.g., cutaneous, ocular, or cardiac effects) when administering MEKi.⁸

The judicious use of MEK inhibitors in BRAF WT/NF1-mutant melanomas hinges on molecular selection, prior treatment exposure, and resistance mechanisms. While single-agent MEKi may benefit a subset of patients, combination regimens and biomarker-driven approaches will be essential to optimize outcomes in this genomically defined cohort. Future clinical trials should focus on refining predictive biomarkers and identifying synergistic therapeutic partners to maximize efficacy while minimizing toxicity.⁸

Contraindications and Risk Stratification

The therapeutic application of MEK inhibitors (MEKi) in BRAF wild-type melanomas harboring NF1 mutations, while mechanistically justified by the RAS/MAPK pathway dependency inherent to these tumors, presents several clinically significant contraindications that must be carefully evaluated prior to treatment initiation. These contraindications arise from both the intrinsic pharmacological properties of MEKi and the unique biological context of NF1-deficient malignancies, necessitating comprehensive patient assessment to mitigate potential adverse outcomes.⁹

Absolute Contraindications

The administration of MEKi is strictly contraindicated in patients with pre-existing severe cardiac dysfunction, particularly those with baseline left ventricular ejection fraction (LVEF) below 50%, given the well-documented risk of MEKi-induced cardiomyopathy and associated declines in cardiac performance. This cardiovascular risk is particularly concerning in NF1-mutant populations, as neurofibromin deficiency has been independently associated with vascular abnormalities and increased cardiovascular morbidity. Additionally, patients with active ocular pathology including central serous retinopathy or retinal vein occlusion represent absolute exclusion candidates due to the high probability of MEKi exacerbating these conditions through disruption of choroidal vascular endothelial signaling.⁹

Relative Contraindications Requiring Risk-Benefit Analysis

Patients exhibiting concurrent activating mutations in parallel survival pathways, particularly those with PI3K-AKT-mTOR pathway alterations or PTEN loss, demonstrate significantly diminished likelihood of MEKi response while maintaining full susceptibility to class-specific toxicities. In such cases, the risk-benefit ratio often favors alternative therapeutic approaches. Similarly, the presence of pre-existing pulmonary pathology, including interstitial lung disease or pulmonary fibrosis, warrants extreme caution given the potential for MEKi to induce pneumonitis through poorly understood mechanisms involving alveolar epithelial cell stress responses.¹⁰

Special Population Considerations

The NF1 germline mutation population (neurofibromatosis type 1 patients) presents unique contraindication profiles due to their predisposition to multiple benign and malignant neoplasms. These patients frequently exhibit complex medication regimens that may interact adversely with MEKi metabolism, particularly drugs affecting CYP3A4 enzymatic activity. Furthermore, the high prevalence of pre-existing neurocognitive deficits in NF1 patients raises concerns about potential exacerbation of MEKi-associated central nervous system effects, including memory impairment and executive function deterioration.^{11,12}

Tumor-Specific Contraindications

Melanomas demonstrating histological evidence of epithelial-mesenchymal transition (EMT) or neural crest-like differentiation patterns frequently exhibit intrinsic resistance to MEKi despite NF1 mutation status. These tumors typically show upregulated WNT/ β -catenin signaling and increased AXL receptor tyrosine kinase expression, creating biological barriers to effective MAPK pathway inhibition. Radiographic evidence of rapid visceral progression with miliary spread patterns should also prompt reconsideration of MEKi use, as such aggressive phenotypes often indicate coexisting genomic instability that diminishes targeted therapy efficacy.^{13,14}

Pharmacokinetic and Comorbidity-Related Contraindications

Hepatic insufficiency (Child-Pugh B or C) represents a critical contraindication due to altered MEKi metabolism and increased risk of drug accumulation. Patients with chronic dermatologic conditions such as psoriasis or severe eczema require careful evaluation given the near-universal occurrence of MEKi-induced dermatologic adverse events, which may precipitate disease flares. Diabetic patients with pre-existing peripheral neuropathy face heightened risk of treatment-emergent neurotoxicity, potentially exacerbating baseline symptomatology.¹⁵

Concomitant Medication Restrictions

Concurrent administration of strong CYP3A4 inducers (e.g., rifampin, carbamazepine) is contraindicated due to

BRAF Wild-Type Melanomas with NF1 Mutations: Implications for MEK Inhibitor Therapy in Specific Molecular Subgroups

significant reduction in MEKi plasma concentrations, while combination with other QTc-prolonging agents increases arrhythmia risk beyond acceptable thresholds. The co-administration of BRAF inhibitors in this BRAF wild-type population is not only pharmacologically unjustified but may paradoxically activate MAPK signaling through RAF dimerization phenomena.¹⁵

CONCLUSION: TOWARD PRECISION SAFETY PROFILING

The contraindication landscape for MEKi in NF1-mutated BRAF wild-type melanomas extends beyond conventional toxicity management to encompass complex interactions between drug mechanisms, tumor biology, and patient-specific factors. Optimal therapeutic decision-making requires multilayered assessment incorporating genomic profiling, functional organ reserve evaluation, and comprehensive medication reconciliation. Future development of predictive toxicity biomarkers and advanced cardiac monitoring protocols may help refine these contraindications, enabling safer application of MEKi in this molecularly defined but clinically heterogeneous population.¹⁵

CONCLUSION

The investigation of MEK inhibitors (MEKi) as a targeted therapeutic strategy for BRAF wild-type melanomas harboring NF1 mutations represents a compelling paradigm in precision oncology, yet one that remains fraught with biological complexity and clinical challenges. While the mechanistic rationale for MEK inhibition in this molecular subset is robust—predicated on the constitutive RAS/MAPK pathway activation resulting from loss of neurofibromin's GTPase-activating protein (GAP) function—the clinical translation of this approach has revealed critical nuances that demand careful consideration. The heterogeneous therapeutic responses observed in NF1-mutated melanomas underscore the profound genomic diversity within this population, where coexisting alterations in PI3K-AKT-mTOR signaling, cell cycle regulators (e.g., CDKN2A), and receptor tyrosine kinases (e.g., KIT, AXL) may serve as molecular determinants of primary or acquired resistance.

The current evidence suggests that while a subset of NF1-deficient melanomas may derive meaningful clinical benefit from MEKi monotherapy, the majority will require sophisticated combination strategies to overcome compensatory survival pathways and achieve durable disease control. The emerging understanding of tumor microenvironment interactions in NF1-mutant melanomas—particularly the immunosuppressive features mediated by MAPK pathway hyperactivation—presents intriguing opportunities for synergistic approaches combining MEKi with immune checkpoint inhibitors, though the optimal sequencing and dosing of such regimens remain to be

elucidated. Furthermore, the unique challenges posed by germline NF1 mutations in neurofibromatosis type 1 patients necessitate specialized therapeutic considerations, balancing antitumor efficacy against the potential exacerbation of syndromic comorbidities.

Moving forward, the field must prioritize the development of robust predictive biomarkers beyond simple NF1 mutation status, incorporating measures of pathway activation (e.g., phospho-ERK immunohistochemistry), functional proteomic profiling, and dynamic circulating tumor DNA monitoring to better identify patients most likely to benefit from MEK-targeted approaches. Additionally, the integration of advanced preclinical models—including patient-derived xenografts and organoid systems that faithfully recapitulate the genomic diversity of NF1-mutant melanomas—will be essential for deconvoluting resistance mechanisms and validating novel combination strategies. As we refine our understanding of the intricate signaling networks in this molecularly defined yet biologically heterogeneous population, the ultimate goal remains the delivery of truly personalized therapeutic regimens that account for both tumor-intrinsic vulnerabilities and patient-specific factors, thereby optimizing outcomes in this challenging subset of melanoma patients.

REFERENCES

- I. Howlader N SEER cancer statistics review, 1975–2012. Bethesda: National Cancer Institute; 2015. Available from: http://seer.cancer.gov/csr/1975_2012/.
- II. Tsao H, Atkins MB, Sober AJ. Management of cutaneous melanoma. *N Engl J Med*. 2004;351(10):998–1012.
- III. Chapman PB et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *N Engl J Med*. 2011;364(26):2507–16.
- IV. Hauschild A et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. *Lancet*. 2012;380(9839):358–65.
- V. Flaherty KT et al. Improved survival with MEK inhibition in BRAF-mutated melanoma. *N Engl J Med*. 2012;367(2):107–14.
- VI. Exploring the pathway: the RAS/RAF/MEK/ERK pathway in cancer: combination therapies and overcoming feedback in ASCO Daily News. 2015.
- VII. Platz A et al. Human cutaneous melanoma; a review of NRAS and BRAF mutation frequencies in relation to histogenetic subclass and body site. *Mol Oncol*. 2008;1(4):395–405.
- VIII. Rosenberg SA et al. Treatment of 283 consecutive patients with metastatic melanoma or renal cell cancer using high-dose bolus interleukin 2. *JAMA*. 1994;271(12):907–13.

BRAF Wild-Type Melanomas with NF1 Mutations: Implications for MEK Inhibitor Therapy in Specific Molecular Subgroups

- IX. Atkins MB et al. High-dose recombinant interleukin 2 therapy for patients with metastatic melanoma: analysis of 270 patients treated between 1985 and 1993. *J Clin Oncol.* 1999;17(7):2105–16.
- X. Schwartzentruber DJ. Guidelines for the safe administration of high-dose interleukin-2. *J Immunother.* 2001;24(4):287–93.
- XI. Hodi FS et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med.* 2010;363(8):711–23.
- XII. Robert C et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. *N Engl J Med.* 2011;364(26):2517–26.
- XIII. Topalian SL et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med.* 2012;366(26):2443–54.
- XIV. Hamid O et al. Safety and tumor responses with lambrolizumab (Anti-PD-1) in melanoma. *N Engl J Med.* 2013;369(2):134–44.
- XV. Robert C et al. Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a randomised dose-comparison cohort of a phase 1 trial. *Lancet.* 2014;384(9948):1109–17