Review

http://www.jcpjournal.org
pISSN 2288-3649 · eISSN 2288-3657
https://doi.org/10.15430/JCP.24.028

JCP

# Therapeutic Strategies for Drug-resistant Melanoma and Their Clinical Implications

**Ke Huang, Myoung Ok Kim**

Department of Animal Science and Biotechnology, Research Institute for Innovative Animal Sciences, Kyungpook National University, Sangju, Korea

Melanoma is a malignant tumor originating from melanocytes, characterized by its high invasiveness and metastasis, leading to poor prognosis and high mortality. Early-stage melanoma is primarily treated with surgery; however, due to its metastatic nature, surgery becomes challenging in advanced stages. Treatment strategies for advanced or metastatic melanoma include chemotherapy, radiation therapy, and targeted therapy. However, melanoma's propensity for rapid drug resistance remains a significant clinical challenge. This review summarizes the developments in the treatment of drug-resistant melanoma over the past decade and discusses the advantages and disadvantages of various therapeutic approaches and their clinical significance implications.

**Key Words** Melanoma, Proto-oncogene proteins B-raf, Drug resistance, neoplasm, Molecular targeted therapy

## INTRODUCTION

Mutations in melanocytes are one of the primary causes of melanoma [1]. Melanoma, a cancer originating from melanocytes, accounts for a small proportion of skin cancers but is the leading cause of skin cancer-related deaths [2,3]. The high mortality rate of melanoma is attributed to its invasive and metastatic potential, making treatment increasingly difficult as the disease progresses [4]. Currently, surgery is the primary treatment for early-stage melanoma; however, as tumor metastasis occurs, surgical treatment becomes increasingly difficult. Chemotherapy and targeted therapies are used for the treatment of advanced melanoma, but their clinical efficacy is often limited by the widespread drug resistance in melanoma [5-7].

Proto-oncogene proteins B-raf (BRAF) is one of the most common oncoproteins mutated in melanoma, with the V600E mutation being the most prevalent [8]. This mutation typically leads to constitutive activation of the BRAF/mitogen-activated protein kinase kinase (MEK)/extracellular signal-regulated kinases signaling pathway [9,10]. In 2011, the US Food and Drug Administration (FDA) approved vemurafenib, the first targeted therapy for melanoma with a BRAF mutation [11]. Its introduction improved the overall survival of patients with BRAF-mutant melanoma. However, the inevitable development of resistance has led to treatment failure [12]. Even with advanced therapies like BRAF and MEK inhibitors that have revolutionized melanoma treatment, the rapid emergence of resistance severely undermines their long-term effectiveness, resulting in patients' lifespan being limited.

In this review, we will discuss the development in treatment strategies for drug-resistant melanoma over the past decade and summarize the current research landscape.

### Application of BRAF and MEK inhibitors

In the past decade, targeted therapies for patients with BRAF V600 mutations, such as vemurafenib and dabrafenib, have significantly improved treatment outcomes. The combination of these therapies with MEK inhibitors has further delayed the onset of resistance. However, most patients receiving monotherapy develop secondary resistance within 6 to 7 months [13,14]. According to Robert et al.'s [15] study, patients with metastatic BRAF-mutant melanoma who received a combination of dabrafenib and trametinib experienced a 33% relative reduction in the risk of death compared to those receiving vemurafenib alone. Additionally, combination therapy can delay the emergence of tumor resistance, thereby improving overall survival. However, nearly all patients undergoing combination treatment experience adverse reactions, with the incidence of grade 3 to 4 adverse events from various com-

Received December 2, 2024, Revised December 16, 2024, Accepted December 17, 2024, Published on March 30, 2025
**Correspondence to** Myoung Ok Kim, E-mail: ok4325@knu.ac.kr, https://orcid.org/0000-0001-6650-7734

binations of BRAF inhibitors and MEK inhibitors ranging from 46% to 69% [15].

## Mechanisms of resistance

While targeted therapies inhibit BRAF V600E or other key driver mutations, resistance often develops through new or bypass mutations in other genes. Some tumor cells achieve resistance by losing the BRAF V600E mutation or truncating the BRAF protein (Fig. 1), thereby activating other members of the rat sarcoma virus (RAS) family, such as RAF proto-oncogene serine/threonine-protein kinase, to continue signaling [16]. Additionally, N-RAS mutations represent a classic example of novel mutations. After BRAF-targeted therapy, tumor cells may acquire mutations in the N-RAS gene (e.g., Q61R and Q61K), leading to the reactivation of the mitogen-activated protein kinase pathway and resistance to treatment [17].

Research by Irvine et al. [18] suggests that overexpression or mutations of proteins such as epidermal growth factor receptor, HER2, and hepatocyte growth factor receptor can enhance resistance by activating downstream signaling pathways, such as the phosphoinositide 3-kinases/protein kinase B pathway. Similarly, phenotypic switching has also been implicated in mediating resistance. Studies have shown that the high-proliferation, low-invasion microphthalmia-associated transcription factor (MITF)-high phenotype can convert to the low-proliferation, high-invasion MITF-low phenotype, enhancing cellular drug resistance [19]. Beyond the MITF axis, other forms of phenotypic plasticity, such as transitions toward neural crest-like states or dedifferentiation to a stem-cell-like phenotype, have also been associated with increased resistance to therapy and immune evasion, thereby further complicating treatment outcomes. These transitions often promote resistance by reducing tumor cell dependency on specific oncogenic pathways targeted by therapy [20,21].

Drug efflux and autophagy, processes occurring within the cells, have recently attracted significant attention in resistance studies. In drug-resistant melanoma, tumor cells increase drug efflux by upregulating ATP-binding cassette (ABC) transporters, such as ABCB1, which lowers intracellular drug concentrations and contributes to resistance. ABCB1, also known as P-glycoprotein, is a membrane-associated multidrug transporter that pumps various anticancer drugs out of cells, reducing drug accumulation within the cells and thereby diminishing therapeutic efficacy [22].

Tumor cells activate autophagy to cope with drug-induced stress, enhancing survival and contributing to resistance. Autophagy plays a dual role in cancer treatment. Most chemotherapy drugs induce autophagy in tumor cells by activating endoplasmic reticulum stress, and excessive autophagy can lead to apoptosis, exerting anti-tumor effects. However, autophagy also serves a protective function for tumor cells, maintaining their viability by degrading and recycling damaged organelles, thus reducing sensitivity to chemotherapy drugs. Therefore, regulators that either promote or inhibit autophagy, in combination with chemotherapy agents, may hold development potential in cancer therapy [23,24]. Targeting autophagy through inhibitors such as chloroquine or hydroxychloroquine in combination with standard therapies could enhance treatment responses. For example, preclinical models of melanoma have demonstrated that autophagy inhibitors can sensitize resistant tumor cells to BRAF/MEK inhibitors, reducing cell viability and tumor growth [25]. These findings suggest that modulating autophagy could represent a promising avenue for overcoming resistance, although clinical validation is still required.

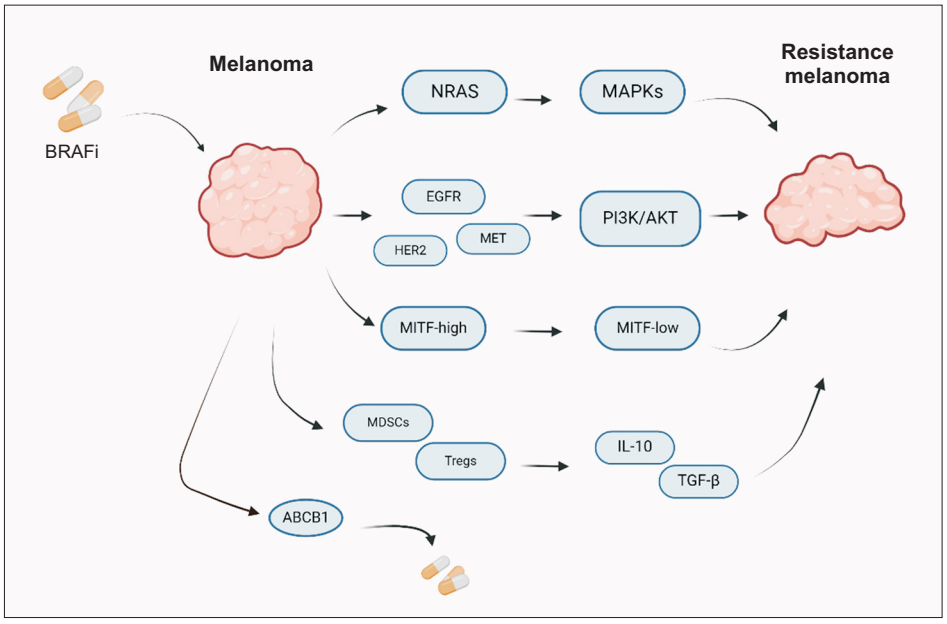


**Figure 1. BRAF inhibitor treatment activates the bypass pathway, ultimately inducing drug resistance.** After treatment with BRAF inhibitor, BRAF V600-mutated melanoma activates specific signaling pathways through various proteins, ultimately inducing drug-resistant melanoma. BRAF, proto-oncogene proteins B-raf; NRAS, oncogene homolog; MAPK, mitogen-activated protein kinase; EGFR, epidermal growth factor receptor; MET, hepatocyte growth factor receptor; PI3K, phosphoinositide 3-kinases; AKT, protein kinase B pathway; MITF, microphthalmia-associated transcription factor; MDSC, myeloid-derived suppressor cell; Tregs, regulatory T cells; IL, interleukin; ABC, ATP-binding cassette.

## Recent advances and challenges in the treatment of drug-resistant melanoma

Over the past decade, significant progress has been made in the treatment of drug-resistant. The combination of immune checkpoint inhibitors, such as programmed cell death 1 receptor (PD-1) and cytotoxic T-lymphocyte associated protein 4 inhibitors, has shown enhanced efficacy in overcoming resistance [26]. However, this approach may lead to an increased incidence of immune-related adverse events, necessitating careful monitoring of patients [27]. At the same time, innovative therapies, such as tumor-infiltrating lymphocyte therapy, have demonstrated promising results in the treatment of advanced melanoma [28]. For example, in February 2024, the US FDA approved lifileucel (Amtagvi) for the treatment of patients with unresectable or metastatic melanoma who had previously received PD-1 blocking antibodies [29]. This represents the first cell therapy approved for adult patients with melanoma that cannot be surgically removed (unresectable) or has spread to other parts of the body (metastatic) [30,31].

Recent studies have also highlighted the potential of combining immune checkpoint inhibitors with small molecule therapies to overcome resistance (Fig. 2). One approach that has gained attention is the combination of PD-1/PD-L1 inhibitors with BRAF/MEK inhibitors. This combination targets both the immune response and the tumor's signaling pathways, showing promise in overcoming the adaptive resistance mechanisms that often develop when BRAF inhibitors are used alone. Recent trials have shown that the combination of pembrolizumab (PD-1 inhibitor) and dabrafenib/trametinib (BRAF/MEK inhibitors) significantly improves overall survival and progression-free survival compared to single-agent therapies, especially in patients with BRAF V600E-mutant melanoma [32].

Tumor microenvironment (TME) plays a critical role in resistance mechanisms (Fig. 3) and its modulation is important in improving treatment outcomes for drug-resistant melanoma patients. In the stroma of TME, cancer-associated fibroblasts (CAFs) secrete factors like TGF-β and interleukin (IL)-6, which activate anti-apoptotic pathways in tumor cells [33]. Additionally, myeloid-derived suppressor cells (MDSCs) and regulatory T cells suppress anti-tumor immune responses by secreting immune-suppressive factors such as IL-10 and TGF-β [34].

Both CAFs and MDSCs contribute to the formation of an immunosuppressive TME, promoting tumor progression and treatment resistance. Targeting CAFs and MDSCs to modulate the TME is a promising strategy to enhance anti-tumor

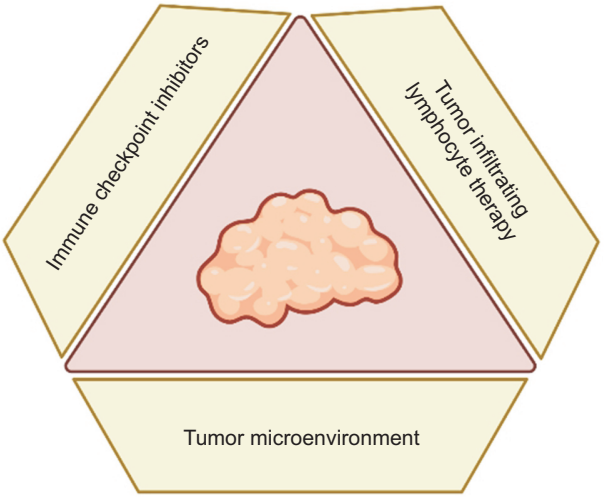


**Figure 2. Treatment approaches for drug-resistant melanoma.** Treatments for drug-resistant melanoma include targeting immune checkpoint and the tumor microenvironment, and the latest research mentions tumor-infiltrating lymphocyte therapy.

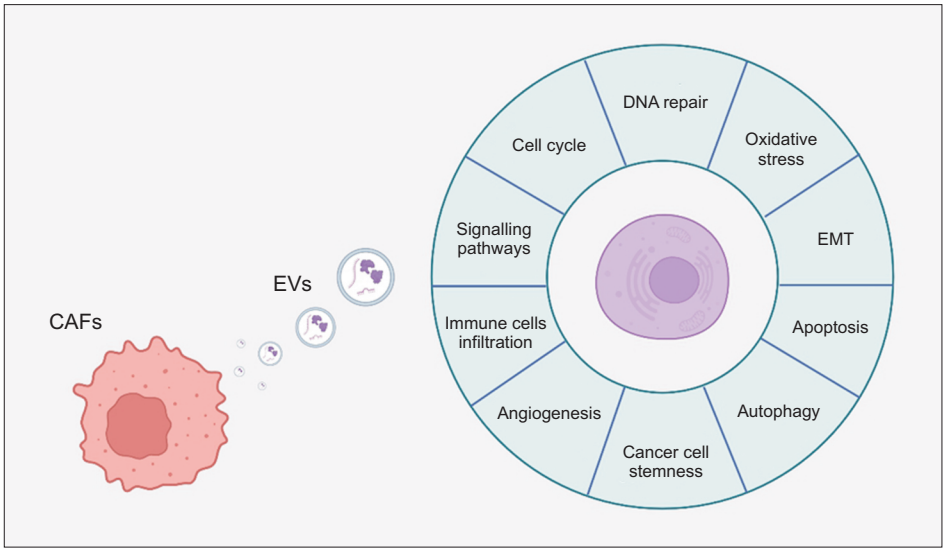


**Figure 3. Role of CAF-derived EVs in cancer chemoresistance.** Exosomes derived from CAFs can transport a variety of biomolecules, including microRNAs, long non-coding RNAs, circular RNAs, and proteins. These exosomal components contribute to the development of chemotherapy resistance in cancer by modulating multiple cellular processes, such as cell cycle progression, DNA repair mechanisms, oxidative stress response, EMT, apoptosis, autophagy, stemness of cancer cells, angiogenesis, immune cell infiltration, and the regulation of diverse signaling pathways. CAF, cancer-associated fibroblast; EV, extracellular vesicles; EMT, epithelial-mesenchymal transition.

immunity and overcome resistance. Recent studies have focused on disrupting the interactions between these cells and tumor cells to improve therapeutic efficacy. For instance, research has explored targeting CAF-derived exosomes and MDSC-mediated immune suppression to enhance the effectiveness of cancer treatments [35]. These approaches represent multifaceted efforts to combat drug-resistant melanoma, aiming to improve patient outcomes through personalized and combination therapies.

## CONCLUSION

In conclusion, we have summarized and discussed the recent research and therapeutic developments for drug-resistant melanoma over the past decade. We have further highlighted studies focused on the mechanisms of resistance, which provide direction for future treatments of drug-resistant melanoma and hold clinical significance. Additionally, we explored the latest treatment strategies for drug-resistant melanoma, with combination immunotherapy and adoptive cell therapy emerging as the two most effective approaches to date. Their development requires ongoing attention. Overall, this review offers new insights into the treatment of drug-resistant melanoma and contributes to the advancement of therapeutic strategies.

## FUNDING

None.

## CONFLICTS OF INTEREST

No potential conflicts of interest were disclosed.

## ORCID

Ke Huang, https://orcid.org/0000-0001-7421-662X
Myoung Ok Kim, https://orcid.org/0000-0001-6650-7734

## REFERENCES

1. Picardo M, Slominski AT. Melanin pigmentation and melanoma. Exp Dermatol 2017;26:555-6.
2. Bertolotto C. Cutaneous and uveal melanoma: two different cancers in therapeutic needs. C R Biol 2021;344:219-31.
3. Liu Y, Sheikh MS. Melanoma: molecular pathogenesis and therapeutic management. Mol Cell Pharmacol 2014;6:228.
4. Sandru A, Voinea S, Panaitescu E, Blidaru A. Survival rates of patients with metastatic malignant melanoma. J Med Life 2014;7:572-6.
5. Markovic SN, Erickson LA, Rao RD, Weenig RH, Pockaj BA, Bardia A, et al. Malignant melanoma in the 21st century, part 2: staging, prognosis, and treatment. Mayo Clin Proc 2007;82:490-513.
6. Rashid S, Shaughnessy M, Tsao H. Melanoma classification and management in the era of molecular medicine. Dermatol Clin 2023;41:49-63.
7. Tuli HS, Sak K, Iqubal A, Choudhary R, Adhikary S, Kaur G, et al. Recent advances in immunotherapy for the treatment of malignant melanoma. Curr Pharm Des 2022;28:2363-74.
8. Ascierto PA, Kirkwood JM, Grob JJ, Simeone E, Grimaldi AM, Maio M, et al. The role of BRAF V600 mutation in melanoma. J Transl Med 2012;10:85.
9. Thomas NE. BRAF somatic mutations in malignant melanoma and melanocytic naevi. Melanoma Res 2006;16:97-103.
10. Oikonomou E, Koustas E, Goulielmaki M, Pintzas A. BRAF vs RAS oncogenes: are mutations of the same pathway equal? Differential signalling and therapeutic implications. Oncotarget 2014;5:11752-77.
11. Kim G, McKee AE, Ning YM, Hazarika M, Theoret M, Johnson JR, et al. FDA approval summary: vemurafenib for treatment of unresectable or metastatic melanoma with the BRAFV600E mutation. Clin Cancer Res 2014;20:4994-5000.
12. Garbe C, Eigentler TK. Vemurafenib. Recent Results Cancer Res 2018;211:77-89.
13. Hauschild A, Grob JJ, Demidov LV, Jouary T, Gutzmer R, Millward M, et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. Lancet 2012;380:358-65.
14. Welsh SJ, Rizos H, Scolyer RA, Long GV. Resistance to combination BRAF and MEK inhibition in metastatic melanoma: where to next? Eur J Cancer 2016;62:76-85.
15. Robert C, Karaszewska B, Schachter J, Rutkowski P, Mackiewicz A, Stroiakovski D, et al. Improved overall survival in melanoma with combined dabrafenib and trametinib. N Engl J Med 2015;372:30-9.
16. Rahman MA, Salajegheh A, Smith RA, Lam AK. BRAF inhibitor therapy for melanoma, thyroid and colorectal cancers: development of resistance and future prospects. Curr Cancer Drug Targets 2014;14:128-43.
17. Dias-Santagata D, Su Y, Hoang MP. Immunohistochemical detection of NRASQ61R mutation in diverse tumor types. Am J Clin Pathol 2016;145:29-34.
18. Irvine M, Stewart A, Pedersen B, Boyd S, Kefford R, Rizos H. Oncogenic PI3K/AKT promotes the step-wise evolution of combination BRAF/MEK inhibitor resistance in melanoma. Oncogenesis 2018;7:72.
19. Muccioli S, Brillo V, Varanita T, Rossin F, Zaltron E, Velle A, et al. Transglutaminase type 2-MITF axis regulates phenotype switching in skin cutaneous melanoma. Cell Death Dis 2023;14:704.
20. Rambow F, Rogiers A, Marin-Bejar O, Aibar S, Femel J, Dewaele M, et al. Toward minimal residual disease-directed therapy in melanoma. Cell 2018;174:843-55.e19.
21. Verfaillie A, Imrichova H, Atak ZK, Dewaele M, Rambow F, Hulselmans G, et al. Decoding the regulatory landscape of melanoma reveals TEADS as regulators of the invasive cell state. Nat Commun 2015;6:6683.

22. Engle K, Kumar G. Cancer multidrug-resistance reversal by ABCB1 inhibition: a recent update. Eur J Med Chem 2022;239:114542.
23. Das CK, Mandal M, Kögel D. Pro-survival autophagy and cancer cell resistance to therapy. Cancer Metastasis Rev 2018;37:749-66.
24. Wei J, Wang X, Yu D, Tu Y, Yu Y. MicroRNA-mediated autophagy and drug resistance in cancer: mechanisms and therapeutic strategies. Discov Oncol 2024;15:662.
25. Ma XH, Piao SF, Dey S, McAfee Q, Karakousis G, Villanueva J, et al. Targeting ER stress-induced autophagy overcomes BRAF inhibitor resistance in melanoma. J Clin Invest 2014;124:1406-17.
26. Wu K, Yi M, Qin S, Chu Q, Zheng X, Wu K. The efficacy and safety of combination of PD-1 and CTLA-4 inhibitors: a meta-analysis. Exp Hematol Oncol 2019;8:26.
27. Boutros C, Tarhini A, Routier E, Lambotte O, Ladurie FL, Carbonnel F, et al. Safety profiles of anti-CTLA-4 and anti-PD-1 antibodies alone and in combination. Nat Rev Clin Oncol 2016;13:473-86.
28. Sarnaik AA, Hamid O, Khushalani NI, Lewis KD, Medina T, Kluger HM, et al. Lifileucel, a tumor-infiltrating lymphocyte therapy, in metastatic melanoma. J Clin Oncol 2021;39:2656-66.
29. Keam SJ. Lifileucel: first approval. Mol Diagn Ther 2024;28:339-44.
30. Parums DV. Editorial: first regulatory approval for adoptive cell therapy with autologous tumor-infiltrating lymphocytes (TILs): lifileucel (Amtagvi). Med Sci Monit 2024;30:e944927.
31. Klobuch S, Seijkens TTP, Schumacher TN, Haanen JBAG. Tumour-infiltrating lymphocyte therapy for patients with advanced-stage melanoma. Nat Rev Clin Oncol 2024;21:173-84.
32. Liu Y, Zhang X, Wang G, Cui X. Triple combination therapy with PD-1/PD-L1, BRAF, and MEK inhibitor for stage III-IV melanoma: a systematic review and meta-analysis. Front Oncol 2021;11:693655.
33. Louault K, Porras T, Lee MH, Muthugounder S, Kennedy RJ, Blavier L, et al. Fibroblasts and macrophages cooperate to create a pro-tumorigenic and immune resistant environment via activation of TGF-β/IL-6 pathway in neuroblastoma. Oncoimmunology 2022;11:2146860.
34. Kumagai S, Itahashi K, Nishikawa H. Regulatory T cell-mediated immunosuppression orchestrated by cancer: towards an immuno-genomic paradigm for precision medicine. Nat Rev Clin Oncol 2024;21:337-53.
35. Lin Z, Li G, Jiang K, Li Z, Liu T. Cancer therapy resistance mediated by cancer-associated fibroblast-derived extracellular vesicles: biological mechanisms to clinical significance and implications. Mol Cancer 2024;23:191.