RESEARCH PAPER

The Role of KIT Mutations in Oral Melanoma and Disease Progression: A Literature Review on Early Detection and Targeted Therapy

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ABSTRACT

Purpose: Oral melanoma is a rare and aggressive malignancy often diagnosed late, leading to poor clinical outcomes. This review aims to highlight the significance of KIT gene mutations in oral melanoma, emphasizing their role in tumor progression and their potential as actionable targets for precision therapy.

Methods: Recent literature on molecular profiling, KIT-related oncogenic pathways and targeted treatment strategies for oral melanoma was examined. Evidence from studies utilizing detection techniques such as tissue biopsy, next-generation sequencing (NGS), RT-PCR and immunohistochemistry (IHC) was analyzed to assess current diagnostic and therapeutic approaches.

Results: KIT mutations were found to contribute to enhanced tumor proliferation, survival, and resistance to conventional therapies. Advanced molecular diagnostic methods provide comprehensive genomic insights, enabling identification of targetable alterations. Targeted therapies including small-molecule inhibitors such as imatinib and sunitinib and emerging combination regimens with immune checkpoint inhibitors shows promising clinical responses in selected patients, although resistance mechanisms limit long term effectiveness. The rarity of oral melanoma continues to restrict large scale clinical trials and robust evidence generation.

Conclusion: KIT mutations play a critical role in the biology and clinical behavior of oral melanoma. Incorporating advanced molecular diagnostics enables accurate detection of these mutations and supports the development of personalized therapeutic strategies. Continued research into resistance mechanisms and combination treatment approaches is essential to improve outcomes for patients with this rare malignancy.

Keywords: Oral melanoma · KIT mutations · NGS · RT-PCR · immune checkpoint inhibitors · MAPK-PI3K Pathway.

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Introduction

Cancer is caused by abnormal and uncontrolled cell growth [1]. Melanoma is a kind of cancerous growth that arises from the melanocytes in the epidermis and is typically detected on the skin [2]. Oral melanoma represents 0.5% of all oral malignancies, according to worldwide reports and is caused by the accumulation of both genetic and epigenetic alterations [3]. Oral melanoma is highly aggressive form of cancer that originates from melanocytes that is the pigment-producing cells in the mucous membranes of the mouth [4]. It accounts for less than 1% of all

melanomas yet it carries a significantly worse prognosis than its cutaneous counterpart [5]. Leukoplakia patches are the frequent symptoms that develop in oral melanomas. Stress and socio-economic factors increase the risk of developing leukoplakia, while acute infections in the oral cavity increase the risk of oral melanoma [6]. Oral melanoma mainly appears on the palate or the gingiva and is often detected only after it has metastasized [7]. This is largely due to the asymptomatic nature of the disease in its early stages and the delayed diagnosis often associated with its non-specific presentation [8]. Clinically, the disease may present as a pigmented, irregular lesion or non-pigmented amelanotic variants which can cause difficulties in diagnosis. Symptoms are often nonspecific like bleeding, pain or tooth mobility that generally appears only after the disease has advanced [9]. Despite undergoing surgical resection and chemoradiotherapy, 50% of patients experience loco-regional recurrence and distant metastasis within 24 months. Treatment primarily involves wide surgical excision with clear margins, while adjuvant therapies such as immunotherapy, radiation are considered depending on the stage and spread of the disease [10].

The oncogene c-KIT codes for KIT a transmembrane tyrosine kinase receptor found in hematopoietic cells, mast cells, germ cells and melanocytes. Mutations in KIT can lead to its continuous activation, driving uncontrolled cellular proliferation and tumor development [11]. Activation of KIT signaling through mutations, amplifications or overexpression can lead to uncontrolled cellular growth and oncogenic transformation [12]. Cutaneous melanomas contains mutations in BRAF or NRAS, mucosal and acral melanomas that exhibit activating KIT mutations particularly within exons 9, 11, 13, 17 and 18 [13]. Genetic changes are connected to the tumor's aggressiveness, its ability to spread and its response to certain tyrosine kinase inhibitors. Clinical studies have explored the efficacy of TKIs such as imatinib, nilotinib and dasatinib in KIT mutant melanomas revealing variable but promising outcomes depending on mutation subtype and tumor burden [14]. Integration of molecular profiling into diagnostic workflows supports early detection of actionable mutations, improving prognostic assessment and therapeutics [15]. This article explores the role of KIT in oral melanoma, influenced signaling pathways and the therapeutic strategies targeting KIT mutations, while addressing the challenges and future directions in managing this aggressive cancer.

Role of kit in oral melanoma

Oral Melanoma studies have increasingly focused on mutations like KIT, BRAF, NRAS, and other genes KIT gene plays a crucial role in several cancer types by driving abnormal cell growth through dysregulated signaling pathways [16]. KIT is a proto-oncogene that encodes a receptor tyrosine kinase, which plays a key role in regulating cell growth, differentiation, and survival [17]. Mutations in KIT gene can activate receptor, causing abnormal cellular proliferation and tumor development [18]. KIT mutations are particularly common in certain subtypes of melanoma, including mucosal, acral, and chronic sun-damaged (CSD) melanomas and oral melanoma [19].

KIT receptor signaling

KIT is a receptor tyrosine kinase (RTK) which remains continuously active when mutated, triggering the downstream activation of multiple signalling pathways [20]. In oral melanoma PI3K pathway activation is more often associated with mutations in RICTOR, KIT and NF1. KIT plays a significant role in controlling several downstream oncogenic signaling pathways within both the MAPK and PI3K pathways as mentioned in Fig. 1. When the ligand SCF attaches to the KIT receptor, MAPK cascade is triggered which attracts GRB2 and SOS. Along with this it also activates Ras by the exchange of GDP for GTP. Then activated Ras triggers Raf , a serine/threonine kinase, which activates MEK and ERK. This gene expression results in cell division, proliferation, and survival. Finally, ERK penetrates the nucleus. PI3K is activated when KIT is activated. PIP2 is changed into PIP3 by PI3K, which then attracts and activates Akt. Akt then triggers mTOR, a key regulator that promotes cell growth, metabolism and prevents cell death. Both of these pathways play a major role in cancer and when KIT signaling is disrupted, it can lead to abnormal cell growth and tumor development [19-20]

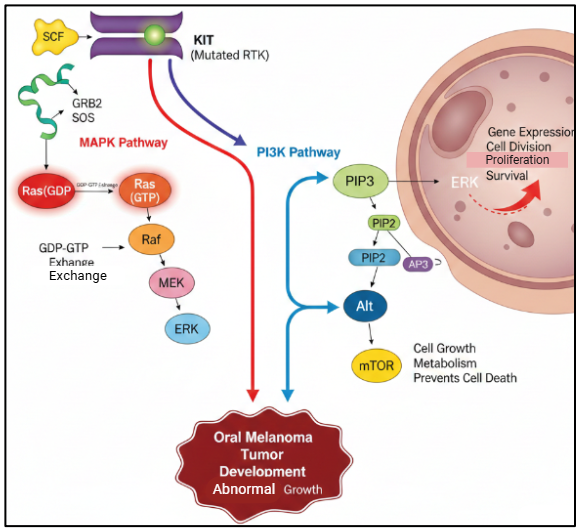


Fig. 1. KIT receptor signaling: MAPK pathway is activated when the ligand SCF binds to the KIT receptor. PI3K pathway: KIT activation leads to the activation of PI3K.

Detection of kit mutations real time polymerase chain reaction (RT-PCR)

RT-PCR is sensitive and specific method used to detect specific KIT mutations at the molecular level. This method starts with isolating RNA from the tumor biopsy sample. The isolated RNA is then converted into complementary DNA (cDNA) through a process called reverse transcription. Once the cDNA is synthesized, PCR amplification is used to target and amplify specific regions of the KIT gene where mutations are likely to occur [21]. RT-PCR allows for rapid detection of specific mutations by amplifying only the regions of interest, making it highly efficient and faster than sequencing methods like NGS. While RT-PCR is highly sensitive for detecting known mutations [22]. RT-PCR is particularly useful for detecting hotspot mutations in the KIT gene, such as those found in exon 11 and exon 17, which are common in certain cancers, including oral melanomas [23]. This method plays a crucial role in clinical decision-making, as the detection of specific KIT mutations can guide the use of targeted therapies such as imatinib, which specifically inhibits mutated KIT proteins [24].

Tissue biopsy and next-generation sequencing (NGS)

Tissue biopsy is the foundational step in detecting KIT mutations. It involves extracting a small sample of tissue from the tumor for genetic analysis. This sample can be obtained using various techniques, such as fine-needle aspiration, core needle biopsy, or excisional biopsy, depending on the tumor's location and size [25]. Next-Generation Sequencing (NGS) is employed for comprehensive genomic profiling. NGS is a highly advanced, high-throughput technology that can sequence large amounts of DNA and RNA quickly and efficiently [26]. For KIT mutation detection, NGS targets specific regions of the genome, focusing on the KIT gene [27]. NGS works by fragmenting the DNA extracted from the tumor tissue and attaching adapters to the fragments. These fragments are then amplified and sequenced to identify mutations at a nucleotide level [28]. NGS allows complete identification of KIT mutations as well as other mutations in genes relevant to cancer progression and treatment response. This comprehensive approach enables personalized treatment plans, especially for oral melanomas where KIT mutations are common drivers of cancer. NGS data can reveal single nucleotide variants (SNVs), insertions, deletions, and other structural variations in the KIT gene [29] The summary of process in given in Fig. 2.

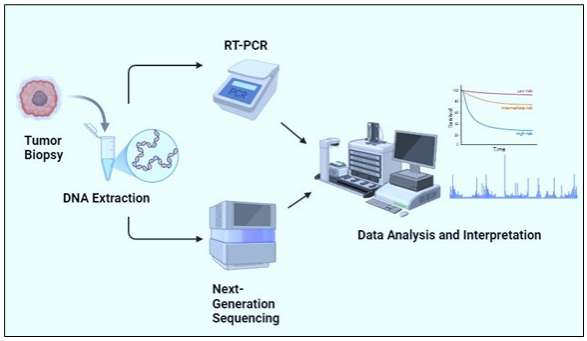


Fig. 2. Sample collection, DNA extraction, early detection of genetic mutation KIT in oral melanoma through real-time PCR .

Precision therapy targeting kit mutations

Oral melanomas show higher prevalence of KIT mutations compared to skin melanomas. This mutation is a promising target for therapies like tyrosine kinase inhibitors. KIT mutations have been identified in 10% to 21% of mucosal melanomas with an overall KIT alteration frequency ranging from 19% to 39%. The L576P mutation is the most prevalent, while KIT amplification occurs in 10% to 26% of cases in Fig. 3. Tumors carrying KIT L576P and K642E mutations can be treated with KIT inhibitors [30].

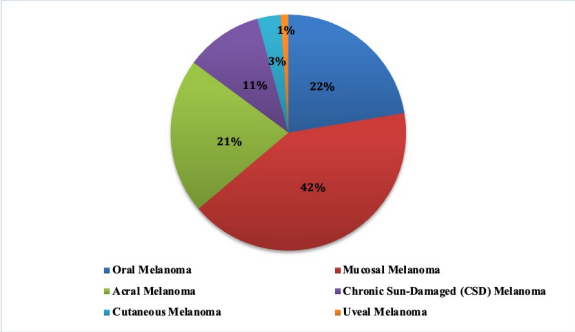


Fig. 3. Distribution of KIT mutation across melanoma subtypes.

Small molecule inhibitors

Oral melanoma contains alterations in KIT, NRAS and NF1 gene which leads to the activation of signaling pathways such as the mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K) [31]. These molecular differences have driven the development of small molecule inhibitors as a targeted therapeutic approach for oral melanoma. Small molecule inhibitors work by inhibiting proteins and kinases that drive tumor progression. KIT mutations, which are present in mucosal melanomas that makes tyrosine kinase inhibitors (TKIs) like imatinib, dasatinib and nilotinib as promising treatment options [32]. These inhibitors block the activation of KIT and interfere with downstream signaling pathways that promote survival and proliferation. MEK inhibitors and PI3K/AKT inhibitors are being explored to target alternative pathways in cases where KIT mutations are absent or resistant [33]. Advantages of small molecule inhibitors is their oral bioavailability, allowing for easier administration compared to traditional chemotherapy or immunotherapy. Also they offer a more targeted approach, reducing systemic toxicity and improving treatment outcomes. Some KIT Mutations in melanoma subtypes and their corresponding targeted inhibitors are mentioned in Table 1. However, drug resistance and tumor heterogeneity remain significant challenges, necessitating combination therapies or next-generation inhibitors. As research progresses, personalized medicine approaches integrating molecular profiling will help identify the most effective small molecule inhibitors, paving the way for more precise and individualized treatment strategies.

Table 1

KIT Mutations in Melanoma Subtypes and Corresponding Targeted Inhibitors.

Melanoma Subtype	Prevalence of KIT Mutations	Common KIT Mutations	Clinical Implications	Approved KIT-Targeting Inhibitors with Year of Approval
Oral Melanoma	10%–21%	L576P, K642E, V559A	Associated with aggressive behavior and poor prognosis. Targeted therapies-imatinib [34].	Imatinib-2001, Sunitinib-2005, Dasatinib-2006, Regorafenib-2012, Avapritinib-2019, Ripretinib-2019.
Mucosal Melanoma	19%–39%	L576P, K642E, V559A	Higher prevalence of KIT mutations compared to cutaneous melanoma, are resistant to conventional therapies [35].	Imatinib-2001, Sunitinib-2005, Dasatinib-2006, Regorafenib-2012, Avapritinib-2019, Ripretinib-2019.
Acral Melanoma	10%–20%	L576P, K642E, V559A	KIT mutations are common in acral melanoma	Imatinib-2001, Sunitinib-2005, Dasatinib-2006,

			, which occurs on palms, soles, and nail beds [36].	Regorafenib-2012, Avapritinib-2019, Ripretinib-2019.
Chronic Sun-Damaged (CSD) Melanoma	5%–10%	L576P, K642E	Lower prevalence of KIT mutations compared to mucosal and acral melanoma [37].	Imatinib-2001, Sunitinib-2005, Dasatinib-2006, Regorafenib - 2012.
Cutaneous Melanoma	1%–3%	Rare	KIT mutations are rare in cutaneous melanoma, commonly driven by BRAF Mutations [38].	Imatinib-2001, Sunitinib-2005.
Uveal Melanoma	<1%	Rare	KIT mutations are extremely rare in uveal melanoma, which is driven by GNAQ/GNA11 Mutations [39].	Imatinib-2001, Sunitinib-2005.

Combination therapies to overcome resistance in kit-mutated melanoma

Oral melanomas exhibit lower immunogenicity and are frequently driven by genetic mutations such as KIT, NRAS, and BRAF. KIT mutations play a pivotal role in tumor growth and progression. Given the limited efficacy of monotherapy approaches, combination therapies involving immune checkpoint inhibitors (ICIs) and other agents such as tyrosine kinase inhibitors (TKIs), chemotherapy, and radiotherapy have been explored to improve patient outcomes.

Combination therapy strategies

In the treatment of KIT-mutated melanoma, several combination therapy strategies have been developed to overcome resistance and improve clinical outcomes. Like KIT inhibitor with a MEK inhibitor, such as imatinib and trametinib. This approach is based on KIT mutations activate the MAPK pathway, so dual inhibition of both KIT and MEK can more effectively suppress tumor growth and delay resistance [40]. Another promising combination is a KIT inhibitor with a PI3K/AKT/mTOR pathway inhibitor, like nilotinib and buparlisib, which targets a parallel survival pathway that cancer cells may exploit when KIT signaling is blocked [41]. By shutting down both pathways simultaneously, this strategy makes it more difficult for melanoma cells to develop escape mechanisms. Finally combination of KIT inhibitors with immune checkpoint inhibitors, such as dasatinib and anti-PD-1 agents nivolumab. KIT inhibition enhance tumor antigen presentation and increase immune cell infiltration, thereby sensitizing the tumor to immunotherapy and enhancing immune-mediated killing [42]. Combining a KIT inhibitor with a CDK4/6 inhibitor, like imatinib and palbociclib, targets both oncogenic signaling and cell cycle regulation. Many KIT-mutated melanomas exhibit dysregulated cell cycle machinery; this combination effectively blocks proliferative signals at multiple levels [43]. Together, these combination strategies aim to tackle both the direct drivers of melanoma and the adaptive mechanisms that lead to treatment resistance explained in Table 2.

Table 2

Integrated Combination Approaches: Rationale, Mechanisms, Drug Choices, and Therapeutic Benefits.

No.	Combination	Rationale	Example	Mechanism	Benefit

			Drugs		
1	KIT Inhibitor + MEK Inhibitor	KIT mutations activate the MAPK pathway; dual inhibition improves effectiveness [44].	Imatinib (KIT) +Trametinib (MEK)	Blocks both KIT and MAPK signaling to reduce proliferation and survival	Delays resistance and enhances tumor regression
2	KIT Inhibitor + PI3K/AKT/mTOR Inhibitor	Activation of PI3K/AKT is a common escape route from KIT Inhibition [45].	Nilotinib (KIT) + Buparlisib (PI3K)	Targets parallel survival pathways, making resistance more difficult	Increases durability of response
3	KIT Inhibitor + Immune Checkpoint Inhibitor	KIT-mutated melanomas are poorly immunogenic; KIT inhibition may boost immune response [46].	Dasatinib (KIT) + Nivolumab (PD-1)	KIT inhibition modifies tumor microenvironment, PD-1 blockade activates T cells	Enhances immune-mediated tumor destruction
4	KIT Inhibitor + CDK4/6 Inhibitor	Cell cycle dysregulation is common in KIT-mutant Melanoma [47].	Imatinib (KIT) + Palbociclib (CDK 4/6)	Blocks proliferative signals and arrests cell cycle progression	Synergistic suppression of tumor growth

Dual pathway inhibition (KIT + MEK) and (KIT + PI3K/AKT)

KIT is a receptor tyrosine kinase whose activating mutations result in the constitutive stimulation of downstream signaling pathways, including the MAPK cascade. Inhibiting KIT alone using tyrosine kinase inhibitors like imatinib or dasatinib can suppress this pathway initially [48]. MEK inhibitors such as trametinib are combined with KIT inhibitors to block both the initiating receptor and the downstream effector node. Preclinical models explains the dual inhibition that not only reduces proliferation but also induces apoptosis in KIT melanoma cells [49]. MEK inhibitors can suppress tumorigenic signals arising from secondary mutations in NRAS or BRAF that co-exist in some KIT-mutant tumors. The use of imatinib and trametinib has shown enhanced antitumor activity in KIT-mutant gastrointestinal stromal tumors, providing a mechanistic rationale for similar application in melanoma. Dual inhibition allows dose reduction of each agent, potentially mitigating toxicity while preserving efficacy [50].

PI3K/AKT pathway serves as a critical regulator of cell survival, metabolism, and resistance to apoptosis. It is often co-activated in KIT-mutant tumors, either through intrinsic cross-talk between pathways or via additional mutations in components such as PIK3CA loss. Inhibiting KIT alone may not fully suppress tumor growth due to redundant survival signals mediated by PI3K/AKT [51]. Dual inhibition using

TKIs along with PI3K or AKT inhibitors has synergistic effects, reducing tumor cell proliferation and increasing apoptosis. Combining dasatinib with PI3K inhibitors like buparlisib or alpelisib show enhanced antitumor activity in melanoma xenograft models. This strategy disrupts multiple nodes in survival signaling, thereby preventing the tumor from adapting and continuing growth despite targeted pressure [52]. It is particularly relevant for patients whose tumors do not respond to MEK inhibition or have molecular features indicative of PI3K/AKT pathway activation. Early-phase clinical trials are currently evaluating these combinations across solid tumors, including melanoma. Some of these therapies are being tested in combination with mTOR inhibitors like everolimus to further disrupt downstream signaling. Thus, the combined inhibition of KIT and PI3K/AKT signaling represents a rational and increasingly viable approach for managing melanomas with complex survival signaling.

Combining kit inhibition with immunomodulation (KIT + ICIs)

Combining KIT inhibition with immunomodulatory therapies particularly immune checkpoint inhibitors (ICIs) is a novel and synergistic strategy in the treatment of KIT mutant melanoma including the aggressive mucosal and oral subtypes [53]. While KIT-targeted tyrosine kinase inhibitors (TKIs) such as imatinib, dasatinib, and nilotinib can directly block tumor proliferation by inhibiting the oncogenic signaling cascades downstream of mutant KIT. Integrating ICIs with TKIs offers the potential to overcome these limitations by reactivating the immune system to sustain tumor control [54]. Immune checkpoint inhibitors, including anti-PD-1 as nivolumab, pembrolizumab and anti-CTLA-4 as ipilimumab antibodies have revolutionized melanoma therapy by inhbiting T cells, allowing them to recognize and destroy tumor cells. In mucosal melanomas including oral melanoma response rates to ICIs alone are lower than in cutaneous subtypes possibly due to lower tumor mutational burden and fewer neoantigens [55]. Combining ICIs with TKIs provides a two-pronged approach direct inhibition of tumor cell growth through KIT blockade and activation of anti-tumor immunity through checkpoint inhibition as shown in Fig. 4.

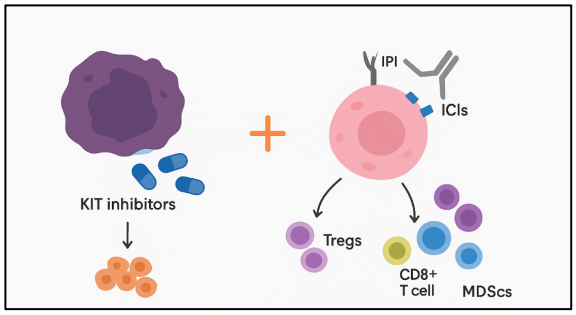


Fig. 4. KIT inhibitors suppress tumor growth and reduce immunosuppressive cells, while ICIs restore T cell activity, together enhancing durable anti-tumor immunity.

KIT inhibitors can modulate the tumor microenvironment in ways that enhance immunotherapy efficacy. Imatinib has been shown to reduce immunosuppressive cells such as myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs) while increasing the infiltration of cytotoxic CD8+ T cells [56]. TKI treatment may upregulate antigen presentation machinery and PD-L1 expression on tumor cells, thereby making them more susceptible to immune-mediated clearance when combined with ICIs. TKIs can sensitize tumors to immunotherapy by inducing immunogenic cell death and promoting T cell infiltration [57]. Early-phase clinical trials have begun exploring these combinations in KIT-mutant tumors. Combination of nilotinib with nivolumab has shown early signs of activity in mucosal melanoma with manageable toxicity profiles. Also, immunological biomarkers such as PD-L1 expression, T cell infiltration or KIT mutation subtype as L576P, K642E help stratify patients and guide treatment choices [58]. This combination emerges as important precision in oncology for KIT-driven melanomas, offering hope for longer-lasting and more novel clinical responses.

ICIs with TKIs, chemotherapy and radiotherapy

KIT mutations are key drivers in oral melanoma, TKIs such as imatinib, dasatinib, and nilotinib have been used as targeted therapies. However, resistance frequently develops due to secondary mutations or compensatory pathways. Combining TKIs with ICIs like nivolumab (anti-PD-1) or ipilimumab (anti-CTLA-4) may enhance therapeutic efficacy by increasing T-cell infiltration and reducing immunosuppressive cells in the tumor microenvironment (TME). TKIs can modulate immune activity by reducing regulatory T cells

(Tregs) and myeloid-derived suppressor cells (MDSCs), making tumors more responsive to immune attack [59]. Recent studies have indicated that combining imatinib with pembrolizumab or nivolumab can lead to improved response rates in KIT-mutant melanomas, including mucosal subtypes. While clinical evidence in oral melanoma specifically is limited, ongoing trials in other KIT-driven melanomas suggest that this combination could be a viable strategy for oral melanoma as well.

Oral melanomas often exhibit poor responses to ICIs alone due to their immunosuppressive TME and low TMB. Chemotherapy can enhance ICI efficacy by inducing immunogenic cell death, increasing tumor antigen presentation and making the tumor more susceptible to immune attack [60]. Platinum-based agents such as cisplatin and dacarbazine have been investigated in combination with pembrolizumab or nivolumab, showing improved survival rates in some mucosal melanomas [61]. Radiotherapy has been explored as a synergistic approach with ICIs in KIT-mutant oral melanomas. Radiation therapy increases PD-L1 expression, stimulates antigen release and enhances immune recognition by shifting the tumor from an immune-resistant state to an immune-responsive one, making it more susceptible to ICIs [62] as mentioned in Fig. 5. Systemic immune response effect where localized radiation triggers a systemic anti-tumor immune response has been observed in patients treated with radiation alongside nivolumab or pembrolizumab. Here we can conclude that monotherapies show limited efficacy in KIT-mutant oral melanomas where it supports a multi-modal approach like integrating TKIs, ICIs, chemotherapy, and radiotherapy as a promising strategy to overcome resistance mechanisms. Ongoing research are essential to validate these combinations and improve clinical outcomes .

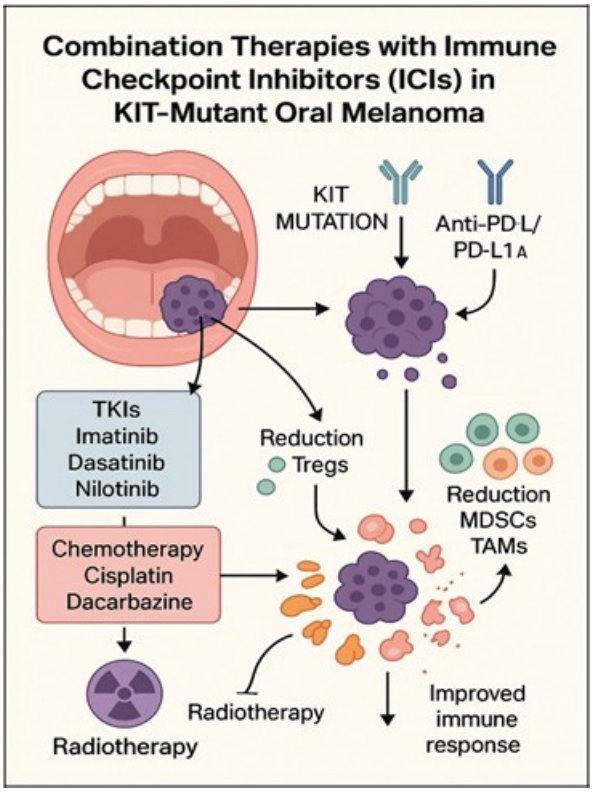


Fig. 5. Integrating ICIs with Tyrosine Kinase Inhibitors, Chemotherapy, and Radiotherapy: Combination Therapy Strategies

Challenges and future directions

Despite the advancements in genomic profiling and targeted therapy, there are several limitations regarding the effectiveness of KIT mutation detection and treatment in oral melanoma. This rare form of melanoma presents unique obstacles in clinical research, treatment resistance, and the applicability of mutation detection techniques. Addressing these issues will be crucial for improving outcomes for patients with this aggressive cancer.

Rarity and resistance mechanisms of oral melanoma

Oral melanoma is a rare and aggressive cancer, accounting for a small percentage of all melanomas. Its rarity poses a significant challenge to conducting large-scale clinical trials or accumulating comprehensive data on KIT mutation prevalence. Due to the limited number of cases, it is difficult to gather a sufficient sample size to conduct statistically studies, making it challenging to establish standardized treatment protocols. While targeted therapies, such as small molecule inhibitors that block the KIT signaling pathway, offer a promising

approach for treating KIT-mutated oral melanoma, resistance to these therapies remains a significant challenge. Cancer cells can adapt to the inhibition of KIT by activating alternative pathways that allow them to bypass the therapeutic blockade, leading to disease progression. Resistance can arise from secondary mutations in the KIT gene itself or through compensatory activation of parallel signaling pathways, such as the MAPK or PI3K/AKT pathways. On identifying the specific resistance mechanisms in oral melanoma and developing combination therapies, target multiple pathways reduces the chances of tumor escape and resistance.

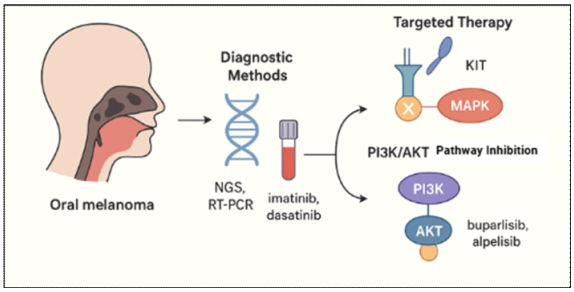
Limitations of mutation detection techniques and future perspectives

Next-generation sequencing (NGS) and real-time PCR (RT-PCR) are highly specific and can only detect the mutations they are designed to amplify or sequence. As a result, they may miss rare or previously unknown mutations that could be driving tumor growth. This limitation restricts the comprehensiveness of mutation detection, especially in cancers like oral melanoma, which may harbor a diverse range of genetic alterations. To overcome this challenge, there is a need for more comprehensive and flexible genomic profiling technologies capable of detecting a broader spectrum of mutations. Advances in whole genome sequencing and whole exome sequencing could provide a more complete picture of the genetic landscape in oral melanoma allowing for the identification of novel mutations and the development of more personalized treatment approaches. Despite promising results, several challenges remain in optimizing combination therapies for KIT-mutant oral melanoma. Resistance to TKIs, immune-related toxicities, and the need for biomarkers to predict response to ICIs are areas of active research. Future strategies may include dual checkpoint blockade like anti-PD-1 + anti-LAG-3 or novel immune-modulating agents to further enhance the anti-tumor response. Increased collaboration through multicentre trials will be essential for gathering the data needed to refine treatment strategies and identify new therapeutic targets. Also improving mutation detection methods will allow for a more comprehensive understanding of the genetic drivers of oral melanoma, enabling more personalized and effective treatments.

Conclusion

Oral melanoma is rare and have significant therapeutic challenges due to its aggressive nature and limited treatment options. The identification of KIT mutations in a substantial subset of cases 10–39% has opened new opportunities for precision therapy with tyrosine kinase inhibitors like imatinib and nilotinib explaining clinical responses. The combination strategies integrating TKIs with immune checkpoint have emerged as promising approach. These combinations leverage the dual benefit of direct KIT pathway inhibition and enhanced immune mediated tumor killing with early trials reporting improved response compared to monotherapy. Patient selection must be refined through comprehensive molecular profiling as next generation sequencing helps to identify predictive biomarkers of response. Next-generation TKIs and novel combinations are under investigation to overcome resistance. The rarity of oral melanoma underscores the need for multicenter collaborations to accelerate clinical trial and validate these strategies. By targeting oncogenic drivers while harnessing the immune system this approach offers the potential for deeper and durable responses. Future research should focus on optimizing treatment sequences, minimizing toxicity and elucidating resistance mechanisms to unlock the full potential of these therapies. For patients with oral melanoma, these advanced treatments provide a hope for improved outcomes and long-term survival.

Graphical Abstract



Author contribution Smitha Nair conducted all writing, review, Formal analysis, Data curation, Conceptualization, Dhanraj Ganapathy conducted editing, Validation, Pitchiah Sivaperumal did Supervision, Data Curation, Project Administration and Funding.

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Data availability Author confirms that all data generated or analyzed during this review are included in this published article.

Declarations

Competing interests The authors declare no competing interest.

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