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ADVANCEMENTS IN UNDERSTANDING AND MANAGING ACRAL LENTIGINOUS MELANOMA: A COMPREHENSIVE REVIEW

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ABSTRACT

Acral lentiginous melanoma (ALM) is a rare subtype of melanoma with distinct clinical, histological, and molecular characteristics. Unlike other cutaneous melanomas, ALM primarily affects non-hair-bearing skin, such as the palms, soles, and nail beds, and is not associated with sun exposure. Its unique epidemiological distribution, being more prevalent in non-White populations, underscores the need for tailored management strategies. Diagnosis of ALM requires careful clinical and histological evaluation, often necessitating specialized techniques such as dermoscopy and nail unit biopsies. Surgical excision remains the mainstay of treatment for localized disease, but challenges in achieving complete excision, especially in subungual melanomas, highlight the importance of alternative approaches. Advancements in molecular profiling have identified key genetic mutations driving ALM, paving the way for targeted therapies and immunotherapy. BRAF/MEK inhibitors have shown efficacy in BRAF-mutant melanomas, while KIT and CDK4/6 inhibitors hold promise in specific genetic subgroups. Immunotherapy, including immune checkpoint inhibitors and oncolytic viruses, offers novel treatment options, either alone or in combination with other modalities. Combination therapies, such as immunotherapy with chemotherapy or antiangiogenic agents, represent a promising approach to overcome resistance mechanisms and improve treatment outcomes in advanced ALM. Further research and clinical trials are warranted to refine treatment algorithms and optimize outcomes for patients with ALM.

KEYWORD: *Acral lentiginous melanoma, Dermoscopy, BRAF/MEK inhibitors, Immune checkpoint inhibitors.*

1. INTRODUCTION

Acral Lentiginous Melanoma (ALM) is a rare subtype of melanoma that develops on non-hair-bearing skin (palms and soles) and in the nail beds. First identified by Reed and Arrington in the 1970s, ALM constitutes about 3% of melanoma cases globally. It is known for being more aggressive and having a worse prognosis than other melanoma types, although there is debate about whether ALM is inherently more aggressive biologically. ALM is not linked to risk factors such as sun exposure, pale skin, a family history of melanoma, or pre-existing melanocytic nevi, in contrast to other kinds of cutaneous melanoma (CM). Compared to CM, ALM has a lower tumour mutational burden (TMB) and distinct oncogenic driver mutations because it is not associated with ultraviolet radiation (UVR) exposure.[1][2][3] ALM accounts for 50–58% of Asian melanomas and 60–70% of Black melanomas, making it rare among Caucasians (1–7%) but more common in non-White groups. Compared to more prevalent subtypes like superficial spreading melanoma, nodular melanoma, and lentigo maligna melanoma, advanced cutaneous melanoma (ALM) has received less attention and representation in large prospective randomised controlled trials that impact current management practices, despite having unique clinical and biological characteristics and causing a significant amount of mortality in Europe and the USA.[4]

2. Epidemiology

Acral melanoma accounts for only 2-3% of all melanomas in Western and European populations, according to several population-based epidemiological studies. On the other hand, it is more common in African, Asian, and Hispanic/Latin American groups. For example, AM accounts for more than 40% of cutaneous melanomas in nations like China, Taiwan, Korea, and Japan, and 20.1% in Latin American nations like Mexico and Peru. Furthermore, compared to those of European ancestry in Latin American nations, AM is more common in genetically heterogeneous or Amerindian-descent communities (such as indigenous Latin Americans). In South Africa, the incidence of AM is 11% in the general population and 65% in Black people.[5][6]

3. Clinical features

ALM typically appears as an asymmetric pigmented macule or papule on the non–hair-bearing skin of distal extremities, such as the soles or palms. These lesions usually have variegated pigmentation and irregular borders. The plantar region is the most common site for ALM, with frequent occurrences in the subungual area, particularly the great toe and thumb. As ALM progresses, lesions may develop into large, exophytic nodules with areas of blue-black pigmentation. Amelanotic lesions, which present as pink nodules or macules, are also common. ALM is often misdiagnosed as other conditions at first, including non-healing wounds, fungal infections, warts, pyogenic granulomas, or hematomas.

Both in situ and invasive acral lentiginous melanomas frequently exhibit irregular diffuse pigmentation with a parallel ridge pattern on dermoscopy. This can help distinguish them from acral nevi, which usually show a fibrillar, lattice-like, or parallel furrow pattern. Partial or complete nail plate melanonychia is a symptom of subungual melanoma. This is referred to as Hutchinson's sign, which is a powerful marker of ALM when combined with periungual skin pigmentation. Subungual melanomas might be confused with subungual haemorrhages because they frequently start off as pigmented streaks in the nail bed. ALM lesions, on the other hand, stay fixed, but subungual haemorrhages will shift with nail growth.[1][2][7]

4. Histological features

- Acral lentiginous melanoma (ALM) differs from other kinds of CM due to its unique histologic features. Along the epidermal-dermal junction, these include confluent epithelioid or dendritic melanocytes, which can be found singly or in nests. Additionally noted are characteristics like extension down adnexal structures and upward pagetoid migration. Atypical epithelioid cords or nests, occasionally combined with spindle cell components, are the typical appearance of dermal invasion in ALM. Like other forms of melanoma, an ulceration and a high mitotic rate are unfavourable prognostic factors.[2][7]

- The majority of tumour cells are found in early lesions as single units that subsequently form nests. Nests are typically a sign of melanocytic nevus; However, they are not a certain way to tell melanoma from melanocytic nevus. Melanocytic nevus nests are cohesive, vertically orientated, uniformly sized, and tightly bounded. ALM nests, on the other hand, are frequently non-cohesive, uneven in size, and poorly bounded, and they frequently run parallel to the epidermis.[1]

- Differentiation is further aided by nuclear size: melanocytic nevus nuclei are usually smaller than nearby keratinocytes, whereas larger nuclei in relation to keratinocytes indicate ALM. Another indicator is the nucleus's form; melanocytic nevus nuclei are typically oval and may have a horizontal arrangement, whereas ALM nuclei that exhibit a horizontal arrangement are more suggestive of melanoma.

- Diagnosing early subungual ALM can be particularly challenging. A key feature is the elevated melanocytes, with ALM often showing around 930 tumor cells in a 1-mm width of epidermis, a finding rare in benign melanocytic nevi. While cellular atypia and ascent are supportive findings for non-subungual ALM, these may not be present in early subungual ALM.[8]

5. Pathogenesis

- Characteristic tumor-promoting mutations involving many genes have been found using ALM sequencing and copy-number profiling studies. The KIT proto-oncogene (KIT), which codes for a tyrosine kinase receptor involved in cell growth and migration; cyclin D1 (CCND1) and cyclin-dependent kinase 4 (CDK4), which together help the cell cycle move from G1 to S phase; cyclin-dependent kinase inhibitor 2A (CDKN2A), which codes for proteins that stabilise TP53; telomerase (TERT), which is necessary for telomere maintenance; and aurora kinase A (AURKA), which controls mitosis, are notable examples.

- A study involving 514 ALM samples which revealed that the CDK4 pathway was frequently dysregulated as a result of either CDK4/CCND1 gains or CDKN2A loss. This promoted the G1 to S cell cycle transition and aided in the growth of tumours.[9] Additionally, investigations have demonstrated a variety of TERT abnormalities, including as promoter mutations and locus amplifications, although the precise function of telomere regulation in ALM remains unclear.[10][11]

- Evidence of DNA damage and YAP signalling pathway activation in mechanically stressed melanoma cells implanted into mouse foot pads has long supported the theory that mechanical stress plays a role in the development of AM. Large-scale genomic amplifications characteristic of AM, "Tyfonas," or "typhoons" of high-JCN junctions and fold-back inversions linked to expressed protein-coding fusion and break-end hypermutations, were not seen in our investigations, despite the emergence of novel single nucleotide variations.[12]

- ALM also exhibits chromothripsis genomic characteristics, which are defined by several chromosomal rearrangements in a single event. Genes such as MAP2K1, CDK4, CCND1, PAK1, GAB2, MDM2, and EP300 are amplified, and CDKN2A and NF1 are deleted.[13]

- In patients with Asian ALM, 14.2% of the genome contained CNVs, with frequent co-amplification of CDK4 and MDM2 and notable increases in KDR, KIT, CCND1, GAB2, PDGFRA, CDK4, YAP1, MDM2, and EP300. When SNVs and CNVs were combined, important pathways like MAPK, histone modification, and cell-cycle progression were found, and immune escape mechanisms were connected to EP300 amplification.[14]

- SKP2 and FER were shown to be oncogenes and PRPRJ to be a putative tumour suppressor gene after an examination of 11 research.[15]

- Key pathways linked to AM were identified using integrated transcriptome data, including MDM2/TP53 (17%), CDK4/CDKN2A (51%), TERT (37%), and MAPK and PI3K/AKT (66%). These pathways are common to all melanomas, suggesting that oncogenic transformation requires certain melanocyte lineages.[10]

6. Diagnosis

- **ALM screening:** Like other malignant melanomas, ALM is detected using the ABCDE rule, which stands for asymmetry, border irregularity, colour variation, diameter higher than 6 mm, and evolving size, shape, or colour. However, it can still be difficult to differentiate between benign melanocytic nevus and early malignant melanoma, particularly in the acral region where pigmentation frequently follows the palm and sole skin patterns, resulting in asymmetry and uneven borders even in benign cases. One crucial technique that improves the sensitivity of ALM diagnosis is dermoscopy.

- **Dermoscopy in ALM Diagnosis:** This procedure has greatly enhanced ALM diagnosis. According to earlier research, in the early stages of ALM, dermoscopic results can be more important than histologic findings. The parallel ridge pattern (PRP), which is pigmentation parallel to the skin ridges, is the most important dermoscopic finding for ALM.[1]

- **Biopsy for suspicious lesions:** Biopsies must be performed on any pigmented lesions on nail apparatus and the acral skin which are suspicious, particularly which do not respond properly to short treatments for suspected benign conditions.

- **Excisional biopsy challenges:** While an excisional biopsy is considered as the gold standard for diagnosing most melanocytic lesions, technical challenges often arise with acral lentiginous melanomas and the ability to fully excise the lesion is limited. The limited acral skin laxity can result in complex wounds, making complete removal difficult or impossible. Nail matrix biopsies can cause permanent nail dystrophy, so techniques like lateral longitudinal excision, 3-mm punch biopsy, or shave biopsy are commonly used depending on the lesion's size and location within the nail matrix.[2]

- **Diagnosing subungual melanoma:** Diagnosing subungual melanoma can be particularly challenging, as collecting a representative biopsy sample may be difficult. Biopsy results should always be assessed with respect to clinical presentation and biopsy location.

- **Longitudinal melanonychia evaluation:** For longitudinal melanonychia, samples should be taken from the nail matrix, marked by the presence of basaloid epithelium. Melanocytes (such as SOX10 or Melan-A) stained by Immunohistochemical helps quantify melanocytes and distinguish between nail unit melanoma and melanocytic activation. Benign processes typically show 15-31 melanocytes/mm, while nail unit melanoma generally shows more than 40 cells/mm.[16]

- **Nail clippings for initial evaluation:** Recently, nail clippings are recommended as a quick initial step in examining pigmented nail lesions, causing minimal discomfort and disfigurement. The presence of melanocyte fragments in an adult's nail plate, seen as hollow areas, may be diagnosed for an underlying melanocytic neoplasm and should prompt a follow-up biopsy of the nail bed or matrix.[17]

7. Management

Surgery

- Complete surgical excision remains the standard treatment for early-stage, localized melanoma, supported by multiple RCTs that have informed the National Comprehensive Cancer Network (NCCN) Guidelines advocating 1- to 2-cm margins based on the primary tumor's maximal depth. However, these studies predominantly involved nonacral cutaneous melanomas, leaving a gap in evidence specifically guiding the surgical management of ALM.[2]

- Due to their locations, ALM excisions often necessitate complex reconstruction, frequently involving skin grafts. In cases of ALM affecting fingers and toes, including subungual melanomas, amputation is often required to achieve adequate surgical margins.

- Recent challenges to the practice of wide-margin excisions and routine amputations for cutaneous and subungual melanomas of the digits have emerged. Nakamura and colleagues studied 62 patients with invasive subungual melanoma who underwent non-amputative wide excisions with 0.5-1 cm peripheral margins extending to the bone. They found that only

4 among 48 patients with the melanoma had local recurrence, necessitating re-resection, and only one required eventual amputation. Notably, no patients with melanoma had local experience or died after undergoing non-amputative wide excision at last follow-up.[18]

- A study by Le et al. assessed excision techniques in situ subungual melanoma. Pooled data from 20 studies revealed local recurrence rates of 8.69% with Mohs micrographic surgery, 2.94% with amputation and 4.72% with nail unit excision. While these differences were not significant statistically, the study's limitations-small sample size, selective outcome bias, publication bias, and retrospective design-preclude using these results to equate Mohs micrographic surgery with the recent recommended surgical treatment.[19]

Sentinel Lymph Node Biopsy and Elective Lymph Node Dissection

- The first nodes in the lymphatic drainage basin from the main tumour, known as sentinel lymph nodes (SLNs), are important prognostic markers in melanoma. For melanoma patients with intermediate-thickness tumours, SLN biopsy is typically advised since the presence or absence of melanoma cells in an SLN is a known independent prognostic factor.[1]

- The guidelines for SLN biopsy in ALM patients are largely extrapolated from broader studies with limited representation of this subtype. Current NCCN Guidelines for SLN biopsy are based on primary tumor depth without considering histologic subtype. In a large retrospective review of over 60,000 melanoma patients, including 959 with ALM, ALM was associated independently with highest risk of SLN positivity. Subgroup analysis further demonstrated this heightened risk for patients with stage IB and II disease. Given these findings and the potential for understaging due to incomplete biopsies, routine SLN biopsy may be prudent even in patients with in situ disease or T1a, particularly when residual pigmentation persists after an initial partial biopsy.[20]

Pharmacotherapy

Over the past years, significant advancements have transformed the landscape of advanced cutaneous melanoma management and prognosis. The advancement of systemic immune checkpoint inhibitors and targeted molecular therapies has played a pivotal role in this transformation.

Immunotherapy

1. Immune checkpoint inhibitors

- T cells are the primary source of expression for PD-1, a protein belonging to the immunoglobulin superfamily that inhibits TCR signalling and CD28-costimulation by binding to two ligands, PD-L1 and PD-L2. Likewise, CTLA-4, which belongs to the immunoglobulin superfamily, suppresses T cell receptor signalling by competing with CD28 for B7. Thus, CTLA-4 and PD-1 are both essential for suppressing T cell activation.[1]

- Several regions have recently approved a number of immune checkpoint inhibitors (ICIs) for the treatment of melanoma, including Ipilimumab, Pembrolizumab, Nivolumab, and Torpalimab. Research has shown that Nivolumab, Pembrolizumab, and Torpalimab monotherapies are more effective than ipilimumab in treating patients with advanced ALM.[22]

- Nakamura and colleagues conducted a retrospective analysis on 193 patients with unresectable stages III and IV AM who received anti-PD-1 therapy. The results showed a median overall survival (mOS) of 18.1 months and an overall response rate (ORR) of 16.6%. Interestingly, compared to patients with subungual melanoma, those with AM of the palms and soles had a noticeably greater response rate and longer OS.[23]

- In addition, Wang et al. evaluated the Apatinib-Camrelizumab combination (an immune checkpoint inhibitor and a tyrosine kinase inhibitor) in patients with advanced AM who had not yet received treatment in a phase 2 trial. Among 30 patients, the trial showed a median progression-free survival (PFS) of 7.39 months and an ORR of 24.1%.[24]

- Finally, Tawbi et al. assessed the effectiveness of Nivolumab-Relatlimab (a lymphocyte activation gene 3 (LAG-3) inhibitor) in conjunction with anti-PD-1 monotherapy in cases of untreated metastatic or previously incurable melanoma. All subgroups, including those with acral melanoma, demonstrated improved PFS with the combined therapy.[25]

2. Imiquimod

- By activating antigen-presenting cells and promoting the development of CD4+ and CD8+ T cells' antitumor response, imiquimod functions as a Toll-like receptor 7 (TLR7) agonist. Through this process, the immune response is steered in the direction of T helper 1 (Th1) cells. Twenty melanoma patients with locoregional cutaneous metastases (LCMM), ten of whom had acral lentiginous melanoma (AM), were included in the retrospective investigation. It examined how well LCMM responded to cryotherapy and local treatment with 5% imiquimod. According to the results, 65% of patients had a locoregional response to the treatment, with 40% exhibiting full responses and 25% displaying partial responses. In terms of overall response, 5% had stable disease, whereas 15% had a full response.[26]

3. Oncolytic virus

- Talimogene laherparepvec (T-VEC) • Taliogene laherparepvec (T-VEC) functions as an oncolytic virus by stimulating T-cell responses specific to tumours through several methods, such as enhancing tumour selective replication, activating viral pathogenicity, and decreasing antigen presentation suppression. Research has confirmed that T-VEC works well for AM sufferers.[28] Additionally, phase 2 clinical research including 26 melanoma patients with incurable tumours in China examined the safety and effectiveness of OrionX010, a type I oncolytic Herpes Simplex Virus. 18 (69.2%) of these patients had AM. According to the research, AM patients had an overall survival (OS) of 19.2 months and a median PFS of 3.0 months.[27]

Targeted Molecular Therapy

1. BRAF/MEK inhibitors

- The most common mutation found in malignant melanoma, accounting for 40–60% of cases, is the serine-threonine kinase BRAF gene mutation. The mitogen-activated protein kinase (MAPK) pathway, which includes Raf, MEK, and ERK, is triggered by this mutation because it activates the B-raf protein. A downstream transcriptional factor is then phosphorylated by activated ERK, increasing tumour cell survival and proliferation. Most individuals with mutations have glutamine at the 600 codons (V600E) instead of valine, with lysine (V600K) or arginine (V600R) occurring less frequently.[1]

- However, BRAF V600E mutations are uncommon in ALM compared to nonacral cutaneous melanoma.[2]

- Between 15% and 20% of patients with ALM have BRAF mutations, which restricts the effectiveness of BRAF inhibitors in these patients. Dabrafenib, Encorafenib, and Vemurafenib are examples of BRAF inhibitors. Patients with BRAF-mutant melanoma have shown promise when treated with a combination of BRAF and MEK inhibitors, with positive results. Trametinib, Bindetinib, and Cobimetinib are MEK inhibitors that are now used to treat melanoma.[4]

- For example, a phase 2 clinical trial in China found that patients with acral melanoma and those with metastatic acral/cutaneous melanoma had good long-term survival results, with an ORR of 83.3% and a 3-year OS of 35.7%.[28]

- An additional retrospective analysis that included 112 patients with advanced melanoma treated with a combination of BRAF-MEK inhibitors showed an ORR of 64.3% for both mucosal and acral melanoma patients.[29]

2. KIT inhibitors

- Compared to other forms of melanoma, ALM has a noticeably higher frequency of KIT mutations. The only KIT inhibitors that have shown effectiveness in AM are Imatinib and Nilotinib, out of the regularly used Sunitinib, Imatinib, Nilotinib, and Dasatinib. Imatinib treatment produced encouraging results in a retrospective examination of 78 individuals with metastatic melanoma, 42 of whom had AM and a c-Kit mutation. At 13.1 and 4.2 months, respectively, the mOS and PFS for every patient were noted. Furthermore, it was reported that the disease control rate (DCR) was 60.3% and the ORR was 21.8%.[30]

3. CDK4/6 inhibitors

- ALM is commonly associated with CDK4/CCND1 mutations and amplifications, suggesting that CDK4/6 inhibitors may be useful in treating it. Palbociclib therapy was assessed in a recent phase 2 trial that included 15 patients with advanced AM who had genetic changes in the CDK pathway. Three patients (20.0%) had tumour shrinkage at 8 weeks, according to the results, and one of them had a documented partial response. OS was 9.5 months, and PFS was observed at 2.2 months.[31]

4. Targeted therapy for NRAS-mutant AM

- By controlling the phosphoinositide 3 kinase (PI3K)/Akt cascade and B-raf activation, which in turn triggers the MAPK pathway, NRAS mutations are essential in melanoma. But as of right now, no medications specifically target NRAS mutations. The first MEK inhibitor to show promise in treating NRAS-mutant melanomas was Binimetinib, although its results were subpar.[4]

Chemotherapy

- Although dacarbazine's effectiveness has been subpar, it has been the main chemotherapy medication used for decades to treat metastatic melanoma. After Dacarbazine-based therapy fails, patients with metastatic acral melanoma (AM) have few alternatives for salvage chemotherapy. However, with an 81.3% DCR, a median PFS of 6 months, and a median OS of 17 months, a clinical trial carried out in China showed that albumin Paclitaxel + Carboplatin was both safe and effective in treating metastatic melanoma.[32]

Interferons

A class of naturally occurring glycoproteins known as interferons (IFNs) are generated by different cells in reaction to viral infections. Immunoregulatory, antiangiogenic, differentiation-inducing, antiproliferative, and antiapoptotic effects are among the biological actions that are induced by type I IFNs (IFN-α and IFN-β) binding to particular receptors and triggering downstream signalling cascades. In terms of immunoregulatory actions, type I IFNs increase cellular-mediated cytotoxicity by promoting antigen cross-

presentation, boosting dendritic cell responses to tumour antigens, and inducing a shift from Th2 to Th1 polarisation. After the original tumour is removed, IFNs are frequently utilised as adjuvant therapy for melanoma patients. Notably, when utilised as adjuvant therapy in combination with IFNs, BRAF inhibitors and immune checkpoint inhibitors have demonstrated notable survival advantages.[1]

Combination therapies

1. Combination of immunotherapies

- In a retrospective analysis conducted in China, patients with resectable advanced melanoma receiving adjuvant Pembrolizumab had a higher median recurrence-free survival if they had previously had PEG-IFN-α therapy. These results imply that IFN-α and PD-1 inhibitors may work well together to treat advanced ALM. Furthermore, it is important to remember that PD-1 and CTLA-4 block anti-tumour immunity via different pathways.[33]

2. Combination of Chemotherapy and Immunotherapy

- By reducing or blocking regulatory T cells (Tregs) in the tumour microenvironment, Temozolomide has been shown to increase the anticancer activity of Pembrolizumab. Pembrolizumab and Temozolomide together produced a considerably higher ORR and median PFS than either medication alone, according to a multicentre retrospective investigation done in China on 69 patients with metastatic melanoma, including 28 cases of AM.[34] According to these results, Temozolomide and Anti-PD1 combination therapy may be a viable first-line therapeutic strategy for advanced melanoma that is incurable, including AM. Furthermore, an additional retrospective investigation of 20 advanced AM patients treated with Albumin Paclitaxel and a PD-1 inhibitor showed a DCR of 75% and an ORR of 20%.[35]

3. Combination of immunotherapy with antiangiogenic therapy

- By promoting antitumor immunity, anti-angiogenic drugs have demonstrated the ability to improve a patient's response to immune checkpoint inhibitors (ICIs). The safety and efficacy of combining Camrelizumab and Apatinib in patients with advanced AM is presently being evaluated in a Chinese clinical trial (NCT03955354). The trial's initial results, which included 27 AM patients, showed a disease control rate (DCR) of 77.8% and an objective response rate (ORR) of 22.2%. Furthermore, the 1-year durable response rate was 83.3%, and the median progression-free survival (PFS) was 8.0 months.[36]

4. Combination of chemotherapy with antiangiogenic therapy

- Chemotherapy and anti-angiogenic treatment administered together may have a synergistic anticancer impact. 29 patients, including 8 cases of AM, participated in phase II clinical research in China to evaluate the safety and effectiveness of combining Apatinib with Temozolomide in patients with advanced melanoma who had not responded to immunotherapy. According to subgroup analysis, AM patients had a median OS of 10.1 months and a median PFS of 4.0 months.[37]

5. Targeted combination therapy

- NRAS-mutated melanomas frequently provide therapeutic problems since MEK-targeting alone might not completely inhibit NRAS-driven downstream signalling, especially through CDK4. Increased CDK4 and cyclin D1 levels are linked to resistance to BRAF inhibitors. It has been shown in earlier studies that CDK4/6 inhibitors can overcome acquired resistance to BRAF/MEK inhibitors. These results provide a theoretical basis for treating metastatic melanoma by combining CDK4/6 inhibitors with BRAF/MEK inhibitors.[38]

8. CONCLUSION

In conclusion, Acral lentiginous melanoma (ALM) poses unique challenges due to its distinct clinical, histological, molecular features compared to other forms of melanoma. In the era of precision medicine, targeted therapies and immunotherapy have shown promise in the management of advanced ALM. While BRAF/MEK inhibitors have demonstrated efficacy in melanomas harboring BRAF mutations, the therapeutic landscape for ALM is evolving, with emerging evidence supporting the use of KIT and CDK4/6 inhibitors in specific genetic subgroups. Immunotherapy, particularly immune checkpoint inhibitors and oncolytic viruses, offers novel treatment options, either as monotherapy or in combination with other modalities. Combination therapies, including immunotherapy with chemotherapy or antiangiogenic agents, represent a promising approach to overcome resistance mechanisms and improve treatment outcomes in advanced ALM.

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