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MELANOMA (K MARGOLIN, SECTION EDITOR)

Mucosal Melanoma: Pathogenesis, Clinical Behavior, and Management

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Abstract Mucosal melanoma represents a rare subtype of melanoma with distinct biological, clinical, and management considerations. Knowledge regarding optimal treatment strategies for mucosal melanoma is limited and based primarily upon small case series and single-institution, retrospective analyses. Surgery remains the standard of care for loco-regional management, but the common presence of multifocal disease and the high rate of distant recurrence should be considered before pursuing aggressive surgical interventions associated with inherent significant morbidity. The role of sentinel lymph node biopsy and lymph node dissection remains unclear. Radiotherapy has not been shown to improve overall survival but may reduce the rate of local recurrence. Significant advances in the treatment of metastatic disease have been made with novel immunotherapeutic agents, the discovery of KIT and BRAF mutations and the development of targeted agents that inhibit these oncogenic pathways.

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Introduction

Melanoma is a potentially life-threatening malignancy arising from the aberrant growth of melanocytes. Though most of the 76,250 cases of melanoma diagnosed each year in the United States arise on cutaneous surfaces, approximately 1 % arise from melanocytes within mucosal surfaces [1, 2]. Any mucosal surface may be affected with melanoma, but most arise from the mucosa of the head and neck, the anorectal mucosa, or the vulvovaginal mucosa.

The biology of mucosal melanoma (MM) differs from the biology of cutaneous melanoma, necessitating a nuanced view of this particular melanoma subset. This review summarizes the epidemiology and clinical features of MM and contrasts them with the more common cutaneous counterpart. We then explore the unique diagnostic and therapeutic considerations relevant for the optimal management of patients with this disease.

Epidemiology

Compared with melanoma arising from cutaneous sites, MM has several distinct epidemiologic features (Table 1). MM generally develops at a later age, with a median age at diagnosis of 70 years. Unlike cutaneous melanoma, which is more prevalent in men, MM is more commonly diagnosed in women, with a female-to-male ratio of 1.85 to 1.0 [1]. The female predominance of MM is likely due to the frequency of vulvovaginal melanoma, the most common subtype affecting women [3]. Among men, the most frequently encountered site of MM is the head and neck. Though the incidence of cutaneous melanoma is rising over time, the incidence of MM remains stable [4].

Table 1 Epidemiology of mucosal and cutaneous melanoma

	Mucosal melanoma[a]	Cutaneous melanoma[b]
Overall incidence [1]	2.2 per million persons-years	153.5 per million persons-years
Incidence trend [3]	Stable	Rising
Female-to-male incidence Ratio	1.85 to 1.0 [1]	0.72 to 1.0 [2]
Demographic group		
• Black	2 per million [1]	22 per million [1]
• White	4 per million [1]	347 per million [1]
• Hispanic (any race)[c]	4 % of all melanoma [3]	86 % of all melanoma [3]
Geographic influence [1]	No geographic difference in incidence rates	Higher incidence in coastal and southern states
Risk factors	Unknown	Ultraviolet light [5]

[a] Includes melanoma arising from anorectal, genital, nasal cavity, and accessory sinuses

[b] All skin (including acral) except skin of the vulva, scrotum, and penis that was considered mucosal

[c] Out of all Hispanic individuals diagnosed with any type of melanoma captured by the database in Chang et al. [3] number in table reflects percentage of Hispanic individuals diagnosed with specific subtype of melanoma

Distinct racial and geographic differences are observed in MM as they are in cutaneous melanoma. As in cutaneous melanoma, MM is more common in people classified as white, compared with those classified as black [1]. Nevertheless, while the rate of cutaneous melanoma among whites is 16 times higher than that among blacks, the rate of mucosal melanoma is only twice that in whites as that observed among blacks. Out of all Hispanic individuals diagnosed with melanoma, 4 % had MM [3]. This is slightly higher than the proportion of MM generally reported [1, 2]. Furthermore, though cutaneous melanoma rates in the United States are higher in individuals from coastal or southern states, this geographic risk did not extend to individuals affected with MM [1]. Taken together, the association between cutaneous melanoma and ultraviolet radiation does not appear to be present with MM [5].

No clear risk factors have been identified for MM. Some reports have indicated that oral MM can be preceded by a phenomenon of oral melanosis [6]. Since cigarette smoking has been shown to increase the prevalence of oral pigmented lesions [7], some believe cigarette smoking may be linked to oral MM. No rigorous proof of this etiologic link has been reported, and the relationship of MM to other commonly considered carcinogens is not clear.

General Clinical Features of Mucosal Melanoma

MM appears to be a particularly aggressive melanoma subtype. Likely because of their often obscured anatomic site of origin, most mucosal melanomas are diagnosed at a late stage [3]. While loco-regional lymph nodes were involved in only 9 % of patients with cutaneous melanoma at the time of diagnosis, nodal involvement was present in 21 % of patients with head and neck MM, 61 % of anorectal MM, and 23 % of vulvovaginal MM at diagnosis [3]. Even when accounting for stage at diagnosis, outcomes for patients with MM appear inferior to those with cutaneous melanoma, suggesting true biological differences between these 2 disease subtypes. Of note, staging of MM is challenging since there is no validated, widely accepted staging system applicable to all cases of MM.

Loco-Regional Management of Mucosal Melanoma

If MM is believed to be localized at diagnosis, initial considerations are typically focused upon loco-regional control with surgery and/or radiation. The rarity of MM has made it challenging to conduct large, randomized controlled trials, and clinical practice is therefore largely based upon data from case series and retrospective analyses.

Local control is complicated by the delicate anatomic issues from affected sites of disease as well as by the multifocal nature of MM. MM displays clinical behavior consistent with a field defect with the frequent development of multiple primary lesions in nearby tissue. In 1 series of 9 patients with vulvovaginal MM, 3 of 9 had more than 1 site of local disease at initial presentation, with 3 additional patients developing additional sites of disease during follow-up [8]. In a larger series of 51 patients with vulvar melanoma, 20 % had evidence of multifocal disease at diagnosis [9]. Multifocality has additionally been seen in patients with MM arising from the male urethra and head and neck [10, 11]. The multifocal nature of MM suggests a shared disorder of melanocytes that inhabit mucosal areas in affected patients and is a significant challenge in the ability to obtain adequate local surgical control.

Aggressive loco-regional management through surgery and radiation can lead to significant local morbidity which

needs to be carefully balanced against the high risk of distant metastatic spread. Since each unique anatomic location of MM requires specific considerations, the clinical features and loco-regional management issues for each of the most commonly encountered subsets of MM are considered individually below.

Head and Neck Mucosal Melanoma

Though MM may arise from any mucosal surface in the head and neck region, there is a slight predominance of disease in the sinonasal region (59 %–80 %) compared with the oral region (16 %–41 %) [11, 12]. The majority (80 %) of patients present to medical attention with localized disease, likely because of the early development of symptoms including epistaxis, nasal obstruction, vision changes, or oral complaints. Oral cavity MM may be slightly more likely to present with regional nodal involvement (25 %) compared with sinonasal MM (6 %) [11]. In 1 series of 59 patients, the presence of vascular invasion on histologic evaluation, tumor thickness greater than 5 mm, clinical stage at presentation, and the development of distal failure were associated with inferior outcomes [11]. Overall survival (OS) is poor, with a reported 2-year OS of 26 % and 5-year OS of 8 % [12].

A variety of staging systems have been proposed [13, 14], including the AJCC staging system for head and neck MM [15]. According to the AJCC staging system, to account for the overall poor prognosis of even local disease, the most limited stage of disease is considered stage III. Advanced disease is considered stage IV, with subtypes IVA, IVB, and IVC, designating various degrees of regional and distant involvement.

Local management of stage III and IVA MM of the head and neck is predominantly surgical. Though craniofacial reconstruction has been pursued with the objective of achieving local control [16], less invasive endoscopic procedures may achieve similar control without as extensive surgical morbidity [17]. Despite aggressive surgical management of the primary site of disease, recurrence rates remain high [11]. Repeat attempts at resection of locally recurrent disease must be considered only after extensive restaging, since local recurrence is associated with the likelihood of distant metastatic disease [18].

Although feasible, the role of sentinel lymph node biopsy in MM of the head and neck is unclear [19]. Should MM even be detected in the sentinel lymph node, there is no clear data that suggest outcomes are improved if adjuvant therapy such as interferon-alpha 2b is pursued. This is not surprising considering the debatable benefit of adjuvant interferon-alpha 2b even for patients with cutaneous melanoma [20]. Additionally, patients with intermediate thickness cutaneous melanoma were not found to have improved overall survival if they underwent sentinel lymph node biopsy compared with observation [21].

For patients with MM, there is no difference in 5-year overall survival between patients who do and do not recur in the lymph nodes, and, given the high rate of early hematogenous spread, aggressive management of the lymph nodes in patients with primary head and neck MM should be carefully considered [22]. Lymph node dissection is, however, recommended when pathologic lymphadenopathy is clinically apparent or symptomatic.

Radiotherapy (RT) is commonly used in the adjuvant treatment of surgically resected head and neck MM, though the precise benefits are unclear, in part because of the difficulty in planning fields that encompass sites at risk. Although 1 retrospective analysis of 69 patients with head and neck MM suggested improved local control for patients treated with postoperative RT [23], the high rate of distant recurrence and the 5-year survival rate of only 20 % reported in this study provided further evidence of the overall poor prognosis of even localized head and neck MM and the low likelihood that RT enhances overall survival. Subsequent reports were also retrospective and contained even fewer patients [24, 25], with similar results that supported the high risk of metastatic spread and the low expected benefit from adjuvant RT.

Anorectal Mucosal Melanoma

Anorectal MM is divided nearly equally between those arising in the anal canal, rectum, and indeterminate sites [26]. The median age at diagnosis is approximately 70 years [26, 27]. The incidence among women is slightly higher (1.6-fold) than that of men, though this finding is likely confounded by the increased frequency of perineal evaluation women undergo as part of routine gynecologic surveillance. Sixty percent of patients with anorectal MM present with loco-regional nodal involvement, and 20 % of are found to have distant metastatic disease at initial diagnosis [3]. Similar to head and neck MM, the long-term prognosis of patients with anorectal MM remains poor. In 1 series of 85 patients with anorectal MM, none of the 14 patients who presented with advanced disease was alive at 5-years [28]. Of the 71 patients who presented with loco-regional, surgically resectable disease, the 5-year survival was 20 %. It is possible that some of the patients in this historic series who were believed to have surgically resectable disease may have had occult metastases that could have been detected by current imaging modalities such as positron emission tomography.

Staging is typically based upon the Ballantyne staging system (stage I–clinically localized disease, stage II–regional nodal involvement, stage III–distant metastatic involvement), as survival for patients with anorectal MM has been shown to depend upon the designated Ballantyne stage [27].

Prognostic histologic features of the primary tumor have been investigated in anorectal MM. In 1 series of 46 patients, the presence of perineural invasion was identified as an independent predictor of disease-specific mortality in multivariate analysis. While tumor thickness, mural involvement, and necrosis were not found to be statistically significant histologic prognostic features, it is likely that larger series and more detailed characterization, for example with molecular studies (see below), will reveal different and more biologically-relevant prognostic factors for this and other primary sites of MM [29].

Historically, APR was the standard surgical approach to anorectal MM. Given the high loco-regional and distant recurrence rate, however, the precise role of APR, is unclear. In 1 review of 85 patients, there was no statistically significant difference in 5-year survival for patients who underwent APR when compared with a more limited, sphincter-sparing wide-local excision [28]. Multiple additional retrospective series suggest that the extent of surgical intervention does not affect long-term outcome [29, 30], and, as a result, the more conservative wide-local excision is recommended in most cases. Though mesorectal, pelvic, and inguinal lymph nodes are at risk for involvement with MM, data suggest that elective lymph node dissection does not affect long-term prognosis [29]. The presence of regional nodal metastasis was not associated with disease recurrence or survival. Thus, there is no clearly defined role for sentinel lymph node biopsy or elective lymph node dissection as part of primary surgical local management of anorectal MM. Clinically apparent or symptomatic nodal disease, however, should be resected.

Because of the risk of local recurrence and its associated morbidity, adjuvant RT may be considered following definitive surgical resection. RT delivered in this setting does not appear to alter long-term survival, though some series have suggested it may improve local control following sphincter-sparing surgery [31, 32]. Any clinical benefit derived from postoperative RT appears to be limited to the primary site. In 1 series, RT delivered to the draining lymph node basins was not found to be helpful and only contributed to increased lymphedema [32].

Vulvovaginal MM

Vulvovaginal MM occurs at a rate of approximately 0.2 per 100,000 women per year [33, 34]. The large majority arise from the vulva, with fewer than 5 % arising from the vagina. The prognosis of vulvar melanoma is generally felt to be better than vaginal melanoma, with 5-year OS rates reported as 50 % and 19 %, respectively [34]. Vulvar melanoma affects slightly older women between 60 and 80 years of age [35] compared with vaginal melanoma, which typically affects women aged 50–70 [36]. In an analysis of 644 patients with vulvar melanoma, age less than 68, extent of lymph node involvement, and localized disease were independent predictors of improved OS in multivariate analysis [35]. Other series have implicated tumor thickness as an important prognostic variable for vulvar melanoma [33]. The 2002 modified AJCC TNM staging system was found to be the best predictor of recurrence-free survival for women with vulvar melanoma and is therefore the staging system of choice for women with this disease. This is not the case for vaginal melanoma, and, as with anorectal MM, the Ballantyne clinical staging system is appropriate for vaginal MM [37].

Loco-regional management of vulvovaginal MM is primarily surgical. Historically, similar to anorectal MM, aggressive surgical procedures such as vulvectomy, vaginectomy, urethrocystectomy, radical hysterectomy, and pelvic exenteration were commonly performed. With growing appreciation of the high risk of distant metastatic spread regardless of the achievement of local control, more conservative surgical approaches are now generally being used. Retrospective series suggest that conservative surgery achieves similar rates of OS when compared with more aggressive surgical intervention [38, 39].

As with anorectal MM, optimal management of the regional lymph nodes is unclear. Several series have described the feasibility of lymph node biopsy and dissection for women with vulvovaginal MM [40, 41], but the therapeutic benefits of lymph node dissection on overall survival remain unknown. As with anorectal MM, lymph node dissection is generally recommended only in the setting of clinically apparent or symptomatic lymphadenopathy.

Less Frequent Sites of MM

Head and neck MM, anorectal MM, and vulvovaginal MM are the most common subsets of MM. Nevertheless, MM have been documented to arise in the mucosa of other tissues including the penile urethra [42], gallbladder [43, 44], esophagus [45], and other parts of the intestine [46]. Given the propensity of melanoma to spread to multiple distant sites, including those of the gastrointestinal tract, it is often challenging to distinguish primary tumors arising in these tissues from metastatic deposits with an unidentified primary site. Clinicopathologic criteria used to distinguish primary from metastatic mucosal melanoma in these unique sites have been proposed [47].

Adjuvant Therapy after Definitive Local Treatment of MM

Immunotherapy with high-dose interferon-alpha is a consideration for the adjuvant treatment of patients with resected, high-risk cutaneous melanoma. Although high-dose α-interferon (IFN) and polyethylene glycol α-IFN have been approved for the adjuvant therapy of high-risk melanoma,

the activity of these forms of nonspecific immunomodulatory therapy for MM is unknown, since the distinct biology of MM and its extreme resistance to systemic therapies have led to its routine exclusion from clinical trials of adjuvant therapy. This exclusion applies to the ongoing adjuvant trial comparing high-dose α-IFN with ipilimumab (NCT01274338) as well as a recently-completed trial of ipilimumab vs placebo (NCT00636168).

Systemic Therapy for Advanced Mucosal Melanoma

Despite limited efficacy, dacarbazine-based chemotherapy has traditionally been the standard approach for patients with advanced melanoma. One series by Yi et al. suggested that patients with MM have worse outcomes following dacarbazine-based chemotherapy than patients with cutaneous melanoma. In this study, 95 patients with melanoma treated with dacarbazine-based regimens from 1997 to 2010 in 3 Korean institutions were retrospectively reviewed. The study was limited by its inherent retrospective nature and by the fact that not all patients received the same dacarbazine containing regimen. Though the response rates between patients with MM and cutaneous melanoma were comparable, MM was found to be a poor prognostic feature for OS in both univariate and multivariate analysis [48]. Given the heterogeneity of the administered regimens and difficulty excluding this confounding feature on the results, however, the efficacy of dacarbazine based chemotherapy for MM compared with cutaneous melanoma remains unclear.

Investigators at MD Anderson retrospectively evaluated the activity of an aggressive biochemotherapy regimen (cisplatin, vinblastine, dacarbazine, interferon-alpha 2b, and interleukin-2) in patients with various subtypes of MM. Bartell et al. reported the results for 14 patients with head and neck MM undergoing biochemotherapy [49], 4 patients (27 %) had a complete response and 3 patients (20 %) had a partial response. After a median follow-up of 13 months, the median survival was reported as 22 months. A second series of 18 patients with anorectal MM treated with biochemotherapy was reported [50]. Six of 18 (33 %) had partial responses and 2/18 (11 %) achieved complete responses. Eleven patients with vulvovaginal melanoma treated with biochemotherapy were reported by Harting et al. [51]. Four (36 %) partial responses were observed, with a median time to progression of 3 months.

Taken together, these small series from a single institution, while suggesting a similar level of activity for biochemotherapy in MM as in cutaneous melanoma [52], need to be interpreted with caution, since they are retrospective data from a single institution with all of the selection and reporting bias inherent in such data. Furthermore, the results of a subsequent phase III U.S. intergroup study demonstrated the lack of benefit for biochemotherapy over identical chemotherapy for advanced melanoma originating in cutaneous sites, adding further doubt to the strength of evidence for biochemotherapy as optimal treatment for MM, although there remains the possibility that a subset of melanoma deriving benefit from this regimen may be identified with additional studies [53].

Significant advances in the treatment of advanced melanoma with immunotherapy have been made in recent years, highlighted by the development of ipilimumab (Bristol-Myers Squibb, Princeton, NJ). Ipilimumab is a fully human monoclonal antibody that enhances antitumor immunity by blocking cytotoxic T lymphocyte antigen 4 (CTLA-4), the normally negative regulator of immunity present on the surface of T cells. Ipilimumab was the first agent to demonstrate an overall survival benefit for patients with advanced cutaneous melanoma in a phase III trial [54••]. Though patients with MM were not excluded from this and other ipilimumab trials, very few patients were treated, and outcome analysis of these cases is planned (personal communication, F. Stephen Hodi). The survival benefit of ipilimumab was confirmed in a second phase III trial. Untreated patients who received ipilimumab with dacarbazine had a significantly improved OS compared with patients receiving dacarbazine alone [55•]. In this trial, however, patients with MM were excluded. Although at our institution we have treated a few patients with MM who achieved partial responses to ipilimumab, its clinical benefit—generally defined as objective responders plus patients experiencing prolonged duration of stable disease—remains to be defined.

In addition to advances in immunotherapy, the treatment of advanced melanoma has significantly improved because of an enhanced understanding of the various genetic abnormalities present in a portion of melanomas. Though mutations in the serine-threonine protein kinase, BRAF are found in approximately 45 % of patients with cutaneous melanoma [56••, 57], BRAF mutations have been found less frequently in patients with MM [58, 59]. Instead, MM tumors have been found to contain a relatively high proportion of activating mutations and/or genetic amplifications involving the receptor tyrosine kinase, c-KIT [60, 61] (Fig. 1)

Small molecule inhibitors of c-KIT such as imatinib have demonstrated activity in patients with MM who have had c-KIT mutations and/or amplifications [62]. A study selecting for patients with KIT genetic aberrations found that 25 % of patients with MM had mutations and/or amplifications of c-KIT [63••]. Of the 13 patients with MM and c-KIT aberrations, 3 patients responded, with 1 durable complete response (mutation and amplification), 1 durable partial response (mutation without amplification), and 1 transient partial response (mutation and amplification).

Of note, not all mutations in c-KIT are felt to be true oncogenic driver mutations. Patients whose tumors have mutations that affect exon 11 (most commonly L576P) which codes for the juxtamembrane domain and exon 13 (most

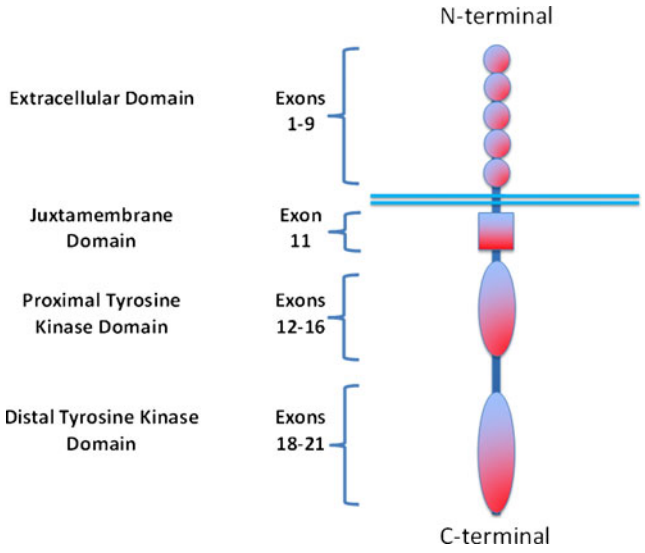

Fig. 1 Model of KIT protein. The N-terminal domain contains an extracellular portion consisting of 5 immunologlobulin-like regions (circles). This domain serves as the binding site for the KIT ligand, stem cell factor. On the intracellular portion near the plasma membrane, the juxtamembrane domain is responsible for preventing activation of the tyrosine kinase domains, unless ligand is present. Following ligand dependent receptor activation, the 2 tyrosine kinase domains become autophosphorylated. Once phosphorylated, they activate a variety of downstream intracellular signaling pathways

commonly K642E) may be particularly sensitive to c-KIT inhibition (Fig. 1), In another phase II study restricted to 43 patients with c-KIT aberrations, 23 % responded to imatinib [64••]. Eleven patients with MM were included, though no subgroup analysis is available regarding clinical response. An ongoing study conducted by the Eastern Cooperative Oncology Group (NCT00700882) is assessing an alternative c-KIT inhibitor, dasatinib, for patients with MM, acral melanoma, and solar melanoma harboring mutations in c-KIT.

Unfortunately most patients who initially respond to c-KIT inhibition develop resistance after relatively brief periods of disease control, in contrast to the often durable remissions occurring in chronic myelogenous leukemia and gastrointestinal stromal tumors, in which activating mutations of critical kinases can be inhibited for prolonged periods by similar agents. The mechanisms underlying resistance to c-KIT inhibitors in MM continue to be elucidated, but recent data supporting the occurrence of new mutations distinct from those mediating drug resistance in the above diseases are providing potential targets for new drugs or combinations.

A recent report described 1 patient with anorectal MM and a KIT W557G mutation who responded for 7 months and then progressed [65]. A biopsy performed at the time of progression revealed an *NRAS* Q61K mutation that was not present in the patient's initial biopsy and may be a mechanism of tumor resistance to c-KIT inhibition. Additional research will be necessary to elucidate the precise mechanisms underlying resistance, looking for both common molecular mechanisms of escape and those which might be unique to individual patients.

For example, a recently described case of MM suggested another mechanism of resistance to c-KIT inhibition involving the upregulation of the mammalian target of rapamycin (mTOR) pathway. After progression on imatinib, 1 patient with sinonasal MM achieved a major response to mTOR inhibition with everolimus [66]. Careful molecular characterization of MM at the time of diagnosis and again upon the development of resistance to therapy should lead to important insights that will inform the development of new approaches with the goal of success in preventing or delaying the onset of resistance in patients with c-KIT mutations and/or amplifications. This strategy is currently being explored in an ongoing clinical trial of nilotinib for patients who have developed resistance (or intolerance) to initial tyrosine kinase therapy. (NCT00788775).

The relatively higher proportion of KIT mutations and lower proportion of BRAF mutations in MM when compared with cutaneous melanoma lends further support to the concept that MM arises from alternative molecular and biological processes than its cutaneous and uveal counterparts. Since BRAF mutations nevertheless occur in patients with MM, we still favor performing molecular testing to assess for this possibility. There is no clear data to suggest that patients with MM whose tumors harbor a BRAF mutation respond differently to vemurafenib than patients with cutaneous melanoma where a survival benefit has been demonstrated [56]. We therefore support vemurafenib for patients with MM and a BRAF mutation.

Activation of the PI3K-Akt pathway, commonly through loss of the tumor suppressor, PTEN and/or activation of RAS has additionally been implicated in melanoma. In a study evaluating 53 cutaneous melanoma cell lines, 30 % had PTEN loss, 21 % had NRAS mutations, and only 1 (2 %) had both [67]. No therapeutic agents are yet approved for blocking the Akt pathway, though clinical trials are underway (NCT01510444). Whether PTEN loss and subsequent Akt activation differs in patients with MM compared with cutaneous melanoma requires further investigation.

We recommend molecular profiling of each patient at diagnosis. In the event that an actionable mutation is not found, we pursue initial treatment with ipilimumab, extrapolating from the data in support of a survival benefit for ipilimumab in patients with cutaneous melanoma. Clinical trial enrollment is encouraged whenever possible.

Conclusions

Mucosal melanoma is clinically and biologically distinct from cutaneous melanoma. Local management of MM remains challenging based upon its common multifocality

and the anatomic considerations of MM arising from delicate anatomic areas. The discovery of c-KIT activating mutations in a substantial fraction of MM has generated great enthusiasm for considering MM as a distinct molecular subtype that may be susceptible to unique, personalized therapeutic approaches. Ongoing efforts will be necessary to optimize systemic treatments for patients with MM and attempt to improve outcomes in this traditionally challenging melanoma subtype.

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- • Of importance
- •• Of major importance

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