Mucosal Melanoma: Epidemiology, Clinical Features, and Treatment

Maria Chiara Sergi[1] · Elisabetta Filoni[1] · Giacomo Triggiano[1] · Gerardo Cazzato[2] · Valeria Internò[3] · Camillo Porta[1] · Marco Tucci[1]

Abstract

Purpose of Review Summarize the writings published in the last years on the management and novel therapies of mucosal melanoma (MM).

Recent Findings New research has demonstrated a difference between MM and cutaneous melanoma (CM) in their genomic and molecular landscapes, explaining the response's heterogeneity. Immunotherapy and targeted therapy have limited benefit, but novel therapies are rapidly expanding.

Summary MM is aggressive cancer occurring in gastrointestinal, respiratory, or urogenital mucosa; whose incidence is greater in the Asian population. The etiology and pathogenesis remain unclear since UV exposure is not a proven risk factor as in cutaneous melanoma. In contrast to CM, lesions on the mucosal surface are less likely to be recognized early; therefore, the disease is diagnosed in an advanced stage. Clinical manifestations, such as bleeding or pain, can help to detect this tumor, although the prognosis remains unfavorable with an overall 5-year survival rate of less than 20%. The mutational landscape of MM includes mutations of BRAF and NRAS, as well as mutations in the c-KIT/CD117 gene (in 50% of patients), thus limiting therapeutic interventions to immunotherapy. However, clinical studies show less responsiveness to immunotherapy compared to CM, therefore novel therapeutic strategies targeting new molecules are needed to improve the survival of patients with MM.

Keywords Mucosal melanoma · Immunotherapy · Targeted therapy · cKIT mutation · BRAF mutation

Abbreviations

MM	Mucosal melanoma
CM	Cutaneous melanoma
KIT	KIT Proto-Oncogene, Receptor Tyrosine Kinase
BRAF	V-RAF murine sarcoma viral oncogene homolog B1
MAPK	Mitogen-activated protein kinase
NRAS	Neuroblastoma ras viral oncogene homolog
NO	Nitric oxide
MSH	Melanocyte Stimulating Hormone
PD-L1	Programmed death-ligand 1
PD-1	Programmed death 1
GNAQ	Guanine nucleotide-binding protein G(q) subunit alpha
GNA11	Guanine nucleotide-binding protein alpha-11
MEK	Mitogen-activated extracellular signal-regulated kinase
VEGF	Vascular endothelial growth factor
CTLA4	The cytotoxic T lymphocyte 4
SLNB	Sentinel lymph node biopsy
ORR	Objective response rate
PFS	Progression Free Survival
OS	Overall Survival
NF1	Neurofibromin 1
ICI	Immune checkpoint inhibitors
MDM2	Murine double minute-2
CDKN2A	Cyclin-dependent kinase inhibitor 2A
CDK	Cyclin-dependent kinases
CCND1	Cyclin D1
TMB	Tumor mutational burden
ATR	Ataxia telangiectasia and rad3-related

✉ Maria Chiara Sergi
sergimariachiara@gmail.com

1 Department of Interdisciplinary Medicine, Oncology Unit, University of Bari "Aldo Moro", P.za Giulio Cesare, 11, 70124 Bari, Italy

2 Section of Molecular Pathology, Department of Precision and Regenerative Medicine and Ionian Area (DiMePRe-J), University of Bari "Aldo Moro", 70124 Bari, Italy

3 Oncology Unit San Paolo Hospital, Bari, Italy

Introduction

Melanoma develops from melanocytes that originate from the neural crest and migrate to many tissues during embryogenesis [1]. The biology and clinical outcome of cutaneous melanoma (CM) is different from that of mucosal or ocular melanoma [2]. MM accounts for 1,3% of all melanomas, and develops in non-sun-exposed areas, including the mucous membranes of the respiratory, gastrointestinal, and genitourinary tracts.

To date, the risk factors are poorly understood and the pathogenesis remains unclear [3], although an association with human papillomavirus and herpesvirus has been described [1]. In contrast to CM, the diagnosis of mucosal evolutive lesions is more difficult and MM is therefore likely to be detected at a late stage [2]. As a result, MM is usually diagnosed late, and malignant cells are often surrounded by a rich vascular and lymphatic network, which is mostly considered to be the cause of aggressive behaviour and poor prognosis. [2]. The molecular landscape includes a lower incidence of BRAF oncogene mutations but a high frequency of KIT mutations, suggesting a distinct genetic origin with respect to CM [2]. The overall five-year survival rate for MM is 10–20% [1]. However, new therapeutic strategies have the potential to improve the outcome of MM, which has a poor response to immunotherapy [1]. Here, we present a comprehensive review of different primary MM, their epidemiological and clinical features, and therapeutic strategies.

Epidemiology

Mucosal melanoma is a rare and aggressive subtype, accounting for 0.8–3.7% of all melanomas in Caucasians [1]. In contrast to CM, whose incidence is steadily increasing, the incidence of MM is almost stable and is more likely to affect women than men (2.8 versus 1.5 per million) [1]. The incidence of MM is also influenced by age, with more than 65% of patients over 60 years of age and less than 3% under 30 years of age. Racial differences in incidence have been reported. Although ethnicity influences the onset of MM, the absolute incidence remains higher in Caucasian populations [1]. The incidence is higher in Caucasians, but Asians have a higher incidence of MM arising from the anorectal tract, whereas non-Hispanic whites have a higher incidence of genitourinary MM [2, 4]. Finally, Hispanics most commonly present with MM of the head and neck [3].

Etiopathogenesis and Clinical Features

Melanocytes are not found exclusively in the epidermis, iris, and hair but also in the inner ear, nervous system, heart as well as mucous membranes [1, 2]. Based on recent studies, melanocytes produce many molecules in consequence of UV exposure as cytokines, melanocortin, amines, and nitric oxide (NO), thus promoting melanogenesis [1]. As recently reported, keratinocytes, lymphocytes, fibroblasts, mast cells, and endothelial cells may represent potential targets of these secretory compounds. In addition, α-MSH controls the production of NO by melanocytes while and melanocortins promote other signals that are considered key regulators of skin and mucous membrane homeostasis [2, 3]. Notably, MM is not associated with UV exposition and those arising from the anorectal tract tend to affect patients with red hair and poor tanning history [5]. Because the pathogenesis of MM is unrelated to typical carcinogens, there is poor evidence to support a link between cigarettes, formaldehyde, or exposure to cancer-causing viruses (i.e., papillomavirus, herpes virus, or polyomavirus) [2, 6]. For example, regarding the head and neck MM, melanocytes could play a key role in the metabolization of polycyclic aromatic hydrocarbons [7, 8]. However, the origin and pathogenetic mechanisms remain still undefined [3]. In the context of clinical presentation, the MM are lesions with irregularity of borders, altered pigmentation, and elevated areas. In contrast to many CM, which in general can be easily detected, lesions occurring in the mucosal surfaces are less likely to be detected early in their evolution [2]. On the other hand, the clinical symptoms depend on the site of onset of melanoma, and in the case of head and neck lesions, blood streaks can be observed in the nasal secretions, epistaxis, proptosis, diplopia, and pain [2].

Mucosal Melanomas of the Respiratory Tract

Mucosal melanomas of the respiratory tract are rare and arise from melanocytes of the ectodermal mucosa. The nasal cavity and sinuses are common sites (about 4% of all sino-nasal neoplasms) [2] whereas it is extremely rare in the larynx and tracheobronchial tract [9]. By contrast, the lung is frequently colonized by melanoma metastases of cutaneous, ocular, or mucosal origin [9].

Most patients suffer from nasal obstruction, visible mass and epistaxis that in some cases cause pain, morphological changes of the face, ptosis, and diplopia. Laryngeal mucosal melanoma is extremely rare and there are approximately 60 cases reported [9]. This subtype affects generally males in the sixth and seventh decade [1]. It causes hoarseness, followed by throat irritation but also sore throat, dysphagia, neck swelling, and pain [10]

Primary tracheal melanoma is a very rare cancer with four cases reported showing clinical manifestations that resemble other tracheal tumors as airway obstruction, dyspnea and stridor as well as hoarseness, cough and hemoptysis. In most cases, the treatment consists of palliative surgery for restoring the airway or tracheal resection [11]. Primary lung melanoma is an extremely rare cancer with around 30 cases described whereas the lung is a common metastatic site. [12]. Endobronchial growth is often peripheral and is detected by bronchoscopy as a pigmented or non-pigmented lesion [1].

Mucosal Melanomas of the Gastrointestinal Tract

Mucosal melanoma frequently affects the oral cavity and the anal canal (33% and 31% of patients respectively), while other sites such as the esophagus, stomach, small intestine, or gallbladder are rarely involved. Only 14% of patients with primary MM of the gastrointestinal tract are under the age of 50, and about 50% are over the age of 70. [12]

The incidence of oral MM is reported to be 0.2 per million [13], and it develops as a de novo asymptomatic melanocytic lesion with the onset of bleeding or pain. Melanoma of the oesophageal mucosa is rare, accounting for only 0.1–0.2% of all oesophageal neoplasms [14]. It is frequently located in the central and distal esophagus, whereas only in 10% of cases is proximal, in 60 years old male patients: males actually have approximately twice the incidence as females. Symptoms include dysphagia but also retrosternal pain, weight loss, and rarely hematemesis or melaena.

On endoscopy, lesions appear hyperpigmented and ulcerated with satellite nodules [15]. The stomach is rarely involved in melanoma and only a few cases have been reported. Symptoms are non-specific and include abdominal pain, weight loss, upper gastrointestinal bleeding and anaemia [3]. Although primary small bowel melanoma is very rare, it is the most common site of gastrointestinal melanoma metastases. Patients typically present with nausea, vomiting, anorexia, abdominal pain, weight loss, gastrointestinal bleeding with secondary anaemia, and intussusception. [1].

The most common type of GI melanoma, with an estimated incidence rate of 0.4 per million, is anorectal mucosal melanoma [2]. It is the third most common site after cutaneous and ocular melanoma due to malignant transformation of anal and rectal melanocytes. Anal and rectal melanoma occurs most commonly in the seventh decade of life, with a higher incidence in women and a prevalence in Caucasians [1, 16]. It causes rectal bleeding, pain or discomfort and is often diagnosed at an advanced or metastatic stage. The tumor is usually polypoid, ulcerated with or without pigmentation. Primary colorectal melanoma is rare. The average age of patients is 60 years, regardless of sex, with a predilection for the right colon [17]. Abdominal pain and weight loss

are common complaints. Primary biliary tract melanoma is extremely rare and may arise in the gallbladder or bile duct. Presenting symptoms are gallstones or cholecystitis, which cause obstructive jaundice, pain, itching and dark urine. Biliary tract melanomas are often metastatic and present as flat, pigmented lesions, whereas primary lesions are often single polypoid lesions on macroscopic examination [18].

Mucosal Melanomas of the Urogenital Tract

Urogenital tract melanoma is more common in females of Caucasian ethnicity in about 90% of cases [19]. They develop in the vulva, vagina, cervix, urethra, and urinary bladder. The female genital tract accounts for 18% of MM and 3% of those of the urinary tract; the most common site is vulvar (76.7%) followed by vaginal (19.8%), while cervical melanoma is the least common [1]. The second most frequent vulvar cancer is vulvar melanoma. [19] Symptoms include bleeding, lumps or masses in the vulvar area, itching, pain or irritation, discomfort, and discharge. [20] Vaginal melanoma affects 80% of postmenopausal older women with an average age of about 60 years are affected by vaginal melanoma [20]. Pain, mass lesions, and vaginal bleeding and discharge are the most typical presenting symptoms [21]. It appears macroscopically as a variety of pigmented lesion that is fragile, easily bleeds, and ulcerated in half of the cases [1]. Melanoma of the cervix is extremely rare [22] and appears as a variously pigmented or amelanotic exophytic cervical mass. Melanoma of the urethra accounts for about 4% of all urethral malignancies [23] and mostly affects elderly women in the distal tract of the urethra.

In about 20% of cases, MM of the urethra is amelanotic and has polypoid growth, therefore is mistaken for a urethral polyp, mucous prolapse, or urothelial tumor [24]. In the literature, 20 cases of urinary bladder melanoma are reported, underlying the rarity of this neoplasm. Clinical manifestations include hematuria and dysuria and it is often locally advanced at diagnosis [25, 26].

The Genetic Landscape of Mucosal Melanoma

Non-cutaneous melanoma shows different genetic alterations compared to CM, without a clear molecular target pathway [1, 8].

Specifically, MM has a lower burden of somatic mutations as well as UV-related genetic mutations that are widely described in CM [27].

As in cutaneous and acral melanoma, the mutational profile categorizes MM into different molecular groups: BRAF-mutated; RAS-mutated; NF1-loss; and triple wild-type
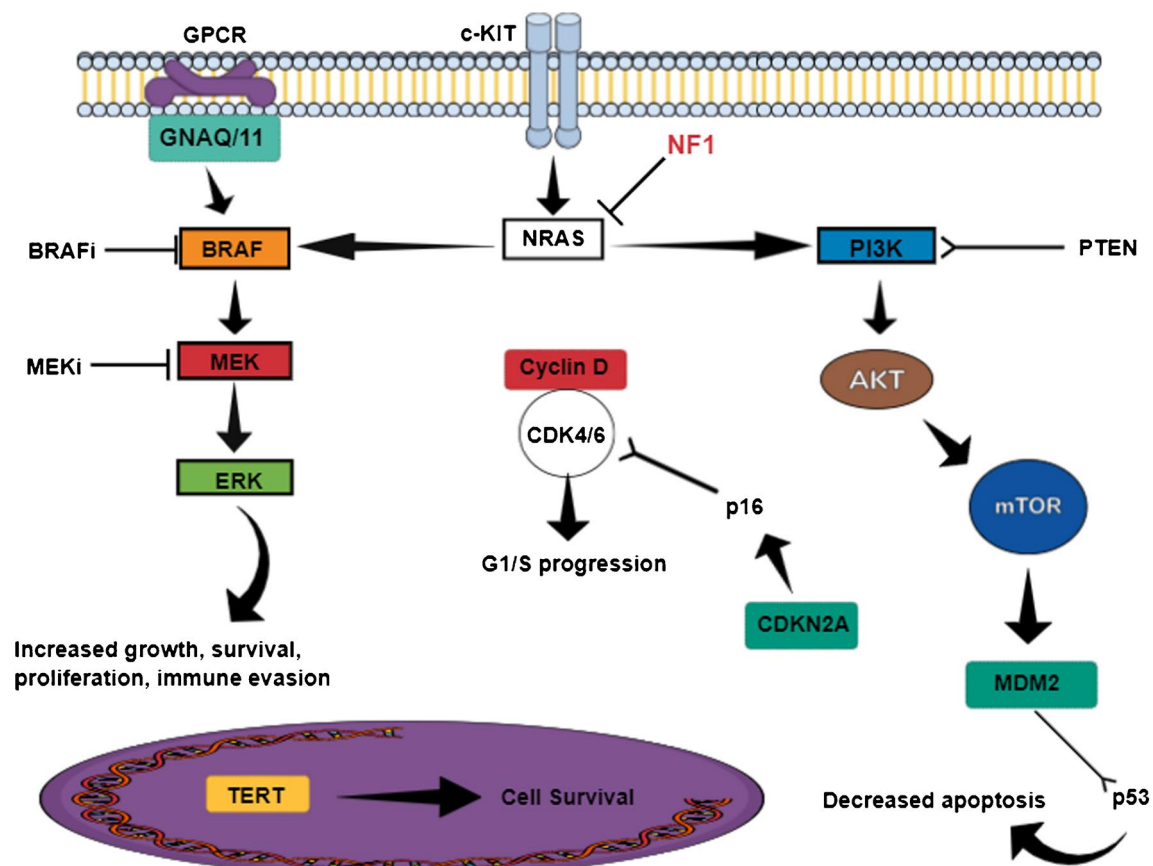
Fig. 1 Main signaling pathways involved in melanoma proliferation: activation of the MAPK signaling cascade and PI3K-AKT-mTOR pathway dysregulation by several oncogenes. Also, TERT promoter mutation is linked to the survival, invasion, and metastasis of melanoma

(absence of mutations in BRAF, RAS and NF1; but the presence of KIT mutations and/or amplifications) [28].

The main pathways involved in the development of MM are summarised in Fig. 1.

The main subtype is characterized by an activating mutation of BRAF, which is involved in MAPK (mitogen-activated protein kinase) signaling, followed by the NRAS mutated group [28].

Activation of MAPK is a major cause of cell proliferation in melanomas that arise on non-chronically sun-damaged skin [29]. However, BRAF/NRAS-activating mutations are less frequently mutated in MM compared to CM [30]: 6% and 8%, respectively, versus 50% and 28% in CM, with a variable incidence depending on the anatomical district of melanoma occurrence [31].

According to Beaudoux's meta-analysis, head and neck MMs have the highest percentage of BRAF mutations, while NRAS mutations are more frequently mutated in MMs of the urinary tract. Surprisingly, the BRAF and NRAS mutations in MM are more similar to those found in tumors such as lung cancer, suggesting an unidentified link to some genotoxic agents [32].

Indeed, MM may present atypical mutations of BRAF (non-V600) and NRAS (located on codons G12, G13, as well as codon Q61), uncovered in patients affected by a more aggressive disease, not responsive to traditional BRAF and MEK inhibitors, but possibly sensitive to next generation of MEK inhibitors [33].

The third subtype, NF1 loss is around 16% of MM [34] and determines the constitutive activation of Ras proteins. Interestingly, co-mutation of NF1 and KIT is found in 32% of MMs (compared to only 4% for CMs), resulting in upregulation of MAPK cascade [2, 35].

KIT/CD117 gene aberrations predominate in MM as opposed to CM [8, 34]. At least 31 mutations involving *c-KIT* affecting exons 9, 11, 13, 17, and 18 have been described [36] in metastatic melanoma. Some research revealed that the disease's early and late stages are both characterized by c-KIT immunoreactivity [36], but whether mutations occur at the onset of melanoma or during the advanced stage due to mutation accumulation, remains unclear. Moreover, Gong et al. showed that similar to BRAF and NRAS mutations, the frequency of c-KIT mutation in melanoma is influenced by the anatomical site of the primary tumor: genitalia and extremities having the highest

mutation rate (of 26 to 35%), anorectal melanoma expresses in 35% of cases cKIT mutations, while in sinonasal tract cKIT mutations are observed in 22% of MM [37].

As mentioned above, cKIT mutations distinguish the subtype of triple-negative melanoma, often associated with the activation of splicing factor 3b subunit 1 (SF3B1), a protein involved in RNA splicing and transcriptomic regulation (with a higher trend of R625C and R625H mutations in vulvovaginal and anal or rectal melanomas) [36] and Telomerase Reverse Transcriptase (TERT) promoter mutations. The overexpression of TERT, which is present in about 30% of head and neck MMs, gives cells the ability to become immortal and therefore aggressive behavior [38, 39].

St.rikingly, some observations uncovered that Sprout-related EVH1 domain-containing protein 1 (SPRED1) loss promotes cell proliferation in KIT-driven melanoma, as a result of SPRED1's function as a tumor suppressor in the MAPK pathway. According to previous studies, SPRED1 acts downstream of KIT but upstream of RAF by directly repressing Ras [39]. The MAPK signal induced by KIT activation may be significantly enhanced by SPRED1 loss, implying the possibility that the co-existence of SPRED1 loss and KIT-activating mutations is linked to resistance to KIT inhibitors [40, 41].

Besides, triple wild-type MMs tend to have CCND1/cyclin D1 or cyclin-dependent kinase (CDK) 4 amplification, acting as an alternative driver in BRAF or NRAS-mediated proliferation signaling mechanisms [2] through activation of MAPK and PI3K pathways. This explains a lack of response to antitumor therapy and a worse prognosis for this melanoma subtype [42].

As reported by Wang et alresearch's, older MM patients who have higher levels of CDK4 protein expression have lower 3-year survival [43]. Other uncommon mutations are in TP53 (9% of cases), ATP-dependent helicase (ATRX) (in 6% of MM), and Phosphatase and tensin homolog (PTEN) inactivation through methylation of the PTEN promoter, a rare occurrence involved in the development of Sinonasal MM [44].

PTEN loss and amplification of CDK4/6 pathways upset the immune system's delicate balance, resulting in immunosuppression and decreased response to immunotherapy [43].

Moreover, the low mutational load described in MM as well as poor expression of death ligand 1 (PD-L1) compared to CM, limits T cell activation contributing to immunotherapy resistance [39, 45].

In conclusion, several reports identified mutations *GNAQ/11* in 9.5% of patients with MM, without clear therapeutic implications. *GNAQ* and *GNA11* are involved in many physiological and pathological processes such as hydrolysis's regulation of GTP [46]. Mutations of *GNAQ* and *GNA11* are relatively low (4.6% and 4.9%, respectively) for MM, unlike the data for uveal melanoma characterized by a frequency of GNAQ mutation ranging from 36 and 53%. Furthermore, metastatic MM patients bearing GNAQ/11 mutations showed

a shorter median survival than wild-type, supporting a probable correlation with clinical progression. [47].

Hence, MMs have a uniquely complex genomic profile that influences their pathogenesis and aggressiveness, explaining the poor response to systemic therapies.

Surgical Treatment and Systemic Treatment

Local Disease

Radical tumor excision is the first approach for locally advanced MM with disease-free surgical margins [48]. However, the anatomical complexity of the region, the metastatic stage at diagnosis, and proximity to vital structures (especially for head-neck tumors) make it difficult to achieve radical surgery [46, 48]. Although challenging surgery procedures, local recurrence is common, particularly in cases of inadequate resection, vascular invasion, and large tumor size [49, 50]. In the head and neck, the median time to first recurrence is 6 to 12 months [51]. Surgery can be paired with adjuvant irradiation to improve local control in patients with clinical lymph node involvement or extracapsular extension [52], although the radiotherapy efficacy is debatable because local failure occurs in half of the patients, and overall survival benefit has not been observed. Sentinel lymph node biopsy (SLNB) is reserved for vulvar and anal melanoma, but its role is controversial because inguinal lymphadenectomy does not improve survival. Therefore, bilateral nodal dissection is performed in patients who have a clinically node-positive disease, eligible for further adjuvant systemic treatment [53].

Due to the diagnostic delay and advanced stage of presentation, systemic therapy is often palliative while adjuvant treatment shows a marginal role. To date, BRAF mutation is mandatory in stage III or IV melanoma [54].

In BRAF wild-type tumors, adjuvant immunotherapy with antibodies targeting PD-1, nivolumab, or pembrolizumab, is a viable choice. In BRAF-mutated MM, targeted therapy with BRAF and MEK inhibitors is an option, in addition to adjuvant immunotherapy [55].

Nevertheless, most trials have enrolled patients with cutaneous melanoma, except for CheckMate 238, whereby 29/906 patients with MM were included, to evaluate adjuvant Nivolumab, or Ipilimumab in resected stage IIIB, IIIC, and IV melanoma. Interestingly, Japanese subgroup analysis revealed a low efficacy of Nivolumab in mucosal melanoma than in cutaneous melanoma (51.7% in the nivolumab arm vs 41.7% in the ipilimumab arm) [56]. Despite the effectiveness advantage of the combination of nivolumab and ipilimumab in CheckMate 067 [57] for metastatic melanoma, no such recurrence-free survival improvement was observed in the adjuvant setting

in CheckMate 915, with lower ipilimumab dose in both cutaneous and mucosal melanoma (7% of the population in the combination arm) [58].

Adjuvant chemotherapy was investigated in a phase III trial of 204 resected MM patients. This trial evaluated temozolomide plus cisplatin versus one year of interferon-alfa-2b [59]. In preliminary evidence, at a median follow-up of 24 months, chemotherapy improved relapse-free survival (median 15.5 versus 9.5 months) and distant metastasis-free survival (median 16.8 months versus 9.6 months). To date, chemotherapy should not be considered the standard of care but exclusively offered to patients not suited for immunotherapy or targeted therapy [60]. Regardless of local diseases, neoadjuvant therapy is evolving. At a median follow-up of 59 weeks, neoadjuvant toripalimab (a humanized antibody targeting PD1) plus axitinib (a selective inhibitor of vascular endothelial growth factor [VEGF] receptor tyrosine kinases 1, 2, and 3) revealed a complete pathologic response rate of 29 percent in a phase II study of 21 patients with resectable MM, representing a new opportunity [61].

Unresectable and Metastatic Disease

In patients with metastatic MM lacking a BRAF mutation, a combination of immunotherapy has provided a promising therapeutic approach, albeit clinical studies show less responsiveness compared to cutaneous melanoma [62]. A 5-year subanalysis of the Checkmate 067 trial about mucosal melanoma patients reported a considerably higher objective response rate (ORR) (43% vs. 7%), and Overall Survival (OS) rate (36% vs. 7%) in 79 patients with MM treated with combined Nivolumab and Ipilimumab vs ipilimumab alone [63], while Nivolumab monotherapy was associated with 30% of ORR and 17 % of OS rate. This data is confirmed by D'Angelo et al. pooled analysis of five trials (CA209-003, CA209-038, CheckMate-037, CheckMate-066, and Check-Mate-067). Despite the median reduction in tumor burden being -34.2% for combination therapy in the subgroup of MM as compared to cutaneous melanoma patients, ORR and PFS are lower (37 vs 60% and 5.9 versus 11.7 months, respectively). Notably, the response rate is higher in patients with an assessment of PDL1 > 5% (53.3% *versus* 12.2% in PD-L1 < 5).

Regarding safety, the most common immune-related events in grades 3 or 4 were rash and diarrhea, higher for combination therapy [58, 64].

A regimen with pembrolizumab was assessed in several studies, confirming Nivolumab data of ORR (19%), the median PFS (2.8 months), and the median OS (11.3 months) [65].

Interestingly, clinical outcomes in Asian patients are less favorable than in Caucasian individuals.

Keynote 041 phase Ib study, evaluating the safety of pembrolizumab in Japanese patients with metastatic melanoma, showed an ORR of 25% for MM [66]. Moreover, in the Keynote-151 trial and Polaris-01 trial, which investigated pembrolizumab and toripalimab, in the Chinese population with advanced/metastatic MM, the anti-PD1 therapy achieved an ORR of 13.3% and 0%, respectively [67]. Probably, these results reflect the immunotherapy resistance in the Asian group, which had a higher rate of KIT mutations, in addition to lower expression of PD-L1, and lower tumor mutational burden [68–70].

Based on c-KIT mutations, agents targeting c-*KIT* have been examined in mucosal melanoma. According to the results of a retrospective study investigating imatinib's (a c-KIT inhibitor) effectiveness in patients with MM who had KIT mutations or amplification., ORR observed was 21.9%, the overall disease control rate of 60%, and an OS of 13 months and PFS of 4 months [71].

In this regard, the *KIT* exon 11 and 13 mutations demonstrate sensitivity to KIT inhibitors, while KIT exon 17 mutations and *KIT* amplifications show no response to imatinib or similar drugs [72]. Another tyrosine kinase inhibitor Dasatinib, targeting mutation in cKIT exon 11-L572P, has been assessed in the ECOG-ACRINE2607 trial, administered 70 mg twice daily in mucosal, acral, or vulvovaginal melanoma. The results were unsuccessful because PFS and OS were low regardless of cKIT status or subtypes [73]. Thus, Imatinib remains a treatment option for patients with a *KIT* mutation who progressed or suffered adverse events after immunotherapy.

Furthermore, the combination of BRAF and MEK inhibitors is less effective in MM, probably as a consequence of NF1 loss of function mutations or deletions linked to BRAF inhibitor resistance, while no effect of NRAS mutation on metastatic melanoma characteristics or outcomes of checkpoint inhibitor immunotherapy is noted [75].

Data from the Italian Melanoma Intergroup underlie the predictive role of intratumoral CD8 + T cells in targeted therapy in terms of PFS and OS [75].

Another promising therapeutic strategy includes targeting NF1. NF1 mutation is associated with better response to immune checkpoint inhibitors, [76] but also worse overall survival for patients with NF1 WT. Jour et al. found a high expression of MK167 (Marker of Proliferation Ki-67) and CDC20 in these patients, thus suggesting a relation between the nuclear accumulation of CDC20 transcripts and worse prognosis. In this study, MAPK pathway and CDC20 co-inhibition resulted in cytotoxic and cytostatic effects, decreasing CDC20 expression in many NF1-mutant cell lines, supporting the idea that inhibition of CDC20 and MAPK pathways may be a new option for NF1 mutated melanoma [77].

Table 1 A summary of clinical studies (recruiting, active or not yet recruiting) for the perioperative and advanced setting of mucosal melanoma (sources: clinicaltrials.gov)

Therapeutic regimen	Molecular target(s)	Clinical phase	Sample size	Primary outcome	Identifier
Neoadjuvant Setting					
Pembrolizumab Plus Lenvatinib	VEGFR1, VEGFR2, VEGFR3, FGFR1-4, PDGFRα, KIT, RET; PD-1	II	44	Change in immune cell expression of HIF1 and immune cell densities; Pathological response rate	NCT05545969
Pembrolizumab plus IMRT	PD-1	II	50	DFS	NCT03313206
Adjuvant Versus NeoAdjuvant Pembrolizumab	PD-1	II	336	Event-free survival	NCT03698019
Nivolumab alone versus Nivolumab plus Ipilimumab versus Nivolumab plus Relatlimab	PD-1; CTLA-4; LAG3	II	53	Pathologic response	NCT02519322
Toripalimab plus Axitinib	PD-1; VEGFR 1-2-3; PDGFRβ and c-Kit	II	30	Pathological response rate	NCT04180995
Adjuvant Setting					
Ipilimumab Plus Nivolumab	PD-1; CTLA-4	II	36	RFS	NCT03241186
Toripalimab plus Temozolomide	PD-1; DNA	II	294	RFS	NCT04462965
Nivolumab alone vs Nivolumab plus Cabozantinib	PD-1; MET, RET, AXL, VEGFR2, FLT3, and c-KIT	II	99	Efficacy of adjuvant nivolumab alone vs combination therapy	NCT05111574
Hypofractionated radiation therapy plus Pembrolizumab	PD-1	II	16	Local tumor control rate	NCT04318717
Dabrafenib plus Trametinib	BRAF; MEK;	NA	150	RFS	NCT04666272
Advanced Setting					
Toripalimab plus chemotherapy plus Endostar	PD-1; M1 macrophages	II	31	PFS	NCT04472806
Atezolizumab plus Bevacizumab	PD-L1; VEGF-A	II	43	ORR	NCT04091217
Oral Decitabine/Cedazuridine plus Nivolumab	PD-1; cytidine deaminase; nucleoside metabolic	I/II	30	Safety of DEC-C	NCT05089370
Nemvaleukin Alfa Subcutaneous vs Intravenous	IL-2R	II	110	Centrally-assessed ORR	NCT04830124
Nivolumab plus Axitinib and Ipilimumab or SBRT in select progressors	PD-1; CTLA-4; VEGFR1, VEGFR2, VEGFR3, PDGFRβ and c-Kit	II	20	Best objective response	NCT05384496
APG-115 plus Pembrolizumab	MDM2; PD-1	I/II	224	Maximum Tolerated Dose; Recommended Phase II Dose, Overall Response Rate	NCT03611868
[212Pb] VMT01	MC1R Receptor	I/II	52	Treatment-related adverse events; DLTs, ORR	NCT05655312
Aldesleukin plus Pembrolizumab	T cells (IL-2); PD-1	II	65	Best overall response rate	NCT02748564
Neoantigen Peptide Vaccine Plus Nivolumab and Poly ICLC	T cell; PD-1;	I	20	Incidence of adverse events	NCT05098210

Table 1 (continued)

Therapeutic regimen	Molecular target(s)	Clinical phase	Sample size	Primary outcome	Identifier
Tebentafusp alone vs Tebentafusp plus durvalumab vs Tebentafusp plus tremelimumab vs Tebentafusp plus tremelimumab plus durvalumab	PD-1; CTLA-4; gp100	I/II	312	DLT and ORR	NCT02535078
Tebentafusp alone vs Tebentafusp plus pembrolizumab	PD-1; gp100	II/III	460	ctDNA reduction on treatment relative to baseline; Overall Survival	NCT05549297
Camrelizumab Plus Anlotinib Plus nab-Paclitaxel	Microtubules; PD-1; VEGFR	II	66	ORR	NCT04979585
Recombinant Vesicular Stomatitis Virus-expressing Interferon-beta and Tyrosinase Related Protein 1	Vaccine	I	12	Maximum-tolerated dose; Incidence of adverse events	NCT03865212
MGD013	PD-1; LAG-3	I	92	ORR	NCT04653038
Ceralasertib alone vs Ceralasertib Durvalumab	PD-(L)1; ataxia telangiectasia and Rad3-related kinase	II	195	Changes in CD8+T cell infiltration of tumours induced by ceralasertib monotherapy; ORR	NCT05061134
Pembrolizumab plus Lenvatinib	PD-1; VEGFR1, VEGFR2, VEGFR3, FGFR1-4, PDGFRα, KIT, RET	III	660	PFS; OS	NCT03820986
YH003 Plus Pebolizumab and Albumin Paclitaxel	CD-40; PD-1; Microtubules	II	43	ORR	NCT05420324
Vactosertib plus Pembrolizumab	PD-1; activin receptor-like kinase 5	II	30	Overall Response Rate	NCT05436990
Olaparib	BRCA1/2 Genes	II	15	ORR	NCT05482074
Intrathecal nivolumab, plus or not intravenous nivolumab in treating patients with leptomeningeal disease	PD-1;	I	50	Safety and/or recommended dose of intrathecal of Nivolumab	NCT03025256
Binimetinib and Encorafenib plus Nivolumab vs Ipilimumab plus Nivolumab	BRAF-V600; PD-1; CTLA-4	II	112	PFS	NCT04511013
Apatinib plus Temozolomide	VEGFR2; DNA	II	30	PFS	NCT03422445
Dinaciclib	CDK	II	72	1-year overall survival rate	NCT00937937
Vorolanib plus toripalimab	VEGFR/PDGFR; PD-1	II	40	ORR	NCT03602547

CTLA-4 cytotoxic T-Lymphocyte Antigen 4; *DLT* dose-limiting toxicities; *DFS* disease-free survival; *FGFR1-4* fibroblast growth factor receptor 4; *HIF1* hypoxia-inducible factor 1-alpha; *IMRT* intensity modulation radiation therapy; *IL-2R* interleukin-2 Receptor; *KIT* stem cell factor receptor; *LAG3* lymphocyte-activation gene 3; *MDM2* murine double minute 2; *NA* not applicable; *ORR* objective response rate; *SO* overall survival; *PDGFRα* platelet-derived growth factor alfa; *PDGFRβ* platelet-derived growth factor receptor beta; *PD-(L)1* programmed death-(ligand)1; *PFS* progression-free survival; *RET* rearranged during transfection; *RFS* recurrence-free survival; *VEGF* vascular-endothelial growth factor

Conclusions and Future Perspectives

Due to the less effectiveness of immunotherapy compared to cutaneous melanoma, numerous ongoing trials are exploring new combination therapies (Table 1). The combination of anti-angiogenic therapy and immunotherapy results in increases in the number of TILs and inhibits tumor growth in murine cancer models [78]. A single-center, phase Ib trial assays the preliminary efficacy and safety of toripalimab in combination with axitinib in patients with advanced Melanoma [79, 80]. Twenty-nine Asian patients with MM received axitinib and toripalimab every 2 weeks, 14 patients had a partial response, the median OS still not reached after (at 1.5 years of follow-up), and a longer PFS and a better ORR were found in PD-L1-positive tumor.

Furthermore, the angiogenesis signatures might be considered an applicable biomarker for anti-VEGF plus immunotherapy, although VEGF signaling has an important immune-modulating function in the microenvironment [80]. Likewise, pembrolizumab plus Lenvatinib (another vascular endothelial growth factor receptor inhibitor) revealed a potential anticancer effect in patients with advanced melanoma. In the LEAP-003 trial, this combination is currently ongoing also for patients with acral and mucosal melanomas [81]. Similar minor clinical studies of combination treatments for mucosal melanoma are also underway and recruiting patients, as well as trials with Immune checkpoint inhibitors (ICI) or apatinib (anti-VEGFR2) plus temozolomide (alkylating agent similar to dacarbazine) [NCT03422445]; radiation plus ICI in mucosal melanoma of the head and neck [NCT04318717]; Camrelizumab (an anti-PD1), plus anlotinib (multitargeted tyrosine kinase inhibitor), and nab-paclitaxel. Promising combinations with ICI under evaluation include MDM2 inhibitor (APG-115) and aldesleukin (NCT03611868, NCT02748564) or single-agent nemvaleukin (NCT04830124). Nevertheless, most of these studies enrolled Asian patients, most frequently affected by this neoplasm. In MM, CDK4 amplification and/or CCND1 amplification and/or p16 (CDKN2A) loss leads to the dysregulation of cell cycle progression, which justifies the rationale of targeting CDK4/6 in some preclinical and clinical trials [82]. Another intriguing target for MM is ataxia telangiectasia and rad3-related (ATR) kinase. An orally available morpholino-pyrimidine-based inhibitor of this molecule is investigated in a phase 2 trial in combination with anti-PD-L-1 in unresectable or advanced melanoma and primary or secondary resistance to PD-(L)1 inhibition, to date an unmet clinical need [NCT05061134].

Hence, even if the combination treatments could enhance long-term outcomes in this rare and aggressive subtype of melanoma, we must consider clinic-pathological features and mutational profiles of a single patient to open the road for novel treatment targets [83]. In this scenario, where traditional therapies are less effective, further prospective umbrella clinical trials are critical to promoting precision medicine and inclusion of the non-Asian population, despite the higher incidence in Orient.

To date, several clinical studies conducted for neoadjuvant and adjuvant therapies are focused on exploring an innovative strategy, dealing with this tumor in the earliest setting.

Declarations

Conflict of Interest The authors declare no competing interests.

References

1. Yde SS, Sjoegren P, Heje M, Stolle LB. Mucosal Melanoma: a Literature Review. Curr Oncol Rep. 2018;20:28 (http://link.springer.com/10.1007/s11912-018-0675-0). Accessed 14 Mar 2023.

2. Ma Y, Xia R, Ma X, Judson-Torres RL, Zeng H. Mucosal Melanoma: Pathological Evolution, Pathway Dependency and Targeted Therapy. Front Oncol. 2021;11:702287. https://doi.org/10.3389/fonc.2021.702287.

3. Spencer KR, Mehnert JM. Mucosal Melanoma: Epidemiology, Biology and Treatment. In: Kaufman HL, Mehnert JM, editors. curatori. Melanoma Cham: Springer International Publishing; 2016. p. 295–320 (https://link.springer.com/10.1007/978-3-319-22539-5_13). Accessed 1 Mar 2023.

4. Postow MA, Hamid O, Carvajal RD. Mucosal Melanoma: Pathogenesis, Clinical Behavior, and Management. Curr Oncol Rep. 2012;14:441–8 (http://link.springer.com/10.1007/s11912-012-0244-x). Accessed 1 Mar 2023.

5. Tomicic J, Wanebo HJ. Mucosal melanomas. Surgical Clinics of North America. 2003;83:237–52 (https://linkinghub.elsevier.com/retrieve/pii/S0039610902001007). Accessed 1 Mar 2023.

6. Altieri L, Wong MK, Peng DH, Cockburn M. Mucosal melanomas in the racially diverse population of California. J Am Acad Dermatol. 2017;76:250–7.

7. Lourenço SV, Fernandes JD, Hsieh R, Coutinho-Camillo CM, Bologna S, Sangueza M, Nico MMS. Head and neck mucosal melanoma: a review. Am J Dermatopathol. 2014;36:578–87. https://doi.org/10.1097/DAD.0000000000000035.

8. Tacastacas JD, Bray J, Cohen YK, Arbesman J, Kim J, Koon HB, et al. Update on primary mucosal melanoma. J Am Dermatology. 2014;71:366–75.

9. Seetharamu N, Ott PA, Pavlick AC. Mucosal melanomas: a case-based review of the literature. Oncologist. 2010;15:772–81.

10. Thompson LD, Wieneke JA, Miettinen M. Sinonasal tract and nasopharyngeal melanomas: a clinicopathologic study of 115 cases with a proposed staging system. Am J Surg Pathol. 2003;27:594–611.

11. Khadka SS, Lee M, Karki A. Primary malignant mucosal melanoma of the larynx: A case report and literature review. J Pathol Nep. 2015;5:872–4 (https://www.nepjol.info/index.php/JPN/article/view/15645). Accessed 3 Mar 2023.

12. Liu G-H, Liu J, Dong H, Tang X-J. Primary malignant melanoma of the lung: a case report. Int J Clin Exp Med. 2014;7:1757–9.

13. Cheung MC, Perez EA, Molina MA, Jin X, Gutierrez JC, Franceschi D, Livingstone AS, Koniaris LG. Defining the role of surgery for primary gastrointestinal tract melanoma. J Gastrointest Surg. 2008;12:731–8.

14. Bisceglia M, Perri F, Tucci A, Tardio M, Panniello G, Vita G, Pasquinelli G. Primary malignant melanoma of the esophagus: a clinicopathologic study of a case with comprehensive literature review. Adv Anat Pathol. 2011;18:235–52.

15 Iwanuma Y, Tomita N, Amano T, Isayama F, Tsu-Rumaru M, Hayashi T, Kajiyama Y. Current status of primary malignant melanoma of the esophagus: clinical features, pathology, management and prognosis. J Gastroenterol. 2012;47:21–8.

16. Wang J, Yang F, Ao W-Q, Liu C, Zhang W-M, Xu F-Y. Primary gastric melanoma: A case report with imaging findings and 5-year follow-up. World J Gastroenterol. 2019;25:6571–8.

17. Coté TR, Sobin LH. Primary melanomas of the esophagus and anorectum: epidemiologic comparison with melanoma of the skin. Melanoma Res. 2009;19:58–60.

18. Khalid U, Saleem T, Imam AM, Khan MR. Pathogenesis, diagnosis and management of primary melanoma of the colon. World J Surg Onc. 2011;9:14 (https://wjso.biomedcentral.com/articles/10.1186/1477-7819-9-14). Accessed 30 Mar 2023.

19. Smith NE, Taube JM, Warczynski TM, Collier KD, Pawlik TM. Primary biliary tract melanoma: Report of a case and review of the literature. Int J Surg Case Rep. 2012 [citato 10 maggio 2023];3:441–4. https://linkinghub.elsevier.com/retrieve/pii/S2210261212001022. Accessed 10 May 2023.

20. Sugiyama VE, Chan JK, Shin JY, Berek JS, Osann K, Kapp DS. Vulvar melanoma: a multivariable analysis of 644 patients. Obstet Gyne-col. 2007;110:296–301.

21. Tucci M, Pasculli A, Sgaramella LI, Cazzato G, Macorano E, Piscitelli D, et al. Severe anemia in a patient with vulvar melanoma. Surgery. 2020;168:e21-2 (https://linkinghub.elsevier.com/retrieve/pii/S0039606020304608).

22. Gungor T, Altinkaya SO, Ozat M, Bayramoglu H, Mollamahmutoglu L. Primary Malignant Melanoma of the Female Genital Tract. Taiwanese J Obstet Gynecol. 2009;48:169–75 (https://linkinghub.elsevier.com/retrieve/pii/S1028455909602813).

23. Pusceddu S, Bajetta E, Carcangiu ML, Formisano B, Ducceschi M, Buzzoni R. A literature overview of primary cervical malignant melanoma: An exceedingly rare cancer. Crit Rev Oncol/Hematol. 2012 ;81:185–95. Recuperato da: https://linkinghub.elsevier.com/retrieve/pii/S1040842811000758. Accessed 12 Mar 2023.

24. Piura B. Management of primary melanoma of the female urogenital tract. Lancet Oncol. 2008, 9:973–81. Recuperato da: https://linkinghub.elsevier.com/retrieve/pii/S1470204508702547. Accessed 14 May 2023.

25. Gupta R, Bhatti SS, Dinda AK, Singh MK. Primary melanoma of the urethra: a rare neoplasm of the urinary tract. Int Urol Nephrol. 2007;39:833–6 (http://link.springer.com/10.1007/s11255-006-9086-5).

26. Pacella M, Gallo F, Gastaldi C, Ambruosi C, Carmignani G. Primary malignant melanoma of the bladder. Int J Urol. 2006;13:635–7 (https://onlinelibrary.wiley.com/doi/10.1111/j.1442-2042.2006.01375.x).

27. Schoenewolf NL, Bull C, Belloni B, Holzmann D, Tonolla S, Lang R, et al. Sinonasal, genital and acrolentiginous melanomas show distinct characteristics of KIT expression and mutations. Eur J Cancer. 2012;48:1842–52 (https://linkinghub.elsevier.com/retrieve/pii/S0959804912002006). Accessed 14 May 2023.

28. Santeufemia DA, Palmieri G, Miolo G, Colombino M, Doro MG, Frogheri L, et al. Current Trends in Mucosal Melanomas: An Overview. Cancers. 2023;15:1356 (https://www.mdpi.com/2072-6694/15/5/1356). Accessed 14 May 2023.

29. Rabbie R, Ferguson P, Molina-Aguilar C, Adams DJ, Robles-Espinoza CD. Melanoma subtypes: genomic profiles, prognostic molecular markers and therapeutic possibilities. J Pathol. 2019;247:539–51 (https://onlinelibrary.wiley.com/doi/10.1002/path.5213).

30. Curtin JA, Fridlyand J, Kageshita T, Patel HN, Busam KJ, Kutzner H, et al. Distinct Sets of Genetic Alterations in Melanoma. N Engl J Med. 2005;353:2135–47 (http://www.nejm.org/doi/abs/10.1056/NEJMoa050092).

31. Newell F, Kong Y, Wilmott JS, Johansson PA, Ferguson PM, Cui C, et al. Whole-genome landscape of mucosal melanoma reveals diverse drivers and therapeutic targets. Nat Commun. 2019;10:3163.

32 Nassar KW, Tan AC. The mutational landscape of mucosal melanoma. Semin Cancer Biol. 2020;61:139–48. https://doi.org/10.1016/j.semcancer.2019.09.013.

33. Dumaz N, Jouenne F, Delyon J, Mourah S, Bensussan A, Lebbé C. Atypical BRAF and NRAS Mutations in Mucosal Melanoma. Cancers (Basel). 2019;11:1133.

34. Beaudoux O, Oudart J-B, Riffaud L, Visseaux L, Marchal A, Lebre A-S, et al. Mutational Characteristics of Primary Mucosal Melanoma: A Systematic Review. Mol Diagn Ther. 2022;26:189–202.

35. Kiuru M, Busam KJ. The NF1 gene in tumor syndromes and melanoma. Labor Investig. 2017;97:146–57 (https://linkinghub.elsevier.com/retrieve/pii/S0023683722022723). Accessed 4 Apr 2023.

36. Satzger I, Schaefer T, Kuettler U, Broecker V, Voelker B, Ostertag H, et al. Analysis of c-KIT expression and KIT gene mutation in human mucosal melanomas. Br J Cancer. 2008;99:2065–9.

37. Wroblewska JP, Mull J, Wu C-L, Fujimoto M, Ogawa T, Marszalek A, et al. SF3B1, NRAS, KIT, and BRAF Mutation; CD117 and cMYC Expression; and Tumoral Pigmentation in Sinonasal Melanomas: An Analysis With Newly Found Molecular Alterations and Some Population-Based Molecular

Differences. Am J Surg Pathol. 2019;43:168–77 (https://journals.lww.com/00000478-201902000-00003). Accessed 5 Apr 2023.

38. Gong HZ, Zheng HY, Li J. The clinical significance of KIT mutations in melanoma: a meta-analysis. Melanoma Res. 2018;28(4):259–70. https://doi.org/10.1097/CMR.0000000000000454.

39. Bell RJA, Rube HT, Xavier-Magalhães A, Costa BM, Mancini A, Song JS, et al. Understanding TERT Promoter Mutations: A Common Path to Immortality. Mol Cancer Res. 2016;14:315–23.

40. Indini A, Roila F, et al. Molecular Profiling and Novel Therapeutic Strategies for Mucosal Melanoma: A Comprehensive Review. Int J Mol Sci. 2022;23:147.

41. Ablain J, Xu M, Rothschild H, Jordan RC, Mito JK, Daniels BH, et al. Human tumor genomics and zebrafish modeling identify SPRED1 loss as a driver of mucosal melanoma. Science. 2018;362:1055–60.

42. Williams GH, Stoeber K. The cell cycle and cancer. J Pathol. 2012;226:352–64.

43. Wang F, Chen G, Quinn MJ, Chen S, Ji X, Shentu Y, et al. Increased CDK4 protein expression predicts a poor prognosis in mucosal melanoma associated with the p16INK4a-CDK4-pRb pathway. Int J Clin Exp Pathol. 2019;12:2819–25.

44. Lee SH, Roh MR, Kang B, Park KH, Kim SH, Lee SE, et al. PTEN Methylation Dependent Sinonasal Mucosal Melanoma. Cancer Res Treat. 2016;48:853–8.

45. Studentova H, Kalabova H, Koranda P, Chytilova K, Kucerova L, Melichar B, et al. Immunotherapy in mucosal melanoma: a case report and review of the literature. Oncotarget. 2018;9:17971–7.

46. Sheng X, Kong Y, Li Y, Zhang Q, Si L, Cui C, et al. GNAQ and GNA11 mutations occur in 9.5% of mucosal melanoma and are associated with poor prognosis. Eur J Cancer. 2016;65:156–63.

47. Kim C-Y, Kim DW, Kim K, Curry J, Torres-Cabala C, Patel S. GNAQmutation in a patient with metastatic mucosal melanoma. BMC Cancer. 2014;14:516. https://doi.org/10.1186/1471-2407-14-516.

48. Bachar G, Loh KS, O'Sullivan B, Goldstein D, Wood S, Brown D, et al. Mucosal melanomas of the head and neck: experience of the Princess Margaret Hospital. Head Neck. 2008;30:1325–31.

49. Nicolai P, Battaglia P, Bignami M, Bolzoni Villaret A, Delù G, Khrais T, et al. Endoscopic surgery for malignant tumors of the sinonasal tract and adjacent skull base: a 10-year experience. Am J Rhinol. 2008;22:308–16.

50. Patel SG, Prasad ML, Escrig M, Singh B, Shaha AR, Kraus DH, et al. Primary mucosal malignant melanoma of the head and neck. Head Neck. 2002;24:247–57.

51. Panje WR, Moran WJ. Melanoma of the upper aerodigestive tract: a review of 21 cases. Head Neck Surg. 1986;8:309–12.

52. Manolidis S, Donald PJ. Malignant mucosal melanoma of the head and neck: review of the literature and report of 14 patients. Cancer. 1997;80:1373–86.

53. Nakashima JP, Viégas CM, Fassizoli AL, Rodrigues M, Chamon LAG, Silva JHC, et al. Postoperative adjuvant radiation therapy in the treatment of primary head and neck mucosal melanomas. ORL J Otorhinolaryngol Relat Spec. 2008;70:344–51.

54. Wechter ME, Gruber SB, Haefner HK, Lowe L, Schwartz JL, Reynolds KR, et al. Vulvar melanoma: a report of 20 cases and review of the literature. J Am Acad Dermatol. 2004;50:554–62.

55. Dhar KK, Das N, Brinkman DA, Beynon JL, Woolas RP. Utility of sentinel node biopsy in vulvar and vaginal melanoma: report of two cases and review of the literature. Int J Gynecol Cancer. 2007;17:720–3.

56. Marconcini R, Pezzicoli G, Stucci LS, Sergi MC, Lospalluti L, Porta C, et al. Combination of immunotherapy and other targeted therapies in advanced cutaneous melanoma. Hum Vaccin Immunother. 2022;18:1980315.

57. Yokota K, Uchi H, Uhara H, Yoshikawa S, Takenouchi T, Inozume T, et al. Adjuvant therapy with nivolumab versus ipilimumab after complete resection of stage III/IV melanoma: Japanese subgroup analysis from the phase 3 CheckMate 238 study. J Dermatol. 2019;46:1197–201.

58. Wolchok JD, Chiarion-Sileni V, Gonzalez R, Grob J-J, Rutkowski P, Lao CD, et al. Long-Term Outcomes With Nivolumab Plus Ipilimumab or Nivolumab Alone Versus Ipilimumab in Patients With Advanced Melanoma. J Clin Oncol. 2022;40:127–37.

59. Weber JS, Schadendorf D, Del Vecchio M, Larkin J, Atkinson V, Schenker M, et al. Adjuvant Therapy of Nivolumab Combined With Ipilimumab Versus Nivolumab Alone in Patients With Resected Stage IIIB-D or Stage IV Melanoma (CheckMate 915). J Clin Oncol. 2023;41:517–27.

60. Tang L, Wei X, Li C, Dai J, Bai X, Mao L, et al. Proliferation Marker Ki67 as a Stratification Index of Adjuvant Chemotherapy for Resectable Mucosal Melanoma. Front Oncol. 2022;12:895672.

61. Zhang L, Hao B, Geng Z, Geng Q. Toripalimab: the First Domestic Anti-Tumor PD-1 Antibody in China. Front Immunol. 2022;12:730666. https://doi.org/10.3389/fimmu.2021.730666.

62. Nakamura Y, Namikawa K, Yoshikawa S, Kiniwa Y, Maekawa T, Yamasaki O, et al. Anti-PD-1 antibody monotherapy versus anti-PD-1 plus anti-CTLA-4 combination therapy as first-line immunotherapy in unresectable or metastatic mucosal melanoma: a retrospective, multicenter study of 329 Japanese cases (JMAC study). ESMO Open. 2021;6:100325.

63. D'Angelo SP, Larkin J, Sosman JA, Lebbé C, Brady B, Neyns B, et al. Efficacy and Safety of Nivolumab Alone or in Combination With Ipilimumab in Patients With Mucosal Melanoma: A Pooled Analysis. J Clin Oncol. 2017;35:226–35.

64. Nigro O, Pinotti G, De Galitiis F, Di Pietro FR, Giusti R, Filetti M, et al. Late immune-related adverse events in long-term responders to PD-1/PD-L1 checkpoint inhibitors: A multicentre study. Eur J Cancer. 2020;134:19–28.

65. Hamid O, Robert C, Ribas A, Hodi FS, Walpole E, Daud A, et al. Antitumour activity of pembrolizumab in advanced mucosal melanoma: a post-hoc analysis of KEYNOTE-001, 002, 006. Br J Cancer. 2018;119:670–4.

66. Yamazaki N, Takenouchi T, Fujimoto M, Ihn H, Uchi H, Inozume T, et al. Phase 1b study of pembrolizumab (MK-3475; anti-PD-1 monoclonal antibody) in Japanese patients with advanced melanoma (KEYNOTE-041). Cancer Chemother Pharmacol. 2017;79:651–60.

67. Si L, Zhang X, Shu Y, Pan H, Wu D, Liu J, et al. A Phase Ib Study of Pembrolizumab as Second-Line Therapy for Chinese Patients With Advanced or Metastatic Melanoma (KEYNOTE-151). Transl Oncol. 2019;12:828–35.

68. Tang B, Chi Z, Chen Y, Liu X, Wu D, Chen J, et al. Safety, Efficacy, and Biomarker Analysis of Toripalimab in Previously Treated Advanced Melanoma: Results of the POLARIS-01 Multicenter Phase II Trial. Clin Cancer Res. 2020;26:4250–9.

69. Sakaizawa K, Ashida A, Uchiyama A, Ito T, Fujisawa Y, Ogata D, et al. Clinical characteristics associated with BRAF, NRAS and KIT mutations in Japanese melanoma patients. J Dermatol Sci. 2015;80:33–7.

70. Rose AAN, et al. Biologic subtypes of melanoma predict survival benefit of combination anti-PD1+anti-CTLA4 immune checkpoint inhibitors versus anti-PD1 monotherapy. J Immunother Cancer. 2021;9(1):e001642. https://doi.org/10.1136/jitc-2020-001642.

71. Wei X, Mao L, Chi Z, Sheng X, Cui C, Kong Y, et al. Efficacy Evaluation of Imatinib for the Treatment of Melanoma: Evidence From a Retrospective Study. Oncol Res. 2019;27:495–501.

72. Hodi FS, Corless CL, Giobbie-Hurder A, Fletcher JA, Zhu M, Marino-Enriquez A, et al. Imatinib for melanomas harboring mutationally activated or amplified KIT arising on mucosal, acral, and chronically sun-damaged skin. J Clin Oncol. 2013;31:3182–90.

73. Kalinsky K, Lee S, Rubin KM, Lawrence DP, Iafrarte AJ, Borger DR, et al. A phase 2 trial of dasatinib in patients with locally advanced or stage IV mucosal, acral, or vulvovaginal melanoma: A trial of the ECOG-ACRIN Cancer Research Group (E2607). Cancer. 2017;123:2688–97.

74. Guida M, Bartolomeo N, Quaglino P, Madonna G, Pigozzo J, Di Giacomo AM, et al. No Impact of NRAS Mutation on Features of Primary and Metastatic Melanoma or on Outcomes of Checkpoint Inhibitor Immunotherapy: An Italian Melanoma Intergroup (IMI) Study. Cancers (Basel). 2021;13:475.

75. Massi D, Rulli E, Cossa M, Valeri B, Rodolfo M, Merelli B, et al. The density and spatial tissue distribution of CD8+ and CD163+ immune cells predict response and outcome in melanoma patients receiving MAPK inhibitors. J Immunother Cancer. 2019;7:308.

76. Eroglu Z, Zaretsky JM, Hu-Lieskovan S, Kim DW, Algazi A, Johnson DB, et al. High response rate to PD-1 blockade in desmoplastic melanomas. Nature. 2018;553:347–50.

77. Jour G, Illa-Bochaca I, Ibrahim M, Donnelly D, Zhu K, Miera EV-SD et al. Genomic and Transcriptomic Analyses of NF1-Mutant Melanoma Identify Potential Targeted Approach for Treatment. J Investig Dermatol

78. Cirenajwis H, Lauss M, Ekedahl H, Törngren T, Kvist A, Saal LH, et al. NF1-mutated melanoma tumors harbor distinct clinical and biological characteristics. Mol Oncol. 2017;11:438–51.

79. Yasuda S, Sho M, Yamato I, Yoshiji H, Wakatsuki K, Nishiwada S, et al. Simultaneous blockade of programmed death 1 and vascular endothelial growth factor receptor 2 (VEGFR2) induces synergistic anti-tumour effect in vivo. Clin Exp Immunol. 2013;172:500–6.

80. Sheng X, Yan X, Chi Z, Si L, Cui C, Tang B, et al. Axitinib in Combination With Toripalimab, a Humanized Immunoglobulin G4 Monoclonal Antibody Against Programmed Cell Death-1, in Patients With Metastatic Mucosal Melanoma: An Open-Label Phase IB Trial. J Clin Oncol. 2019;37:2987–99.

81. Merck Sharp & Dohme LLC, A Phase 3 Randomized, Placebo-controlled Trial to Evaluate the Safety and Efficacy of Pembrolizumab (MK-3475) and Lenvatinib (E7080/MK-7902) Versus Pembrolizumab Alone as First-line Intervention in Participants With Advanced Melanoma (LEAP-003), clinicaltrials.gov, 2022. https://clinicaltrials.gov/ct2/show/NCT03820986 (accessed February 9, 2023).

82. Mao L, Dai J, Cao Y, Bai X, Sheng X, Chi Z, et al. Palbociclib in advanced acral melanoma with genetic aberrations in the cyclin-dependent kinase 4 pathway. Eur J Cancer. 2021;148:297–306.

83. Mannavola F, Tucci M, Felici C, Passarelli A, D'Oronzo S, Silvestris F. Tumor-derived exosomes promote the in vitro osteotropism of melanoma cells by activating the SDF-1/CXCR4/CXCR7 axis. J Transl Med. 2019;17:230. https://doi.org/10.1186/s12967-019-1982-4.