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REVIEW

Management of Advanced Invasive Melanoma: New Strategies

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ABSTRACT

The incidence of cutaneous melanoma (CM) is increasing. CM is defined as melanoma in situ when limited within the epidermis and invasive when atypical melanocytes progressively invade the dermis. Treatment of CM is challenging. On one hand, melanoma in situ does not require further treatment except for a limited secondary excision with reduced margins to minimize the risk of local recurrences; on the other, invasive melanoma requires a personalized approach based on tumor staging. Consequently, an association of surgical and medical treatments is often necessary for invasive forms of the disease. In this scenario, new knowledge on melanoma pathogenesis has led to the development of safe and effective treatments, and several drugs are currently under investigation. However, extensive knowledge is required to offer patients a tailored-tail approach. The aim of our article was to review current literature to provide an overview of treatment options for invasive melanoma, highlighting strategical approaches that can be used in patients with these forms of disease.

Keywords: Melanoma; Management; Invasive melanoma; Immune checkpoint inhibitors; Targeted therapy; Vaccines; Small molecules

Key Summary Points

Why carry out this study?

Treatment of cutaneous melanoma is challenging. On one hand, melanoma in situ does not require further treatments except for a limited secondary excision with reduced margins to minimize the risk of local recurrences; on the other, invasive melanoma requires a personalized approach based on tumor staging

New knowledge on melanoma pathogenesis has led to the development of safe and effective treatments, and several drugs are currently under investigation. However, extensive knowledge is required to offer patients a tailored-tail approach

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What was learned from the study?

The management of metastatic melanoma has been revolutionized by the introduction of immune checkpoint inhibitors and targeted therapies. Moreover, the association of targeted therapies and immunotherapies or their sequential use has been shown to be a valid weapon in melanoma management. Finally, other therapeutic options (e.g., T-cell agonists, intravenous oncolytic virus, vaccines, cytokines, etc.) are currently under investigation

The future of melanoma management will be characterized by the association of surgical and medical interventions as well as several biomarkers, which will allow identifying "at-risk" patients and defining the right treatment at the right moment

INTRODUCTION

Cutaneous melanoma (CM) is a malignant tumor arising from melanocytes located in skin tissue [1] and accounts for > 90% of the deaths caused by cutaneous tumors [2, 3]. Its worldwide prevalence is increasing, with 232,100 new diagnoses and about 55,500 cancer deaths per year [4–6]. Several risk factors have been associated with CM development such as ultraviolet radiation, sunburns, indoor tanning, high socioeconomic status, presence of melanocytic or dysplastic naevi, a familiar or personal history of CM, and phenotypic features (e.g., fair hair, eye, and skin colors and the tendency to freckle) [7, 8]. Of note, melanoma may also derive from melanocyte residents on the meninges, eyes and various mucosal surfaces [9].

Clinically, four common subtypes can be distinguished: superficial spreading melanoma (about 41% of cases), nodular melanoma (about 16% of cases), lentigo maligna melanoma (2.7–14% of cases) and acral lentiginous melanoma (1–5% of cases) [10–12]. Uncommon subtypes include desmoplastic melanoma, spitzoid melanoma and amelanotic or hypomelanotic melanoma [10–12].

CM is defined as melanoma in situ when limited within the epidermis and invasive melanoma when atypical melanocytes progressively invade the dermis [13]. Regarding CM staging, tumor thickness (Breslow score, which measures the depth of the melanoma from the granular layer of the epidermis down through to the deepest point of the tumor) [14], lymph node involvement and the presence of metastasis are the key factors, dividing melanoma severity into four stages: stage I and II (localized disease), stage III (local lymph nodes involvement) and stage IV (distant metastasis) [13]. Moreover, vertical tumor thickness (Breslow's depth), presence of ulceration, mitotic rate and level of invasion (Clark's level, used to determine how many layers of the skin the melanoma has grown into) are the main prognostic factors for CM [13, 15, 16].

Fortunately, the majority of melanomas (about 90%) are diagnosed as primary tumors without metastasis [13, 16, 17].

Regarding management, current guidelines proposed by the American Academy of Dermatology and a collaboration of multidisciplinary experts from the European Association of Dermato-Oncology, the European Organization of Research and Treatment of Cancer and the European Dermatology Forum suggest that local excision with different safety margins, depending on Breslow's thickness, is the mainstay of treatment, followed by sentinel lymph node biopsy if tumor thickness is > 0.8 mm (if histologic examination has revealed additional risk factors) [13, 15, 16].

Although excision with a safety margin and eventual sentinel lymph node biopsy is the standard of care in melanoma patients, this approach may not bring resolution in patients with invasive melanoma.

The aim of our study was to review current literature and provide a complete overview regarding treatment options for invasive melanoma to highlight strategic approaches that can be used in patients with these forms of disease. Of note, we focused our attention on tumor stage to describe and provide the correct

treatment option tailored for each patient at the right time.

MATERIALS AND METHODS

A search of the current literature was performed using the Embase, PubMed, Cochrane Skin and clinicaltrials.gov databases (until 15 March 2023) using the following research terms: "cutaneous melanoma," "invasive melanoma," "surgical treatment," "sentinel lymph node biopsy," "immunotherapy," "checkpoint immunotherapy," "targeted therapies," "ipilimumab," "pembrolizumab," "nivolumab," "BRAF inhibitors," "vemurafenib," "dabrafenib," "MEK inhibitors," "binimetinib," "trametinib," "sequential treatment," "vaccines," "anti-vascular endothelial growth factor," "cytokines," "inhibitory molecules" and "T-cell agonists." Investigated articles included reviews, metanalyses, clinical trials, real-life studies, case series and reports. The most relevant articles were examined. Moreover, the bibliography was reviewed to include articles that could have been missed. Articles regarding treatments for non-invasive CM were not considered. Finally, the research was refined by reviewing the abstracts and texts of collected texts. Of note, only English language articles were considered, while other language manuscripts were excluded. The current article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

RESULTS

In the first part of our review, we reported the current therapeutic scenario while in the second part an overview on the currently used systemic therapies and drugs under development has been discussed.

Current Therapeutic Scenario

Surgical Treatment

Surgery is the gold standard treatment of CM [18]. When melanoma is clinically and dermoscopically suspected, an excisional biopsy should be performed to allow a histologic diagnosis [18]. Of note, the use of reflectance confocal microscopy (RCM) for non-invasively imaging of the skin has shown promising results in cancer diagnosis, limiting use of the surgical approach only to "at risk" cases [19, 20]. However, RCM is currently not available in tertiary referral centers, nor is the knowledge of the pros and cons of this tool, and its clinical applicability is currently under investigation [21].

Generally, incisional biopsies may be considered on large lesions or lesions located on sensitive areas, such as lentigo maligna, acral and genital lesions [13, 15, 16]. In case of histologic confirmation of CM, a subsequent excision should be performed, thus reducing the risk of local recurrences [18]. However, peripheral surgical margins depend on tumor thickness. Indeed, 1-cm margins are recommended for CM with a Breslow thickness < 2 mm (except for melanoma in situ, which is not considered as invasive melanoma when margins are reduced to 0.5 cm), while 2-cm margins are required for CM (Breslow) > 2 mm [13, 15, 16]. Of note, in patients presenting lentigo maligna melanoma or genital and acral melanomas, a microscopically controlled surgery (Mohs micrographic surgery) may be a valuable option to spare tissue, ensuring complete tumor resection [13, 15, 16, 22].

Sentinel Lymph Node Biopsy

Sentinel lymph node biopsy (SLNB) is a standard staging procedure, recommended for patients with CM is thicker than 1 mm or 0.8 mm if histologic examination has revealed additional risk factors such as ulceration, ≥ 1 mitosis/mm^2 and/or lymphovascular invasion, particularly in the setting of younger age [13, 15, 16]. In patients with negative sentinel lymph nodes, no further actions are needed [13, 15, 16]. Contrarily, in case of positive lymph node involvement, complete lymph node dissection, previously routinely practiced, has been replaced by adjuvant therapies after similar outcomes have been reported in clinical trials involving patients with microscopic nodal metastases undergoing or not undergoing complete lymph node dissection [13, 15, 16].

Metastases

CM metastases should be divided into satellite and/or in-transit metastases, defined as lesions occurring within 2 cm of the primary tumor and any cutaneous or subcutaneous metastases that are > 2 cm from the primary lesion but are not beyond the regional nodal basin, respectively, and distant metastases [23]. Indeed, surgery or other destructive therapies (radiotherapy, cryotherapy, electrochemotherapy and laser therapy) can be used for the management of satellite and/or in-transit metastases while distant metastases can be managed with complete resection or other destructive procedures only in cases of oligometastatic disease or as a palliative procedure [13, 15, 16]. For metastatic disease, several systemic therapies are available [13, 15, 16].

Neoadjuvant Treatment

Neoadjuvant therapy is defined as a first step treatment to shrink a tumor before the gold standard treatment [24, 25]. It should be considered in patients with resectable metastases, particularly stage III melanoma [24, 25]. Even if it can be a valid approach, trials investigating the use of adjuvant treatment in CM management are scant [24, 25]. However, preliminary data showed that immunotherapy seems to be superior to targeted therapy, resulting in high response rates, but with lower durability [13, 15, 16]. Moreover, it was reported that combination of ipilimumab [anti-cytotoxic T lymphocyte-associated antigen-4 (CTLA-4)] plus nivolumab [anti-programmed cell death protein-1 (PD-1)] is better than monotherapy with an anti-PD-1 agent and that the initial pathologic response is predictive of recurrence-free survival (RFS) [24, 25].

Adjuvant Treatment

Adjuvant therapy is a treatment given in addition to the primary or initial therapy to maximize its effectiveness [13, 15, 16]. It plays a key role in melanoma management. Indeed, its use has been shown to impact overall survival (OS) and RFS [26]. Historically, interferon-α was used as adjuvant therapy in melanoma patients with tumors > 1.5 mm, despite a significant toxicity profile [26]. Nowadays, new effective and safe drugs such as immune checkpoint inhibitors [PD-1 and its ligand (PDL-1) and anti-CTLA-4] and targeted therapies (BRAF/MEK inhibitors) have replaced its use [26]. Currently, the adjuvant therapy is offered to patients with lymph node involvement using BRAF/MEK inhibitor if BRAFV600 E/K mutation is detected. Of note, anti-PD-1 can be used regardless of the mutation status [26].

Moreover, for patients who develop progressive disease > 6 months after adjuvant therapy, re-challenge can be considered, evaluating BRAF status also in case of acquired resistance setting [26]. For BRAF mutated melanoma, switching from immunotherapy to targeted therapy or vice versa can be considered, whereas combination therapy with anti-PD-1 plus ipilimumab or ipilimumab alone can be an option in patients without BRAF mutation [26].

Management of Systemic Disease

Recent knowledge on CM pathogenesis has led to the development of safer and more effective treatments, leading to an improvement in the RFS, OS, progression-free survival (PFS), disease-free survival (DFS), durable response rate (DRR) and overall response rate (ORR) [17]. The introduction of these drugs has allowed avoiding the use of chemotherapy, which is now only considered as a last-line treatment in patients with resistance to immunotherapies and targeted therapies (if applicable) [17]. However, many patients with stage IV disease do not benefit from these therapies and have died from the disease [17]. Immune checkpoint inhibitors are used as a first-line treatment option, regardless BRAF status, as anti-PD-1 monotherapy or a combination of anti-PD-1 plus anti-CTLA-4 [13, 15, 16]. Targeted therapies are used in patients with resistance to immunotherapy, with BRAF-V600 E/K mutation or as first-line option in selected cases [13, 15, 16]. Currently approved drugs for the management of melanoma, mechanism of action and other therapeutic indications are reported in Table 1.

Table 1 Currently approved drugs* for the management of melanoma, mechanism of action and other therapeutic indications

Drug	Mechanism	Melanoma management	Therapeutic indications
Nivolumab	Anti PD-1	1. Advanced** melanoma in adults: - monotherapy: 240 mg Q2W or 480 mg Q4W - combination with ipilimumab: 1 mg/kg nivolumab plus 3 mg/kg ipilimumab for the first 4 doses, followed by a second phase of nivolumab monotherapy (240 mg Q2W or 480 mg Q4W) 2. Adjuvant treatment of melanoma: - monotherapy: 240 mg Q2W or 480 mg Q4W	Non-small cell lung cancer Malignant pleural mesothelioma Classical Hodgkin lymphoma Renal cell carcinoma Head and neck squamous cell carcinoma Adjuvant treatment of urothelial carcinoma Mismatch repair deficient or microsatellite instability-high colorectal cancer Esophageal squamous cell carcinoma Adjuvant treatment of esophageal or gastro-esophageal junction cancer Gastric, gastro-esophageal junction or esophageal adenocarcinoma
Pembrolizumab	Anti PD-1	1. Advanced** melanoma in adults and adolescents $\geq$ 12 years: - monotherapy: 200 mg Q3W or 400 mg Q6W 2. Adjuvant treatment of adults and adolescents $\geq$ 12 years: with Stage IIB, IIC or III melanoma and who have undergone complete resection: - monotherapy: 200 mg Q3W or 400 mg Q6W	Non-small cell lung cancer Classical Hodgkin lymphoma Urothelial carcinoma Renal cell carcinoma Head and neck squamous cell carcinoma Mismatch repair deficient or microsatellite instability-high cancers Esophageal carcinoma Triple-negative breast cancer Endometrial carcinoma Cervical cancer

Table 1 continued

Drug	Mechanism	Melanoma management	Therapeutic indications
Ipilimumab	Anti-CTLA4	1. Advanced** melanoma in adults and adolescents ≥ 12 years: - monotherapy: 3 mg/kg Q3W for a total of 4 doses - combination with nivolumab: 1 mg/kg nivolumab plus 3 mg/kg ipilimumab for the first 4 doses, followed by a second phase of nivolumab monotherapy (240 mg Q2W or 480 mg Q4W)	Renal cell carcinoma Mismatch repair deficient or microsatellite instability-high colorectal cancer Esophageal squamous cell carcinoma Non-small cell lung cancer Malignant pleural mesothelioma
Dabrafenib	Anti-BRAF	1. Advanced** melanoma with BRAF V600 mutation in adults: - monotherapy: 150 mg twice daily - combination with dabrafenib: dabrafenib 150 mg twice daily plus trametinib 2 mg once daily 2. Adjuvant treatment of melanoma Stage III melanoma with a BRAF V600 mutation in combination with trametinib: - combination with trametinib: dabrafenib 150 mg twice daily plus trametinib 2 mg once daily	Non-small cell lung cancer
Trametinib	Anti-MEK	1. Advanced** melanoma with BRAF V600 mutation in adults: - monotherapy: 2 mg once daily - combination with dabrafenib: dabrafenib 150 mg twice daily plus trametinib 2 mg once daily 2. Adjuvant treatment of melanoma Stage III melanoma with a BRAF V600 mutation in combination with dabrafenib: - combination with dabrafenib: dabrafenib 150 mg twice daily plus trametinib 2 mg once daily	Non-small cell lung cancer
Vemurafenib	Anti-BRAF	1. Advanced** melanoma with BRAF V600 mutation in adults: - monotherapy: 960 mg twice daily	None
Encorafenib	Anti-BRAF	1. Advanced** melanoma with BRAF V600 mutation in adults: - combination with binimetinib: encorafenib 450 mg once daily plus binimetinib 45 mg twice daily	Metastatic colorectal cancer with a BRAF V600E mutation

Table 1 continued

Drug	Mechanism	Melanoma management	Therapeutic indications
Binimetinib	Anti-MEK	1. Advanced** melanoma with BRAF V600 mutation in adults: - combination with encorafenib: encorafenib 450 mg once daily plus binimetinib 45 mg twice daily	None

*Talimogene laherparepvec was not included in the table since its use is not currently clarified in guidelines. Advanced**: unresectable or metastatic. Q2W: every 2 weeks. Q3W: every 3 weeks. Q4W: every 4 weeks
Anti-CTLA-4 anti-cytotoxic T lymphocyte–associated antigen-4, *ANTI-PD-1* anti-programmed cell death protein-1

Overview on the Currently Used Systemic Therapies

Immune Checkpoint Inhibitors

Immune checkpoint inhibitors target small proteins produced by immune cells and cancer cells called "checkpoints" [27, 28]. Among these, PD-1 and CTLA-4 are checkpoints produced by cancer cells to escape from the immune system through the downregulation of T-cell activation, leading to immune tolerance [27, 28]. On one hand, the binding of PD-1, expressed on the surface of monocytes, T and B and natural killer cells, to its ligand PDL-1 promotes the apoptosis of T lymphocytes and activates the regulatory T cells, preventing the inflammation cascade; on the other hand, CTLA-4 is constitutively expressed in regulatory T lymphocytes and prevents the activation of T cells. Thus, targeting these cytokines is a valuable option to reduce melanoma immune escape mechanisms [27, 28].

Nivolumab Nivolumab is an immune checkpoint inhibitor approved for the management of metastatic or unresectable melanoma and as adjuvant therapy. It acts through the blockage of PD-L1 binding to PD-1 [29]. It can be used as monotherapy or combination therapy for melanoma management and is also approved for the treatment of non-small cell lung cancer (NSCLC), malignant pleural mesothelioma (MPM), renal cell carcinoma (RCC), classical Hodgkin lymphoma (cHL), squamous cell cancer of the head and neck (SCCHN), urothelial carcinoma, mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) colorectal cancer (CRC), esophageal squamous cell carcinoma (OSCC), adjuvant treatment of esophageal or gastro-esophageal junction cancer (OC or GEJC) and gastric, gastro-esophageal junction (GEJ) or esophageal adenocarcinoma [30].

Regarding melanoma management, nivolumab is scheduled as an intravenous infusion at a dosage of 240 mg every 2 weeks (Q2W) or 480 mg every 4 weeks (Q4W) as monotherapy or in combination with ipilimumab [(nivolumab 1 mg/kg plus ipilimumab 3 mg/kg every 3 weeks (Q3W) up to four doses followed by nivolumab as single agent at standard dosage of 240 mg Q2W or 480 mg Q4W] [30].

Nivolumab was reported to be superior to chemotherapy in previously treated (ipilimumab and BRAF inhibitor, if BRAF V600 mutation was positive) metastatic melanoma (CHECKMATE-037 study) and in untreated patients with metastatic melanoma (CHECKMATE-066 study) [31, 32].

Moreover, nivolumab as single treatment or combined with ipilimumab was shown to be statistically significantly effective compared with ipilimumab (CHECKMATE-067 study) in untreated patients with unresectable or metastatic melanoma [33].

Finally, it has been reported to be significantly superior to ipilimumab also as adjuvant treatment (CHECKMATE-238 study) [34].

Pembrolizumab Pembrolizumab is an anti-PD-1 drug currently approved for the treatment of metastatic or unresectable melanoma and as adjuvant treatment of patients with melanoma. It is administered at a scheduled dosage of 200 mg every 3 weeks (Q3W) or 400 mg every 6 weeks (Q6W) [35]. Pembrolizumab is also approved for NSCLC, cHL, SCCHN, RCC, urothelial carcinoma, dMMR or MSI-H cancers, esophageal carcinoma, triple-negative breast cancer (TNBC), endometrial carcinoma and cervical cancer [35].

Pembrolizumab has been reported to be significantly superior to ipilimumab for the treatment of untreated metastatic or unresectable melanoma (KEYNOTE-006 study) and to chemotherapy in patients with previously treated metastatic or unresectable disease (KEYNOTE-002 study) [36, 37]. Finally, a statistically significant improvement in RFS was reported in patients receiving pembrolizumab compared to placebo as adjuvant treatment of resected melanoma (KEYNOTE-054 study) [38].

Ipilimumab Ipilimumab is an anti-CTLA-4 antibody targeting CTLA-4 activity, approved at the dosage of 3 mg/kg Q3W for up to four doses [39]. As adjuvant treatment, it has been reported to be significantly superior to placebo in terms of RFS (CA184-029 study) [39]. Studies reporting its effectiveness as combination therapy with nivolumab in metastatic disease have been previously reported. Currently, ipilimumab is also approved for RCC, NSCLC, MPM, dMMR or MSI-H CRC and OSCC [39].

Targeted Therapies

BRAF is a serine/threonine protein kinase that activates the mitogen-activated protein (MAP) kinase/ERK-signaling pathway [39]. This signaling cascade leads to the evasion of apoptosis, senescence and immune response, unchecked replicative potential, angiogenesis, tissue invasion and metastasis [39]. Globally, about 50% of melanomas have BRAF mutations. In particular, over 90% of these are located on codon 600, with > 90% represented by a single nucleotide mutation resulting in substitution of glutamic acid for valine (BRAFV600E: nucleotide 1799 T > A; codon GTG > GAG) [39]. Combining BRAF and MEK inhibition is an innovative strategy for melanoma management [39].

Dabrafenib Dabrafenib is a kinase inhibitor approved for the treatment of metastatic or unresectable melanoma with a BRAF V600E or V600K mutation and as an adjuvant treatment at the dosage of 150 mg twice daily, used either as monotherapy or in combination with trametinib [40]. It was also approved for the management of NSCLC [40]. Dabrafenib was shown to be significantly superior to chemotherapy in melanoma management (BREAK-3 study) [41]. Dabrafenib has also been investigated in metastatic melanoma with brain metastases (COMBI-d study and COMBI-v study) [42].

Finally, the superiority of dabrafenib plus placetinib with respect to placebo as adjuvant treatment has been reported (COMBI-AD study) [43].

Trametinib Trametinib is a kinase inhibitor targeting MEK1 and MEK2, approved for the management of metastatic or BRAF V600E or BRAF V600K mutated unresectable melanoma or as adjuvant treatment at an oral dosage of 2 mg a day, used as either monotherapy or in combination with dabrafenib [44]. It is also approved for NSCLC [44].

Trametinib was shown to be significantly superior to chemotherapy in metastatic melanoma (METRIC study) as well as in combination with dabrafenib in brain metastases or adjuvant therapy (COMBI-d and COMBI-AD studies, respectively) [42, 43, 45].

Vemurafenib Vemurafenib is a targeted therapy approved in monotherapy for the management of patients with metastatic or unresectable melanoma with BRAF V600E mutation at the dosage of four tablets of 240 mg every 12 h [46]. A statistically significative superiority to chemotherapy has been reported (BRIM3 study), also in previously treated patients and in patients with metastatic melanoma BRAF V600E mutation-positive melanoma, with brain metastasis [46].

Encorafenib and Binimetinib Encorafenib is a kinase inhibitor approved for the treatment of unresectable or metastatic melanoma with BRAF V600E or BRAF V600K mutation in combination with binimetinib at the dosage of 450 mg once a day. It is also approved in combination with cetuximab for the treatment of adult CRC patients [47].

Binimetinib is a MEK inhibitor approved for the management of metastatic or BRAF V600E-mutated unresectable melanoma at the dosage of 45 mg twice a day in combination with encorafenib [48].

Encorafenib plus in binimetinib was shown to be statistically significantly superior in terms of PFS compared to vemurafenib (CMEK162B2301 study) [47, 48].

Emerging Treatments

Several treatment strategies or clinical options are currently under investigation for the management of melanoma. First, the combination or sequential use of immune checkpoint inhibitors plus targeted therapies is considered a valuable option due to their high effectiveness. Many trials on this subject are ongoing [24]. However, several drugs are under investigation to fight against the acquired resistance to both targeted therapy and immunotherapy.

Among these, an oncolytic viral immunotherapy [talimogene laherparepvec (T-VEC)] has been recently approved for the local treatment of unresectable metastatic stage IIIB/C and IV melanoma [49]. However, its place in the combined therapy of T-VEC and anti-PD-1 is unclear [49].

Other drugs such as engineered cytokine (e.g., darleukin and bempegaldesleukin), intravenous oncolytic virus (e.g., ICOVIR-5), antivascular endothelial growth factor (e.g., bevacizumab), drugs targeting inhibitory molecules (e.g., colony-stimulating factor 1 receptor inhibitors and indoleamine 2,3-dioxygenase 1 inhibitors), t-cell agonists, Toll-like receptor agonists, agonistic anti-OX40 antibodies, glucocorticoid-induced tumor necrosis factor receptor family-related protein and adoptive T-cell therapy are currently under investigation, opening a new era in the therapy of advanced melanoma [50–60].

Finally, another treatment option could be the combination of immunotherapy and local therapies such as radiotherapy [61]. In particular, radiotherapy may be used when starting immunotherapy peri-induction radiotherapy (PIR) or after systemic treatment failure as post-escape radiotherapy (PER) to increase treatment outcomes [61]. Indeed, radiation can increase tumor antigen visibility and promote priming of T cells but can also exert immunosuppressive action on the tumor microenvironment [61]. To sum up, the combination of immunotherapy and radiotherapy provides an opportunity to increase the immunostimulatory potential of radiation [61].

DISCUSSION

The increasing knowledge on the pathogenesis of skin cancers has led to the development of more effective and safer treatments [62–67]. In particular, new strategies have been adopted for the management of melanoma [68–70]. On one hand, in situ melanomas do not require further treatments except for a limited secondary excision with reduced margins to minimize the risk of local recurrences; on the other hand, invasive melanomas (defined by the presence of atypical melanocytes invading the dermis) require a personalized approach based on tumor staging (tumor thickness + lymph node involvement + presence of metastasis) [13, 15, 16]. Even if a secondary excision with larger margins (1 cm if thickness < 2, 2 cm if thickness > 2 mm) is required for invasive melanoma, sentinel lymph node biopsy is recommended only for patients with CM > 1 or 0.8 mm with peculiar histologic features [13, 15, 16]. Although the therapeutic approach seems standardized up to this point, several strategies may be used to personalize the management of patients with a thick melanoma without lymph node involvement or with an unresectable disease.

In this scenario, some patients may benefit from neoadjuvant therapies. However, neoadjuvant treatments are not yet a standard of care because there is a lack of studies demonstrating the superiority of neoadjuvant approaches over

conventional surgery plus postoperative adjuvant treatment. Indeed, phase III trials are ongoing. Similarly, although adjuvant treatment is well established for patients with stage III or stage IV melanoma, a subgroup of patients with stage II disease may benefit from adjuvant therapies because of the high-risk of tumor recurrence.

Regarding the management of metastatic melanoma, it has been revolutionized by the introduction of immune checkpoint inhibitors and targeted therapies. Moreover, the association of targeted therapies and immunotherapies or their sequential use has been shown to be a valid weapon in melanoma management. Finally, other therapeutic options (e.g., T-cell agonists, intravenous oncolytic virus, vaccines, cytokines, etc.) are currently under investigation to offer a therapeutic opportunity in patients unresponsive to immune checkpoint inhibitors or targeted therapies.

In our opinion, the future of melanoma management will be characterized by the association of surgical and medical interventions as well as several biomarkers that will allow identifying "at-risk" patients and defining the right treatment at the right moment.

Certainly, further studies are required to increase our knowledge on melanoma pathogenesis and treatment in order to offer therapeutic options which may increase survival with a good safety profile.

CONCLUSION

The management of invasive melanoma is challenging. Despite current guidelines that seem to offer a complete overview, there are still many uncovered areas. In this scenario, several studies are needed to establish the role of innovative drugs and surgical procedures in melanoma management at each stage of the disease to increase treatment efficacy and reduce safety concerns.

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Compliance and Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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