Eur J Dermatol 2015; 25(5): 392-403

Alfonso BERROCAL[1]
Enrique ESPINOSA[2]
Severiano MARÍN[3]
Josep MALVEHY[4]
David MORENO[5]
Maria Dolores LOZANO[6]
Salvador MARTIN-ALGARRA[7]
Jose Antonio LOPEZ[8]
Carlos CONILL[9]
Jose Luis RODRIGUEZ-PERALTO[10]

[1] Department of Oncology,
[2] Service of Oncology, Hospital La Paz, Madrid, Spain
[3] Plastic Surgery, Consorcio Hospital General Universitario, Avda, Tres Cruces, 2, 46014 Valencia, Spain
[4] Dermatology Department, Melanoma Unit, Hospital Clinic, Barcelona, Spain
[5] Dermatology Unit, Hospital Universitario Virgen Macarena, Seville, Spain
[6] Department of Pathology,
[7] Department of Oncology, Clinica Universitaria de Navarra, Pamplona, Spain
[8] Department of Oncology,
[9] Department of Radiation Oncology, Hospital Clinic, Institut d'Investigacions Biomédiques August Pi i Sunyer (IDIBAPS), University of Barcelona, Spain
[10] Department of Pathology, Hospital 12 de Octubre, Madrid, Spain

Reprints: A. Berrocal <berrocal.alf@gmail.com>

Spanish Multidisciplinary Melanoma Group (GEM) guidelines for the management of patients with advanced melanoma

Advanced melanoma is a relatively uncommon condition whose therapeutic management has undergone major changes over the past four years. The present article aims to establish recommendations for the management of these patients based on the best available evidence reached by consensus of a group of professionals familiar in the treatment of these patients. These professionals, belonging to Spanish Multidisciplinary Melanoma Group, reviewed the diagnostic process and the incorporation of new techniques of molecular diagnosis of advanced disease; treatment and monitoring of stage III both as adjuvant locoregional treatments have been addressed, as well as new therapies for stage IV. We have reviewed the palliative treatment alternatives for disseminated disease, such as surgery, radiotherapy or non-cytotoxic systemic treatments. Finally, we have also reviewed the most relevant toxicities of new drugs and their management in clinical practice.

Key words: advanced melanoma, diagnosis, therapeutic management

In recent years, the management of advanced melanoma has undergone significant changes, which result from the emergence of new therapeutic strategies. Information on these therapies is quickly changing and this has motivated the Spanish Multidisciplinary Melanoma Group to evaluate the situation and establish a guide for therapeutic action. We have considered as advanced melanoma patients those having stage III or IV disease.
To develop this guide, different specialists involved in the management of this disease formulated a series of questions concerning specific clinical conditions of patients with advanced melanoma. These issues were resolved by reviewing the literature available at the time of developing the guidelines and were agreed on by all members of the guide development committee [1, 2].
Because of the amount of information generated each year in the management of this disease, the authors intend to update this guide on a yearly basis.

Epidemiology

In Spain, melanoma has an incidence of 8.10 cases/100,000 inhabitants, with a standardised mortality ratio of 1.00 recorded deaths/100,000 inhabitants per year (Globocan 2008). At the time of diagnosis, 85% of melanoma patients present with localised disease (stages I and II); 15% present with regional nodal metastatic disease; and 2% present with distant metastasis [3]. With regard to the development of metastasis during follow-up, the few studies related to the Spanish population describe a frequency of lymph node metastasis of 40%, followed by distant metastasis (27%) and locoregional in-transit metastasis (13%) [4].

Recommendations for care

Diagnosis and treatment of malignant melanoma require a multidisciplinary approach in reference centres, in coordination with other professionals from primary care centres or palliative teams. Patients with suspected lesions or risk factors (with atypical nevus syndrome, familial melanoma, etc.) should be referred to specialised centres that use digital dermoscopic imaging techniques [5, 6]. Dermatologists and dermatopathologists should diagnose primary cancer. Sentinel lymph node surgery and staging for melanoma patients should be performed in centres with extensive experience in melanoma [7]. Melanoma committees at reference

doi:10.1684/ejd.2015.2594

To cite this article: Berrocal A, Espinosa E, Marín S, Malvehy J, Moreno D, Lozano MD, Martin-Algarra S, Lopez JA, Conill C, Rodriguez-Peralto JL. Spanish Multidisciplinary Melanoma Group (GEM) guidelines for the management of patients with advanced melanoma. *Eur J Dermatol* 2015; 25(5): 392-403 doi:10.1684/ejd.2015.2594

centres should evaluate surgery for locoregional or distant metastases within an overall treatment strategy for patients [8].
Indication for treatment (adjuvant therapy, treatments in locally advanced disease, immunological therapies and targeted therapies) should preferably be made in reference centres that also have clinical trials [9].

Stage III melanoma

Primary cancer surgery

With regard to treating primary tumours in these cases, the general recommendations are followed, the objective being to completely remove tumours with negative histological margins [10].
The width of these margins has been studied in several prospective, randomised and controlled clinical trials. The current consensus is that the lateral margins should not be less than one centimetre or greater than two centimetres, as measured clinically. *Table 1* shows the currently accepted lateral margins, including grade of recommendation and level of evidence [11-21].
With regard to the depth of enlargement, the classic recommendation consists of resection of the deep muscular fascia. However, there is no evidence to suggest that this is necessary in all cases. In areas with a thick layer of adipose tissue, the superficial fascia that separates the two planes of fat may be sufficient [10].

Sentinel lymph node surgery

This is a diverse group in which at least three patient subgroups can be identified.

Sentinel lymph node-positive patients

Completion lymph node dissection (CLND) is the standard recommendation for sentinel lymph node-positive patients. The objectives would be to improve regional control of the disease, prolong survival and reduce operative morbidity.
With regard to the first objective, in one multi-centre, retrospective study [22], 15% of sentinel lymph node-positive patients who did not later undergo CLND had lymphatic metastasis as the first relapse of the disease. In addition, 16% of sentinel lymph node-positive patients who underwent CLND as part of two prospective, randomised clinical trials [23, 24] had other lymph nodes affected besides the sentinel lymph node. It seems reasonable to conclude that the risk of having lymphatic metastases when not undergoing CLND may be between 15% and 20% [25, 26]. This figure is much higher than the 4.2% of regional relapses after CLND in the Multicenter Selective Lymphadenectomy Trial-I (MSLT-I) [23].
With regard to overall survival, the MSLT-I showed no benefit from CLND for sentinel lymph node-positive patients. However, the 5-year survival rate for sentinel lymph node-positive patients who underwent CLND was 72.3%, compared with 52.4% for sentinel lymph node-positive patients who did not undergo CLND and later developed palpable lymphadenopathy [23].
The MSLT-II is now in progress as a new prospective, randomised clinical trial to determine whether CLND in sentinel lymph node-positive patients improves survival. Although this study has not been completed, the best available evidence suggests that CLND should continue to be done systematically in sentinel lymph node-positive patients.
In addition, the data on operative morbidity support this stance. Local complications and lymphoedema after CLND in sentinel lymph node-positive patients occur significantly less often than after delayed CLND for palpable lymph nodes [27, 28].

Patients with palpable lymph nodes

In patients with suspect lymph nodes, determined clinically or radiologically, histopathological confirmation should be made, including an open biopsy. If a biopsy is done, the incision must not compromise a future CLND. As such, it should preferably be done by the team that performs the lymph node surgery. In any case it should be taken into account that biopsies done before complete basin dissection increase the risk of regional relapse [29].
CLND should be done at the same time as the primary tumour is treated [30]. This procedure, which involves clearing out the basin within anatomical limits, should be done by a team with proven experience in lymph node surgery of the area being operated on [30].

Patients with in-transit disease

For the sub-group of patients with resectable in-transit metastases, with or without palpable lymphadenopathy, surgery remains an option. For in-transit metastases, histopathological confirmation should be made. The primary tumour must be treated in the standard manner and in-transit metastases should be completely resected. If there is no palpable regional lymphadenopathy, sentinel lymph node biopsy may be indicated [30]. This indication should be added to those currently accepted in most clinical practice guidelines, which are shown in *table 2* [10, 30, 31].
If there is palpable regional lymphadenopathy, the stance to be taken would be as described for the previous patient sub-group.

Table 1. Surgical margin recommendations for primary cutaneous melanoma.

	Clinical margins	Grade of recommendation	Level of evidence	References
Melanoma *in situ*	0.5-1 cm	C	III	No clinical trials
≤1.00 mm	1 cm	A	I	13-18
1.01-2 mm	1-2 cm	A	I	13-22
>2 mm	2 cm	B	I-III	19,21-23

Table 2. Recommendations for sentinel lymph node biopsy.

• Sentinel lymph node biopsy is not recommended for patients with melanoma *in situ* or with T1a melanomas.
• Sentinel lymph node biopsy is recommended for patients with melanoma >1 mm in thickness.
• Sentinel lymph node biopsy may be considered in the following cases: - Some T1b melanomas (all those between 0.76 and 1.00 mm in thickness and those ≥0.75 mm with additional negative prognostic factors, such as ulceration, high mitotic index, etc.) - Some stage III melanomas (those with resectable in-transit metastases)

GEM recommendation

All patients with resectable stage III disease should undergo CLND

Histological study

Fine-needle aspiration biopsy (FNAB) is a quick, inexpensive and minimally invasive procedure for diagnosing metastatic melanoma. FNAB requires no invasive procedures and enables molecular studies to be performed. In patients with metastatic melanoma, cytological samples may offer the only chance for tissue to be obtained for the pathologic diagnosis and molecular analysis of these tumours. Several groups, including ours, have shown that FNAB specimens represent an effective platform for studying mutations.
Nowadays, with precise medicine and personalised therapy, the work done by pathologists and in particular by cytopathologists is crucial because they have to obtain cytological material by minimally invasive methods in order to confirm metastasis and conduct molecular studies. The use of cytological material for further molecular analysis means patients with metastatic melanoma can receive effective treatment more quickly.

Adjuvant medical treatment

Adjuvant treatment is indicated in patients with a high risk of relapse, i.e. those with melanoma in stages IIB, IIC and III. Numerous treatment options have been tested, such as immunostimulants, vaccines and conventional chemotherapy, but only alpha-interferon has been shown to have some degree of benefit [32].
Interferon alpha-2b has been studied in numerous clinical trials. Meta-analyses show a moderate efficacy: increase in disease-free survival of 7% and overall survival of 3% [33-35]. Considering each trial separately, the results are more consistent with high doses (20 MU/m^2/day, intravenous ×1 month followed by 10 MU/m^2 3 times a week, subcutaneous ×11 months) than with low doses (3 MU 3 times a week, subcutaneous ×12-60 months [36]), although the meta-analyses do not prove one administration regimen to be superior to the other. Periods of treatment longer than 18 months do not seem to provide advantages over shorter regimens.
In addition, pegylated interferon has also been shown to be beneficial in progression-free survival [37]. It has the advantage of subcutaneous administration once a week. The optimal duration of treatment with this drug is not yet known.
The use of adjuvant interferon is controversial because it is associated with numerous side-effects and the risk-benefit margin is narrow. The factors that predict which patients are most likely to benefit from interferon have not been identified. A retrospective analysis of two trials suggests that the benefit is greater when the tumour is ulcerated and there is microscopic nodal involvement (N1), but this must be tested in prospective studies [38, 39].
Studies have been started with ipilimumab, anti-PD1 antibodies and B-RAF inhibitors, which have shown efficacy in distant metastasis. Ipilimumab has no clearly defined target population, whereas B-RAF inhibitors are highly specific for BRAF V600-mutant melanoma.

GEM recommendation

Patients with stage IIIa melanoma and those with ulceration should receive interferon therapy.

Adjuvant radiotherapy

The prognosis for patients diagnosed with cutaneous melanoma depends on the number of regional lymph nodes affected and the thickness of the primary tumour. Patients with clinical or microscopic involvement of regional lymph nodes have a high risk of relapse following surgery. The percentage of post-lymphadenectomy regional lymph node relapses has been reported to be up to 50% [40, 41]. Because of the increased risk of relapse, radiotherapy has been used in patients with three or more positive lymph nodes greater than three centimetres in size, with extracapsular extension and/or clinical lymph node involvement [42]. The studies published demonstrate a high percentage of local-regional control [43-55] *(table 3)*.
The optimum fractionation regimen is still controversial. Treatment protocols vary from 50 Gy/25fr, 50 Gy/20fr, 48 Gy/20fr, 45 Gy/18fr or 30 Gy/5fr. The hypofractionation regimen (30 Gy/5fr of 600 cGy, twice a week for 2.5 weeks) is considered to improve the therapeutic index of melanoma and has proved to be effective.
Concurrent treatment with IFN-α2b may increase radiation-induced toxicity and so IFN-α2b should be administered at an interval of ≥1 month after radiotherapy [56-59].

GEM recommendation

Adjuvant radiotherapy should not be routinely used but can be considered in extensive nodal involvement.

Treatment of in-transit disease

Locally advanced disease with multiple skin metastases that cannot be treated surgically must be evaluated at specialised centres and treated early on. When skin metastases appear in large numbers, surgery is not the treatment of choice, and the patient may choose other treatments, with high efficacy in palliative care, although no increased survival has been shown.

Table 3. Outcomes in local-regional disease control after postoperative radiation therapy + lymphadenectomy.

Author	Year	No	Dose per fraction	Localisation	5-year LRC*
Ang	1994	174	Hypofractionation	Cervical	88%
Strom	1995 22	Hypofractionation	Axillary	95%	
Burmeister	1995	234	Conventional	multiple	91%
Corry	1999	42	Conventional	multiple	80%
Stevens	2000 139	Hypofractionation	Multiple	89%	
Ballo	2002	89	Hypofractionation	Axillary	87%
Ballo	2003	160	Hypofractionation	Cervical	94%**
Bonnen	2004	157	Hypofractionation	Cervical	89%
Ballo	2004	40	Hypofractionation	Ilioinguinal	74%***
Ballo	2005	36	Hypofractionation	Cervical	93%
Ballo	2006	466	Hypofractionation	Multiple	89%
Chang	2006 56	Both	Multiple	87%	
Conill	2009	77	Both	multiple	90%

(*) LRC: Local-regional control; (**) 10-year actuarial local control; (***) 3-year actuarial local control. Multiple: axillary, cervical, ilioinguinal

Topical treatments or tumour infiltration

There are treatments reported to be efficacious in isolated case studies with imiquimod, cryotherapy, or a combination of the two, or treatment with diphencyprone, a sensitising agent [60-62]. Tumour-infiltrating lymphocytes with IL-2 have shown complete clinical response in 69% of tumours in phase 2 studies, with no distant response in untreated tumours [63].

Electrochemotherapy

Electrochemotherapy consists of the perfusion of cytostatic agents (bleomycin or cisplatin) in low doses and the use of electric fields on tumour tissue to allow for electroporation. This treatment has shown clinical response rates of 90% and complete responses of the treated tumour in one or more cycles greater than 70%, with little toxicity and morbidity [64, 65].

Radiotherapy

In the management of patients with advanced local-regional disease - primary cancer, regional lymph node involvement and unresectable in-transit disease - radiotherapy has palliative and/or adjuvant indications in the following clinical situations: palliative radiotherapy for locally advanced unresectable tumours, palliative radiotherapy of the lymph node area with unresectable metastasis, palliative radiotherapy for unresectable in-transit disease and post-lymphadenectomy adjuvant radiotherapy (evident or microscopic residual disease, previous lymph node surgery, involvement of 2 or more lymph nodes, extracapsular lymph node extension or complete replacement of the damaged lymph node by tumour).

Hyperthermic isolated limb perfusion (HILP)

In patients with unresectable in-transit disease localised in the limbs, HILP is a palliative option where amputating the affected limb can be avoided. HILP involves stopping the circulation in the affected limb by connecting the artery and the vein to an extracorporeal circulation pump in order to administer a dose of chemotherapy up to 10 times higher than those administered in systemic chemotherapy regimens. Melphalan is the most commonly used perfusate, which, for bulky disease, is combined with TNF. HILP studies have demonstrated a median complete response of 60% and a partial response of 25%, with a median non-response of 6% [20]. In terms of prognosis, 5-year disease-free survival of patients treated with HILP has ranged between 16% and 53%, with a median regional disease-free interval of 16 months. Severe and very severe regional toxicity (compartment syndrome and amputation, respectively) is limited to less than 5% and 1% of treated patients, respectively. In the studies available, severe specific target organ systemic toxicity has also had an incidence of less than 5%, with a method-related mortality of less than 1%.

Other options

For local-regional progression, including patients in clinical trials involving tumour infiltration with rose bengal (PV-10), immunotherapy, gene therapy or targeted therapies, amongst others, should be evaluated in referral centres [66, 67].

GEM recommendation

Patients with irresectable in transit metastases should be managed as metastatic patients and locoregional treatments can be offered as palliative if progression happens.

Follow-up of patients with stage III melanoma

There is no consensus on the intensity, duration and studies that should be done after completing adjuvant treatment in high-risk melanoma. However, for reasons of care and management, local multidisciplinary melanoma committees should follow evidence-based criteria when establishing intervals for medical visits and further studies [68].
Follow-up in high-risk melanoma plays a vital role in the prognosis of the disease, not only because surgical resection

of oligometastatic disease is the only proven curative treatment, but also because of the recent addition of new active medical treatments in metastatic melanoma [69].
Following resection and postoperative treatment, all melanoma patients with lymph node involvement should have periodic clinical and radiological follow-up, which, during the first year, is recommended at intervals of 3-4 months and then 6, 8 and 12 months. Annual check-ups should be extended for 5-10 years, as there is no definite consensus on a specific duration [70].
Dermatological follow-up of patients in stages II and III can be used to detect skin relapse and new malignant tumours [71] and assessment of toxicities and response to treatment of skin metastases. A complete physical examination, including an examination of the resected area of the melanoma and the skin lesions, should be performed every 3-6 months. Any skin lesions should be examined dermoscopically to rule out metastasis or new malignant skin tumours [72]. For patients with multiple atypical melanocytic naevi or when assessing the response of skin metastases, digital maps and digital dermoscopy should be obtained [5, 73, 74].
Strategies for follow-up of these patients should include:

– Self-examination, because most relapses are detected by the patient. Report any symptoms associated with relapse and give the basic concepts of regular self-examination focused on the area around the scar and the lymph nodes.
– Patient case history and physical examination: these are required for follow-up and should be systematised, both locally/regionally and by system and organ.
– Blood tests: The determination of LDH is proven as a prognostic factor in metastatic disease.
– Imaging techniques: Currently there is no definitive evidence on radiological techniques for early detection of metastases and their prognostic impact. Nevertheless, regular usage of conventional radiology, ultrasound of soft tissues and lymph nodes and chest and abdomen CT are now routine. In selected cases, FDG PET/CT or MRI may need to be performed. PET is indicated when lesions are operable but there is a doubt regarding its malignancy and also as a preoperative evaluation to rule out further extension.

Unresectable stage IV melanoma

Molecular diagnostics

BRAF mutations
Activating mutations of the BRAF gene are the most common mutation in cutaneous melanoma. BRAF, an oncogene, is located at 7q34 and is involved in the Ras/Raf/MAPK signalling pathways that regulate cell response based on signals emitted by growth factor receptors. Roughly 40% to 60% of malignant melanomas have a single nucleotide change. Most have a mutation that results in the substitution of valine by glutamic acid at position 600 (BRAF V600E); less common mutations include valine 600 to lysine (V600K) or arginine (V600R) residues.
In 2011, the FDA approved the use of two new drugs in metastatic melanoma: ipilimumab (a CTLA-4 inhibitor) and vemurafenib (a BRAF inhibitor). The EMA approved them in 2011 and 2012, respectively. Vemurafenib is aimed at treating unresectable or metastatic melanoma in BRAF-mutation-positive patients, as detected by an FDA-approved test with the CE mark (cobas® 4800 BRAF). In metastatic melanoma, BRAF V600 mutations are biomarkers of treatment response.

c-KIT mutations
In smaller subsets of cutaneous melanoma, other activating mutations, such as NRAS, c-KIT and CDK4, have been described.

– Roughly 15% to 20% of melanomas have oncogenic NRAS mutations.
– c-KIT mutations appear more often in acral or mucosal melanomas (they account for 6-7% of melanomas in the Caucasian population, but are the most common sub-type in the Asian population).
– CDK4 mutations have been described in close to 4% of melanomas and are also more common in acral and mucosal melanomas.

A smaller subset of melanomas shows c-KIT alterations. Unlike the BRAF mutation, c-KIT alterations occur selectively in 17% of melanomas where there is chronic sun damage. Lentiginous and mucosal melanomas show c-kit mutations more often than BRAF mutations.
Though the importance of c-KIT mutations in melanoma is unclear, most point mutations are known to be susceptible to imatinib and other KIT inhibitors. Mutations occur more often in exon 11 and less often in exons 9, 13, and 17. In exon 11, most (34%) of the mutations cause a substitution of a leucine by a proline at codon 576.
A mutation study of the four exons of the gene should be conducted. When the quantity or quality of DNA is a limiting factor, exons 9 and 11 should preferably be evaluated.
The two most widely used methods for determining c-KIT mutations are direct sequencing and real-time PCR.
It should be noted that the immunohistochemical detection of the KIT protein (CD117) is not reliable in predicting mutations, which suggests the need for molecular testing.
Regardless of the technique used and the gene studied, it is important to select the sample with an appropriate percentage of tumour cells. In some cases, microdissection should be used in order to limit the presence of wild-type alleles of non-tumour cells. Cytological samples are also useful. Because cytological specimens are not fixed in formalin, the quality of the DNA is generally superior.

Other genetic alterations
Genetically, melanoma is a highly complex disease, and so it is not surprising that responses to BRAF and c-KIT inhibitors are limited. However, the discovery of mechanisms of resistance to these first-line drugs contributes to the development of new drugs. The resistance mechanisms involved include upregulation of PDGFR-ß, IGF-1R, MAP3K8 and MEK, acquisition of mutations in NRAS and deletions in PTEN. All these mechanisms have the potential ability to circumvent BRAF inhibition and reactivate the MAPK pathway. There is evidence that activation of the PI3K-AKT pathway plays an important role in melanoma, in particular when the Ras-Raf-MEK-ERK pathway is activated concurrently.

At present there is neither clinical consensus nor are there recommendations regarding the determination of these alterations.

GEM recommendation

B-RAF status testing should be done in all metastatic melanoma patients. Other mutation status determinations should be considered experimental.

Staging of patients with metastatic disease and prognostic factors

The prognosis for patients with disseminated melanoma depends on the localisation of the metastases and the tumour burden. The one-year survival rate is 62% when there is only soft-tissue involvement; 53% with lung involvement; and 33% with extrapulmonary visceral involvement or elevated LDH [75]. These survival values are improving as new drugs, like ipilimumab or vemurafenib, are being incorporated [76]. For example, the median survival associated with vemurafenib is 13.6 months, compared with 9.7 months with dacarbazine [77]. For ipilimumab, in patients who have undergone treatment for melanoma, median survival is 10.1 months, compared with 6.4 months for the gp 100 + placebo arm [78] with long-term survival data available at 4 and 5 years.

The standard technique for staging disseminated melanoma is chest, abdomen and pelvis computed tomography (CT). Likewise, CT is the procedure of choice for evaluating drug response. In addition, at the time of diagnosis, a head MRI should be performed, even if there are no neurological symptoms. Positron emission tomography (PET) is indicated when radical surgery for localised metastases is being considered or when the CT scan shows lesions of undetermined significance that might modify the therapeutic approach. The routine use of PET in stage IV beyond these situations is not justified [70, 79].

GEM recommendation

Whole body CT scan is the staging procedure of choice. PET should be reserved for patients who are candidates for surgery.

Surgery for metastases

We can also distinguish sub-groups within this stage: patients with resectable oligometastatic disease and patients with unresectable disseminated disease. Though it is quite likely that there are significant biological differences between the two sub-groups, these are as yet not known [80]. In any case, they could be responsible for the unequal responses of patients in terms of treatment, including surgery [81].

Patients with resectable oligometastatic disease

Many studies, mostly single-centre and retrospective with few patients, suggest that, when possible, metastatic melanoma should be resected because it prolongs survival [82-89].

Moreover, a recent multi-centre, prospective study supports this option [81]. A comparison of the survival figures from this study with those from a meta-analysis of 2100 stage IV patients on systemic therapy and with no surgery is telling (mean overall survival of 21 *vs*. 6.2 months and one-year survival of 75 *vs.* 25.5%) [90].

Even more recent is the huge amount of retrospective data from the MSLT-I [91]. For all types of metastasis (M1a, M1b and M1c), the survival of patients treated with surgery, with or without adjuvant systemic treatment, was higher than that of patients who were not treated with surgery (median survival of 15.8 *vs.* 6.9 months; 4-year overall survival of 20.8% *vs.* 7.0%).

With regard to patients with brain metastases, a clinical trial comparing surgical resection followed by radiation therapy with radiation therapy alone in patients with single brain metastases of various tumours, including melanoma, showed that those treated with surgery lived longer, had fewer local relapses and had a better quality of life [92]. These advantages remain for patients with up to three brain metastases.

Not all patients with metastatic melanoma are candidates for complete surgical resection, however. Only 55% of patients in the MSLT-I with stage IV melanoma were treated with surgery [91]. Surgery may not be indicated, for example, because of a high tumour burden or if the patient is in poor general condition. If surgery is indicated, neither multiple organ metastases nor multiple sequential resections reduce survival. Forty-two per cent (42%) of patients in the MSLT-I [91] and 36% in the SWOG study [81] had more than one surgery.

Therefore, in spite of the limitations of the data available, it seems clear that including surgery in the therapeutic arsenal for patients with resectable stage IV melanoma offers an advantage in terms of survival, as well as the only possibility of a cure [91].

Patients with unresectable disseminated disease

Sometimes a surgery that is meant to achieve complete resection ends up being palliative. The goal is not to eradicate the disease but to reduce tumour mass. In the SWOG study, this happened with 8 out of 77 patients (10%) [81].

At other times, surgery is meant to be palliative from the start. The goal may be to treat symptoms like gastrointestinal bleeding, obstruction, ulcerated skin mass, bulky lymphadenopathy, etc.

Of course, in these cases the indications for surgery should be considered on a case-by-case basis, taking into account various aspects such as the complexity of the procedure or the expectation of survival.

GEM recommendation

In resectable oligometastatic metastatic disease, surgery is the procedure of choice; in other cases it can be a palliative procedure.

First-line treatment

The arsenal of drugs used to treat advanced melanoma is increasing quantitatively and qualitatively *(figure 1)*. Of the various options theoretically available, the following drugs are approved for first-line treatment: dacarbazine, fotemustine, ipilimumab and, in patients with a mutation at codon V600 of the BRAF gene, vemurafenib and

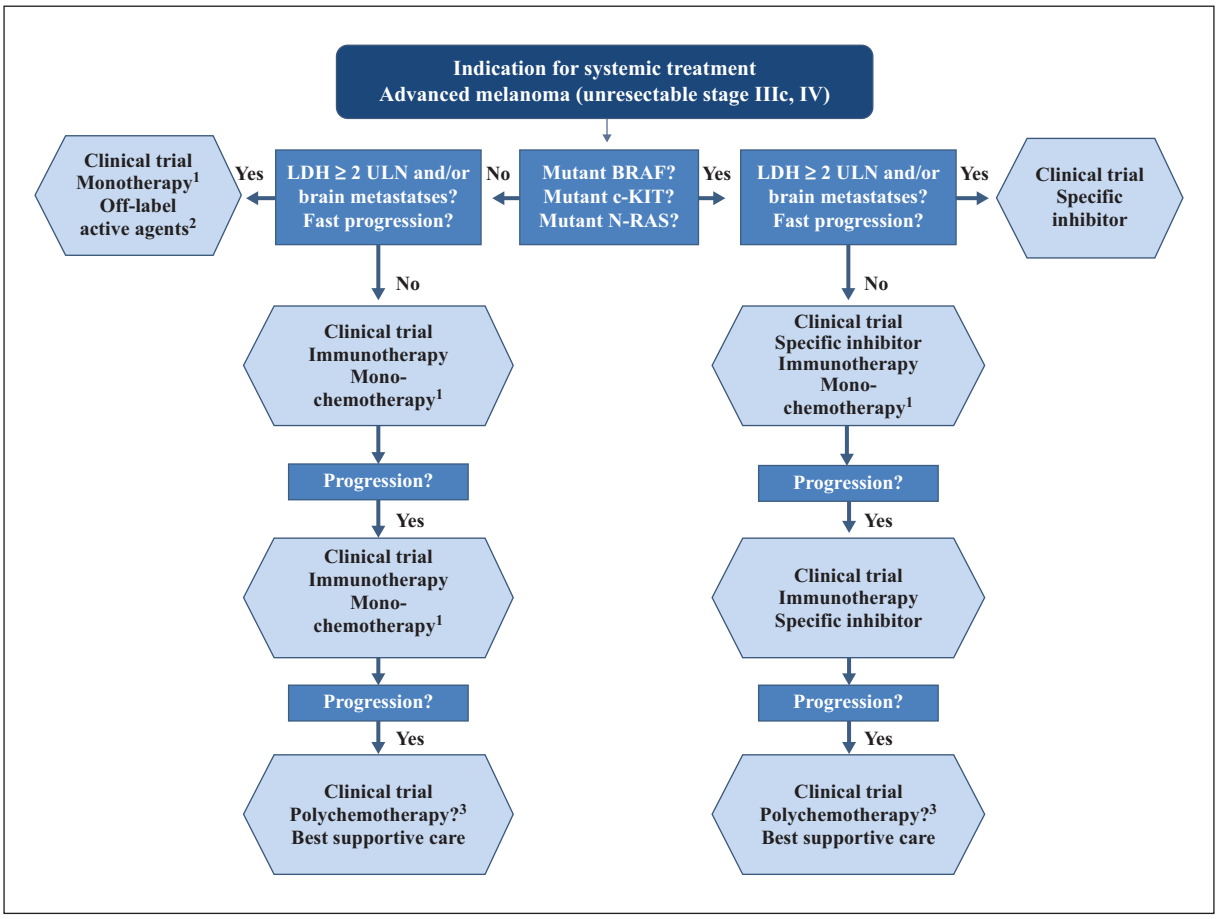

Figure 1. Suggested algorithm for the treatment of patients with advanced melanoma.
1. Dacarbazine and fotemustine
2. Platinum-based agents, taxanes, vinca alkaloids, interferon-α, IL-2
3. Other off-label chemotherapy agents: platinum-based agents, taxanes, vinca alkaloids or synthetic analogues

dabrafenib. There is a group of potentially active drugs (i.e. 10-20% objective responses), such as IL-2, temozolomide, imatinib (for tumours with c-KIT gene abnormalities), platinum-based agents, taxanes (including nab-paclitaxel), vinblastine, vindesine and interferon-alpha that the regulatory authorities in our country have not approved for this indication. Several randomised studies and meta-analyses have shown no benefit in terms of survival from polychemotherapy *versus* dacarbazine in monotherapy, nor between biochemotherapy (chemotherapy with IL-2 and/or interferon) and chemotherapy.

Around 40-60% of patients with metastatic melanoma have *BRAF* gene alterations, most of which are the V600E mutation. Vemurafenib is a specific inhibitor of the resulting abnormal protein. The phase III study that led to the registration of vemurafenib compared it with dacarbazine in 675 previously untreated patients with a mutation at codon V600, as determined by the cobas® test. The most recent data from the study showed the statistical superiority of vemurafenib for all efficacy endpoints: objective response rate (57% *vs.* 8.6%), progression-free survival (6.9 *vs.* 1.6 months; hazard ratio of 0.38) and, in particular, overall survival (median of 13.6 *vs.* 9.7 months; one-year survival of 56% *vs.* 44%; hazard ratio of 0.70). This involves a 30% reduction in the relative risk of death in favour of treatment with vemurafenib.

Response can be seen within days or weeks of starting treatment, with a median duration of response of 6-7 months. Fifteen per cent (15%) of patients are refractory to vemurafenib. This has led to different hypotheses being made about the mechanisms of primary and acquired resistance, and to the design of new clinical trials to treat it quickly.

For patients with advanced BRAF V600-mutant melanoma, treatment with vemurafenib or dabrafenib should be considered, especially if they have associated symptoms, extensive tumour burden and/or rapidly progressive disease, because the chances of achieving objective response and/or disease control increase in a short period of time. Association of a MEK inhibitor to any of these treatments may increase survival according to recent data [93-95]. The incidence of some adverse events is lower with these combinations, such as cutaneous toxicity [95].

Second-line and subsequent treatments

Second-line treatment will be conditioned by what was selected as first-line treatment. Until recently, second-line treatments provided no advantages in terms of survival.

However, ipilimumab has been the first drug to show a benefit in this context in a phase III randomised study [78]. Patients who have received any previous treatment are candidates for receiving treatment with ipilimumab at doses of 3 mg/kg every three weeks for a total of four doses, as this drug has been shown to increase overall survival (median 10.1 months *vs.* 6.4 months; one-year survival of 44% *vs.* 25%; hazard ratio of 0.66) and has survival data at 4 and 5 years [78, 96]. This drug requires a special evaluation of response, because it differs from conventional treatment and not recognising the variants of it may lead to the inadequate discontinuation of treatment [97]. If the patient has a BRAF V600 mutation, the use of vemurafenib is also appropriate, because it has shown activity following treatment with chemotherapy in a phase II uncontrolled study, with a median overall survival of 15.9 months and one- and two-year survival rates of 58% and 32%, respectively [98], whereas dabrafenib has less evidence for use in second-line treatment [99]. There is a lack of data for patients with a BRAF mutation concerning the optimum sequence of second-line treatment between ipilimumab and BRAF inhibitor, although retrospective studies seem to favour starting treatment with ipilimumab [100, 101]. Bristol-Myers Squibb is currently conducting a phase II study assessing the safety of vemurafenib followed by ipilimumab (NCT01673854).

If patients received a BRAF inhibitor in first-line treatment, they may experience a generalised or localised progression. For localised progression, if local treatment is possible it will be given, and the patient may continue with a BRAF inhibitor. For generalised progression, adding MEK inhibitors does not appear to be effective because this combination is associated with low response rates. In these cases, ipilimumab and systemic chemotherapy are the therapeutic alternatives.

Anti-PD1 antibodies have been recently approved by Food and Drug Administration (USA) for patients failing to ipilimumab and the approval by the European Medicines Agency is still pending

GEM recommendations on systemic treatment are summarized in *figure 1*.

Management of treatment-related toxicity

Non-cutaneous toxicity

Chemotherapy is associated with toxicities of routine management by the medical oncologist. However, treatment with recently introduced drugs requires knowledge of specific adverse events and taking appropriate action.

Amongst the most significant non-cutaneous events associated with vemurafenib are fatigue, arthralgia and altered liver function tests. NSAIDs may be required to manage arthralgia. In general, for fatigue and abnormal lab tests the dose of vemurafenib may need to be reduced or delayed. The summary of product characteristics recommends guidelines for this, depending on the severity of the event and whether it is a relapse. Monitoring the electrocardiogram (ECG) and electrolytes (including magnesium) is especially important. This should be done before treatment, a month after starting it, and after changing the dose. In patients with QTc>500 ms, starting treatment with vemurafenib is not recommended. If during treatment the QTc interval exceeds 500 ms, the drug should be discontinued temporarily, electrolyte imbalances corrected and the recommendations for dose modification described in the summary of product characteristics followed.

Ipilimumab may be associated with events relating to lymphocytes infiltrating different organs, including, as well as the skin, the intestines (colitis), the liver (hepatitis) and the endocrine glands (polyglandular autoimmune syndrome). The approved summary of product characteristics contains protocols with guidelines for action during these events. The first measure involves high clinical suspicion and blood test monitoring (liver function and hormone tests, particularly thyroid-stimulating hormone and baseline cortisol). Equally critical is informing the patient and clarifying the guidelines for action, especially against diarrhoea. In general, grade 1-2 events require symptom management and frequent observation, while prolonged grade 2 events or grade 3 events require the use of oral glucocorticoids (e.g. prednisone 1 mg/kg/day). More serious or prolonged toxicities, despite the above measures, usually require i.v. glucocorticoids (e.g. methylprednisolone 2 mg/kg/week). In cases of refractoriness, the use of infliximab (colitis) or mycophenolate (hepatitis) has been described. In general, once the glucocorticoid regimen has been started and improvement in toxicity achieved, the steroids should be continued for at least 1 month in order prevent relapse. It should be noted that anti-infective prophylaxis should be added in cases where long-term use of immunosuppressants is required.

Cutaneous toxicity

The new antineoplastic agents used to treat metastatic melanoma have been associated with dermatological adverse events in between 10% and 40% of treatments [102].

BRAF inhibitors (vemurafenib, dabrafenib) are associated with rash, photosensitivity, squamous cell carcinoma and keratoacanthoma, alopecia, pruritus and hyperkeratotic lesions. MEK inhibitors (selumetinib, trametinib) are associated with papulopustular rash, paronychia, cracking, dry skin, pruritus and facial hypertrichosis. Ipilimumab is associated with dermatological autoimmune conditions in 40% of cases, predominantly papulopustular/maculopapular rash, pruritus, and vitiligo.

The management of skin toxicity is based on the severity of the effects observed. Grade 1-2 adverse events require symptomatic treatment. For prolonged or debilitating grade 2-3 skin toxicity and grade 4 skin toxicity, it will be necessary to reduce the dose or discontinue treatment. For squamous cell carcinoma and keratoacanthoma caused by vemurafenib, any suspicious skin lesions should be removed, submitted for pathologic evaluation and treated according to the local standard protocol, and treatment should be continued without adjusting the dose [103].

With regard to symptomatic treatment, it is recommended to avoid direct exposure to the sun and use sunscreen. Emollients, topical corticosteroids, topical antibiotics (metronidazole, erythromycin) and oral antihistamines will be needed to treat papulopustular/maculopapular rash, dry skin and hyperkeratotic disorders. In cases of grade 2-3 rash, corticosteroids and/or systemic antibiotics (minocycline, doxycycline) may be required. Self-examination and regular dermatological exams will allow for early diagnosis and treatment of non-melanoma cancer in patients treated with BRAF inhibitors.

Follow-up of metastatic melanoma

Clinical and radiological follow-up of patients with unresectable or metastatic melanoma is determined by the number, size and location of the metastases, as well as the general condition, symptoms and functional impairment of organs.

For refractory patients with bulky visceral disease and rapid symptomatic and clinical deterioration, tests other than basic blood tests and conventional radiology procedures are rarely justified.

An increase in circulating LDH levels, and, according to some researchers, S-100,C-reactive protein, MIA serum or tyrosinase levels, may occasionally indicate disease progression and are routinely used in many centres [104].

For oligometastatic patients who respond, and with the option of radical surgery, all further tests needed to confirm the absence of disease in other organs should be performed with ultrasound, chest and abdomen CT, head MRI and/or PET before aggressive surgery.

FDG PET/CT is a proven procedure in metastatic melanoma, and its use is indicated in preoperative staging of resectable disease [105-107]. However, it is vital to conduct a detailed and combined assessment of all images, both CT and PET, since CT is the standard method in this setting The sensitivity, specificity and accuracy of PET/CT in detecting distant metastases improve significantly – from 85%, 96% and 91% to 98%, 94% and 96% ($p = 0.016$), respectively – when a simultaneous and independent assessment of the CT images is considered, especially in lung metastases, and head MRI in CNS metastases.

CT and MRI are the most reliable and widely used procedures in the progressive assessment of patients with metastatic melanoma.

Palliative care for melanoma patients

Extensive skin involvement

Skin metastases should be treated at an early stage to prevent them from growing. Palliative treatment of extensive skin metastases requires specific cancer treatment at a reference centre (tumour infiltration, electrochemotherapy, isolated perfusion, radiotherapy).

Treatment of complications such as pain, swelling or superinfection should be coordinated amongst reference centres and home-care professionals or in their basic area.

Lymphoedema

Lymphoedema can be caused by previous lymph node surgery, involvement due to tumour compression in the inguinal area, and local-regional skin and soft-tissue involvement due to carcinomatous lymphangitis. When lymphoedema is caused by tumour progression, treatment with chemotherapy may temporarily alleviate the condition. Surgery followed by radiotherapy for iliac/inguinal metastases should be assessed. Other treatment options include cytokine infiltration or treatment in a clinical trial. Postural treatment, care (topical treatments with emollients, antibiotic prophylaxis and fomentation) and pain relief are essential. ■

Disclosure. *Financial support: Roche has provided financial support for the editing services of this manuscript, through TFS. BMS has provided financial support for the expert meetings.*

Conflict of interest: Alfonso Berrocal has participated as principal investigator in clinical trials in melanoma promoted by the pharmaceutical industry over the past 5 years with Roche, Bristol Meyers, GSK, MSD, Novartis and Astra Zeneca; has received honoraria for consultancy activities from Roche, Bristol Meyers, GSK, MSD and Astra Zeneca; has received travel expenses for attending scientific meetings from Roche and BMS, and has received speaking honoraria from Roche, BMS and MSD. Enrique Espinosa has received honoraria for consultancy activities and lecturing from Roche, GSK, BMS and Merck, and has participated in clinical trials promoted by these companies. Josep Malvehy has received consultancy honoraria from GSK, AMGEN, Roche, BMS, Almirall, Leo-Pharma, Mavig, Agfa Healthcare, Canfield and Nevisence; and has participated in lectures sponsored by Almirall, Leo-Pharma, Isdin, GSK, Roche, and MEDA Pharma. David Moreno has collaborated in educational and research activities with Roche, GSK and BMS. Salvador Martin-Algarra has participated on advisory boards with BMS, Roche, MSD, GSK, AMGEN and Novartis, and has received honoraria for lecturing from BMS, MSD, GSK and Novartis. Jose Antonio Lopez has participated as principal investigator in clinical trials with vemurafenib, dabrafenib or ipilimumab; and has participated on advisory boards with Roche, GSK and BMS.

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