clinical practice guidelines

Annals of Oncology 26 (Supplement 5): v126–v132, 2015
doi:10.1093/annonc/mdv297

Cutaneous melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

R. Dummer[1], A. Hauschild[2], N. Lindenblatt[3], G. Pentheroudakis[4] & U. Keilholz[5], on behalf of the ESMO Guidelines Committee*

[1]*Department of Dermatology, University Hospital Zürich, Zürich, Switzerland;* [2]*Department of Dermatology, University Hospital Schleswig-Holstein, Kiel, Germany;* [3]*Division of Plastic and Reconstructive Surgery, University Hospital Zürich, Zürich, Switzerland;* [4]*Ioannina University Hospital, Ioannina, Greece;* [5]*Charité Comprehensive Cancer Center, Charité-Universitätsmedizin, Berlin, Germany*

incidence and epidemiology

The European incidence of malignant melanoma varies from 3 to 5/100 000/year in Mediterranean countries to 12–25 (and rising) in Nordic countries. Increased ultraviolet (UV) light exposure of a genetically predisposed population seems to be, at least in part, responsible for an ongoing increase in incidence with signs of stabilisation of mortality over recent decades, except in elderly males [1]. There is a disparity in the mortality-to-incidence ratios between Western and Eastern European countries [2], implying a need to improve prevention, especially in Eastern Europe.

UV irradiation was identified as a major carcinogen involved in melanoma genesis. Prevention of UV exposure, including the regular use of sunscreen, has been shown to diminish the incidence of primary cutaneous melanomas in an Australian population [3].

diagnosis

Suspicious lesions are characterised by ***A***symmetry, ***B***order irregularities, ***C***olour heterogeneity, ***D***ynamics, (dynamics or evolution in colours, elevation or size) ('ABCD rule') [4]. Today, many primary melanomas have a diameter of <5 mm [5].

The ugly duckling 'concept' [6] helps to identify melanomas, because naevi in the same individual tend to resemble one another and melanomas often do not fit the individual's naevus pattern.

Dermoscopy by an experienced physician enhances the diagnostic accuracy [II, B] [7]. An automated video-dermoscopy system can provide improved diagnostic accuracy for patients with multiple atypical naevi in the follow-up.

Diagnosis should be based on a full-thickness excisional biopsy with a minimal side margin. Processing by an experienced pathology institute is mandatory.

The histology report should follow the American Joint Committee on Cancer (AJCC) classification [8], and include: information on the maximum thickness in millimetres (Breslow), information on mitotic rate in case of a tumour thickness below 1 mm, presence of ulceration, presence and extent of regression and clearance of the surgical margins [II, A]. In addition, information on anatomical site (including extra-cutaneous sites, such as mucosa, conjunctiva) and degree of sun damage is necessary. It should also include the melanoma type (superficial spreading melanoma, lentigo maligna melanoma, acral lentiginous melanoma, nodular melanoma and others). In rare situations, melanomas may derive from dermal melanocytes (melanoma arising from giant congenital naevus, malignant blue naevus) [9].

Superficial spreading and nodular melanomas present a higher frequency of BRAF and NRAS mutations than other melanoma types [10]. Acral lentiginous melanoma and mucosal melanomas of the genital region have a certain probability to present c-Kit mutations [11].

Mutation testing for treatable mutations is mandatory in patients with advanced disease (unresectable stage III or stage IV, and highly recommended in high-risk resected disease stage IIc, stage IIIb–IIIc) [V, A]. If the tumour is BRAF-wild type, testing for NRAS mutations c-kit mutation should be considered [V, A].

Mutational testing of primary tumours without metastases is not recommended. Mutation analysis must be carried out in accredited (certified) institutes that have careful quality controls.

staging and risk assessment

Physical examination with special attention to other suspicious pigmented lesions, tumour satellites, in-transit metastases, regional lymph node (LN) and systemic metastases is mandatory.

In low-risk melanomas (pT1a) no other investigations are necessary. In higher tumour stages (pT1b–pT3a), imaging (ultrasound for locoregional LN metastasis) and, in pT stages >pT3a, computed tomography (CT) or positron emission tomography (PET) scans are recommended before surgical treatment and sentinel node biopsy [III, C].

The refined version of the AJCC staging and classification system, which includes sentinel node staging, is the only internationally accepted classification system [8, 12] (Table 1).

Correspondence to: ESMO Guidelines Committee, ESMO Head Office, Via L. Taddei 4, CH-6962 Viganello-Lugano, Switzerland.
E-mail: clinicalguidelines@esmo.org

†Approved by the ESMO Guidelines Committee: February 2002, last update July 2015. This publication supersedes the previously published version—Ann Oncol. 2012; 23 (Suppl. 7): vii86–vii91

Table 1. AJCC staging system of melanoma

T classification	Thickness (mm)	Ulceration status/mitosis
T1	≤1.0	a: without ulceration and mitosis <1/mm²
		b: with ulceration or mitoses ≥1/mm²
T2	1.01–2.0	a: without ulceration
		b: with ulceration
T3	2.01–4.0	a: without ulceration
		b: with ulceration
T4	>4.0	a: without ulceration
		b: with ulceration
N classification	**No. of metastatic nodes**	**Nodal metastatic mass**
N0	0	N/A
N1	1 node	a: micrometastasis[a]
		b: macrometastasis[b]
N2	2–3 nodes	a: micrometastasis[a]
		b: macrometastasis[b]
		c: in transit metastases/satellites 'without' metastatic nodes
N3	4 or more metastatic nodes, or matted nodes, or in transit metastases/satellites 'with' metastatic nodes	
M classification	**Site**	**Serum LDH**
M0	No distant metastasis	N/A
M1a	Distant skin, subcutaneous, or nodal metastases	Normal
M1b	Lung metastases	Normal
M1c	All other visceral metastases	Normal
	Any distant metastasis	Elevated

[a]Micrometastases are diagnosed after sentinel lymph node biopsy and completion lymphadenectomy (if carried out).

[b]Macrometastases are defined as clinically detectable nodal metastases confirmed by therapeutic lymphadenectomy or when nodal metastasis exhibits gross extracapsular extension.

AJCC, American Joint Committee on Cancer; N/A, not applicable; LDH, lactate dehydrogenase.

treatment of localised disease

Wide excision of primary tumours with safety margins of 0.5 cm for *in situ* melanomas, 1 cm for tumours with a thickness of up to 2 mm, and 2 cm for thicker tumours, is recommended [13] [II, B]. Modifications, with reduced safety margins, are acceptable for preservation of function in acral and facial melanomas and should be carried out with micrographic surgery.

Elective lymphadenectomy or irradiation to the regional LNs should not be carried out routinely [II, B].

Sentinel LN biopsy in melanoma with a tumour thickness of >1 mm and >0.75 mm and additional risk factors such as ulceration or mitotic rate (pT1b) are recommended for precise staging [II, B] [14]. A complete lymphadenectomy of regional LNs must be discussed with the patient, if the sentinel node was found positive for metastases [III, C]. However, this procedure offers just a relapse-free survival (RFS) benefit without proven effect on overall survival (OS) [15]. Sentinel LN biopsy should be carried out only in experienced centres.

Many well-designed clinical trials have investigated the impact of adjuvant therapy in patients with high-risk primary melanoma (stage IIB/C) or completely resected LN metastases (stage III) [6]. A number of prospective randomised trials have investigated adjuvant treatment with low, intermediate and high doses of interferon-α (IFN-α) [16, 17].

A meta-analysis of 14 randomised, controlled trials, investigating adjuvant IFN therapy involving 8122 patients, showed statistically significant absolute improvement in both disease-free survival [hazard ratio (HR) 0.82] and OS (HR 0.89), with no clear indication to recommend a certain dose or treatment duration [18]. Since pegylated IFN-α (PegIFN-α) is suitable for long-term therapy, the European Organisation for Research and Treatment of Cancer (EORTC) has initiated a large prospective randomised trial to investigate the protective effect of PegIFN-α-2b in the adjuvant setting [19]. A total of 1256 patients with resected stage III melanoma were randomised to receive observation or PegIFN-α therapy [19]. Randomisation was stratified for microscopic (N1) versus macroscopic (N2) nodal involvement, number of positive nodes, ulceration and tumour thickness. The IFN group received an induction-IFN-weekly dose of 6 μg/kg for the first 8 weeks, and the dose was then reduced to 3 μg/kg per week for 5 years [19]. At 3.8 years of median follow-up, RFS was significantly improved by 18% in the PegIFN-α-2b arm, compared with observation; the 4-year RFS rate was 45.6% versus 38.9%. OS was unchanged in the two groups. In stage III–N1a (micrometastases

detected in the sentinel node), both RFS and distant metastases-free survival (DMFS) were prolonged in the PegIFNα-2b arm, whereas in stage III-N1b (macroscopic metastases), there was no benefit [19]. An update of this trial, with median follow-up of 7.6 years, has shown that IFN therapy had a significant impact on RFS, DMFS and OS (HR 0.59 = 0.006) in a sub-population of patients with micrometastases and primary ulcerated melanomas [20]. Therefore, while awaiting the results of prospective randomised trials, in this patient population, PegIFN-α can be recommended if the individual patient tolerates it well [II, B]. Adjuvant treatment in patients with resected macroscopic node involvement is preferentially applied in the context of randomised clinical trials in specialised centres. However, high-dose IFN-α-2b is an approved indication for this therapeutic situation. A meta-analysis on adjuvant therapy of melanoma with IFNs, however, did not demonstrate an improved efficacy of high-dose IFN compared with low- or intermediate-dose IFNs [18].

Long-term therapy with ipilimumab, an antibody blocking CTLA4 and thus activating T lymphocytes to mount an immune response against tumour cells, has improved RFS (HR 0.75; median RFS 26.1 versus 17.1 months, with 3-year RFS rates of 46.5% versus 34.8%, $P = 0.0013$) in the adjuvant setting also for N1b and higher stages. However, the treatment with a dose of 10 mg/kg every 3 weeks for 4 doses, then every 3 months for up to 3 years, was associated with a number of severe and long-lasting adverse reactions including colitis and endocrinopathies. Therefore, additional trials are mandatory and the respective patient population should be referred to centres offering trial participation [21].

Adjuvant chemotherapy, mistletoe extracts, viscum album and hormone therapies are not beneficial at all [22]. Adjuvant therapy with other cytokines including interleukin-2, tumour vaccination, immunochemotherapy and BRAF inhibitors is experimental and not to be used outside controlled clinical trials. The application of BRAF inhibitors is associated with cutaneous neoplasms such as keratoacanthomas, squamous cell carcinomas and melanomas [23–25], which precludes use outside carefully monitored clinical trials. Radiotherapy for local tumour control should be considered in: cases of inadequate resection margins of lentigo maligna melanoma [26], in R1 resections of melanoma metastases (when surgery is not adequate), or after resection of bulky disease [III, B]. A prospective randomised trial has demonstrated that postoperative irradiation after LN dissection reduces the risk for relapse in the irradiation field by ~50%, but has no impact on RFS and OS [27]. Treatment decisions should be made in an interdisciplinary team.

treatment of locoregional disease

In the case of isolated locoregional LN metastases, surgical removal, including the surrounding LN region is indicated [III, C]; removal of the tumour-bearing LN alone is insufficient. In high-risk situations such as multiple bulky LN metastases, postoperative radiotherapy can improve local tumour control, but has no impact on RFS and OS [27, 28].

However, before undertaking additional aggressive local surgical treatments, a detailed staging investigation, that includes high-resolution imaging techniques, such as PET, CT or magnetic resonance imaging is necessary to exclude distant metastases [4] [III, B]. In unresectable in-transit cases, other locoregional approaches, such as electrochemotherapy [29] or intralesional therapy with replicating herpes virus [Talimogene laherparepvec (T-Vec)] [30], preferentially in the context of a clinical trial, should be considered.

Surgical removal or stereotactic irradiation therapy might be curative in a few patients and is recommended in the case of a single metastasis in parenchymal organs, including the central nervous system.

Non-resectable in-transit metastases or inoperable primary tumours of the limbs, without additional metastases, may be treated with isolated limb perfusion using melphalan and/or tumour necrosis factor-α [III, C]. Such treatment requires major surgery and should be restricted to centres of excellence. Radiation therapy, electrochemotherapy [29] or intralesional therapy, with replicating T-Vec [30], may also be used [V, D], [27, 28].

treatment of systemic metastatic disease (stage IV)

New therapeutic strategies, such as immunotherapy, that utilise antibodies that bind to checkpoint inhibitors of T-cell activation, have demonstrated impressive efficacy. CTLA-4 blocking agents like ipilimumab, the anti PD-1 antibodies, such as nivolumab and pembrolizumab, as well as selective BRAF inhibitors, such as vemurafenib, encorafenib and dabrafenib (used alone and/or in combination with MEK inhibitors like binimetinib, cobimetinib and trametinib [31, 32]), have demonstrated impressive anti-tumour activity [33–39]. Therefore, immunotherapy and kinase inhibitors are the backbone of systemic therapy. Chemotherapy is considered a second-line or bridging treatment option.

Tumour tissues, preferentially of metastatic lesions, should be screened for mutations of BRAF V600. If that is negative, further molecular testing can be carried out for NRAS, c-Kit (mucosal and acrolentigenous primaries) GNA11 or GNAQ (uveal primary); this helps to direct patients to the appropriate targeted treatment or clinical trial. There are early signals from a phase II clinical trial that patients with metastatic melanomas, carrying NRAS mutation, may benefit from MEK kinase-inhibitor therapy [40]. The additional analysis for PDL-1 expression helps to enrich the population of patients who benefit from anti-PD1 therapy, but is not powerful enough to exclude patients from anti-PD1 treatment [39, 41].

The recommendations for first-line treatment of metastatic disease are under debate. Reasonable approaches include anti-PD1 therapies and, for BRAF-mutated melanomas, combinations of BRAF inhibitors with MEK inhibitors. BRAFi/MEKi inhibitor combos offer high response rates (70%) and rapid response induction associated with symptom control, with a progression-free survival (PFS) of ~12 months. Anti-PD1 therapy, and to a lesser extent ipilimumab, offer lower response rates in the range, but many responses are durable [42].

In patients with BRAF-wild-type (wt) disease, ipilimumab has been the standard treatment based on a survival benefit with a ~10% higher survival rate at 1, 2 and 3 years [36]. Based on very recent randomised trial results, comparing anti-PD1 antibody therapies to ipilimumab, anti-PD1 antibody therapy is the preferred first-line treatment of patients with BRAF-wt disease [42]. These therapies also demonstrate efficacy for patients with other

BRAF mutations [37]. Anti-PD1 therapies are also recommended as a second-line treatment, after ipilimumab failure [43, 44].

The anti-PD1 antibody nivolumab was compared with the reference chemotherapy dacarbazine in a double-blind randomised clinical trial with BRAF-wt patients. This trial showed a 1-year survival rate of 72.9% in the nivolumab group, compared with 42.1% in the dacarbazine group (HR for death, 0.42; $P < 0.001$) [39]. Nivolumab and pembrolizumab present an excellent safety profile, resulting in a favourable risk/benefit ratio. The most frequent adverse events included fatigue, pruritus and nausea. Both molecules have been compared with standard chemotherapies in a second-line setting after ipilimumab therapy. They demonstrated favourable efficacy, with prolonged PFS and better response rates, than the chemotherapy option [43–45].

Pembrolizumab (at a dose of 10 mg/kg of body weight) every 2 or 3 weeks was compared with ipilimumab in a randomised clinical trial. The 6-month PFS rates were ~47% for pembrolizumab, independent from the dose, and 26.5% for ipilimumab (HR for disease progression, 0.58; $P < 0.001$ for both pembrolizumab regimens versus ipilimumab). Estimated 12-month survival rates were ~70% for pembrolizumab, versus 58%. The response rate was ~33% for pembrolizumab, compared with 11.9% for ipilimumab [42].

In a double-blinded prospective randomised trial, nivolumab was compared with ipilimumab and the ipilimumab/nivolumab combination. The anti-PD1 antibody alone or in combination demonstrated improved PFS (ipilimumab: 2.9, nivolumab: 6.9, combination: 11.5 months) and response rates.

PDL-1 expression was a relevant marker in this context, because there was no difference in PFS between anti-PD1 antibody therapy versus a ipilimumab/nivolumab combination, in the PDL-1 positive population. The study was not powered to distinguish between the efficacy of nivolumab and the ipilimumab/nivolumab combo. The final clinical implications of this study, including the question about the superiority of combined anti-PD1/CTLA-4 therapy versus sequential anti-PD1/CTLA-4 therapy, remain open until the survival data are mature [41].

If the patient suffers from symptomatic, bulky metastases from a BRAF-V600-mutated melanoma, a combination of BRAFi and MEKi is a valid treatment option in first and second lines. It has a high chance for rapid response and offers improvements in quality of life [37–39, 41]. There are no mature data to guide decision making regarding the sequencing of checkpoint inhibitors and kinase-inhibitor combinations, in patients with BRAF-mutant metastatic melanoma. Emerging data suggest that BRAF inhibition is effective following immunotherapy, and checkpoint inhibitors are still effective in patients who have progressed on kinase-inhibitor therapy. Kinase inhibitors [46] and ipilimumab and/or anti-PD1 antibody therapy [47] can be safely used even in patients with symptomatic brain metastases, in fact it has shown significant efficacy in this area [48]. Stereotactic irradiation of progressive brain metastases is reasonable if systemic therapy can achieve partial disease control.

In the context of new developments and medical progress, there are continuously new experimental treatment options for patients with advanced metastatic melanoma, including combined therapies with anti-CTLA4 and anti-PD1 antibodies, with intralesional therapies and small molecules. Therefore, patients should preferentially be referred to centres of excellence that provide a comprehensive clinical trial programme.

If clinical trials or new compounds are not available, cytotoxic drugs such as dacarbazine (DTIC), temozolomide, taxanes, fotemustine, platin derivatives or others, cytokines (IFNs, interleukin-2) or combinations may be applied. DTIC is still considered a reference drug in this situation. In aggressive metastatic disease, multi-agent polychemotherapy, containing paclitaxel and carboplatin or cisplatin, vindesine, and DTIC may provide mostly short-lived partial responses and/or disease stabilisations in a meaningful number of patients. Despite a better initial control rate, no survival benefit has been shown with polychemotherapy compared with monochemotherapy.

Surgery of visceral metastases may be appropriate for selected cases with good performance status and isolated tumour manifestations. In principal, the goal is R0 resection in these patients.

Palliative radiotherapy should be considered, especially for symptomatic brain or localised and painful bone metastases. Stereotactic irradiation is preferred to whole brain irradiation in case of brain metastases [28].

In general, stage IV melanoma patients need to be treated and discussed in an interdisciplinary tumour board, within centres that have broad experience in this disease (Table 2).

personalised medicine

Biomarkers such as mutations (NRAS, c-Kit, BRAF) are already indispensable today for proper management of advanced melanoma. Additional mutations and the overall mutation rate might provide additional molecular predictive markers in the near future. Based on the recent data of anti-PD1 efficacy in PDL-1-positive advanced melanoma [41], this parameter, which is determined by immunohistochemistry and reflects the presence of T cells in the tumour microenvironment, might soon be relevant. We assume that treatment algorithms for advanced melanoma may evolve in a paradigm for precision medicine in the context of targeted and immunotherapy [42].

patient information and follow-up

Melanoma patients should be advised to avoid sunburn, extended unprotected solar or artificial UV exposure, and to have lifelong, regular self-examinations of the skin and peripheral LNs. Patients must be aware that family members have an increased melanoma risk [III, B]. There is no recommendation for genetic testing.

During melanoma follow-up, patients are clinically monitored in order to detect a relapse and to recognise additional skin tumours, especially secondary melanomas, as early as possible [4] [III, B]. However, it remains to be determined whether this strategy leads to improved survival rates, especially in this new era of systemic therapies for stage IV disease. Eight percent of all melanoma patients develop a secondary melanoma within 2 years of the initial diagnosis [49]. Melanoma patients also have an increased risk for other skin tumours. In patients with lentigo maligna melanomas, 35% of patients develop another cutaneous malignancy within 5 years [26].

Table 2. Treatment modalities for melanoma metastases

Number and localisation of the metastases	Treatment modalities 1st choice 2nd choice 3rd choice	Grade of recommendation
In-transit metastases (few) (pTXN2cM0)	Surgical removal	C
	Radiotherapy	C
In-transit metastases (multiple, >5) (pTXN2cM0)	Perfusion of the extremity[a]	D
	Radiotherapy	D
	T-Vec (Talimogene laherparepvec)	D
	Electrochemotherapy	D
	Systemic therapy[a]	D
Locoregional LNs (pTxN1a, 2a)	Discuss Regional lymph node dissection and trial participation	B
	Additional Interferon alpha treatment[a]	B
Locoregional LNs (pTxN2b, 2c, 3)	Radical lymphadenectomy, in case of incomplete resection: irradiation,	C
	Consider trial participation	C
Solitary central nervous system metastases (pTxNxM3)	Neurosurgical removal	D
	Stereotactic irradiation[a]	D
	(according to localisation this could also be the 1st choice) or other local treatment approaches	
	Consider clinical trial participation	
Solitary lung/liver/kidney and other metastases (pTxNxM1)	Surgical removal	D
	Consider clinical trial participation	
	Systemic therapy[a]	D
Multiple metastases (pTxNxM1a–1c)	Consider clinical trial participation	
	Systemic therapy[a]	B
Painful bone metastases (pTxNxM1a–1c)	Consider clinical trial participation	
	Radiotherapy	C
	Bone-modifying agents	

[a]These therapies should be preferentially carried out at specialised centres.
LNs, lymph nodes.

There is currently no consensus on the frequency of follow-up examinations and the use of imaging techniques. Recommendations vary from follow-up visits every 3 months, during the first 3 years and every 6–12 months thereafter, to no organised follow-up at all. We encourage consultation of the respective national guidelines. Intervals between controls may be tailored according to the individual's risk and the personal needs of the patient [50].

Since patients with a thin primary melanoma have only a small risk of relapse, routine imaging techniques are definitively not recommended for this patient population. In high-risk patients, (e.g. those with thick primary tumours, or following treatment of metastases) ultrasound of LNs, CT or whole-body PET/PET–CT scans may lead to an earlier diagnosis of regional or systemic relapses [51]. The impact of radiological exams upon survival has not been demonstrated so far [52]. However, targeted therapy and immunotherapy demonstrate favourable effects in patients with low tumour burden, who can be identified by high-resolution imaging during follow-up. Rising serum S-100 has a higher specificity for disease progression than lactate dehydrogenase, and is therefore the most accurate blood test in the follow-up of melanoma patients [53], if any blood test is recommended at all [IV, D].

methodology

These clinical practice guidelines were developed in accordance with the ESMO standard operating procedures for clinical practice guidelines development. The relevant literature has been selected by the expert authors. A summary of recommendations is shown in Table 3. Levels of evidence and grades of recommendation have been applied using the system shown in Table 4. Statements without grading were considered justified standard clinical practice by the experts and the ESMO faculty. This manuscript has been subjected to an anonymous peer review process.

conflict of interest

RD has reported research funding from Novartis, Merck Sharp & Dohme (MSD), Bristol-Myers Squibb (BMS), Roche,

Table 3. Summary of recommendations

Diagnosis
• Diagnosis should be based on a full-thickness excisional biopsy with a small side margin [II, A].
• The histology report should include at least: information on the type of melanoma, actinic damage, maximum vertical thickness in millimetres, information on mitotic rate in case of pT1, presence of ulceration, presence and extent of regression and clearance of the surgical margins [II, A].
• Physical examination with special attention to other suspicious pigmented lesions, tumour satellites, in-transit metastases, regional LN and distant metastases is mandatory. In low-risk melanomas (pT1a), no other investigations are necessary. In higher tumour stages, imaging is recommended in order to allow proper staging [III, C].
Treatment of localised disease
• Wide excision of primary tumours with safety margins of 0.5 cm for *in situ* melanomas, of 1 cm for tumours with a tumour thickness up to 2 mm and 2 cm for thicker tumours is recommended [II, B].
• Sentinel LN biopsy in melanoma with a tumour thickness of >1 mm and/or ulceration is recommended for precise staging [II, B]. It should be discussed in patients with a pT1b with a tumour thickness >0.75 mm.
• Patients with resected stage III melanomas should be evaluated for adjuvant interferon therapy [II, B]. Subgroup analyses suggest patients with microscopic regional nodal involvement and/or ulcerated primaries are most likely to benefit from adjuvant IFN. In stage IIIB and higher, participation in clinical trials should be encouraged.
• Surgical removal or stereotactic irradiation of locoregional recurrence or single distant metastasis should be considered in fit patients, as a therapeutic option, offering potential for long-term disease control [III, C].
Treatment of systemic metastatic disease (stage IV)
• Patients with metastatic melanoma should have metastasis (preferably) or the primary tumour screened for detection of BRAF-V600-mutation. Treatment options for the first- and second-line setting include anti-PD1 antibodies (pembrolizumab, nivolumab), ipilimumab, an anti-CTLA4 antibody, for all patients, and BRAF/MEK inhibitor combinations for patients with BRAF-mutant melanoma [II, B].
• If clinical trials or the approved new targeted compounds are not available, cytotoxic drugs such as DTIC or temozolomide may be administered, with modest activity shown [II, C].
Patient information and follow up
• Melanoma patients should be instructed in the avoidance of sunburns, extended unprotected solar or artificial UV exposure, and in lifelong regular self-examinations of the skin and peripheral LNs [III, B].
• There is no consensus on the optimal schedule or frequency of follow-up visits, or on the utility of imaging and blood tests for patients with resected melanoma.

LN, lymph node; IFN, interferon; DTIC, dacarbazine; UV, ultraviolet.

Table 4. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System[a])

Levels of evidence	
I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, experts opinions
Grades of recommendation	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, …), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

[a]By permission of the Infectious Diseases Society of America [54].

GlaxoSmithKline (GSK) and consultant or advisory board with Novartis, MSD, BMS, Amgen, Roche, GSK. AH has reported consultancy, honoraria and trial grants from Amgen, BMS, Celgene, Eisai, GSK, MedImmune, Me-laSciences, Merck Serono, MSD/Merck, Novartis, On-cosec, Roche Pharma. The other authors have declared no potential conflicts of interest.

references

1. Hollestein LM, van den Akker SA, Nijsten T et al. Trends of cutaneous melanoma in The Netherlands: increasing incidence rates among all Breslow thickness categories and rising mortality rates since 1989. Ann Oncol 2012; 23: 524–530.
2. Forsea AM, Del Marmol V, Stratigos A, Geller AC. Melanoma prognosis in Europe: far from equal. Br J Dermatol 2014; 171: 179–182.
3. Green AC, Williams GM, Logan V, Strutton GM. Reduced melanoma after regular sunscreen use: randomized trial follow-up. J Clin Oncol 2011; 29: 257–263.
4. Dummer R, Guggenheim M, Arnold AW et al. Updated Swiss guidelines for the treatment and follow-up of cutaneous melanoma. Swiss Med Wkly 2011; 141: w13320.
5. Bono A, Tolomio E, Trincone S et al. Micro-melanoma detection: a clinical study on 206 consecutive cases of pigmented skin lesions with a diameter < or = 3 mm. Br J Dermatol 2006; 155: 570–573.
6. Grob JJ, Bonerandi JJ. The 'ugly duckling' sign: identification of the common characteristics of nevi in an individual as a basis for melanoma screening. Arch Dermatol 1998; 134: 103–104.
7. Kittler H, Pehamberger H, Wolff K, Binder M. Diagnostic accuracy of dermoscopy. Lancet Oncol 2002; 3: 159–165.
8. Balch CM, Gershenwald JE, Soong SJ et al. Final version of 2009 AJCC melanoma staging and classification. J Clin Oncol 2009; 27: 6199–6206.
9. Whiteman DC, Pavan WJ, Bastian BC. The melanomas: a synthesis of epidemiological, clinical, histopathological, genetic, and biological aspects, supporting distinct subtypes, causal pathways, and cells of origin. Pigment Cell Melanoma Res 2011; 24: 879–897.

10. Bastian BC. The molecular pathology of melanoma: an integrated taxonomy of melanocytic neoplasia. Annu Rev Pathol 2014; 9: 239–271.
11. Schoenewolf NL, Bull C, Belloni B et al. Sinonasal, genital and acrolentiginous melanomas show distinct characteristics of KIT expression and mutations. Eur J Cancer 2012; 48: 1842–1852.
12. Hirakawa S, Kodama S, Kunstfeld R et al. VEGF-A induces tumor and sentinel lymph node lymphangiogenesis and promotes lymphatic metastasis. J Exp Med 2005; 201: 1089–1099.
13. Thompson JF, Scolyer RA, Kefford RF. Cutaneous melanoma. Lancet 2005; 365: 687–701.
14. Han D, Zager JS, Shyr Y et al. Clinicopathologic predictors of sentinel lymph node metastasis in thin melanoma. J Clin Oncol 2013; 31: 4387–4393.
15. Morton DL, Thompson JF, Cochran AJ et al. Sentinel-node biopsy or nodal observation in melanoma. N Engl J Med 2006; 355: 1307–1317.
16. Eggermont AM, Suciu S, Testori A et al. Ulceration and stage are predictive of interferon efficacy in melanoma: results of the phase III adjuvant trials EORTC 18952 and EORTC 18991. Eur J Cancer 2012; 48: 218–225.
17. Kirkwood JM, Ibrahim JG, Sondak VK et al. High- and low-dose interferon alfa-2b in high-risk melanoma: first analysis of intergroup trial E1690/S9111/C9190. J Clin Oncol 2000; 18: 2444–2458.
18. Mocellin S, Pasquali S, Rossi CR, Nitti D. Interferon alpha adjuvant therapy in patients with high-risk melanoma: a systematic review and meta-analysis. J Natl Cancer Inst 2010; 102: 493–501.
19. Eggermont AM, Suciu S, Santinami M et al. Adjuvant therapy with pegylated interferon alfa-2b versus observation alone in resected stage III melanoma: final results of EORTC 18991, a randomised phase III trial. Lancet 2008; 372: 117–126.
20. Eggermont AM, Suciu S, Testori A et al. Long-term results of the randomized phase III trial EORTC 18991 of adjuvant therapy with pegylated interferon alfa-2b versus observation in resected stage III melanoma. J Clin Oncol 2012; 30: 3810–3818.
21. Eggermont AM, Chiarion-Sileni V, Grob JJ et al. Adjuvant ipilimumab versus placebo after complete resection of high-risk stage III melanoma (EORTC 18071): a randomised, double-blind, phase 3 trial. Lancet 2015; 16: 522–530.
22. Kleeberg UR, Suciu S, Brocker EB et al. Final results of the EORTC 18871/DKG 80–1 randomised phase III trial. rIFN-alpha2b versus rIFN-gamma versus ISCADOR M versus observation after surgery in melanoma patients with either high-risk primary (thickness >3 mm) or regional lymph node metastasis. Eur J Cancer 2004; 40: 390–402.
23. Oberholzer PA, Kee D, Dziunycz P et al. RAS mutations are associated with the development of cutaneous squamous cell tumors in patients treated with RAF inhibitors. J Clin Oncol 2012; 30: 316–321.
24. Su F, Viros A, Milagre C et al. RAS mutations in cutaneous squamous-cell carcinomas in patients treated with BRAF inhibitors. N Engl J Med 2012; 366: 207–215.
25. Zimmer L, Hillen U, Livingstone E et al. Atypical melanocytic proliferations and new primary melanomas in patients with advanced melanoma undergoing selective BRAF inhibition. J Clin Oncol 2012; 30: 2375–2383.
26. Farshad A, Burg G, Panizzon R, Dummer R. A retrospective study of 150 patients with lentigo maligna and lentigo maligna melanoma and the efficacy of radiotherapy using Grenz or soft X-rays. Br J Dermatol 2002; 146: 1042–1046.
27. Burmeister BH, Henderson MA, Ainslie J et al. Adjuvant radiotherapy versus observation alone for patients at risk of lymph-node field relapse after therapeutic lymphadenectomy for melanoma: a randomised trial. Lancet Oncol 2012; 13: 589–597.
28. Hong A, Fogarty G. Role of radiation therapy in cutaneous melanoma. Cancer J 2012; 18: 203–207.
29. Campana LG, Testori A, Mozzillo N, Rossi CR. Treatment of metastatic melanoma with electrochemotherapy. J Surg Oncol 2014; 109: 301–307.
30. Andtbacka RH, Kaufman HL, Collichio F et al. Talimogene laherparepvec improves durable response rate in patients with advanced melanoma. J Clin Oncol 2015 [Epub ahead of print].
31. Flaherty KT, Hennig M, Lee SJ et al. Surrogate endpoints for overall survival in metastatic melanoma: a meta-analysis of randomised controlled trials. Lancet Oncol 2014; 15: 297–304.
32. McArthur GA, Chapman PB, Robert C et al. Safety and efficacy of vemurafenib in BRAF (V600E) and BRAF (V600K) mutation-positive melanoma (BRIM-3): extended follow-up of a phase 3, randomised, open-label study. Lancet Oncol 2014; 15: 323–332.
33. Chapman PB, Hauschild A, Robert C et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med 2011; 364: 2507–2516.
34. Guo J, Si L, Kong Y, Flaherty KT et al. Phase II, open-label, single-arm trial of imatinib mesylate in patients with metastatic melanoma harboring c-Kit mutation or amplification. J Clin Oncol 2011; 29: 2904–2909.
35. Hodi FS, O'Day SJ, McDermott DF et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010; 363: 711–723.
36. Robert C, Thomas L, Bondarenko I et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. N Engl J Med 2011; 364: 2517–2526.
37. Long GV, Stroyakovskiy D, Gogas H et al. Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. N Engl J Med 2014; 371: 1877–1888.
38. Robert C, Karaszewska B, Schachter J et al. Improved overall survival in melanoma with combined dabrafenib and trametinib. N Engl J Med 2015; 372: 30–39.
39. Robert C, Long GV, Brady B et al. Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med 2015; 372: 320–330.
40. Ascierto PA, Schadendorf D, Berking C et al. MEK162 for patients with advanced melanoma harbouring NRAS or Val600 BRAF mutations: a non-randomised, open-label phase 2 study. Lancet Oncol 2013; 14: 249–256.
41. Larkin J, Ascierto PA, Dréno B et al. Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. N Engl J Med 2014; 371: 1867–1876.
42. Robert C, Schachter J, Long GV et al. Pembrolizumab versus ipilimumab in advanced melanoma. N Engl J Med 2015; 372: 2521–2532.
43. Weber JS, D'Angelo SP, Minor D et al. Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4-treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial. Lancet Oncol 2015; 16: 375–384.
44. Dummer R, Daud A, Puzanov I et al. A randomized controlled comparison of pembrolizumab and chemotherapy in patients with ipilimumab-refractory melanoma. J Transl Med 2015; 13(Suppl 1): 05.
45. Robert C, Dummer R, Gutzmer R et al. Selumetinib plus dacarbazine versus placebo plus dacarbazine as first-line treatment for BRAF-mutant metastatic melanoma: a phase 2 double-blind randomised study. Lancet Oncol 2013; 14: 733–740.
46. Long GV, Trefzer U, Davies MA et al. Dabrafenib in patients with Val600Glu or Val600Lys BRAF-mutant melanoma metastatic to the brain (BREAK-MB): a multicentre, open-label, phase 2 trial. Lancet Oncol 2012; 13: 1087–1095.
47. Margolin K, Ernstoff MS, Hamid O et al. Ipilimumab in patients with melanoma and brain metastases: an open-label, phase 2 trial. Lancet Oncol 2012; 13: 459–465.
48. Dummer R, Goldinger SM, Turtschi CP et al. Vemurafenib in patients with BRAF (V600) mutation-positive melanoma with symptomatic brain metastases: final results of an open-label pilot study. Eur J Cancer 2014; 50: 611–621.
49. Titus-Ernstoff L, Perry AE, Spencer SK et al. Multiple primary melanoma: two-year results from a population-based study. Arch Dermatol 2006; 142: 433–438.
50. Turner RM, Bell KJ, Morton RL et al. Optimizing the frequency of follow-up visits for patients treated for localized primary cutaneous melanoma. J Clin Oncol 2011; 29: 4641–4646.
51. Bastiaannet E, Wobbes T, Hoekstra OS et al. Prospective comparison of [18F] fluorodeoxyglucose positron emission tomography and computed tomography in patients with melanoma with palpable lymph node metastases: diagnostic accuracy and impact on treatment. J Clin Oncol 2009; 27: 4774–4780.
52. Nieweg OE, Kroon BB. The conundrum of follow-up: should it be abandoned? Surg Oncol Clin N Am 2006; 15: 319–330.
53. Beyeler M, Waldispuhl S, Strobel K et al. Detection of melanoma relapse: first comparative analysis on imaging techniques versus S100 protein. Dermatology 2006; 213: 187–191.
54. Dykewicz CA. Summary of the guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. Clin Infect Dis 2001; 33: 139–144.