SPECIAL ARTICLE

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

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Incidence and epidemiology

The European annual incidence of malignant melanoma varies from 3–5/100 000 in Mediterranean countries to 12–35/100 000 in Nordic countries, whereas it can reach over 50/100 000 in Australia or New Zealand. The incidence of melanoma has been rising steadily over the last 40 years, with a trend towards stabilisation of mortality, except in elderly males [1]. Melanoma incidence peaks at 65 years, though any age can be affected [2]. There is an increase in the mortality-to-incidence ratios in Eastern compared with Western European countries, suggesting a need to improve prevention and early detection in Eastern Europe [3].

Ultraviolet (UV) irradiation was identified as a major carcinogen involved in melanoma genesis. UV irradiation is associated with a distinct DNA damage signature and a high rate of mutations per megabase (Mb) [4]. The best prevention is physical protection with adapted garments. In a randomised trial, 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 [5].

Diagnosis and pathology/molecular biology

Diagnosis

Suspicious pigmented lesions are usually clinically analysed with the 'ugly duckling' concept and the 'ABCD' rule [6]: **A**symmetry, **B**order irregularities, **C**olour heterogeneity, **D**ynamics, (Dynamics or evolution in colours, elevation or size). Today, many primary melanomas have a diameter of <5 mm [7]. Dynamics (or evolution) is a very important criterion because it can also help to identify rapidly growing amelanotic melanomas in educated patients.

The 'ugly duckling' concept helps to identify melanomas, because naevi in the same individual tend to resemble one another and melanomas often do not fit the individuals naevus pattern [8].

Dermoscopy by an experienced physician enhances the diagnostic accuracy [II, B] [9]. An automated videodermoscopy system can provide improved diagnostic accuracy for patients with multiple atypical naevi in the follow-up. Full body imaging with high-resolution pictures has also shown to improve early detection [10].

Machine-learning algorithms trained on either standard or dermatoscopic images have been shown to correctly diagnose pigmented skin lesions, with a success rate comparable to that of a panel of 21 board-certified dermatologists; though early results are very promising, their use in clinical practice remains to be evaluated [11]. The use of patient-operated diagnostic devices without medical supervision is presently not recommended.

Diagnosis should be based on a full thickness excisional biopsy with a minimal side margin [V, A]. Processing of the primary tumour according to international guidelines and by an experienced pathology institute is mandatory.

The histology report should follow the eighth edition of the American Joint Committee on Cancer (AJCC) tumour, node, metastasis (TNM) classification and include: the maximum thickness in millimetres (Breslow) reported to the nearest 0.1 mm (rounding up starting at 0.05), presence of ulceration and clearance of the surgical margins [II, A] [12]. Although no longer included in the eighth edition of the AJCC classification, mitotic rate and regression assessment and recording is recommended for all tumour thickness categories due to its important prognostic determinant when evaluated using its dynamic range across all melanomas [12].

Information on anatomical site (including extra-cutaneous sites, such as mucosa, conjunctiva) and degree of sun damage of the surrounding skin is necessary. It should also include the melanoma type [superficial spreading melanoma, lentigo maligna melanoma (LMM), 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 and spitzoid lesions), which should be reported as well [13]. Atypical spitzoid tumours should be distinguished from spitzoid melanoma as they do not have a metastatic potential. In these melanomas, the prognostic relevance of tumour thickness and sentinel lymph node (SN) involvement is questionable.

Molecular characterisation

Mutation testing for actionable mutations is mandatory in patients with resectable or unresectable stage III or stage IV [I, A], and is highly recommended in high-risk resected disease stage IIC but not for stage I or stage IIA–IIB. *BRAF* testing is mandatory [I, A]. If the tumour is *BRAF* wild-type (WT) at the V600 locus (class I BRAF mutant) sequencing the loci of the other known minor *BRAF* mutations (class II and class III BRAF mutant) to confirm WT status and testing for *NRAS* and *c-kit* mutations are recommended [II, C] [14]. Although no good targeted therapies options exist for these drivers at the moment, they are important to identify for future opportunities and to select patients for clinical trials. Alternatively, a clinically validated next-generation sequencing panel covering all key oncogenic drivers is increasingly being carried out. As drivers are actionable and can impact clinical decision, mutation analysis must be carried out in accredited (certified) institutes that have careful quality controls.

The main melanoma subtypes are associated with different mutational landscapes: frequently mutated genes include [15]:

- *BRAF, CDKN2A, NRAS* and *TP53* in cutaneous melanoma,
- *BRAF, NRAS, NF1 and KIT* in acral melanoma (though with lower frequencies than in cutaneous melanoma),
- *SF3B1* in mucosal melanoma.

In addition to the mutational status, programmed death-ligand 1 (PD-L1) expression, reported as the percentage of positive tumour cells, can be useful to assess and record for all resectable or unresectable stage III and IV [I, B], though its clinical use is very limited at this time (see below). Tumour mutational burden (TMB) computed on full exome sequencing or on a large full length panel and expressed as the number of mutations per Mb can be assessed and recorded [IV, C], though its clinical use is not warranted at this time [16].

Staging and risk assessment

Staging and risk assessment procedures are determined by disease presentation at diagnosis.

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

In low-risk melanomas (pT1a), no additional investigations are necessary. In the other T stages, pT1b-pT4b, ultrasound (US) for locoregional LN metastasis, and/or computed tomography (CT) or positron emission tomography (PET) scans as well as brain magnetic resonance imaging (MRI), represent options for tumour extension assessment before surgical treatment and SN biopsy (SNB). Brain MRI and PET-CT/CT scan should be applied only for very high-risk patients (pT3b and higher [III, C]).

The eighth version of the AJCC staging and classification system, which includes SN staging, is the preferred classification system (Table 1) [12].

Management of local/locoregional disease

Treatment of localised disease (primary tumours)

Wide local excision (WLE) 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 [II, B] (Table 2) [17]. Modifications, with reduced safety margins, are acceptable for preservation of function in acral and facial melanomas and can be carried out with Slow Mohs technique, although prospective randomised trials are missing [18, 19].

For lentigo maligna, radiotherapy (RT) can be curative and represents an option to avoid unacceptable surgery [20]. Definitive RT to the primary tumour is only considered in (rare) palliative cases, when excision is not possible either due to severe comorbidities of the patient (i.e. very old age, end-stage cardiovascular disease etc.) or when the morbidity of the excision is considered too great (i.e. extreme patient delay with a huge non-resectable local disease). RT is not curative in these settings.

Treatment of locoregional disease

A locoregional disease treatment algorithm is provided in Figure 1.

Elective lymph node dissection or primary elective irradiation to the regional LNs should not be carried out [II, B] [21–24]. Again, definitive irradiation can be considered in (rare) palliative cases.

SNB is recommended for precise staging in melanoma of AJCC eighth edition stage pT1b or higher, i.e. with a tumour thickness

Table 1. AJCC TNM eighth edition staging system of melanoma [12]

T—primary tumour

T category		Thickness	Ulceration status
TX	Primary tumour thickness cannot be assessed (e.g. diagnosis by curettage)	Not applicable	Not applicable
T0	No evidence of primary tumour (e.g. unknown primary or completely regressed melanoma)	Not applicable	Not applicable
Tis (melanoma *in situ*)		Not applicable	Not applicable
T1		≤1.0 mm	Unknown or unspecified
T1a		<0.8 mm	Without ulceration
T1b		<0.8 mm	With ulceration
		0.8–1.0 mm	With or without ulceration
T2		>1.0–2.0 mm	Unknown or unspecified
T2a		>1.0–2.0 mm	Without ulceration
T2b		>1.0–2.0 mm	With ulceration
T3		>2.0–4.0 mm	Unknown or unspecified
T3a		>2.0–4.0 mm	Without ulceration
T3b		>2.0–4.0 mm	With ulceration
T4		>4.0 mm	Unknown or unspecified
T4a		>4.0 mm	Without ulceration
T4b		>4.0 mm	With ulceration

M—metastasis

M category[a]	Anatomic site	LDH level
M0	No evidence of distant metastasis	Not applicable
M1	Evidence of distant metastasis	See below
M1a	Distant metastasis to skin, soft tissue including muscle and/or nonregional lymph node	Not recorded or unspecified
M1a(0)		Not elevated
M1a(1)		Elevated
M1b	Distant metastasis to lung with or without M1a sites of disease	Not recorded or unspecified
M1b(0)		Not elevated
M1b(1)		Elevated
M1c	Distant metastasis to non-CNS visceral sites with or without M1a or M1b sites of disease	Not recorded or unspecified
M1c(0)		Not elevated
M1c(1)		Elevated
M1d	Distant metastasis to CNS with or without M1a, M1b or M1c sites of disease	Not recorded or unspecified
M1d(0)		Not elevated
M1d(1)		Elevated

T	N	M	Pathological stage group
Tis	N0[b]	M0	0
T1a	N0	M0	IA
T1b	N0	M0	IA
T2a	N0	M0	IB
T2b	N0	M0	IIA
T3a	N0	M0	IIA
T3b	N0	M0	IIB
T4a	N0	M0	IIB
T4b	N0	M0	IIC

Continued

Table 1. *Continued*

T	N	M	Pathological stage group
T0	N1b, N1c	M0	IIIB
T0	N2b, N2c, N3b or N3c	M0	IIIC
T1a/b–T2a	N1a or N2a	M0	IIIA
T1a/b–T2a	N1b/c or N2b	M0	IIIB
T2b/T3a	N1a–N2b	M0	IIIB
T1a–T3a	N2c or N3a/b/c	M0	IIIC
T3b/T4a	Any N ≥N1	M0	IIIC
T4b	N1a–N2c	M0	IIIC
T4b	N3a/b/c	M0	IIID
Any T, Tis	Any N	M1	IV

[a]Suffixes for M category: (0) LDH not elevated, (1) LDH elevated. No suffix is used if LDH is not recorded or is unspecified.
[b]Pathological stage 0 (melanoma *in situ*) and T1 do not require pathological evaluation of lymph nodes to complete pathological staging; use clinical N information to assign their pathological stage.
AJCC, American Joint Committee on Cancer; CNS, central nervous system; LDH, lactate dehydrogenase; TNM, tumour, node, metastasis.
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Table 2. Local excision margins [17]

Wide local excision margins according to Breslow (pT1a-pT4b Nx M0)

Tumour thickness (Breslow) in mm	Excision margin (cm)
Melanoma *in situ* (pTis N0 M0)	0.5
≤2 mm (pT1a-pT2 N0 M0)	1
>2 mm (pT3a-pT4b N0 M0)	2

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>0.8 mm or with a tumour thickness of <0.8 mm with ulceration [II, B] [25]. SNB is not recommended for pT1a melanomas [26].

In the Multicentre Selective Lympadenectomy Trial I (MSLT-I), there was no significant treatment-related difference between WLE/SN versus WLE/nodal observation in the 10-year follow-up melanoma-specific survival rate in patients with intermediate-thickness melanomas and thick primary melanomas [27]. A criticised subgroup analysis seemed to show a significant benefit for the node-positive patients in the SN arm compared with the node-positive patients in the observation arm. However, any false-positive negative patients or false-positive SN results were not taken into account. Another statistical method was developed on the interim data but was not externally validated [28, 29]. In summary, the MSLT-I validated the staging potential of SNB but did not show any unequivocal survival benefit for this procedure. SNB should therefore not be considered as a therapeutic procedure.

SNB should be carried out only in experienced centres [30]. Quality criteria for centres performing SNB include the following [31]:

- Review and comparison of primary histology with SNB is recommended in difficult cases.
- Histology evaluation of the SNB according to cell morphology and immune profile of the primary.
- SNB procedure carried out simultaneously with the safety margins re-excision of the primary to avoid lymph drainage modifications.
- SNB and re-excision carried out by an experienced surgical team.
- Marking of the scar during the consultation, preferably with photo documentation.
- Single-photon emission CT (SPECT) imaging in cases of unclear sentinel LN localisation.

SN tumour burden has been assessed in different ways, and all different measures conclude that it adds to the accuracy of the prognosis [32, 33]. The most used and best reproducible method between pathologists has been the maximum diameter of the largest lesion (MDLL) according to the Rotterdam Criteria, which the European Organisation for Research and Treatment of Cancer (EORTC) has validated and adopted [34–36]. An MDLL cut-off of 1 mm has been used for adjuvant therapy trials. Therefore, though not formally part of the AJCC eighth edition evaluation, it is recommended to record the EORTC/Rotterdam criteria in the reporting of SN tumour burden.

Complete lymph node dissection (CLND) for SN-positive patients was the standard of care until very recently. Following the MSLT-I trial, both the MSLT-II and the German Dermatologic Cooperative Oncology Group-selective lymphadenectomy (DeCOG-SLT) trials analysed the benefit of performing routine CLND for SN-positive disease. Both studies reported no impact on survival for early CLND compared with nodal observation with periodic US of the SN-positive basin [37, 38]. CLND provides additional staging information, as ~15%–20% of SN-positive patients have additional non-SN involvement. However, upstaging occurs even less frequently at ~6% of cases. Therefore,

considering the morbidity of routine CLND, this practice can no longer be recommended [I, E] [39–41].

In the case of isolated locoregional clinically detectable (macroscopic, non-SN) LN metastases, therapeutic lymph node dissection is indicated [III, C]; removal of the tumour-bearing LN alone is insufficient [42].

However, before undertaking additional aggressive local surgical treatments, a detailed staging investigation that includes high-resolution imaging techniques such as PET, CT or MRI is necessary to exclude distant metastases [III, B] [6]. Evidence of distant metastatic spread will preclude surgery and qualify the patient for systemic therapy (see below).

In-transit disease. Resectable satellite or ITM patients can be candidates for surgery, though the advent of highly effective systemic therapies is now challenging such an approach as it is associated with the risk of rapid progression, jeopardising the chances of long-term benefit from systemic therapies.

Non-resectable satellite, ITM or inoperable primary tumours of the limbs, without additional metastases, may be treated with isolated limb perfusion using melphalan and/or tumour necrosis factor alpha [III, C]. Alternatively, talimogene laherparepvec (T-VEC) has shown an improved durable response rate compared with subcutaneous granulocyte-macrophage colony-stimulating factor, especially in stage IIIB/C, IVM1a (AJCC seventh edition [43]) melanoma patients [44] [I, B]. These local procedures should be carefully weighed against systemic treatment, in order not to lower their chances in providing long-term benefit.

Such local treatments either require major surgery or experience using oncolytic viruses and should therefore be restricted to experienced centres. Since their efficacy data are less established, RT, electrochemotherapy, carbon dioxide (CO_2) laser or other intralesional therapy may also be proposed within clinical trials [V, D] [16, 45–47].

Adjuvant RT. Adjuvant RT for local tumour control can be considered in cases of inadequate resection margins of LMM, in R1 resections (microscopic tumour at the margin) of melanoma metastases (only when second surgery is not adequate) or after resection of bulky disease [III, B] [48]. A prospective randomised trial has demonstrated that adjuvant irradiation after LN dissection reduces the risk for relapse in the irradiation field by ∼50%, but has no impact on recurrence-free survival (RFS) and overall survival (OS) [46]. Since local control is rarely the therapeutic objective in melanoma, adjuvant RT can no longer routinely be recommended in the adjuvant setting [III, D]. It could still be discussed in specific cases where local control is critical, such as in head and neck melanoma.

Adjuvant systemic therapy. 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).

Interferon alpha. A number of prospective randomised trials have investigated adjuvant treatment with low, intermediate and high doses of interferon alpha (IFNα) [49, 50].

A meta-analysis of 14 randomised controlled trials, investigating adjuvant IFNα therapy involving 8122 patients, showed
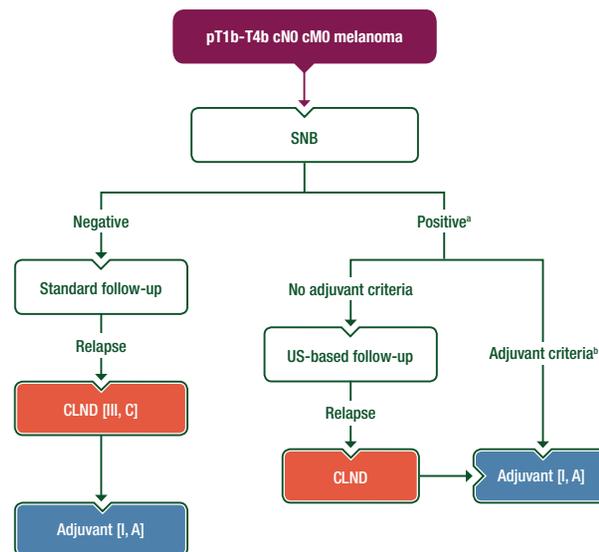

Figure 1. Treatment algorithm for stage I–III melanoma.
[a]For positive SND patients, avoiding CLND is justified based on the results of the MSLT-II and DeCOG-SLT trials. The control arm of both MSLT-II and DeCOG-SLT trials is not standard observation, but US-based follow-up, which should be the strategy proposed to the patient [I, A].
[b]Please refer to main text for a discussion on criteria to propose adjuvant treatment.
CLND, complete lymph node dissection; DeCOG-SLT, Dermatologic Cooperative Oncology Group-selective lymphadenectomy; MSLT, multicentre selective lymphadenectomy; SNB, sentinel lymph node biopsy; SND, sentinel lymph node dissection; US, ultrasound.

statistically significant absolute improvement in both disease-free survival (DFS) [hazard ratio (HR) 0.82] and OS (HR 0.89) [I, C], with no clear indication to specific dose or treatment duration and at the cost of significant toxicity [51].

Considering the most recent developments in adjuvant therapy (see below), adjuvant IFNα can no longer be routinely proposed in the adjuvant setting. Its use might be confined to particular settings like patients with an ulcerated stage IIc primary [52] and where the approved new drugs are not accessible.

Anti-cytotoxic T lymphocyte-associated antigen 4. Long-term therapy with ipilimumab, a monoclonal antibody blocking cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) that promotes T cell priming against tumour cells, resulted in improved RFS (HR 0.75; median RFS 26.1 months versus 17.1 months, with 3-year RFS rates of 46.5% versus 34.8%, $P = 0.0013$) in the adjuvant setting compared with placebo in the EORTC 18071 trial [53]. The rate of OS at 5 years was 65.4% in the ipilimumab group, when compared with 54.4% in the placebo group (HR for death, 0.72; 95.1% CI 0.58–0.88; $P = 0.001$). Contrary to results with IFNα, the benefit was also observed for N1b and higher stages. However, the treatment schedule at 10 mg/kg every 3 weeks for four doses, then every 3 months for up to 3 years, was associated with a number of severe and some long-lasting adverse reactions, including colitis and endocrinopathies. Due to the toxicity profile of anti-CTLA-4, anti-programmed cell death protein

1 (anti-PD-1) adjuvant therapy or dabrafenib/trametinib are the preferred treatment options [I, A] [54]. Ipilimumab has not been approved in the adjuvant setting in the EU by the European Medicines Agency (EMA).

Anti-PD-1. Adjuvant anti-PD-1, nivolumab has very recently shown a significant RFS benefit for stage IIIB/C, IV (AJCC seventh edition; [43]) resected melanoma when compared with adjuvant high-dose ipilimumab, with an RFS HR of 0.66, 70% of patients free of relapse versus 60% at 12 months, 66% versus 53% at 18 months and 63% versus 50% at 24 months, respectively [55]. The RFS HR is very consistent across stage subgroups with 0.68 for IIIB, 0.68 for IIIC and 0.66 for M1a/M1b [55]. Moreover, this adjuvant treatment with nivolumab had far fewer grade 3/4 adverse events compared with the very toxic high-dose ipilimumab; 14.4% versus 45.9%, respectively [56].

In addition, pembrolizumab has been evaluated against placebo for stage IIIA (SN >1 mm), B and C (without ITM) within the EORTC 1325 trial [57]. At a median follow-up of 15 months, pembrolizumab was associated with significantly longer RFS than placebo in the overall intention-to-treat population [1-year rate of RFS, 75.4% (95% CI 71.3–78.9) versus 61.0% (95% CI 56.5–65.1); HR for recurrence or death, 0.57; 98.4% CI 0.43–0.74; $P < 0.001$)].

OS data are not currently available for nivolumab or pembrolizumab.

Based on these RFS data and despite the lack of OS data, the EMA approved nivolumab [I, A; ESMO-Magnitude of Clinical Benefit Scale (ESMO-MCBS) v1.1 score: A] and pembrolizumab [I, A; ESMO-MCBS v1.1 score: A] in the adjuvant setting in August and December 2018, respectively [see Table 3 (58–70)].

Targeted therapy. Efficacy of adjuvant targeted therapy has also been recently reported. The BRIM8 study analysed vemurafenib monotherapy versus a placebo in stage IIC and stage III (AJCC seventh edition [43]) melanoma after complete surgical resection. The study did not meet its primary end point of DFS [71]. Therefore, *BRAF* inhibitor (*BRAFi*) monotherapy cannot be recommended as adjuvant treatment for melanoma.

The COMBI-AD study, however, analysed dabrafenib/trametinib combination therapy versus two placebos in fully resected high-risk stage IIIA (with LN metastasis diameter >1 mm), IIIB or IIIC melanoma (AJCC seventh edition [43]). This study showed a significantly improved estimated RFS of 58% versus 39% at 3 years (HR for relapse or death, 0.47; 95% CI 0.39–0.58; $P < 0.001$), as well as a numerically improved OS of 86% versus 77% (HR for death, 0.57; 95% CI 0.42–0.79; $P = 0.0006$) [I, A] [62]. The P value for the OS HR (0.0006) reported by Long et al. [62] did not meet the prespecified boundary (0.000019). The combination of dabrafenib/trametinib is one of the standards of care for adjuvant *BRAF*-mutated melanoma and was approved by the EMA for adjuvant treatment for melanoma in August 2018 [I, A; ESMO-MCBS v1.1 score: A] (see Table 3).

Summary of recommendations in the adjuvant setting. Table 4 summarises the results from key trials in the adjuvant setting.

The data currently available establish both PD-1 blockade and dabrafenib/trametinib as recommended adjuvant treatments options for stage IIIA (SN >1 mm), B and C for *BRAF*-mutated melanoma. Some of the current approvals include all stage III, regardless of SN deposit. Treatment decisions for stage IIIA SN <1 mm should be made on an individual basis, considering the exact prognosis of the patient. This decision process will be discussed in detail in the upcoming 'ESMO Consensus Conference Recommendations on Melanoma' publication.

Additionally, results from CheckMate 238 suggest that nivolumab had benefits for stage IV no evidence of disease (NED) similar to those of stage III, making it a clear option for this patient population [56]. Combination of nivolumab plus ipilimumab has shown very promising clinical activity compared to nivolumab in stage IV patients rendered NED by surgery or radiotherapy [72] though with increased toxicity.

The added toxicity and the lower efficacy of ipilimumab no longer warrants its use in the adjuvant setting.

In *BRAF* WT patients, PD-1 blockade is the only recommended option.

For *BRAF*-mutated melanoma, as there is no direct efficacy comparison between dabrafenib/trametinib versus PD-1 blockade, individual treatment decisions should be made with the patient, factoring in the toxicity profiles.

Contrary to the initial EORTC 18071 ipilimumab trial, HRs for RFS are robust and consistent across the various subgroups for the PD-1 trial, EORTC 1325 and CheckMate 238, and the dabrafenib/trametinib trial, COMBI-AD [62]. This suggests that the benefit from PD-1 or dabrafenib/trametinib could be similar in lower, not yet evaluated, subgroups, such as some stage II. Indeed, the risk of relapse for SN-negative pT3b, pT4a and pT4b melanoma is quite high, with a mortality of ∼20% at 10-year follow-up [12]. Therefore, such patients should be considered a priority for adjuvant stage II clinical trials.

Management of advanced/metastatic disease

Surgical or ablative treatment of resectable stage IV

Some stage IV patients present with a resectable, oligometastatic disease. Although the value of complete surgery or ablative radiosurgery in such a clinical setting has not been validated in phase III prospective studies, data from phase II are available [73]. 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]. Surgery remains an option for selected patients, preferentially combined with adjuvant systemic therapies [see section on adjuvant systemic therapy].

Systemic treatment of unresectable stage III and IV disease

The therapeutic landscape of unresectable stage III and IV melanoma has been revolutionised by immunotherapies and targeted therapies. Both strategies have shown markedly improved survival compared with the use of chemotherapy (ChT) regimens.

Table 3. ESMO-MCBS table for new therapies/indications in melanoma[a]

Therapy	Disease setting	Trial	Control	Absolute survival gain	HR (95% CI)	QoL/toxicity	ESMO-MCBS score[b]
Nivolumab with ipilimumab	First-line advanced or metastatic melanoma	Phase 3 Study of Nivolumab or Nivolumab Plus Ipilimumab Versus Ipilimumab Alone in Previously Untreated Advanced Melanoma (CheckMate 067) [58, 59] Phase III NCT01844505	Ipilimumab PFS: 2.9 months OS: 19.9 months 3-year OS: 34%	PFS gain: 8.6 months 3-year OS gain: 24%	PFS HR: 0.42 (0.35–0.51) OS HR: 0.55 (0.44–0.68)		4 (Form 2a)
Nivolumab	First-line advanced or metastatic melanoma	Phase 3 Study of Nivolumab or Nivolumab Plus Ipilimumab Versus Ipilimumab Alone in Previously Untreated Advanced Melanoma (CheckMate 067) [58, 59] Phase III NCT01844505	Ipilimumab PFS: 2.9 months OS: 19.9 months 3-year OS: 34%	PFS gain: 4 months OS gain: 17.7 months 3-year OS gain: 18%	PFS HR: 0.53 (0.44–0.64) OS HR: 0.65 (0.53–0.79)		4 (Form 2a)
Cobimetinib with vemurafenib	First-line unresectable or metastatic melanoma with the BRAF V600E mutation	A Study Comparing Vemurafenib Versus Vemurafenib Plus Cobimetinib in Participants With Metastatic Melanoma [60] Phase III NCT01689519	Vemurafenib+placebo PFS: 7.2 months OS: 17.4 months	PFS gain: 5.1 months OS gain: 4.9 months	PFS HR: 0.58 (0.46–0.72) OS HR: 0.70 (0.55–0.90)	9% reduction skin cancer	4 (Form 2a)
Ipilimumab	Adjuvant stage III melanoma	Efficacy Study of Ipilimumab Versus Placebo to Prevent Recurrence After Complete Resection of High Risk Stage III Melanoma [53] Phase III NCT00636168	Placebo OS: 54.40%	Primary outcome 5-year DFS OS gain: 11%	OS HR: 0.76 (0.64–0.89)		A (Form 1)
Trametinib with dabrafenib	First-line unresectable or metastatic melanoma with the BRAF V600 mutation following complete resection	Dabrafenib Plus Trametinib vs Vemurafenib Alone in Unresectable or Metastatic BRAF V600E/K Cutaneous Melanoma [61] Phase III NCT01597908	Vemurafenib PFS: 7.3 months OS: 1-year survival 65%	PFS gain: 4.1 months OS gain: 1-year survival 7%	PFS HR: 0.56 (0.46–0.69) OS HR: 0.69 (0.53–0.89)	17% reduction skin cancer	4 (Form 2b)

Continued

Table 3. *Continued*

Therapy	Disease setting	Trial	Control	Absolute survival gain	HR (95% CI)	QoL/toxicity	ESMO-MCBS score[b]
Dabrafenib in combination with trametinib	Adjuvant treatment of melanoma after surgical resection with BRAF V600 mutation	Dabrafenib With Trametinib in the Adjuvant Treatment of High-risk BRAF V600 Mutation-positive Melanoma (COMBI-AD) [62, 63] Phase III NCT01682083	Placebo RFS: 16.6 months 3-year RFS: 39%	RFS gain: 27.9 months 3-year RFS gain: 19%	RFS HR: 0.47 (0.39–0.58)		A (Form 1)
Trametinib as monotherapy	Unresectable or metastatic melanoma with a BRAF V600E/K mutation	GSK1120212 vs Chemotherapy in Advanced or Metastatic BRAF V600 E/K Mutation-positive Melanoma [64–67] Phase III NCT01245062	Dacarbazine or paclitaxel PFS (crossover allowed): 1.5 months	PFS gain: 3.3 months	PFS HR: 0.45 (0.33–0.63) OS HR: not significant	QoL improved	4 (Form 2b)
Pembrolizumab	Adjuvant treatment of adults with stage III melanoma and lymph node involvement after complete resection	Study of Pembrolizumab (MK-3475) Versus Placebo After Complete Resection of High-Risk Stage III Melanoma (MK-3475-054/1325-MG/KEYNOTE-054) [57] Phase III NCT02362594	Placebo RFS at 1 year: 61%	RFS gain at 1 year: 14.40%	RFS HR: 0.57 (0.43–0.74)		A (Form 1)
Nivolumab	Adult patients with complete resection of stage IIIB/C or IV melanoma	Efficacy Study of Nivolumab Compared to Ipilimumab in Prevention of Recurrence of Melanoma After Complete Resection of Stage IIIb/c or Stage IV Melanoma (CheckMate 238) [56] Phase III NCT02388906	Ipilimumab 10 mg/kg RFS at 1 year: 60.8%	RFS gain at 1 year: 9.7%	RFS HR: 0.66 (0.53–0.81)	Fewer treatment-related grade 3 or 4 adverse events 14.4% versus 45.9%	A (Form 1)

Continued

Table 3. *Continued*

Therapy	Disease setting	Trial	Control	Absolute survival gain	HR (95% CI)	QoL/toxicity	ESMO-MCBS score[b]
Binimetinib with encorafenib	Adult patients with unresectable or metastatic melanoma with the *BRAF* V600 mutation	Study Comparing Combination of LGX818 Plus MEK162 Versus Vemurafenib and LGX818 Monotherapy in BRAF Mutant Melanoma [68, 69] Phase III NCT01909453	Vemurafenib PFS: 7.3 months OS: 16.9 months	PFS gain: 7.6 months OS gain: 16.7 months	PFS HR: 0.51 (0.39–0.67) OS HR: 0.61 (0.47–0.79)	QoL not published as full paper	4 (Form 2a)

[a]EMA approvals since January 2016.
[b]ESMO-MCBS version 1.1 [70]. The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee.
CI, confidence interval; DFS, disease-free survival; EMA, European Medicines Agency; HR, hazard ratio; ESMO-MCBS, ESMO-Magnitude of Clinical Benefit Scale; OS, overall survival; PFS, progression-free survival; QoL, quality of life; RFS, recurrence-free survival.

Table 4. Summary of stage subgroup eligibility criteria and RFS efficacy data for adjuvant trials

| Study | Design | Stage—AJCC seventh edition (all patients NED) | | | | |
		IIC	IIIA	IIIB	IIIC	IV
EORTC 18071 [53]	Ipilimumab 10 mg/kg versus placebo		SN >1 mm HR 0.98	HR 0.75	HR 1.00, 1–3 LNs HR 0.48, ≥4 LNs	
EORTC 1325 [57]	Pembrolizumab versus placebo		SN >1 mm HR 0.38	HR 0.58	HR 0.58	
CheckMate 238 [55, 56]	Ipilimumab 10 mg/kg versus nivolumab			HR 0.68	HR 0.68	HR 0.66 M1a, b HR 0.78 M1c
BRIM8 [71]	Vemurafenib versus placebo	HR 0.0 NE	SN >1 mm HR 0.52	HR 0.63	HR 0.8	
COMBI-AD [62]	Dabrafenib/trametinib versus placebo		SN >1 mm HR 0.44	HR 0.50	HR 0.45	

Note: All trials including stage IIIA patients requested a minimum SN diameter of 1 mm. All stage III patients included in these trials had radical LN dissection.

AJCC, American Joint Committee on Cancer; EORTC, European Organisation for Research and Treatment of Cancer; HR, hazard ratio; LN, lymph node; NE, not established; NED, no evidence of disease; RFS, recurrence-free survival; SN, sentinel node.

Despite progress in treatment of advanced disease, many questions remain unanswered, and for the majority of melanoma patients, prognosis remains poor. Inclusion in clinical trials remains, therefore, the number one priority in all settings.

Systemic treatment algorithms for stage IV are provided in Figures 2–4 (see also Table 5).

First-line treatment. The current first-line standard of care treatments for unresectable stage III/IV are PD-1 blockade (nivolumab, pembrolizumab), PD-1 blockade (nivolumab) combined with CTLA-4 blockade (ipilimumab) and, in addition for *BRAF V600*-mutated melanoma [II, B], BRAF inhibition (vemurafenib, dabrafenib, encorafenib) combined with MEK inhibition (cobimetinib, trametinib, binimetinib) [60]. For unresectable stage IIIB/C, IVM1a (AJCC seventh edition [43]), talimogene laherparepvec (T-VEC) is also an option [I, B] (see 'In-transit disease' section above).

Superiority of nivolumab compared with dacarbazine (DTIC) ChT has been demonstrated for *BRAF* WT melanoma patients in the CheckMate 066, prospective, randomised, first-line trial, with an HR for death of 0.42; 99.79% CI 0.25–0.73; $P < 0.001$ and an HR for death or progression of disease of 0.43; 95% CI 0.34–0.56; $P < 0.001$ [I, A] [74]. Superiority of PD-1 (nivolumab, pembrolizumab) compared with ipilimumab has been shown in two prospective randomised trials, CheckMate 067 and KEYNOTE-006 [58, 75]. CheckMate 067 has an HR for death for nivolumab versus ipilimumab of 0.65 ($P < 0.001$). KEYNOTE-006 has an HR for death for pembrolizumab q2w (10 mg/kg every 2 weeks) versus ipilimumab of 0.63 ($P < 0.001$) and an HR for pembrolizumab q3w (10 mg/kg every 3 weeks) versus ipilimumab of 0.69 ($P < 0.001$) [58, 75]. Based on these trials, PD-1 blockade is now a standard of care for all patients, regardless of their *BRAF* status, in the first-line setting [I, A].
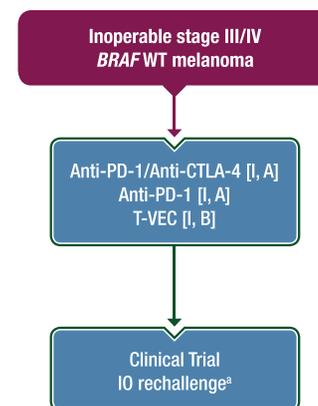

Figure 2. Treatment algorithm for inoperable stage III and IV *BRAF* WT melanoma.
[a]IO rechallenge can be ipilimumab if not given previously, nivolumab or pembrolizumab if another line of treatment was given after IO failure [II, B], or ipilimumab/nivolumab if not given previously [IV, B]. As described in the main text, treatment beyond progression might be an option for selected patients [IV, C].
CTLA-4, cytotoxic T lymphocyte-associated antigen 4; IO, immuno-oncology; PD-1, programmed cell death protein 1; T-VEC, talimogene laherparepvec; WT, wild-type.

The benefit of adding ipilimumab to nivolumab has been assessed in the CheckMate 067 study. The nivolumab and ipilimumab combination arm resulted in numerically higher response rates, response durations, time to subsequent therapies, progression-free survival (PFS) and OS [58]. These numerical differences are maintained in the 4-year survival update [59]. By study design, the two nivolumab-containing arms cannot be compared due to insufficient power. Despite all end points numerically favouring the combination, the OS gain appears limited
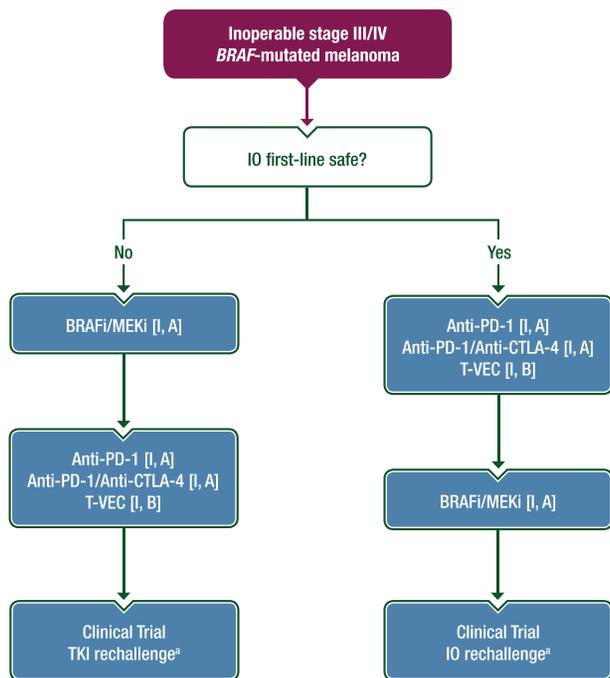
Figure 3. Treatment algorithm for inoperable stage III and IV *BRAF*-mutated melanoma.
[a]IO rechallenge can be ipilimumab if not given previously, nivolumab or pembrolizumab if another line of treatment was given after IO failure [II, B], or ipilimumab/nivolumab again if not given previously [IV, B]. As described in the main text, treatment beyond progression might be an option for selected patients [IV, C].
BRAFi, BRAF inhibitor; CTLA-4, cytotoxic T lymphocyte-associated antigen 4; IO, immuno-oncology; MEKi, MEK inhibitor; PD-1, programmed cell death protein 1; T-VEC, talimogene laherparepvec; TKI, tyrosine kinase inhibitor.

and biomarkers are needed to better select patients that benefit from the combination. PD-L1 provides an imperfect biomarker. Indeed, receiver operating characteristic (ROC) curve analyses show that PD-L1 enriches only marginally the prediction compared with random assignment arguing for its limited value with an area under the curve (AUC) of only 0.56 (see supplementary Figure S1, available at *Annals of Oncology* online) [58].

Some clinical parameters could provide interesting biomarkers to select patients with the highest benefit from the combination, including asymptomatic brain metastases (BMs) that demonstrate an improved PFS and >50% (10 out of 20) response rate with the combination compared with 21% (4 out of 19) for single-agent nivolumab in treatment-naive patients [II, A] [76], or elevated lactate dehydrogenase (LDH) with a PFS/OS HR of 0.69/0.73 favouring the combination in patient with LDH >2× upper limit of normal [58, 77], though evidence for the latter is weaker [III, B].

Current treatment decisions are, therefore, based on several parameters and need to be individualised to the patient when selecting between nivolumab and the combination.

In case of *BRAF*-mutated melanoma, additional first-line options are provided by BRAF and MEK inhibition. BRAF/MEK double inhibition is superior to single-agent BRAF in terms of response rates, PFS and OS [61, 78, 79]. In addition to improved
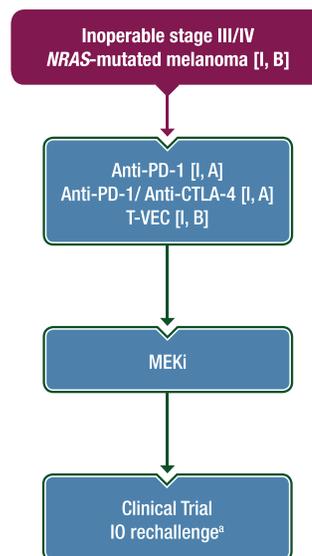

Figure 4. Treatment algorithm for inoperable stage III and IV *NRAS*-mutated melanoma.
[a]IO rechallenge can be ipilimumab if not given previously, nivolumab or pembrolizumab if another line of treatment was given after IO failure [II, B], or ipilimumab/nivolumab again if not given previously [IV, B]. As described in the main text, treatment beyond progression might be an option for selected patients [IV, C].
CTLA-4, cytotoxic T lymphocyte-associated antigen 4; IO, immuno-oncology; MEKi, MEK inhibitor; PD-1, programmed cell death protein 1; T-VEC, talimogene laherparepvec.

efficacy, skin-related side-effects are reduced with the combination, though MEK inhibition adds specific toxicities (e.g. muscle, heart, eye). Single-agent BRAFis should be used only in case of an absolute contraindication for MEK inhibitors (MEKis).

First-line decision between targeted therapies or immunotherapies is currently being studied in prospective trials (SECOMBIT, NCT02631447) to define the best sequencing combination treatment in terms of OS, the primary efficacy variable. No direct randomised comparison exists between the two approaches, but meta-analyses suggest that, despite better outcome within the first 12 months for targeted therapies, immunotherapy patients may have a better survival after 1 year [68, 80, 81]. Patients for whom immunotherapy can be delivered safely for the first few months, i.e. patients with tumours not progressing very quickly and not immediately threatening an important organ or function, should be considered for immunotherapy first, preserving targeted therapies for the subsequent lines.

For *NRAS*-mutated melanoma, due to the limited efficacy of MEKis [82], first-line immunotherapy options identical to those of WT melanoma are the first choice (see Figure 4).

For other drivers such as cKIT or NF1, targeted therapies are of limited activity and first-line immunotherapy options identical to those of WT melanoma are also the first choice. In second-line some specific *c-Kit* mutations suggest a treatment attempt with imatinib or nilotinib [83].

Several simple clinical and laboratory parameters provide predictive and prognostic markers, like the Eastern Cooperative Oncology Group (ECOG) performance status (PS), LDH levels

and the number of metastatic sites. They are negative prognostic and predictive markers for both targeted and immunotherapies [84–86].

Treatment beyond progression. Some retrospective data show that treatment beyond progression can be an option in selected patients both on targeted as well as on immunotherapies [87]. Important biases are expected from these analyses as the decision to treat beyond progression is linked to patient's overall status. No randomised data are available at this time.

Second-line treatment. Standard-of-care second-line selection depends on the strategy used for the first-line and the mutational status of the disease. Clinical trials should always be considered when available.

For *BRAF* WT disease, second-line options are very limited and inclusion in clinical trials and/or personalised approaches could be discussed. If the first-line treatment was anti-PD-1 alone, ipilimumab is an option [II, B] as well as ipilimumab/nivolumab [IV, B] [88, 89]. In some cases, ChT with DTIC or temozolomide can be discussed as a bridging therapy.

For *BRAF*-mutated disease, all the options available for WT melanoma are still valid with the addition of BRAFis/MEKis if not used in the first-line setting. BRAFis/MEKis should not be used too late in the course of the disease, as clinical parameters associated with disease progression, such as LDH, number of metastatic sites and ECOG PS represent strong negative predictive biomarkers [I, A] [85].

In *NRAS*-mutated melanoma, MEKis have a limited activity, providing improved PFS with an mPFS of 2.8 months for binimetinib compared with 1.5 for dacarbazine (HR for PFS 0.62, $P < 0.001$) [82]. cKIT targeting has shown limited activity, though more recent and potent KIT inhibitors are being tested [83]. In the absence of positive phase III data, KIT inhibition remains an option in this molecular subgroup.

Subsequent lines. Subsequent lines of therapy are not evidence-based at this time. Clinical trials or rechallenge, either with targeted or immunotherapies, can be an option [90] (see Figure 2). ChT with DTIC or temozolomide or other drugs remains an alternative for palliation or as a bridging therapy [II, C].

Management of difficult clinical situations: BMs

Management of BMs is particularly challenging, as brain involvement usually dictates a negative outcome for melanoma patients. Therefore, these patients need careful interdisciplinary care in specialised referral centres.

Recent studies confirmed that the preferred systemic treatments, targeted therapies and immunotherapies, can be safely and efficiently applied in BM patients. Thus, four modalities have to be considered and applied depending on the individuals' needs: neurosurgery, stereotactic radiosurgery (SRS), targeted therapy with BRAFi/MEKi combination, as well as immunotherapies. Whole-brain RT (WBRT) should be avoided whenever possible for its lack of efficacy and long-term toxicities that can no longer be justified in the light of the new PFS milestones obtained by combination immunotherapies [91] (see below). The optimal sequence or combination of these modalities has not
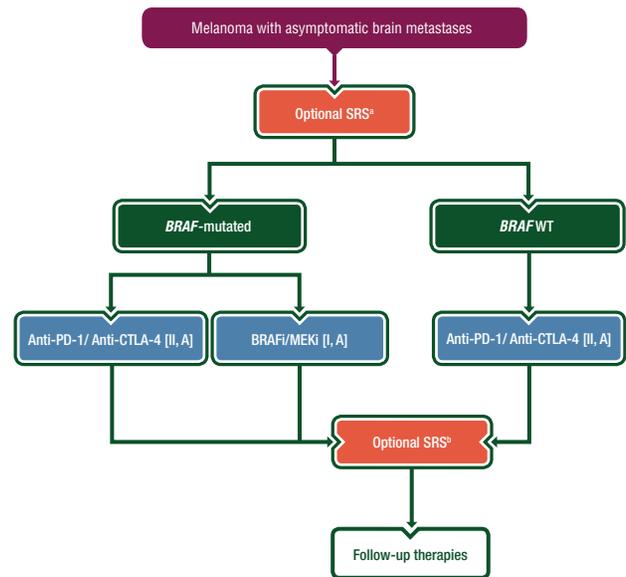

Figure 5. Treatment algorithm for asymptomatic brain metastases (BMs).

This algorithm is restricted to asymptomatic BMs. In case of symptomatic BMs, strategies can be significantly modified due to the use of steroids that can hamper the efficacy of IO treatments or due to additional modalities like neuro-surgery. Such an algorithm should be adapted to the general condition of the patient, e.g. progressing visceral metastasis requiring systemic treatment adaptation, or previous lines of treatment, e.g. patients developing BMs during adjuvant treatment and where a change of systemic treatment might be warranted.
ªFor patients with small number of asymptomatic metastases (<5–10), non-bulky disease (<3 cm), SRS up front is an option. Other patients should be considered for systemic treatment first, keeping SRS for the treatment of non-responding lesions.
ᵇFor patients failing systemic treatment, SRS could be considered as a salvage therapy if the total number of progressing lesions is <5–10 and their maximal size <3 cm.
BRAFi, BRAF inhibitor; CTLA-4, cytotoxic T lymphocyte-associated antigen 4; IO, immuno-oncology; MEKi, MEK inhibitor; PD-1, programmed cell death protein 1; SRS, stereotactic radiosurgery; WT, wild-type.

been fully determined, but recent results can help with decision-making until ongoing clinical trials bring more definitive answers.

Dabrafenib/trametinib combination therapy was investigated in a prospective, multicentre, multicohort, open-label, phase II clinical trial (COMBI-MB) with good ECOG PS of 0 or 1 [92]. The response rate of 58% in asymptomatic untreated BMs is similar to the response rate in other organ sites. However, PFS with a median at 5.6 months seems to be shorter than the 11.0 months median PFS reported in COMBI-d [78].

Immunotherapy with anti-PD-1 monotherapy or ipilimumab plus nivolumab has been investigated in patients with BMs. The outcomes are in favour of the combination with an overall response rate of 46% in patients with asymptomatic BMs, reasonable response duration and PFS of >50% at 18 months [76, 93]. Importantly, the inclusion criteria in these trials are strict which resulted in a selection of patients with low central nervous system (CNS) tumour burden. These results suggest, however,

Table 5. Treatment modalities for melanoma metastases		
Metastases localisation, number (pathological stage)	**Treatment modalities[a]**	**GoR**
Few ITMs (pTXN2cM0)	Surgical removal	C
	T-VEC	C
	Irradiation, electrochemotherapy	D
Multiple ITMs (>5; pTXN2cM0)	T-VEC	B
	Systemic therapy[b]	C
	Perfusion of the extremity[b]	C
	Electrochemotherapy	D
Locoregional LNs (pTxN1a, 2a, N3a)	Consider adjuvant therapy	A
	Consider trial participation	B
Locoregional LNs (pTxN1bN2b, N2c, 3)	Complete surgical removal followed by adjuvant therapy	A
	Irradiation in case of incomplete resection	C
	Consider trial participation	
Solitary CNS metastases (pTxNxM3)	Stereotactic irradiation[b]	B
	Systemic treatment	B
	Neurosurgical removal	C
	Consider clinical trial participation	
Solitary lung, liver, kidney and other metastases (pTxNxM1)	Systemic therapy[b]	A
	Surgical removal	C
	Stereotactic irradiation	C
	Consider clinical trial participation	
Multiple metastases (pTxNxM1a-1c)	Systemic therapy[b]	A
	Consider clinical trial participation	
Painful bone metastases (pTxNxM1a-1c)	Radiotherapy	B
	Bone-modifying agents	C
	Consider clinical trial participation	

[a]Treatment modalities are presented in order of preference.
[b]These therapies should be preferentially carried out at specialised centres.
CNS, central nervous system; GoR, grade of recommendation; ITM, in-transit metastasis; LN, lymph node; T-VEC, talimogene laherparepvec.

ipilimumab/nivolumab combination therapy as the preferred first-line treatment also in *BRAF*-mutated asymptomatic patients [III, A]. Importantly, efficacy of ipilimumab/nivolumab combination seems to be lower in patients with symptomatic BMs with only 22% [94] or 21% intracranial responses on a limited cohort of patients [76].

Since multiple sessions of SRS can be combined with systemic targeted or immunotherapies, close disease monitoring by MRI is recommended in order to add SRS when indicated. For patients with a small number of asymptomatic metastases (<5–10), non-bulky disease (<3 cm), SRS up front is an option. Other patients should be considered for systemic treatment first, keeping SRS for the treatment of non-responding lesions. For patients failing systemic treatment, SRS could be considered as a salvage therapy if the total number of progressing lesions is <5–10 and their maximal size <3cm. First real world data show interesting results between SRS and systemic treatment [95]. Toxicity should also be factored in the decision as data suggest increased risk of symptomatic radio-necrosis with immunotherapies [96]. The place of SRS in the rapidly evolving landscape of systemic treatment must be determined prospectively and several clinical trials are ongoing like the ABC-X trial (NCT03340129) to answer these questions.

Patients with BMs in whom local therapy has failed, or who have neurological symptoms requiring steroids or leptomeningeal disease, infrequently respond to ipilimumab/nivolumab [76, 94]. This population can be treated by WBRT, even in the case of leptomeningeal disease or very extensive disease, and systemically with BRAFi/MEKi in *BRAF*-mutated or temozolomide in *BRAF* WT patients. Nevertheless, the prognosis of this population is extremely poor and palliative care must be discussed and prepared.

A summary of the management of BMs is provided in Figure 5.

Management of toxicities

Management of toxicities from systemic therapies are well documented. Good references exist for immunotherapies [97] as well as for mitogen-activated protein kinase (MAPK) inhibitors [98].

Personalised medicine

Biomarkers such as mutations (*BRAF*, *NRAS*, *c-Kit*) are already indispensable today for proper management of advanced melanoma. Other mutations and the TMB might be additional

Table 6. Summary of recommendations

Diagnosis and pathology/molecular biology
- Diagnosis should be based on a full thickness excisional biopsy with a small side margin [V, 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, presence of ulceration, presence and extent of regression and clearance of the surgical margins [II, A]
- Mutation testing for actionable mutations is mandatory in patients with resectable or unresectable stage III or stage IV and is highly recommended in high-risk resected disease stage IIC but not for stage I or stage IIA–IIB [I, A]. *BRAF* testing is mandatory [I, A]

Staging and risk assessment
- Physical examination with special attention to other suspicious pigmented lesions, tumour satellites, ITMs, regional LNs and distant metastases is mandatory. In higher tumour stages, US, CT and/or PET scans are recommended in order to allow proper tumour assessment [III, C]

Management of local/locoregional disease
- Wide local excision of primary tumours with safety margins of 0.5 cm for *in situ* melanomas, 1 cm for tumours with a tumour thickness up to 2 mm and 2 cm for thicker tumours is recommended [II, B]
- SNB is recommended for all patients with pT1b or higher according to the AJCC eighth edition TNM staging system [II, B]
- CLND is not recommended for SN-positive patients [I, E]. In the case of isolated locoregional clinically detectable (macroscopic, non-SN) LN metastases, CLND is indicated [III, C]; removal of the tumour-bearing LN alone is insufficient
- Patients with resected stage III melanomas should be evaluated for adjuvant therapy
- Adjuvant RT for local tumour control can be considered in cases of inadequate resection margins of LMM, in R1 resections or after resection of bulky disease [III, B]. Adjuvant RT is not recommended in the adjuvant setting [III, D]
- Anti-PD-1 adjuvant therapy, nivolumab [I, A; ESMO-MCBS v1.1 score: A], pembrolizumab [I, A; ESMO-MCBS v1.1 score: A] or dabrafenib/trametinib [I, A; ESMO-MCBS v1.1 score A] are the preferred treatment options

Management of advanced/metastatic disease
- 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]
- 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 settings include anti-PD-1 antibodies (pembrolizumab, nivolumab), PD-1 and ipilimumab for all patients, and BRAFi/MEKi combination for patients with *BRAF*-mutated melanoma [II, B]
- For unresectable stage IIIB/C, IVM1a, T-VEC is also an option [I, B]
- PD-1 blockade or PD-1 and ipilimumab are now a standard of care for all patients, regardless of their *BRAF* status, in the first-line setting [I, A]
- For BRAF WT disease, second-line options are very limited and inclusion in clinical trials and/or personalised approaches could be discussed. If the first-line treatment was anti-PD-1 alone, ipilimumab is an option [II, B] as well as ipilimumab/nivolumab [IV, B]
- For BRAF-mutated disease, all the options available for WT melanoma are still valid with the addition of BRAFis/MEKis if not used in the first-line setting
- For *NRAS*-mutated melanoma, due to the limited efficacy of MEK inhibitors, first-line immunotherapy options identical to those of WT melanoma are the first choice
- If clinical trials or the approved new compounds are not available, cytotoxic drugs such as DTIC or temozolomide may be administered, with modest activity shown [II, C]
- For management of brain metastases, study results suggest, ipilimumab/nivolumab combination therapy as the preferred first-line treatment also in *BRAF*-mutated asymptomatic patients [III, A]. For patients with a small number of asymptomatic metastases (<5–10), non-bulky disease (<3 cm), SRS up front is an option. Other patients should be considered for systemic treatment first, keeping SRS for the treatment of non-responding lesions. For patients failing systemic treatment, SRS could be considered as a salvage therapy if the total number of progressing lesions is <5–10 and their maximal size <3 cm

Follow-up, long-term implications and survivorship
- 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]
- Patients must be aware that family members have an increased melanoma risk [III, B]
- 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 [III, B]
- There is no consensus on optimal schedule, follow-up or the utility of imaging and blood tests for patients with resected melanoma; 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
- SN-positive patients should be followed by regular US examinations
- Rising levels of serum S100 protein is the most accurate blood test in the follow-up of melanoma patients, if any blood test is recommended at all [IV, D]

AJCC, American Joint Committee on Cancer; BRAFi, BRAF inhibitor; CLND, complete lymph node dissection; CT, computed tomography; DTIC, dacarbazine; ESMO-MCBS, ESMO-Magnitude of Clinical Benefit Scale; ITM, in-transit metastases; LMM, lentigo maligna melanoma; LN, lymph node; MEKi, MEK inhibitor; PD-1, programmed cell death protein 1; PET, positron emission tomography; R1, microscopic tumour at the margin; RT, radiotherapy; SN, sentinel node; SNB, sentinel node biopsy; SRS, stereotactic radiosurgery; T-VEC, talimogene laherparepvec; TNM, tumour, node, metastasis; US, ultrasound; UV, ultraviolet; WT, wild-type.

Table 7. 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, etc.), 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 [104].

molecular predictive markers in the near future. PD-L1 has been shown to provide an imperfect predictive biomarker for immunotherapy. Determining the optimal cut-off in melanoma proves challenging and, assessed rigorously with a proper ROC analysis [58], PD-L1 staining has very little predictive value with an AUC of 0.56 for ipilimumab/nivolumab and 0.57 for nivolumab alone.

The authors anticipate that treatment algorithms for advanced melanoma could evolve in a paradigm for precision oncology, where both targeted and immunotherapies are used sequentially or simultaneously according to a highly personalised strategy.

Follow-up, long-term implications and survivorship

Melanoma patients need instructions in avoidance of sunburns, extended unprotected solar or artificial UV exposure, and in life-long regular self-examinations of the skin and peripheral LNs [III, B]. 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 [III, B] [6]. 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 [99]. Melanoma patients also have an increased risk for other skin tumours. In patients with LMM, 35% of patients develop another cutaneous malignancy within 5 years [48].

There is currently no consensus on the frequency of follow-up examinations and the use of imaging techniques and blood tests for patients with resected melanoma. 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. The authors encourage consultation of the respective national guidelines. Intervals between clinical visits and imaging exams may be tailored according to individual risk and personal needs of the patient [100].

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, US of LNs, CT or whole-body PET/PET-CT scans may lead to an earlier diagnosis of regional or systemic relapses [101]. The impact of radiological exams upon survival has not been demonstrated so far [102]. 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 levels of serum S100 protein has a higher specificity for disease progression than LDH, and is, therefore, the most accurate blood test in the follow-up of melanoma patients [103], 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 http://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology. The relevant literature has been selected by the expert authors. A summary of recommendations is shown in Table 6. An ESMO-MCBS table with MCBS scores is included in Table 3. ESMO-MCBS v1.1 [70] was used to calculate scores for new therapies/indications approved by the EMA since 1 January 2016. The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee. Levels of evidence and grades of recommendation have been applied using the system shown in Table 7. 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.

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