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

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Key message (online only): This ESMO Clinical Practice Guidelines provide updated recommendations on management of cutaneous melanoma (diagnosis, treatment and follow-up), compiled by a multidisciplinary author panel and accompanied by level of evidence and grade of recommendation, depending on the strength of supporting data and magnitude of benefit from particular interventions.
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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 forty 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 to 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 8th edition of the American Joint Committee on Cancer (AJCC) tumour, node, metastases (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 8th 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 (NGS) panel covering all key oncogenic drivers is increasingly being performed. As drivers are actionable and can impact clinical decision, mutation analysis must be performed 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 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 8th 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 performed 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

An overview of locoregional disease treatment algorithm is provided in Figure 1.

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

SNB is recommended for precise staging in melanoma of AJCC 8th edition stage pT1b or higher, i.e. with a tumour thickness >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 to 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 that should not be considered as a therapeutic procedure.

SNB should be performed 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 performed simultaneously with the safety margins re-excision of the primary to avoid lymph drainage modifications;
- SNB and re-excision performed by an experienced surgical team;
- Marking of the scar during the consultation, preferable with photo documentation;
- Single-photon emission computed tomography (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]. A MDLL cut-off of 1 mm has been used for adjuvant therapy trials. Therefore, though not formally part of the AJCC version 8 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 to nodal observation with periodic US of the SN-positive basin [37, 38]. CLND provides additional staging information, as approximately 15%-20% of SN-positive patients have additional non-SN involvement. However, upstaging occurs even less frequently at approximately 6% of cases. Therefore, considering the morbidity of routine CLND, this practice can no longer be recommended [I, A] [39-41].

In the case of isolated locoregional clinically detectable (macroscopic, non-SN) LN metastases, therapeutic lymph node dissection (TLND) 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 magnetic resonance imaging (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 (ILP) using melphalan and/or

tumour necrosis factor alpha (TNFα) [III, C]. Alternatively, talimogene laherparepvec (T-VEC) has shown an improved durable response rate (DRR) compared to subcutaneous granulocyte-macrophage colony-stimulating factor (GM-CSF), especially in stage IIIB/C, IVM1a (AJCC 7th edition [43]) melanoma patients [44] [I,B]. These local procedures should be carefully weighed against systemic treatment, in order not to lower their chances to provide 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 2 (CO_2) laser or other intralesional therapy may also be proposed within clinical trials [V, D] [16, 45-47].

Adjuvant radiotherapy

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 approximately 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, B]. It could still be discussed in specific cases where local control is critical like in Head & 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).

INFα

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 (RCTs), investigating adjuvant IFNα therapy involving 8122 patients, showed 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-CTLA-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 to placebo in the EORTC 18071 trial [53]. The rate of OS at 5 years was 65.4% in the ipilimumab group, as 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 4 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-PD1 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 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 7th edition; [43]) resected melanoma when compared to 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 (AEs) compared to 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 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).

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 7th edition [43]) melanoma after complete surgical resection. The study did not meet its primary end point of DFS [58]. Therefore, BRAF inhibitor 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, IIIC melanoma (AJCC 7th 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] [59]. The P value for the OS HR (0.0006) reported by Long et al [59]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 has been approved by the EMA for adjuvant treatment of 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 approval include all stage III, regardless of SN deposit. Decision of treatment for stage IIIA SN <1mm 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].

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 decision should be made with the patients, factoring in the toxicity profiles.

Contrary to the initial EORTC 18071 ipilimumab trial, HR 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 [59]. This suggests that the benefit from PD-1 or dabrafenib/trametinib could be similar in lower, not yet evaluated, subgroups like some stage II. Indeed, the risk of relapse for SN-negative pT3b, pT4a and pT4b melanoma is quite high, with a mortality of about 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 [60]. Surgery remains an option for selected patients, preferentially combined with adjuvant systemic therapies [see 'Anti-programmed cell death 1 (PD-1)' section below].

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. 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.

An overview of systemic treatment algorithm for stage IV is 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)[61]. For unresectable stage IIIB/C, IVM1a (AJCC 7th edition [43]), T-VEC is also an option [I, B] (see 'In-transit disease' section above).

Superiority of nivolumab compared to 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] [62]. Superiority of PD-1 (nivolumab, pembrolizumab) compared to ipilimumab has been shown in two prospective randomised trials, CheckMate 067 and KEYNOTE 006 [63, 64]. 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) [63, 64]. 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].

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 [63]. These numerical differences are maintained in the 4-year survival update [65]. 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 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 to random assignment arguing for its limited value with an AUC of only 0.56 (see Supplementary Figure S1, available at *Annals of Oncology* online) [63].

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 to 21% (4 out of 19) for single-agent nivolumab in treatment-naive patients [II, A] [66], or elevated lactate dehydrogenase (LDH) with a PFS/OS HR of 0.69/0.73 favouring the combination in patient with LDH >2 x upper limit of normal (ULN) [63, 67], 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 [68-70]. In addition to improved efficacy, skin-related side effects are reduced with the combination, though MEK inhibition adds specific toxicities (e.g. muscle, heart, eye). Single-agent BRAF inhibitors (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 one year [71, 72] [73]. 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 MEK inhibitors [74], first-line immunotherapy options identical to those of WT melanoma are the first choice (see Figure 4).

For other drivers like 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 nolitinib [75].

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 [76-78].

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 [79]. 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] [80, 81]. 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] [77].

In *NRAS*-mutated melanoma, MEK inhibitors have a limited activity, providing improved PFS with a mPFS of 2.8 months for binimetinib compared to 1.5 for dacarbazine (HR for PFS 0.62, P<0.001) [74] .

cKIT targeting has shown limited activity, though more recent and potent KIT inhibitors are being tested [75]. 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 [82]. (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: brain metastases

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 radiotherapy (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 [83] (see below). The optimal sequence or combination of these modalities has not 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 [84]. 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 [68] .

Immunotherapy with anti-PD1 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 (ORR) of 46% in patients with asymptomatic BMs, reasonable response duration and PFS of more than 50% at 18 months [66, 85]. 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, 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 brain metastases with only 22% [86] or 21% intracranial responses on a limited cohort of patients [66] .

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. First real world data show interesting results between stereotactic radiosurgery and systemic treatment [87]. Toxicity should also be factored in the decision as data suggest increased risk of symptomatic radio-necrosis with immunotherapies [88]. 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 [66, 86]. 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 [89] as well as for MAPK inhibitors [90].

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 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 [63], PD-L1 staining has very little predictive value with an AUC of 0.56 for ipilimumab/ nivolumab and 0.57 for nivolumab alone.

We 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 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]. 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 [91]. Melanoma patients also have an increased risk for other skin tumours. In patients with LMM, 35% of patients develop another cutaneous malignancy within five 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. We 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 [92].

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 [93]. The impact of radiological exams upon survival has not been demonstrated so far [94]. 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 [95], 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 [96] 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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REFERENCES

1. Hollestein LM, van den Akker SAW, 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. CancerResearch. National Cancer Registration and Analysis Service, Public Health England. In.
3. Forsea AM, Del Marmol V, Stratigos A, Geller AC. Melanoma prognosis in Europe: far from equal. Br J Dermatol 2014; 171: 179-182.
4. Alexandrov LB, Nik-Zainal S, Wedge DC et al. Signatures of mutational processes in human cancer. Nature 2013; 500: 415.
5. 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.
6. 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.
7. 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.
8. 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.
9. Kittler H, Pehamberger H, Wolff K, Binder M. Diagnostic accuracy of dermoscopy. Lancet Oncology 2002; 3: 159-165.
10. Salerni G, Carrera C, Lovatto L et al. Benefits of total body photography and digital dermatoscopy ("two-step method of digital follow") in the early diagnosis of melanoma in patients at high risk for melanoma. J Am Acad Dermatol. 2012; 67: e17-27.
11. Esteva A, Kuprel B, Novoa RA et al. Dermatologist-level classification of skin cancer with deep neural networks. Nature 2017; 542: 115-118.
12. Gershenwald JE, Scolyer RA, Hess KR et al. Melanoma staging: Evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J Clin 2017; 67: 472-492.
13. 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.
14. Yao Z, Yaeger R, Rodrik-Outmezguine VS et al. Tumours with class 3 BRAF mutants are sensitive to the inhibition of activated RAS. Nature 2017; 548: 234-238.
15. Hayward NK, Wilmott JS, Waddell N et al. Whole-genome landscapes of major melanoma subtypes. Nature 2017; 545: 1-18.
16. Snyder A, Makarov V, Merghoub T et al. Genetic basis for clinical response to CTLA-4 blockade in melanoma. N Engl J Med 2014; 371: 2189-2199.
17. Thompson JF, Scolyer RA, Kefford RF. Cutaneous melanoma. Lancet 2005; 365: 687-701.

18. Tzellos T, Kyrgidis A, Mocellin S et al. Interventions for melanoma in situ, including lentigo maligna. Cochrane Database of Systematic Rev 2014.
19. Clark GS, Pappas-Politis EC, Cherpelis BS et al. Surgical Management of Melanoma in Situ on Chronically Sun-Damaged Skin. Cancer Control 2008; 15: 216-224.
20. Fogarty GB, Hong A, Scolyer RA et al. Radiotherapy for lentigo maligna: a literature review and recommendations for treatment. Br J Dermatol. 2014; 170: 52-58.
21. Veronesi U, Adamus J, Bandiera DC et al. Inefficacy of immediate node dissection in stage 1 melanoma of the limbs. N Engl J Med 1977; 297: 627-630.
22. Sim FH, Taylor WF, Ivins JC et al. A prospective randomized study of the efficacy of routine elective lymphadenectomy in management of malignant melanoma. Preliminary results. Cancer 1978; 41: 948-956.
23. Balch CM, Soong SJ, Bartolucci AA et al. Efficacy of an elective regional lymph node dissection of 1 to 4 mm thick melanomas for patients 60 years of age and younger. Ann Surg. 1996; 224: 255-263; discussion 263-256.
24. Cascinelli N, Morabito A, Santinami M et al. Immediate or delayed dissection of regional nodes in patients with melanoma of the trunk: a randomised trial. WHO Melanoma Programme. The Lancet 1998; 351: 793-796.
25. 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.
26. Sondak VK. ASCO Educational Book. In. 2017.
27. Morton DL, Thompson JF, Cochran AJ et al. Final trial report of sentinel-node biopsy versus nodal observation in melanoma. N Engl J Med. 2014; 370: 599-609.
28. Thomas JM. Prognostic false-positivity of the sentinel node in melanoma. Nat Clin Pract Oncol. 2008; 5: 18-23.
29. van Akkooi ACJ. Sentinel node followed by completion lymph node dissection versus nodal observation: staging or therapeutic? Controversy continues despite final results of MSLT-1. Melanoma Res. 2014; 24: 291-294.
30. Nieweg OE. False-negative sentinel node biopsy. Ann Surg Oncol. 2009; 16: 2089-2091.
31. Dummer R, Ramelyte E, Levesque M et al. Critical aspects to achieve a high-quality melanoma clinic. Current Opinion in Oncology 2017; 29: 145-150.
32. van Akkooi ACJ, de Wilt JHW, Verhoef C et al. Clinical relevance of melanoma micrometastases (<0.1 mm) in sentinel nodes: are these nodes to be considered negative? Ann Oncol. 2006; 17: 1578-1585.
33. van Akkooi ACJ, de Wilt JHW, Voit C et al. Sentinel lymph-node false positivity in melanoma. Nat Clin Pract Oncol. 2008; 5: E2-E2.
34. Murali R, Desilva C, Thompson JF, Scolyer RA. Factors predicting recurrence and survival in sentinel lymph node-positive melanoma patients. Annals of surgery 2011; 253: 1155-1164.
35. van der Ploeg APT, van Akkooi ACJ, Rutkowski P et al. Prognosis in patients with sentinel node-positive melanoma is accurately defined by the combined Rotterdam tumor load and Dewar topography criteria. J Clin Oncol. 2011; 29: 2206-2214.
36. van der Ploeg APT, van Akkooi ACJ, Haydu LE et al. The prognostic significance of sentinel node tumour burden in melanoma patients: an international, multicenter study of 1539 sentinel node-positive melanoma patients. Eur J Cancer. 2014; 50: 111-120.
37. Leiter U, Stadler R, Mauch C et al. Complete lymph node dissection versus no dissection in patients with sentinel lymph node biopsy positive melanoma (DeCOG-SLT): a multicentre, randomised, phase 3 trial. The lancet oncology 2016; 17: 757-767.
38. Faries MB, Thompson JF, Cochran AJ et al. Completion Dissection or Observation for Sentinel-Node Metastasis in Melanoma. N Engl J Med 2017; 376: 2211-2222.

39. Madu MF, Franke V, Bruin MM et al. Immediate completion lymph node dissection in stage IIIA melanoma does not provide significant additional staging information beyond EORTC SN tumour burden criteria. European journal of cancer (Oxford, England : 1990) 2017; 87: 212-215.
40. Verver D, van Klaveren D, van Akkooi ACJ et al. Risk stratification of sentinel node-positive melanoma patients defines surgical management and adjuvant therapy treatment considerations. Eur J Cancer. 2018; 96: 25-33.
41. Coit D. The Enigma of Regional Lymph Nodes in Melanoma. N Engl J Med. 2017; 376: 2280-2281.
42. Morton DL, Wanek L, Nizze JA et al. Improved long-term survival after lymphadenectomy of melanoma metastatic to regional nodes. Analysis of prognostic factors in 1134 patients from the John Wayne Cancer Clinic. Ann Surg 1991; 214: 491-501.
43. Balch C, Buzaid A, Soong S et al. Final Version of the American Joint Committee on Cancer Staging System for Cutaneous Melanoma. J Clin Oncol 2001; 19: 3635-3648.
44. Andtbacka RHI, Kaufman HL, Collichio F et al. Talimogene Laherparepvec Improves Durable Response Rate in Patients With Advanced Melanoma. J Clin Oncol. 2015; 33: 2780-2788.
45. Hong A, Fogarty G. Role of radiation therapy in cutaneous melanoma. Cancer journal (Sudbury, Mass.) 2012; 18: 203-207.
46. Henderson MA, Burmeister BH, Ainslie J et al. Adjuvant lymph-node field radiotherapy versus observation only in patients with melanoma at high risk of further lymph-node field relapse after lymphadenectomy (ANZMTG 01.02/TROG 02.01): 6-year follow-up of a phase 3, randomised controlled trial. The Lancet Oncology 2015; 16: 1049-1060.
47. Miura JT, Kroon HM, Beasley GM et al. Long–Term Oncologic Outcomes After Isolated Limb Infusion for Locoregionally Metastatic Melanoma: An International Multicenter Analysis. Ann Surg Oncol 2019.
48. 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.
49. Eggermont AMM, 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.
50. 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.
51. 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.
52. Ives NJ, Suciu S, Eggermont AMM et al. Adjuvant interferon α for the treatment of high-risk melanoma: An individual patient data meta-analysis. European Journal of Cancer 2017; 82: 171-183.
53. Eggermont AMM, Chiarion-Sileni V, Grob J-J et al. Prolonged Survival in Stage III Melanoma with Ipilimumab Adjuvant Therapy. N Engl J Med. 2016; 375(19): 1845-1855.
54. Eggermont AMM, Chiarion-Sileni V, Grob J-J 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 Oncol. 2015; 16: 522-530.
55. Weber JS, Mandalà M, Del Vecchio M et al. Adjuvant therapy with nivolumab (NIVO) versus ipilimumab (IPI) after complete resection of stage III/IV melanoma: Updated results from a phase III trial (CheckMate 238). J Clin Oncol. 2018; 36: 9502-9502.

56. Weber J, Mandalà M, Del Vecchio M et al. Adjuvant Nivolumab versus Ipilimumab in Resected Stage III or IV Melanoma. N Engl J Med. 2017; 1824-1835.
57. Eggermont AMM, Blank CU, Mandalà M et al. Adjuvant Pembrolizumab versus Placebo in Resected Stage III Melanoma. N Engl J Med. 2018; 1789-1801.
58. Maio M, Lewis K, Demidov L et al. Adjuvant vemurafenib in resected, BRAFV600 mutation-positive melanoma (BRIM8): a randomised, double-blind, placebo-controlled, multicentre, phase 3 trial. Lancet Oncol. 2018; 19: 510-520.
59. Long GV, Hauschild A, Santinami M et al. Adjuvant Dabrafenib plus Trametinib in Stage III BRAF-Mutated Melanoma. N Engl J Med. 2017; 1813-1823.
60. Sosman JA, Moon J, Tuthill RJ et al. A phase 2 trial of complete resection for stage IV melanoma: results of Southwest Oncology Group Clinical Trial S9430. Cancer 2011; 117: 4740-4706.
61. Ascierto PA, McArthur GA, Dréno B et al. Cobimetinib combined with vemurafenib in advanced *BRAF* V600-mutant melanoma (coBRIM): updated efficacy results from a randomised, double-blind, phase 3 trial. Lancet Oncol 2016; 17: 1248-1260.
62. Robert C, Long GV, Brady B et al. Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med. 2015; 372: 320-330.
63. Wolchok JD, Chiarion-Sileni V, Gonzalez R et al. Overall Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma. N Engl J Med. 2017; 1345-1356.
64. Robert C, Schachter J, Long GV et al. Pembrolizumab versus Ipilimumab in Advanced Melanoma. N Engl J Med. 2015; 372: 2521-2532.
65. Hodi FS, Chiarion-Sileni V, Gonzalez R et al. Nivolumab plus ipilimumab or nivolumab alone versus ipilimumab alone in advanced melanoma (CheckMate 067): 4-year outcomes of a multicentre, randomised, phase 3 trial. Lancet Oncol 2018; 19: 1480-1492.
66. Long GV, Atkinson V, Lo S et al. Combination nivolumab and ipilimumab or nivolumab alone in melanoma brain metastases: a multicentre randomised phase 2 study. lancet Oncol. 2018; 19: 672-681.
67. Larkin J, Minor D, D'Angelo S et al. Overall Survival in Patients With Advanced Melanoma Who Received Nivolumab Versus Investigator's Choice Chemotherapy in CheckMate 037: A Randomized, Controlled, Open-Label Phase III Trial. J Clin Oncol. 2018; 36: 383-390.
68. Long GV, Stroyakovskiy D, Gogas H et al. Dabrafenib and trametinib versus dabrafenib and placebo for Val600 BRAF-mutant melanoma: a multicentre, double-blind, phase 3 randomised controlled trial. The Lancet 2015; 386: 444-451.
69. 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.
70. Larkin J, Ascierto PA, Dreno B et al. Combined vemurafenib and cobimetinib in BRAF-mutated Melanoma. N Engl J Med. 2014; 141003131120006.
71. Dummer R, Ascierto PA, Gogas HJ et al. Encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with *BRAF*-mutant melanoma (COLUMBUS): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol 2018; 19: 603-615.
72. Liszkay G, Gogas H, Mandalà M et al. Update on overall survival in COLUMBUS: A randomized phase III trial of encorafenib (ENCO) plus binimetinib (BINI) versus vemurafenib (VEM) or ENCO in patients with BRAF V600–mutant melanoma. J Clin Oncol 2019; 37: 9512-9512.
73. Ugurel S, Röhmel J, Ascierto PA et al. Survival of patients with advanced metastatic melanoma: the impact of novel therapies-update 2017. Eur J Cancer. 2017; 83: 247-257.
74. Dummer R, Schadendorf D, Ascierto P et al. Binimetinib versus dacarbazine in patients with advanced NRAS mutant melanoma (NEMO): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol 2017; 18: 435-445.

75. Guo J, Carvajal RD, Dummer R et al. Efficacy and safety of nilotinib in patients with KIT-mutated metastatic or inoperable melanoma: final results from the global, single-arm, phase II TEAM trial. Ann Oncol 2017; 28: 1380-1387.
76. Balch CM, Gershenwald JE, Soong Sj et al. Final version of 2009 AJCC melanoma staging and classification. J Clin Oncol. 2009; 27: 6199-6206.
77. Schadendorf D, Long GV, Stroiakovski D et al. Three-year pooled analysis of factors associated with clinical outcomes across dabrafenib and trametinib combination therapy phase 3 randomised trials. Eur J Cancer. 2017; 82: 45-55.
78. Weide B, Martens A, Hassel JC et al. Baseline Biomarkers for Outcome of Melanoma Patients Treated with Pembrolizumab. Clin Cancer Res. 2016; 22: 5487-5496.
79. Beaver JA, Hazarika M, Mulkey F et al. Patients with melanoma treated with an anti-PD-1 antibody beyond RECIST progression: a US Food and Drug Administration pooled analysis. Lancet Oncol 2018; 19: 229-239.
80. Ascierto PA, Del Vecchio M, Robert C et al. Ipilimumab 10 mg/kg versus ipilimumab 3 mg/kg in patients with unresectable or metastatic melanoma: a randomised, double-blind, multicentre, phase 3 trial. Lancet Oncol. 2017; 18: 611-622.
81. Zimmer L, Apuri S, Eroglu Z et al. Ipilimumab alone or in combination with nivolumab after progression on anti-PD-1 therapy in advanced melanoma. Eur J Cancer. 2017; 75: 47-55.
82. Valpione S, Carlino MS, Mangana J et al. Rechallenge with BRAF-directed treatment in metastatic melanoma: A multi-institutional retrospective study. Eur J Cancer. 2018; 91: 116-124.
83. Glitza Oliva IC, Schvartsman G, Tawbi H. Advances in the systemic treatment of melanoma brain metastases. Ann Oncol. 2018; 1509-1520.
84. Davies MA, Saiag P, Robert C et al. Dabrafenib plus trametinib in patients with BRAFV600-mutant melanoma brain metastases (COMBI-MB): a multicentre, multicohort, open-label, phase 2 trial. Lancet Oncol. 2017; 18: 863-873.
85. Tawbi HA, Forsyth PA, Algazi A et al. Combined Nivolumab and Ipilimumab in Melanoma Metastatic to the Brain. N Engl J Med 2018; 379: 722-730.
86. Tawbi HA-H, Forsyth PAJ, Hodi FS et al. Efficacy and safety of the combination of nivolumab (NIVO) plus ipilimumab (IPI) in patients with symptomatic melanoma brain metastases (CheckMate 204). J Clin Oncol 2019; 37: 9501-9501.
87. Gaudy-Marqueste C, Dussouil AS, Carron R et al. Survival of melanoma patients treated with targeted therapy and immunotherapy after systematic upfront control of brain metastases by radiosurgery. Eur J Cancer 2017; 84: 44-54.
88. Minniti G, Anzellini D, Reverberi C et al. Stereotactic radiosurgery combined with nivolumab or Ipilimumab for patients with melanoma brain metastases: evaluation of brain control and toxicity. J Immunother Cancer 2019; 7: 102-102.
89. Haanen J, Carbonnel F, Robert C et al. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2017; 28: iv119-iv142.
90. Daud A, Tsai K. Management of treatment-related adverse events with agents targeting the MAPK pathway in patients with metastatic melanoma. Oncologist 2017; 22: 823-833.
91. 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.
92. Turner RM, Bell KJL, 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.
93. 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.
94. Nieweg OE, Kroon BBR. The conundrum of follow-up: should it be abandoned? Surg Oncol Clin N Am 2006; 15: 319-330.
95. 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.
96. Cherny NI, Dafni U, Bogaerts J et al. ESMO-Magnitude of Clinical Benefit Scale version 1.1. Ann Oncol 2017; 28: 2340-2366.
97. Hauschild A, Dummer R, Schadendorf D et al. Longer Follow-Up Confirms Relapse-Free Survival Benefit With Adjuvant Dabrafenib Plus Trametinib in Patients With Resected BRAF V600–Mutant Stage III Melanoma. J Clin Oncol 2018; 36: 3441-3449.
98. Latimer NR, Bell H, Abrams KR et al. Adjusting for treatment switching in the METRIC study shows further improved overall survival with trametinib compared with chemotherapy. Cancer Med 2016; 5: 806-815.
99. Robert C, Flaherty K, Nathan P et al. Five-year outcomes from a phase 3 METRIC study in patients with *BRAF* V600 E/K-mutant advanced or metastatic melanoma. Eur J of Can 2019; 109: 61-69.
100. Flaherty KT, Robert C, Hersey P et al. Improved Survival with MEK Inhibition in BRAF-Mutated Melanoma. N Engl J Med 2012; 367: 107-114.
101. Schadendorf D, Amonkar MM, Milhem M et al. Functional and symptom impact of trametinib versus chemotherapy in BRAF V600E advanced or metastatic melanoma: quality-of-life analyses of the METRIC study. Ann Oncol 2014; 25: 700-706.
102. Dummer R, Ascierto PA, Gogas HJ et al. Overall survival in patients with *BRAF*-mutant melanoma receiving encorafenib plus binimetinib versus vemurafenib or encorafenib (COLUMBUS): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol 2018; 19: 1315-1327.
103. Dykewicz CA. Summary of the Guidelines for Preventing Opportunistic Infections among Hematopoietic Stem Cell Transplant Recipients. Clinical Infectious Diseases 2001; 33: 139-144.

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 that trial 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 trial; MSLT, multicentre selective lymphadenectomy trial; SNB, sentinel lymph node biopsy; SND, sentinel lymph node dissection; US, ultrasound.

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 1; T-VEC, talimogene laherparepvec; WT, wild type.

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 1; T-VEC, talimogene laherparepvec.

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 1; T-VEC, talimogene laherparepvec.

Figure 5. Treatment algorithm for asymptomatic brain metastases

This algorithm is restricted to asymptomatic brain metastases. In case of symptomatic brain metastases, 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 brain metastases during adjuvant treatment and where a change of systemic treatment might be warranted.

[a]For 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.

[b]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.

BRAFi, BRAF inhibitor; CTLA-4, cytotoxic T lymphocyte-associated antigen 4; IO, immuno-oncology; MEKi, MEK inhibitor; PD-1, programmed cell death 1; SRS, stereotactic radiosurgery; WT, wild type.

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

Definition of Primary Tumour (T)[a]

T CATEGORY	THICKNESS	ULCERATION STATUS
TX: Primary tumor thickness cannot be assessed (eg, diagnosis by curettage)	Not applicable	Not applicable
T0: No evidence of primary tumor (eg, 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

Definition of Distant Metastasis (M)[a]

	M CRITERIA	
M CATEGORY[b]	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

CNS, central nervous system ; LDH, lactate dehydrogenase.

[a]Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original and primary source for this information is the AJCC Cancer Staging Manual, eighth edition (2017) published by Springer International Publishing (Gershenwald JE, Scolyer RA, Hess KR, et al. Melanoma of the skin. In; Amin MB, Edge SB, Greene FL, et al, eds. AJCC Cancer Staging Manual. 8th ed. New York: Springer International Publishing; 2017:563-585).

[b]Suffixes for M category: (0) LDH not elevated, (1) LDH elevated. No suffix is used if LDH is not recorded or is unspecified.

WHEN T IS...	AND N IS...	AND M IS...	THEN THE PATHOLOGICAL STAGE GROUP IS...
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
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]Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original and primary source for this information is the AJCC Cancer Staging Manual, eighth edition (2017) published by Springer International Publishing (Gershenwald JE, Scolyer RA, Hess KR, et al. Melanoma of the skin. In: Amin MB, Edge SB, Greene FL, et al, eds. AJCC Cancer Staging Manual. 8th ed. New York: Springer International Publishing; 2017:563-585[4]). [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.

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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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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	A phase 3 randomised, double-blind study of nivolumab or nivolumab plus ipilimumab versus ipilimumab alone in previously untreated advanced melanoma (checkmate 067) [63, 65] 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	A phase 3 randomised, double-blind study of nivolumab or nivolumab plus ipilimumab versus ipilimumab alone in previously untreated advanced melanoma	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)

		(checkmate 067) [63, 65] Phase III NCT01844505					
Cobimetinib with vemurafenib	First-line unresectable or metastatic melanoma with the *BRAF* V600E mutation	A phase III, double-blind study comparing vemurafenib versus vemurafenib plus cobimetinib in participants with metastatic melanoma (coBRIM) [61] 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	A randomised, double-blind phase 3 trial: adjuvant immunotherapy with Anti-CTLA-4 monoclonal antibody (ipilimumab) versus placebo	Placebo OS: 54.40%	Primary outcome 5-year DFS OS gain: 11%	OS HR: 0.76 (0.64–0.89)		A (Form 1)

		after complete resection of high risk stage III melanoma [53] Phase III NCT00636168					
Trametinib with dabrafenib	First-line unresectable or metastatic melanoma with the *BRAF* V600 mutation following complete resection	A Phase III, randomised, open-label study comparing the combination of dabrafenib and trametinib to vemurafenib in subjects with unresectable (stage IIIc) or metastatic (stage IV) BRAF V600E/K cutaneous melanoma (COMBI-v) [69] 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)
Dabrafenib in combination	Adjuvant treatment of	COMBI-AD: A phase III	Placebo	RFS gain: 27.9 months	RFS HR: 0.47 (0.39–		A (Form 1)

with trametinib	melanoma after surgical resection with BRAF V600 mutation	randomised double-blind study of dabrafenib in COMBInation with trametinib versus two placebos in the adjuvant treatment of high-risk BRAF V600 Mutation-positive Melanoma after surgical resection [59, 97] Phase III NCT01682083	RFS: 16.6 months 3-year RFS: 39%	3-year RFS gain:19%	0.58)		
Trametinib as monotherapy	Unresectable or metastatic melanoma with a *BRAF* V600E/K mutation	A phase III randomised, open-label study comparing trametinib to chemotherapy in subjects with advanced or metastatic BRAF V600E/K mutation-positive melanoma [98-101] Phase III	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)

		NCT01245062					
Pembrolizumab	Adjuvant treatment of adults with stage III melanoma and lymph node involvement after complete resection	A randomised, double-blind phase 3 trial: adjuvant immunotherapy with Anti-PD-1 monoclonal antibody pembrolizumab versus placebo after complete resection of high-risk stage III melanoma [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	a phase 3, randomised, double-blind study of adjuvant immunotherapy with nivolumab versus ipilimumab after complete resection of stage IIIb/c or stage IV melanoma in subjects who are at high risk for recurrence	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)

		(CheckMate 238) [56] Phase III NCT02388906					
Binimetinib with encorafenib	Adult patients with unresectable or metastatic melanoma with the *BRAF* V600 mutation	A 2-part phase III randomised, open label study of encorafenib plus binimetinib versus vemurafenib and encorafenib monotherapy in patients with unresectable or metastatic BRAF V600 mutant melanoma [71, 102] 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 [96]. The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee.

CI, confidence interval; 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

		Stage – AJCC 7th edition (all patients NED)				
Study	**Design**	**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 LN HR 0.48, ≥ 4 LN	
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 [58]	Vemurafenib versus placebo	HR 0.0 NE	SN >1 mm HR 0.52	HR 0.63	HR 0.8	
COMBI-AD [59]	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.

HR, hazard ratio; LN, lymph node; NE, not established; NED, no evidence of disease; RFS, recurrence-free survival; SN, sentinel node.

Table 5. Treatment modalities for melanoma metastases

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

[a]Treatment modalities are presented in order of preference.

[b]These therapies should be preferentially performed at specialised centres.

CNS, central nervous system; GoR, grade of recommendation; ITM, in-transit metastasis; LN, lymph node; RT, radiotherapy; T-VEC, talimogene laherparepvec.

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 unresctable 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, ITM, regional LN 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

Treatment of localised 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]

Treatment of locoregional disease

- SNB is recommended for all patients with pT1b or higher according to AJCC 8th edition [II, B]
- CLND is not recommended for SN-positive patients [I, A]. 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 [II, B]
- 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, B]

- Anti-PD1 adjuvant therapy or dabrafenib/trametinib are the preferred treatment options [I, A]

Management of advanced/metastatic disease

Treatment of advanced disease (unresectable stage III and IV)

- 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-PD1 antibodies (pembrolizumab, nivolumab), PD-1 and ipilimumab for all patients, and BRAFi/MEKi combination for patients with *BRAF*-mutated melanoma [II, 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 *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 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]

BRAFi, BRAF inhibitor; CLND, complete lymph node dissection; CTLA-4, cytotoxic T lymphocyte-associated-antigen 4; DTIC, dacarbazine; ITM, in-transit metastases; LMM, lentigo maligna melanoma; LN, lymph node; MEKi, MEK inhibitor; PD-1, programmed cell death 1; R1, microscopic tumour at the margin; RT, radiotherapy; SN, sentinel node; SNB, sentinel node biopsy; US, ultrasound.

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])

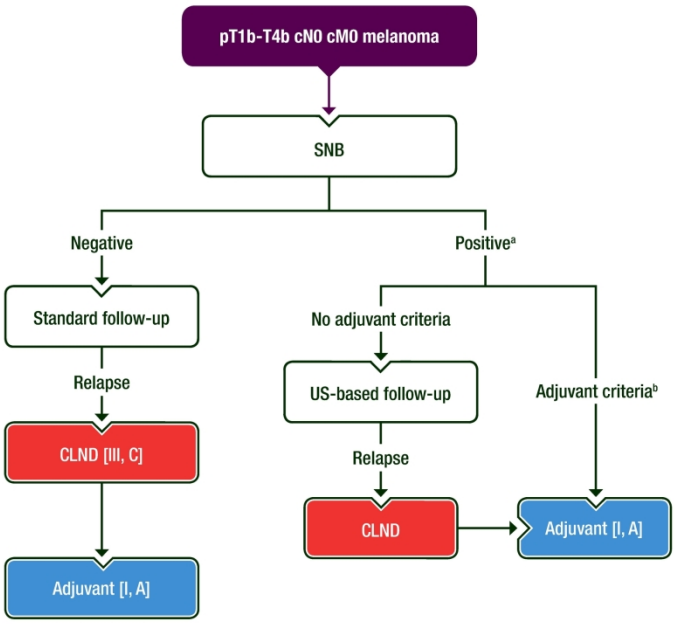
Levels of evidence

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 [103]



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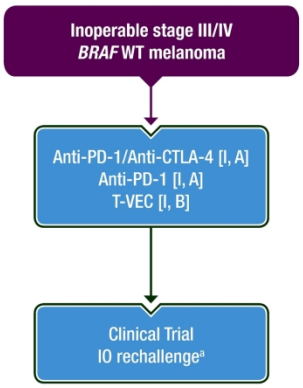

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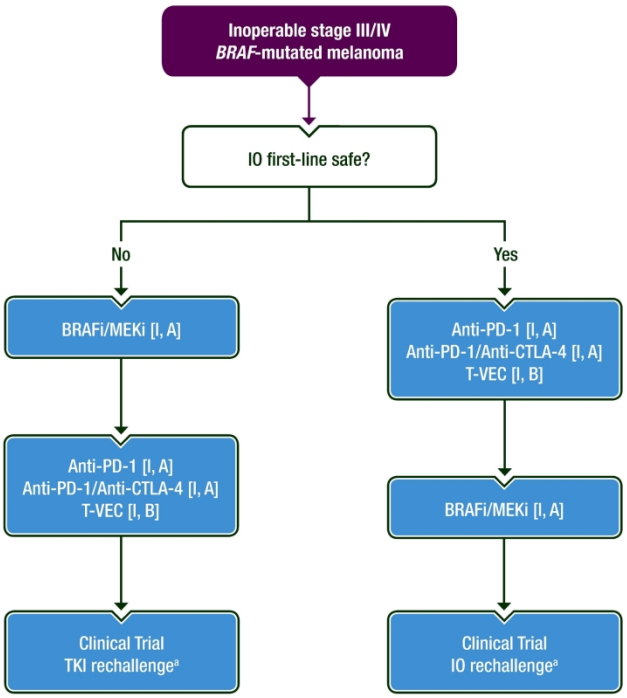

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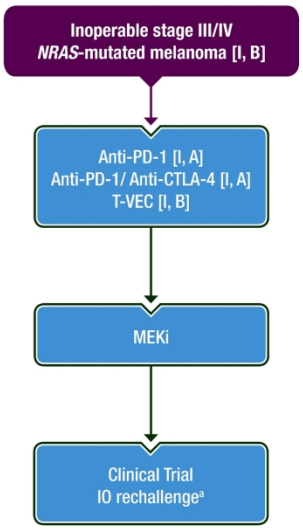

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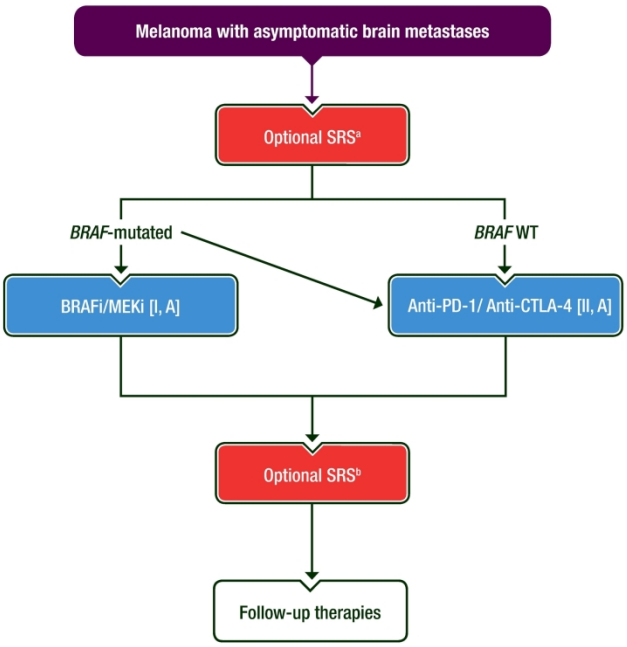

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