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The updated Swiss guidelines for the treatment and follow-up of cutaneous melanoma

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Summary

Despite the globally rising incidence of melanoma, mortality rates have decreased by approximately 18% in Caucasian populations following the introduction of effective systemic treatments.

Thanks to new molecular insights, the management of cutaneous melanoma has undergone several transformations over the past decade. The existing guidelines were last updated in 2016 to provide evidence-based practical recommendations for melanoma specialists across Switzerland. Recent data on surgical, radiotherapeutic and mainly systemic treatment with the implementation of adjuvant and neoadjuvant treatments in the current melanoma management have made modifications of the treatment and follow-up recommendations necessary.

Introduction

The incidence of melanoma in Switzerland is rising with 1721 new cases between 2016 and 2020 and a crude rate of 40.8 per 100,000 per year, representing one of the highest incidences in Europe [1]. The existing guidelines were last updated in 2016 to provide evidence-based practical recommendations to melanoma specialists across Switzerland [2].

Due to the significant advances in the treatment of melanoma in recent years, the recommendations have been revised according to international standards to provide a uniform consensus and ensure optimal patient care. Deviation from these recommendations in special clinical situations should be discussed in multidisciplinary tumour boards. The recommendations presented here have been graded according to the amount of scientific evidence supporting them using the "Level of Evidence" classification [2, 3].

Levels of evidence:

- IA Evidence from meta-analyses of randomised controlled trials
- IB Evidence from at least one randomised controlled trial
- IIA Evidence from at least one controlled study without randomisation
- IIB Evidence from at least one other type of quasi-experimental study
- III Evidence from non-experimental descriptive studies, such as comparative studies, correlation studies and case-control studies
- IV Evidence from expert committee reports or opinions or clinical experience of respected authorities, or both.

Grades of recommendations:

- A Directly based on Level I evidence
- B Directly based on Level II evidence or extrapolated recommendations from Level I evidence
- C Directly based on Level III evidence or extrapolated recommendations from Level I or II evidence
- D Directly based on Level IV evidence or extrapolated recommendations from Level I, II or III evidence

Clinical subtypes

Clinical and histopathological features are the basis of the skin melanoma classification proposed by McGovern and Clark decades ago [4, 5]. Since then, modern technologies,

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such as next-generation sequencing (NGS), have provided numerous new molecular insights into the pathogenesis of melanoma. These are now incorporated in the 5th WHO classification of skin melanoma [6].

Regarding pathogenesis and molecular alterations, the 5th WHO classification introduces the new nomenclature of melanoma with low cumulative sun damage (low-CSD) and high cumulative sun damage (high-CSD) melanoma. Low cumulative sun damage melanoma includes superficial spreading melanoma, whereas high cumulative sun damage melanoma may represent desmoplastic melanoma or lentigo maligna melanoma. High cumulative sun damage typically arises on the chronically sun-exposed skin (face, distal extremities) of individuals usually older than 55 years of age. High CSD melanomas demonstrate a UV radiation-induced signature with a very high tumour mutational burden, defined as 30 mutations per megabase (mut/mb) of DNA or more. Pathogenic alterations involve bi-allelic NF1 inactivation, NRAS, KIT mutations and *BRAF non-pV600E mutations*[7].

In contrast, low cumulative sun damage melanomas typically occur on intermittently sun-exposed skin (back, proximal extremities) of individuals younger than 55 years of age and demonstrate low to moderate solar elastosis. Genomically, *BRAF pV600E*mutations predominate, and they often arise from common or dysplastic naevi through the acquisition of additional pathogenic molecular alterations, such as inactivation of *CDKN2A* and *TERT* promoter mutations [8].

Acral melanoma arises on the glabrous sun-protected skin or nail apparatus. Therefore, they demonstrate a very low tumour mutational burden. However, as well as driver mutations in the MAP-kinase pathway, they show high genomic instability with many copy number gains and losses [9].

Spitz melanomas may develop through genetic inactivation of *CDKN2A* and acquisition of *TERT* promoter mutations from Spitz naevi, which are driven by kinase fusions (*ROS1, NTRK1, NTRK3, ALK, BRAF, MET, MAP3K8* and *RET*) or *HRAS* mutations. Melanomas with Spitz morphology and *BRAF* pV600E mutations do not qualify for a Spitz melanoma diagnosis as *BRAF* pV600E mutations are absent in Spitz naevi [10].

Molecular analysis of melanocytic lesions has also indicated an intermediate group of melanocytic lesions. Therefore, the new concept of 'melanocytoma' is introduced. Importantly, melanocytoma is not a general term indicating that a tumour is diagnostically indeterminate. Besides their specific morphology, this group of lesions has a second distinct mutation in addition to the driver mutation, which is also present in conventional naevi. The melanocytoma category includes *WNT*-activated deep penetrating/plexiform melanocytoma (naevus), pigmented epithelioid melanocytoma, *BAP1*-inactivated melanocytoma and *MITF* pathway-activated melanocytic tumours. Additionally, the atypical Spitz tumour is now named Spitz melanocytoma. Melanocytomas have a low risk of progression to melanoma and therefore belong to class II (same class as melanoma in situ) of the melanocytic pathology assessment tool and hierarchy for diagnosis. Excision with a <1 cm safety margin is recommended[11].

Melanoma diagnosis

Skin examination for melanoma screening requires inspection of the entire body surface under good lighting. Dermoscopy is a non-invasive technique that uses a hand-held magnifying device and immersion technique or polarised light to render the stratum corneum translucent. This technique allows the visualisation of diagnostic features of pigmented skin lesions that are not seen with the naked eye and has been shown to significantly improve diagnostic accuracy compared to naked-eye examination in the hands of an experienced investigator. *Recommendation A, level of evidence IA.*

Lesions that differ from the patient's other lesions (ugly duckling lesions), lesions that have a history of change (dynamic) or lesions with the dermoscopy criteria of severe atypia or malignancy should be excised [12]. Fast growth and ulceration are important features of thick melanomas, including amelanotic melanoma-

Recommendation: Whole-body photography and digital dermoscopy with sequential examinations can improve early detection of melanoma and should be used in high-risk patients with a high total naevus count [13]. *Recommendation B, level of evidence IIA*.

Artificial intelligence-based algorithms have been tested in multiple studies [14, 15]. However, there is insufficient evidence regarding their use in clinical practice.

Diagnosis should be based on a full-thickness excisional biopsy with a small side margin. Processing by an experienced pathology institute is mandatory *(Level of evidence: IV).* The histology report of a primary melanoma should follow the WHO classification and include melanoma type, maximum thickness in millimetres (Breslow), presence of (a) ulceration, (b) mitosis – mitotic rate/1 mm^2 – (c) and extent of regression, as well as clearance of the surgical margins.

Staging

Physical examination with dermoscopy of pigmented lesions and detailed attention to tumour satellites, in-transit metastases, and regional lymph node and systemic metastases is mandatory.

In low-risk melanomas (pT1a), no other investigations are recommended. For higher stages, imaging as suggested in the follow-up section should be performed.

The 8th edition of TNM is the classification of choice.

Surgical treatment of localised primary melanoma

The final surgical therapy should be carried out within 4 to 6 weeks following primary resection, leaving a safety margin of 1–2 cm, depending on the thickness of the tumour (table 1). Special locations, such as the face, may necessitate exceptions from the recommended safety margins, and then micrographically controlled surgery with complete margin evaluation and, if necessary, a staged procedure to secure tumour-free margins by the pathologist should be used.

Histologically complete excision of melanoma in situ (pTis) must be achieved for all localisations [16]. For pTis

of the face and other delicate locations, microscopically controlled surgery (without an additional safety margin) is justifiable. For in situ melanomas at other sites, a safety margin of 0.5 cm is recommended.

Dysplastic naevi with high-grade atypia or dysplastic naevi in chronic sun-damaged skin should be completely excised with clear margins [11, 17, 18].

Sentinel lymph node biopsy

Sentinel lymph node biopsy is currently the most sensitive method for detecting clinically occult nodal disease at the time of primary melanoma diagnosis and therefore the standard for staging cutaneous melanoma. In addition, considering the evolving adjuvant therapy, sentinel lymph node biopsy identifies patients with clinically occult metastases and/or higher tumour load who might benefit from early adjuvant systemic therapy.

The accuracy and reliability of the method make it one of the most important prognostic factors for tumour recurrence in melanoma patients *(level of evidence IV)* [19].

The risk of lymph node spread varies from at least 5% for patients whose melanoma is 0.8–1.0 mm in thickness (Breslow index) with ulceration to over 25% for patients with ulcerated thick (>4 mm) melanomas [20].

Recently, studies have shown the utility of gene-expression profiling and immunohistochemistry of primary tumours to predict sentinel lymph node status and identify patients with an increased risk of relapse [21]. Prospective studies are necessary to validate these results before recommending its use *(level of evidence IV).*

Recommendation: Sentinel lymph node biopsy is recommended for melanoma with ≥1 mm Breslow tumour thickness and melanoma thickness ≥0.8 mm and <1 mm with additional risk factors (ulceration, ≥1 mitosis/mm^2, microsatellites), and clinically normal regional lymph nodes determined by physical examination and ultrasound. *Recommendation A, level IA.*

Indications for sentinel lymph node biopsy should be strictly evaluated in frail patients or older patients with a high geriatric score.

Additionally, based on the risk features of the primary tumour (e.g. T stage) and if the physician and patient are convinced that the patient is a candidate for adjuvant treatment, sentinel lymph node biopsy can be omitted after discussion in multidisciplinary tumour boards *(Level IV).*

In contrast to other malignant tumours, a single melanoma cell identified by immunohistochemistry and confirmed as malignant with HE staining is sufficient for a diagnosis of lymph node metastasis (pN1a). Therefore, the sentinel lymph node (SLN) is meticulously processed. Due to there being many step sections and additional immunohistochemistry, sentinel lymph node biopsy histopathological handling has a significant laboratory workload and costly impact. Unfortunately, there are still too many different protocols for histopathological handling [22, 23]. A previous study showed that melanoma metastases occur globally and are not localised mainly in the hilar region, as initially thought [24]. Therefore, metastases may be missed or the tumour load underestimated if just the hilar region is meticulously investigated with small step sections, as initially proposed by the EORTC and other protocols. Consequently, the EORTC sectioning protocol was revised with the advice to increase the step section distance if the short sentinel lymph node axis is larger than 2 mm [23].

Table 1:
Excision safety margins for surgical treatment of primary melanoma (pT1–4). *Recommendation A, level of evidence I.*

Tumour thickness (Breslow)	Excision safety margin
Melanoma *in situ* (tumour thickness is not indicated) (pTis)	0.5 cm
<2 mm (pT1–2)	1 cm
>2 mm (pT3–4N)	2 cm

A sentinel lymph node biopsy report should include the following information with prognostic impact: location of the metastasis (subcapsular, parenchymal or combined), measurement of the depth of metastasis from the capsule, number of metastases (1, 2–5, 6–10, 11–20 or >20), maximum diameter in mm of the largest metastatic deposit and presence/absence of extranodal involvement. Measurement of the largest deposit is critical, as adjuvant treatment is recommended for IIIA patients with deposits >1 mm. However, a recent EORTC study showed that the inter-observer variability when measuring a metastasis was around 1 mm, even among experienced sentinel lymph node pathologists [25]. Naevi are relatively common in sentinel lymph nodes and differentiating them from melanoma metastasis can be difficult. Comparison with the primary melanoma or p16 immunohistochemistry in initially p16-negative melanomas can be useful in such cases [26]. Histological assessment can be a major diagnostic challenge and should therefore be carried out by an experienced pathologist with a high annual diagnostic biopsy caseload [27].

Completion lymph node dissection

When discussing lymphadenectomy in melanoma treatment, it is important to distinguish the following types:

– Elective lymphadenectomy – performed without previous histological confirmation of lymph node involvement
– Completion lymph node dissection (CLND) – performed after a positive sentinel lymph node has been confirmed histologically
– Therapeutic lymph node dissection (TLND) – performed in cases of clinically manifest, histologically confirmed lymph node involvement

Routine elective lymphadenectomy to the regional lymph nodes is not recommended. *Recommendation B, level of evidence II.*

Following the introduction of sentinel lymph node biopsy as the standard of care in the treatment regimen of cutaneous melanoma, completion lymph node dissection (CLND) was recommended, according to the Augsburg Consensus guidelines for all patients with a positive sentinel lymph node biopsy [28]. The Multicentre Selective Lymphadenectomy Trial (MSLT) I, which compared patients with sentinel lymph node biopsy versus observation found no overall survival (OS) benefit in the sentinel lymph node biopsy group but, in subgroup analyses, could show improved distant disease-free survival (DFS) and

melanoma-specific survival (MSS) for patients with nodal metastases from intermediate-thickness melanomas treated by completion lymph node dissection following Sentinel lymphnode biopsy [29]. Due to the morbidity of completion lymph node dissection, its indication in all cases of positive sentinel lymph node biopsy has frequently been challenged. However, definitive data were not available until recently, when at least two randomised prospective trials, the DeCoG trial of the German Dermatologic Cooperative Oncology Group and the MSLT II, published interim results showing no survival benefit from immediate CLND in patients with positive sentinel lymph node biopsy [30, 31]. While, as expected, the rate of regional disease control was higher in the completion lymph node dissection arms, so were the adverse events, especially regarding lymphoedema, one of the most serious long-term complications of lymphadenectomies.

Recommendation: Routine completion lymphadenectomy is no longer recommended in sentinel lymph node biopsy-positive patients. *(Recommendation A, level of evidence IB).* Each patient with a positive sentinel lymph node biopsy should be discussed at multidisciplinary tumour boards as a candidate for adjuvant treatment.

Therapeutic lymph node dissection

Melanoma patients with clinically (or radiologically) involved lymph nodes are candidates for therapeutic lymph node dissection if neoadjuvant treatment is not feasible. However, before undertaking additional aggressive local surgical treatments, a detailed staging investigation (PET-CT or CT scan) is necessary to exclude the presence of further metastases and a histological diagnosis of the lymph node metastasis should be obtained, ideally by interventional radiological techniques, such as fine-needle aspiration or core biopsy [32].

Therapeutic lymph node dissection in stage III melanoma should include the totality of the involved lymph node basin and should be performed as a radical, en-bloc dissection [33, 34]. *Recommendation C, level of evidence III.*

Node picking is not recommended as therapeutic lymph node dissection in stage III melanoma. Neoadjuvant approaches should be discussed in multidisciplinary boards prior therapeutic lymph node dissection. Otherwise, adjuvant treatment should be evaluated after therapeutic lymph node dissection.

Neoadjuvant treatment

The application of immunotherapy and BRAFi/MEKi was expanded in the neoadjuvant setting and has been intensively studied in recent years [35–42]. It is hypothesised that with neoadjuvant immunotherapy, a higher number of T-cell populations are activated in the tumour bed and thus can better eliminate peripheral micrometastases. Compared to immunotherapy, neoadjuvant therapy with BRAFi/MEKi showed fewer durable remissions, even after pathological complete response [39].

Three randomised phase 2 trials led to early consideration of a neoadjuvant approach: SWOG S1801 (NCT03698019), which evaluated the application of neoadjuvant and adjuvant pembrolizumab; the OpACIN trial with the PRADO expansion cohort, which evaluated a personalised response-driven surgery after neoadjuvant treatment with the combination of ipilimumab and nivolumab; and the application of talimogene laherparepvec (TVEC; NCT02211131) before surgery, which showed better 3-year and 5-year relapse-free survival (RFS) and overall survival vs surgery alone [40, 42, 43].

The SWOG S1801 study showed an improvement in event-free survival when pembrolizumab was applied for three cycles prior to surgery and for 15 cycles thereafter compared to 18 cycles of adjuvant application alone in patients with resectable high-risk melanoma [42]. Event-free survival was significantly longer with a hazard ratio of 0.58 (95% confidence interval [CI]: 0.39–0.87; p = 0.004, event-free survival at 2 years of 72% vs 49%). Overall survival data are preliminary and have not yet been presented. Several advantages favoured a neoadjuvant application; however, an 8% rate of treatment failure was shown in patients who could no longer undergo curative excision. The questions of subsequent treatment in these patients and what kind of surgery should be recommended after neoadjuvant treatment remain unresolved (limited versus therapeutic lymph node dissection). The PRADO expansion cohort attempted, among others, to answer this question, providing a strong rationale for randomised trials testing response-directed treatments.

The randomised phase III trial NADINA establishes neoadjuvant immunotherapy as the new standard of care for stage III melanoma patients with macrometastasis (palpable or confirmed lymph node metastases) [44]. The trial investigated neoadjuvant ipilimumab and nivolumab for two cycles before surgery and adjuvant immunotherapy in cases of partial remission or non-major pathological response (defined as ≤10% vital tumour tissue) versus surgery, and adjuvant immunotherapy showed a significant event-free survival benefit. Eligible patients had stage III melanoma with palpable or enlarged and histologically confirmed lymph node metastases. The difference in mean survival time was 8.0 months (99.9% CI: 4.94–11.05; p < 0.001; HR for progression, recurrence, or death: 0.32; 99.9% CI: 0.15–0.66) [44].

Since pathological evaluation after neoadjuvant therapy and surgery is complex and pivotal for further treatment decisions, the evaluation should be performed by specialised high-volume centres [39].

Recommendation: Neoadjuvant therapy should be considered for patients with macroscopic stage III melanoma in the context of specialised, multidisciplinary tumour boards. Inclusion in clinical trials should be evaluated whenever possible. *Recommendation A, Level of evidence I*

Adjuvant treatment

Adjuvant treatment is considered the standard of care in high-risk completely resected melanoma [34]. Recent studies showed a significant recurrence and distant-metastasis benefit in radically resected stage III and IV melanoma patients treated with either immunotherapy or BRAF and MEK inhibitors (BRAFi/MEKi) in the adjuvant setting [45–52]. Of note, BRAFi/MEKi were not prospectively tested for therapy of stage IV disease. In this context, inter-

feron or pegylated interferon is no longer recommended as adjuvant treatment [51].

Adjuvant treatment in high-risk completely resected stage III and IV melanoma patients

Checkmate 238 compared 1-year nivolumab 3 mg/kg versus ipilimumab 10 mg/kg in AJCC7 stage IIIB, IIIC or IV melanoma patients. In the 4-year analysis, nivolumab was superior to ipilimumab with an HR of relapse-free survival of 0.72 (95% CI: 0.60–0,85) [53]. No difference in overall survival was observed between the two arms. Despite approval of ipilimumab 10 mg/kg by the FDA, given the high toxicity and its inferiority compared to nivolumab, ipilimumab should not be considered as an adjuvant treatment option.

Keynote 054 compared 200 mg pembrolizumab Q3W for 1 year versus placebo in AJCC7 stage IIIA (micrometastasis >1 mm), IIIB and IIIC. With a median follow-up of 5 years, longer relapse-free survival (55.4 months versus 38.03, HR: 0.5) and distant metastasis-free survival (60.6 versus 44.5, HR: 0.62) were demonstrated with pembrolizumab with an absolute relapse-free survival difference of 17% [54]. The 7-year analysis of the Keynote 054 results confirmed a sustained benefit in long-term relapse-free survival and distant-metastasis-free survival [55].

AJCC7 stage IIIA (micrometastasis >1 mm), IIIB and IIIC patients harbouring a *BRAF* V600E or K mutation were randomised to receive either a standard dose of dabrafenib and trametinib or placebo in the Combi-AD trial [47]. The combination resulted in a significant relapse-free survival benefit with an HR of 0.57 and a 13% improvement in overall survival at 3 years (p = 0.0006); however, this was considered non-significant because it did not meet the pre-specified interim analysis significance threshold [56]. More than half (52%) of patients treated with dabrafenib and trametinib did not relapse at 5 years with survival curves ultimately reaching a plateau. In the subgroup analysis of 186 patients with *BRAF* mutations included in the Keynote-054 study, which had the same inclusion criteria as the Combi-AD trial, 54% remained relapse-free at 5 years. In the absence of a direct efficacy comparison, both immunotherapy and targeted therapy should be discussed in patients with *BRAF* mutations. Adjuvant treatment with dabrafenib and trametinib is the only approved target combination and the only trial demonstrating non-significant overall survival benefit after a median follow-up of 100 months with a risk reduction of 20% in the overall population. The *B RAF* V600E population achieved a greater survival benefit than the V600K patients, possibly due to the outperformance of second-line immunotherapy in this patient group [57]. However, given the small size of the V600K subgroup, no conclusions for clinical practice can be drawn.

The combination of ipilimumab and nivolumab was also tested in the adjuvant setting [50]. The randomised phase III CheckMate 915 trial of ipilimumab (1 mg/kg Q6W) and nivolumab (480 mg Q4W) for 1 year against nivolumab (480 mg Q4W) did not reach its dual primary endpoints and failed to show any significant difference in relapse-free survival. However, a smaller phase II study (ImmuNED) in completely resected stage IV patients demonstrated a relapse-free survival of 70% in patients receiving 1 year of ipilimumab 3 mg/kg plus nivolumab 1 mg/kg for four cycles followed by nivolumab 3 mg/kg every 2 weeks [52]. The combination was compared to nivolumab monotherapy (3 mg/kg every 3 weeks) and placebo with relapse-free survival rates of 42% and 14%, respectively, resulting in an impressive HR of 0.23 for the combination over placebo.

Recommendation: Adjuvant treatment with either anti-PD1 monotherapy or BRAFi/MEKi in cases with *BRAF* V600E mutation should be offered (a) in all patients with completely resected stage III melanoma with microscopic disease (positive sentinel lymph node biopsy) who meet the adjuvant criteria and (b) in patients receiving neoadjuvant treatment that do not achieve a major pathological response. Molecular analysis should be available at the time of discussion. For patients with *BRAF*-mutant melanoma, the decision should be made based on the individual patient's preferences, toxicity profiles, comorbidities, comedication and compliance. The different recurrence timings, predominantly in the first 6 months of therapy with anti-PD1 vs after treatment conclusion with the BRAFi/MEKi, should be included in the discussion. In young patients with the desire to have children, the risk of long-term endocrinopathy with potential hypogonadism and impaired fertility related to immunotherapy should be considered. *Recommendation A, level of evidence IB.*

Adjuvant treatment in Stage IIIA melanomas

Both Keynote 054 and Combi-AD trials included melanoma patients with AJCC stage IIIA and a tumour load in the sentinel lymph node biopsy of >1 mm. Since the approval of the adjuvant treatment in Switzerland, there are two major changes that affect decision-making and advice for such patients:

– These trials included patients based on the AJCC7 staging system; however, the currently used AJCC8, introduced in 2018, resulted in a significant improvement in the assigned prognosis for stage IIIA patients upon complete revision of stage III [20].
– All patients in these trials had to undergo completion lymphadenectomy, which is no longer the standard of care and underestimates the current recurrence risk of the IIIA patients as a minority of IIIA patients would have been upstaged to stage IIIB or higher.

Furthermore, although not included as part of AJCC8, tumour load in the sentinel lymph node biopsy is an additional prognostic criterion besides ulceration and the Breslow index. Patients with a sentinel lymph node biopsy tumour load <1 mm have an excellent prognosis with a 5- and 10-year melanoma-specific survival of 90% (8). Nevertheless, a recent German study reported lower survival rates (10-year melanoma-specific survival 82.7% for stage IIIA patients and <1 mm tumour load) [58]. This difference in survival can be partially explained by the lower number of patients in the former study (736 vs >45,000), and by the fact that sentinel lymph node biopsy rates are not always reported and the cause of death is sometimes unclear.

When Keynote-054 and Combi-AD were re-analysed using the AJCC8 edition, no difference in relapse-free survival was demonstrated in the low-number stage IIIA cohort (n = 50).

Recommendation: Adjuvant treatment is not routinely recommended in stage IIIA melanoma patients with a tumour burden in the sentinel lymph node biopsy <1 mm. In the small subset of stage IIIA patients with a higher risk of relapse (sentinel lymph node biopsy ≥1 mm), adjuvant treatment within clinical trials should be considered. In the absence of clinical trials, adjuvant treatment can be offered after a balanced discussion of risk reduction and long-term toxicities. *Recommendation C, D, level of evidence I.*

Adjuvant treatment in stage IIB and IIC melanoma

Many randomised clinical studies have investigated anti-PD1 antibodies in stage IIB and IIC patients at a high risk of relapse. Pembrolizumab 200 mg Q3W for 1 year significantly improved distant metastasis-free survival (stage IIB HR: 0.62; stage IIC HR: 0.57) and relapse-free survival (HR of 0.61 over placebo) with 86% of patients remaining disease-free after 18 months and an absolute 10% relapse-free survival difference [59]. With a minimal follow-up of 24 months, the study also reported a 40% reduction in the number of new primary melanomas [59]. However, 20% of patients treated with pembrolizumab also received long-term hormonal replacement therapy for endocrine toxicities. The majority of these were manageable thyroid toxicities. The CheckMate 76K trial also met its primary endpoint, reporting a 58% reduced risk of recurrence or death (HR: 0.42; 95% CI: 0.30–0.59; $p < 0.0001$) in favour of 1-year nivolumab versus placebo [60]. Currently, no overall survival data are available from any of the above-mentioned studies. The number needed to treat (NTT) was updated to 5.3 for relapse-free survival and 7.8 for distant metastasis-free survival [61].

Recommendation: Anti-PD1 agents are currently approved in Switzerland as adjuvant treatment in stage IIB and IIC melanomas. Risk-benefit analysis, also based on NNT, and the missing overall survival data in the multidisciplinary tumour board's prior treatment decision is mandatory. Stage IIB and IIC patients should be referred to specialised centres for treatment if clinical trial protocols are available. *Recommendation B, level of evidence IB.*

Future directions

Current adjuvant studies focus either on novel combination treatments or on optimising the selection of high-risk patients for adjuvant treatment based on biomarkers. Relativity 098 (NCT05002569) is testing the combination of anti-PD1 and anti-Lag3 in completely resected stage III disease. The study was presented at ASCO this year and did not meet its primary endpoint since the combination anti PD1 and anti Lag3 did not result in a significant recurrence-free survival compared to nivolumab alone (2-y recurrence-free survival rate 62.0 [57.7–66.0] for the combination versus 63.6 [59.4–67.6] for nivolumab alone (HR 1.01) [194]..

Keyvibe-010, a randomised phase III trial that investigated pembrolizumab and vibostolimab versus pembrolizumab alone in high-risk stage completely resected IIB–V melanoma patients was discontinued recently because of lack of superiority and greater toxicity of the combination. The NivoMela study (NCT04309409) randomises patients to 1-year adjuvant treatment with nivolumab based on a gene-expression signature. DETECTION (NCT0491988) is another novel trial in 1050 stage IIB and IIC patients, which uses ctDNA for recurrence monitoring and addresses the question of whether early treatment with nivolumab in cases of molecular recurrence results in a survival benefit. The Columbus-AD-EORTC 2139 trial (NCT05270044) tested encorafenib and binimetinib in the adjuvant setting for stage IIB and IIC *BRAF* V600K/E melanoma. The study was stopped early due to poor recruitment.

Adjuvant mRNA-4157 (an mRNA-based individualised neoantigen vaccine) plus pembrolizumab significantly prolonged relapse-free survival (HR: 0.561) and distant metastasis-free survival in patients with completely resected high-risk cutaneous melanoma compared to adjuvant pembrolizumab alone (phase IIB, Keynote-942) [62]. A multicentric phase III trial with this combination is currently ongoing.

Surgical treatment of locoregional and oligometastatic disease

The surgical treatment of melanoma with only lymphatic metastasis (stage III) is detailed in the therapeutic lymphadenectomy section.

All patients with metastatic melanoma should be discussed by a multidisciplinary board. Historically, surgical treatment in oligometastatic melanoma has been advocated, as some patient populations have shown a long survival time after complete resection [63, 64]. In the era of efficient systemic therapy, complete surgical resection of stage IV melanoma followed by adjuvant therapy can be an option depending on the expected morbidity of the surgical procedure (see paragraph on adjuvant treatment in high-risk complete-resected stage III and IV melanoma patients)

Recommendation: In resectable primary oligometastatic disease, surgery should be offered if limited and acceptable morbidity is expected. *Recommendation B, level of evidence IB.*

(Neo)adjuvant treatment should be evaluated. *Level of evidence I.*

There is limited evidence that patients treated with immunotherapy benefit from surgical resection of metastases. This benefit is higher for patients in whom complete resection is performed and in patients with an oligoprogressing or responding tumour compared with those with multiple progressing lesions [65].

Recommendation: In highly selected cases of patients under immunotherapy, ideally with oligoprogressing or responding tumours, surgical resection can be offered if it is reasonably deemed to obtain a complete resection. *(Recommendation C, level of evidence IIB)*

In the palliative setting for metastatic disease, surgery may be an effective palliative treatment option, if it is technically feasible, if the risk of morbidity and mortality is low and if the patient is likely to live long enough to derive a benefit [2]. *Recommendation C, level of evidence III.*

Radiotherapy

Indications, protocols and radiotherapy of primary melanomas

Surgery remains the standard of care for the local treatment of primary melanoma or cutaneous metastases. Several prospective and retrospective case-series have demonstrated the high efficacy of radiotherapy regarding local control. Therefore, depending on the localisation and the patient's preference, this treatment can be offered as an alternative for irresectable tumours or for patients of advanced age and/or with multiple comorbidities. Especially for lentigo maligna of the elderly, primary, definitive irradiation is a well-established option with long-term experience providing excellent control rates [66–70]. Imiquimod versus radiotherapy was evaluated in a prospective randomised multicentre phase III trial in Australia with 126 patients with a median age of 72 years. Imiquimod (5×/weekly for 12 weeks) was shown not to be inferior to radiotherapy in terms of local relapses after a median follow-up of 24 months [71].

Moreover, the results regarding cosmesis were reported as "good"/"excellent" for the vast majority of patients [68]. Finally, radiotherapy remains a good option for locally recurrent and/or symptomatic primary or secondary lesions after surgery.

Recommendation: Radiotherapy can be offered as a local treatment for non-operable, elderly/frail patients or in the palliative situation for cutaneous primary or metastases. *Recommendation B, level of evidence III.*

Radiotherapy or imiquimod should be offered as a local treatment for inoperable and/or elderly/frail patients with lentigo maligna. *Recommendation A, level of evidence I.*

Prospective randomised trials have demonstrated that extremely hypofractionated irradiation regimens of 3–8 fractions are at least equally effective as longer series and allow for a shorter overall treatment time with only minimal treatment burden for the patients (NCCN guidelines V3.2022) [72, 73].

Data for radiotherapy of the primary tumour bed in the postoperative setting hardly exist for malignant melanoma except for the desmoplastic subtype. This entity is characterised by a higher rate of local recurrence and often narrow resection margins, partly because of a special neurotropism and frequent localisation in the head and neck area [74]. A prospective study and several larger – also multicentric – retrospective studies showed favourable local control rates and sometimes even improved survival for irradiated patients [75–79].

Recommendation: Postoperative radiotherapy should be offered after resection of primary desmoplastic melanoma with high-risk features, such as narrow resection margins or neurotropism/angiotropism when no adjuvant treatment is planned. *Recommendation B, level of evidence IIB.*

Postoperative adjuvant radiotherapy of the nodal basin

Although all published data originate from the pre-adjuvant immunotherapy era, postoperative radiotherapy of the involved lymphatics after nodal dissection generally leads to a significant improvement in the regional tumour control without any impact on survival [80]. Moreover, it is associated with increased toxicity (lymphoedema, fibrosis, etc.), especially in patients with a higher BMI (>25 kg/m^2) or irradiation of the inguinal region. In a large, pooled analysis, the rate of chronic lymphoedema was 20% after adjuvant radiotherapy versus 13% without [81]. Current data still indicate considerable rates of regional recurrence even in the immunotherapy era, e.g. in the adjuvant EORTC trials (1325: pembrolizumab vs placebo and 18071: ipilimumab vs placebo). Such events could have a detrimental impact on quality of life. For example, the rates of isolated 5-year regional recurrence were 21% vs 25% for ipilimumab versus placebo (not statistically significant) and the total 5-year rates for locoregional recurrence were 24% and 31%, respectively. The first data regarding pembrolizumab versus placebo show a slightly lower but still relevant rate of regional recurrence. In conclusion, even in the immunotherapy era, there are subgroups of patients who would benefit from adjuvant radiotherapy. In the presence of one of the risk features, such as parotideal or cervical tumour localisation, extracapsular extension (ECE, especially in combination with the above localisations), incomplete resection, recurrence after first-line treatment and very extensive regional involvement (four or more nodes, bulky disease), adjuvant radiotherapy should be discussed. Naturally, radiotherapy should be recommended in patients not receiving adequate (neo)adjuvant systemic treatment.

Recommendation: Postoperative radiotherapy can be discussed after lymphadenectomy in the presence of one of the following criteria after careful consideration of treatment-related morbidity to improve locoregional control:

- Not eligible for systemic treatment
- ECE (especially head and neck, parotis)
- R1/R2 resection
- Recurrence after first-line treatment
- Bulky lesion
- Four or more involved nodes

Recommendation B, level of evidence IB

Bone metastasis

Palliative percutaneous radiotherapy of bone metastases, regardless of the primary tumour or histology, leads, in most patients, to significant pain relief. Therefore, patients with painful bone metastases should receive analgesic radiotherapy [82, 83]. Furthermore, palliative percutaneous radiotherapy of destabilising skeletal metastases leads to re-calcification and stabilisation of the involved bone within 3–6 months [84–86].

Interestingly, a novel disease-agnostic prospective randomised trial, which did not include melanoma patients, demonstrated not only a significant reduction in skeletal-related events but also an overall survival benefit for polymetastatic (>5 sites of disease) patients after irradiation of asymptomatic high-risk bone metastases. High-risk was defined as meeting one of the following criteria: (a) bulky disease <2 cm, (b) involving the hip, shoulder or sacroiliac joint, (c) disease in long bones with one- to two-thirds cortical thickness, and (d) disease in the junctional spine [87].

Recommendation: Palliative radiotherapy is recommended for symptomatic and asymptomatic but critical – in terms of stability – bone metastases. *Recommendation A, level of evidence IA.*

Oligometastatic extracranial disease

In recent years, several prospective randomised trials demonstrated a potential benefit regarding disease control and survival for patients with oligometastatic disease after stereotactic ablative radiotherapy (SABR) to all lesions compared to standard-of-care only. Although no specific trial for malignant melanoma has been published until now, data from the disease-agnostic SABR-COMET trial, which is investigating this concept for oligometastatic patients with 1–5 lesions, seem very promising after long-term follow-up [88, 89]. In this trial, the 5-year overall survival rate was 17.7% in the standard treatment arm versus 42.3% in the stereotactic ablative radiotherapy arm (stratified log-rank p = 0.006). This strategy can be useful, especially in cases of oligorecurrence or oligoprogression under systemic treatment as defined in the EORTC/ESTRO consensus [90] and could allow for longer intervals without re-challenge or changes in systemic treatment. Importantly, the combination of stereotactic ablative radiotherapy with immunotherapy does not lead to additional toxicity and has been demonstrated to be safe in several studies, but caution is warranted in the case of concomitant BRAF inhibition [91], as increased skin toxicity was reported.

Finally, as there are scarce prospective data regarding applying this concept to malignant melanomas and the number of metastases and setting of oligometastatic disease that would benefit from stereotactic ablative radiotherapy are yet to be defined, inclusion of these patients in ongoing clinical trials is strongly recommended.

Recommendation: Stereotactic ablative radiotherapy for extracranial metastases can be discussed and offered in selected patients with oligorecurrence, oligoprogression or oligopersistence under systemic treatment as defined in the EORTC/ESTRO after interdisciplinary consensus. *Recommendation B, level of evidence IB.*

Systemic treatment

Immune checkpoint inhibitors

The phase III trials establishing anti-PD1 (pembrolizumab, nivolumab) and ipilimumab and nivolumab as the first-line standard of care for unresectable or metastatic melanoma have currently a median follow-up time of approximately 10 years. In the final 10-year analysis of the CheckMate 067 trial, the median overall survival was 71.9, 36.9, and 19.9 months in the ipilimumab and nivolumab combination, nivolumab, and ipilimumab monotherapy arms, respectively [92]. The study was not powered to detect any differences between the nivolumab-containing arms. In the Keynote 006 trial, the median overall survival was 32.7 months for pembrolizumab and 15.9 months for ipilimumab as first- or second-line therapy; 10-year overall survival was 34.0% and 23.6%, respectively [93]. Recently, the fixed-dose combination of nivolumab and the anti-LAG3 antibody relatlimab was approved by Swissmedic as a first-line therapy for advanced melanoma with <1% PD-L1 expression based on a greater median progression-free survival compared to nivolumab (10.1 vs 4.6 months) [94]. The nivolumab-ipilimumab combination is associated with a higher rate of severe (CTCAE grade 3–4) immune-related adverse events (59%) compared with nivolumab-relatlimab (18.9%) or anti-PD1 monotherapy (9.7–21%) [94–97]. In the CheckMate 511 trial, reversing the dosing of ipilimumab (1 mg/kg) and nivolumab (3 mg/kg) resulted in lower grade 3–5 immune-related adverse events compared with the standard dosing (33.9% vs 48.3%) with numerically similar overall survival and response rates; however, the primary endpoint of the trial was grade 3–5 toxicity, and the trial was not designed to demonstrate non-inferiority of the flipped dose [98].

No established biomarkers exist to identify patients who benefit from combination immune checkpoint inhibitor treatment. In a population-based retrospective analysis of over 1000 patients treated in Denmark, patients with PD-L1 expression of ≥1% had similar outcomes after first-line treatment with either a combination of immune checkpoint inhibitors or anti-PD-1 monotherapy [99]. A nomogram to predict response rates to immune checkpoint inhibitors based on clinical and biochemical parameters was recently developed and can help in decision-making [100].

The therapeutic choice between first-line anti-PD1 monotherapy and standard dose nivolumab (1 mg/kg) and ipilimumab (3 mg/kg) should be based on the following prognostic markers:

- Presence of brain metastases
- Presence of liver metastases
- High LDH levels (1.5 × upper limit normal [ULN])
- ECOG (0–1)
- *BRAF* V600E mutation
- Comorbidities and frailty (presence of autoimmune diseases, especially if necessitating immunosuppressive treatment)

Recommendation: In the presence of asymptomatic brain metastases and given the higher progression-free survival and response rate (50%), ipilimumab-nivolumab is the preferred treatment option compared to nivolumab monotherapy (21%). *Recommendation A, level of evidence II*.

In the presence of high LDH and liver metastases, the ipilimumab-nivolumab combination should be favoured over anti-PD1 monotherapy. *Recommendation B, level of evidence I.*

Given their greater risk of immune-related adverse events, patients with preexisting autoimmune diseases should be discussed by a multidisciplinary team to select the treatment with the optimal risk-benefit ratio. *Recommendation A, level of evidence IV.*

In all other cases, anti-PD1 monotherapy or anti-PD1 and anti-Lag3 combination treatments should be evaluated by a multidisciplinary team. *Recommendation A, level of evidence I.*

In a retrospective multicentre analysis of 355 patients resistant to anti-PD-(L)1, the ORR as well as the overall survival was higher with ipilimumab plus anti-PD-1 (31%, 20.4 months) than with ipilimumab monotherapy (13%, 8.8 months) [101]. In a similar analysis of patients with *BRAF* pV600E mutant melanoma who had anti-PD1 ver-

sus ipilimumab plus anti-PD1 after BRAFi/MEKi, the median ORR (34% vs 39%), progression-free survival (3.4 vs 3.6 months) and overall survival (14.4 vs 20.5 months) were not significantly different between groups [102].

Recommendation: The preferred second-line treatment after anti-PD-(L)1 monotherapy for wild-type *BRAF* melanoma should be ipilimumab-nivolumab. *Recommendation A, level of evidence IV.*

The preferred second-line treatment after BRAFi/MEKi in patients with *BRAF* mutations should be ipilimumab-nivolumab. *Recommendation B, level of evidence IV.*

Ipilimumab monotherapy is not recommended as first- or second-line therapy. *Recommendation C, level of evidence I*

BRAF and MEK inhibitors

Three BRAFi/MEKi combinations (vemurafenib-cobimetinib, dabrafenib-trametinib and encorafenib-binimetinib) have been shown to improve progression-free survival and overall survival over BRAFi monotherapy [103, 104].

The optimal sequence of treatment for *BRAF*-mutant melanoma was recently established. In the phase III DREAMseq trial, the sequence starting with ipilimumab-nivolumab resulted in a 20% 2-year overall survival gain (71% vs 51%) compared to that starting with dabrafenib-trametinib [105]. Also, in the phase II Secombit trial [106], 2- and 3-year overall survival, as well as progression-free survival rates, were higher in patients treated with ipilimumab-nivolumab as the first-line therapy and who received encorafenib-binimetinib at progression. In the 'sandwich arm', 8 weeks of encorafenib-binimetib followed by ipilimumab-nivolumab yielded similar results, showing that a short initial induction with targeted therapy followed by an immune checkpoint inhibitor is feasible and associated with a durable benefit. Of note, in several trials, including DREAMseq, Secombit and EBIN, higher rates of brain metastases were observed when targeted therapy was used as the first-line therapy.

Recommendation: The first-line treatment for *BRAF* V600 mutant melanoma should be ipilimumab-nivolumab. *Recommendation A, level of evidence I.*

Given the inferior outcome due to a delayed response, for patients with symptomatic disease in need of a rapid response or incapable of starting ipilimumab-nivolumab (e.g. poor ECOG due to disease burden, symptomatic brain metastases requiring steroid therapy, symptomatic liver metastasis or high LDH >2 ULN), BRAFi/MEKi inhibitors for 8 weeks followed by ipilimumab-nivolumab is recommended. *Recommendation A, level of evidence I.*

Triple combinations: BRAFi/MEKi anti-PD-(L)1

In three randomised trials, the triple combination of BRAFi/MEKi plus anti-PD-(L)1 showed high ORRs (70–80%), a substantial increase in the duration of response by approximately 11–13 months and a prolonged progression-free survival of approximately 4–6 months compared with the BRAFi/MEKi combination [107]. However, this improvement in efficacy comes at the expense of toxicity, with higher grade 3–5 adverse event rates with the triple combination compared with BRAFi/MEKi in the Keynote-022 (58.3% vs 25%) and COMBI-I trials (54.7% vs 33.3%) while in the IMspire-150 trial, both arms had similar safety profiles (79% vs 73%) [107]. In addition, in the final analysis of the IMspire150 trial, no significant improvement in overall survival was observed (86) [108]. Therefore, while the combination of atezolizumab, vemurafenib and cobimetinib is Swissmedic-approved, it is currently unclear which patient populations could benefit from the triple combination. An ongoing trial is comparing the trio of encorafenib, binimetinib and pembrolizumab with pembrolizumab [109].

Recommendation: The combination of atezolizumab, vemurafenib and cobimetinib can be considered as a rescue therapy in exceptional situations in patients with *BRAF*-mutant melanoma. *Recommendation D, level of evidence I.*

Talimogen laherparepvec

Talimogen laherparepvec (TVEC) is an oncolytic viral therapy that is approved for the local treatment of unresectable stage IIIB–C–D and M1a melanoma. TVEC resulted in statistically significant prolonged median overall survival and higher complete response rates compared to the GM-CSF arm and can be discussed in patients with accessible lymph node or skin metastasis in the above-mentioned stages. The addition of pembrolizumab to TVEC did not improve progression-free survival and overall survival compared to pembrolizumab alone in the prospective phase III Masterkey 265 clinical trial [110], and therefore the combination cannot be further recommended.

Chemotherapy

Chemotherapy in metastatic melanoma is increasingly considered obsolete or at least reserved as the last-line option for patients who remain in good health and who have already been treated with immunotherapy (monotherapy or combinations) or BRAFi/MEKi (if applicable) and cannot be included in a clinical trial.

Data about the role of chemotherapy largely stem from the years before the advent of immunotherapy. The most used agent is dacarbazine, which was approved for metastatic melanoma in the 1970s. Response rates varied greatly (5–20%) but responses were largely short-lived (median 4–6 months) and survival barely reached 1 year [111, 112]. Dacarbazine is typically given as an intravenous infusion at 200 mg/m^2 for 5 days and the commonest side effects comprise pancytopenia, nausea with vomiting and anorexia.

Temozolomide is an oral analogue of dacarbazine, which is approved for malignant brain tumours. It was also tested in metastatic melanomas instead of dacarbazine in two large phase III trials and showed similar efficacy [113, 114]. Given its oral formulation, temozolomide can be considered a substitution for dacarbazine provided that its cost can be covered through health insurance.

Further chemotherapeutics, e.g. platinum compounds and taxanes, either alone or in combination, have shown only modest activity and have been not further explored.

Two phase II trials analysed the addition of the vascular endothelial growth factor (VEGF) inhibitor bevacizumab to

either carboplatin or paclitaxel (BEAM trial) or to temozolomide (SAKK 50/07) [115]. The rationale for treating with a VEGF inhibitor is based on the correlation of increased VEGF expression by melanoma cells and/or elevated VEGF serum levels with poor outcomes. Furthermore, VEGF seems to be associated with high LDH levels, which is also a marker of poor prognosis [116–118]. In the randomised BEAM trial, patients received carboplatin-paclitaxel (CP) with or without bevacizumab. Although bevacizumab did not improve the outcome in the intent-to-treat population, survival in the subgroup of high-LDH patients was longer in the bevacizumab arm [119].

Similarly, the SAKK 50/07 single-arm, phase II study analysed the combination of temozolomide and bevacizumab as a first-line treatment in metastatic melanoma and showed a similar survival of LDH-high and LDH-low patients, despite the worse prognosis of the former [115].

In conclusion, chemotherapy has a very limited role in the modern era of melanoma treatment but could still be considered as a last-line option or as a backbone for upcoming clinical trials, e.g. in patients with high LDH.

New combinations, new options

Since the evolution of melanoma therapy is based on immunotherapy and targeted therapy, including BRAF, MEK and multikinase inhibitors, such as lenvatinib, multiple combination strategies are in development.

Recent results of large clinical phase III trials in stage IV patients investigating anti-PD1 inhibitors in combination with talimogen laherparepvec, pegylated IL-2 or lenvatinib did not demonstrate increased clinical benefit in the first-line setting despite some promising phase II data with the pembrolizumab and lenvatinib combination in a PD1-resistant stage IV population [120].

Nevertheless, there are multiple new combinations under investigation. In advanced disease, T-cell-engaging molecules, with tebentafusp as the first-in-class drug, have the potential to improve the treatment repertoire. Tebentafusp and similar molecules targeting peptides derived from gp100 or PRAME in the context of HLA-A2 can be safely combined with immunotherapy, and phase II/III clinical trials have been initiated. In addition, bispecific antibodies and antibody-drug conjugates are promising candidates under investigation in early clinical trials.

Recently, the first autologous tumour-infiltrating lymphocyte product lifileucel was approved by the FDA for the treatment of patients with metastatic or unresectable melanoma who progressed on immunotherapy and BRAFi/MEKi. In a phase II single-arm trial, lifileucel showed an ORR of 36%. The safety profile was consistent with the known toxicities of cyclophosphamide, fludarabine and IL-2 [121].

Recommendation: TIL- treatment should be evaluated for young fit patients after the failure of standard treatment in specialised centres. *Recommendation B, Level of evidence IIA.*

Brain metastasis

Radiotherapy

Melanoma patients with brain metastases should be managed by a multidisciplinary team of melanoma specialists that considers the optimal combination and sequencing of surgery, radiotherapy and systemic therapy. *Recommendation D, level of evidence IV.*

Stereotactic radiosurgery

Stereotactic radiosurgery (SRS) provides high rates of local control in patients with melanoma brain metastases [122–126] and has proven effective in controlling a small number (<4) of melanoma brain metastases with a total tumour volume of <5 cm^3 [127–129]. Notably, stereotactic radiosurgery is also effective for patients with 5–10 brain metastases, presenting a viable, less invasive alternative to whole-brain irradiation (WBRT) with fewer side effects [130]. Studies have even supported the efficacy of stereotactic radiosurgery for patients with 11–20 melanoma brain metastases [131]. Given that, in the indicated studies, patients also received systemic therapy, it is difficult to draw conclusions on the extent of benefit from radiotherapy alone. A systematic review reported a 1-year local control rate of 86% across 31 studies [132]. High-dose stereotactic radiosurgery, with a single fraction of about 24 Gy is associated with local control rates above 90% for melanoma brain metastases [133, 134]. For lesions >4 cm, fractionated stereotactic radiotherapy (SRT) is preferred, with specific dosing regimens based on lesion size [135].

Recommendation: In cases of >10 asymptomatic brain metastases, upfront systemic treatment without stereotactic radiosurgery or stereotactic radiotherapy should be prioritised. *Recommendation A, level of evidence I.*

Stereotactic radiosurgery or stereotactic radiotherapy for 1–10 asymptomatic brain metastases should be discussed in multidisciplinary tumour boards. *Recommendation B, level of evidence I*

Additional stereotactic radiosurgery or stereotactic radiotherapy for 1–10 asymptomatic brain metastases for patients not qualifying for double immunotherapy or BRAFi/MEKi, or for patients with progression after first-line treatment, is recommended. *Recommendation A, level of evidence I.*

Symptomatic patients need to be discussed in multidisciplinary tumour boards. Symptomatic brain metastases with unambiguous sensory-motor deficits and/or intracranial pressures should be treated locally with surgery, radiosurgery or a combination of both, regardless of systemic treatment. In cases of oligosymptomatic patients with planned BRAFi/MEKi treatment, radiosurgery could be delayed for 4–6 weeks upon thorough multidisciplinary discussion. *Recommendation D, level of evidence IV.*

There is no evidence for routine prophylactic use of steroids before/during/after stereotactic radiotherapy and this practice is strongly discouraged in asymptomatic patients. *Recommendation D, level of evidence IV.*

Whole-brain radiation is discouraged because of neurocognitive side effects, as it shows no survival benefit and re-

duces neurocognitive function. *Recommendation A, level of evidence I.*

Stereotactic radiotherapy of the surgical cavity

Several randomised trials demonstrated the benefit of adding stereotactic radiosurgery after resection of a limited number of brain metastases, although these trials did not address the question specifically for melanoma patients [136, 137]. Mahajan et al. demonstrated in a phase III randomised trial that adding stereotactic radiotherapy to the surgical cavity significantly enhances 12-month local control rates in all histologies, including melanoma (72% vs 43%, HR: 0.46, p <0.015) [137]. No overall survival difference was noted between groups. A retrospective series of patients with resected melanoma brain metastases showed similar control rates of above 70% [138, 139].

Adjuvant stereotactic radiosurgery for resection cavities is recommended [137] and also for smaller resection cavities [135].*Recommendation B, level of evidence I.*

Safety of radiation therapy

A systematic review involving 1421 patients found a 2.4% rate of significant treatment-related toxic effects, with a higher incidence of complications (6.2%), especially among patients with melanoma brain metastases, showing a higher rate (33.3%) in a specific subgroup [140]. Another study of 6384 patients reported no significant skin toxicities, bleeding, or clinically impactful radiation necrosis from stereotactic radiosurgery, even when combined with systemic therapies [141]. Concurrent use of immunotherapy and stereotactic radiosurgery did not increase radiation necrosis [142, 143].

Stereotactic radiosurgery with concurrent immunotherapy and BRAFi/MEKi appears to be safe, though prospective trials are lacking. *Recommendation B, level of evidence IV.*

Neurosurgery

Surgery offers high local control rates (80–93%) in patients with melanoma brain metastases [144–147]. Patchell et al. highlighted the benefits of surgery in reducing recurrence and extending survival compared to radiotherapy in a randomised trial [144, 148–150]. Surgery effectively relieves symptoms and improves functionality in symptomatic patients or those with neurological deficits. Complication rates are estimated to be 6–8% [150, 151]. A multidisciplinary approach is advised for melanoma brain metastases management, aside from urgent cases [152].

Exclusive systemic treatments

BRAFi/MEKi treatment resulted in a 58% intracranial response in *BRAF* V600-mutant, untreated, asymptomatic melanoma brain metastases [153]. Anti-PD-1 monotherapy yields a 20% response in systemic treatment-naïve patients with active brain metastases [154, 155].

Combining ipilimumab and nivolumab induces a 55% response in similar patients [155, 156].

Recommendation: Combination treatment with ipilimumab and nivolumab is the recommended first-line treatment for asymptomatic patients not requiring corticosteroids. *Recommendation B, level of evidence II.*

Combination of radiotherapy and systemic treatments

Combining stereotactic radiosurgery with immunotherapy or targeted therapy shows a survival advantage over stereotactic radiosurgery alone in several studies [157–165]. A systematic review and meta-analysis of observational studies suggest that immunotherapy, or immunotherapy plus BRAFi/MEKi with stereotactic radiosurgery, could lead to better outcomes [166], though no significant improvement in overall survival was noted for stereotactic radiosurgery versus whole-brain irradiation, or stereotactic radiosurgery plus BRAFi/MEKi versus stereotactic radiosurgery alone [167–171]. Targeted therapy alongside stereotactic radiosurgery has been found to enhance survival and control in melanoma brain metastases [172, 173]. The ELEKTRA study further indicates that sequential stereotactic radiosurgery followed by immunotherapy might improve immunologic responses and outcomes [174]. The optimal sequence of RT and immunotherapy is currently being prospectively investigated (clinical trial ABC X NCT03340129).

Leptomeningeal disease

Diffuse leptomeningeal disease is associated with a dismal prognosis. Recently, a phase I/IB trial from the MD Anderson Cancer Centre with concurrent intrathecal and intravenous nivolumab demonstrated encouraging results with a mOS of 4.9 months and 26% overall survival rates at 52 weeks [175]. Whole-brain irradiation can be discussed in palliative situations for symptom stabilisation [176]. In a randomised trial of patients with breast and non-small cell lung cancer with leptomeningeal disease, craniospinal irradiation offered superior outcomes compared with whole-brain irradiation [177].

Recommendation: Melanoma patients with leptomeningeal disease should be discussed at multidisciplinary tumour boards. Inclusion in a clinical trial or systemic treatment is the treatment of choice in patients with good performance status (ECOG 0–1).

Intrathecal application of immune checkpoint inhibitors should be performed, ideally in the context of clinical trials in specialised centres. *Recommendation D, Level of evidence IV.*

Whole-brain irradiation may be offered to patients with leptomeningeal disease with the goal of symptom stabilisation in cases where no clinical trials or CNS-active treatments are available, taking into account its toxicity profile. *Recommendation D, level of evidence IV.*

Craniospinal irradiation could be more effective than whole-brain irradiation for treating leptomeningeal disease and should be preferred when radiotherapy is indicated. *Recommendation B, level of evidence II*

Precision oncology biomarkers

Despite intensive research, no predictive biomarkers exist for the management of melanoma aside from *BRAF* mutations for BRAFi/MEKi treatment. Usual immunotherapy predictive biomarkers, such as tumour mutational burden or PD-L1, have very limited predictive power in the advanced clinical setting. In the adjuvant setting, IFN-γ signature and tumour mutational burden have been shown to

play a role in identifying patient subpopulations, though confirmatory trials are missing [178, 179].

Patients who have failed all standard therapies can be proposed for inclusion in precision oncology programs where personalised targeted therapy, immunotherapy or chemotherapy can be proposed based on advanced omics approaches, including genomics, transcriptomics or proteomics. Discussion at institutional molecular tumour boards is recommended. Inclusion in clinical trials or off-label treatment recommendations can be made based on such analyses.

Follow-up

The aims of melanoma follow-up are to identify a local or distant relapse as early as possible and to improve early detection of subsequent melanoma [152, 180]. Additionally, follow-up after melanoma diagnosis should include offering psychosocial support, providing education on primary prevention and regular self-examination of the skin and peripheral lymph nodes. A recent randomised clinical trial revealed that patient-led surveillance after localised melanoma should be considered in patient care [181]. Patients need to be informed that they and their family members are at increased risk for (subsequent) melanoma. The mean absolute risk of developing a subsequent primary melanoma is 8.0% ± SD 4.1% within 5 years after the first primary melanoma, and 46.8% ± 15.0% after the second [152]. However, the diagnosis of multiple primary melanomas seems to not affect patients' overall survival because of earlier diagnosis of the subsequent melanomas [182].

The following assessments are recommended in an individual risk-adapted follow-up [180, 183]:

- Careful anamnesis regarding symptoms
- Clinical and dermatoscopic examination of the total skin, including the scalp and genital and oral mucosa
- Palpation of the scar, in-transit region(s) and peripheral lymph nodes
- Facultative blood testing for S100/LDH
- Locoregional lymph node ultrasound
- Whole-body imaging

The first 3 years after the excision of the primary melanoma are the most important, as 80% of all metastases occur during this period [184]. After risk-adapted follow-up of melanoma patients over a period of 10 years, lifelong surveillance with self-examination and annual full-body examination is generally recommended.

Despite various attempts to achieve international consensus on follow-up guidelines, different follow-up recommendations in melanoma exist worldwide because of a lack of randomised trials [185]. Our proposed schedule of follow-up examinations for melanoma in Switzerland is presented in table 2.

Thin cutaneous melanomas with a Breslow thickness of less than 0.8 mm (pT1a) have only a small risk of relapse and thus no imaging is recommended. Even though some authors support a limited follow-up of 1 year, these patients can nevertheless benefit from follow-up by early detection of sequential melanoma in the first years [180]. Since local, in-transit/satellite and regional lymph node metastases can be detected by ultrasound, it should be routinely performed in all patients except pT1a as the only imaging or alternating with PET-CT examinations [186]. To detect distant metastases in patients with stage IIC and III melanoma, whole-body imaging, preferably with PET-CT or CT and MRI, is suitable.

With new adjuvant therapy options on the horizon, whole-body imaging may soon be extended to stage IIB. Brain MRI should be performed at 6–12 monthly intervals in stage IV patients and at 3-monthly intervals in M1d patients [187]. However, the indication for brain MRI in stage IIC–III needs to be individually discussed by considering the clinical benefit for asymptomatic patients [188]. Rising blood levels of S100B may be a marker of melanoma progression (sensitivity: 86–91%, specificity: 76–91%) and declining concentrations may indicate treatment response in stage IV [189–191]. The pitfalls of serum S100B are false-negative results in patients with a low tumour load and false-positive results in patients with associated comorbidities (e.g. cardiovascular diseases, obesity, chronic kidney disease) warranting cautious re-evaluation [192]. Recent studies underscore the potential implications of ctDNA detection in blood, mainly for patients under systemic treatment in guiding therapeutic decisions for both immunotherapy and targeted therapy agents [193]. Its role in early stages is not yet clear. In non-resected stage IV melanoma patients, the frequency and extent of the follow-up must be individually adjusted depending on symptoms, examinations, and therapy.

For the intermediate group of melanocytic lesions, an individualised follow-up should be based on risk factors. In cases with germline mutations, we recommend including

Table 2:
Recommended follow-up intervals by stage (in months). A blood test for S100 is optional in follow-up care. Research programs for reliable blood markers, such as ctDNA, should be encouraged in the follow-up.

AJCC stage	Clinical dermatological examination				Locoregional lymph node ultrasound			PET-CT and, if applicable, MRI		
Years	1–3	4–5	6–10	>10	1–3	4–5	6–10	1–3	4–5	6–10
IA (pT1a)*	6–12	12	12	12	–	–	–	–	–	–
IA (pT1b)**, IB–IIA	3	6	12	12	12	12	–	–	–	–
IIIA	3	6	12	12	6	12	–	–	–	–
IIB/C and IIIB–D	3	6	12	12	–	12***	–	6	12***	–
IV	Individually				Individually			Individually		

PET: Positron emission tomography; MRI: magnetic resonance imaging.

* pT1a = Breslow <0.8 mm

** pT1b = Breslow <0.8 mm with ulceration, ≥0.8 mm

*** Alternatively, ultrasound and PET-CT

imaging with PET-CT scans in the follow-up because of the risk of other tumours.

Recommendation: Risk-adapted follow-up for detection of recurrence and new primaries should be performed over a period of at least 10 years. *Recommendation B, level of evidence IB.*

Potential competing interests

JM has intermittently been a project-focused consultant for or had advisory relationships with Merck/Pfizer, Merck Sharp and Dohme, Novartis, Roche, Bristol Myers Squibb and Pierre Fabre, and has received travel support from Ultrasun, L'Oreal, Merck Sharp and Dohme, Bristol Myers and Squibb and Pierre Fabre outside the scope of the submitted work.

RD has intermittent, project-focused consulting and/or advisory relationships with Novartis, Merck Sharp and Dhome (MSD), Bristol-Myers Squibb (BMS), Roche, Amgen, Takeda, Pierre Fabre, Sun Pharma, Sanofi, Catalym, Second Genome, Regeneron, T3 Pharma, MaxiVAX SA, Pfizer and Simcere outside the submitted work.

LVM has served as an advisor and/or received speaking fees and/or grants and/or participated in clinical trials sponsored by Almirall, Amgen, Bristol-Myers Squibb (BMS), Canfield, Eli Lilly, Incyte, L' Oreal, Merck Sharp and Dohme (MSD), Novartis, Pierre Fabre, Roche, and Sanofi outside the scope of the current work.

MS, RO and RH report no COI.

YM has served as an advisor for and received travel grants from Roche, BMS, Regeneron, Sanofi, and MSD outside of the current work.

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PB has participated in the data-safety-monitoring board or advisory boards from MSD and Merck outside the scope of the current work.

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NL acts as a scientific advisor and consultant for Medical Microinstruments (MMI).

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