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Guidelines

European consensus-based interdisciplinary guideline for melanoma. Part 2: Treatment – Update 2024

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ABSTRACT

A unique collaboration of multi-disciplinary experts from the European Association of Dermato-Oncology (EADO), the European Dermatology Forum (EDF), and the European Organization of Research and Treatment of Cancer (EORTC) was formed to make recommendations on cutaneous melanoma diagnosis and treatment, based on systematic literature reviews and the experts' experience. Cutaneous melanomas are excised with one to two-centimeter safety margins. For a correct stage classification and treatment decision, a sentinel lymph node biopsy shall be offered in patients with tumor thickness ≥ 1.0 mm or ≥ 0.8 mm with additional histological risk factors, although there is as yet no clear survival benefit for this approach. Therapeutic decisions should be primarily made by an interdisciplinary oncology team ("Tumor Board"). Adjuvant therapies can be proposed in completely resected stage IIB-IV. In stage II only PD-1 inhibitors are approved. In stage III anti-PD-1 therapy or dabrafenib plus trametinib for patients with BRAFV600 mutated melanoma can be discussed. In resected stage IV, nivolumab can be offered, as well as ipilimumab and nivolumab, in selected, high-risk patients. In patients with clinically detected macroscopic, resectable disease, neoadjuvant therapy with ipilimumab plus nivolumab followed complete surgical resection and adjuvant therapy according to pathological response and BRAF status can be offered. Neoadjuvant therapy with pembrolizumab followed by complete surgical resection and adjuvant pembrolizumab is also recommended. For patients with disease recurrence after (neo) adjuvant therapy, further treatment should consider the type of (neo) adjuvant therapy received as well as the time of recurrence, i.e., on or off therapy. In patients with irresectable stage III/IV disease systemic treatment is always indicated. For first line treatment PD-1 antibodies alone or in combination with CTLA-4 or LAG-3 antibodies shall be considered. In stage IV melanoma with a BRAFV600 mutation, first-line therapy with BRAF/MEK inhibitors can be offered as an alternative to immunotherapy, in selected cases. In patients with primary resistance to immunotherapy and harboring a BRAFV600 mutation, this therapy shall be offered as second line. Other second line therapies include therapy with tumor infiltrating lymphocytes and combinations of immune checkpoint inhibitors not used in first line. This guideline is valid until the end of 2026.

Information about the guideline

The European Interdisciplinary Guideline on melanoma was written as a uniform text and then published in two separate but integral parts: Part 1 on diagnosis and Part 2 on treatment. Information about the Guideline is detailed in Garbe et al. Part 1, including the information about societies in charge, financing of the guideline, scope, target population, objectives, methodology, audience and period of validity. The levels of evidence were graded according to the Oxford classification (detailed in Garbe et al. Part 1). Recommendations were based on the level of best quality available evidence. The grades of recommendation were classified as follows: (A) strong recommendation - syntax: 'shall'. Based on good-quality evidence; (B) recommendation - syntax: 'should'. Based on inconsistent or limited quality evidence; (C) recommendation pending - syntax: 'may/can'.

Disclaimer

Medicine is subject to a continuous development process. Therefore, all statements, in particular on diagnostic and therapeutic procedures, can only correspond to the scientific knowledge current at the time of printing of this guideline. The attending physician invoking these guideline recommendations must consider scientific progress since the publication of the guideline

Scope

This guideline has been written in order to assist clinicians in treating patients with invasive cutaneous and metastatic melanoma. This publication was conceptualized mainly due to advances in the medical treatment of patients with cutaneous melanoma, which justify a newer multidisciplinary therapeutic strategy. The use of these guidelines in clinical routine should improve patients' care.

1. Surgical therapy

1.1. General principles

Effective adjuvant and neoadjuvant therapies are presently changing the significance of surgery in the management of cutaneous melanoma, particularly the role of sentinel lymph node biopsy, the extent of lymph node dissections or the removal of distant metastases [1].

Yet, the treatment of primary melanoma remains surgical excision [2–4]. For diagnostic purposes, an excisional biopsy with a minimum clinical margin (1–3mm) is preferred, both to give the dermatopathologist/pathologist an optimal specimen and to allow evaluation of the excision margins for residual tumor. Incisional biopsies should not be performed when an excisional biopsy is technically possible. Such procedures may result in diagnostic error because of incomplete sampling and may compromise the analysis of architectural features or the estimation of Breslow thickness. On occasions incisional biopsy may be necessary to confirm the diagnosis, such as when dealing with a large head and neck lentigo maligna, or with acral or mucosal melanoma. While only one recent analysis found a significantly ($p = .001$) lower 5-year overall survival (OS) for melanomas diagnosed by incisional as compared to shaving biopsies [5], all other large studies did not prove any evidence that either incisional or shaving biopsies worsen prognosis as compared with immediate complete excisional biopsy [6–8].

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Recommendation 1.

Primary excision	Consensus based recommendation
GCP	When melanoma is suspected, the whole lesion should be completely excised with a narrow (1-3mm) margin to perform histological diagnosis. Incisional biopsies can be performed on large lesions such as lesions on the face (e.g., lentigo maligna), acral lesions and on the genitalia.
	Consensus rate: 100% (21/21)

Recommendation 2.

Avoidance of non-surgical treatments	Consensus based recommendation
GCP	If melanoma cannot be excluded, blind destructive treatments such as laser, cryotherapy or topical drugs shall not be used.
	Consensus rate: 100% (21/21)

1.2. Primary melanoma

Excision with a safety margin remains a standard of care in melanoma patients. The current recommendations are based on both prospective, randomized studies and international consensus guidelines [9–13].A randomized, open-label multicenter clinical trial comparing 1 cm versus 3 cm margins in patients with primary cutaneous melanoma on the trunk and limbs suggested that a 1 cm excision margin is inadequate for cutaneous melanoma with Breslow thickness greater than 2 mm [14]. A meta-analysis showed that there is a statistically significant worse melanoma-specific survival (MSS) with narrow (1–3 cm) than with wider margins (3–5 cm) with no treatment effect on recurrence-free survival (RFS) [15]. However, with regard to MSS only 4 trials were eligible and the hazard ratio in favor of wider margins was largely affected by the positive trial of Hayes et al (3 cm versus 1 cm) [14], while another study comparing 4 cm versus 2 cm did not show any statistical difference in thicker melanomas [16]. A further meta-analysis involving 4579 patients' data from seven randomized clinical trials revealed no significant difference between narrow (1–2 cm) and wide (3–5 cm) excision margins in locoregional or distant recurrence, metastasis, death, or death due to melanoma [17]. Moreover, the usefulness of margins above 1 cm still remains unclear in patients with stage II melanoma (pT2b-pT4b, AJCC 8th edition). An ongoing clinical trial comparing 1 cm versus 2 cm margins (MelMart-II) is expected to offer valuable data about this.

Even though a slight variation is observed among guidelines, margins wider than 2 cm are not recommended even in cases of thick primary tumors. The recommendations below are in concordance with the American, United Kingdom and Australian references. In invasive melanomas, the depth of excision should include the subcutaneous tissue. The definitive surgical excision should be performed preferentially within 4–6 weeks of initial diagnosis and simultaneously with the sentinel lymph node biopsy (SLNB).

Recommendation 3 [18-20].

Safety margins for secondary excision (re-excision)	Evidence based recommendation
GCP	In the case of primary melanoma, a subsequent excision should be performed to minimize the risk of local recurrences. The following safety peripheral surgical margins* are recommended: • in situ: 5 mm • ≤ 2mm tumor thickness: 1cm • > 2mm tumor thickness: 2cm Larger excisions are not recommended.
	Guideline adaptation [18-20]
	Consensus rate: 95% (20/21); 1 abstention.

Recommendation 4.

Safety margins for secondary excision (re-excision) in special anatomic locations	Evidence based recommendation
GCP	Narrower margins for re-excision may be considered for special anatomic locations in order to preserve function, maintain cosmesis and to allow reconstruction, particularly in facial, acral and genital lesions.
	Guideline adaptation [18, 19]
	Consensus rate: 100% (21/21)

1.3. Lentigo maligna

Lentigo maligna is a slowly growing melanoma in situ, which occurs typically in UV-exposed areas like the face. A Cochrane review about interventions in melanoma in situ failed to find randomized clinical trials of surgical interventions aiming to optimize margin control (square method, perimeter technique, 'slow Mohs', staged radial sections, staged "mapped" excisions, or Mohs micrographic surgery, which are the most widely used interventions recommended as first-line therapy) [21]. A retrospective study including patients with lentigo maligna melanoma treated through staged surgery with immunohistopathological control of lateral margins showed a higher clearance and a lower recurrence rate than wide excisions [22]. A single-center retrospective study of patients with lentigo maligna concluded that surgical margins of 0.5 cm are inadequate for the treatment of a considerable number of lesions on the head. "Slow Mohs" using routinely stained paraffin-embedded sections was shown to be the treatment of choice in such cases, particularly for recurrent lesions or those with poorly defined borders [23]. Because of unpredictable subclinical extension of the adjacent intraepidermal component, the management of lentigo maligna melanoma may range from a 5 mm margin to wider margins (up to 10 mm). For larger lentigo maligna and lentigo maligna melanoma, microscopically controlled surgery is a recommended option and usually performed following any of the technical variations developed (frozen section Mohs micrographic surgery, paraffin-embedded, "Slow Mohs", 3D-histology) [24]. A systematic review including 27 publications found

a 1.35 % recurrence rate of Mohs micrographic surgery with follow-up times ranging from 1 month – 5 years [25].

As for non-surgical interventions, high-quality evidence does not support the use of imiquimod as primary therapy in non-selected cases [21,26]. However, several retrospective analyses and phase II trials support a role for topical imiquimod as an alternative to surgery in selected cases not eligible for surgery or radiotherapy [27], as well as for incompletely excised tumors or as an adjuvant option for those treated through narrow margins. Further, a randomized phase 3 trial evaluated the efficacy and safety of imiquimod versus radiotherapy for patients with lentigo maligna. Patients (n = 126) with lentigo maligna not suitable for surgery were randomly assigned (1:1) to imiquimod or radiotherapy. The primary endpoint was treatment failure within 24 months. Median follow-up was 27 months. Recurrence at 24 months occurred in 10.5 % of imiquimod patients and 24.0 % in radiotherapy (OR 2.68, p = 0.063). In reflectance confocal microscopy follow-up, radiotherapy had higher failure rates (25.0 % vs. 8.7 %; OR 3.50, p = 0.033). Atypical round cells were linked to higher radiotherapy failure (p = 0.035). No differences in symptoms or QoL were found between treatments [28].

Recently, a 95 % cure rate after a mean follow-up of three years has been reported with adjuvant imiquimod following conventional surgery with narrow margins [29]. The complete response rate to imiquimod treatment is in the range of 75 % to 88 % [26]. Pre-treatment mapping biopsies, or in-vivo reflectance confocal microscopy can be used to assess the extent of the lesion [30].

1.4. Acral and mucosal melanomas

Lentiginous acral and mucosal melanomas have often poorly defined margins and are multifocal leading to discrepancies between the clinically visible and histopathologic margins. Local recurrences are more frequent. Therefore, surgical excision is usually performed with increased safety margins (at least 1 cm) or by narrow margins with micrographic control (e.g., Mohs' technique and variants) [31–33]. The micrographic technique is intended to conserve tissue especially on the hands and feet and also attempts to preserve the digit function as an alternative to amputation in subungual acral melanomas [34].

Recommendation 5.

Microscopically controlled surgery	Consensus based recommendation
GCP	In some melanoma subtypes, such as lentigo maligna melanoma, and nail unit melanomas, microscopically controlled surgery can be used to spare tissue and to ensure complete resection.
	[31-33]
	Consensus rate: 95% (20/21) 1 abstention

1.5. Sentinel lymph node biopsy

SLNB involvement is an independent prognostic factor for MSS and considered a standard staging procedure [35]. It also may improve the accuracy of staging when added to clinicopathological features of the primary tumor [36] and provides superior net benefit when added to a model with primary tumor staging factors alone in estimating patient risk for 5-year melanoma specific death [37]. Recent guidelines and reviews recommend SLNB in clinically node-negative melanoma with Breslow thickness ≥ 1.0mm or ≥ 0.8mm and additional risk factors (e.g. ulceration, ≥1 mitosis/mm^2, microsatellites) [38,39]. Multicenter studies have shown that despite a slight increase in RFS, and a long term regional control in up to 80 % of patients [40] in patients undergoing SLNB, there is no impact on OS [41–43]. However, a positive sentinel lymph node will upstage patients with clinically negative nodes and make them eligible for adjuvant systemic therapy with either immune checkpoint inhibition (see 3.2) or targeted treatment (see 3.3). The availability of approved immune checkpoint inhibitors for adjuvant treatment also in Stage IIB/C disease (see 3.1.) has challenged the value of SLNB for treatment decision making in advanced primary tumors. However, in these clinical settings, ongoing clinical trials on neo-adjuvant therapy in patients with high-risk primary tumors will shed light on the definitive role of SLNB in this subgroup of patients. In the meanwhile, the role of SLNB in these patients rather helps to discuss the alternative option of adjuvant targeted therpay in patients with BRAF mutated tumors, if case they have a positive SLNB.

Recommendation 6 [44,45].

Sentinel lymph node biopsy	Evidence based recommendation
Level of recommendation A	For a correct stage classification and treatment decision, a sentinel lymph node biopsy shall be offered in patients with tumor thickness ≥ 1.0 mm or ≥ 0.8 mm with additional histological risk factors.
Level of evidence: 1a	[44, 45]
	Consensus rate: 95% (21/22), 1 abstention

1.6. Procedure in patients with negative sentinel lymph node biopsy

No further lymph node surgery is required.

1.7. Procedure in patients with micrometastases in sentinel lymph node

Complete lymph node dissection (CLND) has previously been routinely offered to patients having micrometastasis of the SLN. The results of the DeCOG (German Dermatologic Cooperative Oncology Group) and MSLT-II (Multicenter Selective Lymphadenectomy Trial) clinical trials led to the revision of the role of lymphadenectomy in patients with sentinel lymph node metastasis. In patients with microscopic sentinel lymph node metastases both studies failed to show a survival difference between CLND and observation. In the DeCOG study, 68 % of patients in the observation arm and 65 % in the CLND arm were free of distant metastases after 5 years of follow-up [46,47]. In the MSLT-II, 86 % of the patients in both study groups (CLND or observation) were alive after 3 years [43]. Moreover, in the MSLT-II study, the percentage of patients with non-sentinel-node metastases was 20 % at 5 years. Consequently, 80 % of the CLND performed might have been avoided [43].

Considering the previous results, in patients with sentinel lymph node micro-metastasis, CLND shall be abandoned [38]. After earlier retrospective studies suggested effectiveness of adjuvant therapy in sentinel-positive patients foregoing CLND [48,49] several randomized, controlled trials have meanwhile proven its benefit in Stage III melanomas (see 3.2).

Recommendation 7 [50].

Management of micro-metastasis	Evidence based recommendation
Level of recommendation A	In patients with sentinel lymph node micro-metastasis, complete lymphadenectomy shall no longer be performed. Indication for adjuvant systemic therapy should be discussed.
Level of evidence: 1a	[43, 46, 47, 50-52]
	Consensus rate: 100% (22/22)

1.8. Clinically identified regional lymph node metastases

See neoadjuvant therapy below (4.1).

1.9. Regional satellite and/or in-transit metastases

See neoadjuvant therapy below (4.3).

1.10. Distant metastases

Patients with oligo-metastatic disease should be given first line systemic therapy. If technically feasible and reasonable, complete surgical removal of distant metastases may be an option for selected patients, including those with a long disease-free interval and with LDH and protein S100B in the normal range, in case of progressive disease (without new lesions) or lack of response (oligo-residual disease).

Patients with stage IV melanoma with no evidence of disease are eligible for adjuvant PD-1 based therapy [52,53]. See also Section 3.2 - Adjuvant immunotherapy with CTLA-4 and PD-1 antibodies in stage III and resected stage IV disease.

There is no evidence that debulking procedures improve survival. In some circumstances there is a value for palliation of symptoms.

Recommendation 8 [54].

Surgical treatment of distant metastases	Evidence based recommendation
Level of recommendation B	In oligo-metastatic disease systemic therapy should be given first line.
	Guideline adaptation [54]
	Consensus rate: 100% (23/23)

Recommendation 9.

Surgical treatment of distant metastases	Evidence based recommendation
Level of recommendation C	In case of progressive disease or absence of response to systemic therapy, resection or destructive procedures can be considered.
	Guideline adaptation [54]
	Consensus rate: 100% (23/23)

2. Radiotherapy

2.1. Primary melanoma

Radiotherapy of the primary tumor is rarely indicated. However, in elderly or frail patients or where the surgical procedure will lead to severe disfigurement, radiotherapy can be applied with curative intent. This could be considered for lentigo maligna fulfilling these criteria [55].

2.2. Regional lymph nodes

There is no established role for adjuvant radiotherapy of draining lymph nodes after excision of the primary melanoma. Adjuvant radiotherapy after lymphadenectomy has been evaluated in a randomized clinical trial [56], proving the efficacy of radiotherapy in terms of increased locoregional control, but with no impact on survival. Furthermore, the increased locoregional control was accompanied by significant toxicity, with 22 % of the patients receiving radiotherapy, developing grade 3–4 toxicity [57].

2.3. Oligo metastatic disease

In patients with oligo metastatic disease, ablative radiotherapy, e.g., stereotactic radiosurgery (STR) or equivalent, represents a treatment alternative to surgery in cases where surgical access is associated with high risk of significant surgical complications.

2.4. Skin metastases

In patients with in-transit metastases, which are too extensive for a surgical approach, radiotherapy may be an alternative [58].

2.5. Bone metastases

Radiotherapy is effective to palliate patients with bone metastases. The response rate (complete response and partial symptom control) is 67–85 % [59–62]. The major indications for radiotherapy in these cases are pain, loss of structural stability (fracture risk), and compression of the spinal canal with or without neurological symptoms.

2.6. Brain metastases

See below – Local therapy in patients with brain metastases.

3. Adjuvant therapy

A summary of the trials investigating systemic therapy in the adjuvant setting is available in Table 1.

3.1. Adjuvant therapy in stage II disease

Therapy with pembrolizumab 200 mg every 3 weeks for 1 year was compared against placebo in patients with stage IIB and IIC melanoma in the Keynote 716 trial. In the third interim analysis there was a statistically significant RFS benefit for patients treated with pembrolizumab versus placebo- (HR: 0.64) [63].The final distant metastases free survival (DMFS) analysis after a median follow-up of 39.3 months showed that the estimated 36 months DMFS rate was 84.4 % for pembrolizumab and 74.7 % for placebo (HR: 0.59). The median RFS rate was 76.2 % and 63.4 %, respectively, (HR: 0.62). The benefits were consistent across all prespecified subgroups, including stage IIB and stage IIC melanomas [64]. Regarding safety, grade $\geq$ 3 drug-related AEs occurred in 17.2 % of the patients receiving pembrolizumab compared to 5.1 % receiving placebo. Treatment discontinuation associated with AE was seen in 15.9 % and 2.5 % of the patients, respectively. Immune-mediated AEs, mostly grade 1 and 2, occurred in 37.9 % of the patients in the pembrolizumab arm compared to 9.5 % in the placebo arm. The most commonly reported immune-mediated AE were hypothyroidism (17.2 % vs 3.7 %) and hyperthyroidism (10.6 % vs 0.6 %).

The CHECKMATE 076, a randomized, double-blinded, phase 3 trial, evaluated adjuvant nivolumab in patients with fully resected stage IIB/C melanoma. Patients were randomly assigned (2:1 by tumor category) to treatment with nivolumab 480 mg or placebo every 4 weeks for 12 months. At 7.8 months of minimum follow-up, nivolumab significantly improved RFS compared to placebo (HR: 0.42) [65]. The 12-month RFS rate was 89.0 % for nivolumab and 78.4 % for placebo. The benefit was observed across all subgroups. DMFS was also improved with nivolumab therapy (HR: 0.47). There were 10.3 % CTCAE grade 3/4 toxicities in the nivolumab group compared to 2.3 % in the placebo group. One treatment-related death (0.2 %) occurred with nivolumab. The study led to the approval of nivolumab in this indication, by FDA and EMA.

An unpublished study update at the Annual Meeting of the Society of Melanoma Research (SMR) in November 2023 revealed the same magnitude of a benefit for RFS (HR: 0.53) as well as for DMFS (HR: 0.56) after 2 years of follow-up.

A large-sized randomized, placebo-controlled trial was conducted to

Table 1
Key parameters of adjuvant trials with Immune checkpoint Inhibitors or BRAF and MEK inhibitors.

Trial	Treatment	Median FU	Population	HR for RFS/ DMFS	HR for OS	% AE Grade > 3 (treatment vs comparator)
Keynote 716[64, 79]	Pembrolizumab vs placebo	39.4 months	IIB/IIC	0.62/0.59	NA	16/4
Checkmate 76 K [65]	Nivolumab vs placebo	7.8 months	IIB/IIC	0.42/0.47	NA	10.3/23.
Columbus AD[66]	Encorafenib + binimetinib vs placebo	Premature discontinuation due to recruitment issues	IIB/C	Not evaluable	Not evaluable	Not evaluable
EORTC 18071[$] **Checkmate 029** [80,81]	Ipilimumab 10mg/kg vs placebo	6.9 years	IIIA (>1 mm metastases in SLN)/B/C	0.75/0.76	0.73	54.1/26.2
Checkmate 238[52, 70]	Nivolumab 3mg/kg vs Ipilimumab 10mg/kg	62 months	IIIB/C-IV	0.72/0.79	0.86	14.4/45.9
EORTC 1325/ Keynote 054[71, 72]	Pembrolizumab 200 mg vs placebo	6.9 years	IIIA (>1 mm metastases in SLN)/B/C	0.63/0.64	NA	14.7/3.4
BRIM 8[82]	Vemurafenib vs placebo	Cohort 2 - 33·5 months; cohort 1 - 30·8 months	Cohort 2 IIIC; cohort 1 IIIA (>1 mm metastases in SLN)/B	Cohort 2 = 0·80; cohort 1 = 0.54	NA	57/15
COMBI-AD[51,83]	Dabrafenib + Trametinib vs placebo	8.33 years for dabrafenib + trametinib; 6.87 years for placebo	IIIA (>1 mm metastases in SLN)/B/C	0.52/0.56	0.80: BRAF V600E 0.75; BRAF V600K 1.95	41/14

[$]approved only by the FDA; FU = follow-up; RFS = relapse free survival; DMFS = distant metastases free survival, OS = overall survival; AE = adverse events; NA = not available

show a superiority of encorafenib and binimetinib in stage IIB/C. The COLUMBUS-AD/EORTC 2139 trial [66] was, however, prematurely stopped due to a slow recruitment. The main reason was the comparator arm ("placebo") because during the initiation of this trial pembrolizumab and later also nivolumab became available as approved standards of care in this indication.

3.2. Adjuvant immunotherapy with CTLA-4 and PD-1 antibodies in stage III and resected stage IV disease

Ipilimumab: EORTC 18071/Checkmate 029 [67] compared the CTLA-4 blocking antibody ipilimumab 10mg/kg with placebo in patients with stage IIIA (>1 mm SLNB metastasis)/B/C (AJCC 7th edition) [68]. With a median follow-up of 6.9 years, the HR for RFS, DMFS and OS was 0.75 (95 % CI: 0.63–0.88; $P < 0.001$), 0.76, (95 % CI:.64–0.90; $P = 0.002$) and 0.73 (95 % CI: 0.60–0.89; $P = 0.002$), respectively. The benefit observed in the ipilimumab group was durable with an 8.7 % absolute difference at 7 years for OS [69]. Adjuvant ipilimumab was approved by the US-FDA but not by EMA. Ipilimumab is no longer the standard of care in the adjuvant setting, because the survival benefit is significantly inferior to PD-1 monotherapy.

Nivolumab: adjuvant therapy with nivolumab 3mg/kg every 2 weeks for one year was compared to ipilimumab 10mg/kg in the Checkmate 238 trial [70] in patients with completely resected stage IIIB/C-IV (AJCC 7th edition) [68]. After a minimum follow-up of 62 months RFS with nivolumab remained superior to ipilimumab (HR: 0.72). The 5-year rates for RFS were 50 % for nivolumab and 39 % for ipilimumab. The 5-year DMFS rates showed 58 % for nivolumab and 52 % for ipilimumab. The 5-year OS rates were 76 % and 72 %, respectively, but were considered as immature because only 228 of 302 planned events have been observed. Overall survival results showed a non-significant benefit for nivolumab HR 0.86 (95 % CI: 0.66–1.12) which has been most likely impacted by second line therapies. Further, it is important to remember that ipilimumab was an active comparator and that this study included patients with resected stage IV disease [52]. The biomarker analysis showed higher levels of tumor mutational burden (TMB), tumor PD-L1, intratumoral CD8 + T cells and IFNγ-associated gene expression signature as well as lower levels of peripheral serum C-reactive protein as associated with improved RFS and OS with both regimens. As for the safety, grade 3 or 4 adverse events (AE) were reported in 14.4 % of patients in the nivolumab arm compared to 45.9 % of those in the ipilimumab group. Serious adverse events (SAE) of any grade were reported in 17.5 % of patients treated with nivolumab and in 40.4 % receiving ipilimumab.

Pembrolizumab: Pembrolizumab 200 mg every 3 weeks for 1 year was tested against placebo in EORTC1325/Keynote 054 trial [71] in patients with stage IIIA (>1 mm SLNB metastasis)/B/C (AJCC 7th edition). With a median follow-up was 6.9 years, the RFS in the overall population was significantly longer with pembrolizumab (HR 0.63, 95 % CI 0.53–0.74), with 7-year RFS of 50 % vs. 36 % for placebo. Benefits were observed across subgroups, including PD-L1 positive/negative and BRAF mutant/wild-type patients.

DMFS was also prolonged with pembrolizumab (HR 0.64, 95 % CI 0.54–0.76), with 7-year DMFS of 54 % vs. 42 % for placebo.

Progression-free survival 2 was longer in the pembrolizumab group (HR 0.69, 95 % CI 0.57–0.84), with 7-year PRFS2 of 61 % vs. 53 % for placebo [72].

The real measure of this crossover would be a comparison of the OS in those who were treated early in adjuvant compared to those treated later at relapse. Regarding safety, AEs of any grade were reported in 77.8 % of the patients receiving pembrolizumab and in 66.1 % of the patient's receiving placebo. Grade 3,4 or 5 AE occurred in 14.7 % of the patients in the pembrolizumab arm and in 3.4 % in the placebo arm, with one death in the pembrolizumab arm due to myositis.

3.2.1. Pembrolizumab and a personalized vaccine

An open-label, randomized, phase 2b, adjuvant study of mRNA-4157 plus pembrolizumab versus pembrolizumab enrolled patients with completely resected stage IIIB-IV cutaneous melanoma from sites in the USA and Australia [73]. The study aimed to evaluate whether mRNA-4157 (V940), a novel mRNA-based individualized neoantigen therapy, combined with pembrolizumab, improved RFS and DMFS compared to pembrolizumab alone. Patients were assigned 2:1 to receive mRNA-4157 plus pembrolizumab or pembrolizumab. mRNA-4157 was administered intramuscularly (maximum nine doses) and pembrolizumab intravenously (maximum 18 doses) in 3-week

cycles. The primary endpoint was RFS in the intention-to-treat population; 157 patients were assigned to mRNA-4157 plus pembrolizumab combination therapy (n = 107) or pembrolizumab monotherapy (n = 50) and median follow-up was 23 and 24 months, respectively. Recurrence-free survival was not statistically significantly longer with the combination versus monotherapy (HR for recurrence or death, 0.561 [95 % CI 0.309–1.017]; two-sided p = 0·053), with lower recurrence or death event rate (24 [22 %] of 107 vs 20 [40 %] of 50); 18-month RFS was 79 % (95 % CI 69.0–85.6) versus 62 % (46.9–74.3). Most treatment-related adverse events were CTCAE grade 1–2. Grade ≥ 3 treatment-related adverse events occurred in 25 % of patients receiving the combination and in 18 % of patients receiving pembrolizumab alone, with no mRNA-4157-related grade 4–5 events. Immune-mediated adverse event frequency was similar for the combination (36 %) and monotherapy (36 %). The results of this trial led to prospective-randomized, phase-3 trial (V940–001) aiming to demonstrate superiority of the combination over pembrolizumab alone [74].

Ipilimumab and Nivolumab: The Checkmate 915 trial tested a combination of nivolumab at 240 mg every 2 weeks and ipilimumab 1mg/kg every 6 weeks for 1 year against nivolumab 480 mg every 4 weeks in patients with completely resected stage IIIB, C and IV melanoma. This study did not demonstrate a significant difference in its dual endpoints of RFS in the ITT population and in patients with a tumor PD-L1 < 1 % respectively [75]. The combination therapy was associated with more toxicity than nivolumab alone. The rates of grade 3 or 4 AE were 33 % with the combination versus 13 % with nivolumab; 19 % of the patients in the combination arm discontinued therapy due to AE compared to 6 % in the nivolumab arm. Four treatment-related deaths were reported with nivolumab plus ipilimumab and none with nivolumab alone.

In the phase II study ImmuNED, 167 patients with stage IV melanoma with no evidence of disease following surgery or radiotherapy were randomized to receive 1 year of either ipilimumab 3 mg/kg every 3 weeks for 4 doses plus nivolumab, then nivolumab alone, nivolumab or placebo. Although the median time on treatment was only 6.5 weeks in the ipilimumab and nivolumab arm, with treatment discontinuation being mostly due to high grade toxicity, the 4-years RFS rate was 64 % for nivolumab plus ipilimumab, compared to 31 % for nivolumab and 15 % for placebo, resulting in a HR of 0.25 for nivolumab plus ipilimumab over placebo. Median OS was not reached in any treatment group. The HR for OS was significantly in favor of the nivolumab plus ipilimumab compared to placebo (HR 0·41; 95 % CI 0·17–0·99; p = 0·040), but not for nivolumab versus placebo (HR 0·75; 0·36–1·56; p = 0·44 [53].

In the nivolumab plus ipilimumab arm 71 % of patients experienced treatment related Grade 3–4 AEs compared to 29 % in the nivolumab arm; 62 % of the patients discontinued treatment due to AE in the combination arm, compared to 13 % in the nivolumab arm. There were no treatment related deaths. Based on these results nivolumab plus ipilimumab can be offered to selected, high-risk patients with stage IV NED melanoma, although toxicity is a major consideration.

3.3. Adjuvant targeted therapy with BRAF/MEK inhibitors

Vemurafenib: BRIM8 [76] was a trial designed before combined treatment with BRAF/MEK inhibitors became the standard of care for BRAF V600 melanoma. It compared 1 year of treatment with vemurafenib versus placebo in patients with completely resected BRAF V600 mutated melanoma in stages AJCC 7th edition IIC, IIIA/B (cohort I) and IIIC (cohort II). This study did not reach its primary endpoint as defined by the statistical plan, and it is not approved in the adjuvant setting.

Dabrafenib plus trametinib: The COMBI-AD trial compared 1 year of dabrafenib plus trametinib (D+T) with matched placebo in patients with stage IIIA (>1 mm)/B/C melanoma with a BRAF V600E/K mutation.

The OS analysis was published after a median follow-up of 8.33 years for D+T and 6.87 years for placebo [51]. When analyzing the whole BRAF V600 mutated population, there was an OS benefit for D+T over placebo, although the benefit was not significant (HR for death, 0.80; 95 % CI, 0.62 to 1.01; P = 0.06 by stratified log-rank test). Patients with BRAF V600E mutated melanoma had a significant OS benefit (HR for death, 0.75; 95 % CI, 0.58 to 0.96), but patients with BRAF V600K melanoma did not (HR for relapse or death, 0.52; 95 % CI, 0.43 to 0.63). The RFS and DMFS benefit for D+T over placebo was maintained (HR for relapse or death 0.52; HR for distant metastasis or death 0.56). The COMBI-AD OS analysis was done with only 260 of the 597 events included in the initial statistical plan, which may have contributed to the absence of OS benefit.

The D+T combination was associated with pyrexia grade 1–2 in 97 % with chills in 37 %, and grade 3–4 pyrexia in 5 %. Grade 3–4 events occurred in 41 % of the patients, i.e., hypertension (6 %), fatigue (4 %), hepatitis (4 %). Drug related AEs lead to drug discontinuation in 26 % of patients. There were no drug related deaths. The high rate of pyrexia associated with D+T can be reduced by using the management algorithm investigated in the COMBI-A plus trial. The trial met its primary endpoint reducing grade 3/4 pyrexia, pyrexia-related hospitalization, and treatment discontinuation, apparently without compromising therapy efficacy [77].

3.4. Stage IIIA disease

Patients with stage IIIA were either excluded from the trials evaluating adjuvant therapy, e.g., in the Checkmate 238 study, or were included only if there was at least one pathologically confirmed lymph node metastasis > 1 mm, e.g., the Keynote 054 and Combi-AD studies. Besides that, the patients included were classified according to the old AJCC v7 and not the current AJCC v8. Nonetheless, adjuvant therapies are approved in all stage III sub-stages. For stage IIIA with nodal metastasis of less than 1 mm in diameter, the individual risk/benefit of adjuvant therapy is likely to favour observation and should be carefully discussed [78].

3.5. Future directions

Current adjuvant studies in completely resected stage III disease test combinations of various immune-checkpoint inhibitors. Fully recruited and under evaluation is the trial on nivolumab and the LAG3-antibody relatlimab (RELATIVITY-098, NCT05002569) compared to nivolumab alone. Another randomized trial with three treatment arms is using cemiplimab in combination with two different doses of the LAG3-antibody fianlimab versus pembrolizumab alone (HARMONY-adjuvant, NCT05608291).

Finally, the KEYVIBE-010 (NCT05665595) trial compared the vibostolimab, an anti-TIGIT antibody, and pembrolizumab in coformulation with pembrolizumab alone as adjuvant treatment for patients with resected Stage IIB-IV melanoma. The trial completed accrual in March 2024. In a pre-planned analysis, the primary endpoint of RFS was reached. However, a higher therapy discontinuation rate was seen in the coformulation arm compared to pembrolizumab alone, primarily due to immune-mediated adverse events, making it unlikely that the trial would meet a statistically significant improvement in RFS. Following the recommendation of an independent Data Monitoring Committee patients in the vibostolimab and pembrolizumab coformulation were given the option to switch to pembrolizumab monotherapy. Data analysis for this study is still ongoing.

Besides evaluating combination therapies in the adjuvant setting, it is necessary to better select the candidates for such therapies. Using AJCC as a criterion of entry for adjuvant therapy results in two

important limitations: 1) many so-called high-risk patients with stage III, or IIB-C disease are exposed to a treatment although they do not require it, and 2) the AJCC low risk stage I and II A, which account for most of the metastatic deaths because of their very high number, are excluded. The challenge is thus to find biomarkers to identify the patients who will relapse whatever their AJCC group. The ongoing NivoMela trial (NCT04309409) includes patients with resected stage IIA-C and uses a prognostic gene expression signature to limit treatment to a subgroup of patients that is at a higher risk of relapse. Only patients with a positive gene expression score are randomized to treatment with either 12 months of nivolumab or observation, while patients with a negative score are only under clinical observation. Furthermore, the DETECTION Study (NCT04901988) is following 1050 patients with resected Stage IIB/IIC melanoma with regular ctDNA assessment. Patients positive for ctDNA are randomized to either continue (blinded) clinical follow-up and standard of care treatment if they develop metastatic disease, or (unblinded) treatment at the time of molecular recurrence with single agent nivolumab. This study addresses whether recurrence can be detected earlier with ctDNA monitoring than with standard clinical follow-up, and whether early treatment of molecular recurrence with immunotherapy results in a survival benefit.

Recommendation 10.

Clinical trial participation	Evidence based recommendation
GCP	All patients should be considered for clinical trial participation, whenever possible.
	Consensus rate: 100% (26/26)

Recommendation 11.

Multidisciplinary tumor board	Evidence based recommendation
GCP	Management of patients with stage IIB-IV should be discussed in a multidisciplinary tumor board.
	Consensus rate: 100% (26/26)

Recommendation 12 [84].

Adjuvant therapy in stage II	Evidence based recommendation
Level of recommendation A	Adjuvant anti-PD-1 therapy shall be discussed in patients with resected stages IIB – IIC.
Level of evidence: 1b	De novo literature research [65, 84]
	Consensus rate: 100% (22/22)

Recommendation 13 [85,86].

Adjuvant therapy in stage IIIA	Evidence based recommendation
Level of recommendation B	For stage IIIA with nodal metastasis of less than 1 mm in diameter, the uncertainty of the individual risk/benefit of adjuvant therapy should be carefully discussed with the patients.
Level of evidence: 1b	De novo literature research [78, 85, 86]
	Consensus rate: 100% (23/23)

Recommendation 14.

Adjuvant therapy in stage IIIB-D	Evidence based recommendation
Level of recommendation A	Adjuvant anti-PD-1 therapy or BRAF/MEK inhibitor therapy (if BRAF V600 mutated) shall be offered to patients in resected stages IIIB – IIID.
Level of evidence: 1b	De novo literature research [50-52]
	Consensus rate: 100% (22/22)

Recommendation 15.

Adjuvant therapy in stage IV	Evidence based recommendation
Level of recommendation B	In patients with fully resected stage IV melanoma nivolumab should be offered regardless of mutation status.
Level of evidence: 1b	De novo literature research [52]
	Consensus rate: 100% (22/22)

Recommendation 16.

Adjuvant therapy in stage IV	Evidence based recommendation
Level of recommendation C	In patients with fully resected stage IV melanoma nivolumab plus ipilimumab may be an alternative.
Level of evidence: 1b	De novo literature research [53]
	Consensus rate: 100% (22/22)

4. Neoadjuvant therapy

4.1. Systemic neoadjuvant therapies

The survival of patients with clinically detected macroscopic stage III melanoma is poor. 5-year OS and RFS rates for surgery alone range from 40–59 % and 30–39 %, respectively. The standard of care was therapeutic lymph-node dissection (TLND) followed by one year of adjuvant systemic treatment. However, phase 2 clinical trials have shown that neoadjuvant immunotherapy induces high rates of major pathological response (MPR), which translate into durable RFS rates [87].

Pathology response to neoadjuvant therapies should be evaluated according to the recommendations from the International Neoadjuvant Melanoma Consortium – Table 2 [88].

A pooled analysis from the International Neoadjuvant Melanoma Consortium (INMC) [89] evaluated 6 available clinical trials on either anti-PD1-based immunotherapies (PD1-antibodies alone or ipilimumab plus nivolumab) and BRAF+MEK inhibitors. A total of 192 patients were included, of whom 141 received PD-1 based immunotherapy. The vast majority ($n = 104$) were treated with the combination of ipilimumab (1mg/kg) and nivolumab (3mg/kg). The approved dose of 1 mg/kg nivolumab plus 3mg/kg of ipilimumab was previously evaluated in the OpACIN-neo trial [90]. However, this dose had a higher toxicity compared to the 1mg/kg ipilimumab, without added efficacy. Therefore, the lower dose of ipilimumab was chosen for future trials. In the pooled analysis a pathological complete response (pCR) occurred in 40 % of all patients: 47 % with BRAF/MEK inhibitors and 33 % with PD-1 based immunotherapy. However, ipilimumab plus nivolumab demonstrated a response rate of 43 % in contrast to only 20 % with PD-1 monotherapy. The pCR rate correlated with the improved RFS (pCR 2-year: 89 % versus no pCR 50 %, $p < 0.001$) and OS (pCR 2-year OS 95

% versus no pCR 83 %, p = 0.027). Very few relapses have been observed in patients who achieved pCR, near pCR or pathological partial response (pPR) with PD-1 based immunotherapy. The 2-year RFS rate for those patients was 96 %. In contrast, the 2-year RFS rate for the targeted agents was only 79 % and the OS 91 % [91].

The PRADO trial, an extension cohort of the OpACIN-neo trial, addressed the feasibility and effect on clinical outcome of using pathologic response after neoadjuvant ipilimumab and nivolumab as a criterion for further treatment personalization. Ninety-nine patients with clinical stage IIIB-D melanoma and macroscopic lymph-node metastases were included and treated with 2 cycles of neoadjuvant ipilimumab plus nivolumab. In patients achieving MPR in their index lymph node, TLND and adjuvant therapy were not performed. In patients with pPR a TLND, but no adjuvant treatment was foreseen. Only patients with no pathologic response (pNR) underwent TLND and an adjuvant systemic therapy with or without radiotherapy. With this procedure the number of patients with pCR and pPR was 72 % including a rate of 61 % of MPR. Grade 3/4 toxicities within the first 12 weeks of treatment have been observed in 22 % of patients treated. In PRADO in 59 of 60 patients with MPR the TLND was omitted, resulting in a significant lower surgical morbidity and better quality of life. In patients with MPR the 24-month RFS and DMFS rates were 93 % and 98 %, respectively. These findings lead to the phase 3, randomized NADINA trial that tested a pathological response directed treatment personalization.

The NADINA study included 423 patients with macroscopic stage III disease, which were treated with 2 cycles of ipilimumab plus nivolumab followed by surgery or surgery followed by 12 cycles of adjuvant nivolumab [92]. Patients treated with neoadjuvant therapy achieving a pPR or a pNR also received adjuvant treatment. At a median follow-up of 9.9 months, the estimated 12-month event-free survival was 83.7 % (99.9 % CI, 73.8–94.8) in the neoadjuvant group and 57.2 % (99.9 % CI, 45.1–72.7) in the adjuvant group. The difference in restricted mean survival time was 8.00 months (99.9 % CI, 4.94–11.05; $P < 0.001$; HR for progression, recurrence of death, 0.32; 99.9 % CI, 0.15–0.66). In the neoadjuvant group, 59.0 % patients had MPR, 8.0 % a pPR, 26.4 % a pNR and 2.4 % had progression; 4.2 % had not yet undergone or omitted surgery at the time of publication. The estimated 12-month RFS was 95.1 % for MPR, 76.1 % for pPR, and 57.0 % for pNR. Grade 3 or higher adverse events related to systemic treatment occurred in 29.7 % of the neoadjuvant group and 14.7 % of the adjuvant group.

A small pilot study on the LAG-3 antibody relatlimab combined with nivolumab involved 30 patients with melanoma (AJCC stage IIIB/IIIC/D and fully resected stage IV M1a) [93]. The regimen included 2 infusions, 4 weeks apart, leading to a 52 % pCR rate after 8 weeks, with an additional 7 % near-pCR and 7 % pPR. Patients then received 10 months of adjuvant treatment with the same combination. After 16 months, 93 % remained disease-free, and 95 % were alive. Patients with pCR or near-pCR had a 100 % RFS rate. The neoadjuvant treatment was well-tolerated with no grade 3/4 toxicities, though 26 % experienced grade 3/4 toxicities during the adjuvant phase. No new safety signals were identified.

Another approach was evaluated in the SWOG-1801 trial, a randomized phase 2 trial, that included 313 patients with resectable stage IIIB-IV melanoma [94]. Patients received 3 cycles of neoadjuvant pembrolizumab (200 mg every three weeks), followed by complete lymphadenectomy or resection, and 15 additional doses of adjuvant pembrolizumab. This "perioperative treatment" differs from conventional adjuvant therapy by administering 3 cycles before and 15 after surgery, as opposed to 18 cycles post-surgery. The primary endpoint was event-free survival in an intention-to-treat analysis. With a median follow-up of 14.7 months, the perioperative arm showed significantly longer event-free survival compared to the adjuvant-only arm (p = 0.004). At 2 years, event-free survival was 72 % in the perioperative arm and 49 % in the adjuvant arm. The rates of treatment-related adverse events (CTC grade 3/4) were similar between the two arms.

Two articles from global key opinion leaders in the field of melanoma treatment were published in 2023 [95,96]. Both articles review the current status of neoadjuvant and perioperative treatments, advocating for their recognition as best medical practices and reimbursement, despite not being approved. As of March 2024, the perioperative regimen is officially reimbursed in Australia and Ireland. Recently, new phase 3 trials have begun to test the perioperative regimen with combined PD1 and LAG-3 antibodies.

Table 2
Classification of pathological response to neoadjuvant therapy according to the recommendations of the International Neoadjuvant Melanoma Consortium.

Pathological Response Category	Percent Viable Tumour Cells	Category
Pathological Complete Response (pCR)	0 % viable tumour cells	Major Pathological Response (**MPR**)
Near Pathological Complete Response (near-pCR)	0 to ≤ 10 % viable tumour cells	
Pathological Partial Response (pPR)	> 10 % and ≤ 50 % viable tumour cells	**pPR**
Pathological Non-Response (pNR)	> 50 % viable tumour cells	**pNR**

4.2. Intralesional neoadjuvant therapies

In addition to systemic treatments, intralesional immune-modulatory drugs are gaining attention for managing accessible tumors. Talimogene laherparepvec (T-VEC), a herpes simplex virus type 1-based oncolytic immunotherapy, is approved for treating unresectable melanoma. A phase 2 trial assessed neoadjuvant T-VEC's effect on RFS in 150 patients with resectable stage IIIB-IVM1a melanoma [97]. Patients were randomized to T-VEC followed by surgery (arm 1) or surgery alone (arm 2). A 17.1 % pCR was observed in arm 1, with increased CD8 + density correlating with outcomes. Final analysis after a 63.3-month median follow-up showed that the 5-year Kaplan-Meier estimates were 22.3 % versus 15.2 % for RFS and 77.3 % versus 62.7 % for OS, favoring the T-VEC arm [98].

Daromun, a combination of two antibody-cytokine fusions (L19-IL2 and L19-TNF), targets the extra domain-B of fibronectin, prevalent in tumor stroma but absent in normal tissue. A phase 2 study demonstrated intralesional daromun induced responses in both injected and distant uninjected lesions in stage III/IV melanoma patients. The PIVOTAL trial, a phase 3 study across 22 European centers, randomized patients to receive daromun followed by surgery or surgery alone [99]. Eligible patients had cutaneous melanoma with skin and/or lymph node metastases suitable for complete surgical resection. Prior treatments, including surgery and approved adjuvant therapy, were permitted. Patients were randomized (1:1) to receive either 4 weekly intratumoral daromun injections followed by surgery or surgery alone within 4 weeks. Daromun (13 Mio IU of L19-IL2 and 400 μg of L19-TNF) was administered weekly to all injectable lesions. The primary endpoint was RFS. The primary outcome showed an HR of 0.59 [95 % CI 0.41–0.86; p = 0.005] by Blinded Independent Central Review and 0.61 [95 % CI 0.41–0.92; p = 0.018] by investigator assessment. Median RFS was 16.7 months in the treatment arm versus 6.9 months in the control arm (BICR), and the HR for DMFS was 0.60 [95 % CI 0.37–0.95; p = 0.029]. Pathological complete response was observed in 21 % of patients in the treatment arm. Toxicity was primarily low-grade, with 14 % grade 3 local adverse events and no drug-related deaths.

4.3. Satellite and/or in-transit metastases

The number of patients with satellite or in-transit metastases included in the neoadjuvant and perioperative approaches was lower than that of patients with lymph node metastases. Still, if possible, neoadjuvant plus adjuvant or perioperative therapy should be the first choice.

As an alternative, and depending on the number, size and location of satellite and in-transit metastases, different options include surgery or other destructive therapies such as cryotherapy, laser therapy, electrochemotherapy and radiotherapy. Intralesional IL-2 can or topical imiquimod can also be offered. Finally, for inoperable disease isolated limb perfusion with melphalan + /- tumor necrosis factor (TNF) might be considered [100,101]. There is a lack of randomised data evaluating these local treatments and therefore it is not possible to rank them. See advanced disease below for systemic therapeutic options in patients with inoperable disease.

Recommendation 17.

Therapy of clinically detected regional lymph node metastasis	Consensus based recommendation
Level of recommendation A	If regional lymph node macrometastases have been detected clinically or by imaging, and in the absence of distant metastasis, neoadjuvant therapy shall be offered. Ipilimumab plus nivolumab followed by complete surgical resection and adjuvant therapy according to pathological response and BRAF status is one option. Neoadjuvant pembrolizumab followed by complete lymphadenectomy and adjuvant therapy is another option.
Level of evidence 1b	De novo literature research [92, 94, 96]
	Consensus rate: 100% (23/23)

5. First-line systemic therapy for irresectable stage III and stage IV disease

The treatment of metastatic melanoma patients should be discussed in interdisciplinary tumor boards with representation from multiple oncology sub-specialties.

5.1. Immune-checkpoint inhibitors

Serious and irreversible immune related AE can develop in some patients and require multidisciplinary management. Early recognition of these side effects is essential and requires specific training of the treating physicians [102].

5.1.1. Monotherapy with anti-CTLA-4 or anti-PD-1

Blocking immune checkpoint mechanisms with antibodies targeting CTLA-4 and PD-1 prevents the suppression of immune responses, leading to sustained lymphocyte activation and subsequent tumor cell death. Ipilimumab, an anti-CTLA-4 antibody, was the first immunotherapy to demonstrate an OS benefit in two controlled trials for metastatic melanoma [103,104]. Ipilimumab 3mg/Kg every three weeks for 4 cycles is approved for the treatment of stage IV melanoma both by the FDA and EMA.

The response rate to ipilimumab was only about 15 %, but remarkable durable responses were observed in patients with stage IV melanoma previously treated with other drugs [105]. Patients with stable disease or initial disease progression can still experience prolonged survival. However, the advent of PD-1 antibodies has shifted the role of ipilimumab, which is no longer the preferred first line therapy. Currently, ipilimumab is primarily used in combination with PD-1 antibodies or as a second line treatment.

PD-1 antibodies nivolumab and pembrolizumab are approved by both FDA and EMA for the treatment of unresectable melanoma, regardless of BRAF status. Nivolumab was shown to improve PFS and OS as compared to dacarbazine. The 5-year OS rates were 39 % for nivolumab and 17 % for dacarbazine; PFS rates were 28 % and 3 %, respectively [106]. Nivolumab was also superior to ipilimumab. After a minimum follow-up of 6.5 years the mOS was 36.9, and 19.9 months for nivolumab, and ipilimumab, respectively [107].

Pembrolizumab showed improved PFS and OS in comparison to ipilimumab in the KEYNOTE-006 trial. With a median follow-up of 85.3 months, median OS was 32.7 months for pembrolizumab and 15.9 months for ipilimumab (HR 0.70; 95 % CI, 0.58–0.83). The 10-year OS was 34 % for pembrolizumab and 23.6 % for ipilimumab. The 10-year MSS was 45.2 % and 31.3 % for pembrolizumab and ipilimumab, respectively [108]. Pembrolizumab showed a survival benefit across all subgroups, regardless of BRAF status, prior BRAF/MEK-inhibitor treatment, or adverse prognostic factors.

The KEYNOTE-001 evaluated pembrolizumab in previously treated or treatment-naive advanced/metastatic melanoma. Estimated 5-year OS was 34 % in all patients and 41 % in treatment-naive patients; median OS was 23.8 months (95 % CI, 20.2–30.4) and 38.6 months (95 % CI, 27.2-not reached), respectively [109].

The dose of nivolumab and pembrolizumab depends on which type of administration schema is used. Both a body-surface based dose or a flat dose can be offered [110–112]. The difference between these options is the frequency of the therapy, and patients' preferences, and potential previous toxicities should be taken into consideration when discussing which schedule to choose.

5.1.2. Anti-PD-1 plus anti-CTLA-4

The combination of nivolumab with ipilimumab has shown to be superior, in terms of PFS, to ipilimumab and to nivolumab as single drugs in the CheckMate-067 trial and is therefore approved by FDA and EMA. OS data showed a trend, but no significance in a comparison of nivolumab monotherapy with the combination only [113]. The long-term survival data after 10 years indicate the excellent therapeutic potential with a durable, sustained survival benefit, including melanoma specific survival [114].

Checkmate 511 evaluated the difference in toxicity between ipilimumab 3mg/kg plus nivolumab 1mg/kg versus ipilimumab 1mg/kg plus nivolumab of 3mg/kg for four cycles followed by nivolumab 480 mg every 4weeks. The grade 3/4 toxicity was reduced by half, while the efficacy was largely the same in both regimens. The study was powered for response not for OS. The updated data with a median follow-up of more than 40 months show that ipilimumab 1mg/kg plus nivolumab 3mg/kg continue to demonstrate an improved safety profile compared with ipilimumab 3mg/kg plus nivolumab 1mg/kg. In the descriptive analyses, both groups demonstrated similar 3-years OS rates [115].

Finally, the KEYNOTE-029 trial investigated the combination of the standard dose of pembrolizumab with alternate dose of ipilimumab in patients with advanced melanoma [116]. In part 1B, patients (with or without prior systemic therapy) received pembrolizumab 3 mg/kg every 3 weeks for 24 months and four doses of ipilimumab 1 mg/kg every 3 weeks. In part 1 C, therapy-naïve patients were randomized to pembrolizumab 200 mg every 3 weeks for 24 months plus either four doses of ipilimumab 50 mg every 6 weeks (arm A) or ipilimumab 100 mg every 12 weeks (arm B). The latest update reported a 5-year OS rate of 68.3 % for part 1B, with 86.2 % of responses lasting over 48 months. In part 1 C, the 3-year OS was 74.3 % in arm A and 70.4 % in arm B, with response durations over 36 months at 82.3 % and 78.7 %, respectively. Combination therapy was generally well-tolerated, with fewer grade 3–5 adverse events in arm A than in arm B. One patient in arm A died from treatment-related autoimmune myocarditis.

Presently, there are no predictive biomarkers for PD-1 based immunotherapy. The assessment of PD-L1 expression as predictive factor was investigated in the CheckMate 067 trial [117]. Currently available data did not show significant differences in OS according to PD-L1 expression. Therefore, PD-L1 expression determination should not be mandatory and should not be considered for therapeutic decisions in stage IV melanoma.

5.1.3. Anti-PD-1 plus anti-LAG-3

The RELATIVITY-047 trial, is a phase III trial that investigates the

first-line relatlimab plus nivolumab versus nivolumab alone in patients with advanced melanoma [118]. Lymphocyte-activation gene 3 (LAG-3) is an immune checkpoint that inhibits T-cell activity and is upregulated in several tumor types, including melanoma. Relatlimab is a human anti-LAG-3 that restores effector function of exhausted T-cells. In this trial, patients were randomized to receive a fixed-dose combination of relatlimab 160 mg plus nivolumab 480 mg every 4 weeks (RELA+NIVO FDC) or nivolumab monotherapy, until progression or unacceptable toxicity. The primary endpoint was PFS by blinded independent central review, the secondary endpoints were OS and ORR. The median PFS was 10.1 months (95 % CI, 6.4–15.7) with relatlimab–nivolumab, compared to 4.6 months (95 % CI, 3.4–5.6) with nivolumab alone (hazard ratio, 0.75; 95 % CI, 0.62–0.92; P = 0.006). At 12 months, PFS was 47.7 % (95 % CI, 41.8–53.2) with relatlimab–nivolumab versus 36.0 % (95 % CI, 30.5–41.6) with nivolumab. Relatlimab–nivolumab showed a benefit across key subgroups. Grade 3 or 4 treatment-related adverse events occurred in 18.9 % of patients in the relatlimab–nivolumab group, compared to 9.7 % in the nivolumab group.

For patients with PD-L1 expression ≥ 1 %, median PFS was similar between groups: 15.7 months (95 % CI, 10.1–25.8) for relatlimab–nivolumab and 14.7 months (95 % CI, 5.1–NR) for nivolumab (HR, 0.95; 95 % CI, 0.68–1.33). In patients with PD-L1 expression < 1 %, median PFS was 6.4 months (95 % CI, 4.6–11.8) for relatlimab–nivolumab versus 2.9 months (95 % CI, 2.8–4.5) for nivolumab (HR, 0.66; 95 % CI, 0.51–0.84).

Fianlimab plus cemiplimab is another combination of anti-PD-1 and anti-LAG3 that was investigated in a phase 1 trial [119]. Patients with advanced melanoma were enrolled in four cohorts: three for those without and one for those with prior anti–PD-1 therapy. Fianlimab 1600 mg and cemiplimab 350 mg was administered every 3 weeks for up to 51 weeks, with an optional extension of another 51 weeks if needed. The primary endpoint was the ORR per RECIST 1.1 criteria. The ORRs were 63 % for patients with anti–PD-1–naïve melanoma (cohort 6; n = 40; median follow-up 20.8 months) and 63 % for those with systemic treatment–naïve melanoma (cohort 15; n = 40; 11.5 months). In the combined cohorts of patients without prior anti–PD-1 therapy (cohort 6 +15 +16; n = 98), the ORR was 61.2 % (12 % CR, 49 % PR), with a median PFS of 13.3 months (95 % CI, 7.5 to NE). At a median follow-up of 12.6 months (IQR, 8.6–19), the median duration of response was not reached.

In patients with anti–PD-1–naïve advanced melanoma, PD-L1 expression ≥ 1 % (n = 26) showed a higher ORR (73 % vs. 56 %) and longer PFS (24 months [95 % CI, 10 to NE] vs. 10 months [95 % CI, 4 to NE]) compared to those with < 1 % PD-L1 (n = 41). ORR was similar in patients with LAG-3 ≥ 1 % (n = 55) versus LAG-3 < 1 % (n = 14) (64 % vs. 57 %), but PFS data was not mature.

Grade 3 or higher treatment-emergent and treatment-related adverse events occurred in 44 % and 22 % of patients, respectively. Aside from a higher incidence of adrenal insufficiency (12 % for grades 1–4, 4 % for grades 3–4), no new safety signals were observed. A randomized phase III is ongoing evaluating the combination of fianlimab plus cemiplimab versus pembrolizumab is patients with previously untreated unresectable locally advanced or metastatic melanoma (NCT05352672).

A recent publication showed that in an indirect comparison using patient-level trial data from the phase II/III RELATIVITY-047 and phase III CheckMate 067 trials, nivolumab plus relatlimab provided comparable efficacy to nivolumab plus ipilimumab across most, though not all, subgroups, with better safety outcomes in patients with untreated advanced melanoma. Nivolumab plus relatlimab seems to be is a viable alternative to nivolumab plus ipilimumab for treating metastatic melanoma, except in cases of acral melanoma and brain metastases [120].

5.1.4. *Nivolumab + relatlimab + ipilimumab*

The RELATIVITY-048 (NCT03459222) study is a phase 1/2, nonrandomized trial evaluating triple immune checkpoint therapy with nivolumab + relatlimab + ipilimumab in patients with select solid tumors, including melanoma. Patients with advanced melanoma received first-line treatment with nivolumab 480 mg every 4 weeks (Q4W), relatlimab 160 mg Q4W, and ipilimumab 1 mg/kg every 8 weeks (Q8W) until disease progression or unacceptable toxicity. Prior neoadjuvant/adjuvant therapy was allowed if completed more than 6 months before enrollment. Patients with controlled brain metastases were eligible. The primary endpoints were safety, ORR, disease control rate (DCR), and median duration of response (DOR) as assessed by the investigator.

A total of 46 patients were treated, with a median follow-up of 49.4 months (range 0.4–55.0). The triple combination achieved a confirmed ORR of 58.7 % with a 4-year PFS and OS rates of 51.6 % and 71.7 %, respectively. No new safety signals were observed with the triple combination, and its safety profile was consistent with other immunotherapy combinations. Due to the small sample size, further studies are needed to confirm its efficacy and safety.

Recommendation 18 [126].

Immunotherapy in stage IV	Consensus based recommendation
Level of recommendation A	In patients with stage IV melanoma, immunotherapy with checkpoint inhibitors shall be offered as first line, irrespective of BRAF status. The options include anti-PD-1 monotherapy and combination of anti-PD-1 plus anti-CTLA-4 (in different doses and schedules) and anti-PD-1 plus anti-LAG-3, regardless of PD-L1 expression.
Level of evidence 1a	De novo literature research [106, 107, 109, 115, 119, 123-126]
	Consensus rate: 100% (23/23)

5.2. *Targeted therapy*

In melanoma, various activating mutations increase MAP kinase and AKT pathway signaling [127]. About 45 % of cutaneous melanoma patients have a BRAF V600 mutation, for which selective BRAF (vemurafenib, dabrafenib and encorafenib) and MEK inhibitors (cobimetinib, trametinib and binimetinib) exist. The combination of BRAF plus MEK-inhibitors is the standard of care for patients receiving targeted therapies. Monotherapy with BRAF inhibitors alone is not recommended unless MEK-inhibitors are contraindicated.

Testing for *BRAF* mutation status is essential for treatment decisions and should ideally be done on metastatic tissue from AJCC stage III onwards. Additional panel sequencing should be offered if available.

The BRAF inhibitors vemurafenib and dabrafenib showed a rapid tumor response rate of around 50 % and significantly prolong PFS and OS in patients with the BRAFV600E mutation compared to dacarbazine (DTIC) [127–130]. Both therapies are approved for melanoma treatment in the US and EU. Reported adverse events include systemic effects (arthralgia, fatigue), cutaneous reactions, photosensitivity (specific to vemurafenib), and, in rare cases, new primary melanomas or epithelial tumors. Secondary resistance to BRAF inhibitors, developing over variable periods, is common.

MEK inhibitors provide additional inhibition of the MAP kinase pathway. Combinations of BRAF and MEK inhibitors like vemurafenib plus cobimetinib (coBRIM trial [131]) dabrafenib plus trametinib (COMBI-d, COMBI-v [132,133]) and encorafenib plus binimetinib (COLUMBUS [134,135]) were able to show a significantly increased objective response rate, PFS and OS in four independent phase 3 trials (Table 3). The median PFS for the combination in the COMBI-d and the COMBI-v study were 11.1 and 11.4 months; the mOS was 25.1 months

and 26.1 months, respectively. A pooled analysis of COMBI-d/v reported that the 5-year OS rate was 34 % for patients treated with dabrafenib plus trametinib. In patients with normal LDH levels at baseline this increased to 41 % [132]. In the co-BRIM study, the median OS was 22.5 months and 17.4 months, respectively for the combination and monotherapy with vemurafenib (95 % CI: 20.3–28.8 and 15.0–19.8). The 5-year OS rates were 31 % and 26 %, respectively. Also in this study, the OS and PFS were longer in patients with normal baseline LDH levels and low tumor burden, but also in those with complete response [136].

In the COLUMBUS study, the 7-year PFS and OS rates were 21.2 %, 27.4 % in the encorafenib plus binimetinib arm, and 6.4 % and 18.2 % in the vemurafenib arm, respectively [137]. In the encorafenib monotherapy arm, the 7-year PFS and OS rates were 15.8 % and 31.7 %. Median MSS was 36.8 months in the combination arm, 19.3 months in the vemurafenib arm and 22.4 months in the encorafenib arm. Thirty-four long-term responders (complete/partial response ongoing at 7 years) were identified across arms. Considering the similar 7-year outcomes for the combination and encorafenib alone, encorafenib monotherapy can be considered an alternative, especially in case of toxicity associated with the MEK inhibitor.

A small proportion of melanomas in sun-protected areas have c-KIT mutations and have been treated with the c-KIT inhibitor imatinib-mesylate. Responses have been reported in case studies, and a phase II trial showed an objective response rate of 23 % in c-KIT-mutated melanomas (Table 4) [138]., Nilotinib, sunitinib and dasatinib have also been investigated in this setting. A systematic review showed that the pooled ORR for all c-KIT inhibitors was 15 %. Subgroup analysis revealed the highest ORR for nilotinib [139]. Response rates and duration of response vary significantly, likely due to the diverse range of c-Kit mutations and inconsistent responses even with the same mutation.

An NRAS mutation is found in 15–20 % of cutaneous melanomas, but no effective NRAS inhibitors are currently available. MEK inhibitors like binimetinib and pimasertib NCT01693068) have been investigated in clinical trials. A low response rate was observed with no significant impact on OS. Additionally, the MEK inhibitor binimetinib appeared more toxic than single-agent DTIC chemotherapy [140].

5.3. Therapy sequence in BRAF mutated melanoma

Patients with BRAFV600 mutated melanoma may receive first line therapy with BRAF/MEK or immune checkpoint inhibitors. The best sequence of these two therapies was investigated in two studies. The phase II, randomized, noncomparative, SECOMBIT trial evaluated three therapeutic strategies in patients using encorafenib plus binimetinib and nivolumab plus ipilimumab. In arm A, patients received targeted therapy until progression, then switched to immunotherapy. In arm B, patients started with immunotherapy until progression, followed by targeted therapy. In arm C, patients received targeted therapy for 8 weeks, then switched to immunotherapy until progression, at which point had the possibility to be retreated with targeted therapy. A total of 209 patients were randomly assigned: 69 in arm A, 71 in arm B, and 69 in arm C. With a median follow-up of 32.2 months (IQR, 27.9–41.6), median OS was not reached in any arm, and over 30 patients remained alive in all groups. The OS endpoint, assuming a null hypothesis of $\leq$ 15 months, was met in all arms. The 2-year and 3-year OS rates were 65 % (95 % CI, 54–76) and 54 % (95 % CI, 41–67) in arm A, 73 % (95 % CI, 62–84) and 62 % (95 % CI, 48–76) in arm B, and 69 % (95 % CI, 59–80) and 60 % (95 % CI, 58–72) in arm C. No new safety signals were observed [142].

In the phase III DREAMSeq trial, treatment-naïve patients with stage IV BRAF V600 mutated melanoma were randomized 1:1 to receive nivolumab plus ipilimumab (Arm A) or dabrafenib plus trametinib (Arm B) until disease progression. Upon progression, patients entered the second phase to receive the alternate therapy: targeted therapy (Arm C) or immunotherapy (Arm D) [143]. A total of 265 patients were enrolled, with only 73 moving to step 2 (27 in arm C and 46 in arm D). Data was

Table 3
Selected studies investigating immune checkpoint inhibitors in irresectable stage III and stage IV cutaneous melanoma.

Trial	Investigated therapy	PFS	OS
Ipilimumab - CA184 −024 [104]	3 mg/kg i.v. Q3W for four cycles	HR for progression, 0.76; P = 0.006	11.2 vs. 9.1 months. 3-years OS 20.8 % vs. 12.2 %; (HR for death, 0.72; P < 0.001).
Ipilimumab[105]	Pooled analysis of patients treated with ipilimumab	NR	mOS= 11.5 months; 3-year OS 22 % (all patients) 26 % (treatment naive patients) 20 % (previously treated patients);
Ipilimumab NCT01515189 [121]	10mg/Kg versus 3 mg/kg i.v. Q3W for four cycles	NR	median OS was 15.7 months (95 % CI 11.6 to 17.8) at 10mg/kg and 11.5 months (95 %CI 9.9 to 13.3) at 3mg/kg (HR 0.84, 95 %CI 0.71 to 0.99; p = 0.04).
Nivolumab - CheckMate 066 [106]	3 mg/kg i.v. Q2W until tumor progression	PFS rate 28 %	5-year OS rate 39 %
Pembrolizumab - KEYNOTE 006 [108]	2 mg/kg i.v. Q3W until tumor progression	10-year PFS 22 %; mPFS 9.4; HR 064 (95 % CI0.54 −0.75)	mOS 32.7 months; 10-year OS 34 %
Pembrolizumab - KEYNOTE 001 [109]	2 mg/kg Q3W; 10 mg/kg Q3W, or 10 mg/kg Q2W until disease progression	5-year PFS rates 21 % (all patients) and 29 % (treatment-naïve); mPFS was 8.3 and 16.9 months, respectively.	5-year OS 34 % (all patients) 41 % (treatment-naive); mOS 23.8 and 38.6 months; respectively
Nivolumab + Ipilimumab – Checkmate 067 [107,114]	Ipilimumab 3 mg/kg i.v. plus nivolumab 1mg/kg i.v. Q3W for four cycles, continuation with 3 mg/kg nivolumab Q2W until tumor progression	mPFS 11.5 months (95 %CI: 8.7 - 19.3); 10-year PFS rates 31 %	mOS 71.9 months; 10-years OS rate 43 %
Nivolumab + Ipilimumab - Checkmate 511 [115,122]	Ipilimumab 1 mg/kg i.v. plus nivolumab 3mg/kg i.v. Q3W for four cycles, continuation with 3 mg/kg nivolumab Q2W until tumor progression	mPFS 10.2; 3-year PFS rate 38 %	3y OS 59 %
Pembrolizumab + ipilimumab - Keynote 029 [123]	Pembrolizumab 2mg/Kg Q3W for 24 months plus 4 doses ipilimumab 1mg/kg Q3W (part 1B)	5-y PFS rate 51.9 %	6-y OS rate 65.3 %
	Pembrolizumab 200 mg Q3W for 24 months plus 4 doses ipilimumab 50 mg Q6W (part 1 C arm A)	3-y PFS rate 56.5 %	3y OS 74.3 %

(continued on next page)

Table 3 (*continued*)

Trial	Investigated therapy	PFS	OS
	Pembrolizumab 200 mg Q3W for 24 months plus 4 doses ipilimumab 100 mg Q12W (part 1 C arm B)	3-y PFS rate 59.7 %	3y OS 70.4 %
Nivolumab + relatlimab Relativity−047 [124]	Nivolumab 480 mg plus relatlimab 160 mg Q4W versus nivolumab 480 mg Q4W	mPFS 10.2 versus 4.6 mo (HR 0.78)	mOS not reached for nivolumab + relatlimab versus 34.1 months for nivolumab (HR, 0.80; P = 0.059, not statistically significant). 3-year OS rate, 55.8 % versus 48.8 %, respectively
Fianlimab + cemiplimab - NCT03005782 [119]	Fianlimab 1600 mg + cemiplimab 350 mg Q3W for up to 51 W (optional additional 51 W if clinically indicated)	mPFS 13.3 months (cohorts 6, 15, 16)	NR
Nivolumab + relatlimab + ipilimumab – RELATIVITY 048 [125]	NIVO 480 mg Q4W + RELA 160 mg Q4W + IPI 1 mg/kg Q8W until progression or unacceptable toxicity.	4-year PFS rate 51.6 %	4-year OS rate 71.7 %

available for 115 of 145 patients with disease progression, with 60 (52 %) registering for step 2: 21 of 44 (48 %) from arm A and 39 of 71 (55 %) from arm B. Most patients who did not proceed to step 2 died within 6 months of progression, primarily due to brain metastases (arm A = 65.2 %, arm B = 78.1 %). The study was stopped early due to a significant endpoint being reached. The 2-year OS was 71.8 % (95 % CI, 62.5–79.1) for arm A and 51.5 % (95 % CI, 41.7–60.4) for arm B (P = .010). Step 1 PFS favored arm A (P = .054). ORRs were 46.0 % for arm A, 43.0 % for arm B, 47.8 % for arm C, and 29.6 % for arm D. Median duration of response was not reached in arm A and was 12.7 months in arm B ($P < .001$). Grade $\geq$ 3 toxicities were similar across arms, with expected toxicity profiles.

Finally, the phase II EBIN trial compared upfront immunotherapy (arm A: 4 cycles of nivolumab 3mg/Kg + ipilimumab 1mg/kg, followed by nivolumab) with a sequential approach (arm B: 3 months of targeted therapy with encorafenib + binimetinib, followed by the same immunotherapy regimen as arm A) [144]. Total treatment duration in both arms is 2 years, with arm B allowing rechallenge with targeted therapy after progression. A total of 136 patients in arm B and 131 in arm A began treatment. Median follow-up was 21 months. In arm B, 99 % were free of progression at week 12, when targeted therapy ended. In the intention-to-treat analysis, there was no significant difference in PFS between arms (HR = 0.87, 90 % CI 0.67–1.12, p = 0.36). Subgroup analyses showed varied PFS outcomes by LDH levels and metastatic sites, with significant benefit in arm B for patients with liver metastases (HR = 0.48, 95 % CI 0.28–0.80, p = 0.008). ORR was 53 % in arm B and 45 % in arm A, with complete responses of 12 % and 10 %, respectively. Grade $\geq$ 3 adverse events occurred in 58 % of arm B and 51 % of arm A. Overall, EBIN found no PFS difference between the arms in unselected patients, but arm B may benefit those with high LDH or liver metastases.

Table 4
Selected studies investigating targeted therapy in irresectable stage III and IV cutaneous melanoma.

Trial	Investigated therapy	PFS	OS
BRAF V600 mutation			
Dabrafenib + Trametinib – COMBI-d and COMBI-v[132]	2 x 150 mg p.o. daily + 1 x 2 mg p.o. daily	5-year PFS rate 19 %	5y OS 34 %
Vemurafenib + Cobimetinib – CoBRIM[136]	2 x 960 mg p.o. daily + 1 x 60 mg p.o, daily for 21 days, followed by 7 days off treatment	5-year PFS rate 15 %	5y OS 31 %
Encorafenib + Binimetinib – COLUMBUS[137]	1 x 450 mg p.o. daily + 2 x 45 mg p.o. daily	7-year PFS rate 21.2 %	7-year OS rate 27.4 %
cKIT mutation			
Imatinib mesylate [138]	1 x 400 mg p.o. daily until tumor progression	mPFS 3.5 months	1-year OS rate 51 % mOS 14 months
***NRAS* mutation**			
Binimetinib – NEMO [140,141]	2 x 45 mg (3 x 15 mg tablets) p.o. daily until tumor progression	mPFS 3.0 months	mOS 11.8 months

Recommendation 19.

Targeted therapy in stage IV	Consensus based recommendation
Level of recommendation B	For patients with stage IV melanoma with contra-indications to ICI and a BRAF-V600E or V600K mutated tumor, first-line therapy with BRAF/MEK inhibitors should be offered.
Level of evidence 2b	[132, 136, 137]
	Consensus rate: 100 % (26/26)

Recommendation 20.

Targeted therapy in stage IV	Consensus based recommendation
Level of recommendation C	In particular scenarios* for patients with stage IV melanoma and a BRAF V600E or V600K mutation, first line therapy with BRAF/MEK inhibitors for 6-12 weeks can be offered before immunotherapy. * Poor performance status, high LDH, high tumor burden, aggressive course of the disease, symptomatic metastases.
Level of evidence 2a	De novo literature research [142-144]
	Consensus rate: 100 % (26/26)

6. Second-line systemic therapy for irresectable stage III and stage IV disease

Patients with BRAF wild-type melanoma, who do not respond to PD-1-based immunotherapy, particularly to combined anti-PD-1 and anti-CTLA-4, have reduced therapeutic options. It is our opinion that inclusion in a clinical trial is still the best option available for this group of patients. .

6.1. PD-1 rechallenge

Patients treated with anti-PD-1 monotherapy can benefit from a second course of anti-PD-1, particularly when they benefited from the first-line, i.e. when response at discontinuation was at least stable disease. Data from the Keynote 066 trial showed that for patients receiving

second-line pembrolizumab, the mOS was 23.5 (16.8–34.2) and the 5-years OS rate was 30.1 % [145]. Also, in the CheckMate 067 trial, 152 patients included in the nivolumab arm received subsequently systemic therapy with another immunotherapy (n = 105) namely anti-PD-1 (n = 49) [146].

6.2. Ipilimumab and ipilimumab plus anti-PD-1

Ipilimumab alone or in combination with nivolumab can also be a therapeutic option for patients progressing to PD-1-based immunotherapy. In the Keynote 066 trial, the mOS for second-line ipilimumab was 13.6 months (10.7–22.0) and the 5-year OS rate was 27.3 % [147].

In the CheckMate 067 trial, 91 patients in the nivolumab arm received subsequent systemic therapy with ipilimumab, but the survival benefit associated with this second line was not reported. Finally, a multicenter retrospective analysis showed that after progression under PD-1 therapy combined nivolumab plus ipilimumab resulted in a higher response rate and longer PFS and OS compared to ipilimumab monotherapy, with similar toxicity [148]. Therefore, when possible, the combination therapy should be preferred.

6.3. BRAF+MEK inhibitors

For patients with BRAF V600 mutation with resistance to PD-1 based immunotherapy therapy with BRAF/MEK inhibitors can be an alternative, as shown in the EBIN, SECOMBIT and DREAM-Seq trials – see therapy sequence in BRAF mutated melanoma above.

6.4. Adoptive T cell transfer

Adoptive T-cell transfer of tumor-infiltrating lymphocytes (TILs) represents a potential alternative therapy for resistance to immune checkpoint inhibition, which is currently under development. The process of producing TILs is technically challenging, and concomitant administration of interleukin-2 (IL-2) is associated with significant toxicity. Ex vivo-expanded TILs are administered after lymphodepletion chemotherapy followed by high-dose IL-2. High rates of clinical response and long-term survival have been reported for this therapy [149]. An open-label phase 2 study was conducted to determine the efficacy and safety of a lifileucel in 66 patients with unresectable metastatic melanoma and progression on anti-PD-1 therapy or BRAF+MEK inhibitors [150]. Lifileucel (LN-144) is a one-time autologous TIL therapy that uses TIL harvested from a patient's tumor to produce billions of patient-specific cells in a 22-day centralized manufacturing process. The TIL consist mainly of CD8 + and CD4 + T cells with an effector-memory phenotype linked to cytotoxic function. The regimen involved a one-week lymphodepletion with cyclophosphamide and fludarabine, followed by a lifileucel infusion and up to six IL-2 doses. After a median follow-up of 28.1 months, the ORR was 36.4 %, with a 4.5 % complete response rate. Stable disease occurred in 44 % of patients, resulting in an overall disease control rate of 80.3 %. Later, a pooled analysis included 153 patients treated with lifileucel, with extended follow-up on 66 previously reported patients [151]. Patients had a median of 3 prior therapy lines, with 81.7 % having received both anti-PD-1 and anti-CTLA-4. The ORR was 31.4 % (95 % CI: 24.1 %−39.4 %), including 8 complete and 40 partial responses. Median DOR was not reached at 27.6 months of follow-up, with 41.7 % of responses lasting ≥ 18 months. Median OS was 13.9 months, and mPFS was 4.1 months. Patients with normal LDH and lower tumor burden had a higher response likelihood than those with one (OR=2.08) or both (OR=4.42) risk factors. Common grade 3/4 adverse events included thrombocytopenia (76.9 %), anemia (50.0 %), and febrile neutropenia (41.7 %). In February 2024, lifileucel received FDA approval for treating melanoma patients who progressed after PD-1 therapy and BRAF+MEK inhibitors, if they have a BRAF mutation [152]. An ongoing phase 3 study (NCT05727904) will provide confirmatory evidence of benefit.

Table 5
Clinical trials evaluating systemic therapies in irresectable stage III and IV melanoma with progressive disease after first line therapy.

Trial	Investigated therapy	PFS	OS
Pembrolizumab – Keynote 006 [145]	Pembrolizumab 10 mg/kg Q2W, Pembrolizumab 10 mg/kg QW3	NR	mOS 23.5 5-year OS rate 30.1 %
Ipilimumab – Keynote 006 [145]	4 cycles of ipilimumab 3mg/kg Q3W	NR	mOS 13.6 5-year OS rate 27.3 %
Lifileucel C−144 −01 cohort 2 [151]	cyclophosphamide and fludarabine + lifileucel (> 1 × 10^9 TIL cells) + IL−2	NR	mOS 17.4 months 1-year OS rate 58 %
Lifileucel C−144 −01 (cohort 2 +4)[150]	cyclophosphamide and fludarabine + lifileucel (> 1 × 10^9 TIL cells) + IL−2	mPFS 4.1 months	mOS 13.9 months
TIL versus ipilimumab[153]	cyclophosphamide and fludarabine + 5 × 10^9 TILs ' IL−2 or 4 cycles of ipilimumab 3mg/kg Q3W	mPFS 7.2 months	mOS 25.8 months
Nivolumab + relatlimab[155]	D1 - nivolumab and relatlimab 240/80 mg Q2W single-agent vial (SAV) or 1:1 nivolumab and relatlimab 480/160 mg Q4W SAV or nivolumab and relatlimab 480/160 mg Q4W fixed-dose combinationD2 - nivolumab and relatlimab 480/160 mg Q4W SAV	mPFS 2.1 months 1-year PFS rate 21.4 % in cohort D1 pooled mPFS 3.2 months 1-year PFS rate 16.0 % in cohort D2	mOS 14.7 months, 1-year OS rate 56.0 % in cohort D1 pooled mOS 17.1 months 1-year OS rate 60.0 % in cohort D2
Cemiplimab + Fianlimab[119]	fianlimab 1600 mg and cemiplimab 350 mg Q3W 51 W, with an optional additional 51 W	mPFS 1.5 months	NR
Pembrolizumab + Lenvatinib[156]	lenvatinib 20 mg p.o. OD + pembrolizumab 200 mg Q3W	mPFS 4.2 months	mOS 14 months

Table 6
Examples of chemotherapy schemas for advanced cutaneous melanoma.

Medication	Dose	Response rate
Dacarbazine [166–169]	250 mg/m^2 i.v. daily for 5 days every 3 −4 weeks or 800 – 1200 mg/m^2 i.v. daily on one day every 3 −4 weeks	12.1 −17.6 % 5.3 −23 %
Temozolomide[167, 170]	150 - 200 mg/m^2 p.o. daily for 5 days every 4 weeks	13.5 −21 %
Fotemustine[171, 172]	100 mg/m^2 i.v. on days 1, 8 and 15; then 5 weeks pause, then repeat single dose every 3 weeks	7.4 −24.2 %
Carboplatin plus Paclitaxel[173]	Carboplatin AUC6 i.v. day 1, after four cycles reduce to AUC4 Paclitaxel 225 mg/m^2 i.v. day 1 every 3 weeks, after four cycles reduce to 175 mg/m^2	(12.1 % second line)

Another study investigated the therapy with TIL compared to ipilimumab in patients previously treated with PD-1 inhibitors [153]. A total of 168 patients (86 % refractory to anti–PD-1 treatment) were randomized to receive TILs or ipilimumab. In the intention-to-treat population, median PFS was 7.2 months (95 % CI, 4.2–13.1) with TILs and 3.1 months (95 % CI, 3.0–4.3) with ipilimumab (HR, 0.50; 95 % CI, 0.35–0.72; P < 0.001). Objective response rates were 49 % (95 % CI, 38–60) for TILs and 21 % (95 % CI, 13–32) for ipilimumab. Median OS was 25.8 months (95 % CI, 18.2-NR) with TILs and 18.9 months (95 % CI, 13.8–32.6) with ipilimumab. Grade 3 or higher treatment-related adverse events occurred in all TIL patients, primarily due to

chemotherapy-related myelosuppression, and in 57 % of ipilimumab patients. A meta-analysis evaluating TIL therapy in patients who did not benefit from anti-PD-1 therapy included 13 high-dose interleukin-2 studies with OS data for 617 patients [154]. No difference in median OS was found between patients previously treated (n = 238; 17.5 months [95 % CI 13.8–20.5]) and untreated with anti-PD-(L)1 (n = 379; 16.3 months [95 % CI 14.2–20.6]) (P = 0.53). ORR was 34 % (95 % CI 16 %–52 %) with prior treatment and 44 % (95 % CI 37 %–51 %) without. The CRR was 10 % in both groups, with no significant differences for ORR (P = 0.15) or CRR (P = 0.45). The authors conclude that prior anti-PD-(L)1 treatment does not impact clinical response or survival benefits from TIL adoptive T-cell in advanced cutaneous melanoma, supporting its consideration as a second-line treatment for metastatic melanoma.

6.5. PD-1 + LAG-3

Nivolumab and relatlimab has been investigated in patients with progression under immune checkpoint inhibitors. This was investigated in the phase I/IIa RELATIVITY-020 trial part D, which evaluated nivolumab and relatlimab in patients with progression during or within 3 months of 1 (D1) or more (D2) anti-PD-(L)1 regimens [155]. Safety was a primary endpoint. Objective response rate (coprimary endpoint) and PFS by BICR were also assessed. Among 518 patients, the ORR by blinded review was 12.0 % in D1 and 9.2 % in D2, with responses observed regardless of PD-L1 or LAG-3 expression. The median DOR was not reached in D1 and 12.8 months in D2. Median PFS was 2.1 months for D1 and 3.2 months for D2, with 6-month PFS rates of 29.1 % and 27.7 %. Grade 3–4 adverse events occurred in 15.0 % of D1 and 12.8 % of D2, with no treatment-related deaths.

The combination of fianlimab and cemiplimab was also tested in 15 patients pre-treated with PD-1 therapy in a phase 1 study [119]. The ORR was 13.3 % (two partial responses; 95 % CI, 1.7 to 40.5). After a median follow-up of 8 months (IQR, 1–28), the median duration of response was not reached (95 % CI, 3.4 to not estimable), and the Kaplan-Meier estimated median PFS was 1.5 months (95 % CI, 1.3 to 7.7), aligning with prior findings.

6.6. Lenvatinib plus pembrolizumab

The phase 2 LEAP-004 trial evaluated lenvatinib plus pembrolizumab in stage III/IV melanoma patients with confirmed progressive disease within 12 weeks of the last PD-1/L1 inhibitor dose, given alone or with anti–CTLA-4 or other therapies. Among 103 patients, the combination showed potential as a treatment option [156]. With a median follow-up of 15.3 months, the ORR was 21.4 %, and the median duration of response was 8.3 months. For patients previously treated with both anti-PD-1 and anti-CTLA-4, the ORR was 33 %. ORRs for patients with primary and secondary resistance to immunotherapy were 22.6 % and 22.7 %, respectively. The median PFS was 4.2 months, and median OS was 14 months.

Recommendation 21 [157].

Progression after PD-1 based immunotherapy	Consensus based recommendation
Level of recommendation B	In patients with resistance to immunotherapy and harboring a BRAF V600 mutation, BRAF/MEK inhibitors should be offered, if no clinical trial is available.
Level of evidence 1b	[142, 144, 157]
	Consensus rate: 100% (23/23)

Recommendation 22 [158,159].

Progression after PD-1 based immunotherapy	Consensus based recommendation
Level of recommendation B	In patients with resistance to PD-1 monotherapy, combined immunotherapy with anti-PD-1 and anti-CTLA-4, CTLA-4 monotherapy, PD-1 + LAG-3 or TIL therapy should be offered. In patients with BRAF V600 mutated tumors targeted therapy should be offered.
Level of evidence: 2	[119, 155, 158, 159]
	Consensus rate: 100% (26/26)

7. Progression after adjuvant therapy

There is very limited data on the type of therapy to be offered to patients who progress with irresectable disease after adjuvant systemic therapy. A phase 1 study evaluating fianlimab and cemiplimab included patients who were previously treated with anti-PD-1-based (neo) adjuvant therapy [119]. In patients who received any (neo)adjuvant therapy (cohort 16; n = 18), ORR was 56 % (95 % CI, 31 to 79), with complete response and partial response rates of 6 % and 50 %, respectively. In patients (n = 13) who had received adjuvant therapy with an anti–PD–1, ORR was 61.5 % (95 % CI, 32 to 86), median DOR was NR (95 % CI, 6 months to NE), and median PFS was 12 months (95 % CI, 1 to NE).

The type of response to systemic therapy in patients who received adjuvant therapy may vary if the patients have progressive disease on or off adjuvant therapy.

Patients who relapsed after adjuvant BRAF+MEK appeared to respond well to subsequent anti-PD-1 therapy, with outcomes comparable to those seen in first-line or treatment-naïve stage IV melanoma, suggesting that targeted therapy may not affect the response to immune checkpoint inhibitors [160].

Conversely, patients who experience recurrence during PD-1 adjuvant therapy appear to derive limited benefit from PD-1 monotherapy but may respond better to ipilimumab, either alone or combined with PD-1 or BRAF+MEK [161].

Patients with primary resistance to systemic adjuvant therapy, i.e., those who progress while receiving adjuvant therapy or shortly after (<12 weeks after therapy end) [162] have a low likelihood of responding to re-challenge. For patients who recur more than 12 weeks after adjuvant therapy, retreatment can be considered. BRAF status should be considered both in the primary and acquired resistance setting.

Besides systemic therapy, for patients with limited progressive disease that can be treated with local therapy, surgical resection, radiotherapy or a combination of both should be considered [161,163].

Currently, besides BRAF status, there are no other validated biomarkers than can guide therapeutic decision in this setting..

Recommendation 23.

Systemic therapy for unresectable disease after (neo) adjuvant therapy	Consensus based recommendation
Level of recommendation B:	Therapeutic decisions should be based on the time of recurrence and the type of (neo)adjuvant treatment – see Figure 1.
CGP	
	Consensus rate: 100% (26/26)

Recommendation 24.

Systemic therapy for unresectable disease after (neo) adjuvant therapy	Consensus based recommendation
Level of recommendation C:	For patients with primary resistance to PD-1 monotherapy combined immunotherapy with anti-PD-1 and anti-CTLA-4, CTLA-4 monotherapy, PD-1 + LAG-3 or TIL therapy can be offered. For patients with acquired resistance, retreatment with the same type of therapy as in the (neo) adjuvant setting can be considered.
Level of evidence: 3	De novo literature research: [119, 155, 158, 159]
	Consensus rate: 100% (26/26)

8. Chemotherapy

Before the advent of targeted therapies and immunotherapies, chemotherapy was the only systemic option for stage IV melanoma. Today, it is considered a last-line treatment for patients resistant to immunotherapies and targeted therapies or when clinical trial participation is unavailable [164]. Therefore, except in specific cases like locoregional tumor-directed chemotherapy, salvage therapy after first-line failure, when inclusion in clinical trials is not possible, or as a temporary measure until other treatments become accessible, traditional cytotoxic chemotherapy should not be considered standard-of-care in the current management of metastatic melanoma [165]. Various agents with similar effectiveness are used for systemic chemotherapy, which can shrink tumors and reduce symptoms but have not shown any survival benefit beyond symptom control. The longest-used monotherapy, DTIC, has shown response rates of only 5–12 % with few complete responses in multiple trials (Table 4).

Recommendation 25.

Chemotherapy in stage IV	Consensus based recommendation
GCP	Chemotherapy can be considered in patients with good performance status only when there is resistance to immunotherapy and targeted therapies. The alternative is best supportive care.
	Consensus rate: 100% (23/23)

9. Brain metastasis

Patients with melanoma brain metastases, especially untreated and symptomatic, are excluded from the majority of clinical trials. Therefore, the number of prospective studies evaluating therapy in this setting is scarce.

9.1. Immunotherapy

In the first trial of immunotherapy for patients with brain metastases, the CTLA-A4 antibody ipilimumab was tested in an open-label phase 2 study in patients with asymptomatic and symptomatic brain metastases [174]. While an intracranial response rate of 16 % and long-term benefit was seen in asymptomatic patients the response rate deteriorated to 5 % in symptomatic patients.

The CheckMate 204 study investigated combined immunotherapy with nivolumab and ipilimumab in patients with asymptomatic (cohort A) and symptomatic (cohort B) melanoma brain metastases [175]. Of the 165 patients screened, 119 (72 %) were enrolled and treated: 101 asymptomatic (cohort A, median follow-up 34.3 months) and 18 symptomatic (cohort B, median follow-up 7.5 months). Intracranial clinical benefit was seen in 57.4 % of cohort A and 16.7 % of cohort B. Objective response rates were 53.5 % in cohort A and 16.7 % in cohort B, with complete responses in 33 % and 17 %, respectively. In cohort A, 3-year intracranial PFS was 54.1 % and OS was 71.9 %. In cohort B, these rates were 18.9 % for intracranial PFS and 36.6 % for OS.

The Australian ABC trial evaluated ipilimumab and nivolumab in three cohorts: Cohort A involved patients with asymptomatic brain metastases and no prior local brain therapy, randomized to combined immunotherapy followed by nivolumab alone. Cohort B received nivolumab monotherapy. Cohort C was also treated with nivolumab monotherapy and included patients with brain metastases who progressed after local therapy, had neurological symptoms, and/or leptomeningeal disease. The last update showed that the 5-year intracranial PFS and OS were 46 %, 15 % and 6 %, and 51 %, 34 % and 13 % for cohorts A, B and C, respectively. The 5-year OS for patients therapy naïve was 55 %, 40 % and 25 % respectively for cohorts A, B and C [176].

Updated results of the NIBIT-M2 trial showed that for patients treated with ipilimumab plus nivolumab the 7-year OS rate was 42.8 % (95 % CI: 23.4–62.2) in patients with untreated and asymptomatic brain metastases [177].

The benefit of ipilimumab and nivolumab in patients with symptomatic brain metastases is very modest. Investigation of nivolumab plus relatlimab in active melanoma brain metastases is ongoing in a single-arm, open-label, phase II trial NCT05704647 [178].

9.2. Targeted therapy

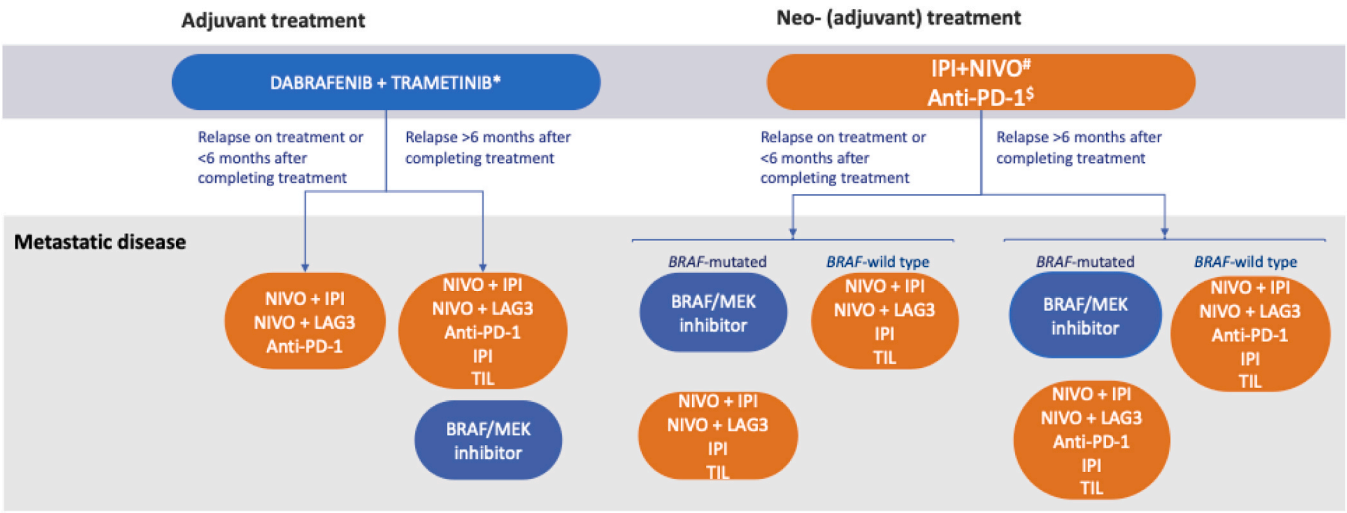
The BREAK-MB trial demonstrated the impact that dabrafenib in brain metastases, with a 39 % and 30 % intracranial response rate in patients without and following progress after previous local treatment of their brain metastases, respectively [179]. In the non-randomized COMBI-MB trial, the combination of dabrafenib and trametinib showed an ORR of 58 % in asymptomatic patients carrying a BRAF V600E mutation (n = 76) and a comparable response rate (56 %) in a small (n = 16) group of patients with symptoms. The DOR was however short 6.5 months and 4.5 months in asymptomatic and symptomatic patients, respectively [180].

Baseline corticosteroid treatment was independently linked to a lower intracranial response rate (ICRR: 39 % vs. 63 %; OR 0.323, 95 % CI 0.105–0.996; P = 0.049) and shorter PFS (HR 1.93, 95 % CI 1.06–3.51; P = 0.031). Multivariate analysis also showed significant associations between improved PFS in patients with a BRAFV600E mutation (HR 0.565, 95 % CI 0.321–0.996; P = 0.048) and better OS in patients with ECOG zero (HR 0.44, 95 % CI 0.25–0.78; P = 0.005) [181].

9.3. Combination of PD-1 inhibitors and BRAF/ MEK inhibitors

TRICOTEL was a multicentre, open-label, single-arm, phase II study that included two cohorts of patients: 1) BRAF wild-type patients and 2) patients harboring a $BRAF^{V600}$ mutation. Patients in the BRAFV600 wild-type cohort received atezolizumab and cobimetinib. For the BRAFV600 mutation-positive cohort, the regimen included atezolizumab, vemurafenib and cobimetinib, with atezolizumab withheld during cycle 1. The primary outcome was the intracranial ORR. Sixty-five patients were enrolled in the BRAFV600 mutation-positive cohort, and 15 in the BRAFV600 wild-type cohort, which closed prematurely. The median follow-up was 9.7 months (IQR 6.3–15.0) and 6.2 months (IQR 3.5–23.0), respectively. The intracranial ORR was 42 % (95 % CI 29–54) for patients with BRAFV600 mutation (IRC assessment) and 27 % (95 % CI 8–55) in the wild-type cohort (investigator assessment) [182].

The triple combination of atezolizumab, bevacizumab and cobimetinib (TACo) was also investigated [183]. Patients were required to have prior PD-1 treatment and at least one non-irradiated lesion (5–30 mm). Those with BRAF mutations could participate after completing BRAF/-MEK therapy with a 3-month washout period. Patients taking up to 4 mg/day of oral dexamethasone or its equivalent were also eligible. Median follow-up was 8.2 months (0.4–39.2). Median duration of



*Only in resected stage III; # only neo-adjuvant (NADINA trial); $ pembrolizumab neoadjuvant plus adjuvant (SWOG S181 trial) and nivolumab or pembrolizumab adjuvant alone
IPI, ipilimumab; IPI, ipilimumab; TIL Tumor infiltrating lymphocytes; MEK, mitogen-activated protein kinase (MAPK) kinase; NIVO, nivolumab; PD-1, programmed cell death protein 1;

Fig. 1. Proposed algorithm for the treatment of melanoma considering the type of adjuvant therapy, and the time point of recurrence on or off adjuvant therapy. All patients should be considered and preferably included in clinical trials, when available.

treatment was 8 weeks (0.6–63.8). Eighteen patients were evaluable for intracranial response: the intracranial response rate was 39 % (1 complete response, 6 partial responses), and the intracranial clinical benefit rate was 56 % (including stable disease). Median PFS was 2.7 months (95 % CI 0.9–7.3), and mOS was 9.3 months (95 % CI 3.8–20.9).

Recommendation 26.

Systemic therapy for brain metastases	Consensus based recommendation
Level of recommendation A:	In patients with brain metastases, combined immunotherapy with PD-1 plus CTLA-4 shall be offered as first line therapy.
Level of evidence: 1b	De novo literature research: [175, 176]
	Consensus rate: 100% (26/26)

Recommendation 27.

Systemic therapy for brain metastases	Consensus based recommendation
Level of recommendation C:	In symptomatic brain disease or in case of resistance to ICI, targeted therapy can be an alternative in patients with BRAF V600 mutation.
Level of evidence: 1b	De novo literature research: [180, 181]
	Consensus rate: 100% (23/23)

9.4. Surgery and radiotherapy

The recommendations below shall not replace the recommendations proposed by the radiotherapy and radio-oncology societies [184].

The literature provides evidence for the use of radiotherapy in the treatment of brain metastases [185].

Clinical trials have shown increased local control in patients with 1–10 brain metastases using adjuvant SRS after surgery, however without any impact on survival [186]. There seems to exist no difference between SRS and surgical resection in terms of the local control of brain metastases. Stereotactic radiosurgery was associated with improved early local control of treated lesions compared with surgical resection, although the relative benefit decreased with time [187]. Both stereotactic single-dose radiation therapy and surgical resection are appropriate for solitary or few (typically up to 5), and smaller lesions (up to 3 cm in diameter), although newer devices allow the treatment of more lesions in selected cases. Treatment of solitary lesions (surgery or stereotactic RT) can be applied several times and appears to prolong PFS, although this has never been established in randomized trials.

There is no data on whole brain radiotherapy (WBRT) used with contemporary systemic therapies, especially immune checkpoint inhibitors. Moreover, WBRT may cause serious long-term cognitive toxicity [188]. This is a palliative therapy, which does not prolong survival, and can no longer be recommended for the treatment of melanoma brain metastases.

9.5. Combined approaches of local and systemic therapy

Preclinical evidence has suggested a positive effect of the combination of immunotherapy and radiotherapy [189,190]. Retrospective studies have shown that the combination of local and systemic therapy improved intracranial control, as well as encouraging PFS and OS data [191–195]. An analysis including eleven studies, and 316 patients showed that the combination of radiotherapy and targeted therapy seems to be safe. The available evidence indicates a better outcome in patients receiving targeted therapy after radiotherapy or targeted therapy accompanied by radiotherapy, although the best time interval is unknown [196].

Definitive results from prospective trials investigating the combination of checkpoint inhibitors or BRAF/MEK inhibitors and local are still missing, and the best sequence remains to be determined in both symptomatic and asymptomatic patients [197–199].

9.6. Leptomeningeal metastases

Patients with leptomeningeal metastases have a dismal prognosis. An ongoing phase 1/1b study is evaluating the safety and efficacy of concurrent intrathecal (IT) and intravenous (IV) nivolumab in patients with melanoma and leptomeningeal disease (LMD) [200]. The primary objectives are to determine safety and establish the recommended IT nivolumab dose, with OS as a secondary endpoint. Patients receive IT nivolumab alone in cycle 1, followed by both IT and IV nivolumab in subsequent cycles. Among 25 patients treated with IT nivolumab doses of 5, 10, 20, and 50 mg, no dose-limiting toxicities were observed. The recommended IT dose is 50 mg, combined with 240 mg IV nivolumab every two weeks. Median OS was 4.9 months, with 44 % survival at 26 weeks and 26 % at 52 weeks. These findings suggest that concurrent IT and IV nivolumab is safe, feasible, and potentially effective, even in patients previously treated with anti-PD1 therapy.

Recommendation 28.

Surgery and radiotherapy for brain metastases	Evidence based recommendation
Level of recommendation C	Patients with brain metastases resistant to immune checkpoint inhibitor therapy can be treated with stereotactic radiotherapy.
	Guideline adaptation [54, 184]
	Consensus rate: 100% (23/23)

Recommendation 29.

Surgery and radiotherapy for brain metastases	Evidence based recommendation
Level of recommendation B	In addition to first line systemic therapy, in patients with symptomatic or life-threatening brain metastases, stereotactic radiotherapy or surgery should be considered.
	Guideline adaptation [54, 184]
	Consensus rate: 100% (23/23)

Recommendation 30.

Whole brain radiotherapy (WBRT)	Evidence based recommendation
Level of recommendation A	Whole brain radiotherapy shall no longer be recommended for the treatment of melanoma brain metastases.
	Guideline adaptation [54, 184]
	Consensus rate: 100% (23/23)

10. Acral melanoma

Patients with acral melanoma should receive the same treatment options as those with other cutaneous melanoma subtypes, though response rates are generally lower. Acral melanoma, found on palms, soles, and nails, is independent of UV exposure and has a similar frequency across ethnic groups. It has a comparatively low tumor mutation burden (TMB), approximately ten times lower than cutaneous melanoma. In a study of metastatic tissue, TMB was 9.5 mut/mB for cutaneous melanoma and 1.5 mut/mB for acral melanoma [201]. Cutaneous melanoma, driven by UV radiation, has a high mutation load, leading to good responses to immunotherapies. Acral melanoma, however, shows significantly lower responses to these treatments. A meta-analysis found an objective response rate of 20 % for metastatic acral melanoma treated with checkpoint inhibitors, which is notably higher than with chemotherapy. Among acral melanoma patients, those treated with anti-PD-1 (n = 330) had better 12-month OS (53 %) compared to those on anti-CTLA-4 therapies (n = 94), who had 34 % survival at 12 months ($P < 0.001$) [202]. The combination therapy of anti-CTLA-4 and anti-PD-1 immunotherapy showed increased efficacy with an ORR of 43 % as compared to single-agent therapy [203]. Up to 20 % of acral melanomas carry a BRAF V600 mutation [204]. In metastatic acral melanomas, mutation testing is essential, and treatment with BRAF+MEK inhibitors should be considered, similar to other melanoma subtypes. cKIT mutations occur in 5–10 % of acral melanomas. Treatment with imatinib has shown some efficacy, with an ORR of 23.3 %, and nilotinib achieved an ORR of 26.2 % in phase II trials [205]. Treatment for metastatic acral melanoma aligns with recommendations for other metastatic cutaneous melanomas. First line therapy includes PD-1 inhibitors or combined PD-1 and CTLA-4 inhibitors. Second line options involve inclusion in clinical trials, BRAF/MEK inhibitors or cKIT inhibitors if relevant mutations are present.

11. Mucosal melanoma

The following information is an abbreviated discussion of the therapeutic options for metastatic mucosal melanoma and does not replace detailed guidelines [206,207].

Mucosal melanoma differs genetically from UV-induced melanomas, showing a lower mutation burden. It has lower rates of BRAF (0 %–21 % vs. 42 %–50 %) and RAS mutations (5 %–25 % vs. 30 %) compared to cutaneous melanoma, but a higher incidence of KIT mutations (10 %–15 % vs. 5 %–10 %) [208].

There is scarce information about systemic therapy in patients with mucosal melanoma, as these patients are frequently excluded from clinical trials. Results from the trials that included mucosal melanoma show, however, that the benefit from the systemic therapies is lower than in cutaneous melanoma. Still, the management recommendations are similar to cutaneous melanoma.

A post-hoc analysis of the Keynote-001, −002 and −006 evaluated the benefit of pembrolizumab in 84 patients with mucosal melanoma, 51 of whom were ipilimumab-naive. ORR was 19 % (95 % CI 11–29 %), with a median DOR of 27.6 months (range 1.1 + to 27.6); mPFS was 2.8 months (95 % CI 2.7–2.8), and mOS was 11.3 months (95 % CI 7.7–16.6). The ORR was 22 % (95 % CI 11–35 %) in ipilimumab-naive patients and 15 % (95 % CI 5–32 %) in those previously treated with ipilimumab [209].

A pooled analysis of five randomized trials (n = 157) showed improved benefit with nivolumab–ipilimumab (n = 35) versus nivolumab (n = 86) or ipilimumab monotherapy (n = 36) in mucosal melanoma, with mPFS of 5.9, 3.0, and 2.7 months, respectively for each therapy [210]. In the phase II C-144–01 trial, lifileucel demonstrated a promising ORR of 50 % in 12 mucosal melanoma patients who had progressed after anti-PD-1 therapy [211].

Phase II/III RELATIVITY-047 trial, where relatlimab–nivolumab showed a PFS advantage over nivolumab alone in this population (n = 51; HR 0.64, 95 % CI 0.32–1.25). Although these therapies offer hope for mucosal melanoma management, more research is needed to enhance outcomes for this underserved patient group [118].

Finally, an indirect comparison between ipilimumab plus nivolumab and relatlimab plus nivolumab in advanced melanoma showed that in patients with mucosal melanoma larger numerical differences were observed favoring nivolumab plus ipilimumab (OR, 1.59 [95 % CI, 0.62 to 4.08]) [212].

Recommendation 31.

Systemic therapy for mucosal melanoma	Consensus based recommendation
Level of recommendation B:	PD-1 based immunotherapy should be offered to patients with metastatic mucosal melanoma. Patients with metastatic mucosal melanoma should be offered combined immunotherapy with anti-PD-1 plus anti-CTLA-4 or anti-PD-1 + anti-LAG-3.
Level of evidence: 1b	De novo literature research: [210, 212]
	Consensus rate: 96% (24/26) – 2 abstain

12. Uveal melanoma

The following information is an abbreviated discussion of the therapeutic options for metastatic uveal melanoma and does not replace detailed guidelines [213].

Uveal melanoma, recognized by the EMA as an orphan disease, is distinct from cutaneous melanoma and typically involves the uvea, ciliary body, or retina. Unlike cutaneous melanoma, uveal melanoma lacks lymphatic spread, leading to metastases almost exclusively in the liver – hematogenous spread. The prognosis for metastatic uveal melanoma is generally worse compared to cutaneous melanoma. However, when comparing patients with liver metastases from both ocular and cutaneous melanoma, disease progression shows no significant differences. Due to the liver being the primary site of metastasis, patients with uveal melanoma and liver metastases may benefit from first-line local-regional treatments such as surgery, isolated hepatic perfusion (IHP), chemoablation, chemoembolization, radiofrequency ablation, or stereotactic radiotherapy (STR) [214–216].

A phase II trial evaluated 4 cycles of ipilimumab and nivolumab followed by nivolumab alone in systemic treatment-naïve patients (n = 52) [217]. Overall, 78.8 % of patients had liver metastases (M1), 56 % had extra-liver metastases (M1), and 32 % had elevated LDH. Stable disease was the most common outcome, observed in 51.9 % of patients. The primary endpoint, 1-year OS, was 51.9 % (95 % CI, 38.3 to 65.5). Median OS was 12.7 months and mPFS was 3.0 months, with higher LDH levels negatively impacting PFS.

Another phase II study evaluated the same combination in 35 patients with previously treated metastatic uveal melanoma [218]. The ORR was 18 %, with one confirmed complete response and five confirmed partial responses. The mPFS was 5.5 months (95 % CI, 3.4 to 9.5 months), and the mOS was 19.1 months (95 % CI, 9.6 months to NR).

The exact sequence and way of combining local and systemic therapy is still unknow in this setting. A phase I study including 18 patients evaluated IHP combined with ipilimumab and nivolumab. Patients were randomized to receive either (Arm A) IHP followed by 4 cycles combined immunotherapy or (Arm B) one neoadjuvant cycle of ipilimumab plus nivolumab prior to IHP followed by three cycles of the combination. In both arms, nivolumab monotherapy was given after the combination. Response was evaluable in 17 patients, with the best clinical responses reported as three complete responses (18 %), four partial responses (24 %), seven stable disease (41 %) and three progressive disease (18 %). The ORR was 63 % in Arm A (5/8) and 22 % in Arm B (2/9). Treatment with IHP and combined immunotherapy demonstrated a high but manageable toxicity profile. While the efficacy of this combination is promising, a single cycle of neoadjuvant therapy administered before IHP did not provide additional benefits [219].

Tebentafusp is a novel T-cell receptor–bispecific fusion protein targeting glycoprotein 100 (gp100) and CD3, designed to redirect T cells to kill gp100-positive melanoma cells. It is currently the only approved systemic therapy for adult HLA-A* 02:01–positive patients with unresectable or metastatic uveal melanoma. The IMCgp100–202 study compared tebentafusp with investigators' therapy of choice in patients with metastatic uveal melanoma HLA-A02 * 01 and systemic therapy naïve. After a minimum follow-up of 36 months, the mOS was 21.6 months for the tebentafusp group versus 16.9 months for the control group (HR 0.68; 95 % CI, 0.54–0.87). The 3-year OS rate was 27 % for tebentafusp and 18 % for the control [220,221]. The particularity of this therapy is that the results for radiographic response and PFS underestimated the OS benefit with tebentafusp. Patients with progressive disease in the first imaging evaluation may still benefit from the therapy. Therefore, if possible, therapy should be continued until the second radiological evaluation.

An indirect comparison between ipilimumab plus nivolumab (n = 45) and tebentafusp (n = 240) showed that the inverse probability of treatment weighting (IPTW)-adjusted OS favored tebentafusp, HR 0.52 [95 % confidence interval (CI) 0.35–0.78]; 1-year OS was 73 % for tebentafusp versus 50 % for N + I. Sensitivity analyses showed consistent superior OS for tebentafusp with all IPTW HRs $\leq$ 0.61 [222].

A phase II trial investigating the combination of pembrolizumab and entinostat - a histone deacetylase (HDAC) inhibitor showed that after a median follow-up of 14.8 months the ORR was 14 % (95 % CI: 3.9–31.7 %). The clinical benefit rate at 18 weeks was 28 %, with a mPFS of 2.1 months and a mOS of 13.4 months. The 1-year PFS rate was 17 % and the 1-year OS rate was 59 %. Better results were seen in patients with BAP1 wildtype tumors [223].

In another phase I/II study combining darovasertib, a protein kinase C inhibitor, with the c-MET inhibitor crizotinib, 30 % of 63 evaluable patients achieved a confirmed partial response, and 92 % showed tumor shrinkage. The mPFS was 6.8 months, with clinical efficacy seen in both HLA-A* 02:01-positive and -negative patients. Additionally, there were significant and sustained reductions in circulating tumor DNA (ctDNA), and the safety profile was manageable [224].

Recommendation 32 [225].

Systemic therapy for metastatic uveal melanoma	Consensus based recommendation
Level of recommendation A	Tebentafusp shall be offered to patients with metastatic uveal melanoma and HLA A02:01 genotype.
Level of evidence: 1a	De novo research: [221, 225]
	Consensus rate: 100% (23/23)

Recommendation 33.

Systemic therapy for metastatic uveal melanoma	Consensus based recommendation
Level of recommendation B	In patients without HLA A02:01 genotype and in patients with HLA A02:01 genotype progressing under or after Tebentafusp, immunotherapy with anti-PD-1 + anti-CTLA4 should be considered.
Level of evidence: 2	De novo research: [217, 218, 222]
	Consensus rate: 78% (18/23); 5 abstain

13. Consensus-building process and participants

The guidelines published here originate from contributors who were previously involved in the development of respective national guidelines. These national guidelines were written by different specialities involved in melanoma management (dermatology, medical oncology, surgical oncology, radiotherapy, pathology, and others).

These European Guidelines are not intended to replace national guidelines that consider the national specificities of health care systems. Rather, they are intended to support the development of national guidelines.

These guidelines were prepared under the auspices of the European Association of Dermato-Oncology (EADO), the European Dermatology Forum (EDF), and the European Organization for Research and Treatment of Cancer (EORTC). In a first-round medical experts who participated in their national guideline development processes were involved. In a second round, the EORTC selected experts from different specialties to contribute to these guidelines. This process was first organized in 2008/2009 and the update was developed by the same groups in 2012, 2016 and 2022. The formal recommendations were discussed and agreed upon at the consensus conferences on the 3rd of November 2023 and 8th November 2024 in Rome by the Guideline Group represented by 20 + European experts. Professor Claus Garbe and Dr Teresa Amaral, MD, PhD, Tübingen, coordinated the activities of the selected experts and the final authors. These guidelines are planned to be updated at least every three years.

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Declaration of Competing Interest

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