

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Guidelines

European consensus-based interdisciplinary guideline for melanoma. Part 2: Treatment – Update 2019

Claus Garbe ^{a,*}, Teresa Amaral ^{a,b}, Ketty Peris ^{c,d}, Axel Hauschild ^e, Petr Arenberger ^f, Lars Bastholt ^g, Veronique Bataille ^h, Veronique del Marmol ⁱ, Brigitte Dréno ^j, Maria Concetta Fagnoli ^k, Jean-Jacques Grob ^l, Christoph Höller ^m, Roland Kaufmann ⁿ, Aimilios Lallas ^o, Celeste Lebbé ^p, Josep Malvehy ^q, Mark Middleton ^r, David Moreno-Ramirez ^s, Giovanni Pellacani ^t, Philippe Saiag ^u, Alexander J. Stratigos ^v, Ricardo Vieira ^w, Iris Zalaudek ^x, Alexander M.M. Eggermont ^y On behalf of the European Dermatology Forum (EDF), the European Association of Dermato-Oncology (EADO), and the European Organization for Research and Treatment of Cancer (EORTC)

^a Center for Dermatooncology, Department of Dermatology, Eberhard Karls University, Tuebingen, Germany

^b Portuguese Air Force Health Care Direction, Lisbon, Portugal

^c Institute of Dermatology, Università Cattolica, Rome, Italy

^d Fondazione Policlinico Universitario A. Gemelli – IRCCS, Rome, Italy

^e Department of Dermatology, University Hospital Schleswig-Holstein (UKSH), Campus Kiel, Kiel, Germany

^f Department of Dermatovenerology, Third Faculty of Medicine, Charles University of Prague, Prague, Czech Republic

^g Department of Oncology, Odense University Hospital, Denmark

^h Twin Research and Genetic Epidemiology Unit, School of Basic & Medical Biosciences, King's College London, London, SE1 7EH, UK

ⁱ Department of Dermatology, Erasme Hospital, Université Libre de Bruxelles, Brussels, Belgium

^j Dermatology Department, CHU Nantes, CIC 1413, CRCINA, University Nantes, Nantes, France

^k Department of Dermatology, University of L'Aquila, Italy

^l University Department of Dermatology, Marseille, France

^m Department of Dermatology, Medical University of Vienna, Austria

ⁿ Department of Dermatology, Venerology and Allergology, Frankfurt University Hospital, Frankfurt, Germany

^o First Department of Dermatology, Aristotle University, Thessaloniki, Greece

^p APHP Department of Dermatology, INSERM U976, University Paris 7 Diderot, Saint-Louis University Hospital, Paris, France

^q Melanoma Unit, Department of Dermatology, Hospital Clinic, IDIBAPS, Barcelona, Spain

^r NIHR Biomedical Research Centre, University of Oxford, UK

^s Medical-&-Surgical Dermatology Service, Hospital Universitario Virgen Macarena, Sevilla, Spain

DOI of original article: <https://doi.org/10.1016/j.ejca.2019.11.014>.

* Corresponding author: Department of Dermatology, Eberhard Karls University, Tuebingen Liebermeisterstr. 25, 72076, Tuebingen, Germany. Fax: +49 7071 29 5187.

E-mail address: claus.garbe@med.uni-tuebingen.de (C. Garbe).

<https://doi.org/10.1016/j.ejca.2019.11.015>

0959-8049/© 2019 The Author(s). Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Please cite this article as: Garbe C et al., European consensus-based interdisciplinary guideline for melanoma. Part 2: Treatment – Update 2019, European Journal of Cancer, <https://doi.org/10.1016/j.ejca.2019.11.015>

[†] Dermatology Unit, University of Modena and Reggio Emilia, Modena, Italy

[‡] University Department of Dermatology, Université de Versailles-Saint Quentin en Yvelines, APHP, Boulogne, France

[§] 1st Department of Dermatology, University of Athens School of Medicine, Andreas Sygros Hospital, Athens, Greece

[¶] Department of Dermatology and Venereology, Centro Hospitalar Universitário de Coimbra, Coimbra, Portugal

^{||} Dermatology Clinic, Maggiore Hospital, University of Trieste, Trieste, Italy

[∞] Princess Máxima Center, 3584, CS Utrecht, the Netherlands

Received 18 November 2019; accepted 18 November 2019

Available online ■ ■ ■

KEYWORDS

Cutaneous melanoma;
Tumour thickness;
Excisional margins;
Sentinel lymph node
dissection;
Interferon- α ;
Adjuvant treatment;
Metastasectomy;
Systemic treatment

Abstract A unique collaboration of multidisciplinary experts from the European Dermatology Forum, the European Association of Dermato-Oncology and the European Organization for 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 1- to 2-cm safety margins. Sentinel lymph node dissection shall be performed as a staging procedure in patients with tumour 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 in stage III/IV patients should be primarily made by an interdisciplinary oncology team ("Tumor Board"). Adjuvant therapies in stage III/IV patients are primarily anti-PD-1, independent of mutational status, or dabrafenib plus trametinib for BRAF-mutant patients. In distant metastasis, either resected or not, systemic treatment is indicated. For first-line treatment, particularly in BRAF wild-type patients, immunotherapy with PD-1 antibodies alone or in combination with CTLA-4 antibodies shall be considered. In particular scenarios for patients with stage IV melanoma and a BRAF-V600 E/K mutation, first-line therapy with BRAF/MEK inhibitors can be offered as an alternative to immunotherapy. In patients with primary resistance to immunotherapy and harbouring a BRAF-V600 E/K mutation, this therapy shall be offered in second-line. Systemic therapy in stage III/IV melanoma is a rapidly changing landscape, and it is likely that these recommendations may change in the near future.

© 2019 The Author(s). Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. 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* [1]. Part 1 includes 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 as per the Oxford classification (detailed in Garbe *et al*. Part 1). Recommendations were based on the level of best quality available evidence. The strength of the recommendations was 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'.

2. 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 take into account scientific progress since the publication of the guideline. In the selection and dosage of the drugs, attention was paid to compliance with the therapeutic recommendations given. Nevertheless, users are requested to use package inserts and technical information from the manufacturers as a backup and, in case of doubt, to consult a specialist. The user remains responsible for all diagnostic and therapeutic applications, drugs and doses.

3. Scope

This guideline has been written to assist clinicians in treating patients with invasive cutaneous and metastatic melanoma. This publication was conceptualized mainly because of 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.

4. Surgical therapy

4.1. General principles

The primary treatment of melanoma is surgical excision [2–4]. An excisional biopsy with a minimum clinical margin (1–3 mm) is preferred, both to give the dermatopathologist/pathologist an optimal specimen and to allow evaluation of the excision margins for residual tumour. Incisional biopsies should not be performed when an excisional biopsy is technically possible. Such procedures may result in diagnostic error because of sampling and may compromise the analysis of architectural features or the estimation of Breslow thickness. On occasion, they are necessary to confirm the diagnosis, such as when dealing with a large lentigo maligna on the face, or with acral melanoma. Large studies have shown no evidence that incisional biopsies worsen prognosis as compared with immediate complete excisional biopsy [5,6].

Recommendation 10 (numbers continued from Part 1)

Primary excision	Consensus-based recommendation
GCP	When melanoma is suspected, the whole lesion should be completely excised with a narrow (1–3 mm) 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%

Recommendation 11

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 performed. Consensus rate: 100%

4.2. Primary melanoma

Excision of safety margins remains a standard of care in patients with melanoma. The current recommendations

are based on both prospective, randomised studies and international consensus conferences [2,7–11]. A randomised, open-label multicenter clinical trial comparing 1 cm vs 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 [12]. A recent meta-analysis also found out that there is a statistically significant worse melanoma-specific survival with narrow margins (1–3 cm) than with wider margins (3–5 cm) with no treatment effect on recurrence-free survival [13]. However, with regard to melanoma-specific survival, only 4 trials were eligible, and the hazard ratio (HR) in favour of wider margins was largely affected by the positive trial of Hayes *et al.* [12] (3 cm versus 1 cm), whereas another study comparing 4 cm versus 2 cm did not show any statistical difference in thicker melanomas [14].

Even though a slight variation is observed among guidelines, margins wider than 2 cm are not recommended even in cases of thick primary tumours. The recommendations in the following section are in concordance with the American, UK and Australian recommendations. 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.

Recommendation 12

Safety margins for secondary excision (re-excision)	Evidence-based recommendation
GCP	In the case of primary melanoma, a subsequent excision should be performed to minimise the risk of local recurrences. The following safety peripheral surgical margins* should be considered: in situ—0.5 cm < 2 mm tumour thickness: 1 cm and >2 mm tumour thickness: 2 cm. Larger excisions are not recommended. Guideline adaptation [15,16] Consensus rate: 100%

*Margins are to be measured clinically and not pathologically.

Recommendation 13

Safety margins for secondary excision (re-excision) in special anatomic locations	Evidence-based recommendation
GCP	Narrower margins for re-excision may be exceptionally considered for special anatomic locations to preserve function and to allow reconstruction, particularly in facial, acral and genital lesions. Guideline adaptation [15,16] Consensus rate: 90%

4.3. Lentigo maligna

Lentigo maligna is a slowly growing melanoma in situ, which occurs typically in UV-exposed areas like the face [17]. A recent Cochrane review about interventions in melanoma in situ failed to find randomised clinical trials of surgical interventions aiming to optimise 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 [18]. 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 [19]. A single-center retrospective study compared conventional surgical excision and 'slow Mohs surgery' for patients with lentigo maligna melanoma. This study concluded that surgical margins of 0.5 cm are inadequate for the treatment of a considerable number of lesions on the head, particularly if these are recurrent. 'Slow Mohs' using routinely stained paraffin-embedded sections was shown to be the treatment of choice in such cases, particularly for recurrent lesions or lesions with poorly defined borders or possible subclinical extension [20]. 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 [20].

As for non-surgical interventions, high-quality evidence does not support the use of imiquimod as a single therapy in non-selected cases [18]. However, several retrospective analyses and phase II trials support a role for topical imiquimod as a potential alternative to surgery in selected cases not eligible for surgery or radiotherapy (RT) [21], as well as for incompletely excised tumours or as an adjuvant option for those treated through narrow margins [22]. The complete response rate to imiquimod treatment is in the range of 75%–88% [23–25]. Pre-treatment mapping biopsies, or likewise in vivo reflectance confocal microscopy can be used to assess the extent of the lesion [26].

4.4. Acral and mucosal melanomas

Lentiginous acral and mucosal melanomas are often poorly defined and multifocal with discrepancies between the clinically visible and histopathologic margins, and therefore local recurrences are more frequent.

Therefore, removal is usually attempted with increased safety margins (at least 1 cm) or by narrow margins

Recommendation 14

Microscopically controlled surgery	Consensus-based recommendation
GCP	In some melanoma subtypes, such as lentigo maligna melanoma, genital and acral melanomas, microscopically controlled surgery can be used to spare tissue and to ensure complete resection. Consensus rate: 100%

with micrographic control (e.g. Mohs' technique and variants) [27–29]. The micrographic technique is intended to conserve tissue especially on the hands and feet.

4.5. Sentinel lymph node biopsy

The sentinel lymph node biopsy (SLNB) was introduced to allow the evaluation of the first draining lymph node(s) in the regional lymphatic system, avoiding the surgical morbidity from unnecessary elective lymph node dissections [30]. SLNB is a staging procedure, appropriate for patients in whom neither palpation nor lymph node sonography has suggested the presence of lymph node metastases. SLNB provides information about survival outcomes of patients with melanoma. As all the adjuvant trials have selected the patients on the basis of positivity of SLNB, the SLNB status is required for the new adjuvant options. As for the impact of SLNB on patients' survival, multicenter studies have shown that despite a slight increase in recurrence-free survival in patients undergoing SLNB, it has failed to show any impact on overall survival (OS) [31,32,33].

Despite this weak background in melanoma ≥ 1 mm thickness, recent guideline updates recommend SLNB as a standard procedure to be offered also to patients with primary melanoma with Breslow thickness ≥ 1.0 mm or ≥ 0.8 mm with additional risk factors (ulceration, ≥ 1 mitosis/mm², microsatellites, etc.) [34,35].

Recommendation 15

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 performed in patients with tumour thickness ≥ 1.0 mm or ≥ 0.8 mm with additional histological risk factors.
Level of evidence: 1a	De novo literature research [36,37] Consensus rate: 100%

4 6. Procedure in patients with negative SLN

No further lymph node surgery is required.

4 7. Procedure in patients with micrometastases in SLN

Complete removal of the regional basin has been routinely offered to patients having micrometastasis of the sentinel lymph node. The results of the recently published DeCOG (German Dermatologic Cooperative Oncology Group) and MSLT-II (Multicenter Selective Lymphadenectomy Trial) clinical trials constrain 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 completion lymph node dissection (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 [38,39]. In the MSLT-II, 86% of the patients in both study groups (CLND or observation) were alive after 3 years [33]. Moreover, in the MSLT-II, the percentage of patients with non-sentinel node metastases was 20% at 5 years. Consequently, 80% of the CLND performed might have been avoided [33].

In view of these findings, the decision-making in patients with metastasis of the sentinel lymph node should start with an exhaustive assessment of clinical criteria and sentinel lymph node pathology findings. In those patients without high-risk criteria (extracapsular extension, >3 metastatic lymph nodes, lymph vascular invasion, microsattelitis and immunosuppression) and with a sentinel lymph node tumour burden of less than 1 mm, current evidence supports abandoning CLND [34]. These patients should be enrolled in intensive follow-up programs based on regional ultrasound. Patients with high-risk criteria mentioned previously were underrepresented in

Recommendation 16

Management of micrometastasis	Evidence-based recommendation
Level of recommendation A	In patients with sentinel lymph node micrometastasis, complete lymphadenectomy shall no longer be performed. There is an indication for adjuvant systemic therapy and stage-specific follow-up.
Level of evidence: 1a	De novo literature research [33,38,39] Consensus rate: 100%

clinical trials. Nevertheless, survival benefits are expected neither in this subgroup.

4 8. Clinically-identified lymph node metastases

If lymph node metastases are diagnosed clinically or by imaging techniques (including ultrasound), complete lymph node dissection is considered standard therapy [34,40].

Recommendation 17

Lymphadenectomy in regional lymph node metastases	Consensus-based recommendation
GCP	If regional lymph node metastases have been detected clinically or by imaging, complete lymphadenectomy shall be performed. Consensus rate: 100%

4 9. Skin metastases

Depending on the number, size and location different options include surgery or other destructive therapies such as cryotherapy, laser therapy electrochemotherapy, but also systemic therapies with targeted therapy (TT) or immunotherapy (IT), intralesional/topical immunotherapy such as talimogene laherparepvec [41], IL-2, or imiquimod, and RT. Isolated limb perfusion with melphalan ± tumour necrosis factor is an invasive technique with only palliative value [42,43].

4 10. Distant metastases

If technically feasible and reasonable (oligo metastatic disease), then complete operative removal of distant metastases should be still seen as an interesting option for patients with tumour markers lactate dehydrogenase (LDH) and protein S100B in the normal range, although it is particularly true that this population is also one of the best respondents to systemic therapies [44]. Many studies show that excision of solitary or few metastases can be associated with a favourable outcome for stage IV patients [45–48]. The possibility of neoadjuvant therapy followed by surgical excision of metastatic lesions can be considered [49]. In case of brain metastases, stereotactic radiation therapy and surgery are considered equally effective for the local control of brain metastases, but stereotactic surgery is non-invasive, applicable to several brain metastases and easily repeatable.

The value of debulking procedures must be viewed critically, as there is no evidence that they improve survival. In some circumstances, there is a value for

palliation, particularly in combination with post-operative RT for local disease control.

Recommendation 18

Surgical treatment of distant metastases	Evidence-based recommendation
Level of recommendation C	In case of oligometastatic disease and if complete resection is feasible, a complete metastasectomy can be considered. Metastasectomy can also be considered as a palliative procedure.
GCP	Guideline adaptation [15,16] Consensus rate: 100%

5. Radiotherapy

5.1. Primary melanoma

Radiotherapy (RT) of the primary tumour is rarely indicated. However, in patients where the surgical procedure will lead to severe disfigurement, RT can be applied with curative intent. This is often the case for lentigo malignant melanoma [50].

5.2. Regional lymph nodes

There is no established role for adjuvant RT of draining lymph nodes after excision of the primary melanoma. Adjuvant RT after lymphadenectomy has been evaluated in a randomised clinical trial [51], proving the efficacy of RT 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 on RT, developing grade III–IV toxicity [52].

5.3. Oligometastatic disease

In patients with oligometastatic disease, RT represents a treatment alternative to surgery in cases where surgical access is associated with high risk of significant surgical complications.

5.4. Skin metastases

In-transit metastases, which are too extensive for a surgical approach, may be controlled by RT alone [53].

5.5. Bone metastases

RT is effective to palliate patients with bone metastases. The response rate (complete response + partial response) is 67–85% [54–57]. The major indications are pain, loss of structural stability (fracture risk) and compression of the spinal canal with or without neurological symptoms.

5.6. Brain metastases

Melanoma has a marked propensity to metastasize to the brain. Systemic treatment strategies for brain metastases with high response rates combined with a short time to response using combination immunotherapy [58,59] or targeted therapies (BRAF-mutated melanomas) [60] must lead to renewed considerations on how to plan the optimal treatment of patients with melanoma with brain metastases.

Preclinical evidence has suggested a positive effect of the combination of immunotherapy and RT, and a number of clinical trials are currently in progress evaluating the possible additive effect of this combination [61,62] or with BRAF + MEK inhibitors in BRAF-mutated melanomas. Recent publications support the concomitant use of immunotherapy and stereotactic radiosurgery (SRS) [63,64].

Whole brain RT (WBRT) may cause serious long-term cognitive toxicity and therefore increased focus on SRS has emerged [65]. Clinical trials have increased local control in patients with 1–10 brain metastases by using adjuvant SRS after surgery [66]. Therefore, WBRT should be restricted to few patients without other systemic and local options.

6. Adjuvant therapy

6.1. General principles

Adjuvant therapy is offered to patients without evidence of macroscopic metastases but at high risk of having microscopic metastases. In published trials, adjuvant therapy is predominantly used in patients with tumours thicker than 1.5 mm, or by American Joint Committee on Cancer (AJCC) staging criteria, in patients with completely resected stage II–IV melanoma. With the effective recently approved drugs in advanced melanoma [67], we have witnessed within a time span of only 4 years (2015–2018), the results of 4 randomised controlled trials, demonstrating a significant and clinically meaningful impact of adjuvant immunotherapy or targeted therapy on relapse-free survival (RFS). Prolonged RFS has been reported for adjuvant therapy with ipilimumab [68], nivolumab [69], pembrolizumab [70] and for therapy with dabrafenib and trametinib in patients with BRAF-mutated melanoma [71]. Data demonstrating a significant impact on OS have been reported for ipilimumab [72] and for dabrafenib and trametinib.

6.2. Adjuvant immunotherapy with interferon- α

Interferon- α was the first substance in the adjuvant therapy of melanoma to have shown a significant improvement of disease-free survival and in some prospective randomised trials, also an impact on OS, albeit

with significant toxicity [73–85]. Based on the superior data for adjuvant therapy with PD-1 and BRAF/MEK inhibitors in stage III melanoma (refer in the following section) interferon- α should not be used any more as a first-line option for adjuvant therapy in this patient group.

6.3. Adjuvant immunotherapy with CTLA-4 or PD-1 antibodies

Based on its successful use in unresectable metastatic melanoma, checkpoint inhibitor–based immunotherapy was also tested in the adjuvant treatment of completely resected locoregional or distant metastatic patients. The following adjuvant immunotherapy trials were conducted (Table 1)

6.3.1. Ipilimumab

The European Organization of Research and Treatment of Cancer (EORTC) 18071/Checkmate 029 [68] compared the CTLA-4 blocking antibody ipilimumab 10 mg/kg given every 3 weeks for the first 12 weeks followed by an infusion every 12 weeks for up to 3 years versus placebo in patients with stage IIIA(>1 mm)/B/C (AJCC 7th edition) [86]. Adjuvant ipilimumab had a modest but significant impact on RFS, with an HR of 0.75, and RFS rates at 12 and 18 months that are 9% and 8% better for ipilimumab [68]. At 5 years, RFS rates were 11% better for RFS as well as for OS [72]. Adjuvant therapy with ipilimumab is however only approved by the US-Food and Drug Administration (FDA), and not by European Medicines Agency (EMA).

6.3.2. Nivolumab

Based on the results of EORTC, 18071 adjuvant 1 year of nivolumab 3 mg/kg every 2 weeks was compared with ipilimumab 10 mg/kg in Checkmate 238 [69] in patients with completely resected stage IIIB/C-IV (AJCC 7th edition) [86]. Nivolumab was superior to ipilimumab

with an HR of 0.65 and RFS rates at 12 and 18 months of 10% and 11%, respectively, better than for Ipilimumab [69]. The curves are a bit lower than in the other trials because the trial population stage IIIB/C-IV has poorer prognosis than the population studied in the other 3 trials (stage IIIA >1 mm/B/C). Furthermore, this is the only trial with an active comparator arm, which also has to be taken into account if comparing between the different trials.

6.3.3. Pembrolizumab

Pembrolizumab 200 mg every 3 weeks for 1 year was tested against placebo in EORTC1325/Keynote 054 [70] in patients with stage IIIA (>1 mm)/B/C (AJCC 7th edition) [86]. RFS was significantly improved with an HR of 0.57 and an RFS rate difference at 12 and 18 months of 14 and 18%, respectively [70].

6.3.4. Consistency across trials

In the EORTC 18071/Checkmate 029 [68] trial of ipilimumab versus placebo for resected, high-risk stage III melanoma, the 1-year RFS rate for ipilimumab was, despite the difference in the patient populations, comparable with the rate observed in the ipilimumab arm of Checkmate 238. Therefore, comparisons were made between the nivolumab arm of Checkmate 238 and the placebo arm of EORTC 18071/Checkmate 029 showing a reduction of RFS with a hypothetical HR of slightly below 0.50, thereby indicating a similar efficacy of both PD-1 antibodies. Further credence to the great consistency of the data of these trials is that in the overlapping stage IIIB/C patient populations, the 18-month RFS rates were virtually identical: 72.2% and 72.3% for the pembrolizumab group (EORTC1325/Keynote 054 [70]) and the nivolumab group (Checkmate 238 [69]), respectively.

6.3.4.1. Treatment-related adverse events. Adjuvant ipilimumab 10 mg/kg was clearly associated with the highest rate of treatment-related AEs. Immune-related adverse

Table 1

Key parameters of adjuvant trials with immune checkpoint inhibitors or BRAF/MEK inhibitors.

Trial	Treatment arm	Comparator arm	Patient population ^a	HR for RFS/DFS	HR for OS	Grade III–IV AEs in % ^b	Reference
EORTC 18071 Checkmate 029	Ipilimumab 10 mg/kg	Placebo	IIIA(>1 mm)/B/C	0.76	0.72	54	[68,72]
Checkmate 238	Nivolumab 3 mg/kg	Ipilimumab 10 mg/kg	IIIB/C-IV	0.65	NA	25.4	[69]
EORTC 1325 Keynote 054	Pembrolizumab 200 mg	Placebo	IIIA(>1 mm)/B/C	0.57	NA	31.6	[70]
BRIM 8	Vemurafenib 960 mg BID	Placebo	IIC, IIIA/B/C	0.54 ^c	NA	57	[87]
Combi-AD	Dabrafenib 150 mg BID & Trametinib 2 mg OD	Placebo	IIIA(>1 mm)/B/C	0.49	0.57	41	[71,88]

DFS = disease-free survival; OS = overall survival; EORTC, European Organization of Research and Treatment of Cancer; HR = hazard ratio; AEs = adverse events.

^a Patients after complete resection of metastases, all trials used AJCC 7th edition.

^b Any AEs regardless of treatment relation.

^c Result not statistically significant.

events (irAEs) occurred in 94% of the patients, with 5 patients who died. In sharp contrast, both the nivolumab and the pembrolizumab trial demonstrated very similar and favourable side-effect profiles with treatment-related grade III–IV. AEs in about 14% of patients and AEs that led to treatment discontinuation are in about 10–14%. In the pembrolizumab trial, however, there was one treatment-related death (myositis), in the nivolumab trial zero. Relatively frequent was grade I–II thyroid-endocrinopathy (20%) that was easy to treat. Although irAEs grade III–IV events were rare in anti-P-1 trials, permanent complications with impact on the survival-like diabetes (1%) are critical in the adjuvant setting.

6.4. Adjuvant-targeted therapy with BRAF/MEK inhibitors

Two large-sized, prospectively randomised trials on either of the BRAF inhibitor vemurafenib alone ('BRIM8') or the combination of the BRAF inhibitor dabrafenib and the MEK inhibitor trametinib ('COMBI-AD') have been performed in patients with completely resected BRAF V600-mutated locoregionally metastatic melanoma (Table 1).

6.4.1. Vemurafenib

BRIM8 [87] was a trial designed before combined treatment with BRAF and MEK inhibitors became the standard of care for BRAF-mutated melanoma. It compared 1 year of treatment with vemurafenib 960 mg BID vs. placebo in patients with completely resected BRAF V600-mutated melanoma in stages IIC, IIIA/B (cohort I) and IIIC (cohort II, all AJCC 7th edition) [86]. No significant benefit was noted for disease-free survival (DFS) in stage IIIC, and DFS was improved only numerically in patients with stage IIC-IIIB disease in cohort 1 with an HR of 0.54 and 12 and 24 DFS rate differences of 18 and 15%, respectively. Results in cohort 1 were not statistically significant, and the study did therefore not reach its primary end-point.

Grade III–IV AEs were observed in 57% of patients with 20% of patients in the vemurafenib arm discontinuing therapy because of AEs, notably keratoacanthomas/cutaneous squamous cell carcinomas, a well-known side-effect of BRAF inhibitor monotherapy.

6.4.2. Dabrafenib plus trametinib

The Combi-AD trial [71] compared 1 year of the combination of 150 mg dabrafenib BID with 2 mg trametinib OD (D + T) against a matched placebo in patients with stage IIIA(>1 mm)/B/C melanoma with a BRAF-V600 E/K mutation. It demonstrated a highly significant benefit in RFS with an HR of 0.47 and 12-month and 18-month RFS rate differences of 32% and 31%, respectively. A cure rate model analysis was performed at a median follow-up of 44 months in the D + T and 42

months in the placebo arm, suggesting a difference of 17% in patients never relapsing for D + T over placebo [88]. An assessment of OS differences at a median follow-up of 2.8 years did demonstrate an improvement in OS for D + T with an HR of 0.54 and a 13% difference in OS rates at 3 years.

The oral drug combination of D + T in the Combi-AD trial was associated with more AEs than the anti-PD-1 trials but less than the ipilimumab trial. The D + T combination was associated with pyrexia grade I–II in 97% with chills in 37%, and grade III–IV pyrexia in 5%. Grade III–IV events occurred in 41% of the patients, i.e. hypertension (6%), fatigue (4%) and hepatitis (4%). Drug related AEs lead to drug discontinuation in 26% of patients.

19

Adjuvant therapy in stage III/IV	Evidence-based recommendation
Level of recommendation A	Adjuvant therapy (anti-PD-1 or targeted therapy) shall be offered to all patients in stages IIIA – IIID and fully resected stage IV. Adjuvant anti-PD-1 therapy can be offered to patients in stages IIIA – IIID and fully resected stage IV irrespective of the mutational status. Adjuvant BRAF/MEK inhibitor therapy can be offered to patients with BRAFV600 E/K mutation in stages IIIA – IIID. For stage IIIA with nodal metastasis of less than 1 mm in diameter, the risk/benefit ratio should be carefully discussed with the patient.
Level of evidence: 1b	De novo literature research [69–71] Consensus rate: 100%

6.5. The new adjuvant landscape and future development

In the moment, the HRs for RFS are in a similar range within the 3 trials. With respect to the distant metastasis-free survival end-point, the data are very consistent with the RFS data. The data are final in the Combi-AD trial and exploratory in the nivolumab and pembrolizumab trials but in essence show HRs consistent with the RFS HRs.

There is a clear difference in the rate and quality of side-effects between PD-1 and BRAF/MEK inhibitors. Although the rate of grade III–IV side-effects is lowest for nivolumab and pembrolizumab both drugs can have long-lasting or life threatening immune-related side-effects (e.g. diabetes, hypophysitis and myocarditis) in a small minority of patients. In contrast, more patients stop therapy because of AEs with D + T, but AEs usually subsiding quickly after discontinuation of the drug(s).

CLND has been a mandatory component in all adjuvant phase III trials but is currently no longer considered mandatory.

6.5.1. The next steps

Current studies in the adjuvant field look at the combination of a reduced dose of ipilimumab with standard doses of nivolumab (Checkmate 915, NCT03068455) or at the adjuvant use of PD-1 antibodies in patients with high-risk primary melanoma i.e. stage IIB and IIC (Keynote 716, NCT03553836; Checkmate 76K, NCT04099251) [89]. Future trials will also assess the use of BRAF and MEK inhibition in stage II disease and the use of sequential therapy of BRAF/MEK and PD-1 inhibition in the adjuvant setting.

Further clinical development may involve neoadjuvant use of pembrolizumab, nivolumab most likely in combination with ipilimumab, or a BRAF/MEK inhibitor combination, especially attractive in palpable nodal stage III disease. One of the advantages of the neoadjuvant setting over adjuvant is that the efficacy of the drug can be confirmed by its direct effect on the nodal disease. Moreover, neoadjuvant therapy may facilitate surgery, reduce RT and increase locoregional control. Impressive results have been obtained with BRAF/MEK combinations, with a 100% response rate and reduced relapse rates [90]. The combination of nivolumab and ipilimumab is highly active as well and, interestingly induces a greater number and variety of T-cell receptor (TCR) clones than adjuvant therapy with the same regimen [91] while PD-1 antibodies alone seem to be less active [92]. Grade III–IV toxicities are observed in 80–90% of patients at approved standard doses of ipilimumab and nivolumab but low-dose ipilimumab (1 mg/kg) with nivolumab at 3 mg/kg showed comparable efficacy but significantly reduced toxicity [93]. Most interestingly, the paradigm that surgery has to be used in every patient following neoadjuvant treatment of palpable nodal disease is, based on the high pathological complete remission observed after neoadjuvant treatment with ipilimumab and nivolumab, currently challenged in the PRADO-extension of the OPACIN-neo trial (NCT02977052).

Currently, most of these trials are however based on small patient groups, and therefore these data will have to be confirmed in larger data sets before they can be introduced into standard clinical care.

7. Systemic therapy for metastatic disease

7.1. General principles

The major indications for systemic therapy are inoperable regional metastases and distant metastases (stage IV). From the long list of available cytostatic drugs, only a few have been able to induce tumour

responses but almost no long-lasting responses with an impact on survival. New targeted compounds and immunotherapeutic drugs have however shown to prolong survival significantly [94,95]. The two main goals of systemic therapy are:

- Prolongation of progression-free survival (PFS) and OS with acceptable drug toxicities
- Reduction of tumour load or specific tumour-related symptoms to increase the quality of life

7.2. Immunotherapy

Cytokines such as interferon-alpha and interleukin-2 were examined in several clinical trials in melanoma and achieved low response rates (10–16%) in non-randomised trials. Randomised clinical trials on these agents are still not available. Vaccination strategies have raised a lot of interest, but so far no efficacious vaccines have been developed [96].

Blockade of immune checkpoint mechanisms with antibodies to CTLA-4 and PD-1 expressed by lymphocytes abrogates down-regulation of immune responses and leads to continued activation of lymphocytes, enabling killing of tumour cells. This immunostimulation is non-specific and can lead to immunologically mediated toxicity. The anti-CTLA-4 antibody ipilimumab was the first immunotherapy that showed a benefit for OS in two controlled trials in metastatic melanoma [95–102]. Ipilimumab is approved for melanoma therapy by the FDA and EMA. It is presently administered as four intravenous infusions at a dose of 3 mg/kg/infusion separated by three weeks. Serious autoimmune reactions including skin rashes, colitis, thyroiditis, hepatitis, hypophysitis and others can develop in some patients and require interdisciplinary management. Early recognition of these side-effects is essential and requires specific training of the treating physicians.

The response rate to ipilimumab is only about 15%, but remarkable durable remissions were observed in stage IV patients previously treated with other drugs. Patients with stable disease or initial disease progression can also benefit with prolonged survival. Meanwhile, the introduction of PD-1 antibodies changed the role of ipilimumab, which is no longer considered as the treatment of choice for first-line therapy, but ipilimumab will be used in combination with PD-1 antibodies or as second-line therapy.

The anti-PD-1 antibodies nivolumab and pembrolizumab are FDA-approved and EMA-approved for the treatment of unresectable metastatic melanoma. Nivolumab was shown to improve PFS and OS as compared with dacarbazine (CheckMate-066 trial [103]) and as compared with ipilimumab (CheckMate-067 trial [104]). Pembrolizumab showed improved PFS and OS in

comparison with ipilimumab (KEYNOTE-006 trial [105]). Objective response rates of 35%–42% were achieved with PD-1 blockade. Long-term survival data after 5 years are now available and show a survival rate of 34% for any line of treatment (KEYNOTE-001 trial) and 43% for treatment-naïve patients (KEYNOTE-006), respectively [105,106]. PD-1 blockade is considered as an effective option for the first-line treatment of patients with both BRAF wild-type and mutated tumours. The dose of nivolumab and pembrolizumab depends on which type of administration schema is used (Table 2). A body surface–based dose or a flat dose can be offered. The difference between these options is the frequency, and patients' preferences should be taken into consideration when discussing which schedule to choose.

The combination of nivolumab with ipilimumab has been shown to be superior, in terms of PFS, to ipilimumab and to nivolumab as single drugs (CheckMate-067 trial [104]) and is therefore approved by the FDA and EMA. However, OS data showed a trend, but no significance in a comparison with nivolumab monotherapy with the combination only. The long-term survival data after 4 years indicate the excellent therapeutic potential with a durable, sustained survival benefit and a hope for cure, both with nivolumab alone and the

combination approach [104]. Because there is substantially more toxicity, including irreversible AEs, with the ipilimumab/nivolumab combination, this treatment needs to be supervised by experienced physicians, who are familiar with immune AE management procedures.

Combining nivolumab with ipilimumab, toxicity can be reduced by choosing a lower dose of ipilimumab with 1 mg/kg and a higher dose of nivolumab of 3 mg/kg in the first four cycles of the induction phase, as shown in the Checkmate 511 trial. The grade III/IV toxicity was reduced by half, whereas the efficacy was largely the same. However, the follow-up in this trial did not yet exceed 18 months, and longer follow-up is needed to confirm the equivalence of the efficacy. Therefore, we listed this schedule in Table 2, and treatment based on this scheme may be considered, but it seems to be too early to give a general recommendation for this scheme.

Table 2

Checkpoint blockade therapies for advanced cutaneous melanoma described in prospective randomised trials.

Medication	Dose	Response rate
Ipilimumab [95,102]	3 mg/kg i.v. every 3 weeks for four cycles	12–19%
Nivolumab [103,110]	3 mg/kg i.v. every 2 weeks until tumour progression	40%–44%
Nivolumab [111]	480 mg i.v. every 4 weeks (flat dose) until tumour progression	
Pembrolizumab [107]	2 mg/kg i.v. every 3 weeks until tumour progression	33%
Pembrolizumab [112,113]	400 mg i.v. every 6 weeks (flat dose) until tumour progression 200 mg i.v. every 3 weeks (flat dose) until tumour progression	
Nivolumab + Ipilimumab [104,108]	Ipilimumab 3 mg/kg i.v. plus nivolumab 1 mg/kg i.v. every 3 weeks for four cycles, continuation with 3 mg/kg nivolumab every 2 weeks until tumour progression	50–58%
Nivolumab + Ipilimumab [109]	Ipilimumab 1 mg/kg i.v. plus nivolumab 3 mg/kg i.v. every 3 weeks for four cycles, continuation with 3 mg/kg nivolumab every 2 weeks until tumour progression	64%

i.v., intravenous.

Recommendation 20

Immunotherapy in stage IV	Evidence-based recommendation
Level of recommendation A	In stage IV patients, immunotherapy with checkpoint inhibitors shall be offered as first-line. The options include anti-PD-1 monotherapy and combination of anti-PD-1 plus anti-CTLA-4.
Level of evidence: 1b	De novo literature research [103,107–110] Consensus rate: 100%

7.3. Targeted therapy

In melanoma, different activating mutations have been described, mainly resulting in an increased signalling of the MAP kinase and AKT pathways [97]. Numerous targeted inhibitors have already been developed or are under clinical investigation.

About 45% of patients with cutaneous melanoma carry an activating BRAF V600 mutation, for which several highly selective inhibitors have been developed. Vemurafenib and dabrafenib were shown to achieve a high rapid tumour response rate (roughly 50%) in patients carrying the V600E mutation and a substantial prolongation of PFS and OS in comparison with dacarbazine (DTIC) [94,95,97,98]. Vemurafenib and dabrafenib are approved for melanoma therapy in the US and the EU. Vemurafenib is administered as an oral drug with a current standard dose of 960 mg twice daily and dabrafenib as an oral drug with a standard dose of 150 mg twice daily. Minor systemic (arthralgia, fatigue) but major cutaneous side-effects have been reported, including photosensitivity (only vemurafenib), development of epithelial tumours and in rare cases new primary melanomas. Development of secondary resistance to BRAF inhibitors with varying time courses is a frequent event. MEK inhibitors meanwhile supplement

the inhibition of the MAP kinase pathway, and combinations of BRAF and MEK inhibitors like vemurafenib/cobimetinib (coBRIM trial [114]) dabrafenib/trametinib (COMBI-d, COMBI-v [115,116]) and recently encorafenib/binimetinib (COLUMBUS [117]) were shown in four independent phase III trials to significantly increase objective response rate, PFS and OS. Therefore, the combination of BRAF and MEK inhibition is the current standard in the treatment of patients with BRAF mutations, where this treatment strategy is indicated (Table 3). A recent update on a pooled analysis of COMBI-d/v reported for the first time 5-year survival data. Thirty-four percent of all patients treated with dabrafenib/trametinib were still alive. If these patients demonstrated normal LDH levels at baseline, this increased to 41% [115].

A small proportion of melanomas arising in sun-protected sites have mutations in cKIT and they have been treated with the cKIT inhibitor imatinib mesylate. Responses have been described in case reports, and a phase II trial revealed an objective response rate of 23% in patients with cKIT-mutated melanoma (Table 3) [118].

A NRAS mutation is detected in 15–20% of cutaneous melanomas. Presently, there are no effective NRAS-inhibiting molecules available. Trials have been performed in these patients with MEK inhibitors such as binimetinib (NEMO trial [119]) and pimasertib

(NCT01693068). A low response rate has been observed but no significant impact on OS. Furthermore, the MEK inhibitor binimetinib appeared to be more toxic than a single-agent treatment with conventional DTIC chemotherapy [119].

Recommendation 21

Targeted therapy in stage IV	Evidence-based recommendation
Level of recommendation A	In particular scenarios* for patients with stage IV melanoma and a BRAF-V600E or V600K mutation, first-line therapy with BRAF/MEK inhibitors can be offered as an alternative to immunotherapy. In patients with primary resistance to immunotherapy and harbouring a BRAF-V600E or V600K mutation, this therapy shall be offered in second-line.
Level of evidence: 1b	De novo literature research [105,114,116,117] Consensus rate: 90%

*particular scenarios: high LDH, high tumour burden or aggressive course of the disease, which will leave not enough time for developing an effective anti-tumour immune response. LDL, lactate dehydrogenase

7.4. Chemotherapy

Chemotherapy was the only available systemic treatment before targeted therapies and immune checkpoint modulators became available. Presently, chemotherapy may only be considered as last-line treatment in patients with resistance to immunotherapies and – where applicable – targeted therapies. However, single-agent and combination chemotherapy may still play a role in countries where the new and more effective drugs are still not available and/or reimbursed.

A number of agents with comparable effectiveness are used for systemic chemotherapy of advanced melanoma. Chemotherapy can lead to the regression of tumours and a reduction in tumour-related symptoms, but no regimen has demonstrated a survival advantage over symptom palliation. The longest established monotherapy is DTIC. Several multicenter trials, however, have demonstrated that response rates are in the range of only 5–12% with few complete responses (Table 4) [126–129].

Recommendation 22

Chemotherapy in stage IV	Consensus-based recommendation
GCP	Chemotherapy should be considered only when there is resistance to immunotherapy and targeted therapies. Consensus rate: 100%

Table 3

Targeted therapy for advanced cutaneous melanoma described in prospective randomised trials or phase II studies, if phase III trials were not available.

Medication	Dose	Response rate
BRAF mutation		
Dabrafenib + Trametinib Long 2014, Robert 2014 [120,121]	2 × 150 mg p.o. daily 1 × 2 mg p.o. daily	64%–67%
Vemurafenib + Cobimetinib Ribas 2014, Larkin 2014, Ascierto 2016 [114,122,123]	2 × 960 mg p.o. daily 1 × 60 mg p.o. daily for 21 days, followed by 7 days off treatment	54–68% 68–76%
Encorafenib + Binimetinib Dummer May 2018, Dummer Oct 2018 [117,124]	1 × 450 mg p.o. daily 2 × 45 mg p.o. daily	
cKIT mutation		
Imatinib mesylate Guo 2011 [118]	1 × 400 mg p.o. daily until tumour progression	23%
NRAS mutation		
Binimetinib NCT01763164; Dummer 2017 [119,125]	2 × 45 mg (3 × 15 mg tablets) p.o. daily until tumour progression	15%

Table 4

Examples of monochemotherapy and polychemotherapy for advanced cutaneous melanoma described in prospective randomised trials or phase II studies, if phase III trials were not available.

Medication	Dose	Response rate
Dacarbazine	250 mg/m ² i.v. daily for 5 days every 3–4 weeks	12.1–17.6%
Ringborg 1989, Middleton 2000	800–1200 mg/m ² i.v. daily on one day every 3–4 weeks	5.3–23%
Chiaroni Sileni, 2001, Young 2001 [129–132]		
Temozolomide	150–200 mg/m ² p.o. daily for 5 days every 4 weeks	13.5–21%
Bleehen 1995, Middleton 2000 [129,133]		
Fotemustine	100 mg/m ² i.v. on days 1, 8 and 15; then 5 week pause, then repeat single dose every 3 weeks	7.4–24.2%
Jacquillat 1990, Mornex 2003 [134,135]		
CarboTax	Carboplatin AUC6 i.v. day 1, after four cycles reduce to AUC4	(12.1% second-line)
Rao 2006 [136]	Paclitaxel 225 mg/m ² i.v. day 1 every 3 weeks, after four cycles reduce to 175 mg/m ²	
DVC	DTIC 450 mg/m ² i.v. days 1 + 8	24%
Verschraegen 1988 [137]	Vindesine 3 mgm ² i.v. days 1 + 8 Cisplatin 50 mgm ² i.v. days 1 + 8 every 3–4 weeks	

i.v., intravenous

7 5. Brief conclusions on stage IV treatment

Presently, insufficient data are available to establish a comprehensive treatment algorithm for stage IV melanoma. That being said some general principles can be applied.

- The treatment of metastatic melanoma patients should be discussed in interdisciplinary tumour boards with representation from multiple oncology sub-specialities.
- Mutation testing of tumour tissue (at least a search for *BRAF* mutations) is a prerequisite for treatment decisions and should be performed preferentially in metastatic tumour tissue from AJCC stage IIIB onwards.
- PD-1 blockade either as monotherapy or in combination with CTLA-4 blockade should be considered as a good option for first-line treatment for all patients with unresectable metastatic melanoma, independent from tumour *BRAF* status.
- The combination of *BRAF* with MEK inhibitors is the standard of care, if patients are treated with targeted therapies. Single-agent therapy with *BRAF* inhibitors alone is not recommended unless MEK inhibitors are contraindicated.
- For patients with *BRAF*-mutated tumours, there are presently no randomised data to judge whether *BRAF*/MEK inhibition should be given in the first- or second-line (before

or after immune checkpoint modulators), but trials on the best sequencing of targeted therapy and immunotherapy are ongoing.

- Chemotherapy may be considered in patients with a good performance status, who are resistant to targeted therapies and immune checkpoint modulators.
- c-KIT inhibitors may play a minor role in the second-line treatment of cKIT-mutant melanomas if PD-1 antibodies with or without ipilimumab have been used already.

7 6. Special case: Brain metastasis

Melanoma has a marked propensity to metastasize to the brain, which is associated with a worse prognosis. Surgery is considered as potentially curative in patients with solitary or few brain metastases (BM). Symptom control may be established in the short term with dexamethasone by reducing secondary oedema. SRS can likewise be potentially curative for brain metastases [138]. No difference for the local control of brain metastases was until now demonstrated between SRS and surgical resection. SRS was associated with improved early local control of treated lesions compared with surgical resection, although the relative benefit decreased with time [139]. Both stereotactic single-dose radiation therapy, and surgical resection are appropriate for solitary or few (typically up to 5), and not too large lesions (up to 3 cm in diameter), although newer devices allow the treatment of more lesions in selected cases. Treating solitary lesions (surgery or stereotactic RT) can be applied several times and appears to prolong DFS, although this has never been established in randomised trials. WBRT is generally palliative and does not prolong survival. In general, nowadays it can no longer be recommended. In symptomatic patients, symptom control may be established in the short term with dexamethasone by reducing secondary oedema.

Recommendation 23

Surgery and radiotherapy for brain metastases	Evidence-based recommendation
Level of recommendation B	Patients with brain metastases should be treated with stereotactic radiotherapy. Surgery can be an option when stereotactic radiotherapy is not possible. Guideline adaptation [15,16]
Level of evidence: 3b	Consensus rate: 90%

Recommendation 24

Whole brain radiotherapy (WBRT)	Evidence based recommendation
Level of recommendation C	WBRT should be abandoned from the treatment of melanoma brain metastases. Guideline adaptation [15,16]
Level of evidence: 3b	Consensus rate: 80%

Until 2010, systemic therapy in melanoma brain metastasis was limited to using chemotherapeutic agents (mainly fotemustine) after failure of local therapies. However, melanoma treatment of brain metastasis has seen a recent surge in novel therapeutics that is effective in treating CNS metastases.

7.6.1. Immunotherapy

In the first trial of immunotherapy for patients with brain metastases, the CTLA-4 antibody ipilimumab was tested in an open-label phase II study in patients with asymptomatic and symptomatic brain metastases [140]. Although an intracranial response rate of 16% and long-term benefit was seen in asymptomatic patients, the response rate deteriorated to 5% in symptomatic patients. Immunotherapy with PD-1 blocking antibodies or in combination with CTLA-4 blocking monoclonal antibodies has been tested in two recent prospective trials. The Checkmate 204 study, showed a 57% intracranial overall response rate (ORR) with 25% complete responses in patients with a limited number of asymptomatic brain metastases [141]. The Australian ABC trial, reported similarly outstanding results for combination immunotherapy with an intracranial ORR of 42% in asymptomatic patients with a slightly higher number of intracranial metastases. With anti-PD-1 monoclonal antibody alone, the response is lower with an intracranial OR of 22% [58]. Intracranial PFS was 63% after 6 months in the 204 trial with a tendency to reach a possible plateau, although follow-up is still limited. OS was reported to be at 82% after 12 months.

In Checkmate 204, a smaller cohort of 18 patients with symptomatic brain metastases was also treated with ipilimumab and nivolumab and showed a significantly lower intracranial response rate of 22% and a 19%, respectively, PFS landmark at 6 months [141].

No prospective trial has been performed combining checkpoint inhibitors and RT/surgery, and the best sequence remains to be determined [142].

7.6.2. Targeted therapy

The BREAK-MB trial demonstrated the impact that a BRAF inhibitor, dabrafenib, had 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 [101]. The COMBI-MB trial, an open trial with dabrafenib and trametinib had an objective response rate of 58% in patients carrying a BRAF V600 mutation without neurologic symptoms and a comparable response rate in a small group of symptomatic patients. The duration of response was however only 6.5 months in asymptomatic patients and 4.5 months in symptomatic patients [60].

In a general manner, the factors associated with shorter OS included male sex, cerebellar involvement, higher number of metastatic brain tumours, concurrent

presence of adrenal metastasis or treatment with whole brain radiation therapy.

7.6.3. Combined approaches

The combination of SRS with modern melanoma treatment (BRAF + MEK inhibition and anti-PD-1-based immunotherapy) has been tested in numerous retrospective studies with improved intracranial control, as well as encouraging PFS and OS data. No prospective trial has been published combining checkpoint inhibitors or BRAF + MEK inhibitors and RT/surgery, and the best sequence remains to be determined [142].

Recommendation 25

Systemic therapy for brain metastases	Consensus-based recommendation
Good clinical practice (GCP)	In patients with brain metastases, combined immunotherapy should be offered preferentially. Targeted therapy can be an alternative in patients with BRAFV600 E/K mutation. Consensus rate: 100%

7.7. Special case: Metastatic uveal melanoma

Melanomas of the eye involve the uvea, ciliary body or the retina. They have a different pattern of metastasis than cutaneous melanomas. Because the eye does not have a lymphatic system, almost all metastases are found in the liver following haematogenous spread. For this reason, the prognosis of metastatic ocular melanoma is in general much worse than that of its cutaneous counterpart. On the other hand, when patients with liver metastases from ocular and cutaneous melanoma are compared, there are no significant differences in the diseases' natural histories from that point.

Because of the preferential metastasis to the liver, patients with ocular melanoma and liver metastases may be candidates for local regional therapeutic measures. Few systemic schedules have been reported with objective responses (Table 5), and the response rates reported for treatment with checkpoint inhibitors are in the lower single-digit range. In the absence of effective systemic

Table 5
Chemotherapy for advanced uveal melanoma.

Medication	Dose
Fotemustine Leyvraz 1997, Egerer 2001, Siegel 2007 [143–145]	Induction cycle 100 mg/m ² intra-arterial (hepatic artery) for more than 4 h weekly for 4 weeks; then 5 weeks pause; then repeat every 3 weeks
Treosulfan/ Gemcitabine Pföhler 2003 [146]	Treosulfan 5 g/m ² i.v. day 1 Gemcitabine 1 g/m ² i.v. day 1 Repeat every 3 weeks

therapies, it is recommended that patients with metastatic disease be offered enrolment in a clinical trial.

8. Consensus building process and participants

These guidelines originate from contributors who were involved in the development of their national guidelines. These national guidelines were elaborated by the different specialities involved in the management of melanoma patients (dermatology, medical oncology, surgical oncology, RT, pathology and others).

These guidelines were prepared under the auspices of the European Dermatology Forum, the European Association of Dermato-Oncology and the EORTC. In the first round, medical experts who participated in their national guideline development processes were involved. In the second round, the EORTC selected experts from different specialities to contribute to these guidelines. This process was first organised in 2008/2009, and the update was developed by the same groups in 2012 and 2016. The formal recommendations were discussed and agreed upon at the consensus conference on the 23rd of September 2019 in Rome by the Guideline Group represented by 20 European experts. Professor Claus Garbe, Tübingen, coordinated the activities of the selected experts and the final authors. These guidelines are planned to be updated at least every two years.

Conflict of interest statement

C.G. reports receiving personal fees from Amgen, Pierre Fabre, Philogen and MSD; and reports receiving grants and personal fees from Novartis, NeraCare, BMS, Roche and Sanofi, outside the submitted work.

T.A. reports receiving personal fees and other grants from BMS, Novartis, Pierre Fabre, Neracare and Sanofi, outside the submitted work.

K.P. reports receiving personal fees from Novartis, Roche, Sanofi, Lilly, Leopharma, Pierre Fabre, Ammirall and Celgene, outside the submitted work.

A.H. reports receiving grants and personal fees from Amgen, BMS, MerckSerono, MSD / Merck, Philogen, Pierre Fabre, Provectus, Regeneron, Roche, Sanofi-Genzyme, and Novartis Pharma; receiving personal fees from OncoSec and Sun Pharma, outside the submitted work.

P.A. reports receiving personal fees from Amgen, MSD, Novartis, BMS and Roche, outside the submitted work.

L.B. reports receiving grants from BMS, during the conduct of the study; personal fees from BMS, Novartis, Merck MSD, Roche, Incyte, Bayer, outside the submitted work.

V.B. reports receiving personal fees from Novartis and Merck MSD, outside the submitted work.

V.d.M. reports receiving personal fees from MSD, BMS and Sanofi; grants and personal fees from ABVIE; grants from Jansen, outside the submitted work.

B.M. reports grants and personal fees from BMS, Roche, Fabre and Sanofi; personal fees from MSD, outside the submitted work.

M.C.F. reports receiving grants and personal fees from Ammirall, Leo Pharma, Novartis, Sanofi, Abbvie and Galderma; personal fees from Janssen, Lilly, UCB, Celgene, Pierre Fabre, Mylan, Medac Pharma, Roche, Sun Pharma, outside the submitted work.

J.J.G. reports receiving personal fees from Amgen, MSD, Novartis, BMS, Roche, Pierre fabre, Merck / Pfizer, outside the submitted work.

C.H. reports receiving personal fees from Amgen, MSD, Novartis, Incyte, BMS, Pierre Fabre, Roche, Sanofi, outside the submitted work.

R.K. reports receiving grants and personal fees from Novartis and Roche; and grants from AbbVie, Amgen, Bionteck, BMS, Celgene, Galderma, Janssen, Leo, Lilly, Merck, MSD, Pierre Fabre, Regeneron and Wyeth, outside the submitted work.

A.L. reports personal fees from Amgen, Novartis, BMS and Sanofi grants and personal fees from Roche, outside the submitted work.

C.L. reports receiving grants and personal fees from Bristol-Myers Squibb and Roche; personal fees from MSD, Novartis, Amgen, Avantis Medical Systems, Pierre Fabre, Pfizer, Incyte, outside the submitted work.

J.M. reports personal fees from Amgen, personal fees from MSD, grants from Novartis, grants and personal fees from BMS, grants and personal fees from Roche, grants and personal fees from Ammirall, personal fees from Sun Pharma, outside the submitted work.

M.M. reports receiving personal fees from Amgen and BiolineRx; grants and personal fees from Roche and GSK; grants from Astrazeneca; personal fees and other from Novartis, Eisai, Array Biopharma (now Pfizer), Rigotec (acquired by MSD), and BMS; other from Millennium, Regeneron Pfizer; personal fees, non-financial support and other from Immunocore, Replimun and Merck / MSD, outside the submitted work.

D.M.-R. has nothing to disclose.

G.P. reports receiving personal fees from Novartis, personal fees from Sanofi, grants from Novartis, instruments from 3Gen, Vidix, Fotofinder and MAVIG GmbH, outside the submitted work.

P.S. reports receiving personal fees from Amgen, MSD and Pierre Fabre / array; grants and personal fees from Novartis, NeraCare, BMS, Roche, and Sanofi, outside the submitted work.

A.J.S. reports personal fees and/or research support from Novartis, Roche, BMS, Abbvie, Sanofi, Regeneron, Genesis Pharma, outside the submitted work. Dr. Vieira has nothing to disclose.

I.Z. reports receiving personal fees from Difa Cooper, MSD, Sanofi, Ammirall Hermal, Novartis,

Mylan and Sunpharma; grants and personal fees from Roche, outside the submitted work.

A.M.M.E. reports receiving personal fees from Biocad, Biovent, BMS, CatalYm, Ellipses, GSK, Incyte, IO Biotech, ISA Pharmaceuticals, Merck GmbH, MSD, Novartis, Pfizer, Polynoma, Regeneron, Sanofi, SkylineDx, Stellas; other from RiverD, SkylineDx, Theranovir, all outside the submitted work.

References

- [1] Howick J, Garbe, Chalmers I, Glasziou P, Greenhalgh T, Heneghan C, et al. Group OLoEW. In: The Oxford levels of evidence 2, Guideline Part 1. Oxford Center for Evidence-Based Medicine; 2016. <https://www.cebm.net/index.aspx?o=5653>. [Accessed 23 April 2019].
- [2] Eggermont AM, Spatz A, Robert C. Cutaneous melanoma. *Lancet* 2014;383:816–27.
- [3] Saiag P, Bosquet L, Guillot B, Verola O, Avril MF, Bailly C, et al. Management of adult patients with cutaneous melanoma without distant metastasis. 2005 update of the French Standards, Options and Recommendations guidelines. Summary report *Eur J Dermatol* 2007;17:325–31.
- [4] Hauschild A, Rosien F, Lischner S. Surgical standards in the primary care of melanoma patients. *Onkologie* 2003;26:218–22.
- [5] Martin 2nd RC, Scoggins CR, Ross MI, Reintgen DS, Noyes RD, Edwards MJ, et al. Is incisional biopsy of melanoma harmful? *Am J Surg* 2005;190:913–7.
- [6] Pflugfelder A, Weide B, Eigentler TK, Forschner A, Leiter U, Held L, et al. Incisional biopsy and melanoma prognosis: facts and controversies. *Clin Dermatol* 2010;28:316–8.
- [7] Coit DG, Andtbacka R, Bichakjian CK, Dilawari RA, Dimaio D, Guild V, et al. Melanoma. *J Natl Compr Cancer Netw* 2009;7:250–75.
- [8] SaNZGGW TcCAaACN Australian cancer network melanoma guidelines revision working party. Clinical practice guidelines for the management of melanoma in Australia and New Zealand. 2008.
- [9] Negrier S, Saiag P, Guillot B, Verola O, Avril MF, Bailly C, et al. Guidelines for clinical practice: standards, options and recommendations 2005 for the management of adult patients exhibiting an M0 cutaneous melanoma, full report. National federation of cancer campaign centers. French dermatology society. Update of the 1995 consensus conference and the 1998 standards, options, and recommendations. *Ann Dermatol Venerol* 2005;132:10S3–10S85.
- [10] Marsden JR, Newton-Bishop JA, Burrows L, Cook M, Corrie PG, Cox NH, et al. Revised U.K. guidelines for the management of cutaneous melanoma 2010. *Br J Dermatol* 2010;163:238–56.
- [11] Garbe C, Hauschild A, Volkenandt M, Schadendorf D, Stolz W, Reinhold U, et al. Evidence-based and interdisciplinary consensus-based German guidelines: systemic medical treatment of melanoma in the adjuvant and palliative setting. *Melanoma Res* 2008;18:152–60.
- [12] Hayes AJ, Maynard L, Coombes G, Newton-Bishop J, Timmons M, Cook M, et al. Wide versus narrow excision margins for high-risk, primary cutaneous melanomas: long-term follow-up of survival in a randomised trial. *Lancet Oncol* 2016;17:184–92.
- [13] Wheatley K, Wilson JS, Gaunt P, Marsden JR. Surgical excision margins in primary cutaneous melanoma: a meta-analysis and Bayesian probability evaluation. *Cancer Treat Rev* 2016;42:73–81.
- [14] Gillgren P, Drzewiecki KT, Niin M, Gullestad HP, Hellborg H, Mansson-Brahme E, et al. 2-cm versus 4-cm surgical excision margins for primary cutaneous melanoma thicker than 2 mm: a randomised, multicenter trial. *Lancet (London, Engl)* 2011;378:1635–42.
- [15] Onkologie L. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): diagnostik, Therapie und Nachsorge des Melanoms, Langversion 3.1, 2018. 2018. AWMF Registernummer: 032/024OL, [http://www.leitlinienprogramm-onkologie.de/leitlinien/melanom/\(abgerufenam:05.11.2019\)](http://www.leitlinienprogramm-onkologie.de/leitlinien/melanom/(abgerufenam:05.11.2019)).
- [16] Pflugfelder A, Kochs C, Blum A, Capellaro M, Czeschik C, Dettenborn T, et al. Malignant melanoma S3-guideline "diagnosis, therapy and follow-up of melanoma. *J der Deutschen Dermatol Gesellschaft = J German Soc Dermatol : JDDG*. 2013;11(Suppl 6):1–116. 1-26.
- [17] Moehrl M, Dietz K, Garbe C, Breuninger H. Conventional histology vs. three-dimensional histology in lentigo maligna melanoma. *Br J Dermatol* 2006;154:453–9.
- [18] Tzellos T, Kyrgidis A, Mocellin S, Chan AW, Pilati P, Apalla Z. Interventions for melanoma in situ, including lentigo maligna. *Cochrane Database Syst Rev* 2014. Cd010308.
- [19] de Vries K, Greveling K, Prens LM, Munte K, Koljenovic S, van Doorn MB, et al. Recurrence rate of lentigo maligna after micrographically controlled staged surgical excision. *Br J Dermatol* 2016;174:588–93.
- [20] Hilari H, Llorca D, Traves V, Villanueva A, Serra-Guillen C, Requena C, et al. Conventional surgery compared with slow Mohs micrographic surgery in the treatment of lentigo maligna: a retrospective study of 62 cases. *Actas Dermo-Sifiliográficas* 2012;103:614–23.
- [21] Tio D, van der Woude J, Prinsen CAC, Jansma EP, Hoekzema R, van Montfrans C. A systematic review on the role of imiquimod in lentigo maligna and lentigo maligna melanoma: need for standardization of treatment schedule and outcome measures. *J Eur Acad Dermatol Venerol : JEADV* 2017;31:616–24.
- [22] Swetter SM, Chen FW, Kim DD, Egbert BM. Imiquimod 5% cream as primary or adjuvant therapy for melanoma in situ, lentigo maligna type. *J Am Acad Dermatol* 2015;72:1047–53.
- [23] Buettiker UV, Yawalkar NY, Braathen LR, Hunger RE. Imiquimod treatment of lentigo maligna: an open-label study of 34 primary lesions in 32 patients. *Arch Dermatol* 2008;144:943–5.
- [24] Mahoney MH, Joseph MG, Temple C. Topical imiquimod therapy for lentigo maligna. *Ann Plast Surg* 2008;61:419–24.
- [25] Cotter MA, McKenna JK, Bowen GM. Treatment of lentigo maligna with imiquimod before staged excision. *Dermatol Surg : off Publ Am Soc Dermatol Surg* 2008;34:147–51 [et al].
- [26] Yelamos O, Cordova M, Blank N, Kose K, Dusza SW, Lee E, et al. Correlation of handheld reflectance confocal microscopy with radial video mosaicing for margin mapping of lentigo maligna and lentigo maligna melanoma. *JAMA dermatology* 2017;153:1278–84.
- [27] Moehrl M, Metzger S, Schippert W, Garbe C, Rassner G, Breuninger H. Functional" surgery in subungual melanoma. *Dermatol Surg : off Publ Am Soc Dermatol Surg* 2003;29:366–74 [et al].
- [28] Breuninger H, Schlagenhauß B, Stroebel W, Schaumburg-Lever G, Rassner G. Patterns of local horizontal spread of melanomas: consequences for surgery and histopathologic investigation. *Am J Surg Pathol* 1999;23:1493–8.
- [29] Temple CL, Arlette JP. Mohs micrographic surgery in the treatment of lentigo maligna and melanoma. *J Surg Oncol* 2006;94:287–92.
- [30] Morton DL, Wen DR, Wong JH, Economou JS, Cagle LA, Storm FK, et al. Technical details of intraoperative lymphatic mapping for early stage melanoma. *Arch Surg* 1992;127:392–9.

- [31] Thompson JF, Shaw HM. Sentinel node mapping for melanoma: results of trials and current applications. *Surg Oncol Clin N Am* 2007;16:35–54.
- [32] Morton DL, Cochran AJ, Thompson JF, Elashoff R, Essner R, Glass EC, et al. Sentinel node biopsy for early-stage melanoma: accuracy and morbidity in MSLT-I, an international multicenter trial. *Ann Surg* 2005;242:302–11. discussion 11–3.
- [33] Faries MB, Thompson JF, Cochran AJ, Andtbacka RH, Mozzillo N, Zager JS, et al. Completion dissection or observation for sentinel-node metastasis in melanoma. *N Engl J Med* 2017;376:2211–22.
- [34] Wong SL, Faries MB, Kennedy EB, Agarwala SS, Akhurst TJ, Ariyan C, et al. Sentinel lymph node biopsy and management of regional lymph nodes in melanoma: American society of clinical oncology and society of surgical oncology clinical practice guideline update. *J Clin Oncol : off J Am Soc Clin Oncol* 2018;36:399–413.
- [35] Cordeiro E, Gervais MK, Shah PS, Look Hong NJ, Wright FC. Sentinel lymph node biopsy in thin cutaneous melanoma: a systematic review and meta-analysis. *Ann Surg Oncol* 2016;23:4178–88.
- [36] Morton DL, Thompson JF, Cochran AJ, Mozzillo N, Elashoff R, Essner R, et al. Sentinel-node biopsy or nodal observation in melanoma. *N Engl J Med* 2006;355:1307–17.
- [37] Morton DL, Thompson JF, Cochran AJ, Mozzillo N, Nieweg OE, Roses DF, et al. Final trial report of sentinel-node biopsy versus nodal observation in melanoma. *N Engl J Med* 2014;370:599–609.
- [38] Leiter U, Stadler R, Mauch C, Hohenberger W, Brockmeyer N, Berking C, et al. Complete lymph node dissection versus no dissection in patients with sentinel lymph node biopsy positive melanoma (DeCOG-SLT): a multicentre, randomised, phase 3 trial. *Lancet Oncol* 2016;17:757–67.
- [39] Leiter U, Stadler R, Mauch C, Hohenberger W, Brockmeyer NH, Berking C, et al. Final analysis of DeCOG-SLT trial: No survival benefit for complete lymph node dissection in patients with melanoma with positive sentinel node. *J Clin Oncol : off J Am Soc Clin Oncol* 2019;Jco1802306.
- [40] Morton DL, Wanek L, Nizze JA, Elashoff RM, Wong JH. Improved long-term survival after lymphadenectomy of melanoma metastatic to regional nodes. Analysis of prognostic factors in 1134 patients from the John Wayne Cancer Clinic. *Ann Surg* 1991;214:491–9. discussion 9–501.
- [41] Andtbacka RH, Kaufman HL, Collichio F, Amatruda T, Senzer N, Chesney J, et al. Talimogene laherparepvec improves durable response rate in patients with advanced melanoma. *J Clin Oncol : off J Am Soc Clin Oncol* 2015;33:2780–8.
- [42] Lienard D, Eggermont AM, Kooops HS, Kroon B, Towse G, Hiemstra S, et al. Isolated limb perfusion with tumour necrosis factor-alpha and melphalan with or without interferon-gamma for the treatment of in-transit melanoma metastases: a multicentre randomized phase II study. *Melanoma Res* 1999;9:491–502.
- [43] Deroose JP, Eggermont AM, van Geel AN, de Wilt JH, Burger JW, Verhoef C. 20 years experience of TNF-based isolated limb perfusion for in-transit melanoma metastases: TNF dose matters. *Ann Surg Oncol* 2012;19:627–35.
- [44] Weide B, Elsasser M, Buttner P, Pflugfelder A, Leiter U, Eigentler TK, et al. Serum markers lactate dehydrogenase and S100B predict independently disease outcome in melanoma patients with distant metastasis. *Br J Canc* 2012;107:422–8.
- [45] Petersen RP, Hanish SI, Haney JC, Miller 3rd CC, Burfeind Jr WR, Tyler DS, et al. Improved survival with pulmonary metastasectomy: an analysis of 1720 patients with pulmonary metastatic melanoma. *J Thorac Cardiovasc Surg* 2007;133:104–10.
- [46] Sanki A, Scolyer RA, Thompson JF. Surgery for melanoma metastases of the gastrointestinal tract: indications and results. *Eur J Surg Oncol : the J Eur Soc Surg Oncol Br Assoc Surg Oncol* 2009;35:313–9.
- [47] Chua TC, Saxena A, Morris DL. Surgical metastasectomy in AJCC stage IV M1c melanoma patients with gastrointestinal and liver metastases. *Ann Acad Med Singapore* 2010;39:634–9.
- [48] Wasif N, Bagaria SP, Ray P, Morton DL. Does metastasectomy improve survival in patients with Stage IV melanoma? A cancer registry analysis of outcomes. *J Surg Oncol* 2011;104:111–5.
- [49] Moschos SJ, Edington HD, Land SR, Rao UN, Jukic D, Shipe-Spotloe J, et al. Neoadjuvant treatment of regional stage IIIB melanoma with high-dose interferon alfa-2b induces objective tumor regression in association with modulation of tumor infiltrating host cellular immune responses. *J Clin Oncol : off J Am Soc Clin Oncol* 2006;24:3164–71.
- [50] Farshad A, Burg G, Panizzon R, Dummer R. A retrospective study of 150 patients with lentigo maligna and lentigo maligna melanoma and the efficacy of radiotherapy using Grenz or soft X-rays. *Br J Dermatol* 2002;146:1042–6.
- [51] Burmeister BH, Henderson MA, Ainslie J, Fisher R, Di Iulio J, Smithers BM, et al. Adjuvant radiotherapy versus observation alone for patients at risk of lymph-node field relapse after therapeutic lymphadenectomy for melanoma: a randomised trial. *Lancet Oncol* 2012;13:589–97.
- [52] Henderson MA, Burmeister BH, Ainslie J, Fisher R, Di Iulio J, Smithers BM, et al. Adjuvant lymph-node field radiotherapy versus observation only in patients with melanoma at high risk of further lymph-node field relapse after lymphadenectomy (ANZMTG 01.02/TROG 02.01): 6-year follow-up of a phase 3, randomised controlled trial. *Lancet Oncol* 2015;16:1049–60.
- [53] Olivier KR, Schild SE, Morris CG, Brown PD, Markovic SN. A higher radiotherapy dose is associated with more durable palliation and longer survival in patients with metastatic melanoma. *Cancer* 2007;110:1791–5.
- [54] Rate WR, Solin LJ, Turrisi AT. Palliative radiotherapy for metastatic malignant melanoma: brain metastases, bone metastases, and spinal cord compression. *Int J Radiat Oncol Biol Phys* 1988;15:859–64.
- [55] Katz HR. The results of different fractionation schemes in the palliative irradiation of metastatic melanoma. *Int J Radiat Oncol Biol Phys* 1981;7:907–11.
- [56] Konefal JB, Emami B, Pilepich MV. Analysis of dose fractionation in the palliation of metastases from malignant melanoma. *Cancer* 1988;61:243–6.
- [57] Kirova YM, Chen J, Rabarijaona LI, Piedbois Y, Le Bourgeois JP. Radiotherapy as palliative treatment for metastatic melanoma. *Melanoma Res* 1999;9:611–3.
- [58] Long GV, Atkinson V, Lo S, Sandhu S, Guminski AD, Brown MP, et al. Combination nivolumab and ipilimumab or nivolumab alone in melanoma brain metastases: a multicentre randomised phase 2 study. *Lancet Oncol* 2018;19:672–81.
- [59] Tawbi H. Safety of nivolumab (NIVO) plus ipilimumab (IPI) in patients with advanced melanoma(MEL) metastatic to the brain: initial results from phase 2 CheckMate 204. *SMR*; 2016.
- [60] Davies MA, Saiag P, Robert C, Grob JJ, Flaherty KT, Arance A, et al. Dabrafenib plus trametinib in patients with BRAFV600-mutant melanoma brain metastases (COMBI-MB): a multicentre, multicohort, open-label, phase 2 trial. *Lancet Oncol* 2017;18:863–73.
- [61] Grimaldi AM, Simeone E, Giannarelli D, Muto P, Falivene S, Borzillo V, et al. Abscopal effects of radiotherapy on advanced melanoma patients who progressed after ipilimumab immunotherapy. *OncoImmunology* 2014;3:e28780.
- [62] Crittenden M, Kohrt H, Levy R, Jones J, Camphausen K, Dicker A, et al. Current clinical trials testing combinations of immunotherapy and radiation. *Semin Radiat Oncol* 2015;25:54–64.
- [63] Lehrer EJ, Peterson J, Brown PD, Sheehan JP, Quinones-Hinojosa A, Zaorsky NG, et al. Treatment of brain metastases

- with stereotactic radiosurgery and immune checkpoint inhibitors: an international meta-analysis of individual patient data. *Radiother Oncol* : j Eur Soc Ther Radiol Oncol 2019;130:104–12.
- [64] Rauschenberg R, Bruns J, Brutting J, Daubner D, Lohaus F, Zimmer L, et al. Impact of radiation, systemic therapy and treatment sequencing on survival of patients with melanoma brain metastases. *Eur J Cancer* 2019;110:11–20.
- [65] Brown PD, Ballman KV, Cerhan JH, Anderson SK, Carrero XW, Whitton AC, et al. Postoperative stereotactic radiosurgery compared with whole brain radiotherapy for resected metastatic brain disease (NCCTG N107C/CEC.3): a multicentre, randomised, controlled, phase 3 trial. *Lancet Oncol* 2017;18:1049–60.
- [66] Mahajan A, Ahmed S, McAleer MF, Weinberg JS, Li J, Brown P, et al. Post-operative stereotactic radiosurgery versus observation for completely resected brain metastases: a single-centre, randomised, controlled, phase 3 trial. *Lancet Oncol* 2017;18:1040–8.
- [67] Ugurel S, Rohmel J, Ascierto PA, Flaherty KT, Grob JJ, Hauschild A, et al. Survival of patients with advanced metastatic melanoma: the impact of novel therapies-update 2017. *Eur J Cancer* 2017;83:247–57.
- [68] Eggermont AM, Chiarion-Sileni V, Grob JJ, Dummer R, Wolchok JD, Schmidt H, et al. Adjuvant ipilimumab versus placebo after complete resection of high-risk stage III melanoma (EORTC 18071): a randomised, double-blind, phase 3 trial. *Lancet Oncol* 2015;16:522–30.
- [69] Weber J, Mandala M, Del Vecchio M, Gogas HJ, Arance AM, Cowey CL, et al. Adjuvant nivolumab versus ipilimumab in resected stage III or IV melanoma. *N Engl J Med* 2017;377:1824–35.
- [70] Eggermont AM, Blank CU, Mandala M, Long GV, Atkinson V, Dalle S, et al. Adjuvant pembrolizumab versus placebo in resected stage III melanoma. *N Engl J Med* 2018;378:1789–801.
- [71] Long GV, Hauschild A, Santinami M, Atkinson V, Mandala M, Chiarion-Sileni V, et al. Adjuvant dabrafenib plus trametinib in stage III BRAF-mutated melanoma. *N Engl J Med* 2017;377:1813–23.
- [72] Eggermont AM, Chiarion-Sileni V, Grob JJ, Dummer R, Wolchok JD, Schmidt H, et al. Prolonged survival in stage III melanoma with ipilimumab adjuvant therapy. *N Engl J Med* 2016;375:1845–55.
- [73] Pehamberger H, Soyer HP, Steiner A, Kofler R, Binder M, Mischler P, et al. Adjuvant interferon alpha-2a treatment in resected primary stage II cutaneous melanoma. Austrian Malignant Melanoma Cooperative Group. *J Clin Oncol* : off J Am Soc Clin Oncol 1998;16:1425–9.
- [74] Garbe C, Radny P, Linse R, Dummer R, Gutzmer R, Ulrich J, et al. Adjuvant low-dose interferon {alpha}2a with or without dacarbazine compared with surgery alone: a prospective-randomized phase III DeCOG trial in melanoma patients with regional lymph node metastasis. *Ann Oncol* : off J Eur Soc Medical Oncology/ESMO. 2008;19:1195–201.
- [75] Kleeberg UR, Suci S, Brocker EB, Ruiter DJ, Chartier C, Lienard D, et al. Final results of the EORTC 18871/DKG 80-1 randomised phase III trial. rIFN-alpha2b versus rIFN-gamma versus ISCADOR M versus observation after surgery in melanoma patients with either high-risk primary (thickness >3 mm) or regional lymph node metastasis. *Eur J Cancer* 2004;40:390–402.
- [76] Hancock BW, Wheatley K, Harris S, Ives N, Harrison G, Horsman JM, et al. Adjuvant interferon in high-risk melanoma: the AIM HIGH Study–United Kingdom Coordinating Committee on Cancer Research randomized study of adjuvant low-dose extended-duration interferon Alfa-2a in high-risk resected malignant melanoma. *J Clin Oncol* : off J Am Soc Clin Oncol 2004;22:53–61.
- [77] Cascinelli N, Belli F, MacKie RM, Santinami M, Bufalino R, Morabito A. Effect of long-term adjuvant therapy with interferon alpha-2a in patients with regional node metastases from cutaneous melanoma: a randomised trial. *Lancet* (London, England) 2001;358:866–9.
- [78] Cameron DA, Cornbleet MC, Mackie RM, Hunter JA, Gore M, Hancock B, et al. Adjuvant interferon alpha 2b in high risk melanoma - the Scottish study. *Br J Canc* 2001;84:1146–9.
- [79] Kirkwood JM, Ibrahim JG, Sondak VK, Richards J, Flaherty LE, Ernstoff MS, et al. High- and low-dose interferon alfa-2b in high-risk melanoma: first analysis of intergroup trial E1690/S9111/C9190. *J Clin Oncol* : off J Am Soc Clin Oncol 2000;18:2444–58.
- [80] Grob JJ, Dreno B, de la Salmoniere P, Delaunay M, Cupissol D, Guillot B, et al. Randomised trial of interferon alpha-2a as adjuvant therapy in resected primary melanoma thicker than 1.5 mm without clinically detectable node metastases. French Cooperative Group on Melanoma. *Lancet* (London, Engl) 1998;351:1905–10.
- [81] Hansson J, Aamdal S, Bastholt L, Brandberg Y, Hernberg M, Nilsson B, et al. Two different durations of adjuvant therapy with intermediate-dose interferon alfa-2b in patients with high-risk melanoma (Nordic IFN trial): a randomised phase 3 trial. *Lancet Oncol* 2011;12:144–52.
- [82] Eggermont AM, Suci S, MacKie R, Ruka W, Testori A, Kruit W, et al. Post-surgery adjuvant therapy with intermediate doses of interferon alfa 2b versus observation in patients with stage IIb/III melanoma (EORTC 18952): randomised controlled trial. *Lancet* (London, England) 2005;366:1189–96.
- [83] Kirkwood JM, Strawderman MH, Ernstoff MS, Smith TJ, Borden EC, Blum RH. Interferon alfa-2b adjuvant therapy of high-risk resected cutaneous melanoma: the Eastern Cooperative Oncology Group Trial 1684. *J Clin Oncol* : off J Am Soc Clin Oncol 1996;14:7–17.
- [84] Creagan ET, Dalton RJ, Ahmann DL, Jung SH, Morton RF, Langdon Jr RM, et al. Randomized, surgical adjuvant clinical trial of recombinant interferon alfa-2a in selected patients with malignant melanoma. *J Clin Oncol* : official journal of the American Society of Clinical Oncology 1995;13:2776–83.
- [85] Eggermont AM, Suci S, Santinami M, Testori A, Kruit WH, Marsden J, et al. Adjuvant therapy with pegylated interferon alfa-2b versus observation alone in resected stage III melanoma: final results of EORTC 18991, a randomised phase III trial. *Lancet* (London, Engl) 2008;372:117–26.
- [86] Balch CM, Gershenwald JE, Soong S-J, Thompson JF, Atkins MB, Byrd DR, et al. Final version of 2009 AJCC melanoma staging and classification. *J Clin Oncol* : off J Am Soc Clin Oncol 2009;27:6199–206.
- [87] Maio M, Lewis K, Demidov L, Mandala M, Bondarenko I, Ascierto PA, et al. Adjuvant vemurafenib in resected, BRAF(V600) mutation-positive melanoma (BRIM8): a randomised, double-blind, placebo-controlled, multicentre, phase 3 trial. *Lancet Oncol* 2018;19:510–20.
- [88] Hauschild A, Dummer R, Schadendorf D, Santinami M, Atkinson V, Mandala M, et al. Longer follow-up confirms relapse-free survival benefit with adjuvant dabrafenib plus trametinib in patients with resected BRAF V600-mutant stage III melanoma. *J Clin Oncol* : off J Am Soc Clin Oncol 2018. JCO1801219.
- [89] Carlino MS, Ascierto PA, Eggermont AM, Gershenwald JE, Grob JJ, Hauschild A, et al. Pembrolizumab versus placebo as adjuvant therapy in resected high-risk stage II melanoma: phase 3 KEYNOTE-716 study. *J Clin Oncol* 2019;37. TPS9596-TPS.

- [90] Amaria RN, Prieto PA, Tetzlaff MT, Reuben A, Andrews MC, Ross MI, et al. Neoadjuvant plus adjuvant dabrafenib and trametinib versus standard of care in patients with high-risk, surgically resectable melanoma: a single-centre, open-label, randomised, phase 2 trial. *Lancet Oncol* 2018;19:181–93.
- [91] Blank CU, Rozeman EA, Fanchi LF, Sikorska K, van de Wiel B, Kvistborg P, et al. Neoadjuvant versus adjuvant ipilimumab plus nivolumab in macroscopic stage III melanoma. *Nat Med* 2018;24:1655–61.
- [92] Amaria RN, Reddy SM, Tawbi HA, Davies MA, Ross MI, Glitza IC, et al. Neoadjuvant immune checkpoint blockade in high-risk resectable melanoma. *Nat Med* 2018;24:1649–54.
- [93] Rozeman EA, Menzies AM, Van de Wiel BA, Adhikari C, Sikorska K, Krijgsman O, et al. OpACIN-neo: a multicenter phase 2 study to identify the optimal neo-adjuvant combination scheme of ipilimumab and nivolumab. 2018 ESMO congress. 2018. Abstract LBA42. Presented.
- [94] Chapman PB, Hauschild A, Robert C, Haanen JB, Ascierto P, Larkin J, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *N Engl J Med* 2011;364:2507–16.
- [95] Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med* 2010;363:711–23.
- [96] Morton DL, Mozzillo N, Thompson JF, Kelley MC, Faries M, Wagner J, et al. An international, randomized, phase III trial of bacillus Calmette-Guerin (BCG) plus allogeneic melanoma vaccine (MCV) or placebo after complete resection of melanoma metastatic to regional or distant sites. 25 ed 2007. p. 8508.
- [97] Ko JM, Fisher DE. A new era: melanoma genetics and therapeutics. *J Pathol* 2011;223:241–50.
- [98] Sosman JA, Kim KB, Schuchter L, Gonzalez R, Pavlick AC, Weber JS, et al. Survival in BRAF V600-mutant advanced melanoma treated with vemurafenib. *N Engl J Med* 2012;366:707–14.
- [99] Greger JG, Eastman SD, Zhang V, Bleam MR, Hughes AM, Smitheman KN, et al. Combinations of BRAF, MEK, and PI3K/mTOR inhibitors overcome acquired resistance to the BRAF inhibitor GSK2118436 dabrafenib, mediated by NRAS or MEK mutations. *Mol Cancer Ther* 2012;11:909–20.
- [100] Falchook GS, Long GV, Kurzrock R, Kim KB, Arkenau TH, Brown MP, et al. Dabrafenib in patients with melanoma, untreated brain metastases, and other solid tumours: a phase 1 dose-escalation trial. *Lancet* 2012;379:1893–901.
- [101] Long GV, Trefzer U, Davies MA, Kefford RF, Ascierto PA, Chapman PB, et al. Dabrafenib in patients with Val600Glu or Val600Lys BRAF-mutant melanoma metastatic to the brain (BREAK-MB): a multicentre, open-label, phase 2 trial. *Lancet Oncol* 2012;13:1087–95.
- [102] Robert C, Thomas L, Bondarenko I, O'Day S, Weber J, Garbe C, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. *N Engl J Med* 2011;364:2517–26.
- [103] Robert C, Long GV, Brady B, Dutriaux C, Maio M, Mortier L, et al. Nivolumab in previously untreated melanoma without BRAF mutation. *N Engl J Med* 2014;372:320–30.
- [104] Hodi FS, Chiarion-Sileni V, Gonzalez R, Grob JJ, Rutkowski P, Cowey CL, et al. Nivolumab plus ipilimumab or nivolumab alone versus ipilimumab alone in advanced melanoma (CheckMate 067): 4-year outcomes of a multicentre, randomised, phase 3 trial. *Lancet Oncol* 2018;19:1480–92.
- [105] Robert C, Ribas A, Schachter J, Arance A, Grob JJ, Mortier L, et al. Pembrolizumab versus ipilimumab in advanced melanoma (KEYNOTE-006): post-hoc 5-year results from an open-label, multicentre, randomised, controlled, phase 3 study. *Lancet Oncol* 2019;20:1239–51.
- [106] Hamid O, Robert C, Daud A, Hodi FS, Hwu WJ, Kefford R, et al. Five-year survival outcomes for patients with advanced melanoma treated with pembrolizumab in KEYNOTE-001. *Ann Oncol* : official J Eur Soc Medical Oncology/ESMO 2019;30:582–8.
- [107] Robert C, Schachter J, Long GV, Arance A, Grob JJ, Mortier L, et al. Pembrolizumab versus ipilimumab in advanced melanoma. *N Engl J Med* 2015;372:2521–32.
- [108] Larkin J, Hodi FS, Wolchok JD. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. *N Engl J Med* 2015;373:1270–1.
- [109] Lebbé C, Meyer N, Mortier L, Marquez-Rodas I, Robert C, Rutkowski P, et al. Evaluation of two dosing regimens for nivolumab in combination with ipilimumab in patients with advanced melanoma: results from the phase IIIb/IV CheckMate 511 trial. *J Clin Oncol* 2019;37:867–75.
- [110] Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med* 2012;366:2443–54.
- [111] Long GV, Tykodi SS, Schneider JG, Garbe C, Gravis G, Rashford M, et al. Assessment of nivolumab exposure and clinical safety of 480 mg every 4 weeks flat-dosing schedule in patients with cancer. *Ann Oncol* : official J Eur Soc Medical Oncology/ESMO 2018;29:2208–13.
- [112] Lala M, Li M, Sinha V, de Alwis D, Chartash E, Jain L. A six-weekly (Q6W) dosing schedule for pembrolizumab based on an exposure-response (E-R) evaluation using modeling and simulation. *J Clin Oncol* 2018;36:3062.
- [113] Freshwater T, Kondic A, Ahmadi M, Li CH, de Greef R, de Alwis D, et al. Evaluation of dosing strategy for pembrolizumab for oncology indications. *J Immunother cancer* 2017;5:43.
- [114] Ascierto PA, McArthur GA, Dreno B, Atkinson V, Liszakay G, Di Giacomo AM, et al. Cobimetinib combined with vemurafenib in advanced BRAF(V600)-mutant melanoma (coBRIM): updated efficacy results from a randomised, double-blind, phase 3 trial. *Lancet Oncol* 2016;17:1248–60.
- [115] Robert C, Grob JJ, Stroyakovskiy D, Karaszewska B, Hauschild A, Levchenko E, et al. Five-year outcomes with dabrafenib plus trametinib in metastatic melanoma. *N Engl J Med* 2019;381:626–36.
- [116] Grob JJ, Amonkar MM, Karaszewska B, Schachter J, Dummer R, Mackiewicz A, et al. Comparison of dabrafenib and trametinib combination therapy with vemurafenib monotherapy on health-related quality of life in patients with unresectable or metastatic cutaneous BRAF Val600-mutation-positive melanoma (COMBI-v): results of a phase 3, open-label, randomised trial. *Lancet Oncol* 2015;16:1389–98.
- [117] Dummer R, Ascierto PA, Gogas HJ, Arance A, Mandala M, Liszakay G, et al. Encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with BRAF-mutant melanoma (COLUMBUS): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol* 2018;19:603–15.
- [118] Guo J, Si L, Kong Y, Flaherty KT, Xu X, Zhu Y, et al. Phase II, open-label, single-arm trial of imatinib mesylate in patients with metastatic melanoma harboring c-Kit mutation or amplification. *J Clin Oncol* : official J Am Soc Clinical Oncology 2011;29:2904–9.
- [119] Dummer R, Schadendorf D, Ascierto PA, Arance A, Dutriaux C, Di Giacomo AM, et al. Binimetinib versus dacarbazine in patients with advanced NRAS-mutant melanoma (NEMO): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol* 2017;18:435–45.
- [120] Robert C, Karaszewska B, Schachter J, Rutkowski P, Mackiewicz A, Stroiakovski D, et al. Improved overall survival in melanoma with combined dabrafenib and trametinib. *N Engl J Med* 2015;372:30–9.
- [121] Long GV, Stroyakovskiy DL, Gogas H, Levchenko E, de Braud F, Larkin JMG, et al. COMBI-d: a randomized, double-blind, Phase III study comparing the combination of dabrafenib and trametinib to dabrafenib and trametinib placebo as first-line therapy in patients (pts) with unresectable or metastatic

- BRAFV600E/K mutation-positive cutaneous melanoma. *J Clin Oncol* 2014;32:9011.
- [122] Larkin J, Ascierto PA, Dreno B, Atkinson V, Liskay G, Maio M, et al. Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. *N Engl J Med* 2014;371:1867–76.
- [123] Ribas A, Gonzalez R, Pavlick A, Hamid O, Gajewski TF, Daud A, et al. Combination of vemurafenib and cobimetinib in patients with advanced BRAF(V600)-mutated melanoma: a phase 1b study. *Lancet Oncol* 2014;15:954–65.
- [124] Dummer R, Ascierto PA, Gogas H, Arance AM, Mandalà M, Liskay G, et al. Overall survival in COLUMBUS: a phase 3 trial of encorafenib (ENCO) plus binimetinib (BINI) vs vemurafenib (VEM) or enco in BRAF-mutant melanoma. *J Clin Oncol* 2018;36:9504.
- [125] Dummer PA R, Ascierto PA, De Groot JW, Hallmeyer S, Lotem M, Long GV, et al. 1130TiP- NEMO: a phase 3 trial OF binimetinib (MEK162) versus dacarbazine IN patients with advanced NRAS-mutant melanoma WHO are untreated or have progressed after any number OF immunotherapy regimens. *Ann Oncol* 2014;25(suppl 4):iv392.
- [126] Bedikian AY, DeConti RC, Conry R, Agarwala S, Papadopoulos N, Kim KB, et al. Phase 3 study of docosahexaenoic acid-paclitaxel versus dacarbazine in patients with metastatic malignant melanoma. *Ann Oncol : official J Eur Soc Medical Oncology/ESMO* 2011;22:787–93.
- [127] Patel PM, Suci S, Mortier L, Kruit WH, Robert C, Schadendorf D, et al. Extended schedule, escalated dose temozolomide versus dacarbazine in stage IV melanoma: final results of a randomised phase III study (EORTC 18032). *Eur J Cancer* 2011;47:1476–83.
- [128] Bedikian AY, Millward M, Pehamberger H, Conry R, Gore M, Trefzer U, et al. Bcl-2 antisense (oblimersen sodium) plus dacarbazine in patients with advanced melanoma: the Oblimersen Melanoma Study Group. *J Clin Oncol : official journal of the American Society of Clinical Oncology* 2006;24:4738–45.
- [129] Middleton MR, Grob JJ, Aaronson N, Fierbeck G, Tilgen W, Seiter S, et al. Randomized phase III study of temozolomide versus dacarbazine in the treatment of patients with advanced metastatic malignant melanoma. *J Clin Oncol : off J Am Soc Clin Oncol* 2000;18:158–66.
- [130] Ringborg U, Rudenstam CM, Hansson J, Hafstrom L, Stenstam B, Strander H. Dacarbazine versus dacarbazine-vindesine in disseminated malignant melanoma: a randomized phase II study. *Med Oncol Tumor Pharmacother* 1989;6:285–9.
- [131] Chiarion Sileni V, Nortilli R, Aversa SM, Paccagnella A, Medici M, Corti L, et al. Phase II randomized study of dacarbazine, carmustine, cisplatin and tamoxifen versus dacarbazine alone in advanced melanoma patients. *Melanoma Res* 2001;11:189–96.
- [132] Young AM, Marsden J, Goodman A, Burton A, Dunn JA. Prospective randomized comparison of dacarbazine (DTIC) versus DTIC plus interferon-alpha (IFN-alpha) in metastatic melanoma. *Clin Oncol* 2001;13:458–65.
- [133] Bleeher NM, Newlands ES, Lee SM, Thatcher N, Selby P, Calvert AH, et al. Cancer Research Campaign phase II trial of temozolomide in metastatic melanoma. *J Clin Oncol : off J Am Soc Clin Oncol* 1995;13:910–3.
- [134] Jacquillat C, Khayat D, Banzet P, Weil M, Avril MF, Fumoleau P, et al. Chemotherapy by fotemustine in cerebral metastases of disseminated malignant melanoma. *Cancer Chemother Pharmacol* 1990;25:263–6.
- [135] Mornex F, Thomas L, Mohr P, Hauschild A, Delaunay MM, Lesimple T, et al. A prospective randomized multicentre phase III trial of fotemustine plus whole brain irradiation versus fotemustine alone in cerebral metastases of malignant melanoma. *Melanoma Res* 2003;13:97–103.
- [136] Rao RD, Holtan SG, Ingle JN, Croghan GA, Kottschade LA, Creagan ET, et al. Combination of paclitaxel and carboplatin as second-line therapy for patients with metastatic melanoma. *Cancer* 2006;106:375–82.
- [137] Verschraegen CF, Kleeberg UR, Mulder J, Rumke P, Truchetet F, Czarnetzki B, et al. Combination of cisplatin, vindesine, and dacarbazine in advanced malignant melanoma. A phase II study of the EORTC malignant melanoma cooperative group. *Cancer* 1988;62:1061–5.
- [138] Gaudy-Marqueste C, Carron R, Delsanti C, Loundou A, Monestier S, Archier E, et al. On demand Gamma-Knife strategy can be safely combined with BRAF inhibitors for the treatment of melanoma brain metastases. *Ann Oncol : official J Eur Soc Medical Oncology/ESMO* 2014;25:2086–91.
- [139] Churilla TM, Chowdhury IH, Handorf E, Collette L, Collette S, Dong Y, et al. Comparison of local control of brain metastases with stereotactic radiosurgery vs surgical resection: a secondary analysis of a randomized clinical trial. *JAMA Oncol* 2019;5:243–7.
- [140] Margolin K, Ernstoff MS, Hamid O, Lawrence D, McDermott D, Puzanov I, et al. Ipilimumab in patients with melanoma and brain metastases: an open-label, phase 2 trial. *Lancet Oncol* 2012;13:459–65.
- [141] Tawbi HA, Forsyth PA, Algazi A, Hamid O, Hodi FS, Moschos SJ, et al. Combined nivolumab and ipilimumab in melanoma metastatic to the brain. *N Engl J Med* 2018;379:722–30.
- [142] Galli G, Cavalieri S, Di Guardo L, Cimminiello C, Nichetti F, Corti F, et al. Combination of immunotherapy and brain radiotherapy in metastatic melanoma: a retrospective analysis. *Oncology Res Treat* 2019;42:186–94.
- [143] Leyvraz S, Spataro V, Bauer J, Pampallona S, Salmon R, Dorval T, et al. Treatment of ocular melanoma metastatic to the liver by hepatic arterial chemotherapy. *J Clin Oncol : off J Am Soc Clin Oncol* 1997;15:2589–95.
- [144] Egerer G, Lehnert T, Max R, Naeher H, Keilholz U, Ho AD. Pilot study of hepatic intraarterial fotemustine chemotherapy for liver metastases from uveal melanoma: a single-center experience with seven patients. *Int J Clin Oncol* 2001;6:25–8.
- [145] Siegel R, Hauschild A, Kettelhack C, Kahler KC, Bembenek A, Schlag PM. Hepatic arterial Fotemustine chemotherapy in patients with liver metastases from cutaneous melanoma is as effective as in ocular melanoma. *Eur J Surg Oncol : the J Eur Soc Surg Oncol Br Assoc Surg Oncol* 2007;33:627–32.
- [146] Pfohler C, Cree IA, Ugurel S, Kuwert C, Haass N, Neuber K, et al. Treosulfan and gemcitabine in metastatic uveal melanoma patients: results of a multicenter feasibility study. *Anti Cancer Drugs* 2003;14:337–40.