ESMO consensus conference recommendations on the management of metastatic melanoma: under the auspices of the ESMO Guidelines Committee


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The European Society for Medical Oncology (ESMO) held a consensus conference on melanoma on 5—7 September 2019 in Amsterdam, The Netherlands. The conference included a multidisciplinary panel of 32 leading experts in the management of melanoma. The aim of the conference was to develop recommendations on topics that are not covered in detail in the current ESMO Clinical Practice Guideline and where available evidence is either limited or conflicting. The main topics identified for discussion were (i) the management of locoregional disease; (ii) targeted versus immunotherapies in the adjuvant setting; (iii) targeted versus immunotherapies for the first-line treatment of metastatic melanoma; (iv) when to stop immunotherapy or targeted therapy in the metastatic setting; and (v) systemic versus local treatment for brain metastases. The expert panel was divided into five working groups to each address questions relating to one of the five topics outlined above. Relevant scientific literature was reviewed in advance. Recommendations were developed by the working groups and then presented to the entire panel for further discussion and amendment before voting. This manuscript presents the results relating to the management of metastatic melanoma, including findings from the expert panel discussions, consensus recommendations and a summary of evidence supporting each recommendation. All participants approved the final manuscript.

Key words: consensus, immunotherapy, melanoma, metastatic, targeted therapy, treatment

INTRODUCTION

The management of metastatic melanoma has changed significantly following the introduction of targeted therapy and immunotherapy. However, despite these advances, evidence is limited and/or conflicting in some areas and the optimal approach remains controversial.

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In 2019, the European Society for Medical Oncology (ESMO) held a consensus conference on melanoma to gain insights from a multidisciplinary group of experts and develop recommendations on controversial topics that are not adequately addressed in the current ESMO Clinical Practice Guideline.1

METHODS
On 5–7 September 2019, ESMO held a consensus conference in Amsterdam, The Netherlands, which was organised by the ESMO Guidelines Committee. The aim of this consensus conference was to discuss controversial issues relating to the management of patients with melanoma. The conference included a multidisciplinary panel of 32 leading experts from 14 countries and was chaired and co-chaired by U. Keilholz and O. Michielin, respectively. All experts were allocated to one of five working groups. Each working group covered a specific subject area and was appointed a chair as follows:

1. Management of locoregional disease (Chair: A. van Akkooi)
2. Targeted versus immunotherapies in the adjuvant setting (Chair: P. Lorigan)
3. Targeted versus immunotherapies for the first-line treatment of metastatic melanoma (Chair: P. A. Ascierto)
4. When to stop immunotherapy or targeted therapy in the metastatic setting (Chair: C. Robert)
5. Systemic versus local treatment for brain metastases (BMs) (Chair: R. Dummer).

Planning, preparation and execution of the consensus conference was conducted according to ESMO standard operating procedures, available at https://www.esmo.org/content/download/77792/1426729/1. No systematic literature search was undertaken. All recommendations compiled by the group were accompanied by a level of evidence and strength of recommendation based on the ‘Infectious Diseases Society of America-United States Public Health Service Grading System’ (supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2020.07.004).2 Recommendation 6.1 failed to reach a consensus at the meeting during an online vote, in accordance with ESMO methodology. Results from Working Groups 3–5 of this consensus conference (i.e. the management of metastatic melanoma), including all recommendations and a summary of supporting evidence, are described in this article. The final manuscript was reviewed and approved by all panel members.

RESULTS

Targeted versus immunotherapy for the first-line treatment of metastatic melanoma

1. In patients with BRAF-mutated metastatic melanoma, which treatment should be used as first option: targeted therapy or immunotherapy? Immunotherapy induces durable clinical responses in 45%–50% of patients but often with a slow onset.3 For BRAF-mutated melanoma, combination treatment with BRAF and MEK inhibitors offers rapid symptom control and the highest chances of response (~70%).4–10 While patients with good prognostic features may achieve long-term disease control with front-line BRAF/MEK inhibitors,11 patients with poor prognostic features are most likely to progress and require further treatment after front-line BRAF/MEK inhibitors or ipilimumab plus nivolumab.9

The first-line decision between targeted therapies and immunotherapies is being studied in prospective trials [SECOMBIT (NCT02631447), DREAMseq (NCT02224781)]. Meta-analyses suggest that, despite better progression-free survival (PFS) and 12-month outcome for targeted therapies, front-line immunotherapy may yield a superior long-term outcome.12,13 Overall, the best sequencing combination is yet to be established. Long-term/durable disease control even after stopping treatment is the most important observation favouring immunotherapy as the first-line choice.14

**Recommendation 1.1.** Current treatment decisions need to be individualised to the patient and should be based on treatment goals (short-term benefit versus long-term benefit) as well as clinical characteristics [lactate dehydrogenase (LDH), organs involved, performance status (PS), tumour burden, disease progression kinetics], comorbidities and patient preference. Patients for whom immunotherapy can be delivered for the first few months should be considered for immunotherapy first, as it may provide very long-term disease control even after stopping the treatment.

Level of evidence: IV
Strength of recommendation: C
Level of consensus: 93% (25) yes, 7% (2) no (27 voters)

Potential for combination treatment with targeted therapy and immunotherapy. High objective response rates (ORRs) of 70%–80% and manageable toxicity were reported with the triple combination of BRAF/MEK inhibitors plus programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) inhibitors.15–17 Preliminary results from randomised studies suggest improved outcomes but greater toxicity with BRAF/MEK inhibitors plus immunotherapy.16,18

Current trials are investigating the option of a planned switch from targeted therapy to immunotherapy or immunotherapy with intermittent targeted therapy [NCT02631447 (SECOMBIT), NCT03235245 (EORTC-1612-MG), NCT02625337 (IMPemBra), NCT02224781 (DREAMseq)].

**Recommendation 1.2.** The combination of targeted therapy with anti-PD-1 therapy is not recommended outside of clinical studies.

Level of evidence: II
Strength of recommendation: E
Level of consensus: 100% (29) yes (29 voters)
2. Are there clinical characteristics that can help in treatment decisions?

In patients with metastatic disease and elevated LDH, which treatment should be used as first line? Are patients with LDH level $>2 \times$ the upper limit of normal different from those with LDH $>1 \times$ and $\leq 2 \times$ the upper limit of normal? Elevated serum LDH and distant metastases are independent prognostic factors in patients with stage IV disease, with LDH reflecting tumour burden.19

A subset of patients treated with dabrafenib and trametinib achieved durable outcomes, mostly having normal LDH levels and a lower number of organ sites.15,16,20,21 In a post-hoc analysis of KEYNOTE-006, LDH had an incremental negative impact on overall survival (OS), PFS and ORR.22 In CheckMate 067 and 069, patients with elevated LDH receiving nivolumab (n = 507) or ipilimumab and nivolumab (n = 407)23 had an incrementally lower PFS and ORR compared with patients with LDH $\leq$ the upper limit of normal (ULN).

**Recommendation 2.1.** For BRAF-mutated patients with metastatic melanoma and elevated LDH, first-line therapy with ipilimumab plus nivolumab is generally preferred over BRAF/MEK inhibitors, depending on the presence of other adverse prognostic factors. Patients with LDH $>1 \times$ and $\leq 2 \times$ ULN, anti-PD-1 monotherapy is an additional option.

Strength of recommendation: C
Level of evidence: V
Level of consensus: 89% (25) yes, 7% (2) no, 4% (1) abstain (28 voters)

In patients with metastatic disease and high tumour burden, which treatment should be used as first line? What is the definition of metastatic disease with high tumour burden? There is no uniform definition of tumour burden and although it is of prognostic relevance, it is not contemplated in the American Joint Commission on Cancer 8th edition (AJCC8) staging manual for stage IV disease.19 Pooled analyses of phase III trials of BRAF/MEK inhibitors20,24 and part C of the BRF113220 phase II/II study21 identified patients with $<3$ metastatic organ sites, a lower sum of lesion diameters and normal LDH as the best prognostic group. The magnitude of immune response to anti-PD-1 agents was also related to tumour burden.22 In KEYNOTE-001, patients were stratified according to baseline tumour size, which was shown to be an independent predictor of OS [hazard ratio (HR) 0.61; $P < 0.001$] but not ORR. BRAF genotype was not associated with OS or response.26 CheckMate 067 revealed no obvious pattern regarding the benefit of ipilimumab and nivolumab over nivolumab based on tumour burden.3

**Recommendation 2.2.** In metastatic melanoma, there is no clear definition for tumour burden. As such, there is no consensus regarding how this should be used to select treatment.

Level of evidence: IV

Strength of recommendation: E
Level of consensus: 93% (26) yes, 4% (1) no, 4% (1) abstain (28 voters)

3. What is the best treatment for patients who have progressed after adjuvant therapy? Limited data are available and prospective trials are ongoing [NCT02631447 (SECOMBIT) and NCT03235245 (EORTC EBIN)] to guide sequence selection of BRAF-targeted therapy and immunotherapies in metastatic disease and following failure of adjuvant therapy (see also question 15). Should different options be considered in cases where progressive disease occurred during treatment or $>6$ months from the end of adjuvant therapy? In patients with primary resistance, a benefit of retreatment with the same agent(s) is unlikely. Patients with acquired resistance in the metastatic setting, however, may benefit from BRAF-directed retreatment,27 although long-term benefit remains unlikely. There are very limited data regarding the efficacy of single-agent PD-1 inhibitors in metastatic disease with acquired resistance.28

**Recommendation 3.1.** Progression on or soon after adjuvant treatment ($<6$ months) implies a low likelihood of significant clinical benefit if re-exposed to the same agent. Alternative agents should therefore be given priority.

Level of evidence: IV
Strength of recommendation: B
Level of consensus: 100% (28) yes (28 voters)

**Recommendation 3.2.** Progression $>6$ months after adjuvant treatment can be retreated using the same agent or treated with an alternative agent class.

Level of evidence: IV
Strength of recommendation: C
Level of consensus: 100% (27) yes (27 voters)

Are there biomarkers that can drive the decision? With the exception of BRAF mutational status as a validated biomarker for BRAF therapy, there are currently no established predictive biomarkers.

**Recommendation 3.3.** The only currently available validated biomarker is the presence of BRAF mutation.

Level of evidence: I
Strength of recommendation: A
Level of consensus: 100% (29) yes (29 voters)

**Summary of treatment options for patients who progressed to unresectable disease after adjuvant therapy.** Choice of first-line metastatic treatment following adjuvant treatment failure should be influenced by the adjuvant treatment received and time until relapse (Table 1).

4. Is there a role for a short course of targeted therapy followed by immunotherapy outside of clinical trials? Immunotherapy has proven to induce durable clinical responses, but often with a slow onset. The rapid clinical
responses seen with BRAF/MEK inhibitors and modulation of the tumour microenvironment may provide a window of opportunity for an early switch to immunotherapy.29

A small retrospective study suggested favourable OS for patients who switched from targeted therapy to immunotherapy in the absence of progressive disease (PD).30 Two ongoing clinical trials [NCT02631447 (SECOMBIT Arm C) and NCT03235245 (EORTC-1612-MG)] include a planned switch from BRAF/MEK inhibitors after 8–12 weeks to ipilimumab and nivolumab. Currently, switching from BRAF/MEK inhibitors to immunotherapy in the metastatic setting in the absence of PD carries the risk of discontinuing an effective treatment in favour of another treatment with potentially lower efficacy.

**Recommendation 4.1.** In metastatic melanoma, switching to immunotherapy in the absence of PD with targeted therapy should not be routinely considered outside of clinical trials until additional evidence is available. Level of evidence: V Strength of recommendation: E Level of consensus: 100% (28) yes (28 voters)

5. For patients with metastatic disease who have progressed after targeted therapy and immunotherapy, can rechallenge with targeted therapy or immunotherapy be considered as a subsequent line of therapy?

**Can patients with metastatic disease who have progressed after first-line targeted therapy and second-line immunotherapy be treated with rechallenge of targeted therapy?** Acquired resistance mechanisms to BRAF inhibition can be reversible after treatment interruption. Moreover, immune infiltrates have been documented in melanoma metastases at the time of response to BRAF inhibitors.29,31 Strengthened antitumour immunity might therefore contribute to the success of rechallenge after exposure to immune checkpoint inhibitors (ICIs). BRAF inhibitor rechallenge in patients who previously progressed on targeted therapies was associated with a 28%–50% ORR, 57%–72% disease control rate and a 4–5-month median PFS.27,32–34 Most of these patients were initially treated with BRAF inhibitor monotherapy and received combination BRAF/MEK inhibition as rechallenge. The time between first treatment and rechallenge did not seem to impact treatment response.32,33,35

**Recommendation 5.1.** Patients who progressed after targeted therapy as first line and immunotherapy as second line can be rechallenged with targeted therapy. Level of evidence: IV Strength of recommendation: C Level of consensus: 100% (28) yes (28 voters)

**Can patients with metastatic disease who progressed after first-line immunotherapy and second-line targeted therapy be treated with rechallenge of immunotherapy?** Treatment with BRAF/MEK inhibitors may impact on the immune system and facilitate new effective action of immunotherapy, although lower efficacy of immunotherapy after progression from targeted therapy has been reported.36–39

Randomised phase II and III studies demonstrated successful treatment with anti-PD-1 agents following first-line ipilimumab followed by BRAF/MEK inhibitors.

**Recommendation 5.2.** Patients initially treated with ipilimumab (immunotherapy used as first line and targeted therapy as second line) may benefit from anti-PD-1 therapy. No data are available regarding the efficacy of ipilimumab plus nivolumab in this setting. Level of evidence: II Strength of recommendation: A Level of consensus: 100% (28) yes (28 voters)

However, after first-line anti-PD-1 and second-line targeted therapy, responses to third-line anti-PD-1 therapy were observed but duration was often very short.28 Several studies42–44 support ipilimumab after nivolumab failure. However, most patients were BRAF wild type and poorer outcomes were suggested in the case of primary resistance to PD-1 inhibitors.45 In some (but not all) studies, the efficacy of ipilimumab plus nivolumab was limited after prior anti-PD-1 treatment (ORR 21% and 12-month OS 55%).46 Again, only few patients had received BRAF/MEK inhibitors.

**Recommendation 5.3.** Patients initially treated with anti-PD-1 therapy (immunotherapy used as first line and targeted therapy as second line) might benefit from ipilimumab-based treatments.

### Table 1. Treatment options for patients who progress to unresectable disease after adjuvant therapy

<table>
<thead>
<tr>
<th>Adjuvant treatment</th>
<th>First-line metastatic Relapse on treatment or &lt;6 months after completing adjuvant treatment</th>
<th>First-line metastatic Relapse &gt;6 months after completing adjuvant treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-PD-1</td>
<td><em>BRAF</em> mutated&lt;br&gt;• Anti-BRAF/MEK&lt;br&gt;• Ipilimumab + nivolumab&lt;br&gt;• Ipilimumab</td>
<td><em>BRAF</em> mutated&lt;br&gt;• Anti-BRAF/MEK&lt;br&gt;• Ipilimumab + nivolumab&lt;br&gt;• Anti-PD-1&lt;br&gt;• Ipilimumab</td>
</tr>
<tr>
<td>Anti-BRAF/MEK</td>
<td><em>Anti-PD-1&lt;br&gt;• Ipilimumab + nivolumab</em></td>
<td><em>Ipilimumab + nivolumab&lt;br&gt;• Anti-PD-1&lt;br&gt;• Anti-BRAF/MEK&lt;br&gt;• Ipilimumab</em></td>
</tr>
</tbody>
</table>

PD-1, programmed cell death protein 1; WT, wild type.
Level of evidence: IV
Strength of recommendation: C
Level of consensus: 100% (28) yes (28 voters)

Case reports on rechallenge after first-line ipilimumab and nivolumab suggested favourable outcomes despite stopping treatment for toxicity in the setting of initial response.45

Recommendation 5.4. After all alternative agents have been explored, rechallenge with drugs which showed clinical activity can be considered.
Level of evidence: V
Strength of recommendation: C
Level of consensus: 100% (28) yes (28 voters)

When to stop immunotherapy or targeted therapy in the metastatic setting

6. Can therapy be stopped (considering both immunotherapy and targeted therapy) in the case of a favourable outcome: complete response, partial response and stable disease?

Complete response with immunotherapy. The possibility of stopping therapy in the phase I KEYNOTE-001 trial was offered following a protocol amendment for (i) a confirmed complete response (CR); (ii) > 6 months of pembrolizumab; (iii) at least two injections of pembrolizumab after confirmed CR.46 In 67 patients who stopped pembrolizumab after a CR, 24-month disease-free survival from the time of CR was ~90%.46 Extended follow-up did not modify the relapse rate.47

Real-life experience confirmed a low relapse rate for patients with a CR but relapse was more likely with < 6 months of treatment.14 In KEYNOTE-006,48 patients with a CR stopped treatment at 2 years and 85.4% did not relapse.

Recommendation 6.1. Patients with a CR that persists at the following radiological evaluation (at least 4 weeks after), and who have received at least 6 months of anti-PD-1 treatment, can be considered for stopping therapy.
Level of evidence: IV
Strength of recommendation: B
Level of consensus: 84% (21) yes, 12% (3) no, 4% (1) abstain (25 voters)

Partial response and stable disease with immunotherapy. The maximum duration of pembrolizumab treatment was 24 months in KEYNOTE-006.48 For patients with a partial response (PR) or stable disease (SD), there was no change in the HR for PD after the 2-year landmark. In CheckMate 067,49 in which patients continued nivolumab treatment, recurrence-free survival was similar to KEYNOTE-006.

In a real-life evaluation of 185 patients who electively discontinued anti-PD-1 therapy (pembrolizumab N = 167, nivolumab N = 18), in the absence of PD or toxicity, relapse rate was lower after CR than after PR or SD.14

Recommendation 6.2. Stopping treatment with anti-PD-1 therapy should be considered after 2 years of treatment in the case of PR.
Level of evidence: III
Strength of recommendation: B
Level of consensus: 100% (30) yes (30 voters)

Recommendation 6.3. Stopping treatment with anti-PD-1 therapy can be considered after 2 years of treatment in the case of SD.
Level of evidence: III
Strength of recommendation: C
Level of consensus: 97% (29) yes, 3% (1) no (30 voters)

CR, PR and SD with targeted therapy. There are limited data regarding stopping targeted therapy in patients with a CR, PR or SD. Relapse rates of ≥50% were reported from cohort studies of <20 patients and a short follow-up after stopping BRAF or BRAF/MEK inhibitors.50,51

Recommendation 6.4. Stopping targeted therapy followed by observation in patients with clinical benefit (CR, PR or SD) outside of a clinical trial is not recommended.
Level of evidence: IV
Strength of recommendation: E
Level of consensus: 100% (30) yes (30 voters)

7. If stopping immunotherapy in the case of a favourable outcome, what are the required criteria in terms of duration of therapy, duration of response, imaging and pathology? Dual modality imaging with fluorodeoxyglucose positron emission tomography and computed tomography (CT) may allow stratification of patients under anti-PD-1 immunotherapy according to their risk for subsequent progression. The PFS rate in patients with a PR on CT at 1 year and a metabolic CR was 93% in contrast to 48% for those without a metabolic CR.52

The role of biopsy or resection of metastases in the absence of PD has not been formally established, although a pathologic CR may define low risk for progression.

Recommendation 7.1. Stopping anti-PD-1 treatment before 2 years can be considered after at least 6 months of treatment in patients with confirmed radiological control (SD or PR) in case of a complete pathological and/or metabolic response.
Level of evidence: V
Strength of recommendation: C
Level of consensus: 97% (29) yes, 3% (1) no (30 voters)

Follow-up after stopping therapy. Given the risk of early progression after elective discontinuation (~10%–30% in the first 24 months), clinical examination and whole-body imaging follow-up should be carried out every 3–6 months for up to 3 years (or earlier in case of clinical indications for progression). Intervals between follow-up visits can be increased after 3 years of remission.

Recommendation 7.2. Clinical and imaging follow-up after stopping anti-PD-1 therapy should be performed every...
3–6 months for up to 3 years, and then the follow-up intervals can be increased.
Level of evidence: V
Strength of recommendation: B
Level of consensus: 93% (28) yes, 7% (2) abstain (30 voters)

8. Can the same criteria be applied for stopping in cases of non-spontaneous responses, that is, when radiotherapy, surgery or any other local treatment was used to eradicate one or several tumours that did not respond as well as the others? No data are available on patients with a CR achieved by surgical resection or stereotactic irradiation of one or a few metastases. As such, no formal recommendation can be made and a multidisciplinary team decision is likely the best approach, considering the type of therapy and whether the lesions treated by surgery/radiotherapy (RT) have been progressing or stagnating under systemic therapy. Stopping therapy might be possible for some patients on immunotherapy but this should probably be avoided for patients on targeted therapy.

9. Can therapy be stopped and when should therapy be stopped in the case of progression?

Immunotherapy. Data regarding treatment beyond progression are only available from pooled analyses for anti-PD-1 agents [CheckMate 066 and 06753 and a Food and Drug Administration (FDA) analysis of eight clinical trials of pembrolizumab or nivolumab involving 2624 patients54]. In the FDA analysis, patients were evaluated by Response Evaluation Criteria In Solid Tumours (RECIST) version 1.1 and were authorised to receive treatment beyond PD (i.e. RECIST PD). Subsequent responses appeared similar between patients treated beyond progression and those who were not [19% (95/500) and 16% (10/64), respectively],54 although the group treated beyond progression had better Eastern Cooperative Oncology Group (ECOG) PS and lower LDH levels. Moreover, survival was similar between patients treated beyond progression in the nivolumab and dacarbazine groups in the CA209066 trial.54

Atypical progression or pseudoprogression using RECIST has been observed in 7% of patients treated by anti-PD-1 therapy,55 highlighting the interest of immune-modified criteria of response and the necessity to confirm progression.

Recommendation 9.1. Continuing immunotherapy beyond confirmed progression is not generally recommended.
Level of evidence: III
Strength of recommendation: D
Level of consensus: 93% (28) yes, 7% (2) no (30 voters)

Targeted therapy. Puzanov et al.56 reported on 20 (45.5%) patients treated after progression with vemurafenib for a median of 3.8 months. Scholtens et al.57 reported a favourable survival in 35/70 patients treated beyond progression with vemurafenib. Patients treated beyond progression, however, had better prognostic factors (LDH and PS) compared with those not treated beyond progression.57

In a retrospective study,58 37/95 patients (39%) progressing on dabrafenib or vemurafenib continued BRAF inhibitor therapy beyond progression and had a better OS, but again better prognostic factors. In contrast, a retrospective analysis of 180 patients with BRAF-mutated melanoma, mostly treated with vemurafenib or dabrafenib, did not suggest a benefit of treatment beyond progression.59

It is worth noting that discontinuing targeted therapy in progressive patients who have no further treatment options available is potentially followed by a rapid flare-up of the disease (experts’ opinion).

Recommendation 9.2. Continuing targeted therapy beyond confirmed progression can be considered in the absence of appropriate alternative treatment.
Level of evidence: IV
Strength of recommendation: B
Level of consensus: 97% (29) yes, 3% (1) abstain (30 voters)

10. Are there adverse events that definitely prevent resuming therapy, and when an ‘unacceptable’ adverse event occurs with ipilimumab/nivolumab, is it possible to rechallenge with an anti-PD-1 therapy? Depending on the individual clinical situation and a very careful risk—benefit assessment, resuming therapy can be considered after any adverse event (AE) of any grade in patients with metastatic melanoma. Shared decision making is warranted. Severe immune-related AEs (irAEs) can occur with ICIs and must be adequately treated and resolved. Fatal irAEs affect <1% of ICI-treated patients.60 By percentage, cardiac or neurological irAEs are most frequently fatal, whereas colitis or endocrinopathies rarely cause treatment-related death. However, based on absolute numbers, the latter contribute substantially to treatment-related mortality.60 Thus, no specific irAE can be defined that prohibits resuming therapy.

In patients who received ipilimumab 3 mg/kg plus nivolumab 1 mg/kg that was stopped for toxicity reasons, not resuming therapy did not result in an inferior survival outcome.61 Resuming anti-PD-1 monotherapy after ipilimumab and nivolumab can lead to recurrent irAEs in ~20% of patients.62 Recurrent anti-PD-1 monotherapy-related AEs can also happen after resuming anti-PD-1 monotherapy.63 Limited data are available on survival outcomes after permanent discontinuation of anti-PD-1 monotherapy due to an irAE, but current evidence suggests that it is not inferior.65

Recommendation 10.1. In case of resolved severe AEs, treatment should only be resumed after careful risk—benefit assessment by an experienced clinical team.
Level of evidence: IV
Strength of recommendation: B
Level of consensus: 100% (28) yes (28 voters)

Recommendation 10.2. When a treatment-limiting AE occurs with ipilimumab/nivolumab, rechallenge with anti-PD1 monotherapy can be considered after resolution or control of the AE and after careful risk—benefit assessment by an experienced clinical team.
Level of evidence: III
Strength of recommendation: B
Level of consensus: 100% (29) yes (29 voters)

**Systemic versus local treatment for BMs**

11. If immunotherapy is given to patients with central nervous system metastases, is ipilimumab/nivolumab always preferred over anti-PD-1 monotherapy? Small, single-arm, phase II studies of immunotherapy have been reported in patients with central nervous system (CNS) metastases. For example, in a phase II study evaluating ipilimumab in patients with melanoma BMs (MBMs), intracranial responses were achieved in 16% of 51 patients who were neurologically asymptomatic and not receiving corticosteroid treatment, and in 5% of 21 patients who were symptomatic and on a stable dose of corticosteroids.66

The activity of ipilimumab and nivolumab versus nivolumab monotherapy in MBMs was evaluated in the randomised phase II Australian Brain Collaboration (ABC) study.67 Among the 76 treated patients, 60 were asymptomatic, and of these, 35 received the combination of ipilimumab and nivolumab (cohort A) and 25 received nivolumab monotherapy (cohort B). Sixteen patients who had failed local therapy or were neurologically symptomatic and/or had leptomeningeal disease (LMD) received nivolumab monotherapy (cohort C). Intracranial responses were achieved in 51%, 20% and 6%, and 12-month OS was 63%, 60% and 31% in cohorts A, B and C, respectively. The intracranial response rate (RR) in cohort A was 59% for treatment-naïve patients and 25% in patients previously treated with BRAF inhibitors. However, ABC was not designed/powered to be comparative between treatment arms.

The safety and efficacy of nivolumab and ipilimumab was also evaluated in CheckMate 204.68 In the most recent update, 119 patients had been treated: 101 patients with asymptomatic MBMs and 18 patients with either symptomatic MBMs or who were receiving up to 4 mg of oral dexamethasone. The intracranial RR was 54% in patients with asymptomatic MBMs, including CRs in 29%. The 6-month intracranial PFS was 63% and the median PFS was not reached. In patients who were either symptomatic or requiring steroids at the time of treatment initiation, the RR was 22%, although only 1/11 patients (9%) receiving steroids experienced a response.

The safety profile of immunotherapy in these studies was consistent with that for patients without BMs. Furthermore, intracranial and extracranial responses were largely concordant, as confirmed by a recent meta-analysis.69 However, it is unclear whether the efficacy of immunotherapy holds true for all patients with BMs, because in both BM trials, the size of the lesions was very small. In CheckMate 204, patients had to be asymptomatic with a low tumour burden.

**Recommendation 11.1.** Combination immunotherapy over single-agent therapy is recommended for patients with asymptomatic MBMs not requiring steroids.

Strength of recommendation: B
Level of consensus: 100% (30) yes (30 voters)

12. For patients with BRAF-mutated disease who require concomitant medications for BMs, would targeted therapy or immunotherapy be the preferred approach? In the COMBI-MB trial (dabrafenib and trametinib in patients with BRAF-mutated MBMs), the main cohort A of asymptomatic patients not receiving local treatment was not allowed to be taking antiepileptic medication related to the BMs. This restriction was also applied to cohort B (patients previously treated with local therapy) and cohort C (patients with mutations other than V600E/K), thereby reducing the possibility of their use in cohort D (symptomatic patients).70 There was no noted difference in efficacy between cohorts. Thus, if a patient requires antiepileptic medication, there is no evidence of an impairment in efficacy of targeted therapy. However, strong inhibitors of CYP3A or CYP2C8 (e.g. carbamazepine, oxcarbazepine, phenobarbital and phenytoin) could increase the concentration of both drugs (especially dabrafenib), thereby increasing toxicity. Levetiracetam could be safer due to its low interaction with cytochromes.

The use of antiepileptic drugs was not an exclusion criterion in clinical trials evaluating ipilimumab and nivolumab (ABC69 and CheckMate 20471). There is no evidence that antiepileptic agents impact on immunotherapy efficacy outcomes.

Given the above, it seems reasonable that for patients with BRAF-mutated MBMs who require an antiepileptic medication that is a strong inhibitor of CYP3A or CYP2C8, the preferred treatment option in terms of safety is immunotherapy.

The COMBI-MB trial allowed the use of a stable or decreasing dose of corticosteroids,70 which was excluded in the ABC study (except prednisone <10 mg or equivalent).39 In the cohort of symptomatic patients, CheckMate 204 allowed up to 4 mg of dexamethasone, provided the dose was stable 10 days before starting study treatment. In the asymptomatic cohort, patients were excluded unless corticosteroids had been stopped 10 days before starting immunotherapy.71 The RR in CheckMate 204 was 22%68 compared with 59% in COMBI-MB.70

Table 2 provides a summary regarding the potential for immunotherapy and targeted therapy use in patients with BMs who require concomitant corticosteroids and/or antiepileptic drugs.

**Recommendation 12.1.** Antiepileptic therapy appears to be safe during immunotherapy but can interact with targeted therapy (with the exception of levetiracetam).

Level of evidence: IV
Strength of recommendation: B
Level of consensus: 100% (30) yes (30 voters)

**Recommendation 12.2.** If there is continuous dependency on corticosteroids (>10 mg prednisolone or equivalent) at initiation of systemic treatment, then targeted therapy is preferred over immunotherapy.

Level of evidence: III
Strength of recommendation: B
Level of consensus: 90% (27) yes, 10% (3) no (30 voters)
### Table 2. Potential use of immunotherapy and targeted therapy in patients receiving concomitant corticosteroids and/or antiepileptic medication

<table>
<thead>
<tr>
<th>Condition and concomitant treatment</th>
<th>Targeted therapy can be used</th>
<th>Immunotherapy can be used</th>
<th>Preferred treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiepileptics with strong effect on CYP</td>
<td>No</td>
<td>Yes</td>
<td>Immunotherapy</td>
</tr>
<tr>
<td>Antiepileptics with no effect on CYP</td>
<td>Yes, but most evidence in symptomatic patients</td>
<td>Yes</td>
<td>Immunotherapy</td>
</tr>
<tr>
<td>Corticosteroids ≤4 mg dexamethasone</td>
<td>Yes, but must be stable</td>
<td>Yes, but most evidence in symptomatic patients</td>
<td>Targeted therapy for symptomatic patients and immunotherapy for asymptomatic patients</td>
</tr>
<tr>
<td>Corticosteroids &gt;4 mg dexamethasone</td>
<td>Yes, but must be stable</td>
<td>No evidence</td>
<td>Targeted therapy</td>
</tr>
</tbody>
</table>

CYP, cytochrome P450.

#### 13. How should stereotactic radiosurgery or whole-brain RT be combined with targeted therapy and immunotherapy: sequential versus simultaneous application?

**Immunotherapy in combination with RT.** The potential synergy of RT with immunotherapy has become an exciting field of investigation with the introduction of ICIs.

In clinical trials, the timing, dose and schedule of RT, as well as the dose, schedule and type of ICI are heterogeneous. Two prospective phase I trials and several retrospective studies have investigated a potential synergism between RT and ICIs in patients with MBMs.

Prospective studies to evaluate stereotactic radiosurgery (SRS) plus immunotherapy are ongoing (NCT03340129 and NCT02107755); however, the optimal timing for the introduction of systemic therapy (before or after SRS), the optimal RT dose and early and delayed toxicities, including the incidence of radionecrosis, remain to be elucidated. Furthermore, changes in neurocognitive function with such combinations should be investigated.

**Targeted therapy in combination with RT.** SRS can be used as a rescue strategy in patients treated with BRAF/MEK inhibitors in cases of local progression despite overall disease control and can be repeated if needed. Alternatively, SRS can be used for immediate control of threatening BMs, while BRAF/MEK inhibitors can be started at the same time to treat metastases in other organs and possibly also to control undetectable BMs. Although the biological rationale to combine SRS with BRAF/MEK inhibitors is less robust than with immunotherapy, retrospective series suggest that it improves outcomes. Importantly, neither immediate radiotoxicity nor radiation recall has been observed in patients treated with SRS and BRAF/MEK inhibitors. Hence, while it is still advised to stop BRAF/MEK inhibitors during whole-brain RT (WBRT), interruption of treatment with BRAF/MEK inhibitors is not recommended during SRS.

**Recommendation 13.1.** SRS with concurrent immunotherapy or targeted therapy appears to be safe, although strong evidence is lacking.

Level of evidence: IV

Strength of recommendation: B

Level of consensus: 90% (27) yes, 3% (1) no, 7% (2) abstain (30 voters)

#### 14. What is the best sequencing strategy for immunotherapy, targeted therapy and SRS in patients with MBMs?

SRS is the preferred local treatment modality for limited asymptomatic BMs, with ‘limited’ BMs defined as 1–4 BMs with a maximum diameter of 4 cm or 5–10 BMs with the largest tumour <10 mL in volume and <3 cm in the longest diameter and a total cumulative volume of ≤15 mL.

SRS has been shown to achieve durable local metastases control and improved OS in the RTOG 9508 study, which included 4%–5% of patients treated for MBMs. However, local efficacy of SRS appears equal in MBMs compared with other tumour entities without an excessive risk of post-SRS haemorrhage.

For patients with melanoma presenting with asymptomatic BMs, ipilimumab plus nivolumab is a treatment option with a high ORR in the brain (51%–54%). Although dabrafenib plus trametinib shows clear activity in patients with BRAF V600-mutated asymptomatic BMs (ORR 58%), the durability of these responses appears shorter, with a 1-year PFS of 19%. Therefore, there is consensus to use combination immunotherapy in patients with asymptomatic MBMs irrespective of BRAF mutational status unless there is a strong contraindication to immunotherapy.

Whether immunotherapy should follow SRS or be given concomitantly has not been prospectively addressed. Delaying SRS carries the risk of neurological symptoms. A recent meta-analysis of mostly single-agent ICI treatment and SRS, as well as CheckMate 204, suggests early SRS in the course of single-agent immunotherapy results in better brain control and survival. In CheckMate 204, only 2% of patients (with SD) received SRS during immunotherapy, whereas 33% of patients had intracranial PD, requiring additional treatment (SRS and targeted therapy). Starting with combination immunotherapy requires careful follow-up (4–6 weeks after starting immunotherapy) to allow early SRS for relevant residual disease. Upfront SRS or concurrent immediate immunotherapy and SRS may decrease the risk of CNS progression, although it may increase the risk of radionecrosis. The size and location of BMs should be considered in the decision-making process. Upon significant progression in patients with BRAF V600-mutated disease, a switch to targeted therapy is advised.
For patients with symptomatic BMs not requiring corticosteroids, a small subset analysis of CheckMate 204 showed that combination immunotherapy resulted in a similar ORR to that seen in patients with asymptomatic BMs. Based on the limited data available for systemic therapy alone in this patient cohort, combining immunotherapy with immediate SRS should be considered to achieve the best local response and symptom improvement.

Approaches for patients with symptomatic BMs requiring corticosteroids depend on BRAF status. In patients with BRAF wild-type disease, upfront SRS to allow tapering of corticosteroids and treatment with combination immunotherapy, or a combined approach of SRS and immunotherapy, is advised. The low ORR of 22% in patients with symptomatic BMs in CheckMate 204 \( (N = 18) \) indicates that this is a patient population with a poor prognosis. In patients with BRAF-mutated disease, combined targeted therapy with immediate SRS should be considered to achieve the best local response and symptom improvement.

**Recommendation 14.1.** For patients with multiple asymptomatic BMs, combination treatment with ipilimumab and nivolumab is recommended due to its more durable disease control compared with targeted therapy.

Level of evidence: V
Strength of recommendation: B
Level of consensus: 100% (32) yes (32 voters)

**Recommendation 14.2.** In BRAF-mutated cases, combination targeted therapy with dabrafenib and trametinib is recommended in patients with rapid PD or contraindications for immunotherapy.

Level of evidence: V
Strength of recommendation: B
Level of consensus: 100% (32) yes (32 voters)

**Recommendation 14.3.** For limited BMs, if SRS is considered along with immunotherapy or targeted therapy, early (within 2–3 months) concurrent SRS is preferred over late SRS as salvage treatment.

Level of evidence: III
Strength of recommendation: B
Level of consensus: 97% (31) yes, 3% (1) no (32 voters)

**15. What is the role of WBRT or SRS after resection of MBMs?** WBRT has been the standard of care for BMs after neurosurgical resection or SRS, but there are few studies on MBMs. A recent phase III trial of either WBRT or observation after BM-directed local therapy in 215 MBM patients showed that WBRT improved local metastases control but did not reduce distant intracranial failure or improve time to ECOG PS deterioration or OS, and increased the risk of neurocognitive decline.

More conformal techniques for WBRT that avoid the hippocampus, with the aim of preserving neurocognitive function, are currently under investigation. Based on the lack of OS benefit and the negative effect on neurocognition, WBRT should not be carried out after SRS or neurosurgical resection in the treatment of limited MBMs.

Two randomised trials evaluated the use of SRS to the resection cavity after neurosurgical resection of BMs with multiple histologies. In the first, WBRT and SRS (1 × 12–20 Gy) did not differ in OS, but a cognitive function decline was more frequent after WBRT versus SRS. The second study of SRS (1 × 12–16 Gy) versus observation reported a significantly improved 12-month freedom from local recurrence with SRS [72%, 95% confidence interval (CI) 60–87] compared with observation (43%, 95% CI 31–59). Based on these data, postoperative SRS to the resection cavity should be considered after complete resection of MBMs. For larger resection cavities, distributing the total dose over 3–5 fractions is encouraged, which might improve local metastases control.

**Recommendation 15.1.** WBRT is not recommended after complete resection or SRS of MBMs.

Level of evidence: I
Strength of recommendation: E
Level of consensus: 100% (30) yes (30 voters)

**Recommendation 15.2.** Postoperative SRS to the resection cavity should be considered after complete resection of MBMs.

Level of evidence: I
Strength of recommendation: B
Level of consensus: 97% (29) yes, 3% (1) abstain (30 voters)

**16. What dosing schedule is recommended for stereotactic radiosurgery?** The dose of single-fraction SRS is based on the RTOG 9005 study, which was not melanoma specific, and reported maximum tolerated doses of 24, 18 and 15 Gy for tumours ≤2.0, 2.1–3.0 and 3.1–4.0 cm in maximum diameter, respectively. The dose of single-fraction SRS is based on the RTOG 9005 study, which was not melanoma specific, and reported maximum tolerated doses of 24, 18 and 15 Gy for tumours ≤2.0, 2.1–3.0 and 3.1–4.0 cm in maximum diameter, respectively. No prospective study has tested alternative dose and fractionation schedules in a comparative design. This holds true for SRS alone as well as the combination with systemic therapy.

Studies have reported that SRS combined with ICIs and with BRAF inhibitors might be associated with an increased risk of radionecrosis and haemorrhage, respectively; however, these preliminary findings do not justify a change to standard treatment.

In cases of BMs larger than 2–3 cm, a risk-adapted fractionation is recommended where the total dose is distributed, usually over 3 or 5 fractions.

**Recommendation 16.1.** The dose of single-fraction SRS is 20–24, 18 and 15 Gy for tumours ≤2.0, 2.1–3.0 and 3.1–4.0 cm in maximum diameter, respectively.

Level of evidence: I
Strength of recommendation: A
Level of consensus: 90% (27) yes, 3% (1) no, 7% (2) abstain (30 voters)

**Recommendation 16.2.** In cases of BMs larger than 2–3 cm, a risk-adapted fractionation appears to achieve a better risk–benefit ratio and is recommended with a few (usually 3 or 5) RT fractions (e.g. 3 × 9 Gy).

Level of evidence: III
Strength of recommendation: A
Level of consensus: 90% (27) yes, 3% (1) no, 7% (2) abstain (30 voters)
CNS-active systemic therapy and the toxicity profile of WBRT

Currently, the value of WBRT is challenged by several developments: (i) CT and magnetic resonance imaging (MRI) for (re)staging result in frequent diagnosis of asymptomatic BMs; (ii) stereotactic RT and radiosurgery of BMs have become standard clinical practice; (iii) effective systemic treatment options (i.e. ICIs and targeted therapy) show relevant CNS activity. Based on these developments and the potential consequences of WBRT on neurocognition, the routine use of WBRT in multiple BMs not amenable to SRS is discouraged.

The use of WBRT in patients with multiple BMs needs to consider patient symptoms, the choice and availability of CNS-active systemic therapy and the toxicity profile of WBRT.

In asymptomatic patients, BRAF/MEK inhibitors and combined ICIs achieve RRs and intracranial PFS that support initial treatment with systemic therapy, close follow-up using cranial MRI and deferred local RT (SRS preferred).

In symptomatic patients, activity of systemic therapy alone is limited. Vemurafenib alone achieved an intracranial PR of 16% with a median PFS of 3.9 months and OS of 5.3 months in 24 patients with BRAF V600-mutated symptomatic MBMs. Dabrafenib and trametinib in BRAF V600-mutated MBMs resulted in an intracranial RR of 59% in 17 patients with symptomatic BMs, but with a median intracranial response duration of only 4.5 months. Nivolumab monotherapy achieved an intracranial response in only one of 16 patients with symptomatic MBMs. The intracranial clinical benefit rate (i.e. CR + PR + SD ≥6 months) with nivolumab and ipilimumab in CheckMate 204 was only 22% in 18 patients with symptomatic BMs.

Diffuse LMD is associated with a dismal prognosis, with a median survival of weeks in untreated patients and 2–3 months in treated patients. Treatment algorithms for LMD are similar to those for MBM and the consideration of WBRT needs to take into account patient symptoms, the choice and availability of CNS-active systemic therapy and the toxicity profile of WBRT.

**Recommendation 17.1.** The routine use of WBRT in MBMs not amenable to SRS and in LMD is discouraged and should be restricted to carefully selected patients.

**Recommendation 17.2.** What is the role of WBRT for multiple MBMs not amenable for SRS and in cases of LMD? WBRT has traditionally been a mainstay in the treatment of MBMs, with symptom improvement reported in 75% of patients. Currently, the value of WBRT is challenged by several developments: (i) CT and magnetic resonance imaging (MRI) for (re)staging result in frequent diagnosis of asymptomatic BMs; (ii) stereotactic RT and radiosurgery of BMs have become standard clinical practice; (iii) effective systemic treatment options (i.e. ICIs and targeted therapy) show relevant CNS activity. Based on these developments and the potential consequences of WBRT on neurocognition, the routine use of WBRT in multiple BMs not amenable to SRS is discouraged.

**Recommendation 17.3.** The use of WBRT in patients with multiple BMs needs to consider patient symptoms, the choice and availability of CNS-active systemic therapy and the toxicity profile of WBRT.

**Recommendation 18.1.** The use of inactivated influenza vaccine appears safe.

**Recommendation 18.2.** Several studies suggest that antibiotics may be detrimental to outcomes in patients receiving immunotherapy and may possibly interact pharmacologically with targeted therapies as well as other drugs such as antiemetics. We recommend restrictive use of empirical antibiotics.
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