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SPECIAL ARTICLE

ESMO consensus conference recommendations on the management of locoregional 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 of brain metastases. The expert panel was divided into five working groups in order 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 locoregional 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: melanoma, consensus, treatment, immunotherapy, targeted therapy, adjuvant

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INTRODUCTION

Although melanoma accounts for less than 10% of skin cancer cases, it is the deadliest form of skin cancer due to its aggressive nature and high mortality rate.[1] Thus, early

diagnosis and effective treatment at a stage when a cure is readily achievable are the most important success factors.

Various organisations and societies, including the European Society for Medical Oncology (ESMO),[2] produce Clinical Practice Guidelines (CPGs) that provide guidance to health care professionals (HCPs) regarding the optimal management of patients with melanoma based on the latest evidence and expert opinion. However, evidence is limited and/or conflicting in some areas and the optimal approach remains controversial. For example, in patients with resectable melanoma, recommended safety margins for the wide local excision (WLE) of primary melanomas have been defined for localised disease, but with recent advances in adjuvant systemic therapy, it is unclear if the same safety margins should be applied for WLE of resectable stage III primary tumours. In terms of staging, sentinel lymph node (SLN) biopsy (SLNB) is recommended for patients with melanoma of American Joint Commission on Cancer 8th edition (AJCC8) stage pT1b or higher (i.e. with a tumour thickness of $>$0.8 mm or $<$0.8 mm with ulceration[2]); but additional risk factors exist and it is not known which features are significant predictors of SLN metastases and to what degree. Moreover, subsequent completion lymph node dissection (CLND) in the event of SLN-positive disease has not been shown to offer an improvement in overall survival (OS) versus observation.[3,4] As such, clear criteria for CLND need to be defined.

In terms of adjuvant treatment, a number of clinical studies have shown that immunotherapy and targeted therapy are effective[5–10] but long-term survival data are still lacking and no direct comparison studies have been carried out. Moreover, given the recent introduction of the AJCC8 staging system, the optimal approach for stage IIIA disease is unclear. A further concern is the management of toxicities with adjuvant therapies, with grade 3/4 adverse events (AEs) reported in up to 41% of patients in adjuvant trials.[11] Pilot studies and phase I/II trials have demonstrated promising preliminary results for the use of targeted therapies and immunotherapies as neoadjuvant treatment in resectable disease[12–15] but optimal approaches to integrate neoadjuvant therapy in the current landscape require further investigation.

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 in the treatment of melanoma 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 of brain metastases (Chair: **R. Dummer**).

Planning, preparation and execution of the consensus conference was conducted according to ESMO standard operating procedures (SOPs), 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 as shown in supplementary Table S1 available at https://doi.org/10.1016/j.annonc.2020.07.005.[16] Recommendation 10.3 failed to reach a consensus at the meeting; this statement was modified post-meeting and an online vote was undertaken in order to reach a consensus in accordance with ESMO methodology.

Results from Working Groups 1 and 2 of this consensus conference (i.e. management of locoregional 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

Management of locoregional disease

1. What is the correct indication/threshold to offer an SLNB? SLNB is an established, minimally invasive surgical procedure, which provides essential staging information that impacts on the clinical management of patients with melanoma.[2] The presence of SLN metastasis indicates a significantly worse prognosis and this appears true across all tumour thicknesses.[17–23] However, the rate of SLN positivity varies with primary tumour thickness and influences the recommendation for performing the procedure. In addition to tumour thickness, other primary tumour factors have been shown to be associated with the rate of SLN metastasis and are considered important for patients with primary melanomas $<$1 mm in thickness. These factors include ulceration, mitotic rate, Clark level, tumour infiltrating lymphocytes (TILs), lymphovascular invasion (LVI), vertical growth phase and regression. Patient factors, including age and sex, have also been associated with nodal metastasis.[19,24–27] There is, however, significant variability in the literature as to which features are significant predictors and to what degree. A meta-analysis of SLNB in thin melanomas found thickness ($\geq$0.75 mm), Clark level (IV/V), mitotic rate and microsatellitosis to be significant factors.[28] Ulceration was an uncommon finding but was correlated with SLN metastasis in an unadjusted analysis [odds ratio

(OR) 2.27, 95% confidence interval (CI) 0.98—5.24]. However, this was a study-level meta-analysis. A patient-level meta-analysis could be carried out to help clarify the variability in reporting of some predictors (e.g. mitosis). A meta-regression could also be carried out in order to define the independent effect of high-risk features of the primary tumour on SLN positivity.

The AJCC8 staging system defines T1b tumours as those with a thickness of <0.8 mm with ulceration or 0.8—1.0 mm with or without ulceration.[17] However, the committee noted that ulceration in melanomas that are <0.8 mm is an uncommon finding and that data regarding the frequency of SLN metastasis in that specific group are lacking. The predicted rate of SLN metastasis in T1b melanomas is between 5% and 10%, which was felt to be sufficient to discuss SLNB with those patients. The committee discussed the threshold probability of SLN metastasis that would warrant SLNB but did not come to a formal consensus due in part to the evolving adjuvant therapy landscape. Additional research is needed into the frequency of larger metastases (longest diameter ≥1 mm) among patients with thin melanomas and SLN disease which might influence future consideration of the procedure.

Recommendation 1.1. SLNB is recommended for staging in melanomas of AJCC8 stage pT2a or higher (>1.0 mm Breslow thickness).
Level of evidence: I
Strength of recommendation: A
Level of consensus: 100% (27) yes (27 voters)

Recommendation 1.2. SLNB should be discussed with patients with a melanoma of AJCC8 stage pT1b (i.e. with a tumour thickness >0.8—1.0 mm or with a tumour thickness of <0.8 mm with ulceration).
Level of evidence: III
Strength of recommendation: B
Level of consensus: 96% (27) yes, 4% (1) no (28 voters)

Recommendation 1.3. SLNB is not routinely recommended for patients with a melanoma of AJCC8 stage pT1a (e.g. with a tumour thickness <0.8 mm and no ulceration).
Level of evidence: II
Strength of recommendation: E
Level of consensus: 100% (29) yes (29 voters)

Recommendation 1.4. SLNB can be discussed in pT1a for special cases [e.g. ≥3 mitoses/mm^2, a positive deep margin or when Breslow thickness cannot be reliably determined (pTx)].
Level of evidence: III
Strength of recommendation: D
Level of consensus: 100% (29) yes (29 voters)

2. Which margins should be followed for WLEs?

Should standard WLE safety margins be used for primary melanoma in the context of resectable clinical stage III disease, and should WLE be used for primary melanoma in the context of clinical stage IV disease?. The concept of WLE in melanoma was developed in the early 20th century when it was hypothesised that WLE could improve local control after melanoma by removal of undetected microsatellites and thereby potentially reduce progression to regional nodes and/or distant sites. Indeed, WLE reduced local relapses significantly but relapse-free survival (RFS) and OS were not improved. At the same time, treatment of resectable stage III melanoma has changed due to recent advances in adjuvant therapy whereby the majority of patients with resectable stage III disease will receive adjuvant systemic therapy. Given these advances, the question is raised as to whether WLE with the same safety margins should be used to treat primary melanoma in the context of resectable clinical stage III disease? Although the committee recognised that there are no robust data on this topic, it seems sensible to recommend conservative treatment, thus accepting lesser clinical safety margins than would normally be advised based on the Breslow thickness. For patients with stage IV disease, in most circumstances, no surgical treatment of the primary melanoma is recommended since the patient will be receiving systemic therapy. However, in those circumstances where the primary melanoma is symptomatic or when surgical removal is necessary for diagnostic tissue then the surgical resection should be with clear margins but with no additional safety margins.

Recommendation 2.1. In the context of resectable clinical stage III disease, primary melanomas should be removed with clear margins to ensure local control. WLE with primary closure to avoid reconstruction whenever possible, ideally with a clinical 1 cm margin, is advised with reconstruction avoided whenever possible.
Level of evidence: V
Strength of recommendation: B
Level of consensus: 100% (31) yes (31 voters)

Recommendation 2.2. In the context of clinical stage IV disease, in the absence of symptoms or need for diagnostic tissue, there is no need to resect the primary tumour. If there is an indication to resect the primary lesion, resection should be with clear margins but without additional safety margins.
Level of evidence: V
Strength of recommendation: D
Level of consensus: 100% (29) yes (29 voters)

3. Radical lymph node dissection

Indication for radical lymph node dissection in case of clinically-detected lymph node metastases in resectable stage III disease. For patients with nodal metastases detected by physical examination or imaging, radical dissection of the associated nodal basin has been the standard treatment. In an era when the MSLT-II and DeCOG-SLT trials have changed practice for CLND in patients with SLN-detected metastases, the committee evaluated recommendations in patients with clinically-detected (sonography/palpable nodal) disease. It was noted that management of patients whose metastases are detected in pre-SLN ultrasounds may be different, but the committee did not specifically address that population in the current recommendation. It was also highlighted that this is not routine practice in most institutes since the results of pre-SLN ultrasound have been variable.[3,4] The increased effectiveness of systemic therapy was also noted, particularly with regard to whether patients with clinically-detected nodal metastases could undergo a smaller surgical procedure, as discussed in the questions below.

Recommendation 3.1. Radical lymph node dissection is recommended for cases of clinically-detected lymph node metastases in resectable stage III disease after pathological assessment (cytology or histology of lesion preoperatively) and adequate staging.
Level of evidence: IV
Strength of recommendation: B
Level of consensus: 100% (31) yes (31 voters)

Node picking versus node dissection (in the absence of neoadjuvant therapy). As noted above, the possibility of a more limited dissection or removal of only lymph nodes with clinically-apparent disease was considered. Complete dissection has been standard therapy up to this point. There are currently no high-level data to recommend a reduction in the extent of surgery. A trial comparing node picking followed by adjuvant systemic therapy versus node dissection followed by adjuvant systemic therapy would be required. It was also noted that the number of involved lymph nodes in this setting is significantly greater than in the positive-SLN setting and that the location of additional involved nodes within the basin cannot be accurately predicted.[29] There are also data from the MSLT-I study showing that the extent of dissection, as measured by the number of removed nodes, is not related to the risk of subsequent lymphoedema.[30] Additional research may be able to provide guidance, with ongoing improvements in imaging, particularly nodal ultrasound.[31] In the absence of clinical trial data establishing the safety of a 'node-picking' approach, there was broad consensus that full dissection of the affected nodal basin is indicated.

Recommendation 3.2. When lymph node surgery is indicated, radical node dissection is recommended over 'node picking'.
Level of evidence: III
Strength of recommendation: B
Level of consensus: 100% (29) yes (29 voters)

Inguinal versus ilio-inguinal dissection, levels of axilla and levels of neck dissection. When node dissection is indicated for regionally metastatic melanoma, complete removal of node-bearing tissue within the anatomic boundaries of the nodal basin has been the standard approach. In other diseases such as breast cancer, the extent of nodal dissection has been reduced, for example sparing the level III axillary lymph nodes. The committee did not feel such an approach could be recommended for patients with melanoma at this time. Drainage patterns from primary melanomas are highly variable,[32] making reliable algorithms for inclusion or exclusion of areas within the basin very challenging. In general, it was felt that the addition of more levels within a given nodal basin is not broadly associated with substantially increased procedural morbidity. Specifically, the number of excised nodes has not been associated with morbidity in melanoma, and inclusion of a pelvic dissection in the case of groin metastasis was found not to increase the long-term risk of lymphoedema in the MSLT-I trial.[30] This led to some lack of agreement among the panel regarding the inclusion of iliac/pelvic lymph nodes when macroscopic inguinal metastases are present. It was felt that inclusion of those nodes would be unlikely to influence OS and that re-operation into that previously undisturbed field could be safely carried out upon recurrence as long as the patient could be reliably followed with imaging and would not receive adjuvant radiotherapy (RT), which makes a pelvic/iliac dissection much more susceptible to complications. There is a prospective trial ongoing (EAGLE-FM; NCT02166788) that might guide this decision in the future.

In the cervical nodal basin, superficial parotidectomy carries additional morbidity risk relative to neck dissection alone. It was therefore felt that those nodes should only be included if there is direct evidence of metastasis there. There was some discussion about whether certain cervical nodal levels could be preserved based on the location of the primary tumour. In some instances—for example, occipital lymph nodes for anterior primary melanomas or level I lymph nodes for posterior primary tumours—consideration could be given to tailoring the extent of dissection, although prospective data are not available to provide specific recommendations. It was also noted that preservation of all important functional components of the neck (e.g. motor nerves) should be carried out, with rare exceptions for direct tumour involvement of those structures.

Recommendation 3.3.

Groin: If imaging does not show any iliac involvement, an inguinal dissection is sufficient. If iliac disease is also present, a combined ilio-inguinal dissection should be carried out.

Axilla: Complete clearance of the axilla, including level I—III, should be carried out.

Neck: Modified radical neck dissection is recommended. Parotidectomy should only be carried out if there is evidence of involvement of the parotid.

Level of evidence: IV
Strength of recommendation: B
Level of consensus: 87% (26) yes, 13% (4) no (30 voters)

4. Treatment of satellite/in-transit metastases

Treatment of satellite/in-transit metastases in case of resectable disease. Approximately 5%—10% of patients with high-risk melanoma will develop satellite or in-transit metastases.[33] This is a form of tumour spread within intradermal and subcutaneous lymphatic channels between the primary site and the regional lymph nodes. When there are only a few resectable lesions, simple radical surgical excision without the need for any extra margin is recommended. Resectability is a complicated definition and there is no single agreement. This recommendation focuses on in-transit metastases that can be regarded as few, small and non-rapidly recurrent.

These patients are considered stage III and they are at high risk for both locoregional and systemic recurrences. Imaging for staging—preferably with positron emission tomography-computed tomography (PET-CT)—and adjuvant systemic therapy are recommended. In a recent neoadjuvant trial using BRAF/MEK inhibitors, seven patients with in-transit only metastases were treated and four patients (57%) had a pathological complete response (CR).[34] Future research will need to evaluate if omitting surgery in this group of patients is safe.

Results of a randomised phase II study (NCT02211131), which is evaluating neoadjuvant talimogene laherparepvec (T-VEC) versus resection, were also discussed by the panel. Initial results demonstrated an increase in microscopically margin-negative resection (R0) rate with the use of T-VEC,[35,36] and a recent update also showed improvements in RFS [hazard ratio (HR) 0.66, $P = 0.04$] and OS (HR 0.49, $P = 0.05$) at 2 years.[37] However, as mature OS results had not been reported at the time of the consensus meeting, the committee felt it would be premature to recommend neoadjuvant T-VEC in these cases but recognised that this might be an option for the future.

Recommendation 4.1. For in-transit metastases that can be regarded as few, small and non-rapidly recurrent lesions, resection with clear margins, but without additional safety margins, is recommended. Extensive and multiple repeated resections and reconstructions should be avoided.

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

Treatment of satellite/in-transit metastases in case of unresectable disease. For patients with unresectable satellite or in-transit metastases (e.g. multiple, bulky or rapidly recurrent metastases), there are several treatment options. The major aim of treatment is to gain locoregional control but also to reduce systemic recurrences and ultimately improve survival.

Randomised trials of systemic immunotherapies for inoperable stage III disease have included patients presenting with in-transit metastases together with lymph node involvement; however, no subgroup analyses have specifically evaluated outcomes in this population.[38,39] Systemic treatment with targeted therapy or immunotherapy is often used in clinical practice, but no outcomes data have been published specifically for patients with in-transit or satellite metastases.

There are numerous locoregional treatment options available. However, most studies are retrospective case series with significant heterogeneity in patient populations and there are no direct comparisons between the treatments.

T-VEC is a local injection therapy for unresectable metastatic melanoma lesions (stage IIIB—IVM1a) that was approved globally based on results from the phase III OPTiM trial.[40] This trial reported a durable response rate (objective responses lasting $\geq$6 months; primary end point) of 16.3% with T-VEC versus 2.1% with granulocyte macrophage colony-stimulating factor[41] (19.0% versus 1.4% in the final analysis[42]). CR rates were 15% for injected lesions and 6% for non-injected lesions.[43]

Isolated limb perfusion (ILP) is a technique carried out by open surgical access to the central venous and arterial blood flow of the limb, which is proximally isolated by a tourniquet and then connected to an extracorporeal perfusion circuit. A high concentration of a chemotherapeutic drug is thereafter circulated through the limb, limiting the systemic side-effects of the drug. ILP has proven to be effective and safe with a high CR rate of 58% and low rates of regional and systemic toxicity.[44] Isolated limb infusion (ILI) is a similar procedure, based on the percutaneous placement of arterial and venous catheters passing through the contralateral groin without a surgical isolation of the vessels. Using a high-flow three-way stopcock syringe, melphalan is infused manually over approximately 20 min.[45] No randomised trials have compared ILI with ILP, but a retrospective study including 203 patients showed a CR rate of 29% for ILI compared with 60% for ILP.[46]

Electrochemotherapy (ECT) is a locoregional technique based on selective permeability produced by short electric pulses which can open ionic membrane channels that are otherwise impermeable to the chemotherapeutic agent bleomycin.[47] A recent prospective cohort study reported that this technique can achieve a CR in 48% of patients (58% of lesions).[48]

PV-10 is another local injection therapy containing a 10% solution of the xanthene dye rose bengal disodium. PV-10 results in a phototoxic reaction in injected lesions potentially increasing the uptake of cancer antigens by dendritic cells and leading to activation of T lymphocytes.[49] A recently published multicentre, single-arm, phase II trial including patients with unresectable stage III ($n = 62$) and stage IV ($n = 18$) disease reported a CR rate of 26% with PV-10.[50]

Given the aforementioned, the committee agreed that unresectable satellite/in-transit metastases, or inoperable primary tumours of the limbs without additional metastases, may be treated with locoregional treatments (e.g. ILP, ILI, T-VEC, ECT or PV-10). The use of these local procedures should be carefully weighed against systemic treatment in order to not lower the chance of providing long-term benefit. These recommendations are commensurate with those already included in the ESMO CPG.[2]

5. Is there an indication for adjuvant RT after node dissection? Lymphadenectomy is still the primary treatment for patients with clinically-detected stage III melanoma (see question 3), but there is a high regional recurrence rate in patients with high-risk features (e.g. extracapsular extension, large size of the metastatic node, multiple metastatic lymph nodes, head and neck melanoma and recurrent disease after prior nodal surgery).[51] This might change in the near future with the introduction of neoadjuvant treatments; neoadjuvant BRAF/MEK inhibition[34] and immunotherapy[52] have shown high CR rates of 46% and 43%, respectively.

Several retrospective studies have analysed the effect of adjuvant RT and have shown improved locoregional control without an improvement in survival.[53] This was confirmed by the ANZMTG 01.02/TROG 02.01 trial in which patients who had undergone lymphadenectomy due to clinically-detected lymph node metastases were randomised to receive adjuvant RT (48 Gy in 20 fractions) or observation. The results showed significantly fewer regional recurrences with adjuvant RT (21% versus 36% with observation) with an adjusted HR of 0.52; however, there was no difference in either RFS or OS between the two treatment arms.[54]

Recommendation 5.1. For patients with advanced stage III disease that has been treated with lymphadenectomy, the primary recommendation is adjuvant systemic therapy and observation, reserving additional surgery and RT for any recurrent disease. However, adjuvant RT could be useful for high-risk patients where regional control is a major issue and/or where systemic therapy is not possible.
Level of evidence: II
Strength of recommendation: D
Level of consensus: 100% (30) yes (30 voters)

6. When can neoadjuvant strategies be discussed? The committee acknowledged recent encouraging reports on the results of neoadjuvant therapy for resectable stage III melanoma but did not feel that these data warrant the mainstream use of this approach as yet. However, if agents become available that can only be delivered in a neoadjuvant context (e.g. intralesional injection) and/or demonstrate improved survival then these should be considered before surgical resection.

Recommendation 6.1. For easily resectable stage III disease with acceptable surgical morbidity, neoadjuvant strategies should be considered only in the context of a clinical trial. Neoadjuvant strategies outside of the context of a clinical trial should be considered for technically resectable but bulky nodal and/or in-transit disease when surgery will be associated with significant morbidity, likely to result in positive resection margin status or necessitate the need for postoperative RT.
Level of evidence: III
Strength of recommendation: B
Level of consensus: 100% (30) yes (30 voters)

Recommendation 6.2. Continuing treatment after surgery should be considered based on the pathological response evaluation of the surgical specimen.
Level of evidence: III
Strength of recommendation: C
Level of consensus: 90% (27) yes, 10% (3) no (30 voters)

Does a complete node dissection still need to be carried out in patients receiving neoadjuvant therapy or can the extent be reduced? When neoadjuvant therapy is undertaken for nodal disease that would normally be resectable by a standard radical dissection, the committee felt that until more data are available from prospective clinical trials, the standard surgical approach in the post-neoadjuvant treatment setting should remain as a standard dissection using the same surgical approach as would be used for untreated nodal disease. However, if neoadjuvant therapy is used to downstage locally advanced disease that extended outside the nodal basin, and neoadjuvant therapy resulted in a major radiological or pathological response rendering the tumour operable, then the surgery should be tailored according to the post-treatment disease volume.

Recommendation 6.3. In principle, the standard surgical approach should be used after neoadjuvant therapy until studies show that it is safe to omit or modify surgery. Tailoring of the extent of surgery can be considered if there is a major radiological or pathological response for disease that extends outside of the nodal basin.
Level of evidence: V
Strength of recommendation: B
Level of consensus: 100% (30) yes (30 voters)

Targeted versus immunotherapies in the adjuvant setting

7. What is the optimum adjuvant therapy for patients with a *BRAF* mutation? Three recent studies showed a significant benefit with adjuvant therapy in patients with radically resected *BRAF* V600E/K-mutated stage III or stage IV melanoma.

Two randomised controlled trials [CheckMate 238[6] and the European Organisation for Research and Treatment of Cancer (EORTC) 1325 trial[7]] evaluated the impact of anti-programmed cell death protein 1 (anti-PD-1) therapy in patients regardless of *BRAF* mutation status. CheckMate 238 included patients with American Joint Committee on Cancer 7th edition (AJCC7) stage IIIB, IIIC or IV melanoma

and compared 1 year of nivolumab 3 mg/kg every 2 weeks versus ipilimumab 10 mg/kg. The EORTC 1325 trial (also known as KEYNOTE-054) compared 1 year of pembrolizumab 200 mg every 3 weeks versus placebo in patients with AJCC7 stage IIIA (micrometastasis >1 mm if N1a), IIIB or IIIC melanoma. The COMBI-AD trial compared 1 year of dabrafenib 150 mg twice daily plus trametinib 2 mg once daily versus placebo in patients with AJCC7 stage IIIA (lymph node metastasis >1 mm), IIIB or IIIC *BRAF* V600E/K-mutated melanoma.[8]

Given that EORTC 1325 and COMBI-AD had similar inclusion criteria (apart from the requirement for *BRAF* mutation in COMBI-AD) and were carried out at similar times (EORTC 1325 started after COMBI-AD was closed but before adjuvant targeted therapy was approved), a comparison of the efficacy of targeted therapy and immunotherapy in *BRAF*-mutated patients may be of interest.

Subgroup analyses of EORTC 1325 showed that 186 patients treated with pembrolizumab had a *BRAF* V600E/K mutation. The HR for RFS in this patient subgroup was 0.57 compared with 0.47 for COMBI-AD.[7,8] This difference may well be explained by the smaller number of patients (186 versus 438) and the shorter follow-up in the EORTC 1325 study. Comparing the shapes of the RFS curves for both trials, we see a 15%—20% higher attrition rate in the first 3 months with pembrolizumab compared with dabrafenib plus trametinib, translating to a better RFS rate at 12 months for targeted therapy (88% versus 75.4%). Once treatment was complete at 1 year, the shapes of the curves change, with a higher attrition rate for targeted therapy than immunotherapy, which may suggest greater long-term efficacy of immunotherapy versus targeted therapy.

In COMBI-AD, an absolute advantage in RFS of 16% was still observed at 4 years of follow-up with targeted therapy.[55] The interim analysis for OS also suggested an improvement (HR 0.57, 95% CI 0.42—0.79; $P = 0.0006$), although it did not meet the prespecified interim analysis significance threshold ($P = 0.000019$). Further comparisons are precluded by the still too-short follow-up and lack of survival data for the EORTC 1325 study.

Many molecular biomarkers have been studied with the aim of helping to inform treatment choice. These appear to be more prognostic than predictive and applicable to both targeted therapy and immunotherapy treatment approaches. As yet, there is no biomarker to help adjuvant treatment selection for patients with *BRAF*-mutated melanoma.

Thus, as current evidence suggests that patients with *BRAF*-mutated melanoma can derive an RFS benefit from either adjuvant BRAF/MEK inhibition or adjuvant PD-1 blockade, in the absence of a direct efficacy comparison, and in accordance with the ESMO CPG,[2] individual treatment decisions should be made with the patient, factoring in the toxicity profiles for the different adjuvant treatment approaches.

8. Adjuvant therapy in stage IIIA melanoma. The three phase III adjuvant trials in stage III melanoma—nivolumab versus ipilimumab (CheckMate 238), pembrolizumab versus placebo (EORTC 1325) and dabrafenib plus trametinib versus placebo (COMBI-AD)—all reached their primary end points and so there are three potential new treatment options for these patients.[6—8]

While CheckMate 238 included patients with stage IIIB to resectable stage IV disease according to AJCC7, EORTC 1325 and COMBI-AD included patients with AJCC7 stage IIIA—IIIC. All trials showed RFS benefits, but none has as yet demonstrated an OS benefit (either not shown to-date or not meeting the prespecified interim analysis boundaries).[6—8]

Quality of life (QoL) data from EORTC 1325 and COMBI-AD show that both treatment options (i.e. pembrolizumab or dabrafenib plus trametinib) are very well tolerated and do not hamper the QoL of this potentially curatively-treated patient population.[56,57]

The question of how to advise patients with stage IIIA melanoma is particularly challenging for several reasons. Firstly, the three randomised trials which led to the approval of adjuvant therapy were based on the AJCC7 staging system.[58] The revised AJCC8, introduced in 2018, included a further stage III subgroup (stage IIID) and revised the criteria for the others, resulting in a significant improvement in assigned prognosis for stage IIIA patients.[17] Furthermore, the pivotal trials required a minimum metastatic tumour burden of 1 mm diameter (EORTC 1325 and COMBI-AD) or an ulcerated primary (CheckMate 238) for SLN-positive patients to be eligible.[6—8] All of the trials required that SLN-positive patients had a completion lymphadenectomy, which is no longer the standard of care, implying that some patients would have been upstaged from stage IIIA to IIIB or higher by the pathological findings at completion lymphadenectomy. A review of data from the EORTC database showed that this would be expected to be the case for 5%—6% of patients.[59]

Both EORTC 1325 and COMBI-AD have been re-analysed using AJCC8.[55,60] In both trials, a maximum of 50 patients with stage IIIA disease remained in the study arms, making reliable conclusions challenging. Both trials failed to show a significant RFS benefit for AJCC8 stage IIIA patients. Considering the low numbers of patients remaining in these cohorts, the consensus group felt that this is unlikely to change with a longer follow-up. However, a numerical difference might become detectable as the data mature further. This is based on the observation that for AJCC7 stage IIIA patients, half of the relapses occur beyond 12 and 24 months for local/lymph node relapses and systemic relapses, respectively.[61]

There are reports of differing outcomes for some patient cohorts restaged according to AJCC8 which could potentially impact on the advice given to patients regarding prognosis and the impact of adjuvant therapy. Indeed, AJCC8 reported 5- and 10-year melanoma-specific survival (MSS) rates in stage IIIA disease of 93% and 88%, respectively,[17] but two

other published studies have restaged patients according to AJCC8 and reported worse outcomes.

A Swedish population-based registry reported 5- and 10-year MSS rates of 87% and 80%, respectively, for stage IIIA disease.[62] Similarly, a German study reported a 5-year MSS rate of 89% for stage IIIA disease.[63] Other groups are reviewing their data and further publications are expected.

There are many possible explanations for these differences in reported outcomes. There are challenges associated with comparing data across different patient populations (institution series, population-based studies, clinical trial patients, etc.); the guidelines for SLNB and biopsy rates are not always reported and the cause of death is not always clear. Of particular importance is that SLN tumour burden is a key prognostic factor that drives outcome but is not included as part of AJCC8 and is not reported in the other series. There is no reason though why the distribution of tumour burden should be different in the different patient populations. Data from the AJCC and other series show that patients with a tumour deposit of <1 mm within the sentinel node have an excellent prognosis with an expected 10-year survival of 80%–90%, and this has informed entry criteria for adjuvant studies focusing on higher-risk patients.[64,65] Therefore, to more accurately assign a prognosis to patients with stage IIIA disease, data on tumour burden within the sentinel node need to be considered.

Consideration should also be given to the absolute risk reduction for stage IIIA disease, where the absolute benefit will be low but the risk of toxicity remains the same (i.e. higher toxicity per unit of benefit). Furthermore, what is accepted as a clinically meaningful benefit in other tumour types (e.g. lung, breast and colorectal cancer) should be considered. In addition, in these tumour types, adjuvant treatment is approved based on OS benefit, which is not available for this melanoma subgroup.

The fact that adjuvant ipilimumab has shown an OS benefit versus placebo,[5] CheckMate 238 showed improved RFS with nivolumab compared with ipilimumab[6] and COMBI-AD has already shown a potentially meaningful OS benefit for dabrafenib plus trametinib versus placebo (despite not meeting the prespecified boundaries),[8] makes it likely that all three treatment options will improve 5-year OS. Therefore, the consensus group recommends accepting RFS as a surrogate marker for OS improvement. The group considered that the minimum clinically meaningful OS benefit to justify currently available adjuvant therapies would be 5% at 5 years.

Recommendation 8.1. An absolute survival benefit of 5% at 5 years would be considered strong evidence to recommend adjuvant therapy in stage III melanoma. However, surrogate markers of OS benefit are currently acceptable.
Level of evidence: I
Strength of recommendation: A
Level of consensus: 100% (30) yes (30 voters)

Recommendation 8.2. There is currently insufficient evidence to support the routine use of adjuvant therapy in AJCC8 stage IIIA melanoma.
Level of evidence: I
Strength of recommendation: D
Level of consensus: 97% (29) yes, 3% (1) no (30 voters)

Recommendation 8.3. There may be some subsets of stage IIIA patients with a higher risk of relapse (e.g. tumour burden in sentinel node >1 mm). In these patients, a balanced discussion of risk reduction and long-term side-effects of adjuvant therapy can be considered.
Level of evidence: II
Strength of recommendation: C
Level of consensus: 97% (29) yes, 3% (1) no (30 voters)

9. What is the optimal approach for management of toxicity in the adjuvant setting? Adjuvant immunotherapy in completely resected stage III–IV melanoma leads to treatment-related side-effects in 77%–99% of patients, with grade 3/4 AEs reported in 14.4% of patients receiving nivolumab (CheckMate 238[6]) and in 14.7% of patients receiving pembrolizumab (EORTC 1325[7]). Discontinuation of treatment due to toxicity was necessary for 9.7% of patients receiving nivolumab and in 13.8% receiving pembrolizumab. Immune-related side-effects typically appear within a few weeks or months of starting treatment but can develop at any time during or after adjuvant immunotherapy. Endocrine toxicities (hypophysitis, diabetes mellitus, adrenalitis), although rare, are largely irreversible.

The COMBI-AD study reported grade 3/4 AEs in 41% of patients receiving dabrafenib plus trametinib, with 26% of patients stopping treatment early due to toxicity.[8] The toxicity profile was similar to that seen in the metastatic setting, although the incidence of AEs seemed to be higher in the adjuvant setting. There was no evidence of permanent toxicity after treatment discontinuation.

There are limited data on dose modification due to toxicity and impact on outcomes in the adjuvant setting. For immunotherapy in the metastatic setting, there is no evidence that the management of significant toxicity with immunosuppressive drugs or treatment withdrawal impacts on outcomes,[66] and treatment algorithms based on these have been developed and are widely used.[67,68] Data from the EORTC 1325 study with adjuvant pembrolizumab showed that patients who experienced an immune-related AE had a better RFS, although this benefit appears higher in patients who did not receive steroids or those who received <30 days of steroids compared with those who received >30 days of steroids.[69] In the metastatic setting, it is common to consider restarting treatment or changing from combination to single-agent immunotherapy after a grade 2/3 toxicity, largely because of concerns associated with advanced disease and the lack of other useful treatment options. A number of series have looked at the risk of recurrence of toxicity or development of new toxicity in this situation.[70,71] The risk–benefit balance is very different in

the adjuvant setting, where a substantial proportion of patients will never relapse after surgery. Therefore, in the adjuvant setting, the decision about restarting therapy should be made with caution after assessment of the potential risk and benefit. The important factors for consideration include the type and severity of toxicity, patient biological age, other comorbidities and the duration of the adjuvant treatment before complication. When toxicity is severe, there is no indication to restart treatment even if the toxicity completely resolves.

For targeted therapy, there are limited data on toxicity, its management and outcomes. Management algorithms have evolved over time with a current focus on early dose reductions and delays to minimise toxicity and keep patients on treatment.[72–75] While there is some evidence that more potent inhibition of mutated *BRAF* is associated with a better outcome in the metastatic setting,[76] there has been no analysis of dose intensity in the COMBI-AD study.

Recommendation 9.1. The management of toxicity from adjuvant therapy should be done according to the established management algorithms for metastatic disease.
Level of evidence: I
Strength of recommendation: A
Level of consensus: 100% (30) yes (30 voters)

Recommendation 9.2. For adjuvant immunotherapy, where treatment is withheld because of severe toxicity, the recommendation is neither to restart treatment nor to start an alternative adjuvant therapy.
Level of evidence: V
Strength of recommendation: D
Level of consensus: 97% (29) yes, 3% (1) abstain (30 voters)

10. Adjuvant therapy for in-transit metastases and resected stage IV disease

The role of targeted therapy and immunotherapy in resected stage IV disease. Patients with completely resected stage IV melanoma are at very high risk of further relapse and death from melanoma. This risk equals or exceeds the risk of relapse and death for any category of stage III melanoma for which adjuvant therapy is indicated. Relatively few modern adjuvant therapy trials have included patients with resected stage IV disease, almost always including only selected subpopulations of such patients. The CheckMate 238 trial, which compared adjuvant nivolumab to adjuvant high-dose ipilimumab, included 169 patients with resected stage IV melanoma, 128 of whom had M1a or M1b disease.[6] The HR for RFS was 0.65 in favour of nivolumab for the trial overall; it was 0.63 for patients with M1a or M1b disease and 1.00 for M1c. Hence, there is clear evidence that adjuvant therapy with nivolumab is appropriate for most patients with resected stage IV melanoma and it should be considered the preferred adjuvant therapy approach when patients with resected stage IV melanoma are considered for adjuvant therapy. A recently-reported randomised phase II study compared adjuvant therapy with ipilimumab plus nivolumab, nivolumab alone or placebo in 167 patients with resected stage IV disease. There was a clear advantage in terms of RFS for combination therapy over single-agent nivolumab (HR 0.40, 95% CI 0.22—0.73) or placebo (HR 0.23, 95% CI 0.13—0.41).[77]

For patients with resected stage IV melanoma harbouring a *BRAF* mutation, there is no prospective clinical trial involving BRAF or BRAF/MEK inhibition in the adjuvant setting. In the COMBI-AD trial, adjuvant dabrafenib plus trametinib showed a significant benefit for improved RFS as well as a trend towards improved OS in patients with completely resected stage III *BRAF*-V600-mutated melanoma, but patients with completely resected stage IV melanoma were not included in this study.[8] Subset analyses of RFS demonstrated similar treatment benefit regardless of stage III disease substage, nodal metastatic burden and ulceration. On a biological basis, there is no reason to expect that outcomes with adjuvant dabrafenib plus trametinib would be substantially different in patients with resected stage IV disease compared with patients with resected stage III disease.

Finally, it should be mentioned that there are no data to show whether the use of adjuvant therapy in this particular subgroup of patients, where distant metastatic disease is accessible to surgery (i.e. a very favourable group), is superior to the same medical treatment upfront without surgery.

Recommendation 10.1. Adjuvant dabrafenib plus trametinib can be considered in patients with completely resected *BRAF*-V600-mutated stage IV melanoma if there is a contraindication to immunotherapy.
Level of evidence: V
Strength of recommendation: C
Level of consensus: 96% (26) yes, 4% (1) no (27 voters)

Adjuvant therapy for in-transit metastases. Most modern adjuvant therapy trials in stage III melanoma included only melanoma with metastases to regional lymph nodes, so patients with in-transit metastases that had been completely resected, while technically considered to be stage III, were excluded in the absence of nodal involvement. Moreover, patients with microscopic satellitosis within 2 cm of the primary tumour are also stage III but have also been excluded from virtually all modern adjuvant therapy trials. Patients with completely resected in-transit melanoma in the absence of proven nodal metastases are at high risk of further relapse and death from melanoma, similar to the risk of relapse and death for other categories of stage III melanoma for which adjuvant therapy is indicated. The prognostic significance of microsatellites in the absence of nodal metastasis, considered N1c and hence stage III in AJCC8, is subject to some debate. However, the large AJCC8 dataset suggests that the prognosis for these patients is similar to that for patients with in-transit

metastases.[17] On a biological basis, there is no reason to expect that outcomes with adjuvant immunotherapy or targeted therapy would be substantially different in patients with resected in-transit or microsatellite disease compared with patients with resected nodal disease.

Recommendation 10.2. Adjuvant therapy may be considered for patients with completely resected in-transit melanoma or microsatellites, including patients without evidence of nodal metastasis.
Level of evidence: V
Strength of recommendation: C
Level of consensus: 100% (29) yes (29 voters)

In case of resectable local relapse in patients receiving adjuvant therapy, what should be done after surgery: continue, change or stop treatment? In some older adjuvant therapy trials, patients with resectable locoregional recurrences were allowed to resume treatment and complete therapy after recovery from surgery. However, most modern adjuvant trials did not specifically incorporate rules for continued treatment in the event of resectable local or regional relapse. Moreover, virtually all adjuvant therapy trials reported to-date required patients with nodal metastases to undergo CLND. Since the publication of the results of the MSLT-II trial,[3] many patients with SLN-positive melanoma are now treated with adjuvant therapy without undergoing CLND. This increases the risk of isolated regional recurrence and such recurrences might well occur during the period when adjuvant therapy is being administered. The optimal management of patients who did not undergo CLND and who relapse despite adjuvant therapy is not known and very limited data are available regarding these patients. It seems logical to consider them as resistant to the strategy used in the adjuvant setting. Still, it cannot be excluded that 'mixed' responses can be observed with adjuvant therapy, as seen in metastatic melanoma treated with either immunotherapy or targeted therapy, which do not always indicate that continued therapy after surgery is futile.

Oligoprogression is another manifestation of mixed response to therapy, and in some cases of stage IV melanoma with oligoprogression, resection of the progressing lesion(s) is carried out with continuation of the systemic therapy. Given the absence of prospective clinical trial data, decisions about continuing, stopping or switching therapy in patients with resectable locoregional recurrence occurring while on adjuvant systemic therapy need to be individualised, taking into consideration patient preferences, tolerance to the initial adjuvant therapy before recurrence, *BRAF* mutation status and other factors.

Recommendation 10.3. Resuming adjuvant therapy for patients with completely resected locoregional recurrent melanoma occurring during adjuvant treatment remains controversial in the absence of prospective clinical data.
Level of evidence: IV
Strength of recommendation: C
Level of consensus: 86% (19) yes, 9% (2) no, 5% (1) abstain (22 voters)

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