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Update on adjuvant melanoma therapy

Florentia Dimitriou[a], *Ralph Peter Braun*[a,b], *and Joanna Mangana*[a]

Purpose of review
We review the results from relevant clinical trials and discuss current strategies in the melanoma adjuvant setting.

Recent findings
The favorable therapeutic efficacy and the significant less toxicity of nivolumab compared with ipilimumab, fully substitutes today's approval of ipilimumab, regardless mutation status, whereas in BRAF-mutated patients, dabrafenib and trametinib seem to confirm their high efficacy also in adjuvant setting. The use of interferon is restricted to patients with ulcerated melanoma and countries with no access to the new drugs.

Summary
Systemic adjuvant treatment after complete disease resection in high-risk melanoma patients aims to increase relapse-free survival (RFS) and overall survival (OS). According to the eighth edition of melanoma classification of American Joint Committee on Cancer (AJCC), the prognosis in stage III patients is heterogeneous and depends not only on N (nodal) but also on T (tumor thickness) category criteria. Recent data from randomized, phase-3 clinical trials analyzing the use of adjuvant anti-programmed death-1 and targeted therapies ultimately affect the standard of care and change the landscape of the adjuvant treatment.

Keywords
adjuvant, immunotherapy, melanoma, targeted therapy

INTRODUCTION

Checkpoint inhibitors as well as inhibitors of the mitogen-activated protein kinase pathway (MAPK) revolutionized the treatment era of advanced melanoma patients leading to their approval for metastatic disease [1–8,9▪▪,10–16,17▪▪,18,19▪,20]. Recently, spectacular outcomes were equivalently demonstrated in the adjuvant setting of patients with high risk for recurrence; however, choosing the right treatment at the right time remains an important clinical challenge [21,22▪▪,23▪▪,24]. Taking into account the high heterogeneity in stage III population and based on the American Joint Committee on Cancer (AJCC) staging system, the likelihood of recurrence or systemic disease correlates closely with tumor thickness and ulceration, microscopic versus macroscopic disease, the number of positive nodes as well as with presence of (micro)satellites or intransit metastasis [25,26]. Furthermore, the outcome of the sentinel lymph node biopsy (SLNB) is used for identification of high-risk groups, and decisions on frequency of follow-up, adjuvant therapy and enrollment into clinical trials [27–29].

This review will focus on the recent advances and the impact of immunotherapies and MAPK pathway-targeted therapies on clinical outcomes of high-risk melanoma patients. It will also examine the rationale behind current treatment choices in the real-life adjuvant setting.

RADIOTHERAPY

Radiotherapy provides an important variant in the treatment of patients with recurrent, in-transit or nodal metastatic melanoma requiring local control [30]. In the ANZMTG 01.02/TROC 02.01 phase 3, randomized controlled trial, 250 patients were enrolled to receive adjuvant radiotherapy of 48 Gy in 20 fractions or observation (OBS) [31]. The use of adjuvant radiotherapy after complete surgical resection significantly reduced the melanoma relapse in

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KEY POINTS

- The disease prognosis in stage III patients is heterogeneous and depends not only on N but also on T category criteria, according to the eighth edition of melanoma classification of American Joint Committee on Cancer (AJCC).
- According to the recent clinical trials outcomes, current adjuvant treatment options are nivolumab for all patients regardless mutation status and dabrafenib/trametinib for BRAF-mutated patients.
- The use of interferon is restricted to patients with ulcerated melanoma in countries with no access to the new drugs.
- Neoadjuvant therapy, upcoming adjuvant treatment combinations, for example, nivolumab with ipilimumab and identification of new biomarkers are expected to maximize the antitumor response.

the adjuvant radiotherapy group compared with OBS, but no differences regarding relapse-free survival (RFS) and overall survival (OS) were noted [31]. Long-term follow-up data support the primary findings. After a median follow-up of 73 months, 21% relapses occurred in the adjuvant radiotherapy group compared with 36% in the OBS group [hazard ratio 0.52, 95% confidence interval (CI) 0.31–0.88, $P = 0.023$] [32]. However, no significant difference regarding OS (hazard ratio 1.27, 95% CI 0.89–1.79, $P = 0.21$) and RFS (hazard ratio 0.89, 95% CI 0.65–1.22, $P = 0.51$) was noted.

IMMUNOTHERAPY

Melanoma has been long considered an immunogenic cancer inducing significant antitumor responses and in some cases, spontaneous regression after immune-stimulating agent treatment [33–35]. As a result, multiple efforts in cytokine therapy, tumor vaccines, oncolytic viruses, adoptive immunotherapy and immune check point inhibition have been evaluated [33]. Some of these agents showed impressive activity not only in metastatic but also in the adjuvant setting and will be discussed here in further detail.

Interferons

Over the last 30 years, interferon (IFN) has been extensively investigated in patients with high-risk melanoma [36–44] (Table 1). Despite showing a rather modest activity – particularly whenever balanced against toxicity – it was the first agent worldwide approved in this setting. However, and partly because of substantial toxicity and treatment costs, there is a significant variation in different geographic locations regarding its use. High-dose IFN (HDI) for 12 months was until recently the

Table 1. Adjuvant trials determining adjuvant treatment in melanoma

Study	Stage at study entry	Treatment arms (N)	Median follow-up (years)	RFS	OS	Reference
ECOG E1684	II and III (T4N0M0/TanyN+M0)	High-dose IFNα2a (HDI) versus observation (287)	6.9	0.61	0.67	Kirkwood *et al.* [45]
			12.6	0.72	0.82	
ECOG E1690	II and III (T4N0M0/TanyN+M0)	HDI or LDI versus observation (642)	4.3	0.78	1.0	Kirkwood *et al.* [46]
			6.6	0.81	1.0	
ECOG E1694	II and III (T4N0M0/TanyN+M0)	HDI versus GMK vaccine for 96 weeks (880)	1.3	0.67	0.72	Kirkwood *et al.* [47]
			2.1	0.75	0.76	
EORTC 18991	III [Tany, N1(occult)/N2 (bulky), M0]	Pegylated IFNα2b versus observation (1256)	3.8	0.82	0.98	Eggermont *et al.* [37]
			7.6	0.87	0.96	
EORTC 18071	IIIA (N2a)/IIIB/IIIC (except in transit)	Ipilimumab 10 mg/kg versus placebo (951)	5.3	0.76	0.72	Eggermont *et al.* [24]
COMBI-AD	IIIA (>1 mm)/IIIB/IIIC	Dabrafenib 150 mg b.i.d. with trametinib 2 mg q.d. versus placebo (870)	2.8	0.47	0.57	Long *et al.* [23▪▪]
Checkmate-238	IIIB/IIIC/IV	Nivolumab 3 mg/kg versus ipilimumab 10 mg/kg (906)	1.5	0.65	?	Weber *et al.* [22▪▪]

OS, overall survival; RFS, relapse-free survival.

standard of care in the United States and Australia, whereas intermediate and low doses are used in Europe and pegylated IFN is only approved in Switzerland for patients with micrometastasis and ulcerated primary tumors.

The E1684 clinical trial was the first trial demonstrating an improvement both in OS and RFS after a median follow-up time of 6.9 years. It investigated an induction phase of HDI intravenously administered at 20 MU/m^2 for five consecutive weeks followed by subcutaneous administration of 10 MU/m^2 of IFN three times a week for 48 weeks versus placebo. 5-year RFS was 37% (95% CI 30–46%) compared with 26% (95% CI 19–34%), and 5-year OS was 46% (95% CI 39–55%) versus 37% (95% CI 30–46%) in favor of HDI [45]. HDI for 1 year and low-dose IFN for a treatment period of 2 years were compared with postoperative OBS in the E1690 trial [46]. HDI significantly improved RFS ($P = 0.03$) compared with OBS after a median follow-up of 4.3 years, but no differences were seen in OS. E1694 trial followed and tested HDI for 1 year versus the ganglioside vaccine GMK (Progenics pharmaceuticals) for 96 weeks [47]. Herein, OS and RFS were significantly improved in favor of HDI (hazard ratio 0.72 and 0.67, respectively). Subsequently, a number of trials trying to identify the optimal dose, schedule and duration of adjuvant IFN have followed [38,41,48–52]. In a pooled meta-analysis of nearly 2000 patients including E1684, E1690 and E1694 trials, HDI maintained substantial RFS but not OS benefit ($P = 0.006$) [39]. Other meta-analyses demonstrated a modest impact in OS (approximately 3%, 95% CI 1–5%) with ulceration being the most predictive factor for response to IFN [37,40,42,48,53–55].

CTLA-4 inhibition

Ipilimumab, a fully human monoclonal antibody that blocks CTLA-4, was approved by the Federal Drug Administration (FDA) for treatment of patients with advanced melanoma in 2011 [11]. The efficacy of ipilimumab in the adjuvant setting has been evaluated in two randomized phase III clinical trials either compared with placebo (EORTC 18071) [21] or HDI (ECOG 1609, NTC01274338).

The EORTC 18071 clinical trial enrolled 951 melanoma patients with stage IIIA (N2a), IIIB and IIIC disease after complete resection and high risk of recurrence [21]. Patients were 1 : 1 randomly assigned to receive ipilimumab at a dose of 10 mg/kg or placebo every 3 weeks for four doses, following every 3 months for up to 3 years. The study met its primary endpoint of RFS in 2.7 years. Ipilimumab was shown to significantly improve RFS at 26.1 months (95% CI 19.3–39.3) compared with 17.1 months (95% CI 13.4–21.6) in the placebo group (hazard ratio 0.75, 95% CI 0.64–0.90, $P = 0.0013$) [21]. Recent data of 5.3 years' median follow-up confirm the RFS and OS benefit (RFS 40.8 versus 30.3%, hazard ratio 0.76, 95% CI 0.64–0.89, OS 65.4 versus 54.4%, hazard ratio 0.72, 95% CI 0.58–0.88) [24] (Table 1). Benefit was consistent in all subgroups, though patients with ulcerated primary lesions seem to benefit the most.

As current dose of ipilimumab 10 mg/kg in the adjuvant setting is significantly higher than the dose approved for metastatic melanoma (3 mg/kg), questions have been raised regarding the dose relation to higher toxicity [56]. The ECOG-E1609 clinical trial compares ipilimumab 10 or 3 mg/kg versus high-dose recombinant IFNα in resected stages IIIB and IIIC (including in-transit metastases) and stage IV melanoma with primary endpoints, the OS and progression-free survival (PFS). An unplanned RFS analysis was recently presented, showing no substantial difference in PFS for patients treated with 3 mg/kg compared with 10 mg/kg [57]. Updated results of this trial are expected in May 2018.

PD1 inhibition

Anti-programmed death-1 (anti-PD1) blockade has demonstrated significant benefits in RFS and OS in metastatic melanoma with superior efficacy to ipilimumab [8,16,19▪]. These encouraging data along with a favorable toxicity profile prompted their application in the adjuvant setting.

The phase 3 clinical trial comparing ipilimumab 10 mg/kg to nivolumab 3 mg/kg in fully resected stage IIIB/IIIC–IV melanoma patients reformed the adjuvant treatment era (Checkmate-238) [22▪▪]. Nine hundred and six patients were 1 : 1 randomized to nivolumab 3 mg/kg every 2 weeks versus ipilimumab 10 mg/kg every 3 weeks for 4 doses and then every 12 weeks for 1 year till disease recurrence or unacceptable toxicity. After 18 months of follow-up, nivolumab showed a significant superiority over adjuvant ipilimumab treatment, with RFS of 70.5% (95% CI 66.1–75.4) versus 60.8% (95% CI 56.0–65.2), hazard ratio 0.65; $P < 0.001$ [22▪▪]. Adjuvant treatment with nivolumab seems to have higher benefit in patients with stage IIIB/IIIC and PD-L1 expression more than 5%, regardless of BRAF status.

Other ongoing clinical trials investigating the application of anti-PD1 agents in the adjuvant setting are the EORTC 1325 (KEYNOTE-054) comparing pembrolizumab 200 mg flat dose versus placebo (NCT02362594) and the SWOG S1404 protocol comparing pembrolizumab 200 mg flat dose to HDI [58].

As combination of CTLA-4 with PD-1 blockade has been proved to augment the immune response compared with each agent alone in metastatic melanoma [17▪▪], the Checkmate-915 clinical trial is currently underway, comparing adjuvant nivolumab combined with ipilimumab versus nivolumab monotherapy (NCT03068455). This phase-3 study enrolls patients after complete resection of stage IIIB/IIIC/IIID or stage IV melanoma, according to the eighth AJCC edition.

TARGETED THERAPY

In addition to immunotherapy, inhibition of the MAPK pathway resulted in outstanding activity in the adjuvant setting as recently presented in the European Association of Medical Oncology Meeting (ESMO), this year in Madrid. The Combi-AD randomized double-blind phase III clinical trial enrolled 870 patients with completed resected stage III melanoma harboring the BRAF V600E or V600K mutation to receive either dabrafenib 150 mg twice daily with trametinib at a dose of 2 mg once daily or two matched placebo. Patients were treated for a maximum of 1 year in the absence of disease progression or until unacceptable toxicity or study withdrawal. Among the study population, 18% (154 patients) had a stage IIIA disease with a micrometastasis in SLNB of more than 1 mm. At a median of 2.8 years follow-up, investigation-assessed RFS was significantly longer in the combination group resulting in a 53% lower risk for death or relapse (hazard ratio 0.47; 95% CI 0.39–0.58; $P < 0.0001$). Estimated rates for RFS at the first, second and third year were 88, 67 and 58% for the combination group in comparison with 56, 44 and 39% for the placebo group, respectively. Combination treatment resulted in higher rates of OS and distant-metastasis-free survival (DMFS) with a 3-year OS of 86% in the combination group versus 77% in the placebo group and a 3-year DMFS of 71 versus 57%, respectively (Table 1). Clinical benefit was consistent across all subgroups of patients regardless of ulceration of primary tumor or lymph-node involvement.

The randomized BRIM8 trial of adjuvant vemurafenib versus placebo, however, in patients with resected BRAF-mutant melanoma and high risk of recurrence did not manage to improve the primary endpoint of RFS but seems to be effective with manageable safety profile in patients with stage IIC–IIIB melanoma [59].

TOXICITY

The toxicity profile in the adjuvant setting is confirming the existing experience in advanced melanoma. Adverse events occur less frequent with anti-PD1 antibodies than with ipilimumab with a comparable toxicity profile, including diarrhea, colitis, endocrinologic adverse events (hypophysitis, hyperthyroidism and hypothyroidism, adrenal dysfunction), vitiligo, pruritus, rash and fatigue [60,61]. Patients enrolled in the EORTC 18071 trial developed a high rate of grade 3–5 immune-related adverse events (irAEs; 43 compared with 2% in placebo group), including five treatment-related deaths (colitis, $n = 3$; myocarditis, $n = 1$; multiorgan failure with Guillan–Barre syndrome, $n = 1$) [21]. Comparing the safety profile of the Checkmate-238 trial, nivolumab showed significantly less toxicity. Grade 3–4 adverse events occurred in 14.4% of the patients in the nivolumab group and in 45.9% in the ipilimumab group and led to discontinuation in 3.5 and 30%, respectively [22▪▪]. These irAEs are, however, manageable through early application of high-dose corticosteroids or other immune modulatory agents.

Albeit, immunotherapy and targeted therapy have different toxicity profiles. Taking a closer look into the Combi-AD trial, the most common adverse events appear to be pyrexia, fatigue and nausea, whereas grade 3–4 toxicities occurred in 41% in the combination group versus 14% in the placebo group [23▪▪]. The number of treatment discontinuations seems to be higher compared with stage IV melanoma (26 versus 16%, respectively, though no new adverse events were observed.

High-dose interferon-α2b is associated with high toxicity, such as chronic fatigue (96%), myelosuppression (92%), elevated liver enzyme levels [63% increased aspartate aminotransferase (AST)] and neurologic symptoms (40%), which affect the majority of patients and can lead to premature treatment discontinuation [62].

INTEGRATING CURRENT ADJUVANT TREATMENT INTO CLINICAL PRACTICE

Putting this data together, there is yet no consensus available for treatment selection in melanoma patients with high risk for recurrence. As neither nivolumab nor dabrafenib and trametinib combination therapy have been so far approved by the regulatory authorities for this indication, the suggestions that follows are hinged on the results of the available studies. However, and considering that the surgical procedures and the staging system have changed since the initiation of these trials, there is a certain gap of knowledge affecting the adjuvant field. The recommendations that follows have been adapted to the new AJCC, eighth edition.

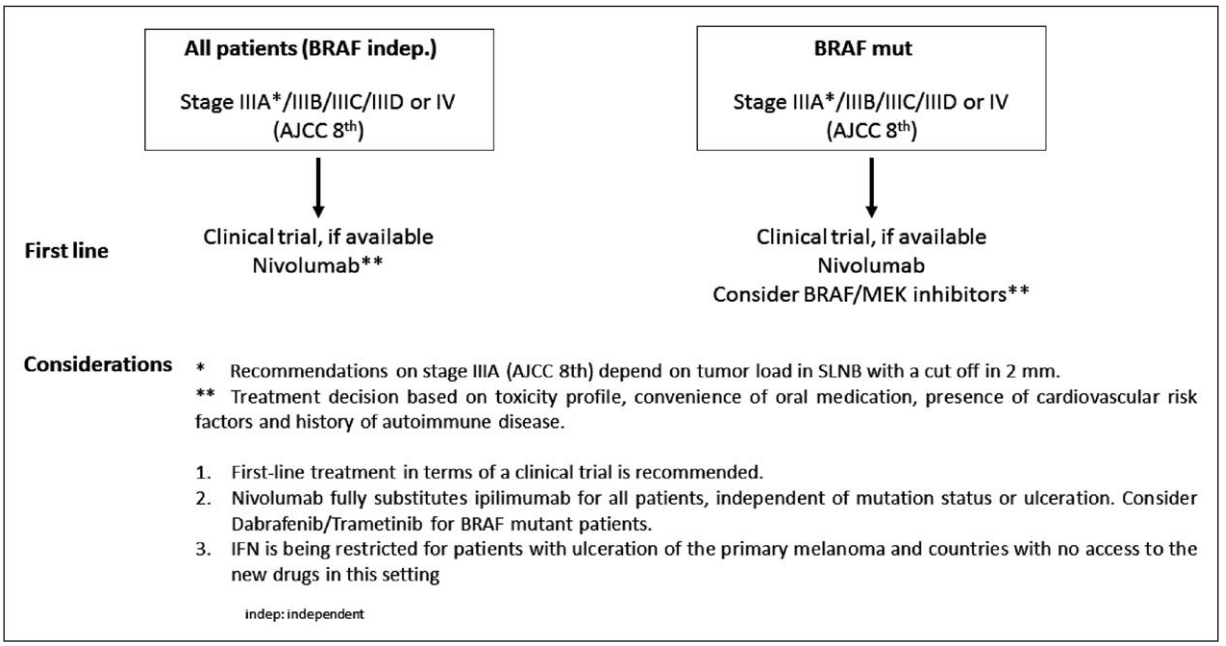

FIGURE 1. First-line choice recommendation for adjuvant treatment.

Taking into account, the modest impact in OS and the substantial toxicity related to IFN and based on the impressive new data, we believe that the role of IFN will be restricted for patients with ulceration of the primary melanoma for countries with no access to the new drugs in this setting. For the same reasons and owing to the superior efficacy of nivolumab compared with ipilimumab, the future of the latter as monotherapy seems scanty. Whether combination of low-dose ipilimumab with nivolumab would have a place in the adjuvant setting remains an open question, and BMS-219 will definitely give new insights with early results expected in the following 2–3 years.

In addition to enrollment into clinical trials, which is the first-line choice for melanoma patients with high-risk of recurrence, nivolumab would be the appropriate adjuvant therapy for all patients independent of mutation status or ulceration (Fig. 1). For V600 mutant patients, combination dabrafenib and trametinib is a considerable alternative (Fig. 1). Whenever comparing the available evidence, the data of Combi-AD are more mature, although consistent to Checkmate 238 (Table 1). Decision should be based on individual factors such as toxicity profile, convenience of oral medication, or presence of cardiovascular risk factors and history of autoimmune disease.

One important question arising is whether all stage III or M1a patients should receive adjuvant therapy. Both DECOG and MSLT 2 trials showed no differences in clinical outcome after complete lymphadenectomy (CLND) [63,64]. Several countries do not currently recommend CLND whenever micrometastasis of less than 1 mm in SLNB (clinically occult disease) is present; instead patients undergo more intensive surveillance. We favor adjuvant treatment in high-risk patients from stage IIIB/IIIC, whereas the recommendations on stage IIIA (T1a/b-T2a N1a or N2a) depend on tumor load in SLNB with a cut off of 2 mm (Fig. 1). In general, and according to the AJCC eighth edition, IIIA patients have a favorable prognosis compared with IIIB and IIIC patients with a 10-year survival of 88 versus 77 and 60%, respectively. Five-year survival for patients with metastasis of a maximum dimension of 2–4 mm in SLNB was similar to that of 1–2 mm (86 versus 89%, respectively). In IIIB–IIIC stages with clinically occult N disease only (pT2b-4b N1a/N2a) the approach is similar to clinically detectable disease (pN1b-N3c), where adjuvant treatment is strongly recommended, as ulceration and tumor thickness are both strong predictors of impaired outcome in patients with N-positive disease.

CONCLUSION

Taking into consideration the limited maturity of the data available, a definite suggestion of the first-line adjuvant treatment remains onerous. Nivolumab seems to fully substitute ipilimumab with a statistically significant improvement in RFS and less

toxicities. Combination dabrafenib and trametinib presents an important alternative in BRAF mutant patients (Fig. 1). Additionally, the use of both agents in neo-adjuvant setting offers very attractive choices for future clinical trial design.

All in all, the ongoing evaluation of antitumor antigens, the identification of new biomarkers and the understanding of treatment resistance mechanisms is expected to guide the selection of treatment and maximize the antitumor response.

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Conflicts of interest

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