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Skin Cancer (T Ito, Section Editor)

Adjuvant Therapy for Melanoma

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Abbreviations *MAPK* mitogen-activated protein kinase · *OS* overall survival · *RFS* relapse-free survival · *RCT* randomized controlled trial · *FDA* Food and Drug Administration · *HR* hazard ratio · *IFN-α2b* interferon-α2b · *PD-1* programmed cell death protein 1 · *ECOG* Eastern Cooperative Oncology Group · *EMA* European Medicines Agency · *AE* adverse event · *CTLA-4* cytotoxic T lymphocyte-associated antigen 4 · *HRQoL* health-related quality of life · *PD-1* programmed death-1 · *AJCC* American Joint Committee on Cancer · *DFS* disease-free survival

Opinion statement

In recent years, the number of patients with malignant melanoma has continued to increase globally; surgery remains the first treatment option for patients with resectable melanoma. Adjuvant therapy for patients with stage III and IV melanoma following surgical resection has gradually been approved. After complete resection, these patients can probably derive significant benefit from adjuvant therapy. New treatments that improve the long-term survival of patients with unresectable advanced or metastatic melanoma are currently under evaluation in adjuvant therapy to increase relapse-free survival and overall survival. We here review several relevant clinical trials of radiotherapy, systemic immune therapies, molecular-targeted therapies, and neoadjuvant therapies in order to shed light on most suitable adjuvant therapy. The findings of this review include the following: The use of interferon-α2b will be restricted for patients with ulcerated primary melanoma in countries with no access to new drugs in adjuvant therapy. Ipilimumab should not be considered as the first-line therapy due to its lower efficacy and severe toxicity. The use of anti-programmed death-1 antibody would be a relevant adjuvant therapy for patients without BRAF mutation. If the BRAF mutation status is positive, the combination of dabrafenib and trametinib is a plausible option. The establishment of appropriate therapeutic planning and clinical endpoints in adjuvant therapy should affect the

standard of care. The choice of optimal adjuvant therapy for individual patients is an important issue.

Introduction

In recent years, the number of patients with malignant melanoma has continued to increase globally; surgery remains the first option of treatment for patients with resectable melanoma [1]. Owing to disease relapse and poor prognosis following resection among most of these patients, there was an obvious need to improve the option of adjuvant therapy for melanoma. Since 2011, multiple new treatment options including immune checkpoint inhibitors and molecular inhibitors of the mitogen-activated protein kinase (MAPK) pathway have improved the treatment responses and long-term survival of patients with unresectable advanced or metastatic melanoma [2–8, 9•, 10–14]. In adjuvant therapy for patients with resected high-risk melanoma, these treatments also showed favorable outcomes [15, 16••, 17••, 18••, 19]. However, whether melanoma patients following resection should receive adjuvant therapy depends on multiple factors, such as the specific character of the tumor, presence of melanoma genome mutation, risks associated with treatment, and their individual ability to tolerate treatment [20]. In this review, which includes findings of completed and ongoing clinical trials, we examine both the validity of adjuvant therapy in this clinical setting and preferable options of such therapy that are now available.

Radiotherapy

Radiotherapy is provided for patients with unresectable mucosal melanoma or limited brain, visceral, or bone metastasis [21–26]. In the ANZMTG 01.02/TROG 02.01 randomized controlled trial (RCT), 250 melanoma patients who had a high risk of relapse were randomly assigned to adjuvant radiotherapy or observation, the results of which were then evaluated [27, 28]. Patients had undergone complete lymphadenectomy for metastases to the cervical, inguinal, or axillary lymph nodes, and were at high risk of relapse in the multiple involved lymph nodes and large nodes, along with the presence of extracapsular extension of the tumor. At a median follow-up of 73 months, relapse in the lymph-node field had occurred at a rate of 21% in the adjuvant radiotherapy group compared with 36% in the observation group (HR 0.54; 95% CI 0.33–0.89; $P = 0.021$). However, overall survival (OS) (HR 1.27; 95% CI 0.89–1.79; $P = 0.21$) and relapse-free survival (RFS) (HR 0.89; 95% CI 0.65–1.22; $P = 0.51$) did not differ between the two groups. Radiotherapy commonly caused fibrosis of the skin or subcutaneous tissue, pain, nerve damage, and increased lower limb volume as the predominant toxic effects; 22% of patients in the adjuvant radiotherapy group had grade 3–4 toxic effects. These findings suggested that the risk of relapse in the lymph-node field would be reduced by adjuvant radiotherapy following resection. A few trials suggested that adjuvant radiotherapy following resection had an effect on OS [29], but most trials failed to show prolonged OS [30–35]. However, these trials were conducted before the era of molecular-targeted therapy or immune therapy, when interferon was the only

treatment modality in the setting of adjuvant use; moreover, the efficacy of radiation therapy in combination with molecular-targeted therapy or immune therapy has yet to be elucidated.

Immune therapy

Interferon

High-dose interferon-α2b (IFN-α2b) adjuvant therapy for melanoma patients at stage IIB/III showed benefits on both RFS and OS in the ECOG1684 trial [36]. In comparison with observation alone, high-dose IFN-α2b (20 MU/m^2/day intravenously 5 days per week for 1 month and then 10 MU/m^2 subcutaneously 3 days per week for 48 weeks) significantly improved 5-year RFS (37% versus 26%) and OS (46% versus 37%) [36]. As a result of this, high-dose IFN-α2b was approved as adjuvant therapy for the treatment of high-risk melanoma by the US Food and Drug Administration (FDA) in 1996 [36]. High-dose IFN-α2b was used as the standard adjuvant therapy for high-risk melanoma in many countries until adjuvant ipilimumab was approved in 2015. After a median follow-up of 12.6 years, an RFS benefit associated with high-dose IFN-α2b versus observation was still evident (HR 1.38; $P = 0.02$), but an OS benefit was not confirmed (HR 1.22; $P = 0.18$) [37]. The ECOG1690 trial comparing high-dose IFN-α2b and low-dose IFN-α2b (3 MU/day three times per week subcutaneously for 2 years) versus observation in stage IIB/III patients showed an RFS improvement for high-dose cases, but no OS benefit for either high- or low-dose cases [38]. Low-dose IFN-α2b was approved for stage II patients based on a French trial, which showed an RFS benefit and a trend for improved OS [39]. Moreover, the European Organization for Research and Treatment of Cancer (EORTC) 18991 trial showed that the 7-year RFS rate was 39.1% for those treated with a pegylated form of IFN (PEG-IFN), which has a longer half-life in circulation than the parent drug, versus 34.6% for an observation group ($P = 0.055$) [40–42]. However, there was no difference in OS ($P = 0.57$) [42]. PEG-IFN was approved by the FDA in 2011 based on this trial. However, neither IFN-α nor PEG-IFN has been widely used due to their frequent and serious side effects [43, 44]. A previous meta-analysis of IFN-α2b indicated that it had a consistent effect on RFS, but no clear effect on OS [37, 45, 46]. However, a meta-analysis in 2017 showed that IFN-α2b had a clear significant effect on both RFS (HR 0.90; $P < 0.00001$) and OS (HR 0.90; $P = 0.003$), compared with those in a group with observation alone [47]. In addition, there was no causal relationship between the benefit of IFN-α2b and dose, duration, age, gender, site of primary tumor, disease stage, Breslow thickness, or presence of clinical nodes; only patients with ulcerated tumors received a significant benefit of IFN-α2b. It was also shown that there was no benefit of high-dose IFN-α2b compared with low-dose IFN-α2b.

Immune checkpoint inhibitors

Anti-CTLA-4 checkpoint inhibitors

CTLA-4 is a negative feedback control factor of T cell activation. Anti-CTLA-4 antibodies block the regulatory signal to T cells and inhibit the activity of regulatory T cells (Tregs), to promote antitumor immune

reactions [48, 49]. In 2011, ipilimumab (3 mg/kg every 3 weeks for four doses) was approved as a treatment for unresectable or metastatic melanoma by the FDA and European Medicines Agency (EMA) based on a study that showed a significant OS benefit of ipilimumab compared with gp100 vaccine [50].

Ipilimumab showed efficacy in adjuvant therapy in two randomized phase III clinical trials, compared with either placebo (EORTC 18071) or high-dose IFN-α (ECOG 1609) [51••, 52]. In the EORTC 18071 trial, completely resected high-risk melanoma patients ($n = 951$) at stage IIIA (lymph node metastasis >1 mm, no in-transit), IIIB, or IIIC were randomly assigned at a 1:1 ratio to receive ipilimumab (10 mg/kg every 3 weeks for four doses, and then every 3 months for up to 3 years) versus placebo [51••]. At a median follow-up of 5.3 years, ipilimumab significantly improved RFS and OS versus placebo. The rate of RFS was 40.8% in the ipilimumab group compared with 30.3% in the placebo group (HR 0.76; 95% CI 0.64–0.89; $P < 0.001$). Moreover, the rate of OS was 65.4% in the ipilimumab group compared with 54.4% in the placebo group (HR 0.72; 95% CI 0.58–0.88; $P = 0.001$). Drug-related adverse events (AEs) of grade 3 or 4 occurred in 41.6% of the patients in the ipilimumab group, only 13.4% of the patients completed their treatment, and 5 patients (1.1%) died due to drug-related AEs. However, health-related quality of life was similar between the two groups despite the toxicity and high rate of discontinuation due to AEs with ipilimumab; no clinically relevant differences regarding global health status were reported [15]. Based on the results of this trial, the FDA approved ipilimumab as adjuvant therapy for high-risk resected stage III melanoma patients in 2015.

Different dose regimens were investigated to improve the tolerability and decrease the toxicity of the drug while maintaining its efficacy. For example, in the ECOG 1609 clinical trial, completely resected high-risk melanoma patients ($n = 1670$) at stage IIIB/C or IV (M1a, M1b) were randomly assigned to receive ipilimumab at 10 mg/kg ($n = 511$) or 3 mg/kg ($n = 523$) versus IFN-α2b ($n = 636$) [52].

At a median follow-up of 3.1 years, an unplanned RFS analysis showed no difference between ipilimumab at 10 mg/kg and at 3 mg/kg. However, compared with ipilimumab at 3 mg/kg, that at 10 mg/kg was associated with significantly higher toxicity (grade ≥ 3 AEs, 57% versus 36.4%) and more drug-related deaths (1.6% versus 0.4%). Because of its rate of severe toxicity and the fact that other adjuvant therapies showed superior efficacy and less toxicity, ipilimumab will not be recommended as the first adjuvant therapy.

Anti-PD-1 checkpoint inhibitors

The cell surface PD-1 receptor is expressed on T cells and negatively regulates their immune function. Anti-PD-1 antibodies are monoclonal antibodies to the PD-1 receptor, which potentiate the immune response to tumors by blocking PD-1/PD-L1 binding [53]. In 2014, nivolumab and pembrolizumab were approved for treating unresectable or metastatic melanoma by the FDA and EMA, based on studies that showed their significant efficacy compared with chemotherapy or ipilimumab [8, 54, 55, 56•].

CheckMate 238 was a randomized phase III double-blind adjuvant study of nivolumab (3 mg/kg every 2 weeks) versus ipilimumab (10 mg/kg every 3 weeks for four doses and then every 12 weeks) for completely resected high-risk melanoma patients at stage IIIB, IIIC, or IV (AJCC v7) [16••]. A total of 906 patients were randomly assigned at a 1:1 ratio to receive nivolumab or ipilimumab and treated for up to 1 year until disease relapse or unacceptable toxic effects. At a minimum follow-up of 24 months, the 18-month rate of RFS was 66.4% (95% CI 61.8–70.6%) in the nivolumab group versus 52.7% (95% CI 47.8–57.4%) in the ipilimumab group; adjuvant nivolumab treatment significantly improved RFS compared with ipilimumab (HR 0.65; 97.56% CI 0.51–0.83; $P < 0.0001$) [57]. Drug-related AEs of grade 3 or 4 occurred in 14.4% of the patients in the nivolumab group and 45.9% of those in the ipilimumab group; treatment was discontinued due to any AEs in 9.7% and 42.6% of the patients, respectively.

There were no drug-related deaths in the nivolumab group and two deaths (0.4%) from toxic effects in the ipilimumab group [16••]. Regardless of PD-L1 expression, nivolumab showed a sustained efficacy benefit versus ipilimumab. In December 2017, the FDA approved nivolumab as adjuvant therapy for high-risk resected melanoma patients based on the preliminary results of this trial.

Another anti-PD-1 antibody, pembrolizumab, was also studied in a randomized phase III double-blind adjuvant study. In the EORTC 1325 trial, 1019 patients with completely resected stage IIIA melanoma (lymph node metastasis > 1 mm) or stage IIIB/IIIC (no in-transit metastases) were randomly assigned at a 1:1 ratio to receive pembrolizumab (200 mg every 3 weeks for a total of 18 doses) or placebo [18••]. At 18 months, the rate of RFS was 71.4% (95% CI 66.8–75.4%) in the pembrolizumab group versus 53.2% (95% CI 47.9–58.2%) in the placebo group; adjuvant pembrolizumab treatment significantly improved RFS compared with placebo (HR 0.57; 98.4% CI 0.43–0.74; $P < 0.001$). Pembrolizumab was also effective in patients with PD-L1-negative tumors and in those with undetermined tumor PD-L1 expression. Drug-related AEs of grades 3 to 5 occurred in 14.7% of the patients in the pembrolizumab group and 3.4% of those in the placebo group [18••]. There was one death (0.2%) from toxic effects in the pembrolizumab group. On February 15, 2019, the FDA approved pembrolizumab for the adjuvant therapy of patients with melanoma with lymph node involvement following complete resection based on this study. Recently, SWOG 1404 was also established as a randomized trial comparing high-dose IFN-α to pembrolizumab as an adjuvant therapy for stage III/IV melanoma after resection, but the results are pending [58].

Another example of a trial that is CheckMate 067, which was a randomized trial comparing the combination of ipilimumab and nivolumab with each agent alone for unresectable or metastatic melanoma patients. It demonstrated that this combination significantly improved RFS and OS compared with the single treatments, although the toxicity increased [59]. The findings proved that the combination of CTLA-4 and PD-1 blockade for metastatic melanoma enhances the immune response compared with the use of each agent alone. CheckMate 915 clinical study is a randomized trial comparing the combination of ipilimumab and nivolumab with each agent alone as an adjuvant therapy for completely resected melanoma patients [60••]. At present, no results of this study have been reported.

Molecular-targeted therapy

Oncogenic BRAF mutations are found in approximately 40% of melanomas and lead to constitutive activation of the MAPK pathway [61–64]. Combination therapy with the BRAF inhibitor dabrafenib plus the MEK inhibitor trametinib was shown to improve survival over BRAF inhibitor monotherapy in patients with BRAF V600E/K mutations and unresectable or metastatic melanoma [2, 4, 65–68]. BRAF and MEK inhibitors showed efficacy in adjuvant therapy in two randomized phase III clinical trials, compared with placebo (BRIM8, COMBI-AD) [17••, 19].

BRIM8 was a randomized phase III double-blind adjuvant study of vemurafenib (960 mg twice daily) versus placebo for completely resected high-risk melanoma patients at stages IIC, IIIA, and IIIB (cohort 1), or stage IIIC (cohort 2) [19]. A total of 498 patients were randomly assigned at a ratio of 1:1 to receive vemurafenib or placebo and treated for 52 weeks. The primary endpoint was disease-free survival (DFS). In cohort 1, median DFS was not reached (95% CI, not evaluable) in the vemurafenib group versus 36.9 months (95% CI 21.4, not evaluable) in the placebo group (HR 0.54; 95% CI 0.37–0.78; log-rank $P = 0.0010$). In cohort 2, median DFS was 23.1 months (95% CI 18.6–26.5) in the vemurafenib group versus 15.4 months (95% CI 11.1–35.9) in the placebo group (HR 0.80; 95% CI 0.54–1.18; log-rank $P = 0.26$). Although the study did not reach the primary DFS endpoint in cohort 2, there was a significant improvement in DFS compared with that for placebo in cohort 1. Drug-related AEs of grade 3 or 4 occurred in 57% of the patients in the vemurafenib group and 15% of those in the placebo group; treatment was discontinued due to any AEs in 20% and 2% of the patients, respectively.

COMBI-AD was a randomized phase III double-blind adjuvant study of dabrafenib (150 mg twice daily) plus trametinib (2 mg once daily) or two matched placebos for completely resected stage III melanoma patients harboring BRAF V600E or V600K mutation [17••].

Overall, 870 patients were randomly assigned at a ratio of 1:1 to receive dabrafenib plus trametinib or placebo and treated for 12 months in the absence of disease progression or until unacceptable toxicity or study withdrawal. The primary endpoint was RFS. At a median follow-up of 2.8 years, investigation showed a significant RFS benefit in the combination group, with an estimated 3-year RFS rate of 58% in that group versus 39% in the placebo group (HR 0.47; 95% CI 0.39–0.58; $P < 0.001$). The 3-year OS rate was 86% in the combination therapy group versus 77% in the placebo group (HR 0.57; 95% CI 0.42–0.79; $P = 0.0006$). Subanalyses demonstrated a significant RFS benefit in the combination therapy group, regardless of disease stage, presence of micrometastases or macrometastases, and ulceration status. Severe AEs occurred in 36% of the patients in the combination therapy group and 10% of those in the placebo group; treatment was discontinued due to any AEs in 26% and 3% of the patients, respectively, and one fatal serious AE was reported in the combination therapy group. The safety of dabrafenib plus trametinib accorded with a previous report on metastatic melanoma. These preliminary results of the COMBI-AD trial demonstrated that adjuvant therapy involving the combination of BRAF and MEK inhibitor could significantly improve long-term prognosis in patients with completely resected high-risk melanoma harboring BRAF mutation versus the adjuvant use of placebo. Adjuvant vemurafenib alone is no longer recommended due to the results of COMBI-AD and the PD-1 trials.

Neoadjuvant therapy

The significant effect of neoadjuvant therapy in melanoma patients is to improve control and surgical resectability of regional disease. Biochemotherapy is a combination of chemotherapy and immunotherapy, and usually involves dacarbazine and either IFN-α2b or interleukin-2 [69]. Several phase II clinical trials provided results with low response rates and related toxicities; biochemotherapy was not treated as a standard neoadjuvant therapy for advanced resectable regional disease [70–72]. To investigate the RFS or OS benefit of neoadjuvant therapy, phase I/II clinical trials of immune therapy, such as high-dose IFN-α2b, ipilimumab, anti-PD-1 antibodies, and BRAF-targeted therapies, were performed for resectable stage III/IV melanoma patients; these showed promising results for the use of immune checkpoint inhibitors and BRAF-targeted therapies. Early data from trials revealed that resection can be completed in the overwhelming majority of patients, and trials proved that agents available in neoadjuvant therapy are safe and effective. A new target in neoadjuvant therapy is to increase the response rates with less toxicity. A number of trials testing neoadjuvant therapies for melanoma are currently ongoing [73–81]. The results from these trials should clarify whether neoadjuvant therapy improves survival and local disease control in patients with stage III and IV melanoma [82–96].

Discussion

Immune checkpoint inhibitors and molecular-targeted therapy will improve the standard adjuvant therapy for high-risk advanced melanoma. However, the stages of patients were not consistent between the previously mentioned adjuvant therapy trials (Table 1). In CheckMate 238, AJCC v7 stage IIIA (no ulceration of primary tumor and micrometastasis of lymph node, diagnosed after sentinel lymph node biopsy or completion of lymphadenectomy) patients were not studied [57]. In COMBI-AD, stage IIIA patients were included, but stage IV patients were not [17••]. Compared with the background of patients in these clinical trials, there are some differences in some of the patients now treated with adjuvant therapy. We should thus perform careful observation of the clinical outcomes for patients treated with adjuvant therapy with backgrounds different from those in trials.

Considering the slight improvement in the OS and the severe toxicity related to IFN-α2b, the use of IFN-α2b will be restricted for patients with ulcerated primary melanoma in countries with no access to the new drugs in adjuvant therapy. Ipilimumab was approved by the FDA for adjuvant therapy of melanoma using checkpoint inhibitor for the first time in 2015. However, ipilimumab should no longer be considered to be the first-line therapy given its lower efficacy and severe toxicity, in view of the FDA approval for anti-PD-1 antibodies and BRAF plus MEK inhibitor for adjuvant therapy of melanoma [16••]. Anti-PD-1 antibody would be a relevant adjuvant therapy for patients without BRAF mutation. PD-L1 expression is presently not considered in the decision-making process regarding adjuvant therapy, except in clinical trials [59]. If the BRAF mutation status is positive, the combination of dabrafenib and trametinib is an option for consideration. When resecting a metastasis of stage III or IV surgically, we should check the BRAF mutation status even if the

Table 1. Summary of adjuvant trials for patients with cutaneous melanoma

Study	Year published	Disease stage	Treatment	*N*	Median follow-up (years)	Hazard ratio RFS	*P* value	Hazard ratio OS	*P* value	Reference
ECOG 1684	1996	IIB, III	HDI vs. observation	287	6.9	0.61	0.023	0.67	0.0237	[36, 37]
					12.6	1.38*	0.02	1.22*	0.18	
ECOG 1690	2000	IIB, III	HDI or LDI vs. observation	642	4.3	HDI 1.28 LDI 1.19	HDI 0.05 LDI 0.17	HDI 1.00 LDI 1.04	HDI 0.995 LDI 0.813	[37, 38]
					6.6	HDI 1.24	HDI 0.09	HDI 1.00	HDI 0.98	
ECOG 1694	2001	IIB, III	HDI vs. GMK vaccine	880	1.3	1.49	0.00045	1.38	0.023	[37, 98]
					2.1	1.33	0.006	1.32	0.04	
EORTC 18991	2008	III	PEG-IFN vs. observation	1256	3.8	0.82	0.01	0.98	0.78	[41, 42]
					7.6	0.87	0.055	0.96	0.57	
EORTC 18071	2015	III (lymph node metastasis > 1 mm, except in-transit)	Ipilimumab vs. placebo	951	2.7	0.75	0.0013	NR	NR	[15, 51••]
					5.3	0.76	< 0.001	0.72	0.001	
CheckMate 238	2017	IIIB, IIIC, IV	Nivolumab vs. ipilimumab	906	1.6	0.65	< 0.001	NR	NR	[16••, 57]
COMBI-AD	2017	III (lymph node metastasis > 1 mm)	Dabrafenib plus trametinib vs. placebo	870	2.8	0.47	< 0.001	0.57	0.0006	[17••]
EORTC 1325	2018	III (lymph node metastasis > 1 mm)	Pembrolizumab vs. placebo	1019	1.3	0.57	< 0.0001	NR	NR	[18••]
BRIM8	2018	IIC, IIIA, IIIB (cohort 1)	Vemurafenib vs. placebo	498	2.6 (cohort 1)	0.54	0.001	NR	NR	[19]
		IIIC (cohort 2)			2.8 (cohort 2)	0.8	0.26	NR	NR	

ECOG Eastern Cooperative Oncology Group, *EORTC* European Organisation for Research and Treatment of Cancer, *HDI* high-dose interferon-α2b, *LDI* low-dose interferon-α2b, *GMK* GM2-KLH/QS-21, *PEG-IFN* pegylated IFN-α2b, *RFS* relapse-free survival, *OS* overall survival, *NR* not reached
*HR for observation vs. HDI

mutation status of the primary lesion is negative because there might be a discrepancy in this regard between the primary lesion and metastasis [97].

Because the patient populations are slightly different and there are various primary endpoints in each RCT, it is difficult to compare the efficacy of anti-PD-1 antibodies with BRAF plus MEK inhibitor. The 12-month RFS rates for stage III patients were 63.5% (ipilimumab in EORTC 18071) [15], 72.3% (nivolumab in CheckMate 238) [57], 75.4% (pembrolizumab in EORTC 1325) [18••], and 88% (dabrafenib plus trametinib in COMBI-AD) [17••]. As previously mentioned, COMBI-AD and EORTC 1325 included stage IIIA patients, but CheckMate 238 did not. In terms of the favorable prognosis of IIIA patients compared with that of IIIB and IIIC patients, direct comparison of the results of each RCT is impossible. In addition, staging was significantly changed in AJCC v8 compared with that in v7, which might hinder the application of trial results in actual clinical settings. Moreover, whether all patients at stage III or IV should receive adjuvant therapy and how to treat patients at stage IIB, IIC, or IIIA in adjuvant therapy remain controversial issues. For decision-making regarding appropriate adjuvant therapy for patients with resected stage III or IV melanoma, we should consider not only the efficacy but also the toxicity profile, cost, route of administration, and medical history of the patient. The toxicity profile of checkpoint inhibitors differs from that of targeted therapy in adjuvant therapy, but the comprehensive rates of AEs are notably similar between these two therapies. An important consideration in this context is the ability of patients to complete treatment and to tolerate any side effects. Additional reports of ongoing trials and further studies are necessary to improve the efficacy of neoadjuvant and adjuvant therapy and determine the standard adjuvant therapy for patients with high-risk advanced melanoma.

Compliance with Ethical Standards

Conflict of Interest
Maiko Wada-Ohno, Takamichi Ito, and Masutaka Furue declare they have no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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This study showed that durable responses under kinase inhibitors are possible. Baseline LDH and number of organ sites with metastasis associated with predictive of PFS and OS.

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This study showed that adjuvant therapy with nivolumab resulted in significantly longer RFS and a lower rate of high grade adverse events than adjuvant therapy with ipilimumab.

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