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Review

Which adjuvant treatment for patients with *BRAF*^{V600}-mutant cutaneous melanoma?

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ABSTRACT

Treatment of patients with melanoma has considerably improved over the past decade and more recently with adjuvant therapies for patients with American Joint Committee on Cancer (AJCC) stage III (loco-regional metastases) or IV (distant metastases) totally resected melanoma, in order to prevent recurrence. In the adjuvant setting, two options are available to patients with *BRAF*^{V600}-mutant AJCC stage III totally resected melanoma: anti-PD-1 blockers (nivolumab or pembrolizumab) or BRAF plus MEK inhibitors (dabrafenib plus trametinib). In the absence of comparative studies, it is difficult to determine which of these options is best. Our aim was to review published studies focusing on the management of patients with *BRAF*^{V600}-mutant melanoma in the adjuvant setting. We also reviewed the main clinical trials of BRAF plus MEK inhibitors and immunotherapy in advanced (i.e. unresectable metastatic) BRAF-mutant melanoma in an attempt to identify results potentially affecting the management of patients on adjuvants. More adverse events are observed with targeted therapy, but all resolve rapidly upon drug discontinuation, whereas with immune checkpoint blockers some adverse events may persist. New therapeutic strategies are emerging, notably neoadjuvant therapies for stage III patients and adjuvant therapies for stage II patients; the place of the adjuvant strategy amidst all these options will soon be re-evaluated. The choice of adjuvant treatment could influence the choice of subsequent treatments in neo-adjuvant or metastatic settings. This review will lead clinicians to a better understanding of the different adjuvant treatments available for patients with totally resected AJCC stage III and IV *BRAF*^{V600}-mutant melanoma before considering subsequent treatment strategies.

1. Introduction

Considerable progress has been made in advanced cutaneous melanoma treatment over the past decade and more recently with new adjuvant therapies in patients with American Joint Committee on Cancer (AJCC) stage III or IV totally resected melanoma. These adjuvant therapies have demonstrated benefit in reducing the risk of recurrence in these patients. Thus, the latest version of AJCC melanoma staging now distinguishes 4 sub-stages of stage III, from IIIA to IIID, with 5- and 10-year survival rates for melanoma of 93% and 88% respectively for stage IIIA and 32% and 24% respectively for stage IIID [1]. However, a recent European study has reported less favourable overall survival rates over the entire stage III (particularly for stages IIIA and IIIB) than reported in the AJCC report and suggests incomplete reporting of outcomes in the database used [2].

Two largely mutually exclusive groups of melanomas should be distinguished: those harbouring a *BRAF*^{V600} mutation, which represent 40–50% of all melanoma patients, and those harbouring other mutations. Only patients with *BRAF*^{V600}-mutant melanoma can be treated successfully with the combination of BRAF and MEK inhibitors.

In the adjuvant setting, two options are available to patients with *BRAF*^{V600}-mutant AJCC stage III totally resected melanoma:

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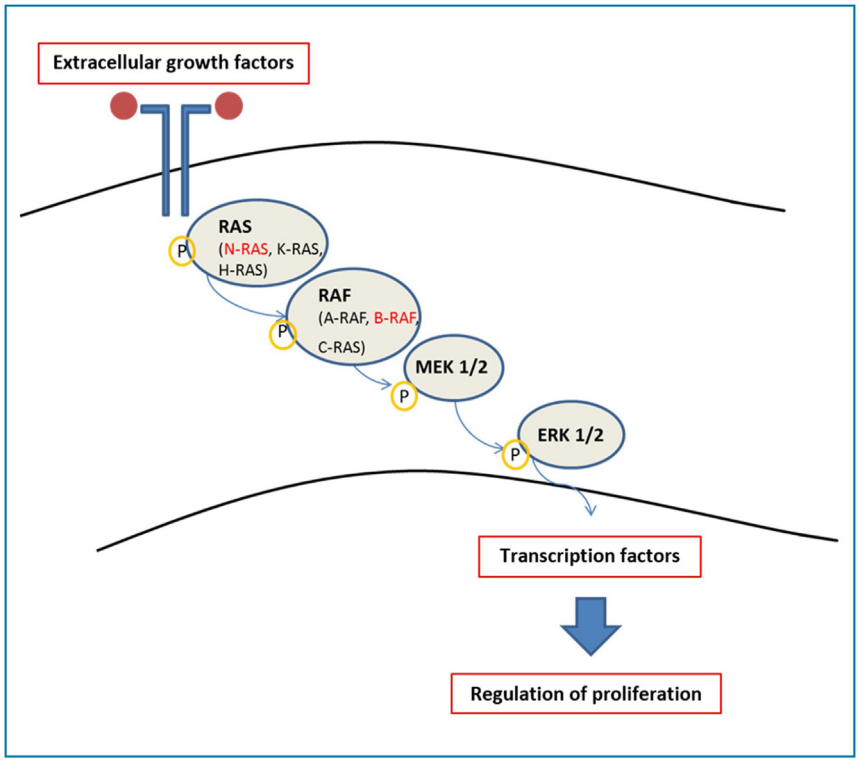

Fig. 1. MAPK pathway: phosphorylation cascades resulting in activation of transcription factors having an impact on cell proliferation. The most frequently mutated proteins in melanoma are shown in red.

anti-PD-1 blockers (nivolumab or pembrolizumab) or a combination of BRAF and MEK inhibitors: dabrafenib plus trametinib. The choice between the 2 options is not easy in the absence of comparative studies.

Our aim was to review published studies focusing on the treatment of patients with *BRAF*^{V600}-mutant melanoma in the adjuvant setting. To better understand the therapeutic options, all of which rely on drugs first tested in patients with unresectable advanced melanoma, we also reviewed the main results of pivotal trials with targeted and immune therapies in patients with *BRAF*^{V600}-mutant metastatic melanoma.

2. Methods

We set up a working group consisting of 11 dermatologists from academic skin cancer centres. Equal work was distributed between five pairs of one senior (professor) and one junior (assistant) dermatologist. EFB coordinated and supervised each part and participated in the introduction and conclusion sections. Each pair of authors conducted a review of the literature of published studies of systemic therapies in cutaneous melanoma that led to validated drugs or prospect therapies. EFB and PS reviewed all contributions and suggested corrections to all pairs of authors until a consensus version was approved.

3. BRAF/*BRAF* mutations and *BRAF*-mutant melanoma

BRAF is a proto-oncogene located on chromosome 7q, encoding BRAF, a serine-threonine kinase protein of the mitogen-activated protein kinase (MAPK) pathway (Fig. 1) [3].

3.1. BRAF-*activating mutations and consequences*

The most common *BRAF*-activating mutation is V600E, a single-base mutation on exon 15, with T1796A leading to the substitution of valine by glutamic acid at position 600 (inducing an increase in kinase activity of up to 500 times the normal values). *BRAF* activating mutations are present in many human cancers such as melanoma and colorectal, lung, pancreatic, thyroid and ovarian cancers [4]. They are also found in benign lesions, including nevi [5]. *BRAF*-activating mutations are found in 35 to 50% of melanomas (V600E in 75 to 85% and V600 K in 10 to 20%) [3].

3.2. *Methods of detection*

In France, *BRAF* mutations are detected in tumour cells from tumour samples (formalin-fixed, paraffin-embedded or frozen tissue from either primary tumour or, preferably, metastasis), mainly using one of the molecular techniques validated by the Institut National du Cancer (INCa) after morphological assessment of the lesion performed by a trained pathologist on a hematein-eosin-stained tumour slide (i.e. diagnosis confirmation, definition of tumour area for further macro-dissection, assessment of the percentage of tumour cells and level of pigmentation) [6,7]. Tumour DNA is then extracted using manual or automated techniques, either from a tumour block where sufficient tumour material is available or from unstained sections where limited tumour material is available. DNA genotyping is performed using different techniques, either individually or in combination: Sanger sequencing, pyrosequencing, high-resolution melting (HRM), allele-specific real-time polymerase chain reaction (PCR), SNAP shot and Cobas® (Roche Molecular Diagnostics). New-generation sequencing (NGS) techniques are now used more and more frequently. *BRAF*^{V600E} mutation can also be detected with high specificity and sensitivity by immunochemistry using anti-VE1 antibody, which stains only mutated BRAF V600E protein [8]. Detection of *BRAF*^{V600} mutation in circulating DNA is a method that is still under evaluation [9].

Table 1
Phase III trials of targeted therapy in unresectable advanced melanoma with a *BRAF*^{V600} mutation.

Phase III studies	Treatment arms[b] (*n* = number of patients)	ORR (%)	Median DOR (months)	Median PFS (months)	Median OS (months)	OS rate (%)			
						2-year	3-year	4-year	5-year
BRIM 3 [10,11]	Vemurafenib (*n* = 337)	48	5.9	6.9	13.6	30.2	20.8	17	–
	Dacarbazine (*n* = 338)	5	–	1.6	10.3	24.5	18.9	15.6	–
BREAK 3 [12]	Dabrafenib (*n* = 187)	50	5.5	5.1	20	–	–	–	24
	Dacarbazine (*n* = 63)	6	–	2.7	15.6	–	–	–	22
CoBRIM [13–15]	Vemurafenib + cobimetinib (*n* = 247)	70	13	12.3	22.3	48.3	38.5	34.7	30.8
	Vemurafenib + placebo (*n* = 248)	50	9.2	7.2	17.4	38	31.1	29.2	26.3
COMBI-d [16]	Dabrafenib + trametinib (*n* = 211)	69	12.9	11	25.1	51	44	–	27
	Dabrafenib + placebo (*n* = 212)	53	10.6	8.8	18.7	42	32	–	–
COMBI-v [17]	Dabrafenib + trametinib (*n* = 352)	66	13.8	11.4	25.6	51	45	–	23
	Vemurafenib (*n* = 352)	53	7.9	7.3	18	38	32	–	–
COLUMBUS[a] [18,19]	Encorafenib 450 + binimetinib (*n* = 192)	64	18.6	14.9	33.6	57.6	47	39	–
	Encorafenib 300 (*n* = 194)	52	15.2	9.6	23.5	49.1	41	–	–
	Vemurafenib (*n* = 191)	41	12.3	7.3	16.9	43.2	31	25	–

BID: twice daily; DOR: duration of response; IV: intravenously; PFS: progression-free survival; OS: overall survival; ORR: objective response rate. Chemotherapy: dacarbazine 1000 mg/m^2/3 weeks intravenously. Comparisons of primary endpoints (PFS and OS) were significant in all these studies.
MEK inhibitors: cobimetinib: 60 mg/day for 21 days followed by a 7-day rest period, trametinib: 2 mg/day, binimetinib: 45 mg BID.
[a] Columbus study: patients were either naïve or previously treated with first-line immune checkpoint inhibitors. The primary endpoint was PFS for encorafenib 450 + binimetinib vs. vemurafenib.
[b] Targeted therapies (orally): BRAF inhibitors: vemurafenib 960 mg BID, dabrafenib 150 mg BID, encorafenib 300 or 450 mg/day.

4. Therapeutic options for *BRAF*^{V600}-mutant melanomas in the adjuvant setting

4.1. Targeted therapy

Only melanomas carrying a *BRAF*^{V600} mutation can be treated with targeted therapy. Vemurafenib was the first selective inhibitor of BRAF (pV600) to be granted marketing authorization (MA) in France in 2012 for the treatment of advanced melanoma carrying the *BRAF*^{V600} mutation [10,11]. In 2013, a second BRAF inhibitor was approved in the same setting: dabrafenib [12]. Although BRAF inhibitors constituted a true revolution in advanced melanoma treatment, response duration was short, with multiple mechanisms of acquired resistance, mainly reactivation of the MAPK-signalling pathway. In order to reduce or delay this escape, studies combining BRAF and MEK inhibitors were conducted. Data from phase II and III clinical trials resulted in regulatory approval in 2016 of two therapeutic combinations of BRAF and MEK inhibitors: vemurafenib plus cobimetinib and dabrafenib plus trametinib [13–17]. More recently, in 2019, a third association was authorized in advanced *BRAF*^{V600}-mutant melanoma: encorafenib plus binimetinib (Table 1) [18,19]. Encorafenib has interesting pharmacokinetic characteristics, with a 10-fold longer half-life of dissociation (> 30 hours) than either dabrafenib or vemurafenib, enabling sustained target inhibition. The synergistic combination of BRAF and MEK inhibitors is now the standard targeted treatment in patients with a *BRAF*^{V600}-mutant metastatic melanoma.

Patients with stage III disease presenting regional involvement at diagnosis are at high risk of recurrence after locoregional resection, and many will ultimately die from metastatic melanoma [1]. In order to reduce this risk, and given the remarkable efficacy of combined targeted therapies in the metastatic setting, studies have been conducted to determine whether combined BRAF plus MEK inhibitors in adjuvant therapy would improve outcomes in *BRAF*^{V600}-mutated patients with resected stage III melanoma. The aim of this adjuvant therapy was to prevent local recurrence or metastases while achieving an acceptable side-effect profile.

To date, the only targeted combination therapy approved by the European Medicines Agency (EMA) as adjuvant treatment in patients with totally resected AJCC stage III *BRAF*^{V600}-mutant melanoma is the dabrafenib plus trametinib combination (July 2018), since Combi-AD was the first positive clinical trial to investigate this targeted therapy combination as adjuvant treatment [20]. Indeed, no studies of either vemurafenib plus cobimetinib or encorafenib plus binimetinib have been reported in the adjuvant setting. A study with the latter combination is, however, planned in stage II melanomas. The dosage of dabrafenib and trametinib used in the adjuvant setting is the same as in the metastatic indication, and patients should be treated for 12 months unless recurrence of the disease or unacceptable toxicity occurs (Table 2) [20]. In the event of adverse events occurring during use of dabrafenib plus trametinib, one possible strategy is to substitute the latter with the combination of encorafenib plus binimetinib, which has shown high efficacy in a randomized clinical trial of patients with distant metastatic disease coupled with a more favourable safety profile than that reported for dabrafenib plus trametinib [21].

4.2. Immune checkpoint inhibitors

The development of immune checkpoint inhibitors to stimulate T-cell-mediated tumour killing has also considerably improved the prognosis of advanced melanoma patients. The targets of currently commercially available monoclonal antibodies (mAb) are two key receptors involved in central and peripheral immune tolerance: cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed cell death-1 (PD-1). While CTLA-4 is primarily involved in lymph nodes during the priming phase of the immune response to stop potentially auto-reactive T-cells at the initial stage of naïve T-cell activation, PD-1 regulates previously activated T-cells in the later stages of the immune response, mostly in peripheral tissue. To the best of our knowledge, there is currently no evidence that

Table 2
Targeted therapy with BRAF and MEK inhibitors.

Combined BRAF + MEK inhibitors		Dosage	Administration	If dose missed, recommended time to following dose	Registered indication	
					Metastatic disease	Adjuvant setting
1	Vemurafenib	960 mg BID	Continuously, preferentially during meals	Up to 4 hours	Yes	No
	+					
	Cobimetinib	60 mg 1/day	Sequentially, 3 tablets per day for 21 days then 7-day break	Up to 12 hours		
2	Dabrafenib	150 mg BID	Continuously, 1 hour before or 2 hours after meals; 12 hours apart	Up to 6 hours	Yes	Yes
	+					
	Trametinib[a]	2 mg 1/day	Continuously, same hour daily, simultaneously with one of the doses of dabrafenib	up to 12 hours		
3	Encorafenib	450 mg 1/day	Continuously	Up to 12 hours	Yes	No
	+					
	Binimetinib	45 mg BID	Continuously, 12 h apart	Up to 6 hours		

[a] Trametinib must be kept refrigerated (2–8°C) and stored away from light.

BRAF mutations can have a direct impact on response to immune checkpoint inhibitors.

Ipilimumab, a fully human mAb that blocks CTLA-4, was the first immune checkpoint inhibitor assessed in clinical trials in advanced melanoma patients [22–25]. Nivolumab and pembrolizumab are fully human IgG4 PD-1 immune checkpoint inhibitor mAbs with broad anti-tumour activity in many cancers, including melanoma. The results of phase II and III clinical trials led to regulatory approval in 2014 of pembrolizumab and nivolumab for the treatment of patients with metastatic melanoma [26–32]. Nivolumab in combination with ipilimumab was approved by the Food and Drug Administration (FDA) and the EMA in 2016 for the treatment of patients with unresectable or metastatic melanoma, regardless of BRAF-mutation status [31].

The favourable progression-free survival (PFS) and overall survival (OS) outcomes achieved by checkpoint inhibitors in phase III clinical trials in advanced melanoma patients (summarised in Table 3) have also led to their development in the adjuvant setting, with substantial improvements in recurrence-free survival (RFS).

Alpha interferon is approved in both the USA and Europe as an adjuvant therapy for resected melanoma [33]. However, this drug is no longer used as an adjuvant therapy owing to the marginal benefit in OS and the frequency of adverse events (AE) [34,35].

In 2015, the FDA, but not the EMA, approved ipilimumab as adjuvant therapy in patients with fully resected stage III melanoma at high risk of recurrence based on the results of a randomised, placebo-controlled, phase III trial (EORTC 18071) [36]. In the adjuvant setting of this study, patients received ipilimumab at a dose of 10 mg/kg, which is higher than the FDA-recommended a dose of 3 mg/kg, every 3 weeks for the first 4 doses, then every 3 months for up to 3 years or until either disease recurrence or unacceptable toxicity.

The anti-PD-1 mAbs nivolumab and pembrolizumab gained FDA and EMA approval for the adjuvant treatment of melanoma patients with involvement of lymph nodes (or distant metastatic disease for nivolumab) previously undergoing complete surgical resection, based on a statistically significant improvement in RFS in phase III comparative trials [37,38]. The recommended dose and schedule in the adjuvant setting is 200 mg/3 weeks (or 400 mg/6 weeks) for pembrolizumab and 240 mg/2 weeks (or 480 mg/4 weeks) for nivolumab, given by intravenous infusion over 30 minutes, until disease recurrence or unacceptable toxicity, up to a maximum of 1 year.

These results put an end to the use of interferon and ipilimumab in the adjuvant setting. In countries with access to interferon alone, its use can be restricted to patients with ulcerated melanoma, based on recent meta-analysis data [39].

5. Efficacy of adjuvant treatments in *BRAF*-mutant melanoma patients

5.1. *Efficacy of targeted therapy in adjuvant treatment of* BRAF-*mutant melanoma patients*

Two phase III clinical trials evaluated the efficacy of BRAF inhibitors or combined BRAF plus MEK inhibitors administered for one year in the adjuvant setting in fully resected high-risk melanoma patients (stage IIC to IIIC, according to the criteria of AJCC 7th edition). The results are summarised in Table 4.

The BRIM 8 trial evaluated adjuvant vemurafenib monotherapy versus placebo in patients with fully resected *BRAF*^{V600}-mutant melanoma, in either stage IIC-IIIB (cohort 1) or stage IIIC (cohort 2). Although vemurafenib monotherapy was active in patients with stage IIC-IIIA-IIIB disease (median disease-free survival of 23.1 months versus 15.4 months in vemurafenib and placebo respectively, hazard ratio (HR): 0.80, 95% confidence interval (95% CI) 0.54–1.18; $P = 0.026$), no significant improvement in RFS was observed in stage IIIC patients, and the study did not achieve its primary endpoint. While vemurafenib monotherapy achieved a reduction in risk of RFS events in patients with resected stage IIC-IIIA-IIIB disease (cohort 1), the result could not be considered significant due to the study design [40].

The COMBI-AD phase III trial included patients having undergone complete resection of histologically confirmed AJCC 7th edition-stage IIIA (limited to lymph-node metastasis of > 1 mm), IIIB or IIIC cutaneous melanoma. This adjuvant combination resulted in a 53% lower risk of relapse than placebo and a significant improvement in the 3-year RFS rate (59% versus 40%); the risk of death was 43% lower (HR: 0.57; 95% CI 0.42–0.79, $P = 0.0006$), and the risk of distant metastasis or death was reduced by 47% [20,41]. An updated OS analysis from the COMBI-AD trial has not been reported because the number of events needed for the next prespecified interim analysis of OS has not yet been reached. Moreover, subgroup analysis of RFS demonstrated that therapeutic benefits were observed regardless of baseline factors, including AJCC 8th edition disease stage, nodal metastatic burden, or tumour ulcera-

Table 3
Phase III trials of anti-CTLA-4 and anti-PD-1 monoclonal antibodies in unresectable advanced melanoma patients.

Phase III studies	Treatment arms[b] (*n* = number of patients; % BRAF-mutant melanoma)	ORR (%)	Median DOR (months)	Median PFS (months)	Median OS (months)	OS rate (%)			
						2-year	3-year	4-year	5-year
CA184-169 [24]	Ipilimumab 10 mg/kg (*n* = 365; 22%)	15	16.3	2.8	15.7	–	31.2	–	–
	Ipilimumab 3 mg/kg (*n* = 362; 22%)	12	15.9	2.8	11.5	–	23.2	–	–
NCT00094653 [25]	Ipilimumab 3 mg/kg + gp100 (*n* = 403)	5.7	11.5	–	10	21.6	–	–	–
	Ipilimumab 3 mg/kg (*n* = 137)	10.9	NR	–	10.1	23.5	–	–	–
	Gp100 (*n* = 136)	1.5	NR	–	6.4	13.7	–	–	–
NCT01515189 [22]	Ipilimumab 10 mg/kg + dacarbazine (*n* = 250)	15.2	19.3	–	11.2	–	20.8	–	–
	Dacarbazine + placebo (*n* = 252)	10.3	8.1	–	9.1	–	12.2	–	–
CHECKMATE 037 [27]	Nivolumab 3 mg/kg (*n* = 403; 22%)	27	32	3.1	16	38.7	–	–	–
	Chemotherapy (*n* = 133; 22%)	10	13	3.7	14	33.9	–	–	–
CHECKMATE 067 [31]	Nivolumab + ipilimumab (*n* = 314; 32.2%)	58	50.1	11.5	NR	–	58	58	55
	Nivolumab (*n* = 316; 31.6%)	45	NR	6.9	36.9	–	52	45	44
	Ipilimumab (*n* = 315 (30.8%)	19	14.4	2.9	19.9	–	34	19	26
KEYNOTE 002 [32]	Pembrolizumab 10 mg/kg (*n* = 181; 31.6%)	28	NR	2.9	14.7	38	–	–	–
	Pembrolizumab 2 mg/kg (*n* = 182)	22	22.8	2.9	13.4	36	–	–	–
	Chemotherapy (*n* = 179)	4	6.8	2.7	11	30	–	–	–
KEYNOTE 006 [29]	Pembrolizumab (*n* = 556; 35%)	42	53.5	8.4	32.7	–	–	–	38.7
	Ipilimumab (*n* = 278; 38%)	17	NR	3.4	15.9	–	–	–	31

DOR: duration of response; PFS: progression-free survival; OS: overall survival; ORR: objective response rate; NR: not reached. Comparisons of primary endpoints (PFS and OS) were significant in all of these studies, except for studies performed in second line therapy (CheckMate 037, OS in Keynote 002). In CheckMate 067, no comparison of the nivolumab vs. nivolumab + ipilimumab groups was planned.

tion status [1]. The estimated cure rate at a median follow-up of 3.5 years was 54% (95% CI: 49–59) in the dabrafenib plus trametinib arm versus 37% (95% CI: 32–42) in the placebo arm [41].

5.2. Efficacy of immunotherapy in the adjuvant setting in BRAF-mutant melanoma patients

Data from phase III trials assessing the efficacy of the anti-CTLA-4 and anti-PD-1 mAbs in the adjuvant setting in fully resected high-risk melanoma patients are summarised in Table 5.

Adjuvant ipilimumab therapy at the dose of 10 mg/kg/3 weeks for 4 doses then every 3 months for up to 3 years for patients with high-risk stage III melanoma resulted in significantly higher levels of RFS, OS and distant metastasis-free survival than placebo at the cost of substantial toxic effects [36]. The risk of death was 28% lower with ipilimumab than with placebo while the risk of distant metastasis or death was reduced by 24%. No data are currently available regarding the efficacy of adjuvant ipilimumab therapy according to *BRAF*-mutation status. Grade 3–4 AEs occurred in 54.1% of the ipilimumab group and 26.2% of the placebo group respectively. In the ipilimumab group, 5 patients died owing to immune-related AEs. More than half of patients treated with adjuvant ipilimumab had a relapse and about one third had died at 5 years.

The anti-PD-1 mAbs have also been compared to ipilimumab or placebo as adjuvant therapy for patients with resected high-risk melanoma in randomized phase III trials. Of 905 patients undergoing complete resection of stage IIIB, IIIC or IV melanoma, adjuvant therapy with nivolumab resulted in significantly longer RFS and a better safety profile than adjuvant therapy with ipilimumab [37]. The 1-year RFS rate was 70.5% in the nivolumab group and 60.8% in the ipilimumab group respectively. Grade-3 or -4 AEs were reported in 14.4% of the nivolumab group and 45.9% of the ipilimumab group respectively. As previously shown in patients with metastatic disease, patients who received nivolumab as adjuvant therapy after tumour resection derived benefit regardless of *BRAF* status, providing additional options for patients with $BRAF^{V600}$ mutations. The recent data showed 4-year recurrence-free survival rates of 51.7% and 41.2% for the nivolumab and ipilimumab arms respectively [42].

Similarly, pembrolizumab (200 mg/3 weeks for up to 1 year) as adjuvant therapy for high-risk stage III melanoma (inclusion criteria similar to those in the COMBI-AD adjuvant trial) resulted in significantly longer RFS than placebo, with no new toxic effects being identified [38]. The 1-year RFS rate was 75.4% in the pembrolizumab group and 61% in the placebo group, with an HR of 0.57 for recurrence or death. AEs of grades 3 to 5 were reported in 14.7% of the pembrolizumab group and 3.4% of the placebo group, with one treatment-related death due to myositis in the pembrolizumab group. *BRAF*-mutation status did not significantly influence the difference in RFS between the pembrolizumab and placebo groups.

Owing to the superiority of combined immunotherapy in unresectable stage IV disease, the efficacy and safety of nivolumab plus ipilimumab have also been assessed in the adjuvant setting. Results from a phase 2 trial evaluating the safety and efficacy of adjuvant nivolumab plus ipilimumab or nivolumab monotherapy versus placebo in patients with stage IV melanoma with no evidence of disease after surgery or radiotherapy have recently been published [43]. The HR for recurrence for the nivolumab plus ipilimumab group versus placebo group was 0.23 (97.5% CI 0.12–0.45; $P < 0.0001$) and for the nivolumab group versus placebo group was 0.56 (0.33–0.94; $P = 0.011$). Treatment-related adverse events of any grade led to treatment discontinuation in 34 (62%) of 55 patients in the nivolumab plus ipilimumab group and seven (13%) of 56 in the nivolumab group. Other clinical trials are currently ongoing (NCT02656706 and NCT03068455).

Table 4
Phase III trials of adjuvant targeted therapy in *BRAF*-mutant melanoma patients.

Adverse events (%)		Treatment arms[b] (*n* = number of patients)	Median RFS (months)	RFS rate (%)				Hazard ratios [95%CI] *P*-value		OS rate (%)			Adverse events (%)
				1-year	2-year	3-year	4-year	Relapse or death	DFMS	1-year	2-year	3-year	Grade 3 or 4
BRIM 8 [40] *n* = 498	COHORT 1 Stage IIC-IIIB *n* = 314	Vemurafenib *n* = 157	NR	84.3	72.3	–	–	0.54 [0.37–0.78] *P* = 0.0010	0.58 [0.37–0.90] *P* = 0.013	–	93	–	57[c]
		Placebo *n* = 157	36.9	66.2	56.5	–	–			–	87	–	15[c]
	COHORT 2 Stage IIIC *n* = 184	Vemurafenib *n* = 93	23.1	78.9	46.3	–	–	0.80 [0.54–1.18] *P* = 0.26	0.91 [0.57–1.44] *P* = 0.68	–	84	–	57[c]
		Placebo *n* = 91	15.4	58	47.5	–	–			–	85	–	15[c]
COMBI AD [20,41] Stage IIIA[a]/IIIB/IIIC *n* = 870	Dabrafenib + trametinib *n* = 438	NR	88	67	59	54	0.47 [0.39–0.58] *P* < 0.001	0.53 [0.42–0.67] *P* < 0.001	97	91	86	41	
	Matched placebo *n* = 432	16.6	56	44	40	38			94	83	77	14	

BID: twice daily, NR: not reached; RFS: relapse-free survival; DMFS: distant-metastasis free survival; OS: overall survival. In COMBI AD, comparison of the primary endpoint (RFS) was significant. In BRIM 8, comparison of the primary endpoint (RFS) could not be considered significant due to the study design (hierarchical analysis of cohort 2 before cohort 1).

[a] Stage IIIA limited to lymph node metastasis > 1 mm.

[b] Dabrafenib: 150 mg BID p.o., Trametinib: 2 mg p.o., Vemurafenib: 960 mg BID p.o.

[c] Cohorts 1 + 2.

Table 5
Phase III trials of adjuvant immunotherapy in stage III melanoma patients.

Phase III studies Patients previously untreated	Treatment arms (n = number of patients)	Median RFS (months)	RFS rate (%)					Hazard ratios [95% CI] p value		OS rate (%)			Adverse events (%)	
			1-year	2-year	3-year	4-year	5-year	Relapse or death	DFMS	1-year	2-year	5-year	Grade 3 or 4	Grade 5 (death)
EORTC 18071 [36] Stage III	Ipilimumab 10 mg/kg (n = 475)	26.1	–	–	46.5	–	40.8	HR 0.76 [0.64–0.92] P = 0.002	–	–	–	65.4	54.1	0.9
	Placebo (n = 476)	17.1	–	–	34.8	–	30.3			–	–	54.4	20.2	0
Chekmate238 [37] Stage IIIB/IIIC or IV	Nivolumab 3 mg/kg (n = 453)	NR	70.5	–	60	–	–	0.65 [0.51–0.83] P < 0.001	0.73 [0.55–0.95]	–	–	–	14.4	0
	Ipilimumab 10 mg/kg (n = 453)	NR	60.8	–	48	–	–			–	–	–	45.9	2.2
NCT02362594 [38] Stage IIIA/IIIB/IIIC	Pembrolizumab 200 mg (n = 514)	-	75.4	–	–	–	–	0.57 [0.43–0.74] P < 0.001	–	–	–	–	14.7	0.2
	Placebo (n = 505)	-	61	–	–	–	–			–	–	–	3.4	0

NR: not reached; RFS: relapse-free survival; DMFS: distant-metastasis free survival; OS: overall survival.

6. Adverse events with currently approved adjuvant therapy (dabrafenib plus trametinib and anti-PD1 mAb)

Standard practice is to grade side effects according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 [44]. Similar rates of AEs occurred on adjuvant therapy with either immune or targeted therapy, but the treatment discontinuation rate was higher than in unresectable metastatic disease. This finding could be related to the nature of adjuvant therapy; the balance between the risk of AE and the benefits of the treatment is not the same in the adjuvant as in the distant metastatic setting. Thus, the risk of AEs must be taken into account in the choice of adjuvant therapy, and it is essential to inform patients about these different possible adverse events.

6.1. Safety profile of dabrafenib plus trametinib

The main specific AE observed in patients treated with dabrafenib plus trametinib in the COMBI-AD trial was acute pyrexia (63%), which can be treated with paracetamol, followed by corticosteroids, in addition to transitory drug withdrawal; in most cases, pyrexia disappears after a few months. The other most common AEs were fatigue (47%) and nausea (40%). Grade 3 or 4 adverse events occurred in 41% of patients and one fatal AE (pneumonia) was reported. AEs led to permanent discontinuation of treatment in 26% of patients, which is higher than that observed in patients treated in the metastatic setting (14 to 16%) [16,17,20]. CTCAE grade 3 toxicities require discontinuation of therapy until they return to grade 1 or 2, and therapy can be re-introduced with dosage adaptation.

6.2. Safety profile of anti-PD-1 mAb

Immune-related AEs observed in the adjuvant setting are similar to those in the metastatic setting and are summarized in Table 6. In the CheckMate 238 study evaluating nivolumab versus ipilimumab as adjuvant therapy, AEs of any grade resulting in the discontinuation of a trial drug were reported in 9.7% of the patients in the nivolumab group and 43% in the ipilimumab group. No deaths were reported with nivolumab, but two deaths occurred with ipilimumab (bone-marrow aplasia and colitis, both occurring more than 100 days after the last dose) [37]. Discontinuation of pembrolizumab as adjuvant therapy was reported in 13% of patients, and one (treatment-related) death was reported (myositis) [38].

AEs may occur at any time during treatment, but with a general pattern of occurrence. The first AEs to appear are cutaneous adverse events, seen on average three to four weeks after the first administration. After six to seven weeks, AEs affecting the gastrointestinal tract and/or liver occur, with most endocrine-related side effects developing only after nine weeks (Fig. 2) [45].

Some patients can develop immune toxicities even after drug discontinuation due to the long half-life of these mAbs (nivolumab: 26 days; pembrolizumab: 22 days; ipilimumab: 15 days).

Serious immune-related endocrine AEs such as hypophysitis and adrenal insufficiency usually present with nonspecific symptoms and can be difficult to diagnose. Symptoms such as fatigue, headaches and visual field changes are suggestive of hypophysitis. Pulmonary toxicity is variable in onset and severity. Symptoms usually begin as a dry cough, progressive dyspnoea, and fine inspiratory crackles. Gastrointestinal toxicity can be severe, such as severe colitis. Diarrhoea is the first symptom and it is crucial to warn every patient about initial assessment of diarrhoea/colitis (since early management might prevent progression to more severe toxicity). Cardiac toxicity has been reported: heart failure, cardiomyopathy, heart block, myocardial fibrosis and myocarditis. Myocarditis (< 1%) is very rare, and can be initially poorly symptomatic, but is always associated with elevation of blood troponin. Steroids should be administered where the severity of an immune-related AE warrants reversal of inflammation. Other immunomodulatory medications used in steroid-refractory cases include the anti-TNF-alpha mAb, infliximab.

The Society for Immunotherapy of Cancer (SITC) set up a multidisciplinary Toxicity Management Working Group, which convened for a full-day workshop to draft recommendations to enable standardised management of immune-related AEs [46].

7. Data interpretation and conclusions

In real life, we currently have several therapeutic options for patients with a *BRAF*^{V600}-mutant melanoma in the adjuvant setting, and it is necessary to know whether this mutation is present or absent in order to choose the appropriate treatment strategy.

The choice will depend on each individual case, while keeping in mind that combined targeted therapy has the advantage of eliciting a rapid response, with less frequent very early progression, while anti-PD-1 therapy achieves a durable response.

In stage III resected patients, because of the absence of studies comparing anti-PD-1 therapy with targeted therapy and of biomarkers to predict the best response, the choice of adjuvant treatment depends on several criteria, including the presence of a contraindication (e.g. history of auto-immune disease, immunosuppressive treatment, kidney or liver failure, etc.) and must be discussed with the patient (intravenous treatment versus oral, different tolerance profiles, etc.). For targeted therapy, only the combination of dabrafenib plus trametinib is currently available in this indication (a study of encorafenib plus dabrafenib in AJCC stage II melanoma patients is planned). For anti-PD-1 mAbs, in the absence of comparative studies there is no valid argument in favour of one molecule or administration schedule over another (nivolumab 240 mg or 3 mg/kg/2 weeks, or 480 mg/4 weeks, *versus* pembrolizumab 2 mg/kg/3 weeks or 400 mg/6 weeks).

Patients with AJCC 7th edition stage IIIA melanoma (with node micrometastasis > 1 mm) were included in phase III trials comparing dabrafenib plus trametinib versus placebo and comparing pembrolizumab versus placebo, but they were excluded from a phase III study comparing nivolumab versus ipilimumab [20,37,38]. However, in the French melanoma guidelines, all patients with AJCC 8th edition stages III (from IIIA to IIID) are eligible to receive adjuvant treatment with these drugs, although MSS data are very heterogeneous in this patient population [47]. Even within AJCC 8th edition stage IIIA, disparities are marked, with the tumour burden within the sentinel lymph node(s) appearing to be a good stratification factor; 5-year OS ranged from 91% for metastasis < 0.1 mm, 61% for metastasis of 0.1–1.0 mm, and 51% for metastasis > 1.0 mm ($P < 0.001$) [1]. Interestingly, in a recent study reporting data for European cohorts, OS rates in AJCC 8th edition stage IIIA patients at 5 and 10 years were poorer than melanoma-specific survival data from AJCC 8th edition (80% versus 93% and 71% versus 88% respectively), which could encourage clinicians to treat these patients using adjuvant therapies [2].

In stage IV resected patients, the choice is simpler because only nivolumab is allowed; these patients were included only in the phase III study comparing nivolumab versus ipilimumab while being excluded from other studies [37].

At present, the most effective duration of adjuvant therapy in patients with melanoma is unknown; however, there is no evidence to suggest that a treatment duration superior to one year provides any additional clinical benefit.

Nowadays, we have very few data to predict response to the next treatment(s) in patients with recurrence of melanoma during or after adjuvant therapy, and or to determine the best strategy.

Table 6
Common adverse events with immune checkpoint inhibitors. Non-comparative data from the various pivotal studies.

Phase III studies with immune checkpoint inhibitors	KEYNOTE 006 [29] Pembrolizumab			CheckMate 067 [31] Nivolumab			CheckMate 067 [31] Ipilimumab			CheckMate 067 [31] Nivolumab + ipilimumab		
Adverse event grades	All grades	Grade 3 or 4	Grade 5 (death)	All grades	Grade 3 or 4	Grade 5 (death)	All grades	Grade 3 or 4	Grade 5 (death)	All grades	Grade 3 or 4	Grade 5 (death)
Any adverse events (%)	80	17	0.2	86	22	0.3	86	28	0.3	96	59	0.6
Diarrhoea	17	2	0	22	3	0	34	6	0	45	10	0
Fatigue	25	< 1	0	37	1	0	29	1	0	38	4	0
Pruritus	20	< 1	0	22	< 1	0	36	< 1	0	36	2	0
Rash	17	0	0	23	< 1	0	23	2	0	30	3	0
Nausea	13	1	0	13	< 1	0	17	< 1	0	28	2	0
Vomiting	–	–	0	7	< 1	0	7	< 1	0	14	0	0
Pyrexia	–	–	0	7	0	0	6	< 1	0	20	< 1	0
Decreased appetite	–	–	0	11	0	0	13	< 1	0	19	< 1	0
Hypothyroidism	10	0	0	10	0	0	5	0	0	17	< 1	0
Arthralgia	13	< 1	0	11	< 1	0	7	< 1	0	14	< 1	0
Increased AST/ALT	–	–	0	7	2	0	7	2	0	20	10	0
Vitiligo	13	0	0	10	< 1	0	5	0	0	9	0	0.3
Hypophysitis	–	–	0	< 1	< 1	0	4	3	0	8	2	0
Colitis	–	–	0	3	1	0	11	8	0.3	14	9	0

KEYNOTE 006: pembrolizumab 10 mg/kg/2 or 3 weeks. CheckMate 067: nivolumab 3 mg/kg/2 weeks, ipilimumab 3 mg/kg/3 weeks or nivolumab 1 mg/kg + ipilimumab 3 mg/kg/3weeks (4 infusions). KEYNOTE 006: 1 death with pembrolizumab (sepsis); CheckMate 067: 1 death with nivolumab (neutropenia), 1 death with ipilimumab (colon perforation), 2 deaths with nivolumab + ipilimumab (cardiomyopathy ($n = 1$); liver necrosis ($n = 1$)).

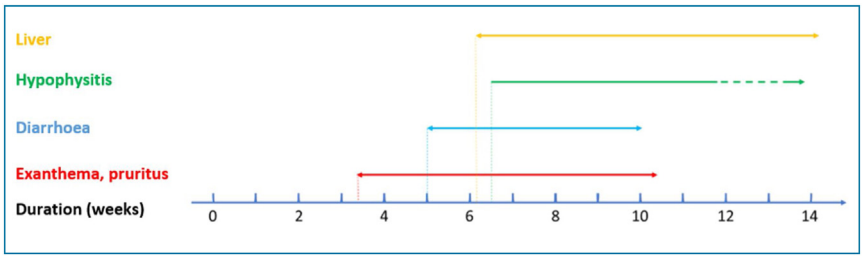

Fig. 2. Time course of typical adverse events during therapy with immune checkpoint inhibitors [45].

The possibility that patients presenting distant metastasis during or after adjuvant therapy have developed resistance mechanisms to this treatment cannot be ruled out. The choice of adjuvant treatment could influence the choice of subsequent treatments in either neo-adjuvant (before surgery) or metastatic settings.

Safety profiles differ between targeted and immune therapy; whereas with targeted therapy, AEs are more common but none are irreversible, with immune checkpoint blockers, some AEs may persist indefinitely. This risk of persistent immune AEs must be explained to patients and must be taken into account in the choice of adjuvant treatment.

We lack head-to-head comparative studies enabling us to choose between these different strategies of adjuvant treatment. In the metastatic setting, it has been shown that benefits can continue after anti-PD-1 mAbs have been discontinued [26], whereas discontinuing targeted therapy is not recommended due to high risk of relapse [48]. However, in the adjuvant setting, treatment is discontinued after 12 months in both treatment strategies (anti-PD-1 and dabrafenib plus trametinib), and the update of the COMBI-AD trial (after median follow-up of 5 years) showed a long-term benefit of the dabrafenib plus trametinib option, with an HR of 0.51 (95% CI: 0.42–0.61) and a recurrence-free survival rate of 52% in the population of patients treated with dabrafenib plus trametinib vs. 36% in the placebo group [49]. Long-term benefits at 4 years and 3 years respectively have also been demonstrated with pembrolizumab vs. placebo (HR 0.56; 95% CI 0.47–0.68) [50] and with nivolumab vs. ipilimumab (HR 0.68; 95% CI (0.55–0.84) in stage III patients) [42].

New therapeutic strategies are emerging and we await the results of several clinical trials of adjuvant treatment for stage II disease and of neoadjuvant treatment in patients with lymph macrometastasis prior to lymph-node resection. It is difficult to envisage the place that these (neo)adjuvant treatments will have in future treatment strategies; the constant updates on clinical trial results in melanoma in reality undermine the sustainability of therapeutic strategies, thus setting them up for failure.

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