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The new era of adjuvant therapies for melanoma

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New treatment options for patients with resected stage III melanoma have been established with the publication of the results of four pivotal randomized clinical trials, resulting in three drug approvals, with a forth expected, all within only 4 years. Herein, we put these advances into context.

Refers to Eggermont, A. M. et al. Adjuvant pembrolizumab versus placebo in resected stage III melanoma. *N. Engl. J. Med.* **378**, 1789–1801 (2018).

After an almost 20-year era of adjuvant interferon (IFN) therapies with marginal benefits for patients with high-risk stage II–III melanoma, we have now entered a new epoch of effective adjuvant therapies for this disease. Following the FDA approval of a number of therapies for advanced-stage melanoma[1], the past 4 years have witnessed the results from four randomized controlled trials (RCT) demonstrating substantial improvements in recurrence-free survival (RFS) in patients with resected melanoma who received adjuvant ipilimumab[2], nivolumab[3], dabrafenib plus trametinib[4], or pembrolizumab[5]. Indeed, ipilimumab, nivolumab, and most recently dabrafenib plus trametinib have been approved in the adjuvant setting, and a similar approval of pembrolizumab is expected soon.

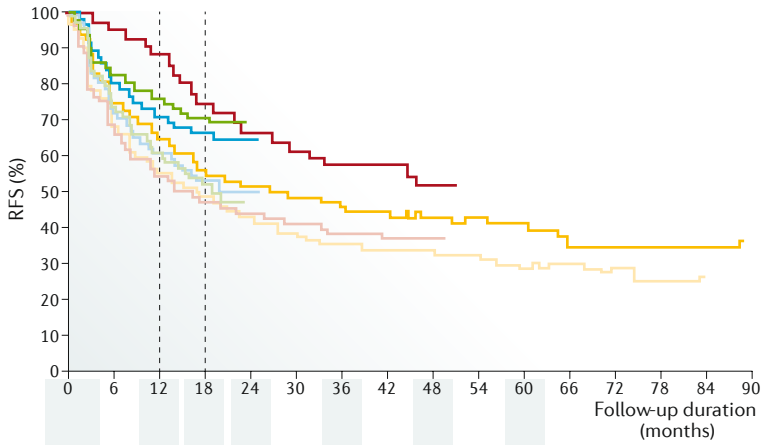
Strikingly consistent outcomes are observed across the pivotal adjuvant RCTs of ipilimumab[2] (EORTC 18071/CA184-029), nivolumab[3] (CheckMate 238), dabrafenib plus trametinib[4] (COMBI-AD), and pembrolizumab[5] (EORTC 1325/KEYNOTE-054). Ipilimumab has a modest but statistically significant RFS benefit (FIG. 1). At 5 years, ipilimumab treatment increased both RFS and overall survival by 11%[2]. Nivolumab, pembrolizumab, and dabrafenib plus trametinib all seem to provide a greater degree of clinical benefit than ipilimumab. Of note, the data for nivolumab and pembrolizumab are from interim analyses[3,5], with most patients censored after 12–18 months, whereas the ipilimumab[2] and dabrafenib plus trametinib[4] data are reported after the pre-specified number of RFS events had occurred.

In the direct comparison performed in CheckMate 238 (REF.[3]), nivolumab was found to be superior to ipilimumab (FIG. 1). In this trial[3], RFS was lower than in the other three RCTs because the trial population had a poorer prognosis (stage IIIB, IIIC, or IV versus stage IIIA (diameter >1 mm), IIIB, or IIIC disease). Interestingly, 18-month RFS in the placebo arms of the EORTC 18071, COMBI-AD, and KEYNOTE-054 trials was almost identical (FIG. 1), facilitating cross-trial comparisons. In EORTC 1325/KEYNOTE-054 (REF.[5]), pembrolizumab improved RFS, with an absolute benefit over placebo of 18% at 18 months, compared with the 8% benefit observed with ipilimumab in EORTC 18071 (FIG. 1). These observations support the conclusion that pembrolizumab is also more effective than ipilimumab, in keeping with findings with nivolumab in CheckMate 238. In fact, 18-month RFS with pembrolizumab and nivolumab was virtually identical in the subgroups of patients with stage IIIB–IIIC disease: 72.2% versus 72.3%[3,5].

In COMBI-AD[4], patients with *BRAF*$^{V600E/K}$-mutant melanoma derived substantial benefit from dabrafenib plus trametinib (FIG. 1). Very few patients relapsed within 9 months of treatment with this combination, suggesting an immediate benefit — akin to the very rapid responses observed in the advanced-stage disease setting. With the caveat that the current data are immature, the RFS curve of patients in the dabrafenib plus trametinib arm seems to drop steadily: RFS at 12 months and 18 months is 88% and 73% versus 75% and 71% with pembrolizumab in a similar population (FIG. 1); the RFS curves with pembrolizumab as well as nivolumab drop more rapidly within the first 6 months, but more slowly thereafter. At 18 months, RFS is virtually identical (~71–73%) with all three of these treatments in comparable patient subgroups[3–5]. These patterns are reminiscent of those observed with these treatments in patients with advanced-stage melanoma, whereby the progression-free survival curves cross at 18 months, with the anti-programmed cell death protein 1 (PD-1) antibodies (pembrolizumab and nivolumab) potentially having greater efficacy beyond this point[1]. Whether the latter observation will also be seen in the adjuvant setting is currently uncertain. With regard to distant metastasis-free survival, the hazard ratios are very consistent with the RFS data.

Among the four different treatments, ipilimumab has been associated with highest frequency of treatment-related adverse events (AEs; 94%); immune-related AEs (irAEs) occurred in 90% of patients and were grade >3 in 43% and 5 patients died of colitis, myocarditis, or Guillain-Barré syndrome. By contrast, adjuvant nivolumab and pembrolizumab had very similar and favourable safety profiles, with grade ≥3 treatment-related AEs in ~14% of patients and grade ≥3 irAEs in ~7%. Nivolumab and pembrolizumab have frequently been associated with grade 1–2 thyroid AEs, mostly hypothyroidism in ~20%[3,5]. Of note, anti-PD-1 antibody-induced hypothyroidism can persist and might necessitate lifelong hormone-replacement therapy; however, other endocrinopathies, such as diabetes and hypophysitis, are very rare (grade ≥3: each ~1%)[3,5]. Pembrolizumab was associated with one grade 5 AE (myositis), whereas no fatal toxicity occurred with nivolumab. In COMBI-AD[4], dabrafenib plus trametinib therapy was associated with a higher frequency of AEs than anti-PD-1 therapy, but a lower frequency than with ipilimumab. Dabrafenib–trametinib was associated with pyrexia of grade 1–2 in 97% of patients, with chills in 37%, and of grade ≥3 in 5%; grade ≥3 AEs occurred in 41% of patients overall. Notably, drug-related AEs led to treatment discontinuation rates of 50% with ipilimumab (in EORTC 18071)[2], 26% with dabrafenib plus trametinib[4], and 14% with nivolumab or pembrolizumab[3,5].

Thus, a new adjuvant therapy landscape for high-risk melanoma has emerged with



Placebo (EORTC 18071)	100%	56%	49%	–	–	–	30%	HR 0.76, 95% CI 0.64–0.89
Ipilimumab (EORTC 18071)	100%	65%	57%	–	–	–	41%	
Placebo (COMBI-AD)	100%	56%	49%	44%	39%	–	–	HR 0.47, 95% CI 0.39–0.58
Dabrafenib + trametinib (COMBI-AD)	100%	88%	73%	67%	58%	–	–	
Ipilimumab (CheckMate 238)	100%	61%	53%	–	–	–	–	HR 0.65, 97.6% CI 0.51–0.83
Nivolumab (CheckMate 238)	100%	71%	66%	–	–	–	–	
Placebo (KEYNOTE-054)	100%	61%	53%	–	–	–	–	HR 0.57, 98.4% CI 0.43–0.74
Pembrolizumab (KEYNOTE-054)	100%	75%	71%	–	–	–	–	

Fig. 1 | **Kaplan–Meier curves of estimated RFS in key trials of adjuvant therapies for melanoma**[2–5]**.** RFS, relapse-free survival.

the advancement of pembrolizumab and nivolumab into this setting, with the additional option of dabrafenib–trametinib for *BRAF*$^{V600E/K}$-mutant disease. The effects of these treatments on RFS are so substantial that overall survival benefits are expected; however, only EORTC 1325/KEYNOTE-054 was designed to formally address this question[5]: upon disease relapse, patients from the placebo arm can crossover to receive up to 2 years pembrolizumab treatment, enabling formal assessment of overall survival while also addressing the question of whether adjuvant pembrolizumab for all patients is a better strategy than treating only those who have disease relapse after tumour resection. Overall survival is also the primary end point of the ongoing S1404 trial (NCT02506153), in which pembrolizumab is being compared with adjuvant therapies that were the standard of care at the time of patient accrual (high-dose IFN or ipilimumab).

These recent results put an end to adjuvant therapy with ipilimumab or IFN. In many countries, however, access to the new drugs will remain limited for years; therefore, the use of IFN might continue, but can be restricted to patients with ulcerated stage II–III melanoma, as demonstrated in a number of large trials of IFN versus observation as well as a meta-analysis encompassing all 15 trials of this comparison[6].

In all adjuvant phase III RCTs to date, completion lymph-node dissection (CLND) has been mandatory, but on the basis of the results of the MSLT-II and DeCOG trials[7,8], is no longer considered compulsory. Only 5% of patients with stage III melanoma are upstaged after CLND compared with the use of two other criteria: ulceration versus non-ulceration of the primary tumour and diameter of sentinel node metastasis >1 mm versus <1 mm (REF.[9]); thus, CLND is not necessary for the decision to recommend adjuvant therapy. The RFS of patients with positive sentinel nodes in the nivolumab, pembrolizumab, and dabrafenib plus trametinib RCTs are outstanding[3–5], therefore, recommending adjuvant therapy for these patients without CLND is logical and can reduce the associated risk of morbidity.

Future clinical advances might involve neoadjuvant use of pembrolizumab, nivolumab alone or in combination with ipilimumab, or a BRAF–MEK inhibitor combination, especially for patients with stage III disease and palpable nodes. Impressive results have been obtained with the BRAF–MEK inhibitor combination, with a 100% response rate and reduced relapse rates compared with the standard of care[10]. Moreover, neoadjuvant therapy can facilitate surgery, reduce the need for radiotherapy, and improve locoregional control. Anti-PD-1 therapy and the nivolumab plus ipilimumab combination also have evidence of activity in the neoadjuvant setting, but definitive reports have not been published to date.

In conclusion, adjuvant therapy with anti-PD-1 antibodies (nivolumab or pembrolizumab) for patients with melanoma, regardless of mutational status, or with dabrafenib plus trametinib for those with *BRAF*$^{V600E/K}$-mutant disease, are the new standards. Additionally, promising neoadjuvant therapies are in development.

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Competing interests

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