Adjuvant immune checkpoint inhibition (ICI) with anti–PD-1 antibodies in high-risk resected melanoma has improved recurrence-free survival by about 50 percent, but there is still a proportion of patients who develop recurrence despite adjuvant anti-PD1 treatment, many of them unscorable or metastatic disease. Overall, in stage III to IIB around 40% of patients may develop a recurrence according to the long-term result of the KEYNOTE-054 trial. This may occur while still on the 6 months of adjuvant treatment or later in the course of the disease and may be related to late and early late recurrence.

Available data on the efficacy of ICI therapy in advanced patients who have relapsed after anti-PD1 therapy is sparse, and it unclear whether adjuvant pre-treatment with anti–PD1 antibodies would impair IC therapy in patients with metastatic recurrence. This study was performed to evaluate the clinical outcomes of patients with metastatic or non-resectable melanoma treated with or without upfront anti–PD1 monotherapy treatment in the adjuvant setting.

Methods

Cohorts with non-resectable stage III or stage IV melanoma who were treated with non-adjuvant immune checkpoint inhibition after failure from adjuvant anti-PD1 treatment were selected from the EU-MELAReg database. Patients were excluded if they had a usual or minor type of melanoma, while acral and melanoma of unknown primary were included. Both, 1st line anti–PD1 therapy (pembrolizumab or nivolumab) and combined anti–PD1/CTLA4 therapy were included.

Primary outcomes of interest were (1) the overall response rate (ORR) of 1st line ICI treatment and (2) progression-free survival (PFS) from start of non-adjuvant ICI.

Further analysis included stratifications for the time of the preceding recurrence (‘early’: up to 3 months after end of adjuvant treatment) and the impact of several prognostic covariates.

In order to prevent statistical bias from selection of patients, matching was performed with a nearest neighborhood algorithm using Mahalanobis distance as distance metric. Samples were matched for ECOG, AJCC stage, baseline serum LDH, number of metastatic sites, sex, BRAF status, and age and Charlson comorbidity score. The type of 1st line ICI was included as exact 1:1 match.

Results

389 cases with 1st line ICI after failure from adjuvant anti-PD1 therapy were successfully matched with metastatic cases receiving 1st line ICI without adjuvant anti-PD1 treatment (anti-PD1 naive cohort). The goodness of matching is demonstrated by only non-significant differences in key prognostic variables (Table 1) as well as by only small standardized differences in the respective parameters (Figure 3).

Response rates in cases after adjuvant PD1 failure were significantly lower (ORR: 31.6% vs. 69.9%; p<0.0001) than in treatment naive cases (Table 2), which was also reflected in a shorter PFS (6 months vs. 15.5 months; p < 0.0001) (Figure 1).

The results were influenced by the time of the preceding recurrence (ORR: 28.8% in early vs. 38.5% in late recurrences; Figure 4). For the early recurrence, this was most pronounced in recurrence during the first 6 months of adjuvant treatment (Figure 4B).

The effect of decreased response rate in 1st line after failure of adjuvant anti-PD1 could be seen in both, combined anti-PD1/CTLA4 as treatment in single-agent anti–PD1 re-treatment (Figure 6).

Conclusions

Adjuvant pre-treatment with anti-PD1 antibodies was related to an inferior response and progression-free survival in patients with metastatic or non-resectable melanoma receiving ICI in the 1st line setting after failure from adjuvant anti-PD1 treatment. This effect was seen irrespective of whether combined or single-agent ICI or treatment was used. There is no general direct impact of these results on current clinical practice, but it points to the need for further developments of immune-based treatments but may also impact treatment decisions in BRAF V600D mutated cases.

A major limitation of our study is the observational nature of our database and despite matching a major differences persisted in follow-up times of both cohorts (Figure 1). In order to check whether this could have biased our findings, we reproduced the procedure for patients with 1st line BRAF/MEK therapy. Notably, there was no evidence of bias due to different follow-up times as shown by the analogous Kaplan-Meier analysis with unstrapped efficacy of BRAF/MEK inhibition after adjuvant anti-PD1 failure (Figure 7).

In conclusion, the potential of ICI in metastatic disease may be impaired by preceding adjuvant ICI in high-risk melanoma.