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Activity and safety of first-line treatments for advanced melanoma: a network meta-analysis

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BACKGROUND

Treatment options for advanced melanoma have increased with the Food and Drug Administration (FDA) approval of the anti-LAG3 and anti-PD-1 relatlimab/nivolumab combination. To date, ipilimumab/nivolumab is the benchmark of overall survival (OS), despite a high toxicity profile. Furthermore, in *BRAF*-mutant patients, BRAF/MEK inhibitors and the atezolizumab/vemurafenib/cobimetinib triplet are also available treatments, making the first-line therapy selection even more complex. To address these issues, we conducted a systematic review and network meta-analysis comparing the activity and safety of ipilimumab/nivolumab with relatlimab/nivolumab and all the other available first-line treatment options in metastatic melanoma.

METHODS

Randomised clinical trials (RCTs) of patients with unresectable stage III or IV, previously untreated melanoma, were included if at least one intervention arm contained a targeted (BRAF with or without MEK) or an immune checkpoint (CTLA-4 or PD-(L)1) inhibitor. The aim was to indirectly compare the ICIs combinations ipilimumab/nivolumab and relatlimab/nivolumab, and these combinations with all first-line treatment options for advanced melanoma (irrespective of BRAF status) in terms of activity and safety. The co-primary endpoints were progression-free survival (PFS), overall response rate (ORR), and grade ≥3 treatment-related adverse events (≥ G3 TRAEs) rate, defined according to Common Terminology Criteria for Adverse Events (CTCAE). PROSPERO registration number: CRD42022303279.

RESULTS

A total of 9070 patients treated in 18 RCTs of metastatic melanoma were included in the network meta-analysis (**Figure 1**).

No difference in the risk of disease progression (**Figure 2**) and response (**Figure 3**) between ipilimumab/nivolumab and relatlimab/nivolumab was observed (HR=0.99 [95%CI 0.75 – 1.31] and RR=0.99 [95%CI 0.78 – 1.27], respectively).

The PD-(L)1/BRAF/MEK inhibitors triplet and BRAF/MEK inhibitors combinations were superior to ipilimumab/nivolumab in terms of PFS (HR=0.56 [95%CI 0.37 – 0.83] and HR=0.73 [95%CI 0.50 – 1.06], respectively) (**Figure 2**) and ORR (RR=3.07 [95%CI 1.61 – 5.85] and RR=2.99 [95%CI 1.58 – 5.67], respectively) (**Figure 3**).

Ipilimumab/nivolumab showed the highest probability to have the highest risk of developing ≥ G3 TRAEs. Relatlimab/nivolumab trended to a lower risk of ≥ G3 TRAEs (RR=0.71 [95%CI 0.30 – 1.67]) vs. ipilimumab/nivolumab (**Figure 4**).

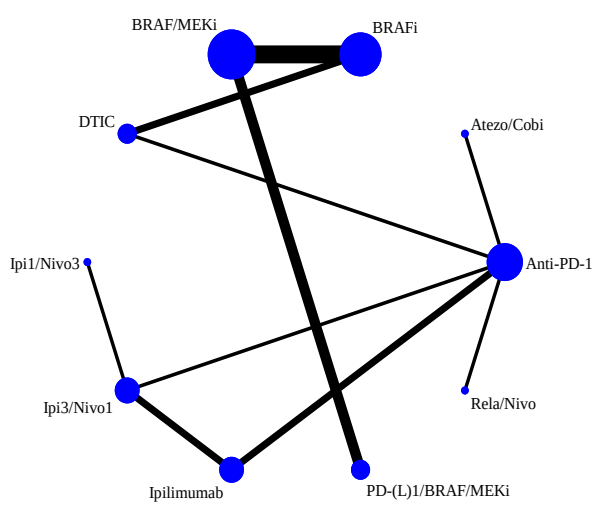

Figure 1. Network of evidence per treatment class for progression-free survival, overall response rate and safety.

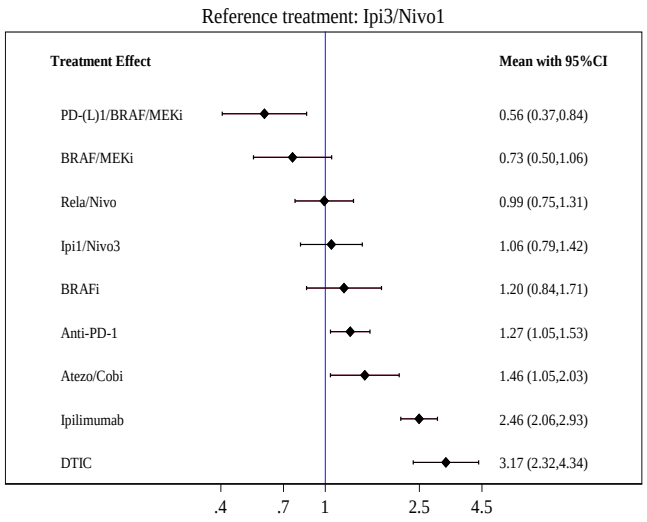

Figure 2. Forest plot of hazard ratios for **progression free survival** of all treatment classes versus reference treatment ipilimumab 3 mg/kg plus nivolumab 1 mg/kg.

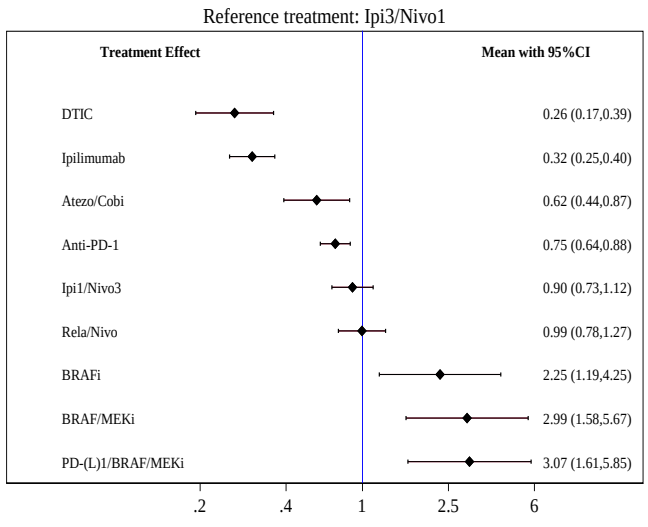

Figure 3. Forest plot of risk ratios for **overall response rate** of all treatment classes versus reference treatment ipilimumab 3 mg/kg plus nivolumab 1 mg/kg. RR <1 favours ipilimumab 3 mg/kg plus nivolumab 1 mg/kg.

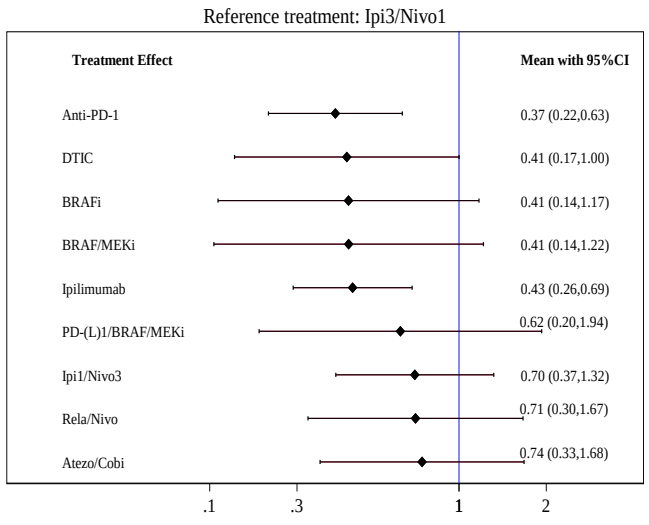

Figure 4. Forest plot of risk ratios for **≥ grade 3 treatment-related adverse events** of all treatment classes versus reference treatment ipilimumab 3 mg/kg plus nivolumab 1 mg/kg. RR >1 favours ipilimumab 3 mg/kg plus nivolumab 1 mg/kg.

CONCLUSIONS

Relatlimab/nivolumab showed similar PFS and ORR compared to ipilimumab/nivolumab, with a trend for a better safety profile. The triplet combinations were superior to ipilimumab/nivolumab in terms of both PFS and ORR. These results should take into account the absence of a comparison in terms of survival.

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