Introduction

The treatment landscape in metastatic melanoma has recently expanded with the FDA approval of the combination of anti-LAG3 and anti-PD-1 relatlimab/nivolumab. To date, the treatment demonstrating the best overall survival results is ipilimumab/nivolumab, despite a high toxicity profile. Furthermore, in BRAF-mutant patients, BRAF/MEK inhibitors combinations and the atezolizumab/ vemurafenib/cobimetinib triplet are also possible treatments of choice, making the selection of the best first-line therapy even more complex.

To address the complexity of first-line treatment choices, 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

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-L1) inhibitor.

The aim of our study was to indirectly compare the ICIs combinations ipilimumab/nivolumab and relatlimab/nivolumab, and both these combinations with all possible first-line treatment options for advanced melanoma (irrespective of BRAF status) in terms of activity and safety.

The co-primary endpoints were PFS, ORR, and grade ≥3 TRAEs rate, defined according to Common Terminology Criteria for Adverse Events (CTCAE). PROSPERO registration number: CRD42022303279.

Results

1. A total of 9070 patients treated in 18 first-line clinical trials of metastatic melanoma were included in the network meta-analysis (Figure 1).

2. No difference in PFS nor ORR 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). (Figure 2 and Figure 3)

3. The PD-(L)1/BRAF/MEK inhibitors triplet was superior to ipilimumab/nivolumab in terms of PFS (HR=0.56 [95%CI 0.37 – 0.84]) and ORR (RR=3.07 [95%CI 1.61 – 5.85]). (Figure 2 and Figure 3)

4. Ipilimumab/nivolumab showed the highest probability of grade ≥3 TRAEs. Compared to the reference treatment ipilimumab/nivolumab, the PD-1 inhibitor monotherapy had the best safety profile (RR 0.37 [95%CI 0.22 – 0.63]), and relatlimab/nivolumab showed a trend to a lower risk of grade ≥3 TRAEs (RR=0.71 [95%CI 0.30 – 1.67]) (Figure 4).

Conclusions

- Compared to the ipilimumab/nivolumab combination, relatlimab/nivolumab showed similar PFS and ORR, while the PD-(L)1/BRAF/MEK inhibitors triplets showed the most favourable outcomes in terms of PFS and ORR.
- The ipilimumab/nivolumab combination was the least favourable treatment in terms of safety, while the PD-1 inhibitor monotherapy showed the most favourable safety profile.

Abbreviations CI: confidence interval; HR: hazard ratio; FDA: Food and Drug Administration; PFS: progression-free survival; ORR: overall response rate; RCT: randomized clinical trial; RR: risk ratio; TRAE: treatment-related adverse event.


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