Editorial Commentary

Lessons from clinical trials on triple combination of immune checkpoint inhibitors and BRAF/MEK inhibitors in BRAF-mutant melanoma

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Immune checkpoint inhibitors (ICIs) and BRAF/MEK-targeted therapies have dramatically improved the prognosis of patients with unresectable or metastatic melanoma since the 2010s, and now, patients in good condition can expect a 5-year overall survival (OS) rate of 50% or more (1-3). Among ICIs, combined nivolumab plus ipilimumab therapy is considered the most promising therapy according to current long-term use data, with a reported overall response rate (ORR) of 58% and a median OS of 72.1 months (1). Among targeted therapies, the combination of dabrafenib plus trametinib is the most widely used, with a high ORR of 68% and a favorable 5-year OS rate of 71% for the 19% of patients who achieve complete response (2). However, the median progression-free survival (PFS) for all patients is only 11.1 months, and the response is not sustained for the majority of patients (2).

The choice of ICIs or targeted therapies as the first-line therapy has been frequently debated, and recently the results of two important clinical trials have been published: the DREAMseq (4) trial and the SECOMBIT trial (5). Both of these demonstrated better OS for melanoma patients treated with a first-line combination of nivolumab and ipilimumab therapy. The Kaplan-Meier OS curves for these trials reflect the characteristics of targeted therapies, which have a high response rate but a short response duration, and ICIs, which have a relatively low response rate but a long response duration. To maximize the benefits of both treatments, the possibility of combining them has been explored.

Several preclinical and translational studies have suggested synergistic effects of the combination of ICIs and targeted therapies (6-10). Following this evidence, the KEYNOTE022 (pembrolizumab or placebo with dabrafenib and trametinib, phase II) (11), IMspire150 (atezolizumab or placebo with vemurafenib and cobimetinib, phase III) (12), and COMBI-i (spartalizumab or placebo with dabrafenib and trametinib, phase III) (13) studies have investigated the clinical efficacy of a triple combination of an ICI plus targeted therapy of a BRAF inhibitor and a MEK inhibitor in patients with advanced BRAF-mutant melanoma. In each trial, the treatment group received an ICI and targeted therapy, while the control group received a placebo and the same targeted therapy. The KEYNOTE022 study and the COMBI-i study did not meet the primary endpoint of PFS, but the IMspire150 study did meet the primary endpoint of the investigator-assessed PFS (15.1 *vs.* 10.6 months, hazard ratio 0.78, 95% CI: 0.63–0.97, P=0.025). However, no statistical significance was observed when the PFS was assessed by an independent review (P=0.16). A similar trial of triple combination therapy, STARBOARD, is under way, but it is unique in that it does not use targeted therapy for the control arm (14). In a short-term PFS comparison, the

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high response rate of targeted therapies will probably favor the treatment arm. However, the fact that previous studies have already shown a small additional benefit and increase in toxicity of triple therapy should make doctors cautious when interpreting the results.

The latest subgroup analysis of the COMBI-i study presented in 2022 showed that clinical characteristics, such as ECOG PS 1, age ≥65 years, negative PD-L1 status, sum of lesion diameters ≥66 mm at baseline, and metastatic sites ≥3 were associated with prolonged OS for the triple-therapy arm (15). The COMBI-i trial has consistently shown a higher frequency of dose reductions and discontinuations due to treatment-related adverse events (AEs) in the triple-therapy group than in the control group. The dose reduction rates of dabrafenib and trametinib due to AEs were 47.2% and 45.7% in the triple-therapy arm *vs.* 25.4% and 25.4% in the control arm. The discontinuation rate of all trial drugs due to treatment-related AEs was 13.5% in the triple-therapy arm and 8% in the control arm (15). Even so, it is noteworthy that there may be a group of patients for whom triple therapy is more effective. The characteristics of the patient groups that benefited from triple therapy in the COMBI-i study were not consistent with the subgroup analysis of KEYNOTE022 (16). As more data is gathered in the future and further post-hoc analyses are reported, it may be possible to predict which patients will benefit from triple therapy.

In the discussion section of the first report on the COMBI-i trial, the authors made the very interesting suggestion that the investigators' experience in managing targeted therapies may have led to differences in how AEs, including pyrexia, were handled, resulting in the better-than-expected outcomes in the control arm (13). In fact, although simple numerical comparisons are impossible because these clinical trials are different, the COMBI-i and COMBI-d/v trials showed that patients treated with the combination of dabrafenib and trametinib had a median PFS of 12.0 and 11.1 months, and a 2-year PFS rate of 36% and 31%, respectively (2,13). Furthermore, although the impact of the dramatic evolution of second-line therapies for advanced malignant melanoma should be taken into account, a comparison of the two trials shows a 2-year OS rate of 61.9% *vs.* 44%, and a 3-year OS rate of 52.9% *vs.* 37% for patients treated with dabrafenib plus trametinib (13,15).

As described above, treatments for malignant melanoma have changed dramatically in recent years, but it is inevitable that the patient's condition and the treatment strategy will differ between clinical trials and actual clinical practice. In actual clinical practice, there are many different parameters for each patient, such as the effectiveness of prior adjuvant therapy, metastatic lesions including brain metastases, and pre-existing medical conditions; also, clinicians go through a process of trial and error to see how well the results of clinical trials apply to the patient in front of them. Findings from actual clinical practice are crucial for the appropriate use of new therapies.

Unfortunately, the results of clinical trials reported to date suggest that the combination of ICIs and targeted therapies is still difficult to apply in clinical practice. However, there is no doubt that both treatments play an important role in the treatment of patients with advanced malignant melanoma, and the possibility of combining these treatments should continue to be investigated. Protocols that allow for the appropriate management of adverse events and the avoidance of dose reductions or discontinuations may further enhance the therapeutic effectiveness of combination therapy. To this end, post-hoc analyses of these trials are warranted, including a search for further biomarkers and clinical trials with more restricted populations.

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