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## RESIDENT'S FORUM

### [Translated article] RF – Can Targeted Therapy Be Combined With Immunotherapy for Melanoma?



### FR – ¿Es posible combinar la terapia diana y la inmunoterapia en el tratamiento del melanoma?

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Target therapy

#### PALABRAS CLAVE

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Inhibidores del punto de control inmune;  
Terapia dirigida

Immunotherapy and targeted therapy have revolutionized the treatment of advanced melanoma in the past decade.<sup>1</sup> Targeted therapy is only useful in patients with *BRAF*-mutated melanoma. Three combinations of *BRAF* and *MEK* inhibitors are available: dabrafenib/trametinib, vemurafenib/cobimetinib, and encorafenib/binimetinib.<sup>1,2</sup>

One of the main advantages of targeted therapy is its rapid action, whilst its main drawback is a progressive loss of effectiveness, with less than 20% of patients maintaining response 2 years after treatment initiation.<sup>2</sup>

In immunotherapy, immune checkpoint inhibitors (ICIs) are used to stimulate the immune system.<sup>1,2</sup> Three ICIs are approved for use in melanoma: ipilimumab, nivolumab, and pembrolizumab.<sup>1,2</sup> ICIs provide better long-term effectiveness, but they are associated with slower responses and possible immune-mediated adverse events.<sup>1,2</sup>

The possibility of combining targeted therapy – to induce a faster response – and immunotherapy – to maintain this response – is clearly tempting, but is this simultaneous use of therapeutic classes, known as triple or triplet therapy, feasible?

The phase 2 KEYNOTE 0223 trial in which patients were randomized to receive dabrafenib/trametinib plus either pembrolizumab or placebo was the first trial to evaluate triplet therapy.<sup>3</sup> The results for the triplet therapy arm showed no improvements in overall survival, a nonsignificant improvement in disease-free survival,

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and greater toxicity (58.3% of patients experienced grade 3 or higher adverse events). Very similar results were observed in COMBI-1, a phase 3 trial comparing triplet therapy with dabrafenib/trametinib plus spartalizumab (an anti-programmed death receptor 1 antibody) vs. dabrafenib/trametinib.<sup>4</sup> Subgroup analyses, however, showed better disease-free survival for triplet therapy in patients with characteristics indicative of a higher tumor burden, possibly justifying the risk–benefit ratio of this treatment.

In the phase 3 IMspire150 trial, the only trial to date to demonstrate the superiority of triplet therapy,<sup>5</sup> patients were randomized to receive vemurafenib/cobimetinib plus atezolizumab (an anti-PD-1 ligand 1 inhibitor) or placebo. The findings showed an improvement in median disease-free survival (15.1 months for triplet therapy vs. 10.6 months for placebo) and an initial improvement in overall survival. The adverse effects were similar in both groups, with a respective 79% and 73% of patients experiencing grade 3 or higher adverse effects.

Toxicity appears to be the main limiting factor for triplet therapy. Sequential rather than simultaneous use of these drugs has been proposed as a means of overcoming this limitation, with several trials currently exploring sequencing options for different combinations of immunotherapy and targeted therapy. The recent findings of the phase 2 SECOMBIT6 trial showed that sequential treatment using a “sandwich” strategy consisting of 8 weeks of induction therapy with encorafenib/binimetinib followed by ipilimumab and nivolumab was associated with better 3-year overall disease-free survival (54%) than either targeted therapy (41%) or immunotherapy (53%). Although immunotherapy followed by targeted therapy appears to achieve better results than the other way round, in certain cases where a rapid response is needed, it might be better to start with a short round of targeted therapy and then use immunotherapy for maintenance.

The need for continued investigation of the potential benefits of triplet therapy and sequencing strategies will

largely be determined by the emergence of new drug combinations that are both safer and more effective than existing options. The promising results reported for relatlimab (an anti-LAG3 antibody)<sup>6</sup> plus nivolumab may also cause a shift in interest from triplet and sequential therapy.

## Conflicts of interest

The authors declare that they have no conflicts of interest.

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