

## Immune Suppression and Response to Ipilimumab: Assessing Risk-to-Benefit Ratio

**TO THE EDITOR:** In their recent article, Horvat et al<sup>1</sup> evaluated the effects of immune-related adverse events (irAEs) in about 300 patients with metastatic melanoma treated with ipilimumab. In recent years, accumulating data suggested that ipilimumab supports the activation of the immune system, thus promoting antitumor immunity.<sup>2,3</sup> However, immune system activation may induce in turn normal tissue injury (ie, irAEs), which occurs in about 60% to 80% of patients treated.<sup>1,2</sup> The authors observed that both irAEs (any severity) and the administration of systemic immunosuppressive therapies (ie, corticosteroids) did not influence survival outcome.<sup>1</sup> This information is useful in clinical practice for patients affected by metastatic melanoma treated with ipilimumab, in whom corticosteroid use is generally avoided.<sup>1</sup>

However, the following points of this paper deserve to be addressed. There is growing evidence showing that an (excessive) activation of the immune response, leading to immune-related toxicities, is associated with an improved response to immunotherapy.<sup>3,4</sup> By this point of view, it would be interesting to assess the prognosis of patients who experienced severe irAEs with corticosteroid rescue. In addition, the authors should clarify if the patients with irAEs achieved a response to ipilimumab before the start of corticosteroid rescue. In the latter case we can hypothesize that, when an efficient immune reaction is activated by ipilimumab, administration of immunosuppressive therapies does not influence response to treatment. In fact, although the efficacy of systemic steroids in suppressing immune response is well known, the kinetics of development (time and dose relation) of such immunosuppressive effect are not completely clear.<sup>5,6</sup> In this regard, knowledge of the schedule and the dose of corticosteroid that had been used would be useful information.

Improving knowledge of the relationship between systemic immune activation and clinical responses to immune therapies would be helpful from a clinical point of view. In fact, an effective immunotherapy should be continued even if patients experience irAEs, making rescue with corticosteroids not harmful for their activity. Further attempts are needed to improve the care of patients and their quality of life.

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### AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at [www.jco.org](http://www.jco.org).

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