

Checkpoint inhibitors are a form of immunotherapy that have revolutionized treatment for malignant melanoma, resulting in longer survival and better disease control. Multiple autoimmune disorders can occur with the use of checkpoint inhibitors, including severe, potentially fatal neurologic complications. Although neurologic complications are uncommon, their early recognition and treatment is required. The purpose of this article is to present information on neurologic complications of ipilimumab and nivolumab to inform nursing practice. Recommendations for evaluation and treatment of neurologic complications are reviewed.

#### AT A GLANCE

- Immunotherapy has resulted in significantly improved survival rates for melanoma. However, it has caused immune-related neurologic complications.
- The combination of ipilimumab and nivolumab increases the risk of neurologic complications compared to single-drug therapy.
- Prompt recognition and treatment of neurologic complications can decrease mortality.

#### KEYWORDS

melanoma; immunotherapy; side effects; management; neurologic complications

#### DIGITAL OBJECT

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# Neurologic Complications

## Effects of ipilimumab and nivolumab therapy in patients with metastatic melanoma

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**M**elanoma is the fifth most common cancer among U.S. men and women (American Cancer Society [ACS], 2019). In 2019, there will be an estimated 96,480 new cases of melanoma and 7,230 deaths from melanoma in the United States (ACS, 2019). The use of immunotherapy has been one of the most successful approaches for the treatment of advanced melanoma because it enhances the antitumor response. The development of immunotherapy checkpoint inhibitors has led to impressive clinical outcomes, including longer survival rates with the possibility of a cure (Achkar & Tarhini, 2017; Spain et al., 2017).

Immunotherapy stimulates an individual's immune system to destroy cancer cells (Lee, Thomas, & Ng, 2017). The immune system has internal regulatory mechanisms to identify abnormal cells that need to be attacked while protecting normal cells (Bayer et al., 2017). Malignant cancer cells work by taking advantage of the decreased expression of checkpoint proteins (Bayer et al., 2017; Lee et al., 2017). The cancer cells disguise themselves so they cannot be identified, which allows them to multiply. Ipilimumab, nivolumab, and other checkpoint inhibitors prevent cancer cells from using these pathways. The immune checkpoints that are targeted are cytotoxic T lymphocyte-associated antigen 4 (CTLA4), programmed cell death protein

1 (PD-1), and programmed cell death protein ligand 1 (PD-L1).

Checkpoint inhibitors are some of the newest drugs used to treat metastatic melanoma. There are three checkpoint inhibitors approved for use in melanoma: ipilimumab, nivolumab, and pembrolizumab (Bayer et al., 2017; Spain et al., 2017). Combining ipilimumab and nivolumab results in better response rates than either drug alone, but also dramatically increases grade 3 and 4 toxicities (Hodi et al., 2018; Spain et al., 2017) (see Figure 1). Neurologic toxicities are well documented in individuals receiving combination therapy.

Ipilimumab is a human CTLA4 blocking antibody (Bayer et al., 2017; Lee et al., 2017). It binds to CTLA4 and blocks the interaction of CTLA4 with its ligands, cluster of differentiation (CD) 80 and CD86. With the blocking of this pathway, there is an increase in T-cell formation and an antitumor effect (Bayer et al., 2017; Lee et al., 2017).

Nivolumab is a human monoclonal antibody and its action is directed toward the PD-1 receptor (Lee et al., 2017). Nivolumab binds to the receptor and blocks the binding of PD-L1 and PD-L2 (Lee et al., 2017). With this action, T-cell activation and proliferation are disrupted, and an antitumor response is released (Bayer et al., 2017; Carlo, Voss, & Motzer, 2016; Lee et al., 2017).

### Neurologic Complications

The overall incidence of autoimmune neurologic complications associated