CORRESPONDENCE

Nivolumab for Squamous-Cell Cancer of Head and Neck

TO THE EDITOR: A new class of toxic effects has emerged with cancer immunotherapy. Endocrine immune-related adverse events are especially interesting because they are frequent but rarely require the discontinuation of treatment. Moreover, immunotherapy offers a promising model for the study of some autoimmune endocrinopathies that are rare in the general population and whose pathophysiological mechanisms are not fully known. In this regard, precise definitions of endocrine immune-related adverse events in immunotherapy trials are a pending issue in this field.

Ferris et al. (Nov. 10 issue)[1] report the results of nivolumab treatment in patients with squamous-cell carcinoma of the head and neck. They report three possible cases of autoimmune hypophysitis as three separate endocrine immune-related adverse events (hypophysitis, hypopituitarism, and secondary adrenocortical insufficiency). Regarding thyroid-related adverse events, events of "blood TSH [thyrotropin] increased" and hypothyroidism were reported independently. Furthermore, "abnormal thyroid-function test" was considered to be a separate endocrine immune-related adverse event; this ambiguous term could include patients with the sick euthyroid syndrome, which is considered to be a physiological response to illness.[2] These imprecise terms, which have been used recurrently in various studies,[3,4] contribute to the underdiagnosis or overdiagnosis of endocrine immune-related adverse events. These terms hinder the appropriate investigation of endocrine immune-related adverse events, so it would be prudent to avoid them in future trials of cancer immunotherapy.

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TO THE EDITOR: Ferris et al. report promising results from a large, phase 3 trial in which nivolumab outperformed standard therapy in patients with platinum-refractory squamous-cell cancer of the head and neck. However, the monotherapies that were identified as standard treatment (i.e., cetuximab, methotrexate, and docetaxel) led to varied overall survival. Moreover, the median difference of 1.7 months in overall survival between docetaxel and nivolumab treatment was equal to the difference between docetaxel and cetuximab. This finding is further reflected in the nonsignificant

THIS WEEK'S LETTERS

difference between nivolumab and docetaxel in the hazard ratio for death (hazard ratio [in favor of nivolumab], 0.82; 95% confidence interval, 0.53 to 1.28).

Therefore, we believe that it is not correct to conclude that nivolumab is superior to all three drugs that are used in patients with platinum-refractory squamous-cell cancer of the head and neck. Because the overall survival benefit was especially prominent in patients who had not received cetuximab previously, this subgroup is likely to be biologically different from patients who were pretreated with cetuximab. Since the comparison between nivolumab and docetaxel is likely to be underpowered in this study, we believe that this cohort should be expanded to detect the true additive value of nivolumab in this line of treatment.

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THE AUTHORS REPLY: Checkpoint inhibitors are a new class of agents for cancer that restore antitumor immunity, and their efficacy has been shown in a variety of solid and hematologic tumors. Owing to their mechanism of action, they are associated with a unique safety profile, with some adverse events that are thought to be related to autoimmune effects. In our trial (CheckMate 141), standard reporting conventions were followed, as are required in any clinical trial. Adverse events were reported by the treating physician by means of verbatim terms and were categorized with the use of preferred terms in accordance with the *Medical Dictionary for Regulatory Activities*, a clinically validated international medical terminology dictionary. Preferred terms are then grouped according to organ systems (e.g., endocrine) in order to identify relationships to potential class effects. This information may also be useful for the physician when managing adverse events.

Overall survival was the primary end point of the randomized, phase 3 CheckMate 141 trial. The trial was designed and powered to compare the nivolumab group with the standard-therapy group and was not designed to evaluate it against each individual comparator agent. Subgroup analyses, including those according to individual agent in the standard-therapy group, were exploratory in nature, and comparisons were not sufficiently powered for the investigators to draw definitive conclusions. In the overall trial population, nivolumab was associated with significantly longer overall survival, a more favorable toxic-effect profile, and a quality-of-life benefit as compared with standard therapy.

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Acute Pancreatitis

TO THE EDITOR: We would like to emphasize the association between acute pancreatitis and pancreatic cancer, which was not addressed in the review of acute pancreatitis by Forsmark et al. (Nov. 17 issue).[1] In rare cases, acute pancreatitis can be the first presentation in patients with pancreatic cancer.[2,3] We recently found a 0.4% risk of pancreatic cancer during a median follow-up of 55 months after a first episode of acute pancreatitis. The median time between the first episode of acute pancreatitis and the detection of pancreatic cancer, in patients free from chronic pancreatitis, was 12 months. After a first episode of acute pancreatitis without a clear cause, physicians should be aware of the possibility of pancreatic cancer as the underlying disease and patients should undergo follow-up with endoscopic ultrasonography and computed tomography.

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