A Cautionary Note: “Real-World” Toxicity of Checkpoint Inhibitors

Maurie Markman^{a, b}

^aCancer Treatment Centers of America, Philadelphia, PA, USA; ^bDrexel University College of Medicine, Philadelphia, PA, USA

The introduction of checkpoint inhibitors into the systemic antineoplastic armamentarium has resulted in a clinically meaningful impact on both the survival (time to disease progression and overall survival) and quality of life for individuals found to have a number of advanced malignancies (e.g., melanoma, non-small cell lung, renal cell, bladder, and head and neck cancers). While today it remains the minority of patients who will exhibit prolonged disease-free survival following treatment with one of several commercially available checkpoint inhibitors, ongoing research examining a variety of biomarkers continues to improve the ability of clinicians to predict the specific population of individuals most likely to experience clinical benefit from the delivery of this novel class of antineoplastic agents.

Not surprisingly, based on both past experience with cytotoxic chemotherapy and preclinical laboratory investigation, increasing clinical trial data have revealed the superiority of the administration of a combination of immunological agents which individually “target” specific components of pathways revealed to inhibit the immune system from optimally killing tumor cells. Unfortunately, existing data also indicate a marked increase in the risk of serious treatment-related side effects associated with such drug combination approaches [1–3].

In this issue of *Oncology*, Zarrabi and Wu [4] present an analysis of the current published experience with liver toxicity associated with the delivery of the checkpoint inhibitor nivolumab. The overall incidence of aspartate

aminotransferase (ALT) elevations, a well-established liver function test, following single-agent nivolumab administration was 4% (95% confidence interval 2.6–6.1%). However, when combined with a second checkpoint inhibitor (ipilimumab), the incidence increased to >25%. It is also relevant to acknowledge here that while liver toxicity may be reversible and often only a laboratory test abnormality, serious liver dysfunction can occur.

Centers with considerable experience dealing with the side effects associated with the delivery of combination checkpoint inhibitors have noted a high risk of serious toxicity, including required hospitalizations and emergency room visits [3]. However, it can be anticipated that when patients are treated in the real-world setting outside the realm of clinical trials (e.g., older patients, patients with existing clinically relevant comorbidities, etc.) and where there is considerably less experience with the management of complex immunological side effects (e.g., colitis, thyroiditis, hepatitis, carditis, or severe skin rashes) treatment-related morbidity and even mortality will become even more of an issue [5].

It will be important that future research document the clinically relevant magnitude of the side effect profile of individual checkpoint inhibitors and combination regimens (both currently employed and proposed for future use) and that the clinical research community works to develop strategies to mitigate or minimize these negative effects of this highly beneficial approach to cancer management [6].

References

- 1 Sznol M, Ferrucci PF, Hogg D, et al: Pooled analysis safety profile of nivolumab and ipilimumab combination therapy in patients with advanced melanoma. *J Clin Oncol* 2017;35:3815–3822.
- 2 Hammers HJ, Plimack ER, Infante JR, et al: Safety and efficacy of nivolumab in combination with ipilimumab in metastatic renal cell carcinoma: The CheckMate 016 study. *J Clin Oncol* 2017;35:3851–3858.
- 3 Shoushtari AN, Friedman CF, Navid-Azarbaijani P, et al: Measuring toxic effects and time to treatment failure for nivolumab plus ipilimumab in melanoma. *JAMA Oncol* 2018;4:98–101.
- 4 Zarrabi K, Wu S: Risk of liver toxicity with nivolumab immunotherapy in cancer patients. *Oncology* 2018, DOI: 10.1159/000486679.
- 5 Topalian S: Targeting immune checkpoints in cancer therapy. *JAMA* 2017;318:1647–1648.
- 6 Postow MA, Sidlow R, Hellmann MD: Immune-related adverse events associated with immune checkpoint blockade. *N Engl J Med* 2018;158–168.