

## Selecting Patients for Combination Immunotherapies

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**R**ecent advancements in the understanding of the genetic, molecular, cellular, and immunologic features of tumors have led to a remarkable evolution in the way we think about and approach cancer treatment. The discovery of immune checkpoint blocking drugs, which act on a patient's innate immune

*How are you educating your patients and their loved ones to recognize and report symptoms related to their IO treatment? How do they know who to call and when?*

system and stimulate T cells to recognize and attack cancer cells, have offered the promise of durable treatment for tumors that were previously felt to be incurable. Since 2014, six immune checkpoint inhibitor drugs have been approved by the U.S. Food and Drug Administration for the treatment of 13 different tumor types, including 2 approvals for the use of these drugs in combination with other immunotherapeutics. The use of immune checkpoint blocking drugs such as the CTLA-4 inhibitor, ipilimumab, in combination with the PD-1 inhibitor, nivolumab, for the treatment of metastatic melanoma has been shown to increase response rates by a modest 14% over the use of nivolumab alone (57.6% vs. 43.7%) per the Checkmate 067 trial. However, this increased efficacy comes at the cost of increased toxicity with a severe (grade 3 and 4) treatment-related adverse event rate of 55% in the combination group compared to 16.3% for nivolumab alone. My clinical experience has reflected that about 50% of patients receiving combination immune checkpoint blockade for the treatment of melanoma require hospital admission for the management of acute, life threatening immune-related toxicity. Given the high rate of toxicity,

careful clinical assessment must be undertaken to select patients that are both fit and appropriate for combination treatments.

Our understanding of biomarkers to predict response to immune checkpoint blockade is rapidly evolving. When considering a patient for combination immunotherapy one must take into account relevant biologic, immunologic, and genetic determinates of response. PD-1 and PD-L1 antigens remain inconsistent markers for predicting which patients will or will not show a response to anti-PD-1 drugs; however, data suggests that PD-L1 status should be considered when deciding which patients may benefit from the addition of a second immunotherapy agent. In the case of melanoma, the PD-L1 <5% population seems to benefit from the addition of ipilimumab to nivolumab compared to nivolumab alone. Tumor mutational burden (TMB) is rapidly gaining acceptance as a more robust clinical marker for response to checkpoint blockade and has been shown in lung cancer to select for a subset of tumors more likely to respond to combination immunotherapy. General "fitness" of a patient to receive treatment must be considered. In my practice, a patient who is ambulatory < 50% of the waking day is not fit enough to receive combination immunotherapy. In today's clinic the most relevant predictor of well-being while receiving combination therapy is a patient's understanding of immune related toxicity and ability to promptly recognize and report adverse events to the clinical team. A forthright conversation between the treating clinician, patient and family members on the importance of self-reporting adverse events must take place prior to consideration of combination immunotherapy.



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