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The standard of care for the treatment of patients with metastatic melanoma has changed fundamentally based on two new treatment strategies that are, conceptually and biologically, largely independent: the blockade of immune regulatory molecules with monoclonal antibodies (termed “immune checkpoint blockade”) and the inhibition of \( BRAF \) V600 mutation–driven mitogen-activated protein kinase (MAPK) signaling using small-molecule kinase inhibitors. Based on improved overall survival documented in phase III trials, the monoclonal antibody ipilimumab (Yervoy) and the tyrosine kinase inhibitor vemurafenib (Zelboraf) received regulatory approval, providing accessible opportunities for patients.[1,2] While the previously established treatments, such as chemotherapy with dacarbazine, biochemotherapy, high-dose interleukin 2 (IL-2), and adoptive T-cell transfer, remain in the therapeutic armamentarium of the clinician treating patients with advanced melanoma, ipilimumab and vemurafenib have become primary treatment modalities due to their proven survival benefits.

Yushak and colleagues provide a comprehensive review of the treatment landscape in melanoma in 2013 and discuss many of the key issues that are important in the clinical and research arenas. As the authors note, there is a striking contrast between the response durability at a modest rate that is achieved with immune checkpoint blockade, and the unprecedented response rates, yet modest durability, seen with BRAF inhibition in \( BRAF \) V600-mutated melanoma. These characteristics define two of the most important challenges for both the clinician and the research community in advanced melanoma treatment today.

For the practicing oncologist, awareness of the different patterns and kinetics of responses, appropriate patient selection, and correct sequencing of treatments are of critical importance. Due to its potential to induce durable benefit, ipilimumab should be considered in the first line (regulatory approval allowing) for patients whose tumors harbor a \( BRAF \) V600 mutation, with the exception of those with rapidly progressing disease or with poor performance status and symptomatic disease who would benefit from rapid palliation. Given the limitations of the currently approved agents (modest response rate with ipilimumab, and near-universal emergence of treatment resistance with vemurafenib), it remains reasonable and necessary that a clinical trial be considered for every melanoma patient at the time of diagnosis of metastatic disease.

Remarkably, within 2 years of the introduction of ipilimumab and vemurafenib into the clinic, major new advances have been reported in both the immune checkpoint blockade and small-molecule kinase inhibition arenas. As Yushak and colleagues discuss, these advances include improved progression-free survival documented with BRAF-plus-MEK inhibition compared with BRAF inhibition alone, and durable objective responses with programmed death 1 (PD-1)/PD-1 ligand (PD-L1) inhibition, which was seen in a higher proportion of patients than has been the case with ipilimumab.[3-5] We envision that this new class of checkpoint inhibitors, as well as combined BRAF/MEK inhibition, will change the standard of care for melanoma patients yet again in the near future.

Several PD-1 and PD-L1 antibodies are currently in different stages of clinical development. As a class, these agents appear to be very well tolerated. Importantly, the anti-PD-1 monoclonal antibody MK-3475, by preliminary report, induced objective responses in a large percentage of patients whose disease had progressed on ipilimumab.[6] However, it appears likely that complementary therapies will be necessary to further improve the benefits of these treatments. Early studies indicate that BRAF inhibition may have a favorable effect on the immune response in the tumor, providing a strong rationale for combined therapy with MAPK inhibition and immune checkpoint blockade.[7-9]
Furthermore, there is preclinical evidence for synergies between cytotoxic T-lymphocyte antigen 4 (CTLA-4) and PD-1/PD-L1 blockade[10]; combined CTLA-4 and PD-1 inhibition, given concurrently and in sequence, is being assessed in clinical trials. Other partnering agents and targets under investigation include cytokines such as interferon alfa (IFN-α), IL-2, and granulocyte macrophage colony-stimulating factor (GM-CSF), as well as anti-angiogenesis and vaccines.

As Yushak and colleagues rightly point out, a challenge for both clinicians and investigators, particularly with regard to patients with BRAF-mutant tumors, is the choice of the most effective and least toxic sequence or combination of active agents. Given the long history of relatively ineffective and fairly toxic therapeutics in melanoma, this is a challenge the melanoma community should be happy to meet.

The development of appropriate biomarkers to help select agents is an area of intense investigation. Early data on tumor PD-L1 expression as a predictive marker for PD-1/PD-L1-directed therapy has shown some promise in the phase I studies, but these results need to be validated prospectively. Tumor PD-L1 expression should also be better defined in terms of what is considered a positive biomarker result (percent cells, membranous vs cytosolic staining, etc, as well as the clinical positive predictive value and negative predictive value) and in terms of the clinical benefit of a response and of prolonged stable disease in this context.

Caution is warranted when developing combined approaches. Inflammatory toxicity is a particular concern with checkpoint blockade and may be increased with a combination of antibodies blocking both CTLA-4 and PD-1/PD-L1. Increased skin toxicity was reported in a series of patients who received vemurafenib after ipilimumab, and the phase I combination study of the two drugs administered synchronously was halted because of liver toxicity.[11,12]

These are certainly exciting times for the melanoma clinical and research communities. The durable responses achieved with PD-1/PD-L1 blockade in multiple tumor types, including lung cancer, suggest that the treatment approach of immune checkpoint blockade first defined in melanoma has broad applicability, a discovery that is particularly exciting for the immunotherapists among us.

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