

# MELANOMA IN FOCUS

Current Developments in the Management of Melanoma

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## Reversing Resistance to Checkpoint Inhibitors and Targeted Therapy in Metastatic Melanoma



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### **H&O** How often do patients with metastatic melanoma experience primary or secondary resistance to checkpoint inhibitors?

**MS** An estimated 40% to 50% of patients with metastatic melanoma experience primary resistance to checkpoint inhibitors, and get little or no benefit from ipilimumab (Yervoy, Bristol-Myers Squibb), pembrolizumab (Keytruda, Merck), or nivolumab (Opdivo, Bristol-Myers Squibb). Of the 50% to 60% of patients who respond initially, approximately 30% experience progression over time. Therefore, approximately 15% of patients overall with metastatic disease end up with secondary resistance at some point. Secondary resistance includes responders who progress while on treatment and responders whose disease progresses at some point after they stop checkpoint inhibitor treatment.

Among patients who initially respond to checkpoint inhibitors but develop disease progression after treatment ends, approximately 15% to 30% may respond to a second course. Not all patients need more checkpoint inhibitors, however. Some patients who experience secondary resistance to checkpoint inhibitors will have long progression-free intervals with salvage radiation or surgery.

### **H&O** What causes resistance to checkpoint inhibitors?

**MS** I do not believe we will know the whole story until we have more data regarding the activity of multiple agents in the resistance setting, and more data from biopsies of resistant lesions. If you can extrapolate from animal models and information from baseline biopsies in treated

patients, several mechanisms could explain resistance or lack of response. Some patients do not have enough T cells in the tumor microenvironment, which may occur if the immune system is not primed adequately. In other patients, the T cells are primed to respond but cannot get in the tumor, for example, because of overproduction of vascular endothelial growth factor (VEGF). There may be metabolic factors that block the function of the T cells. The T cells in the tumor microenvironment could be too far along in the differentiation pathway—they are exhausted. Another possible explanation is that other immune checkpoints besides cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) or programmed death 1 (PD-1)/programmed death ligand 1 (PD-L1) are at work.

Many potential mechanisms of resistance exist, but we do not have very good biomarkers to identify the most critical mechanisms of resistance in any individual patient. These factors make clinical drug development difficult in these patients.

### **H&O** Is there a way to predict which patients will experience resistance to checkpoint inhibitors in melanoma?

**MS** Not with absolute confidence. Measuring levels of PD-L1 is useful in some types of tumors, but not in melanoma because patients who are PD-L1-negative still seem to benefit from anti-PD-1 therapy or from a combination of ipilimumab and nivolumab. Some researchers have looked at T-cell infiltration, but that does not correlate completely with who responds and who does not respond. Tumor mutation burden does not seem to be important in melanoma, but most patients have a high

tumor mutation burden at baseline. Overall, combining PD-L1 status or a T-cell inflamed gene signature with tumor mutation burden appears to distinguish between patients with a higher or a lower chance for response, at least in some tumor types. Some clinical factors are useful; in melanoma, patients with high levels of lactate dehydrogenase (LDH) have a lower chance of responding to checkpoint inhibitors, but some of these patients still derive substantial benefit. Therefore, we do not have reliable predictive biomarkers to tell us who will be a responder and who will be a nonresponder. At best, we can identify a group that has a higher response rate and a group that has a lower response rate.

### H&O How long does it take to determine that a patient is not going to respond to a particular agent in the up-front setting?

**MS** Almost all patients on ipilimumab/nivolumab who are not responding at 12 weeks, which is when most oncologists determine disease stage, are not going to respond. A small number of patients on an anti-PD-1 agent—perhaps 5% to 10% of the overall responders—will demonstrate some form of pseudoprogression, and will have late responses. As noted, patients who are receiving a combination of ipilimumab and nivolumab are unlikely to benefit if they have clear disease progression at week 12. However, not all progression is the same; in mixed responders, the discordant progressing lesions may subsequently regress, or they can be radiated or resected with a chance for long-term benefit.

Some oncologists are starting to perform early biopsies at 3 weeks in the research setting in an effort to predict which patients will respond, but that is not the standard of care at this time.

### H&O What steps can be taken for patients who develop resistance?

**MS** If the tumor has a *BRAF* mutation, BRAF/MEK inhibition can control the disease for some time, although it does not offer a cure. If the tumor is wild-type for *BRAF*, we could look for other mutations that may represent a druggable target. For example, tumors with a *KIT* mutation can respond to KIT inhibitors. But for the patients who do not have a *BRAF* mutation (or BRAF fusion protein) or a *KIT* mutation, no effective standard-of-care second-line therapy exists, particularly if first-line therapy was ipilimumab/nivolumab. If first-line therapy was nivolumab, then a combination of ipilimumab and nivolumab may be effective in the second-line setting.

Several years ago, I would consider chemotherapy for patients with melanoma, but the response rate is so low and the responses are so short-lived that I no longer do. The best

approach is often a clinical trial—we hope that an investigational therapy might be effective. Along these lines, there are reports of activity with tumor-infiltrating lymphocyte (TIL) cell therapy, and occasional responses have been seen with various investigational immune therapies.

### H&O How often do patients with metastatic BRAF-mutated melanoma experience resistance to targeted therapy?

**MS** We generally begin with immunotherapy for metastatic melanoma, and move to targeted therapy only if immunotherapy is ineffective. Most of the available data suggest that immunotherapy is more likely than targeted therapy to cure disease. Targeted therapies are relatively ineffective in patients who have high LDH levels or more than 3 sites of metastatic disease, when considering not just objective response but also durability of response. Initially, the conventional thinking was to start with targeted therapy in patients with a high burden of disease or rapidly progressive disease because it produces such rapid responses, but in the long run patients appear to fare better if we begin with immunotherapy. There are exceptions, of course.

When we treat patients with a combination of a BRAF and a MEK inhibitor as first-line therapy, the response rate is quite high—probably in the 70% range. The rates are similar whether patients are receiving dabrafenib (Tafinlar, Novartis)/trametinib (Mekinist, Novartis), vemurafenib (Zelboraf, Genentech/Daiichi Sankyo)/cobimetinib (Cotellic, Genentech), or encorafenib (Braftovi, Array BioPharma)/binimetinib (Mektovi, Array BioPharma). Very few patients experience primary resistance to targeted therapies, and the progression-free survival (PFS) curves do not fall much at 3 months. Most patients will develop secondary resistance at some point, however, so the overall PFS rate at 5 years is closer to 20%. For patients with high LDH, the PFS rate at 5 years is less than 10%. I do not know what the PFS curves look like over the long-term in patients treated with BRAF/MEK inhibitors who have received initial treatment with immunotherapy.

### H&O What causes resistance to targeted therapy if the patient does have BRAF-mutated melanoma?

**MS** A number of researchers have looked at this question extensively. In most cases, the BRAF/MEK signaling pathway becomes reactivated, which may occur through a variety of mechanisms. To my knowledge, attempts to reverse resistance have not been successful so far. But there are several approaches in clinical trials; one example that is being initiated by investigators at the University of Pennsylvania is adding autophagy inhibitors to treatment.

## H&O How can oncologists adjust treatment in patients who experience resistance to targeted therapy?

**MS** In a research setting, the best approach is to perform biopsies of lesions that are resistant to BRAF/MEK inhibitors, then attempt to determine the mechanism of resistance and enroll patients in trials of agents that could target that specific mechanism. Some patients will have multiple mechanisms of resistance to targeted therapy. One approach is to continue the BRAF/MEK inhibitors in this situation, and enroll the patient in a trial that allows adding an agent. But there is no standard of care, and my impression is that few trials are pursuing this important unmet medical need.

## H&O What other trials of note are looking at overcoming resistance to either immune therapy or targeted agents?

**MS** A recent phase 2 trial presented by Dr Amod Sarnaik at the 2020 annual meeting of the American Society of Clinical Oncology has shown response rates of 36% with adoptive transfer of TILs. Some of these responses are durable, which is an exciting development, but of course this approach is still investigational.

Several investigational immunotherapy agents have shown a small amount of activity in the treatment-resistant setting. Each of these agents has a low or very low response rate. If we had good predictive biomarkers, we could target just those patients who might respond. That would produce higher response rates and could expedite subsequent drug approval studies. There are many agents in trials that are being combined with immune checkpoint inhibitors to improve outcome in the frontline or resistant settings. These include anti-CD40, anti-lymphocyte activation gene 3 (LAG-3) agents, anti-T cell immunoglobulin mucin 3 (TIM-3) agents, and anti-T cell immunoreceptor with Ig and ITIM domains (TIGIT), among many others. There is also substantial interest in agents that are administered by intratumoral injection, such as talimogene laherparepvec, also known as T-VEC (Imlygic, Amgen); stimulator of interferon genes (STING) agonists; and Toll-like receptor (TLRs) agonists.

One of the nice aspects of studying agents in the treatment-resistant setting is that any observed activity is likely a true effect of the investigational agent, especially if the resistance to prior therapy has been verified using strict criteria. If resistance or lack of response to a PD-1 inhibitor was well documented and subsequent activity is demonstrated when a new agent is combined with anti-PD1, there is reasonable certainty that the new agent added is at least contributing to the activity. This is a good

way to pick up signals that are clinically meaningful.

There are pitfalls in evaluating new agents among patients who progress after treatment with standard immune checkpoint inhibitors. As previously discussed, patients who respond, go off therapy, and progress while off treatment have the ability to re-respond to an anti-PD-1 agent. A few patients experience pseudoprogression and can develop late responses. For example, lymph node enlargement may just be an inflammatory response rather than true disease progression. That is why the Society for Immunotherapy of Cancer (SITC) published guidelines in 2020 to better define clinical resistance to anti-PD-1 agents, which will hopefully lead to more informative trials.

### Disclosure

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### Suggested Readings

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