

Treatments and Response Monitoring in Melanoma

In this **CancerNetwork® OncView™** program, faculty panelist John M. Kirkwood, MD, explains the treatment options in this disease space and discusses recent drug approvals.



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In a recent OncView™ program hosted by CancerNetwork®, **John M. Kirkwood, MD**, director of the Melanoma Center at the University of Pittsburgh Medical Center’s Hillman Cancer Center, in Pittsburgh PA, detailed immunotherapeutic and targeted treatment options and response monitoring in patients with melanoma.

To start, Kirkwood acknowledged the development of melanoma therapies over the last 50 years. “It’s become a diametrically opposite situation to what we had just 10 years ago when we were still giving chemotherapy. We were still giving combinations of chemotherapy, which were toxic and had no demonstrable survival benefit in this disease,” he said.

Therapeutic Options in Melanoma

The year 2011 saw the emergence of second-generation checkpoint inhibitors for the treatment of patients with melanoma, which, according to Kirkwood, “became available only a few years after the advent of first-generation [inhibitors]. The benefit was more than several times better, with a response rate of 30% to 40% [compared with] a response rate of 10% [for first-generation inhibitors].”

Outside of single-agent PD-1 inhibitors like pembrolizumab (Keytruda), which is a recommended frontline treatment option for melanoma, or immunotherapeutic combinations, Kirkwood

also focused on therapy selection based on baseline characteristics, namely the presence of a *BRAF* mutation.

For patients with a *BRAF* mutation, the *BRAF*/MEK inhibitor combination of dabrafenib (Tafinlar) and trametinib (Mekinist) have shown a durable survival benefit over 3 years, according to Kirkwood. “The benefit has been one of the truly remarkable stories of progress in this disease in the advanced and adjuvant settings over the past decade,” he said.

Looking again to immunotherapy, Kirkwood reviewed data presented in June 2021 regarding inhibition of LAG-3 with a third-generation checkpoint molecule from the phase 2/3 RELATIVITY-047 trial (NCT03470922). The trial showed a benefit of relatlimab plus nivolumab (Opdivo) vs the PD-1 inhibitor alone for patients with previously untreated or unresectable advanced melanoma.¹

“Now with the second-generation and third-generation agents, and the lesser toxicity seen in RELATIVITY-047, we are able to offer patients benefits that we may have previously thought unattainable from first- and second-generation agents with these second- and third-generation immunotherapies combined,” Kirkwood explained.

When deciding on treatment options, Kirkwood emphasized the need to work with a patient to weigh the safety and efficacy of a particular drug. “It’s a shared journey with the patient, where

we need to go through the description of all of the potential toxicities, all of the potential benefits in terms of [survival]," he described. "Then, we let the patient decide whether they want to pursue a very aggressive therapy with potentially significant immune-related adverse events or a single-agent therapy."

For immunotherapy, specifically with the combination of nivolumab and ipilimumab (Yervoy), Kirkwood focused on the sites of disease for patients with metastatic melanoma.

"The combination of ipilimumab and nivolumab has been shown to have benefits in patients with brain disease similar to the benefits that we've seen in peripheral non-central nervous system disease. That has nudged us all to consider the doublet in the treatment of any patients who have brain disease," Kirkwood explained.

Response Monitoring and Incorporating ctDNA

For monitoring, Kirkwood emphasized the need to watch for toxicities in patients as they continue through their treatments. Additionally, being aware of potential biomarkers for inflammation and immune-related therapy effects remains significant, according to Kirkwood.

Kirkwood also discussed response monitoring, which can be effectively achieved with surveillance of the molecular characteristics in the blood.

"Monitoring the tumor is something that we have considered important [for successful] treatment. One of the truly promising approaches to monitoring disease response in patients, both on targeted therapies and immunotherapies, may be to monitor ctDNA [circulating tumor DNA] in the blood," Kirkwood explained.

Kirkwood said he sees the potential for regularly incorporating ctDNA into monitoring for patients with melanoma, including those with active

measurable disease and those who are in the adjuvant setting where no measurable disease remains.

In patients with active measurable disease, where correlations can be made more quickly because the disease is radiologically accessible, ctDNA allows providers to confirm findings on radiographs and CT and PET scans. However, Kirkwood explained that those in the adjuvant setting stand to gain the most potential benefit from ctDNA monitoring. "If evidence of disease relapse could be monitored [with ctDNA, it has the potential to] indicate the need for additional alternative therapies in a subset of patients who are relapsing," he noted.

Even more, Kirkwood sees the potential to stop therapy early for patients with no clinical evidence of disease progression. "With sensitive molecular markers that are precise, it would be possible to intelligently, rationally approach this and limit the therapy that we're giving to our patients," he speculated.

Ultimately, Kirkwood acknowledged there is still much unknown about ctDNA, specifically how changes in ctDNA levels correlate with patient outcomes like overall or progression-free survival. "That is currently under study, and that's what we need to see in prospective trials," he declared.

Impact of Drug Holidays on Outcomes

To wrap the discussion, Kirkwood touched on the idea of drug holidays and what that means for a patient undergoing therapy.

Specifically, Kirkwood mentioned the SWOG S1320 trial (NCT02196181) that examined intermittent vs continuous dosing of dabrafenib and trametinib. The trial did not show a significant benefit with intermittent treatment vs continuous dosing.²

"We try to limit the period of time

[patients are] off treatment to alleviate the symptoms of fatigue or fever that we see with dabrafenib and trametinib," Kirkwood explained. "Then we can often resume therapy without dose attenuation and carry the patient through the period of treatment, especially in the adjuvant setting where we think perhaps doing this has curative potential."

In terms of its impact, though, Kirkwood still sees some value in a drug holiday when done carefully for patients who are struggling with treatment.

"If a drug holiday winds up being repeated and associated with dose attenuation, it can [cause us to] lose the benefit that we hoped to gain from the BRAF/[MEK] inhibitor pair a patient is being treated with. But when it's done judiciously, it allows the patient to stay with therapy through the entire prescribed period of treatment. The hope is that interruptions, not wholesale and not for long periods of time, may allow the patient to complete therapy," Kirkwood said. ■

REFERENCES

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