Expert Insights on Strategies for Managing Advanced Melanoma With Ryan J. Sullivan, MD

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***AJMC®*: What do you feel is the optimum treatment duration for immunotherapy?**

DR SULLIVAN: The optimal treatment duration depends on several factors, such as single-agent therapy or combination therapy, what immunotherapy agent or agents are being used, etc. The standard therapy with ipilimumab, for example, is 4 doses over 12 weeks. For patients on combination immunotherapy of ipilimumab with nivolumab, we typically treat with combination therapy every 3 weeks for 4 doses followed by single-agent nivolumab. With that said, there are certainly some data showing that a very brief time on therapy is sufficient; however, we do not know what is the optimal amount of time on therapy. There is currently no clear answer to the question of how long do we treat patients who are responding to anti–PD-1 [programmed cell death protein 1] antibody therapy. In my practice, if a patient is receiving anti–PD-1 antibody monotherapy (either upfront or after combination therapy) and is having a complete response, a near-complete response, or a good response, I would generally treat them for 1 year. If they have stable disease, I would consider 2 years of therapy.

***AJMC®*: How and when do you evaluate response to treatment? At what time points do you evaluate response to treatment?**

DR SULLIVAN: In terms of routine surveillance for response, I usually do scans (eg, torso imaging) every 12 weeks or so, unless the patient is in a clinical trial that mandates more frequent imaging or the patient is experiencing symptoms, in which case I would monitor them sooner. If a patient does not have brain metastases, I would conduct a brain MRI every 24 weeks to monitor for any signs of a brain mass.

***AJMC®*: How can we quantify cure rates for melanoma in the advanced setting?**

DR SULLIVAN: It is hard to define which patients are cured in this anti–PD-1 antibody era because there are very little long-term data on efficacy. Long-term benefit is typically measured by a plateaued Kaplan-Meier curve that extends past 5 years. Thus, you may consider it a possible cure if that plateau occurs and it extends beyond 5 years. The "cure" rate for ipilimumab is approximately 20%. Currently, anti–PD-1 antibody monotherapy cure rates are estimated at approximately 30% to 35%, but this is difficult to determine with certainty without longer-term data. With combination immunotherapy or sequential immunotherapy, cure rates are probably 40% or more.

***AJMC®*: What are your thoughts on 5-year survival as a proxy measure for a cure in advanced melanoma?**

DR SULLIVAN: It was a decent number to use when high-dose IL-2 [interleukin-2] was the standard therapy, and I think it is still a fair metric today. We have yet to see a scenario where a 5-year proxy did not predict longer survival. For example, for high dose IL-2 and ipilimumab, a 5-year proxy predicts 10-year survival. I do not think it will be much different with the anti–PD-1 antibodies, but we have not gotten to that point yet. The largest studies currently are still in only the 3- to 5-year range. Currently, we do not have long-term data on the newest agents, which are also the most effective agents. Therefore, I believe that 5-year survival is a reasonable metric to predict where the patient will be at 10 years. »

***AJMC®*: What are the challenges in dealing with mutations that occur in metastatic melanoma?**

DR SULLIVAN: The biggest challenge is determining whether we should only use immunotherapy or consider targeted therapy that blocks the mutations. In melanoma, the most common mutations seen are *BRAF* mutations, so we are deciding between molecular targeted therapy with a *BRAF* mutation inhibitor or immunotherapy. The biggest challenge with having several options is determining whether there is an optimal first-line therapy and whether there is an optimal sequence or combination. These questions are answerable with clinical trials, but there are currently insufficient data to make these determinations. There are some retrospective data available, but not substantial enough to change clinical practice.

***AJMC®*: What do you typically use for treatment in the second-line *BRAF*-mutated population?**

DR SULLIVAN: Generally, if immunotherapy was used [as first-line treatment], then my second-line therapy would usually be BRAF inhibitor therapy, and if I started with a BRAF inhibitor, my second-line therapy would usually be combination immunotherapy. However, it depends on the patient. Most oncologists will give frontline immunotherapy for patients who are *BRAF* mutant. If we happened to start with BRAF inhibitor therapy, we would likely use combination immune therapy as second-line therapy, such as nivolumab plus ipilimumab, if the patient is able to tolerate the therapy.

***AJMC®*: What strategies can be used to overcome mechanisms of resistance to targeted therapy?**

DR SULLIVAN: There are many potential mechanisms of resistance, which makes overcoming resistance challenging. There are strategies to target resistance and strategies to delay resistance. Many resistance mechanisms reactivate the pathway, so one strategy would be to treat with a drug that targets the pathway downstream. There is some data that show ERK [extracellular signal-regulated kinase] inhibitor therapy may be beneficial in some populations. Some resistance mechanisms activate the PI3 [phosphatidylinositol-4,5-bisphosphate 3]-kinase pathway, and there are strategies that target inhibiting that pathway. We are starting to research approaches that target more broadly in the resistance setting as well as the up-front setting. For example, we conducted a clinical trial targeting apoptosis to make the tumors more vulnerable to BRAF inhibition. We have also researched the use of molecular chaperones, such as heat shock protein, to target several potential [resistance] mechanisms.

Another strategy that is being studied in a larger cooperative group is the use of intermittent therapy to delay acquired resistance, which would allow for longer [duration of] therapy. There are preclinical data that show intermittent *BRAF* therapy may be associated with better outcomes versus continuous therapy. Theoretically, if a patient is on therapy without interruption, it is more likely that acquired resistance pathways will develop. Therefore, the rationale behind intermittent therapy is that stopping therapy for a period will limit the growth of cells with the acquired resistance mechanism and allow [therapy-]sensitive cells to repopulate, at which time therapy would be restarted.

***AJMC®*: In patients with metastatic melanoma, what are the most clinically significant adverse events?**

DR SULLIVAN: For *BRAF*-targeted therapy, such as dabrafenib and trametinib, fever syndrome tends to be the most common issue, and it occurs in about half of the patients. There are strategies that minimize the risk, but it is still a major issue. For vemurafenib and cobimetinib, photosensitivity is the major issue, especially in the summertime when patients are frequently outside. However, most adverse events are transient and resolve when therapy is stopped. If they occur, we can hold therapy, reduce the dose, or adjust the schedule.

On the other hand, adverse events related to immune therapy are more complex to manage. We commonly see immune-related adverse events in almost every type of tissue—for example, colitis, hepatitis, nephritis, gastritis, myocarditis. The earlier that immune-related toxicities are diagnosed and managed, the better the outcome for the patient. But the biggest challenge is catching these adverse events early. More resistant toxicities have also been seen in some patients. These adverse events require a team to manage, especially if the patient is on combined immune checkpoint inhibitor therapy. Specialists are often needed to manage these adverse events, including gastroenterologists, rheumatologists, cardiologists, and others. These specialists are heavily invested in trying to learn more about preventing and treating these adverse events so that patients have better outcomes.

***AJMC®*: How do you quantify these adverse events?**

DR SULLIVAN: As far as incidence, we try and document each event either pathologically or radiographically. For example, if it is a rash, we would document it and maybe take a picture to monitor its resolution. If it is itchiness, we would document and quantify how much it is bothering the patient. If a patient has diarrhea, we will document and consider a colonoscopy to rule out colitis.

Methods for determining the severity of the adverse event differ between clinical trials and clinical practices (outside of clinical trials). Clinical trials commonly use the CTCAE [Common Terminology Criteria for Adverse Events] version 4 criteria to quantify the severity. Outside of clinical trials, those categories have less of an impact.

For example, in clinical practice, chronic grade 2 is functionally treated like grade 3 and you may consider treating grade 1 as if it were grade 2 if it was bothersome to the patient. The actual severity level based on CTCAE v4 is less critical in terms of driving management outside of clinical trials; thus, we tend not to give it a grade and instead document the symptoms and frequency of symptoms. We try to ask more relevant questions. For example, are they eating? Do they have pain? Is there blood? These are things that may not fall into the criteria but can be quite actionable even if the patient is not experiencing a lot of diarrhea. The same goes for other toxicities.

***AJMC®*: What types of costs do you see associated with treatment-related adverse events?**

DR SULLIVAN: The biggest cost is hospitalization. Some of these hospital stays tend to be long and can quickly result in a substantial hospital bill. We tend to intervene early with corticosteroids, which are pretty cheap, but may confirm pathology with biopsies, scopes, or imaging. The cost of laboratory tests is not something we think about often, but that can have an impact on overall cost. We would conduct more imaging in patients who are experiencing toxicities. We may have to obtain expensive blood tests in patients with abnormal side effects that we cannot quite characterize, so the cost of diagnostic blood tests can certainly add up. For the patient, I think the biggest cost is the loss of productivity, especially if the patient needs to be out of work for a few weeks.

***AJMC®*: How do you define cost-effectiveness? Do you take into account adverse events when evaluating cost-effectiveness?**

DR SULLIVAN: Cost effectiveness is not a major consideration when we are determining therapy. We do not design our treatment decision making around a cost-effectiveness model in the sense that we do not think about what is the most efficient and least expensive option. We are not thinking about how to apply cost-effectiveness data for a patient population to an individual patient when we are deciding what drug is best for that individual patient.

Determining which treatment to use is more complex than evaluating which agent is more cost-effective. For example, anti–PD-1 antibodies may cause substantial toxicities that require interventions in approximately 20% of patients; however, there is a significant probability the patient will be cured. I believe there is some value in having broader discussions regarding cost-effectiveness. Cost-effectiveness research evaluating these factors may impact and help guide our clinical decisions.

In terms of preventative therapy, there is a great unmet need for methods to identify a patient's risk of toxicity. If we could identify which patients are at high risk of toxicity, we could try to proactively prevent or lessen the toxicity with prophylactic therapy. If a patient is at low risk, we could avoid giving unnecessary and costly prophylactic therapy. We need better data and more research on potential biomarkers that can predict what therapy (eg, single agent versus combination) is optimal for an individual patient and predict which patients are at greater risk for drug toxicity.

To be truly cost-effective, we need data that can guide us in selecting the best agent for an individual patient and help predict the risk of toxicity in a specific patient. Incorporating stop dates into clinical trials can help us determine when to the stop therapy. Also, the development of blood assays and radiographic imaging that are more accurate and less costly would help increase cost-effectiveness.

***AJMC®*: What type of patient outcomes reflect "effectiveness"?**

DR SULLIVAN: The obvious one is overall survival. The patient's quality of life, productivity, and ability to work are important outcomes as well; however, many patients are willing to sacrifice quality of life and productivity if a drug provides them with a higher chance of being cured. In my opinion, survival, productivity, and quality of life are important, but the most important factors are how well a patient tolerates and responds to therapy and their long-term benefits from therapy.

***AJMC®*: How do you evaluate the cost-effectiveness of first-line immuno-oncology monotherapy and combination therapies? How do you evaluate cost-effectiveness of new immunotherapies entering the market?**

DR SULLIVAN: Most oncologists do not think about what is the most cost-effective way of treating our patients. Rather, we would determine the most effective way of treating our patients first and then [factor in cost] later. That may or may not be the "right" approach, but it is the current approach.

It is difficult to think about cost-effectiveness on a single-patient basis. For example, one patient is given single-agent therapy for 12 months and they have a great response with little to no toxicity. Another patient receives 4 doses of ipilimumab or nivolumab, experiences substantial toxicity requiring hospitalization for 2 months, but has a great response and does not require retreatment with ipilimumab or nivolumab. Both scenarios result in a cure and are similarly cost-effective regarding the total cost of drug delivered, but one therapy is obviously better for the patient than the other. It may be preferable to give the 12-month therapy that minimally impacts the patient's quality of life rather than have them come in every 3 weeks. Also, societal costs must be considered along »

with the direct cost of the drug. Substantial societal costs may negate the costs saved with a certain therapy. Toxicity is an important issue with combination therapy and management of toxicities can be costly. If combination therapy with newer agents is more effective and less toxic than current combination therapy options, it could be seen as more cost-effective than current therapies.

AJMC®: How does mutation status (eg, *BRAF* wild-type) impact your evaluation?

DR SULLIVAN: It certainly is a consideration, but when treating a patient with melanoma, most oncologists will start with immunotherapy. There is no consensus on the level of impact *BRAF* status has in selecting first-line therapy. Some of my colleagues strongly believe that patients with a *BRAF* mutation should receive frontline immunotherapy, while others feel less strongly. It is another piece of information that should be taken into account, but there are not enough data to determine how it can be utilized.

AJMC®: How does the use of doublet and triplet regimens fit into current treatment and what are the ideal settings for their use?

DR SULLIVAN: Triplet regimens are only experimental at this point, so they do not exist in a standard-of-care setting. There are insufficient data to determine whether they will have a role in melanoma treatment. Currently, triplet regimens are being evaluated against the standard of care as control and only phase 1 and phase 2 data are available. The limitation with comparing a triplet regimen against standard of care is that it does not take into consideration long-term effects. The influence [triplet therapy] may have on next-line therapy is an important consideration. Right now, there are not enough data to know how to incorporate [triplet therapy] into practice, and it may be a while before we have the answers.

AJMC®: Will there be a greater place for doublets and triplets in the treatment of patients who have relapsed?

DR SULLIVAN: Doublets definitely have a role in that setting. If a patient relapses after PD-1 inhibitor therapy, they may receive nivolumab plus ipilimumab therapy (if they do not have a *BRAF* mutation) or be enrolled in clinical study of a PD-1 agent plus another agent. The ultimate goal for oncologists is to identify the best therapy up front. A combination of immune therapy and targeted agents or different immune agents or different targeted therapy agents has a role in post-frontline therapy. However, the only combination currently available is nivolumab and ipilimumab. Other doublets and triplets are experimental.

AJMC®: What is the role of immuno-oncology in the adjuvant setting? What is the value of immuno-oncology in the adjuvant setting?

DR SULLIVAN: We now have data from 2 compelling phase 3 trials using immune checkpoint inhibitors for patients with melanoma in the adjuvant setting. The older trial evaluating ipilimumab against placebo showed [an] overall survival benefit but severe toxicity in nearly half of patients. The toxicity rate was unpalatable to most of us; thus, ipilimumab was not commonly used when it was approved. The recent CheckMate 238 trial compared adjuvant ipilimumab [with] adjuvant nivolumab in patients with high risk of recurrence. It showed nivolumab was superior from a relapse-free survival point of view. These data are changing the way we think about treatment for patients with high risk of recurrence. Because the duration of treatment was only 1 year, the study's findings are limited to short-term therapy. Patients can invariably relapse and become PD-1 resistant by the time they are diagnosed with metastatic disease. This would essentially be a different disease, newly metastatic melanoma that is PD-1 resistant, a variant that has not been studied in clinical trials. However, the data from this trial are compelling enough that [nivolumab] should be considered as an option for patients with high-risk melanoma.

AJMC®: The eighth edition of the American Joint Committee on Cancer's (AJCC's) Cancer Staging Manual will be implemented on January 1, 2018. Important updates are planned for the staging criterion for T1 tumors and additional evidence-based prognostic factors are incorporated. Please comment on what changes this revision to the AJCC Cancer Staging Manual will bring to treatment and how these changes may potentially affect the cost-effectiveness of therapy.

DR SULLIVAN: Truthfully, it is hard to make that determination at this time. I think from a treatment standpoint, we will be less likely to offer adjuvant therapy for the new stage IIIa because they are low-risk and we will be more likely to offer adjuvant therapy for stage IIId and maybe IIIb and IIIc.

It is important to note that staging systems are always changing. Even this new system is not accurate because it was developed before the anti–PD-1 antibody era and the data come from trials that were treating according to the old staging system. However, it is the best we have, so it is important to consider the data showing benefits in the adjuvant setting to help sort out which patients may benefit.

Another important change that complicates this new staging system is the changes in guidelines regarding which patients should receive [complete] lymph node dissection. This makes staging more challenging in some patients because the true nodal status will not be known in stage III melanoma patients who do not have a completion node dissection. ◆