MELANOMA IN FOCUS

Current Developments in Melanoma

Section Editor: Sanjiv S. Agarwala, MD

New Evidence for Neoadjuvant Therapy in Advanced Melanoma

Sapna P. Patel, MD
Associate Professor
The University of Texas
MD Anderson Cancer Center
Houston, Texas

H&O What was the history behind the SWOG S1801 study that you presented at the most recent European Society for Medical Oncology congress?

SP The benefits of neoadjuvant immunotherapy have been theorized across multiple solid tumors. We hypothesized that we would be able to generate a larger and more diverse population of tumor-specific T cells by administering immunotherapy before removing a tumor, rather than after. The seminal preclinical study that postulated this was by Teng and colleagues in a mouse model of breast cancer. In a pilot study of melanoma patients, Blank and colleagues in the Netherlands randomly assigned 20 patients to either adjuvant or neoadjuvant immunotherapy also found that neoadjuvant immunotherapy led to a much richer expansion of T cells in the blood compared with adjuvant immunotherapy. Leaving a tumor in place educates the immune system to generate an antitumor immune response better than if the tumor was removed first.

This work led to further small, pilot studies investigating the use of neoadjuvant therapy in melanoma. Our goal was to find out if the benefits of neoadjuvant therapy would outweigh any risks that might occur from delaying surgery by 6, 8, or even 10 weeks. These pilot studies included both single-agent immunotherapy and combination treatment with immunotherapy plus BRAF-targeting therapy.

A pooled analysis of 192 patients from 6 clinical trials by Menzies and colleagues for the International Neoadjuvant Melanoma Consortium found that the pathologic complete response (pCR) rate to neoadjuvant therapy was 40% overall, 47% with targeted therapy, and 33% with immunotherapy. The pCR rate correlated with improved relapse-free survival and overall survival, suggesting the use of pCR as an early surrogate endpoint in clinical trials.

S1801 was the first randomized trial designed to investigate whether immunotherapy was more beneficial when given before and after surgery rather than only after surgery. Our hypothesis was that the neoadjuvant/adjuvant use of anti–programmed death 1 therapy would lead to better event-free survival (EFS) compared with the adjuvant-only administration of that same treatment.

H&O Could you describe the design of the SWOG S1801 study?

SP S1801 was a randomized phase 2 study that enrolled patients with stage IIIB to IV resectable melanoma. Patients were randomly assigned in a 1:1 ratio to receive either standard treatment, which consisted of surgery to remove the tumor followed by fixed doses of pembrolizumab (Keytruda, Merck) every 3 weeks for a total of 18 doses; or experimental treatment, which consisted of 3 doses of pembrolizumab, followed by surgery, and then 15 additional doses of pembrolizumab.

One of the factors that makes S1801 important is that it is the first study in oncology to compare 2 groups that received precisely the same treatments—surgery

and systemic therapy—but in a different order. Patients were deemed operable prior to enrollment, and the surgical approach did not change based on the response to neoadjuvant therapy. That is important to note because S1801 was not designed to assess the effects of decreasing or deescalating surgery—we did not want to have that as an additional variable that could affect outcomes. Likewise, the dose and number of cycles of immunotherapy remained consistent in both groups.

Another factor that makes S1801 important is the use of EFS as the primary endpoint, which is not typical in melanoma trials. EFS was measured from the time of randomization to the first protocol-defined event, including documented progression that rendered patients unable to receive planned protocol surgery, failure to begin adjuvant therapy within 84 days of surgery, relapse after surgery, or death from any cause. This study counted melanoma events starting from the time a patient entered the study, whereas every study of adjuvant therapy in melanoma has started the clock postoperatively. Starting the clock postoperatively means you are not including patients who experience disease progression before surgery or before initiation of adjuvant therapy—which may apply to 15% to 20% of the melanoma population. Melanoma studies have never captured that population before.

Our study had an event-driven endpoint, meaning we were waiting for a specific number of events to occur that would achieve statistical significance. For our study, that number was 104 events. We hit that 104 number at just 14.7 months, which is what triggered the final analysis. We found that EFS was statistically significantly longer in the neoadjuvant arm compared with the adjuvant arm, with a hazard ratio of 0.58 and a 2-sided *P* value of .004. Additionally, the 2-year EFS was significantly higher in the neoadjuvant arm than in the adjuvant arm, at 72% and 49%, respectively.

H&O How did the rates of toxicity and adverse events compare between the neoadjuvant and adjuvant groups?

SP Whenever we change standard treatment, we are always concerned that we might be increasing toxicity and adverse events. Our study included 3 settings during which adverse events could occur: the neoadjuvant period for patients who received experimental treatment, the surgical period for all patients (including the postoperative time leading up to adjuvant therapy), and the adjuvant period for all patients.

We saw very limited toxicities during the neoadjuvant period, with less than 2% of patients in that population experiencing a grade 3 or 4 adverse event. A handful of patients experienced immune-related adverse events that delayed surgery, but surgery was rarely canceled for this reason. The main reason for a surgery cancelation in the neoadjuvant arm was a worsening of melanoma, which raises the question of whether earlier surgery would have been beneficial. Most of these cases of worsening melanoma occurred as newly developed distant tumors, which suggests that earlier surgery (local therapy) to address the tumor(s) may not have made a difference because the tumor had already spread.

With this study, we have shown for the first time that we can improve outcomes by using the same treatment as before, just sequenced differently.

The rates of adverse events were identical in the surgical and adjuvant periods. As a result, we can conclude that administering systemic therapy with single-agent pembrolizumab before surgery does not increase the rate of adverse events before surgery or complications during and immediately after surgery. It is important to note this may not be true for all neoadjuvant regimens, as the rate of toxicity is certainly higher with combination immunotherapy.

H&O What makes these results important?

SP With this study, we have shown for the first time that we can improve outcomes by using the same treatment as before, just sequenced differently. The fact that we have not added to the treatment, only re-ordered it, is especially important for those of us who practice in a nationalized health care setting, such as in the United Kingdom, in Australia, and across Europe, where cost considerations play an important role. If we had introduced more or less treatment than the standard of care, that could have led to a change in cost. But in this case, the treatment that improves outcomes is financially identical to the standard of care. This fact makes it much easier for health ministries to adopt this neoadjuvant/adjuvant regimen.

H&O What ongoing studies are looking at the use of neoadjuvant therapy in melanoma?

SP There is an ongoing, phase 3 international study sponsored by The Netherlands Cancer Institute called NADINA, which is similar to S1801 (NCT04949113). In NADINA, 420 patients with stage III melanoma are being randomly assigned to receive either neoadjuvant immunotherapy followed by surgery or up-front surgery followed by adjuvant immunotherapy. Notably, NADINA differs from S1801 in that the response to neoadjuvant immunotherapy can be used to de-escalate surgery and adjuvant therapy. It also allows the option of adjuvant immunotherapy or adjuvant targeted therapy for eligible patients.

H&O What additional studies would you like to see conducted?

SP I would love to see a head-to-head trial of single-agent vs combination treatment in the neoadjuvant setting. Is this a situation where more drugs are better or do more drugs lead to toxicity that delays surgery, leads to the use of immune suppression, and results in worse outcomes? It would also benefit the field to know whether we can offer these patients far less surgery than we are currently performing. In the SWOG S1512 study, which was identical to S1801 except that it enrolled patients with desmoplastic melanoma, 56% of patient experienced a pCR with neoadjuvant pembrolizumab, suggesting that surgery might be able to be eliminated for many patients with desmoplastic melanoma. Dr Kari Lynn Kendra presented the results of S1512 at the 2022 American Society of Clinical Oncology annual meeting.

H&O Is there anything you would like to add?

SP It behooves us to talk about the endpoint of pathologic response, which is a more general term than pCR. A standard measure of treatment response in oncology has been radiographic response, which measures change in tumor burden, but the pooled analysis by Menzies and colleagues for the International Neoadjuvant Melanoma Consortium described the different categories of pathologic response—pCR, pathologic major response, pathologic response, and pathologic non-response. These pathologic response categories can be validated in S1801 and used to design future studies.

Disclosures

Dr Patel has received honoraria from Delcath Systems; has served in a consulting or advisory role to Castle Biosciences, Delcath Systems, Bristol Myers Squibb, Novartis, Pfizer, Immatics, Replimune, Immunocore, and TriSalus Life Sciences; has received research funding from Bristol Myers Squibb, Foghorn Therapeutics, InxMed, Lyvgen Biopharma, Novartis, Provectus, Seagen, Syntrix Bio, and TriSalus Life Sciences; and has received travel, accommodations, or expenses from TriSalus Life Sciences and InxMed.

Suggested Readings

Blank CU, Rozeman EA, Fanchi LF, et al. Neoadjuvant versus adjuvant ipilimumab plus nivolumab in macroscopic stage III melanoma. *Nat Med.* 2018;24:1655-1661.

Kendra KL, *Moon J,* Eroglu Z, et al. Neoadjuvant PD-1 blockade in patients with resectable desmoplastic melanoma (SWOG 1512) [ASCO abstract 9502]. *J Clin Oncol.* 2022;40(16)(suppl).

Liu J, Blake SJ, Yong MC, et al. Improved efficacy of neoadjuvant compared to adjuvant immunotherapy to eradicate metastatic disease. *Cancer Discov.* 2016;6:1382-1399.

Menzies AM, Amaria RN, Rozeman EA, et al. Pathological response and survival with neoadjuvant therapy in melanoma: a pooled analysis from the International Neoadjuvant Melanoma Consortium (INMC). *Nat Med.* 2021;27:301-309.

Patel S, Othus M, Prieto V, et al. Neoadjvuant versus adjuvant pembrolizumab for resected stage III-IV melanoma (SWOG S1801) [ESMO abstract LBA6]. *Ann Oncol.* 2022;33(7)(suppl).