

MELANOMA IN FOCUS

Current Developments in Melanoma

Section Editor: Sanjiv S. Agarwala, MD

Is Neoadjuvant Therapy Ready for Prime Time in Melanoma?



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H&O What is the rationale for using neoadjuvant therapy in solid-organ cancers?

MR Multimodality therapy has been shown to improve treatment outcomes vs surgery alone in the management of most advanced-stage solid-organ cancers that are still surgically resectable. The traditional multimodality care model has been up-front surgical resection followed by systemic adjuvant therapy. Over the last 15 years, however, we have seen a major shift toward the use of neoadjuvant strategies—up-front systemic therapy followed by surgical consolidation—in many solid tumors.

The neoadjuvant treatment strategies that have been established as new standards of care or are being evaluated in clinical trials have been designed so that either all or a portion of the planned systemic therapy is given up-front. In the latter scenario, the response in situ may dictate whether the same systemic therapy or an alternative one will be used in the adjuvant setting; this is often referred to as a “neoadjuvant-plus-adjuvant” or “response-driven” approach.

Neoadjuvant therapy has several advantages over the traditional model of purely adjuvant therapy. First, after the tumor has responded to systemic therapy, a more complete surgical resection may be possible, leading to more durable locoregional disease control and possibly less-extensive surgery. Second, neoadjuvant therapy means earlier treatment of systemic micrometastatic disease, fewer delays in systemic therapy caused by surgical complications, and a higher likelihood of completion of the planned course of multimodality treatment. All these factors translate into the potentially more effective eradication of micrometastatic disease, improving survival

outcomes. Finally, the use of neoadjuvant therapy allows physicians to assess the tumor response to treatment in situ within a short period. If a response to therapy is lacking or disease progresses during therapy, further exposure of the patient to an ineffective therapy can be avoided, limiting toxicity and potentially allowing an effective alternative therapy to be administered before surgery. An observed clinical response supports the use of the same therapy in the adjuvant setting.

Neoadjuvant therapy also permits researchers to acquire a better understanding of tumor biology. The examination of serial biospecimens taken before and during therapy can help identify biomarkers of drug response and resistance and provides a potential pathway for the evaluation and registration of new drugs.

H&O What are the disadvantages of neoadjuvant therapy?

MR One potential disadvantage is that a delay in standard surgical therapy may result in progression of disease and a missed opportunity for a surgical cure. Although progression during neoadjuvant therapy is concerning, it likely reflects unfavorable biology or inherent resistance to systemic therapy. These are the same patients who undergo upfront surgery and then relapse early either before initiation of, or during, systemic adjuvant therapy.

H&O What is the rationale for and status of research on the use of neoadjuvant therapy in melanoma?

MR The current standard of multimodality care for

patients with high-risk melanoma is for them to receive adjuvant therapy with either single-agent checkpoint inhibition or—if they have a *BRAF* V600E or V600K mutation—combination BRAF/MEK inhibition after complete surgical resection of advanced regional (stage III) lymph node or in-transit metastases, or distant (stage IV) oligometastatic disease. Although these approaches have resulted in significant improvements in survival outcomes in comparison with surgery alone—or in comparison with the earlier approved adjuvant systemic therapy regimen of ipilimumab (Yervoy, Bristol Myers Squibb)—a significant percentage of patients will still have a relapse and will succumb to their disease. Therefore, more effective therapy is clearly an unmet need for patients with high-risk disease. Given the recent approval of highly effective combination therapy with systemic agents in the setting of widely disseminated stage IV metastatic disease, the growing off-label use of combination therapies with potential synergy in patients with borderline resectable disease, and the recognized success and approval of neoadjuvant therapy for other solid tumors, a significant interest has developed in neoadjuvant clinical trials.

H&O How did you become interested in neoadjuvant therapy for melanoma?

MR My initial interest in neoadjuvant therapy for melanoma derived from the results of a phase 1 trial of ipilimumab/nivolumab (Opdivo, Bristol Myers Squibb) in patients with stage IV melanoma; these were presented at the 2013 American Society of Clinical Oncology (ASCO) annual meeting and subsequently published by Wolchok and colleagues in the *New England Journal of Medicine*. The patients showed remarkable responses to combination checkpoint inhibition with ipilimumab and nivolumab, which made me think about how valuable it might be to use this regimen as neoadjuvant therapy for patients with advanced stage III disease. It is important to note that the standard adjuvant therapy for melanoma at the time was ipilimumab or high-dose interferon, neither of which was embraced by the melanoma community because of low to moderate efficacy, a questionable effect on overall survival, and significant toxicity. Approximately 2 years after the presentation, our team at MD Anderson had set up 2 randomized phase 2 trials of neoadjuvant therapy in tandem: one comparing combination checkpoint inhibition vs single-agent programmed death 1 (PD-1) inhibition, and one comparing BRAF/MEK inhibition vs up-front surgery plus standard adjuvant therapy for patients with a *BRAF* mutation. By this time, BRAF/MEK inhibition, single-agent checkpoint blockade, and combination checkpoint blockade with ipilimumab and nivolumab had been approved in the setting of stage IV metastatic disease. All of these regimens were identified

as excellent candidates to be studied in the neoadjuvant setting for patients with advanced stage III disease.

H&O What did your study of neoadjuvant BRAF/MEK inhibition study find?

MR Our phase 2 study, which appeared in *Lancet Oncology* in 2018 with Amaria as the first author, looked at BRAF/MEK inhibition in a small number of patients with *BRAF* V600-mutated stage III melanoma; the patients were randomly assigned to either neoadjuvant plus adjuvant dabrafenib (Tafinlar, Novartis) and trametinib (Mekinist, Novartis; n=14) or standard care with up-front surgery followed by adjuvant treatment (n=7). As mentioned earlier, adjuvant therapy was not nearly as effective in 2014, when the study began, as it is now. As a result, we had to halt the trial after an interim analysis showed that the patients who had received surgery followed by adjuvant treatment were doing very poorly, whereas the pathologic complete response (pCR) rate was very high among the patients who had received BRAF/MEK inhibition and was associated with favorable survival.

Shortly after the publication of our trial in *Lancet Oncology*, Long and colleagues in Australia published the results of the NeoCombi trial in the same journal. In this single-arm phase 2 study of 35 patients with *BRAF* V600-mutated stage III melanoma, neoadjuvant dabrafenib plus trametinib led to a complete response according to Response Evaluation Criteria in Solid Tumors (RECIST) in a high proportion of patients; in addition, a high proportion of patients achieved a pCR.

H&O What specific studies have looked at neoadjuvant immunotherapy in melanoma?

MR One hypothesis for the advantage of neoadjuvant over adjuvant therapy that is specific to checkpoint inhibitors is that the presence of an established tumor microenvironment could enhance T-cell activation, improving the effectiveness of the agents. The fact that immunotherapy used only in the adjuvant setting is not exposed to the same established tumor microenvironment because the tumor has already been removed provides further motivation to study checkpoint blockade in the neoadjuvant setting.

Our group at MD Anderson conducted a randomized phase 2 study of neoadjuvant nivolumab alone vs nivolumab plus ipilimumab in 23 patients with high-risk resectable melanoma; this study appeared in *Nature Medicine* in 2018, with Amaria as the first author. We found that the overall response rates and pCR rates were higher with the combination than with nivolumab alone, but at the cost of more frequent and severe toxicity.

The ongoing phase 1b OpACIN study compared

adjuvant ipilimumab and nivolumab with the same agents split between neoadjuvant and adjuvant treatment in 20 patients with stage IIIB melanoma (NCT02437279). According to results that Dr Christian Blank presented at the 2020 American Association for Cancer Research (AACR) annual meeting, a trend was noted toward better estimated relapse-free survival at 3 years with neoadjuvant treatment. An open-label phase 2 study called OpACIN-neo compared 3 neoadjuvant regimens with various combinations of ipilimumab and nivolumab in 86 patients with stage III melanoma. In the same presentation at the AACR annual meeting, Dr Blank stated that OpACIN-neo has strengthened the finding that neoadjuvant ipilimumab plus nivolumab can lead to high pCR rates.

A collaboration among 3 institutions on 3 continents led to the formal establishment of the International Neoadjuvant Melanoma Consortium (INMC) in 2016. We currently have more than 100 institutions as active members and meet twice annually. In 2018, the consortium published a White Paper (with Tetzlaff as the first author) on the pathologic assessment of resection specimens after neoadjuvant therapy for metastatic melanoma, and in 2019 we set forth recommendations to formalize and standardize neoadjuvant clinical trial design; these were published in *Lancet Oncology* in 2019 (with Amaria as the first author).

Another significant INMC clinical research endeavor has been validating the use of pCR as a surrogate endpoint for survival in neoadjuvant studies of melanoma. A pCR likely reflects the extent of eradication of micrometastases. In an analysis by Menzies and colleagues of pooled data from 6 neoadjuvant clinical trials of either checkpoint blockade or BRAF/MEK inhibition in melanoma, 40% of patients had a pCR, which was shown to correlate with improved relapse-free and overall survival. Although any response less than a complete response to BRAF therapy showed little correlation with favorable survival outcomes, even a partial response to immunotherapy was associated with durable favorable outcomes.

Other clinical neoadjuvant trials initiated and supported by the INMC are ongoing. One strategy employs checkpoint inhibition in conjunction with an injectable oncolytic such as talimogene laherparepvec, which is known as T-VEC (Imlygic, Amgen). The idea behind using intratumoral injections of oncolytic therapy before surgery is to enhance T-cell activation in an established tumor microenvironment, attracting cytokines and dendritic cells that can enhance the systemic response to immunotherapy. Injecting oncolytics adds very little toxicity to single-agent checkpoint inhibition, whereas combining 2 checkpoint inhibitors significantly increases toxicity. In a phase 1b/2 study of patients who had stage IV and unresectable stage III melanoma, with some sites

of disease accessible for direct intralesional injection, Chesney and colleagues randomly assigned 198 patients to either T-VEC plus ipilimumab or ipilimumab alone. The overall response rate was significantly higher in the patients in the combination arm than in those in the ipilimumab-alone arm, at 39% vs 18%, respectively. In updated results of this trial, presented at the 2020 ASCO annual meeting, the complete response rate was significantly higher with combination therapy than with ipilimumab alone, at 21% vs 6%, respectively. In addition, complete response was associated with better overall survival in the combination therapy arm. This experience provided the rationale for evaluating the combination in the neoadjuvant setting in patients with resectable stage III and IV disease that had relapsed after adjuvant anti-PD-1 therapy. Because anti-PD-1 agents have replaced the anti-cytotoxic T-lymphocyte antigen 4 agent ipilimumab as the standard adjuvant therapy for patients with resected stage III disease, neoadjuvant trials of nivolumab or pembrolizumab (Keytruda, Merck) plus T-VEC as frontline therapy for patients with resectable stage III disease are currently active.

The most important recent development in neoadjuvant therapy with combination checkpoint inhibition is the addition of the experimental agent relatlimab to nivolumab; this combination of a PD-1 inhibitor and a lymphocyte activation gene 3 (LAG-3) inhibitor is much better tolerated than ipilimumab plus nivolumab. In the phase 2/3 RELATIVITY-047 trial, which was published in the *New England Journal of Medicine* by Tawbi and colleagues earlier this year, median progression-free survival among patients with previously untreated metastatic or unresectable melanoma was 10.1 months with nivolumab plus relatlimab vs 4.6 months with nivolumab alone. We expect to see nivolumab plus relatlimab in the stage IV setting approved in the next few months.

On the basis of the impressive activity of this novel combination, our group at MD Anderson collaborated with Memorial Sloan Kettering on a single-arm study of neoadjuvant plus adjuvant treatment with nivolumab plus relatlimab in 30 patients with advanced melanoma. In results that Dr Rodabe Amaria presented at the 2021 ASCO annual meeting, we found a high pCR rate—59%—with much less toxicity than what is seen with ipilimumab plus nivolumab.

H&O Should overall survival be the gold standard endpoint for neoadjuvant trials?

MR Right now, the US Food and Drug Administration is using disease-free survival as the standard endpoint for the approval of agents in melanoma. An overall survival endpoint is impractical because we have effective therapies that can be used after patients have a recurrence. We do

not really need to demonstrate improved overall survival with neoadjuvant therapy vs standard adjuvant therapy (although this might ultimately be demonstrated) because neoadjuvant therapy offers other advantages. These include the ability to ensure that patients receive as much of their multimodality therapy as possible, better surgical outcomes, and translational opportunities for biomarker discovery. All we need to prove is that neoadjuvant treatment does not have a negative effect on survival outcomes in comparison with current adjuvant therapy strategies.

H&O Are any studies looking at neoadjuvant vs adjuvant treatment in melanoma?

MR The Southwest Oncology Group is conducting S1801, which is comparing neoadjuvant vs adjuvant therapy with pembrolizumab (NCT03698019). This phase 2 trial is designed to randomize patients before treatment begins, as opposed to after surgery. As a result, the investigators can avoid the problem of improving outcomes artificially by screening out patients who have a poor prognosis and will have a relapse after surgery before receiving adjuvant therapy. This is the only fair way to compare neoadjuvant with adjuvant therapy.

H&O Is there any way to predict which patients will respond to neoadjuvant therapy?

MR We know that the first factor to look at is *BRAF* mutation status because combination targeted therapy is approved for use only in patients with a *BRAF* mutation. Patients with a *BRAF* mutation also seem to have a better response to immunotherapy, possibly because they have an elevated mutational burden. *BRAF* mutation status may be an even better marker of response to immunotherapy than programmed death ligand 1 (PD-L1) positivity.

Beyond that, the only way to determine which patients will respond is through biomarker discovery on therapy. It is critical that all neoadjuvant trials include tandem translational research studies that incorporate baseline biopsies, then administer therapy, and then obtain additional tumor tissue biopsy specimens and serum in an attempt to correlate pCR—and ultimately survival—with markers that we identify either before or during therapy.

H&O How has the concept of neoadjuvant therapy been received by the surgical community?

MR There was some resistance initially because of concern about delaying standard surgical resections, which was in part the motivation for the S1801 study design directly comparing neoadjuvant with adjuvant therapy. What is clear is that both surgical and medical oncologists are now

strongly motivated to enroll their patients in clinical trials of neoadjuvant therapy.

H&O Do you consider neoadjuvant therapy to be ready for prime time in melanoma?

MR I consider the standard of care for patients with advanced stage III melanoma to be either enrollment in a clinical trial of neoadjuvant therapy or up-front surgery followed by established adjuvant therapy. So in that sense, neoadjuvant therapy is ready for prime time.

Disclosure

Dr Ross is a member of the global advisory board of MSD, is a paid speaker for MSD and Amgen, and has received a research grant from Amgen.

Suggested Readings

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