IMMUNOTHERAPY HAS REVOLUTIONIZED THE treatment for melanoma, but much of that progress has come among patients who have metastatic disease and are not candidates for surgery. For this group, combination therapy is common and typically lasts 2 years. This means high costs for payer and patient alike, along with months of living with adverse effects that can range from shortness of breath to fatigue to organ dysfunction.1,2

What if some patients with locally advanced melanoma, as opposed to metastatic disease, could get better results by receiving immunotherapy before surgery? Trials involving immunotherapy in the neoadjuvant setting are gaining attention, both with individual agents and with combinations. Results from 3 immunotherapy trials were included in a review article by Liu and Lowe in the December 27, 2018, *Journal of Surgical Oncology,* which also listed 7 more trials in progress.3

Before that review article made it to press, one of those trials made headlines after appearing in *Nature Medicine.*4 The results, the first of their kind, showed what could be possible for patients with high-risk, advanced melanoma if they were treated with immunotherapy before surgery. Investigators at The University of Texas MD Anderson Cancer Center treated 2 small groups of patients with high-risk, stage III melanoma for 8 to 9 weeks before surgery—one with combination ipilimumab with nivolumab and the other with nivolumab only.

Although many patients in the combination arm had strong responses—45% had no sign of disease by the time of surgery—severe adverse effects forced investigators to conclude that the toxicities of this regimen keep it from being the optimal neoadjuvant regimen.

Rodabe Amaria, MD, assistant professor in the Department of Melanoma Medical Oncology, Division of Cancer Medicine, at MD Anderson and a lead author on the study, explained to *Evidence-Based Oncology* in an interview that evidence has been accumulating in preclinical models that neoadjuvant treatment may be superior to treatment after surgery.

A separate review article that Amaria coauthored in 2018 explained the need to build on the success seen with immune checkpoint inhibitors and targeted therapies: “While adjuvant therapies have improved [relapsed-free survival versus] ipilimumab or placebo, up to 50% of patients are still relapsing at 24 months of follow-up. Additionally, patients that present with in-transit or bulky, locally advanced disease are difficult surgical candidates.”5

The study in *Nature Medicine* featured the combination of cytotoxic T-lymphocyte antigen-4 checkpoint inhibitor ipilimumab and the programmed cell death 1 (PD-1) inhibitor nivolumab, which is the current standard of care in metastatic melanoma. Results showed that 8 of 11 patients (73%) who had the ipilimumab/nivolumab combination saw their tumors shrink, and 5 had no evidence of disease by surgery—a pathological complete response (pCR). By contrast, only 3 of 12 patients who were treated with nivolumab (25%) had their tumors shrink and demonstrated pCR, whereas 2 patients reached stage IV disease before they could have surgery.4

In the combination arm, 73% of patients experienced a grade 3 adverse effects, causing some to delay doses or surgery. None had grade 4 adverse effects. In the nivolumab arm, only 8% of patients had grade 3 adverse effects. Patients in both groups received nivolumab after surgery.

As for survival, all who had a pCR remained disease free at the time the study was published. “Overall survival was 100% at 24 months in the combination arm and 75% in the nivolumab arm,” according to a statement from MD Anderson.6

**Trying a New Combination**

Now the MD Anderson team will rework the trial, replacing ipilimumab with a lymphocyte-activation gene 3 (LAG3) inhibitor, a molecule being developed by Bristol-Myers Squibb and described by He et al in *Cancer Science* as “another vital checkpoint that may have a synergistic interaction with PD-1/PD-L1 [programmed death ligand 1].”7

In the interview, Amaria said selecting LAG3 inhibitors made sense for a few reasons: The molecule has had some promising preclinical data, and results from a study involving nivolumab presented for a LAG3 inhibitor showed a 10% response rate for patients with PD-1–refractory disease; although the rate is low, this “is the most important patient population,” she said.8

More important, Amaria said, the study uncovered a biomarker that showed “if you have LAG3-positive T cells, then you may be more likely to respond.”

Because the data looked promising, “there’s more...
work being done in the treatment-naïve setting as well as the refractory setting, and so we thought this would be a good opportunity to explore this combination in the neoadjuvant setting," she said.

**Taking Advantage of Neoadjuvant Trials**

Amaria said clinical trials that treat patients before surgery can offer answers regarding whether a drug works very quickly. Patients are given therapy for 6 to 9 weeks, and investigators then have answers from pathology at the time of surgery. "You get a good sense [of whether] patients are deriving benefit or not, and you can do detailed biospecimen analyses from the blood and tumor that [are] collected," she said. This allows the research team to identify "why some people did well and why some people did not do as well."

The study at MD Anderson yielded a bounty of biomarker data, including evidence that early on-treatment biopsies were more predictive of who would respond to both therapies compared with baseline biopsies.

Some biomarker information turned out not to be as straightforward as it first appeared. Patterns based on PD-L1 expression seemed to correlate, but there were also responses from patients who were PD-L1 negative. "The initial reports were that the higher the total mutation burden, the better you’re going to respond to immunotherapy. Further analysis shows that doesn’t always bear out…., What we know is that we don’t know a lot.

"I think neoadjuvant trials are something that should be used with any novel drug combination because the readout is very quick," Amaria said. "You can get high-quality data with a small number of patients in a really rapid manner."

**Bringing Data Together to Predict Outcomes**

The MD Anderson team is just one of many worldwide looking at neoadjuvant therapy in melanoma. Amaria said an important task now is to develop protocols for trials that will allow data to be analyzed together so that investigators can come to conclusions about pCR that could be collectively presented to regulators. The goal, she said, "is to have a marker in the surgical resection sample that correlates with long-term outcomes, a marker of pathological complete response.

"My sense is that pCR from an immunotherapy-treated patient is likely going to be correlated better, and I can say that because we have done both immunotherapy neoadjuvant trials and BRAF-targeted therapy trials," Amaria said. "I can tell you from that experience that people who are getting pathological complete response after immunotherapy—are those the people who really seem to be deriving the long-term benefit and, hopefully, are cured."

The initial results reported in *Nature Medicine* were released alongside findings from the Netherlands that compared the ipilimumab/nivolumab combination in the neoadjuvant setting with treatment in an adjuvant setting in similar patients. According to the article's senior author, Jennifer Wargo, MD, associate professor in the Departments of Surgical Oncology and Genomic Medicine at MD Anderson, those findings demonstrated "a higher number of tumor-resistant [T-cell receptors] expanded in the peripheral blood of patients receiving neoadjuvant as opposed to adjuvant checkpoint blockade—supportive of what was seen in clinical models," which she said, "suggests that the neoadjuvant approach may be superior."³

Could the work at MD Anderson someday mean less therapy, less time with adverse effects, and lower overall costs for payers and patients? Amaria believes the answer to all 3 is yes. With the annual cost of combination ipilimumab/nivolumab at $256,000 according to the Association of Community Cancer Centers, the implications are enormous.

"People are more accepting of neoadjuvant therapy as an option in melanoma," Amaria said. The possibility of an approval in the neoadjuvant setting based on pCR "would be a big ask in melanoma," she added, but the precedent was set in breast cancer in 2013, when pertuzumab received such an approval from the FDA.⁴

Amaria explained that because there are so many more cases of breast cancer, it is easier to collect such data; doing so in melanoma would be impossible unless investigators collaborate worldwide. That collaboration process is under way, she said.

Despite all the progress in melanoma over the past decade, Amaria said the explosion in neoadjuvant trials reflects the need for good surrogate markers because melanoma remains so deadly. "Especially for those in the high-risk population, if this population is not relapsing, then we have definitely positively affected the natural history of their disease."