VDM VASCULAR DISEASE MANAGEMENT

INTERVIEW

# Perioperative Immune Checkpoint Inhibition and Cryoablation in Women With Triple-Negative Breast Cancer

*An Interview With Heather McArthur, MD, MPH*

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Heather McArthur, MD, MPH, clinical director of the breast cancer program at UT Southwestern in Dallas, Texas, and the Komen Distinguished Chair in clinical breast cancer research, speaks about her work examining the impact of perioperative cryoablation and immune checkpoint inhibition (ICI) on 3-year event-free survival in women with triple-negative resectable breast cancer after taxane-based neoadjuvant chemotherapy.

***How are current treatments falling short in their approach to women with triple-negative breast cancer (TNBC)?***

We have seen a lot of successful drug development and innovation in the metastatic TNBC setting with antibody drug conjugates, and immune therapy in selected patients. Recently, we have seen improvement in the curative intent setting, with the addition of immune therapy to neoadjuvant or preoperative chemotherapy for patients with stage 2 or 3 TNBC per the KEYNOTE-522 study, which improved 3-year event-free survival by essentially 8% and improved overall survival. So, we are seeing incremental improvements.

That being said, among patients who do not achieve a complete response to neoadjuvant or preoperative chemotherapy with immune therapy, about a third of them will experience a distant recurrence, typically within 2 to 3 years, then succumb to complications of that recurrence soon thereafter. So, there is still a lot of work to be done, particularly in that very high-risk population.

***What was the rationale for combining cryoablation with ICI in this patient population, and how is ICI supplementing the cryoablation procedure?***

When I worked at Memorial Sloan Kettering many years ago, I had the privilege of working with Dr Jim Allison, who later received the Nobel Prize for his work in identifying checkpoint targets and his role in successful development and checkpoint inhibitor therapy for the treatment of solid tumors, which became paradigm-changing for the treatment of cancer in general. He was doing in his lab at the time studies looking at combining cryoablation or tumor freezing together with immune therapy, and my mentor at the time, Larry Norton, said we need to be doing this in breast cancer because the data were so compelling. So, in 2011, we began enrolling in the first study, to my awareness, using immune therapy for the treatment of early-stage breast cancer and we treated patients with immune therapy vs tumor freezing or cryoablation vs the combination, and had no recurrences in that early effort, including in our TNBC cohorts.

The idea with cryoablation is that you are doing a couple things in that you are creating inflammation, thereby drawing immune cells into the environment. But you are also breaking down the tumor into tiny fragments that might be more easily digested by those immune cells. The overarching goal is to create a vaccine-like effect because you are able to train those immune cells to ingest those tiny tumor fragments and remember them. So, if a patient were faced with that same tumor-specific information at a later date, hopefully, one would not even know that that recurrence occurred because one's immune cells would go into attack mode and eradicate that recurrence.

We have undertaken a couple of pilot studies as proof of principle to show that we could combine cryoablation and immune therapy safely in an early-stage breast cancer setting, and we are currently wrapping up a multicenter phase 2 study that is applying this strategy in patients with residual TNBC after neoadjuvant therapy but before surgery. In short, we work backward from the surgery

date and apply the cryoablation or tumor freezing 7 to 10 days before surgery. Again, this is for that very high-risk population where a third of them are going to experience metastatic disease within the next 2 to 3 years. So, a very high-risk population and a population that really needs hope for a different outcome.

***Can you elaborate on why pembrolizumab was selected for this study?***

The study was originally supported by a sponsor that provided immune therapy in the form of ipilimumab and nivolumab as partners for cryoablation. When pembrolizumab was approved by the FDA, we updated the protocol to allow that new standard of care. We have a handful of patients who were treated with ipilimumab for 1 dose and nivolumab for 4 doses together with cryoablation and a second group of patients treated with pembrolizumab together with cryoablation.

***How do you anticipate the results of this study might influence the standard of care for patients with TNBC?***

The primary endpoint for this study is event-free survival, so, demonstrating improved cure rates with this approach. It is an approach that is done in radiology; it takes about 20 minutes to do the procedure, local anesthesia, so it is very easy to administer. Our hope is that this strategy will improve cure rates and will negate the need for additional chemotherapy in the adjuvant setting, and, if successful, may be moved earlier on in the course of disease to mitigate the need for all of the efferent chemotherapy that is currently being administered. I think there is a lot of promise and possibility for this approach depending on the results of this study.

***Looking ahead, do you foresee this combined approach being applicable to other tumor types or subtypes of breast cancer?***

Absolutely. The beauty of this approach is that it overcomes tumor heterogeneity and biologic uniqueness. So, if you have 100 patients with TNBC, that is simply an umbrella term that describes the absence of 3 biologic features but does not tell you anything about the unique biologic features that drive the biology for those 100 patients. So, you can imagine that if it can address unique biology in TNBC that it could be applicable as an approach to treating other cancer types as well. So, it could be broadly applicable. Again, we are hoping that this study that is underway will demonstrate improved curability that will increase enthusiasm for applying this approach more broadly across tumor types.

***Aside from what you have already mentioned, can you share any other research or projects you are working on?***

Certainly; we are working on a number of other studies that are looking at other elements of the tumor microenvironment. So not just T cells, we are looking at strategies that influence dendritic cells and natural killer cells. And we are also looking at strategies applying novel antibody drug conjugates in the curative intent setting as a potential replacement for chemotherapy, or as an add-on to immune therapy in the adjuvant setting for high-risk populations. So, there are a number of very exciting efforts that are ongoing, particularly in the curative intent, TNBC setting. ■

***Click here to see a video of this interview.***