The future role of immunotherapy in breast cancer is currently being actively investigated, so we anticipate that we will soon have further clues about the role of immunotherapy in breast cancer patients.

In this issue of ONCOLOGY, Cimino-Mathews and colleagues present a timely review on immune targeting in breast cancer.[1] Unlike other solid tumor types, such as melanoma, breast cancer has not traditionally been thought of as amenable to immune approaches. However, an increasing volume of correlative biomarker research and preclinical studies, as described in the review, support the concept that the immune microenvironment can be favorably altered in breast cancer in order to improve outcomes. The critical issue facing us now is figuring out which specific immunotherapies and combinations will be the most effective in breast cancer and in whom they will have the biggest effect. Tumor-infiltrating lymphocytes (TILs) have been reported to be positively associated with improved survival, but only in the triple-negative and human epidermal growth factor receptor 2 (HER2)-positive breast cancer subtypes and in early-stage disease.[2-5] This suggests that these breast cancer subtypes may be the groups to target; however, it is not clear why these subtypes present with higher levels of TILs.

High mutational burden, as observed in melanoma and non–small-cell lung cancer, has thus far also been associated with the best responses to T-cell checkpoint inhibitors. This could be due to the likelihood that some mutant peptides can present to major histocompatibility complex (MHC) class I molecules and can activate an antitumor immune response.[6] It is thought that this preexisting immune response is either exhausted or suppressed but can be reactivated by the T-cell checkpoint inhibitors. In general, breast cancer does not have the magnitude of mutational burden seen in other tumor types, although it is usually higher in the triple-negative and HER2-positive groups, as compared with the luminal breast cancers. Therefore, it is likely that only a minority of breast cancer patients will have enough robust preexisting immunity that can be “reactivated.” Indeed, the population that has high levels of TILs (≥ 50%) is small (< 10%), unlike the “programmed cell death ligand 1 (PD-L1)-strong” populations seen in lung and head and neck cancers, which comprised > 20% of the cohorts that had significantly higher objective response rates.[7,8] As discussed in the review, while early efficacy data on agents targeting the programmed death 1 (PD-1)/PD-L1 axis look promising in advanced triple-negative breast cancer, at this stage the total number of breast cancer patients who have received T-cell checkpoint inhibitors is low compared with other solid tumor types. What is encouraging is that in the small number of patients who did respond, the responses seemed to be durable.[9] There is still much to learn about the immune microenvironment in breast cancer. Why do some patients with breast cancer have TILs while others do not? What is the landscape of T-cell checkpoints in breast cancer patients with TILs? Characterization of the landscape of T-cell–negative regulators in breast cancer may help us design rational future combination studies.

Patients with TILs in their tumor at diagnosis have greater sensitivity to chemotherapy, as evidenced by increased pathologic complete response rates.[10,11] While the exact mechanism is unclear, this suggests that traditional cytotoxic chemotherapy can be immune-enhancing, rather than being immunosuppressive, as was conventionally believed. Preclinical data also support this hypothesis, particularly with regard to agents such as anthracyclines, oxaliplatin, and cisplatin.[12] This implies that cytotoxic chemotherapy can also stimulate immune effects and/or relieve immunosuppression. Hence, it is plausible that future immunotherapeutic strategies in breast cancer are likely to involve combinations, since we already have very effective treatments for breast cancer (eg, trastuzumab, doxorubicin) that are likely to be immune-promoting and have effects that could be enhanced with specific immunotherapy combinations.

The future role of immunotherapy in breast cancer is currently being actively investigated. T-cell checkpoint inhibitors are in phase II/III studies; combinations of T-cell checkpoint inhibitors, adoptive T-cell therapy, and vaccines are also under study by numerous groups. Let us hope that these trials
make the effort to collect the necessary correlative biological materials. Performing “immune profiling” of the tumor, including exome-guided neoantigen determination, evaluation of TILs[13] and PD-L1 protein assessment, as well as immune profiling of the peripheral blood, will help us understand the differences between responders and nonresponders. It is likely that these studies will enroll patients rapidly, so we anticipate that we will soon have further clues about the role of immunotherapy in breast cancer patients.  

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References:


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