From the Editor

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This issue of *The American Journal of Hematology/Oncology* contains a forward-looking review of immunotherapy and future trends in lung cancer, one of several malignancies that have for decades eluded efforts to effectively unleash the immune system for clinical benefit. Breast and lung cancers are among the most common cancers and leading causes of cancer mortality in men and women. In the past few years (and in the case of breast cancer, just in the last year), responses are being seen with the latest revolution in immunological therapy—checkpoint inhibition—which has allowed the crossing of the barrier from responses in melanoma and renal cell cancer to more common cancers. Malignant cells express foreign antigens, but due to similarities to other human proteins, as well as suppressive factors elicited by the tumor itself, the immune response is dampened. Furthermore, the immune system possesses "checkpoint" mechanisms to tamp down exuberant responses following infections. Attempts to goad the immune system into action with tumor or purified antigens, or nonspecific stimulation with interferons, interleukins, and more recently, activated dendritic cells, have worked only on cancers that are more immunogenic, such as melanoma.

A major breakthrough came with the discovery of checkpoint receptors on T-cells—initially the CTLA-4 receptor, and more recently the programmed cell death (PD-1) receptor. Ipilimumab, the first CTLA-4 antibody in the clinic, was approved for melanoma on the basis of enhanced survival, and has also shown modest activity in other tumor types. Antibodies to PD-1 and one of its ligands, PD-L1, have been shown to be even more effective in melanoma, and with fewer autoimmune side effects. Importantly, these are the first immune therapies to show a clear benefit in lung cancer and responses in early-phase trials for triple-negative breast cancer. Of note: the next issue of *AJHO* will feature a review of immunotherapeutic options and trends in the area of breast cancer.

Which patients will benefit the most from checkpoint inhibition? Mounting data show that a higher mutational tumor rate and more "neoantigens" may predict better response, consistent with a high degree of environmental DNA damage seen in ultraviolet-driven melanoma and smoking-related lung cancer. Triple-negative breast cancer is also known to harbor more genomic aberrations, and correspondingly, a higher incidence of naturally occurring immunity evidenced by tumoral lymphocytic infiltrates. Evidence also exists showing that the presence of tumor or stromal PD-L1 expression may predict a better response; however, this varies among tumor types, and optimal indices have not been defined.

Finally, there is much interest in further modulating the overall immunological thrust with combination therapies that include vaccines, hematopoietic and other cytokines, and alternate immunostimulatory pathways. As pointed out in our immunotherapy feature article on lung cancer in this issue, we are at the dawn of a new era of immunotherapy that holds promise for more sustainable responses across a spectrum of malignancies yet to be defined.