New Year's Resolution: Work to Do

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As 2015 begins, it is with great anticipation that we await the results of ongoing work in the field of melanoma therapy. We have come a long way, as immunotherapy with PD-1/PD-L1 checkpoint inhibition has gained approval as a standard therapy. Multiple phase 3 trials have expediently reached accrual, and the results of these studies could thrust PD-1 axis blockade into the first-line setting as standard therapy. We have moved past single-agent targeted BRAF therapy, with improved progression-free and overall survival with combined BRAF/MEK inhibition.[1,2] These are game changers; higher response rates and faster kinetics of response seen with the PD-1/PD-L1 checkpoint and BRAF/MEK inhibitors translate into an overall survival advantage. While the targeted agents may have higher response rates, we have not seen responses as durable as those seen with immunotherapy. In the past, this would be enough. Fortunately, today we realize that there is more. We have just begun to touch on the promise of immunotherapy. The future will elucidate optimal combinations of checkpoint inhibition and other immune-oncologic modalities and targeted agents. Answers will not only seek most favorable combinations but also appropriate dose, sequence, and schedule.

The field of checkpoint inhibition began with ipilimumab and progressed to PD-1/P-L1 inhibition. Today, there exist phase 1 trials testing novel inhibitory targets such as TIM-3 and LAG-3, with preclinical data proposing the benefit of combination therapy. Agonistic antibodies against T-cell co-stimulatory receptors (OX-40, GITR, CD137) have also burst onto the scene with multiple phase 1 trials in their early stages. These agents will look to replicate the success of their predecessors and will provide further options for our patients. We now know that lack of response to one immune therapy does not preclude subsequent response to another.

Oncologists today have the mandate to reconfigure their preconceived notions of immunotherapy. The toolbox has expanded past just interleukin-2, interferon, and ipilimumab. Newer cytokines (IL12, IL21), vaccines, immune suppressive enzyme inhibitors (IDO inhibitors), adoptive cell transfer, oncolytic immunotherapy, and T-cell engineering have expanded our armamentarium. The need to familiarize oneself with these options is tantamount. For example, the oncolytic therapy talimogene laherparepvec (T-VEC) utilizes an attenuated herpes virus that can only replicate in malignant cells. Unfettered viral replication leads to focal cancer cell lysis while secreting GM-CSF, more virus capable of infecting other malignant cells, and tumor antigens creating an immune stimulatory environment. Today, T-VEC therapy has shown local and distant tumor response, improved response rates and tumor control, and a trend toward improved survival. The minimal side effects seen with this therapy have made it an ideal candidate for combination immunotherapy. It is no surprise that recent data in combination with ipilimumab have shown improved response rates, and clinical trials of T-VEC with PD-1 therapy will begin in the near future.

Combinations hold the potential to overcome multiple barriers that tumor cells possess to evade a host immune response and provide an overall survival benefit to a greater proportion of patients. Initial forays into combination therapies for melanoma resulted in toxicity and discouragement.[3] This is not the current state of combination therapy. With the multitude of targeted therapies, immune modulators, and checkpoint inhibitors/agonists, extensive options exist. Early attempts in melanoma at combining radiotherapy and immunotherapeutics have shown promise of improvement in local and systemic control.[4]

Our mandate now emphasizes the importance of translating the advances made in the field toward the best patient outcomes. The major impetus toward this goal is based predominantly on predictive biomarkers that accurately foretell response to tumor immunotherapy. This dynamic paradigm holds the promise of appropriate patient selection and improved response rates while sparing patients valuable time and the expense of treatment-related morbidity. Recent trials have focused on requirements of tumor specimens (both archival and fresh) in addition to blood samples at multiple time points in therapy, including response and progression, in an effort to unlock this holy grail. We have also begun to retrospectively look for these markers in established therapies, including CTLA-4 blockade.[5] Initial data with PD-1/PD-L1 checkpoint inhibition indicating tumor PD-L1 staining as a go-no-go predictor was premature. PD-L1-negative tumors respond, but they do so at a lower rate, and therefore we continue to develop improved biomarkers. Wolchok et al[6] have indicated that dual checkpoint blockade may offer the ability to increase response rates in this population. Newer techniques focusing on pre-existing $CD8^+$ T cells distinctly located at the invasive tumor margin[7] and PD-L1 expression by tumor-infiltrating immune cells[8] have indicated a more sensitive predictive approach.

Led by the advances made in melanoma, immuno-oncology is burgeoning into a separate discipline amidst all cancers. This approach is actively investigated for its potential to translate from melanoma into similar breakthroughs in long-term survival in multiple tumor types. Currently, PD-1 and PD-L1 checkpoint inhibitors have garnered "breakthrough designation" in lung cancer, bladder cancer, and Hodgkin lymphoma. Checkpoint inhibition has already shown survival advantage versus chemotherapy in both lung cancer[9] and melanoma.[10] As the field of immuno-oncology expands, so does our need to understand the best candidates for its benefit, and the most optimal combinations and sequences. We have only begun this journey. It is clear that today we have many more tools in the tool box, and there is still much work to do.

In the special melanoma section that follows, we will take a more in-depth look at some of these advances and what they may mean to the treatment of patients with melanoma.

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Disclosure: Dr Hamid reports no relevant financial conflicts of interest to disclose.
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