



# IMMUNOTHERAPY: A REVOLUTION IN THE TREATMENT OF CANCER

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## INTRODUCTION

Immunotherapy has made big news this past year. It is impossible to watch a sporting event or news program without seeing a television advertisement for Opdivo® (*nivolumab*). There has also been a lot of press about the treatment of Jimmy Carter's metastatic melanoma with Keytruda® (*pembrolizumab*). Traditional treatment for cancer has been chemotherapy, which unselectively targets rapidly dividing cells, killing both malignant and normal cells. Over the past decade there has been a shift toward molecularly targeted therapy and immunotherapy. The immune system plays a critical role in surveillance and elimination of cancer cells. The goals for immunotherapy are to aid in detection of malignancy, augment immune responses, and overcome immune inhibition by tumor cells. Some of the current modalities employed to augment the immune system to achieve those goals are manipulation of T cells, and use of cytokines, oncolytic viruses, vaccines, monoclonal antibodies, and checkpoint inhibitors. The focus of this article will be on checkpoint inhibitors, which have become a practice-changing breakthrough in advanced lung cancer.

## CHECKPOINT INHIBITION

Immune checkpoints are molecules expressed on multiple tissue types that serve to down regulate the immune system to prevent damage from excessive inflammation and autoimmunity. Tumor cells can also use immune checkpoints to evade the immune system and promote tumor expansion and growth. The programmed death 1 (PD-1) receptor is an immune checkpoint expressed on activated T cells. Tumor cells express the programmed death ligand 1 (PD-L1) which can interact with the PD-1 receptor on T cells, leading to inactivation of T cells, inhibition of apoptosis of the tumor cells, and immune escape.<sup>1</sup> PD-1 and PD-L1 inhibitors have been developed which can overcome the immune checkpoint implemented by tumor cells and restore the immune system's anti-tumor effects. *Nivolumab* and *pembrolizumab* are IgG4 subclass PD-1 antibodies that have been approved for the treatment of

non-small cell lung cancer and melanoma based on clinical trials demonstrating a survival advantage. *Nivolumab* is also approved for renal cell carcinoma for the same reason. PD-1 and PD-L1 antibodies are showing promising responses in clinical trials in multiple other cancers including colorectal carcinoma, head and neck cancer, bladder cancer, triple negative breast cancer, non-Hodgkin lymphoma, and Hodgkin lymphoma.

## PD-1 ANTIBODIES IN LUNG CANCER

Until last year most of the advancements in the treatment of metastatic lung cancer were limited to targeted therapy, which is only beneficial to a small percentage of patients with an identifiable driver mutation. Systemic chemotherapy has been shown to improve survival in patients with stage IV disease versus supportive care alone,<sup>2</sup> but all patients unfortunately develop progressive disease, and second line options are limited. Cytotoxic chemotherapy with docetaxel had been the standard since the early 2000s, which illustrates the lack of progress.<sup>3</sup>

## SQUAMOUS CELL LUNG CANCER

In July of 2015 the landscape changed for the second line treatment of advanced squamous cell non-small cell lung cancer when the CheckMate 017 trial was published in the *New England Journal of Medicine*.<sup>4</sup> It was a phase III trial in which 272 patients with advanced squamous cell lung cancer who progressed after standard first line chemotherapy with a platinum doublet were randomized to either docetaxel or nivolumab. Overall survival (the primary endpoint) for nivolumab was 9.2 months compared to 6.0 months for docetaxel. One year survival was 42% for nivolumab and 24% for docetaxel. The risk of death was 41% lower with the nivolumab group. The improvement in overall survival is significant but the really exciting finding was the duration of response, which was 8 months in the docetaxel group, but has not been reached yet in the nivolumab group. There was a tail to the survival curve in that some patients were still having durable responses some years

later. The other significant advantage was tolerability. Nivolumab is not chemotherapy and therefore is not cytotoxic to normal cells. Treatment-related adverse events that were severe grade 3 or higher occurred in only 7% of the nivolumab group compared with 54% in the docetaxel group. The benefit of nivolumab was seen regardless of PD-L1 tumor expression. Nivolumab became the first PD-1 inhibitor approved by the FDA for the treatment of advanced squamous cell lung cancer that had progressed after a platinum doublet.

#### NON-SQUAMOUS NON-SMALL CELL LUNG CANCER

We knew that immunotherapy was effective in squamous cell lung cancer but was it effective in non-squamous non-small cell lung cancer (adenocarcinoma)? We got that answer from CheckMate 057.<sup>5</sup> It had an identical design to CheckMate 017 except it was for non-squamous lung cancer. Overall survival was significantly prolonged for nivolumab (12.2 months) compared with docetaxel (9.4 months). One year survival was 51% for nivolumab vs 39% for docetaxel. Nivolumab was well tolerated with similar rates of treatment-related adverse events compared with CheckMate 017. An interesting finding on subset analysis suggested there was a benefit to nivolumab compared with docetaxel in patients with a smoking history, but no difference in never smokers. In contrast with CheckMate 017, PD-L1 expression on tumor cells was associated with improved survival with nivolumab. In PD-L1 negative tumors, survival was similar between nivolumab and docetaxel. Nivolumab is now also approved for the second line treatment of advanced non-squamous non-small cell lung cancer.

*Pembrolizumab* is a PD-1 inhibitor that was granted accelerated approval by the FDA in October 2015 for the treatment of patients with advanced PD-L1 positive squamous and non-squamous non-small cell lung cancer that progressed after standard platinum-based chemotherapy. The approval was based on the phase I dose expansion KEYNOTE-001 trial.<sup>6</sup> The majority of patients were required to be PD-L1 positive. The percent of tumor cells with positive membranous staining correlated with the response. Patients with at least 50% positivity had a response rate of 44% and progression free survival of 6.1 months. Patients with less than 50% positivity had a response rate of 16.5% and progression free survival of 4.1 months. Patients who were PD-L1 negative had a response rate of 10.7% and progression free survival of 4 months. The treatments were well tolerated with a 10% incidence of adverse events that were grade 3 or higher.

#### PSEUDO-PROGRESSION

Immunotherapy can have unique response patterns that differ from chemotherapy or targeted therapy. Patients may have apparent progression of tumors or even appearance of new sites of disease but have symptomatic improvement. Subsequent imaging then shows regression of disease. This has been termed pseudo-progression and is probably due to an inflammatory response around the tumors. It can sometimes be difficult to differentiate between true-progression and pseudo-progression, but in general true-progression is characterized by rapidly progressive symptoms. Responses can take longer to observe than with cytotoxic agents, and some patients can have durable, stable disease without an objective response. Clinicians should not readily abandon immunotherapy and deem it a treatment failure unless the patient's symptoms are progressing. The traditional Response Evaluation Criteria in Solid Tumors (RECIST) may not be the optimal means of evaluating response for immunotherapeutic agents. New immune-related response criteria have been developed and are beginning to be incorporated into clinical trials.<sup>7</sup>

#### PD-L1 EXPRESSION AND RESPONSE

The ability to identify those patients who respond to immunotherapy would have a significant clinical and economic impact. The trend in most trials suggests that PD-L1 positivity correlates with response,<sup>6,8</sup> but some trials have shown a survival benefit in PD-L1 negative tumors.<sup>4</sup> Why the conflicting data? There are many possible reasons:

First, there is not one standard assay and most trials used different tests and cutoffs for positivity. Second, tumors are heterogeneous and a small core biopsy may not reflect the true PD-L1 status. A third possible factor is that most testing is done on archived samples; tumors are known to adapt and to acquire new mutations, so the original biopsy may not represent the current status of the tumor. Fourth, the expression of PD-1 and PD-L1 changes, based on cytokines and the local micro-environment. The bottom line is that until these issues are sorted out immunotherapy should not be withheld based on lack of PD-L1 expression alone.

#### CHECKPOINT INHIBITOR TOXICITIES

The toxicities associated with immune checkpoint inhibitors is unique to this class of drugs and is immune-mediated.<sup>9</sup> PD-1 inhibitors are generally well tolerated with serious adverse events occurring in only 10% of

patients, but when they occur they can be life threatening if not recognized and treated appropriately. Low grade events are generally treated by withholding the drug until symptoms return to grade 1 or less. For more serious adverse events (grade 3 or 4), treatment includes withholding the drug plus the addition of immunosuppression with corticosteroids, infliximab, or mycophenolate.

The most common side effect is fatigue, which is usually mild. Dermatologic toxicity is also common, resulting in a rash, pruritus, dry mouth, or occasionally vitiligo. Diarrhea/colitis is the most frequent gastrointestinal toxicity and is usually mild. Grade 3 or 4 adverse events are rare, and require treatment with high dose corticosteroids, with the addition of Infliximab or mycophenolate for patients who do not respond to steroids. Endocrine toxicities include hypophysitis, hypothyroidism, hyperthyroidism, and adrenal insufficiency. Serious cases of hepatitis and renal insufficiency have been reported rarely. Immune mediated pneumonitis occurs in only 3-5% of patients, but it can be life threatening; there were some patient deaths in early trials.<sup>8</sup>

#### THE FUTURE.

In addition to the PD-1 inhibitors nivolumab and pembrolizumab, PD-L1 inhibitors (atezolizumab and durvalumab) have been developed and show promising results in ongoing clinical trials. Trials are now looking at combination immunotherapy, immunotherapy in conjunction

with chemotherapy as first line therapy, and adjuvant treatment of early stage disease. We have several of those trials available for patients at the Ann B. Barshinger Cancer Institute. Research is also focused on identifying biomarkers such as PD-L1 expression for response.

#### CONCLUSION

Lung cancer is a global epidemic. It is the leading cause of cancer worldwide, and the leading cause of cancer deaths worldwide and in the United States. Globally, in the index year of 2008 there were 1.6 million new lung cancer diagnoses and 1.4 million lung cancer deaths.<sup>10</sup> Unfortunately 75% of patients present with advanced stage disease that is not curable.<sup>11</sup> Immunotherapy, a rapidly evolving treatment paradigm that is demonstrating dramatic and durable responses, has the potential to revolutionize our treatment of cancer in general, and lung cancer in particular.

Despite the advances with immunotherapy, however, the most effective treatment for lung cancer remains prevention of smoking initiation and emphasis on smoking cessation.

*“The awareness that health is dependent upon habits that we control makes us the first generation in history that to a large extent determines its own destiny.”*

—Jimmy Carter, *Everything to Gain*

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